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EXCELLENCE IN RESEARCH IS NOT ENOUGH*

PHILIP K. RUSSELL†
Walter Reed Army Institute of Research, Washington, D.C. 20307

Members of the Society, Distinguished Guests, Ladies and Gentlemen—

First, I would like to thank the Society for the privilege of being President for the past year and give special thanks to our Secretary-Treasurer, Dr. John Scanlon, for doing so much of the work necessary to the successful functioning of the Society.

I found that one of the most difficult tasks as President is choosing a topic for today's speech. I had an initial impulse to discuss field research and use my experiences in Pakistan, Southeast Asia, the Caribbean, and the eastern shore as a basis for the talk. That approach would have allowed me to give proper credit and recognition to several colleagues who have been very important in my research career. However, that approach would have been, of necessity, anecdotal and on some reflection I discarded the idea.

I also considered an in-depth analysis of a scientific issue, but I decided that no matter which subject I chose I would run an almost certain risk of boring a large segment of the audience who do not share my personal scientific interests.

Having rejected those options I did what I suspect some of my predecessors may have done. I read many of the earlier presidential addresses seeking either inspiration or a challenge to which I might respond. A presidential address that captured my attention was presented just over a decade ago and met both criteria of being inspiring and challenging. The message in that address is as important today as it was when it was delivered to the Society by Doctor William C. Reeves at the 1972 meeting. The title of Doctor Reeves' address was "Can the War on Infectious Disease Be Lost?" Doctor Reeves' paper dealt with some of the major public health issues facing the world, and expressed a realistic concern about the serious threats posed by the traditional enemies of health in the tropics—yellow fever, plague, dengue, the arboviral encephalitides, other vector-borne virus diseases, malaria, cholera, and a long list of other infectious diseases so well known to this audience.

Doctor Reeves went on to discuss the deterioration of our collective abilities to deal with the increasing infectious disease threat using the traditional weapons available to public health authorities—sanitation, vector control, insecticides, antibiotics and anti-parasite drugs, and the available vaccines. Burgeoning populations in the developing world, social changes, increased mobility due to modern transportation, rapidly increasing drug resistance by parasites, and insecticide resistance by arthropod vectors all contributed to a world-wide situation which led Doctor Reeves to pose the question in the title of his address. And that question is as important today as it was in 1972.

In the decade that has passed since that scholarly and farsighted analysis the overall situation has become even worse in many respects. There have been some major accomplishments, most notably the global eradication of smallpox through the efforts of WHO and several member nations, some national successes such as excellent control of Japanese encephalitis in Japan, and some major advances in therapy such as oral rehydration for cholera and diarrheal diseases, but for every victory in the war on infectious diseases, we have had major defeats.

Malaria is clearly one of the most important problems. During the 1970s the world-wide incidence of malaria increased significantly, peaking I believe in 1978. In 1980 over 8 million cases were recorded by WHO outside of Africa in addition to an estimated 6 million cases in sub-Saharan Africa. It is certainly probable that these figures underestimate true incidence. In Africa, by one estimate, over a million deaths per year in children are associated with malaria.

Forty-six percent of the world's population remain at risk of malaria. Some progress has been made in control of malaria in the past 5 years

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† Present address: Fitzsimmons Army Medical Center, Aurora, Colorado 80045.

by intensified national control efforts, but these have been costly and difficult and the overall picture remains bleak.

Drug resistance of *Plasmodium falciparum* is a continually increasing and expanding problem. Chloroquine resistance is spread from Eastern India throughout Southeast Asia. Resistant strains of *P. falciparum* are widespread in South America occurring in 10 countries. Africa has recently become an area where drug resistance is a serious problem. Between 1978 and 1982, chloroquine resistance was confirmed in seven east African countries. Mutiple drug resistance is now widespread in Southeast Asia and South America, and we are reduced to relying on combinations of expensive drugs for treatment in some areas. The combined effects of insecticide resistance, vector biology, drug resistance, and economic factors produce a very unsatisfactory situation.

Dengue is another disease for which epidemiologic studies have very impressively recorded a continuous series of losses to the dengue viruses and their *Stegomyia* vectors—principally *Aedes aegypti.* This year, 1983, marks 2 decades of my personal interest in dengue. In 1963 the first major Caribbean epidemic since World War II began with a serious island-wide outbreak on Puerto Rico. Our group at Walter Reed identified the epidemic strain as a unique subtype of dengue-3. That serotype subsequently became widely disseminated in the Caribbean Islands.

The dengue-3 epidemic was followed by an outbreak of dengue-2 in Puerto Rico in 1969 which subsequently involved all of the Caribbean Islands except Cuba, as well as Colombia and Venezuela. This spread of dengue, and the fear that these events signaled a potential danger of even more dengue and the possibility of an outbreak of dengue hemorrhagic fever or an *Aedes aegypti*-borne epidemic, led to the establishment by the Pan American Health Organization of a Scientific Advisory Committee on Dengue. The committee later became the Scientific Advisory Committee on Dengue, Yellow Fever and *Aedes aegypti.* This committee enabled PAHO and the international community of scientists most interested in the problem to do a much better job of surveillance and epidemiologic studies. Thus, the next dengue epidemic in the Caribbean, which occurred following the introduction of an African strain of dengue-1 virus into Jamaica, was very well studied and excellent epidemiologic and virologic data documented the spread of that virus to all the previously dengue-affected countries and, in addition, we saw the invasion of Cuba, Honduras, Guatemala, El Salvador, Mexico, and a few cases in south Texas. Huge areas where *Aedes aegypti* had previously been eradicated or well controlled became endemic. The dengue-1 epidemic in Cuba was followed by the introduction in 1981 of a dengue-2 strain which caused a disastrous dengue hemorrhagic fever (DHF) epidemic with hundreds of deaths and thousands of cases which required an immense effort by the Cuban health structure to care for cases and control the vector.

I neglected to mention the introduction of dengue-4 virus into the Caribbean, probably from the Western Pacific, which also became widespread. We now have a situation in the Caribbean in which four serotypes of dengue have established endemicity.

To extend Doctor Reeves' analogy of a war on infectious diseases—the campaign against dengue in the Americas has been about as successful as Napoleon's invasion of Russia—a resounding defeat.

During the same past 2 decades, parallel events in Asia saw the extension of severe DHF epidemics into Burma, Indonesia and Vietnam with continuous increases in morbidity due to DHF in the Southeast Asian and Western Pacific regions as a whole. Other areas of the world, the Pacific Islands, India, and East Africa also have seen large dengue epidemics.

This has all occurred during an era in which laboratory and field research has produced a wealth of new information on vectors, the viruses, the immunology on the pathogenesis of disease, and on the quantitative epidemiology of dengue. Excellence in research on dengue has so far produced elegant explanations of why we are losing the war.

I have used two examples, malaria and dengue, to illustrate the point that the many infectious diseases are very successful opponents. There are many other examples where we are losing ground.

Other arthropod-borne virus diseases have also been expanding their impact in recent years. Ross River virus, previously confined to Australia, joined the dengue viruses in producing epidemics in the Pacific Islands.

A few years ago, Rift Valley fever virus moved out of its traditional endemic region and caused an unprecedented epidemic in Egypt with a tremendous impact on human life and also on the livestock industry.

Japanese encephalitis is another disease which

is causing major problems in spite of impressive research on the virus and on the epidemiology and immunology of the disease. Development and use of killed virus vaccines have been associated with excellent control of the disease in Japan and have probably had a significant effect in China. However, we are seeing major outbreaks of Japanese encephalitis in India and Nepal, and a very serious emerging pattern of annual outbreaks in northern Thailand. Current control technology is inadequate. A more effective and more inexpensive vaccine is very badly needed for Japanese encephalitis, and I am sure that one could be developed using either current technology or technical options which will soon evolve from cloning of the Japanese encephalitis virus genome.

These events in which we appear to be consistent losers in the war on infectious diseases have occurred in an era in which we have seen amazing advances in scientific research. This is an era in which molecular biology came of age, and the terms genetic engineering, gene cloning, monoclonal antibiodies and synthetic peptides have become commonplace, and "biotechnology" has become a bureaucratic buzzword. One might think from reading the scientific news report and the popular press that solutions to many of the world's major public health problems are near at hand.

For myself and, I suspect, most members of this Society, the past decade has been an exciting time to be involved in scientific research. Society meetings have been important forum for presentation and discussion of major advances in immunology, molecular biology, pathogenesis and epidemiology of tropical diseases. Every field has been intellectually very exciting, and the membership of the Society can be justly proud of the excellent research being done.

Excellence in research, however, is not enough. Basic research, no matter how good, provides only the information on which to base the essential follow-on actions. The actions I refer to are the steps needed to develop the useful products and practical methodology, and to get them into operational use in the field. In order to harvest the immense potential benefits of the recent and soon-to-come advances in basic research, a national and international effort in developmental research will be needed. The technology required for the development of new vaccines, drugs, or other approaches to disease control lies largely in the developed countries and, in my view, the moral obligation also resides within the developed countries. At the present time, however, I see in the United States a serious deficiency of resources and lack of national commitment to the development of new products and new methodology for control of diseases in the developing countries. The existing programs of private foundations, the National Institutes of Health (NIH), the U.S. Agency for International Development (USAID) and the Department of Defense are commendable as far as they go, but they are very limited in both dollars and, especially, in scientific manpower committed to development programs.

A partial explanation lies in the fact that basic research is largely public funded and carried out in academic and some government institutions. The development of drugs and vaccines and insecticides has been heavily dependent on investment by industry and to a large extent carried out by industrial firms. The industrial sector has, in the past, made the major investment of dollars and human resources necessary to put new products into use. A notable exception has been the drug and vaccine development done or underwritten by the U.S. Army where government funds covered the early phases of development and subsidized the end-stage industrial development. Here, the needs of the military were the critical factor which caused government funding of product development.

The heavy reliance on industrial investment for development of the products needed in the tropical medicine field is, I believe, a thing of the past. I will not go into the reasons for the decline of vaccine development and manufacturing in the United States but it is a well recognized problem, and leaves this country with a serious deficiency in the ability to undertake development of new products such as malaria vaccines, and new viral and bacterial vaccines, especially those needed principally by the developing countries. If we are to exploit the potential of our research, we cannot rely heavily on industry to make the investments. The profit motive is simply not sufficient for many of the potential products needed in the tropical medicine field and disincentives, such as product liability, are great. A greater responsibility for product development must be borne by the public sector through government agencies and by foundations.

This poses an important problem because funds for development efforts will, unfortunately, be in competition with funds for basic research. It is

also true that undertaking major developmental efforts increases rather than decreases the necessity for basic research, at least in the short term. Those experienced in vaccine development realize that development efforts inevitably raise new questions that need to be answered by basic scientists. Thus, in any field a product development effort must be in addition to, and not replace, basic research in the same field. For research managers this is a restatement of the old adage—there is no such thing as a free lunch.

The recent advances we have all seen in basic research have provided, or very soon will, the scientific basis on which to develop new disease control technologies. The creation of new scientific information which holds potential for development into practical disease control methods, I believe, carries with it an obligation to follow through with developmental research and, ultimately, the development of new control programs.

These advances in research are producing an almost dismaying number of new options which need to be pursued through the development process. Malaria is a prime example of this. Several antigenic proteins from various stages of the parasite which are related to protective immunity are being ientified and characterized. Very sound theoretical concepts of vaccination of individuals and populations have been developed which appear very promising and are currently being tested. However, we are facing an immense developmental effort. Consider the fact that for *P. falciparum* alone we foresee the possibility of three types of vaccines—anti-sporozoite, anti-blood stage, and transmission-blocking vaccines. Each of these antimalarial vaccines may have an important future role in malaria control and all need developing. For each of these different vaccine concepts a developmental research effort will have to evaluate and test several options. For each malaria protein which has been shown to play a role in protective immunity there will be a need to deal experimentally with the issue of using peptide synthesis to reproduce critical antigenic domains, or to use cloned genes and produce fusion proteins as immunogens, or possibly use other approaches such as carrier organisms. Development of a synthetic peptide vaccine will require a large amount of work on configuration of the peptides, on carrier proteins, on adjuvants, and on formulation of vaccines. Pursuing the development of malaria vaccines through gene cloning will require extensive work on expression and purification as well as on carriers, adjuvants, and vaccine formulation. This developmental work is of necessity largely empirical, and is very costly and time-consuming.

Just following through on the brilliant research on sporozoite immunity by Doctor Ruth Nussensweig and her collaborators at New York University will be a formidable development task. We should keep in mind that we need to do more than develop a reasonably effective vaccine which costs $25.00 a dose for use by travelers and the U.S. military. The developing countries need very inexpensive and very effective long-lasting vaccines. I am quite sure they can be developed, but it will require some major investments in both immunologic research and in development of manufacturing technology.

The sporozoite vaccine will be the first real challenge in the malaria field, but soon we will be faced with the problem of even more complex blood-stage vaccines and transmission-blocking vaccines. Vaccine developers will have to deal with the several separate proteins associated with protective immunity. These will have to be developed into vaccines individually and in combinations. I'm sure you can see the magnitude of the problems if we are to do the work necessary to eventually produce the best vaccines possible for the developing countries.

Other fields face similar problems with multiple development options that need to be fully explored. Research on the pathogenesis of bacterial diarrheas and on the genetics of the bacterial pathogens has produced some very exciting possibilities. Insertion of *Shigella* genes into the attenuated typhoid type 21A vaccine strain to produce a typhoid-shigella vaccine is a very promising approach that can be extended to other *Shigella* species. Similar approaches using genetically engineered *Escherichia coli* strains to carry *Shigella* antigens are also very promising. Add to that the potential of vaccination with pilus proteins, adherence factors, and toxin subunits of enteric bacteria one can readily see an overload of our existing capabilities to do the development work.

I might mention here the very exciting recent studies by Moss and his colleagues at NIH in which they inserted hepatitis B genetic material into vaccinia virus, producing an infectious virus which immunizes against both. The whole concept of using carrier organisms, either viruses or bacteria, for immunizing adds another large new dimension to options for vaccine development.

Use of carrier organisms may ultimately prove to be an excellent method for producing inexpensive vaccines for the developing world. It is certainly an area in which exploratory development efforts are well justified.

The list of potential development options is a long one, and extends to most areas of our interest. In the case of Rift Valley fever, genetic engineering appears to offer a very good opportunity for development of a second generation vaccine that, if properly developed, can be manufactured without the necessity of phase 4 biocontaminant and may ultimately be inexpensive enough to be of real value to the African nations. The emerging new concepts on the basic reservoir of Rift Valley fever in floodwater *Aedes* may offer yet another important opportunity to control the virus at its source. Again, to exploit these options will take resources and dedicated people to do the development and carry out the work in the field.

The U.S. Army Medical Research and Development Command has long recognized the necessity to follow up basic research with product development efforts. The history of military medical research, with its long list of successfully developed vaccines from typhoid through Venezuelan equine encephalitis, adenovirus and meningoccal polysaccaride vaccines attests to the fact that the Department of the Army expects a return on its investments in research in terms of useful products and practical disease control methods.

A good example of this view of research management is the antimalarial drug program, which extends from very basic research to field trials. It is important to note here that the final industrial development of drugs requires close collaboration with private industry usually in the form of collaborative development agreements which recognize the needs of the government and the needs of the industrial developer.

This type of collaboration with private industry is also essential in vaccine development. Industrial development must depend on the technical expertise which only experienced manufacturers can provide. Given the fact that, for many of the drugs and vaccines that need to be developed, the private sector cannot or will not take the initiative and the financial risks alone, collaboration between government agencies and industrial developers becomes a necessity.

I might add here that the many ethical manufacturing firms appear to be willing and anxious to undertake development efforts in collaboration with national and international agencies.

In the Army Medical Research and Development Command over the past several years we have come to a realization that options for product development—whether drugs, vaccines, or vector control measures—far exceed our current resources to exploit them. We are finding that we do not have the dollars or the scientific manpower to handle all the possibilities emerging from basic research that need to be explored—and do a thorough job.

Current work on dengue vaccines, on meningococcal type B, gonorrhea, anti-parasitic drugs, and enteric bacterial vaccines, is extending our developmental resources to the limit in both drug development and vaccine development. Some very painful decisions and prioritizations have to be made. In the civilian sector I see an even bigger problem. The investment in basic research is not balanced by an appropriate investment in development. Nor do the current programs of USAID and the funds in the World Health Organization's Tropical Disease Research Programme fill the need. As I said earlier, I do not believe private industrial investment will fill the need *and,* unless there are some significant changes in our national policies, new disease control methods will not be forthcoming in the time frame that is possible.

Let me digress for a few minutes to comment on the current role of tropical medicine in regard to international politics. I believe that this country has a potential in tropical medicine that is not being effectively used. In the current Caribbean scene the U.S. has been using political, economic and military initiatives as instruments to achieve national policy objectives. I do not quarrel with what has and is being done, but I personally feel that we have not utilized the potential of medicine and public health as an effective tool to further our own national interest and to improve the quality of life in the Caribbean countries which are in the news every day. This country has an immense potential to develop better public health technology and capabilities, and to get them into the field to do some real good. Our most important adversary in the Caribbean—Cuba—has a national policy to use medical research, training and public health to further Cuban political goals, and I believe they are having an impact. The U.S. can and should do much more in this field. Investing in an institution with a defined mission of research,

training, and developing public health technology for the Americas south of Florida and Texas may well be an excellent long term investment, considering the political problems we are facing in the Americas.

Investing in public health initiatives for the underdeveloped countries based on exploitation and development of technologic options could be a very wise long-range policy for the U.S.

This Society has had and can have a significant role in effecting national policy. For many years, unfortunately, a main role of the Society, both through its Committee on Public Affairs and as individuals, has been defensive and reactive. We have been in the position of defending various segments of the research community against budget and manpower cuts. At one time or another we have collectively spoken out to defend the Army and Navy overseas laboratories, the Gorgas laboratory, NIH overseas programs and USAID programs, and we have been very helpful in many instances.

In the future, though, I think we have the opportunity to be proactive rather than reactive, and do more than just defend the status quo. There are some favorable political signs of more national interest, at least at the Congressional level, in the potential of tropical medicine. In the recent Office of Technology Assessment study of the Gorgas Memorial Laboratory (GML), a statement was made that it was ironic that the GML was in danger of extinction at a time when tropical medicine in Latin America has never been more relevant to the U.S. Happily the funding for GML funds has been restored.

Two years ago the Society appointed an ad hoc Committee on the Future of Tropical Medicine, headed by Doctor Robert Shope. This committee was charged to seek ways to focus the attention of the political hierarchy on our national position on tropical medicine. This committee approached the Institute of Medicine of the National Academy of Sciences and convinced the Institute to conduct a study on the U.S. Capacity of Addressing Tropical Disease Problems. This study will get underway soon, supported by several government agencies and foundations. If the study does as the Society intends, it can produce a blueprint for an effective national policy in tropical medicine research, development and overseas initiatives.

I'm sure that many Society members will participate in the study, and if it is done well it can be very important in helping to achieve the objectives of the Society. We need to take that study very seriously, and see to it that it is comprehensive and takes on the difficult national issues. It will fail if it turns out to be just another defense of the status quo and current programs. It can also fail if there is no follow-through. The scientific community will have to find ways to use its influence to obtain political support for our collective views. The Society will have to work hard if we want to see some real progress in this area.

In closing, I would like to summarize a few central points.

The research achievements of the recent past, and the new information that is coming so rapidly, are producing exciting possibilities for new disease control measures which need to be developed and put into use in the field. This is a major challenge to the U.S. scientific community, the Society and to the several agencies and institutions which must support the work.

At the present time the manpower and dollar resources are inadequate to do the necessary developmental research to fully explore the options to produce the best and most inexpensive vaccines and drugs, and to put new disease control technologies into effective use. This issue must be addressed jointly by the Society and the funding agencies, and brought to the attention of national leadership. It will be all too easy to fail, and to take 50 years to accomplish what may be possible in a decade.

I believe that the members of this Society, collectively and as individuals, will have an opportunity to develop the plans for a national effort in tropical medicine that will exploit the opportunities made available for research and to put in the field some really effective new weapons in the war on infectious diseases.

As a final answer to Dr. William Reeves' question, "Can the war on infectious disease be lost?" Not if we realize the potential of the results of our research, and if we carry out our responsibilities to the developing world.