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VACCINES FOR THE 21ST CENTURY

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INTRODUCTION

It is a pleasure for me to be here with you in San Antonio and to have the opportunity to visit a city and a health department whose reputation extends far beyond Texas -- in fact, even to Washington D.C., which I would point out is like Texas -- a country affiliated with the United States. In particular, I would pay special tribute to Dr. Guerra whom I have come to know well over recent years -- and whose imagination, creative genius and thoughtfulness have impressed me immensely. San Antonio is a special place!

But, I welcomed the invitation to visit the city for quite selfish reasons. During the eleven years I spent in Geneva, I occupied a spectacular office on the 6th floor of the World Health Organization (WHO) building which itself was perched on a hill overlooking the city, Lake Lemman and the Alps. It is hard to imagine an ambiance which could have been further removed from the realities of health and disease in such as Bangladesh or the Sudan -- and, in truth, there were some in that building who were both physically and mentally on another planet. In Geneva, I quickly learned that the daily stream of reports and data from around the world conveyed a wholly different picture from the realities being experienced by those at work in the field -- by those actually delivering the services. Visits to the field offered quite a different perspective as to what was important and what was not but, more than this, I quickly learned that there were exceptionally bright, creative people dealing imaginatively with problems and innovating solutions which had never occurred to us at headquarters. It was their creative genius which inspired our smallpox eradication program; it was their ideas which I brought back to Geneva. This was the essential secret of the program -- and what led me throughout the program to spend upwards of 60 percent of my time in the field.

Now that I have taken up responsibilities in Washington -- inside the notorious Beltway, I perceive the need, as never before, to meet and talk with the truly important people -- those on the firing line. Thank you for inviting me. I expect to return with far more wisdom than I can convey.

VACCINES FOR THE 21ST CENTURY

My career in public health began with immunization -- indeed, my baptism was during the heady, exciting days of 1955 when, at long last, a weapon became available to combat the dreaded poliomyelitis. Not all of you experienced the all too vivid and terrifying summers before that year when theaters closed -- and swimming pools -- and summer camps. When parents hovered anxiously over every febrile illness fearing that it might be the prodrome of poliomyelitis. Hospitals devoted whole wards to patients in respirators -- the so-called iron lungs. But, fortunately, scientists at the National Foundation for Infantile Paralysis opted to fund basic research on viruses and on poliovirus in particular and subsequently on polio vaccine research. (There were precious few NIH funds then available.) These priorities would seem obvious but the funds could have been expended for improved respirators -- and far better hospital care for patients. And those systems, parenthetically, would more closely parallel some of our misplaced funding priorities in medical research over recent decades -- but I shall return to that point later.

The vaccine, when it became available, initially had to be rationed. Demand was so high. Also, I would note that there was no shortage of resources to purchase it. For everyone, the purchase of polio vaccine and the delivery of polio immunization was very high priority indeed.

Oral polio vaccine came along some 6 years later and with it, the well-known "Sabin on Sunday" programs (i.e., S.O.S.) in which volunteer physicians, nurses, Boy

Scouts, Rotary Clubs and all manner of groups organized community-wide programs to vaccinate everyone. Communities united in an unprecedented effort to stamp out polio. Where vaccination had once been the exclusive province of physicians, it quickly became apparent that many conscientious persons could drop 3 drops of vaccine on a sugar cube and give it to a child. Not many years later, polio vanished -- as did thousands of respirators.

A few years later a measles vaccine was perfected and in rapid succession -- mumps and rubella. But then the pace of development abruptly slowed. Product liability suits emerged; many pharmaceutical companies folded their vaccine production operations -- and their research and development programs as well; those funding research saw curative and diagnostic opportunities as the great opportunity. Interest in prevention ebbed.

Just about the time measles vaccine was licensed, I left the Centers for Disease Control to assume direction of smallpox eradication for WHO. Building on that program we launched in 1974 the inelegantly named -- Expanded Program on Immunization (EPI) and 10 years later, this was transformed by UNICEF into the "Child Survival Revolution," for the developing countries, in particular.

It was a long overdue response to Mahatma Ghandi's lament near the end of his life when he said, "I am hard hearted enough to let the sick die if you could only show me how to prevent others from becoming sick." The universal childhood immunization program is a global effort in which nations throughout the world are

participating, joined by such disparate groups as the World Health Organization, UNICEF, the international and regional development banks, our own Agency for International Development and other national assistance agencies and by Rotary International, which itself has raised more than \$200 million for the effort.

The immunization campaign, the foundation of the Child Survival Revolution represents a renewed recognition of the potential of simple, inexpensive interventions to prevent disease and death and to promote the well-being of children. No less important has been a growing appreciation by political leaders that improved health plays a vital role in development, that healthy children offer a better hope for achieving their country's aspirations.

The genesis of the Child Survival Revolution has its origin in not one but several developments. However, the most important component and its foundation, is the objective of providing well-established vaccines against six major diseases to all of the world's children — the diseases being poliomyelitis, measles, tetanus, whooping cough, diphtheria and tuberculosis. This initiative followed inexorably from our experience gained in smallpox eradication. The smallpox program, coordinated by WHO, succeeded in only a decade, and at a total cost of less than \$8 million per year in international support, in eliminating from the earth one of the most feared diseases known to man. Today the U.S. no longer needs to vaccinate 15 million citizens annually; and because of this it saves each year the equivalent of four times its total annual contribution to WHO.

Smallpox was a disease which, when the program began, claimed more than 10 million victims each year despite the fact that an effective vaccine had been known and available for more than a century and a half. However, an intensified program eradicated the disease in a little over ten years. What accounted for this abrupt change? First was the observation that in most countries, trained health personnel were in surprisingly plentiful supply and that even with moderately effective supervision, they were capable of a remarkably high standard of performance. The numbers needed were really very small. Competent, motivated leadership, even though few in number, made the difference. Second was the finding that villagers, when properly approached, were usually willing, in fact eager, to cooperate in the program and often could serve as volunteer workers. Third was the discovery that a system for the routine notification and investigation of cases and outbreaks could be reasonably easily established and that the findings were invaluable in stopping spread, in guiding strategy, in monitoring progress and in allocating resources.

During the early years of the program, I was dumbfounded to discover, in country after country, whole wards of hospitals for the treatment of smallpox victims and other wards dedicated to patients with whooping cough, tetanus, polio and measles. When I asked about vaccines, the responses were monotonously the same -- no foreign currency and thus no vaccine. As we discovered, less than 5 percent of children were then being vaccinated. And yet, there were numerous costly drugs of foreign origin in every country. It seemed paradoxical that so little attention had been directed to providing vaccination, the single most cost-effective, most innocuous procedure in our entire medical armamentarium -- and the simplest to administer.

Indeed one had to ask the question if a health service could not effectively deliver the simplest and most effective of all procedures, what did it suggest about other aspects of the health care system? What it said was that Ministries of Health were basically operating sickness-care systems, not health care systems. More appropriately, they should have been called Ministries of Sickness. Their primary concern -- and, indeed, virtually all medical training -- was focused on treating those who reached a sickness care facility -- a doctor's office, a primary health center, a hospital. And, sometimes, providing vaccines, if they were available, to those who happened to come. However, when the EPI started and vaccines began to be taken out to the villages, when school teachers, village and religious leaders were recruited to help, immunization levels began to rise dramatically. Today, 80 percent of the world's children are receiving vaccines against six primary diseases. In the Western Hemisphere, polio cases have plummeted to such low levels that in 1985, an eradication campaign was proposed and four years ago, it began in earnest. An extensive system for reporting and investigating cases is now in place. More than two years have elapsed since the last case was found in Brazil, more than three years since indigenous cases have occurred in Central America and more than four years in the whole of the southern cone of South America. In fact, there has been only one confirmed case of poliomyelitis this year in the whole of the Western Hemisphere -- a case occurring in Columbia in early January. And now, a global eradication effort has begun.

When the recent problems with measles began to occur in the U.S.A., I was asked by the media about the immunization program in the Americas and how U.S. immunization levels compared with other countries. I had just returned from a

meeting in Guatemala where each country had provided reports on progress and so the most recent data were available to me. I was able to point out that U.S. immunization levels among preschool children were not the lowest in the hemisphere — those in Haiti and in Bolivia were lower — but they were the only ones.

Leadership in immunization was once a priority and a source of pride in America. It must be again. You in San Antonio are showing what can be done when a community unites to declare that vaccine-preventable diseases are unacceptable. Other cities — New York, Los Angeles, Philadelphia and many others — could learn a great deal from your accomplishments. Throughout much of the country, barriers to immunization have been erected. During the National Vaccine Advisory Committee's review of immunization practices this past year, we learned that many so-called health insurance programs fail to cover costs of immunization — in consequence, children are referred to already over-burdened public clinics. Unbelievably as it may seem, even some so-called Health Maintenance Organizations fail to provide for vaccination. The single and seemingly obvious concept that a child's vaccination record should be checked each time he is seen seems to be the exception not the rule. Emergency rooms and acute care centers where most poor and minority children receive primary care seldom, if ever, provide vaccination and yet it is precisely in these settings where many infections are acquired. Physicians have been insisting on full physical examinations before vaccination — contrary to all recommendations. Vaccination with more than one vaccine is denied — again, counter to recommendations. Those with mild illnesses are denied vaccinations — again, counter to recommendations. What a

difference between the practices of 30 years ago -- and what a difference between these practices and those in other countries of the Americas.

The one central and salient point about which I would again remind you is that immunization is the single most cost-effective, most innocuous procedure in our entire medical armamentarium and the simplest to administer. This is the acid test of a health system -- if it cannot effectively deliver the simplest and most effective of all procedures, what does it say about other components of its health delivery system.

Throughout the developing countries, this is a fact which is increasingly appreciated. In consequence, UNICEF, the World Bank, the Rotary Foundation, the United Nations Development Program and many other agencies have begun to support immunization efforts as no other program before. And it is succeeding.

However significant the progress, more is promised. Just over the horizon are a whole gamut of new and improved vaccines. As one speaker at a recent conference observed, there are few important diseases for which vaccines are not now moving through the development process. With the new techniques available to contemporary science, the time required for their development has been greatly abbreviated and field application is possible far sooner than ever before.

It is not surprising that those who know of these developments have been captivated. In consequence, increased funds for health programs have been made

available and the commitment of politicians is greater than it has ever been. Last September, a global meeting of heads of State -- the largest number ever assembled -- occurred in New York. Its purpose -- to enhance the commitment to child health, especially through immunization. In conjunction with this, a major research program was launched -- the Children's Vaccine Initiative. Vaccine research has been too long neglected. To program managers, a plea for research is too often labeled as the irrelevant cry of academics concerned more about their own careers than "getting on with the task." We must not forget, however, that those once engaged in malaria eradication viewed that problem as entirely an administrative one -- to apply DDT to the walls of houses. Deliberately, research programs were terminated when the eradication program began. A decade later, with increasing mosquito and parasite resistance and a global program foundering, there were no alternatives for either pesticides or drugs and no research laboratories to take up the task. Politicians argued similarly when the global smallpox eradication program began. As they saw it, a good vaccine was available, the problem was entirely an administrative one -- to apply it to the field. We resisted this view and promoted research throughout the program. By the time it concluded, little was the same as it had been -- vaccine strains had changed, vaccine production methods had improved, new vaccinating devices were in universal use, our understanding of the epidemiology of smallpox had greatly changed and the campaign strategy and tactics substantially altered. Indeed, without the research component, smallpox eradication would have failed.

In the Child Survival Revolution, we need to seek constantly for simpler, more effective tools and for better means for applying them. For example, none of the

vaccines now in use are fully satisfactory. All could be improved but none have been improved over the past 25 years. Meanwhile, candidate vaccines are beginning to emerge from the laboratory; others are needed. Support is required for testing them in the field and for the development of simpler preparations for administration. Thus the decision was reached last autumn to launch a broad-based global program whose objective would be a Children's Vaccine -- ideally, a preparation which could be given by mouth at or shortly after birth and which would protect against as many as 30 to 40 infectious agents. Now, in fact, some of the scientists who have looked at the opportunities and options before us believe that such a utopian objective is feasible, but there is general consensus that we should come close to that ideal. All agree that the foundation has already been laid for advances in immunization over the coming decade which should far surpass all developments of the past 200 years. As tangible evidence that those in the commercial sector share that view has been a recent decision by one of the major pharmaceutical producers to:

- o Create a new vaccine division which would have the autonomy to more freely explore these new opportunities;
- o A decision to invest a quarter of a billion dollars in new plant construction;
- o A commitment to provide \$5 million in support of this country's national vaccine program.

But let me speak briefly about the Children's Vaccine Initiative. (May I apologize for the graphics -- my Harvard graphics model misfired so you will be treated to Henderson graphics.)

Broadly, what are its objectives:

1. "Children's Vaccine Initiative -- September 10"
2. Vaccines to be Available -- 2000
3. New Vaccine Presentations

With a rapidly expanding understanding of immunology, molecular biology and biotechnology, the unimaginable of yesterday becomes the feasible today and the routine tomorrow. The next two decades hold promise to be the decades of immunization -- decades marked by disease prevention. I would hope that challenge of devising a user-friendly vaccine delivery system will not prove to be so great a challenge as developing the new vaccines -- but evidence to date suggests that it just may be.

CHILDREN'S VACCINE INITIATIVE - Sept 10

(WHO, UNICEF, UNDP, World Bank)

◦ New Vaccines —

AIDS, acute resp. infection, diarrhea, parasite dis

◦ Better Vaccines

- + 1 or 2 vs. multiple doses
- + Heat stable
- + Combinations of vaccines
- + Oral administration
- + Immunization soon after birth

◦ Affordable vaccines

VACCINES TO BE AVAILABLE - 2000

Universal use

- * Diphtheria
- * Pertussis
- * Tetanus
- * Measles
- * Polio
- Rubella
- Hepatitis B
- Hem. influenzae
- Mumps

Varicella
Resp syncytial
Rotavirus
Hepatitis A, E
Pneumococcus
AIDS

Regional

- * Tuberculosis
- Yellow fever
- Mening. A, C
- Dengue
- Jap. encephalitis
- Typhoid
- Shigella
- Cholera
- Leprosy

NEW VACCINE PRESENTATIONS

• BIODEGRADABLE MICROSPHERES (DL-lactide-co-glycolide)

- + Biocompatible
- + Sustained or pulsed release 200⁺ days
- + Subcutaneous or oral
- + Adjuvant effect

? DPT / Hemophilus / Hepatitis B, A, E / Mening. A, C
and pneumococcus

• LIVE VECTOR OR BACTERIAL CARRIERS

(Vaccinia, adenovirus, yellow fever, salmonella, BCG)

• NEW STABILIZERS