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NEW CHALLENGES FOR TROPICAL MEDICINE

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**The Charles Franklin Craig Lecture
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The Charles Franklin Craig Lecture

I count it a special privilege and an honor to be asked to deliver the Charles Franklin Craig Lecture -- a lecture series which, I discover, dates back to the third year of Franklin Roosevelt's first term in office. It is a series which, over the years, has highlighted an impressive and diverse array of important discoveries and developments relevant to tropical medicine. The topics, which have been presented, reflect aptly the breadth and depth of Charles Craig himself who bestrode the field of tropical medicine for much of the first half of this century. ¹²He was a professor at the Army Medical School and at Tulane University; an administrator at many different Army Hospitals; an editor of the American Journal of Tropical Medicine; and a scholar -- author of more than 200 publications and 10 books.

All of us, and in many different venues, have regularly deplored the now dwindling numbers of Charles Franklin Craigs, scientists and physicians broadly schooled in tropical medicine. That this is so remains for me, a subject of the greatest concern.

The most recent comprehensive examination of personnel and resources devoted to tropical medicine paints a reasonably dismal picture. I refer, of course, to the

publication, The U.S. Capacity to Address Tropical Infectious Disease Problems. This presented the findings of a study undertaken by a Committee of the Institute of Medicine and the National Research Councils' Board on Science and Technology for International Development.³ I was privileged to serve on that Committee. The Committee concluded that "(U.S. expertise is) insufficient to ensure U.S. ability to cope with more than occasional domestic cases of these (tropical) diseases...and that expertise is not being adequately renewed." A national survey conducted by Committee staff revealed fewer than 300 specialists with clinical competence in tropical medicine and only 4 academic centers with more than 30 full or part-time faculty in tropical health work.

The Committee provided a thorough justification for increased resources being devoted to tropical medicine and offered many thoughtful recommendations. However, their invocations as with so many previous ones, met with little response. Let's face it. Tropical medicine in the abstract, with its wondrous array of polysyllabic diseases does not have the sex appeal of a disease problem, however rare, which afflicts Americans at home. Diseases of the tropics -- however important to residents of other parts of the world, to tourists or to the military, or however compelling the case for dealing with them because of humanitarian or global economic reasons -- are simply of far less interest than diseases perceived to be an immediate threat to our own national community.

How then can the case be made for garnering needed resources for research and control of many of the world's most serious and important problems -- problems which by any objective standard we should be addressing. Given the state of the economy and the deficit, this would hardly seem to be a propitious time to endeavor to make a compelling case for augmenting resources devoted specifically to tropical medicine, be it research capacity building or control programs. Indeed, I would, absent a special case being made, warrant that such an effort would be even less successful than such efforts have been over recent decades. Is there cause for making such a case? I believe there is and, I should like today to draw to your attention, new challenges and problems now becoming apparent in three different arenas, each of which commands urgent attention. Each demands approaches involving infrastructure development, research and training. All involve development of component activities which bear specifically on our capacities in the broader field of tropical medicine. Certain of the component activities are overlapping in character. Specifically, these new or newly perceived challenges are: (1) the threat posed by new and emerging microbial agents; (2) increasing concerns about the possible use of biological warfare agents, and; (3) recent crises and challenging opportunities posed by the current global immunization program. Let me briefly refer to each of these.

The emergence and progressive spread of the Human Immunodeficiency Virus has proved to be a singularly humbling experience both for those engaged in research as well as for those engaged in public health. I believe it is fair to say that we as a nation

had grown implicitly, if not explicitly, arrogant in the belief that serious infectious disease problems were a concern of the past in our well-sanitized industrial world. The HIV epidemic shattered that confidence. But, it went further than this. It demonstrated that even with extraordinary funding to expand biomedical research efforts, effective weapons to combat the problem were not readily forthcoming. In fact, as you know, neither a curative drug nor an effective vaccine is at hand or even imminent.

Inevitably, the question had to be asked whether this was an exceptional, aberrant phenomenon or whether we might anticipate other microbial challenges of catastrophic proportion. With Josh Lederberg's encouragement, a meeting was convened in 1989 to survey the field of this and other new and emergent infections and to ascertain the potential risk which new agents might pose.⁴ To me, the meeting offered a number of sobering reflections, the most pointed of which was offered by Lederberg himself who concluded the meeting with these words: "Our only real competition for domination of the planet remains the viruses" and "the survival of humanity is not preordained." Subsequently, an Institute of Medicine Committee on Emerging Microbial Threats to Health was convened under the chairmanship of Lederberg and Bob Shope. Many here participated in those deliberations. The Committee's report was released this autumn.⁵

The simple fact, amply explicated in the book, is that all human pathogens -- whatever their origin, whether new or recently emergent -- now have an increasing

likelihood of survival and epidemic potential, given the factors of increasing population, crowding in ill-sanitated urban areas, and greatly heightened population mobility. The world of today, containing twice the population of a generation ago, with many times more than that now living in urban areas, offers an increasingly rich locus for transmission of microbial agents. Likewise, the potential for these agents to be disseminated widely and rapidly throughout the world is unprecedented. Indeed, such dissemination is precisely what we have witnessed -- not only with HIV but, as you know, with dengue, Lassa, Ebola and Marburg viruses, Lyme disease, parvovirus, and many others. It is a certainty that over the coming years we will be challenged by many more agents for which we do not now possess adequate diagnostic methods or vaccines and for which effective therapeutic and other preventive measures are deficient or lacking. These conclusions and perceptions are not now widely known. They must be and articles such as Richard Preston's recent vivid portrayal in the New Yorker of Marburg and Ebola virus disease are especially valuable in educating both the scientific and lay publics.⁶

A well-defined blueprint for response is difficult to contrive given the breadth and complexity of the challenge. The Committee, however, has identified critical elements. I should like to refer only to a few of the most important.

Surveillance is identified as the most important of the initiatives if, indeed, new or emerging infectious diseases are to be detected in a timely manner so as to permit

preventive or therapeutic measures to be developed. Ironically, this hearkens back to the subject of the first Craig lecture presented by Charles Franklin Craig himself.⁷ In that lecture 56 years ago, he argues the need for more accurate statistics regarding the distribution and incidence of tropical diseases in the United States itself citing, in particular, malaria, dengue, amoebiasis, and bacillary dysentery. Surveillance today is better than it was then but, as the report points out, it remains far from satisfactory even today in this country.

Globally, surveillance is woefully lacking. Even for well-recognized conditions, surveillance has been low among the priorities even of special programs. In illustration, I cite the World Health Organization's Expanded Program on Immunization which began in 1974, but which for the next 15 years, elected not to develop a surveillance program, even for the vaccine-preventable diseases included in that program.

One can't help but wonder what might have been the history of AIDS had that disease been detected earlier. Our antennas, however, were few. Little known is the fact that, beginning in 1972 and extending through 1986, WHO supported an extensive surveillance program throughout the rain forests of northern and central Zaire to detect cases of monkeypox and to characterize them epidemiologically. This, of course, was the earliest locus of emergent HIV. Mobile teams working with transponder radios were in continuing contact with an extensive network of government clinics and mission stations in an effort to detect smallpox-like cases. More than 300 cases of monkeypox were

identified. Given the superb quality of surveillance which was established, it was superb --, it seemed to us wasteful not to extend the scope of the team's activities to embrace other diseases. Among those of known and obvious interest were the newly recognized hemorrhagic infections, Lassa, Marburg, and Ebola virus diseases, among others. And this area, of course, as I noted, was the presumed epicenter for HIV. Our resources were limited and so we communicated with a variety of groups in WHO, USA, and Japan offering an opportunity for special studies to be undertaken if anyone would bear the necessary incremental costs. None expressed interest.

A global surveillance program is recommended by the IOM Committee which embraces four basic components: (1) A mechanism for detecting clinically new or unusual diseases or syndromes; (2) a supporting diagnostic laboratory; (3) a data system for reporting of cases and analysis of reports, and; (4) a response mechanism to investigate outbreaks and to mobilize control efforts. To me, this defines well the characteristics of a needed network of tropical medicine centers. To function effectively, such centers would have to be well versed in the expected in order to identify the new or unique.

The Committee identified a second important problem -- provision of vaccines. It recommended that mechanisms be found to support vaccine research and development as well as production. Vaccines are singled out, in particular, because of the obvious

implications for prevention and the limited incentive for the private sector to assign resources. For those concerned with tropical medicine, this must also strike a sympathetic note.

In brief, it is difficult to conceive of how we could possibly address the challenge of new and emerging microbial agents without strengthening and developing a framework well-suited to a better understanding and control of the tropical diseases as a whole.

The second challenge to which I should like to refer is that posed by biological warfare agents. In contrast to open discussion of the threats posed by the use of nuclear and chemical weapons, comparatively little has been said about the potential for use of biological weapons. I suspect this can be attributed, in part, to the fact that biological weapons are not thought to have been deployed in warfare perhaps since Lord Jeffrey Amherst distributed smallpox infected blankets during the Pontiac rebellion of 1763.⁸ This has led some to suggest, hopefully, that a higher moral imperative would preclude the use of such agents. Moreover, many engaged in biomedical research understandably regard BW with such repugnance as to make the subject itself an improper one for discussion. I believe the time has come for us to take this threat seriously and to begin serious discussions of the threat posed.

Many believed and hoped that the BW specter had been laid to rest when

President Nixon decided in 1969 to cease research and development on offensive BW weapons. Recall, however, that in part, this decision was predicated on the availability of nuclear retaliation should any country resort to the use of BW agents. This, itself, is a chilling thought. In 1972, an international Biological Weapons Convention was adopted which prohibited the development, production, and stockpiling of biological weapons. More than 100 countries ratified the treaty, among them Iraq, but the treaty made no provision for verification. U.S. government support for BW research, even for defensive purposes, has been under continuing attack -- when not totally ignored -- and, recently, we have witnessed a major loss of key scientists at USAMRID. However, the events of the past two years indicate that a major reappraisal of both our attitudes and our program are necessary. This has important ramifications for tropical medicine as many of the agents of concern are disease agents of importance to the tropics.

Other countries at present regard BW as having a greater potential than what I sense to be the prevalent view among US scientists and policy makers. Twenty years ago, there were only two countries with BW programs; today there are 10 and 20 others are known to be seeking the technology. As we learned after Desert Storm, Iraq had been engaged in large-scale production of BW weapons with every indication that they expected to employ them. Russia has had an extensive program which, as we have recently learned, continued in operation at least into the early part of 1992.

As the microbiologists here would know, BW poses special problems. Reasonably

large scale production requires comparatively little space and buildings so used have no distinctive characteristics such as do production facilities for chemical and nuclear weapons. Verification of adherence to a treaty is thus extremely difficult. Moreover, needed equipment for production has alternative and perfectly legitimate applications making it impossible to deter development of BW capability by embargo of critical production equipment. Finally, the costs of producing quantities of all manner of possible agents are affordable to even the poorest of third world nations. Those concerned with arms control measures label BW as potentially "the poor man's nuclear bomb." Couple these facts with a post Cold War era now beset with a host of small, politically unstable countries, some of whom espouse and practice terrorism as a legitimate weapon and it becomes apparent why there has been a sudden awakening of interest in BW.

To define a defensive strategy is quite as difficult as attempting to deter or verify the development of BW capacity in a country. Efforts to interdict possible perpetrators are unlikely to succeed given the small volumes of material needed. Thus, the key elements of defense must rely on early detection, prompt investigation and an analytic capacity to deduce the probable origin of the epidemic, perhaps through analysis of the genetic structure of the organism involved.⁹ Wheelis argues the need for a global network of clinical-epidemiological centers of a character similar to that which the IOM Committee outlined as being needed to deal with new or emerging organisms.

Basic and applied research would also be vital to better understand organism pathogenicity, to identify rapid diagnostic methods and to develop and produce vaccines. Such research is, of course, wholly relevant to tropical disease problems.

Neither of the two challenges I have discussed have, as yet, a well-articulated strategy or, as yet, a vocal constituency either in Congress or the Executive. A broader public appreciation of the problems is yet to come. It is absolutely imperative, however, that these problems be addressed.

There is a third challenge of interest, however, which does have broad support and interest but which must now experience major redirection. I refer to the global program on immunization and the new Children's Vaccine Initiative. The program, begun in 1974, was a direct outgrowth of smallpox eradication, and has, as its objective, the provision of six antigens to children throughout the world. The antigens are diphtheria, pertussis, tetanus, measles, poliomyelitis and BCG. With substantial and increasing support from UNICEF, Rotary International, WHO, USAID, and other agencies, it reached the point where by 1990, 80 percent of all children were receiving these vaccines. This is an unprecedented achievement in public health. An estimated two to three million deaths are being averted every year and, in the Americas, polio transmission appears now to have been interrupted. The last known case occurred in August 1991 in a small town 50 kilometers east of Lima Peru.

The extraordinary advances in biomedical sciences now offer real promise for the development of many more effective vaccines. And vaccines occupy a special role among the panoply of health interventions. Geoffrey Edsall said it most aptly, "Never in the history of human progress has a better and cheaper method of preventing illness been developed than immunization at its best."¹⁰ Accordingly, in 1990, a consortium of international and bilateral agencies agreed to embark on the Children's Vaccine Initiative to develop new vaccines or improve existing ones which: (1) require only one or two doses; (2) can be given at or soon after birth; (3) can be given as a multiagent preparation, preferably by mouth; (4) are effective against the major causes of child mortality, and; (4) are affordable.

Efforts are being made to expand the capacity of developing countries both for vaccine research and production¹¹; task forces are developing the research agendas to bring selected vaccines to market; and global strategic plans for production and quality control are being developed.

As the strategic planning group has progressed in its work, however, it became apparent that unsuspected serious deficiencies are extant. Vaccine production for many vaccines is nowhere near what is needed and resources for vaccine purchases are diminishing; vaccine quality control for locally produced vaccines is negligible to non-existent; and surveillance, the foundation for disease control, remains seriously deficient and for many diseases, totally absent. Present leadership of the immunization program

has as yet scarcely begun to seriously address any of these issues.

A series of urgent meetings are now taking place in an effort to redirect this gargantuan undertaking. The deficits, however, are readily apparent -- deficient surveillance, lack of capacity for producing effective and safe vaccines and a need for human and institutional research and development capacity throughout the third world. Generically, these are very similar to the needs identified to meet the two great challenges to which I referred earlier.

Where does all this take us? The clarion call echoing through Congress, NSF and NIH today is the need for relevance of basic research. Personally, I feel this has been overstated and regrettably distorted. There is an element of reality, however, to the fact that research and development programs which are more cogently described in terms of identifiable needs and products have a better chance of success in being supported than do those couched in less explicit terms of research for the sake of research.

If we are to rebuild our expertise in tropical medicine, I believe the prospects for success are best if justified, as I believe they can be, in terms of programs designed to meet challenges of domestic relevance. I have identified two for you. They could also be justified in relationship to an international challenge which presently does command interest and support such as the program on immunization. As one reviews the needs

for each of these, the responses are broadly overlapping and the development of each holds real promise for advancing our efforts in tropical medicine. They may not bear the precise labels you would like or I would like but it seems to me that the product, not the label, is what really matters. I look forward to an opportunity to work with you in devising a needed strategic plan and in persuading a broader audience of the importance of implementing it.

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