THE MIRACLE OF VACCINATION*

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Many ~~therapeutic~~ advances in medicine have been proclaimed to be ~~Among the pantheon of medical procedures, a number are regularly cited as~~ medical miracles--cardiac surgery, cancer chemotherapy, organ transplantation, and ~~the~~ many others. ~~brilliant spectrum of pharmacological interventions for all manner of infections, aches, pains and arrhythmias.~~ Seldom is vaccination accorded such respect and, yet, I believe it is safe to say that more lives are saved and more disabling diseases prevented every year by vaccines alone than ~~by all of these~~ by many other medical interventions ~~combined.~~ The incredible difference which vaccination has made to health throughout the world is surprisingly little appreciated--and, no less its potential for an even greater impact over the coming decades. I would like to reflect on this in three brief ~~capsules~~ chapters beginning with the dramatic ~~chapter~~ success of smallpox vaccination--from its discovery just 200 years ago to its banishment in 1980 coincident with smallpox eradication; second, I would like to describe the miracle of the Child Survival revolution and the impending eradication of poliomyelitis; and, finally, I would propose to look briefly to the future.

We quite forget what a grim life our forefathers endured--and not so long ago. I rather like a quotation from Rousseau, dated 1762, which conveys something of the flavor of the times in so far as health was concerned (**SLIDE 1**)

> "Half of all the children will die by eight years of age. This is an immutable figure. Do not try to change it."

I.C. 50 of 100 children born ~~would die~~ survive their 8th birthday. In contrast, today in the U.S. 99 of 100 children who are born are alive at 8 years.

On May 14, 1796, however, there occurred that truly momentous event in the annals of medicine--the first vaccination performed by an English physician, Edward Jenner. It was to prevent smallpox. (SLIDE 1B) (Elaborate on the nature of the vaccine)

We need to be reminded that Jennerian vaccination began long before it was recognized that microbes caused disease. It was a time, in fact, when cholera and malaria and yellow fever were thought to arise in the ~~malodorous~~ bad air of swamps and sewage. It was a time when throughout Europe--indeed the world--everyone could expect to acquire smallpox at some time in their lives. Commonly, at least 20 to 25% died. In some parts of Central Europe, it is said that it was customary to delay naming a child until after he had recovered from smallpox. Macauley in his history of England wrote at the time (SLIDE 2):

> "That disease was the most terrible of all the ministers of death. The horror of the Plague....visited our shores only once or twice within living memory but the smallpox was always present, filling the churchyards with corpses....and making the eyes and cheeks of the betrothed maiden objects of horror to the lover."

Smallpox left permanent deeply pitted scars on the face (SLIDE 3) and as shown here in a more recent victim in Asia, it often caused blindness (SLIDE 4). In fact, it was the leading cause of blindness in ~~England~~ Europe in the 18th century.

Edward Jenner's discovery of a method to protect against mankind's most feared disease was understandably hailed as one of the most important advances in medical history. Within five years, the cowpox vaccine had been sent by sailing vessel to countries on every continent. Even by today's standards, this was an incredibly rapid dispersion of technology.

(It was greatly feared for good reason)

Smallpox was an ugly ~~disease~~ disease. It was caused by a virus which was transmitted from person to person by droplets. After 10-12 days, the individual developed high fever and aching pains, like severe influenza & usually took to his bed.

SLIDES (2B, 2C, 2D)

Over the following 150 years, vaccination prevented many cases and deaths of smallpox but it failed to achieve its initial promise. Until late in the 19th century, the vaccine virus was maintained by arm-to-arm vaccination but, frequently, the virus was lost when vaccination proved unsuccessful, and sometimes hepatitis, syphilis and tetanus were transferred with the vaccine virus.

Smallpox continued to ravage the developing countries--a disease so dreaded that special deities were worshipped as in Africa (SLIDE 5) and Asia (SLIDE 6). Eventually, it was discovered that the vaccine virus could be grown in large quantity on the skin of calves and methods were developed to purify the product, to package it and to preserve it.

Through the 1950s and 1960s, smallpox remained a major problem throughout most developing countries. All tried to control the disease but resources were limited. The vaccine quality was poor and it was readily destroyed by heat. Smallpox-free countries feared importations of smallpox and continued to vaccinate their citizens. All travellers had to carry yellow vaccination certificates stating that successful vaccination had been performed within the preceding three years; and in some countries--England and Germany, for example--special smallpox hospitals were maintained, to be opened only when cases of smallpox were imported into the country.

A vaccine which would retain its potency even at tropical temperatures was sorely needed and, in 1953, Leslie H. Collier of the Lister Institute, England, succeeded in freeze-drying smallpox vaccine--much as one would freeze-dry coffee (SLIDE 7). The vaccine proved to be stable even when exposed to tropical climates for months. The Lister Institute generously shared this technology with the world and eventually, one of its most

senior scientists, Professor Colin Kaplan, travelled widely helping to establish vaccine production centers in the third world.

In 1966, a political commitment was made to deal seriously with smallpox. That year, delegates to the World Health Assembly decided that the World Health Organization should undertake a global program for the eradication of smallpox. They suggested a ten-year goal (SLIDE 8) At the time, some 43 countries recorded cases of smallpox. It was endemic in 31 which had a combined total population of more than one thousand million persons. An estimated 10 to 15 million cases were occurring annually with approximately two million deaths. The entire budget allotted for the effort was $2.4 million or roughly $50,000 per year for each country where programs were needed.

I will touch on only a few highlights and findings of the program, notably those which were important to the subsequent development of global immunization programs.

The objective was nil cases of disease--a mission familiarly referred to as "Target Zero" (SLIDE 9). The strategy was to break the chain of transmission--to stop spread. It was comprised of two parts: 1) A vaccination campaign in each endemic country which was intended to assure that at least 80% of all persons had been vaccinated; and b) The development of a surveillance-containment system--a system in which all health units reported cases of smallpox weekly and special teams undertook to vaccinate all contacts of cases in order to prevent spread.

As field operations got under way, we encountered, almost immediately, two unexpected findings.

The first related to manpower. We discovered in essentially all developing countries surprisingly large numbers of underemployed, unsupervised health staff who responded eagerly to a challenge, given even modest direction. Many, for the first time ever, were visited in the field for supervision and training by WHO advisers and senior national staff. Most responded with enthusiasm to the leadership. In places where staff had vaccinated 20 to 50 persons per day, productivity increased to as many as 500 to 1200 per day. And some of these areas were unbelievably difficult to reach (**SLIDES 10 & 11**) Special measures were taken to assure that all vaccine, wherever produced, met international standards; independent assessment teams checked progress to assure that vaccination teams reached at least 80% of all persons, and that all health units reported cases regularly. ~~Implementing such quality controls proved remarkably easy.~~

~~A second surprise~~ was the discovery that smallpox did not spread rapidly and easily like measles or influenza, as the textbooks indicated. Rather, an infected patient seldom transmitted disease to more than four or five others, primarily to relatives and friends. It spread as a chain of infection. By detecting cases early and vaccinating all contacts, disease transmission was stopped and the chain was broken. With this approach, it was possible to eliminate smallpox from large areas even when half or less of the population was protected.

We were astonished by how rapidly progress was made (**SLIDES 12, 13, 14, 15**) Finally, on 26 October 1977, the last case occurred--in Somalia (**SLIDE 16**) We had missed our ten-year goal by nine months and 26 days! But for the first time in history, a

disease had been eradicated (**SLIDE 17**). Vaccination everywhere could cease--and it did, in 1980.

The fact of eradication was notable but how the victory was achieved and what was required proved catalytic for future programs. First, the program was remarkably inexpensive. International assistance of all types for all countries amounted to only $8 million per year over a 12-year period--to sustain one clinical department of a modest-sized medical school in your country or mine. The endemic countries spent little more than what they were spending already for ineffective control programs. Nor were there armies of smallpox staff continually at work in the field. Our international staff numbered no more than 100 persons at any one time, and our total headquarters contingent in Geneva consisted of only six professionals. The total international investment was $100 million; the savings each year amount to several thousand million dollars. It is difficult to identify any other medical procedure or advance which approach smallpox vaccination in its cost-effective impact.

During the smallpox campaign, it was customary for us find in virtually every hospital, whole wards filled with children with tetanus, polio, measles and whooping cough--all diseases which are wholly preventable with inexpensive vaccines. These vaccines were then in routine, widespread use throughout the industrialized world. Almost none of the developing countries, however, provided vaccines other than for smallpox and some for tuberculosis. In fact, surveys made just 20 years ago, revealed that less than 5% of children in the developing world were being given diphtheria, pertussis, tetanus, polio or measles vaccines.

In 1974, therefore, we proposed to the World Health Assembly that a next stage in immunization activities be launched--a program we called the Expanded Program of Immunization, i.e., an expansion of the smallpox vaccination activity to include six additional antigens SLIDE 18

At first, progress was slow. By 1983, coverage rates scarcely exceeded 20% SLIDE 19 But about this time, two organizations, in particular, stepped forward to play critical roles. UNICEF identified childhood immunization as the primary element in its new Child Survival Initiative. And Rotary International began a world-wide $100 million fund-raising drive in support of polio eradication. The Rotarians amazed themselves and indeed the world by raising not $100 million but more than $300 million. And individual Rotary members participated in vaccination campaigns in countries around the world. About this time, other organizations, such as Save the Children, began to take a special interest, and bilateral assistance programs joined the effort. The program rapidly gained momentum. By 1990, 80% of children throughout the world were receiving vaccines against the six diseases. The result--three million fewer deaths annually. And note that is in addition to the two million deaths prevented by smallpox eradication.

Even today, few appreciate the extraordinary magnitude of this effort. As Jim Grant, the late director of UNICEF pointed out, this unquestionably has been the most extensive social mobilization and prevention program in history.

The success of the program relies substantially on the principles which made smallpox eradication possible--planning, outreach to involve community groups, delivery of vaccines in villages and in other sites convenient to the people, and surveillance.

What has this meant in more quantitative terms? (SLIDE 20)

Over the past 25 years, we have witnessed throughout the developing world unprecedented decreases in mortality rates among children under five years of age. Between 1970 and 1994, the rates fell from 168 per 1000 children to 101. That these decreases occurred throughout a long period of stagnation or declining growth in GDP in most developing countries is all the more astonishing. Now, it is known that other factors beyond immunization contributed, but it was immunization that played the dominant role in effecting these decreases. As childhood mortality rates began to fall, fertility rates did so as well. The end result is healthier children but in smaller families.

As immunization rates increased, the incidence of the vaccine preventable diseases began to plummet, most notably cases of poliomyelitis. In 1985, WHO staff in the Americas proposed to the countries of the Western Hemisphere that a hemisphere-wide eradication campaign begin with a target of eliminating polio by the year 1990.

Events in Brazil had an important bearing on this decision. Until 1980, Brazil had depended on staff in its health centers and hospitals to vaccinate children when they came to the clinics; the results were poor. Vaccination levels hovered around 60%. So Brazil decided to hold two National Immunization Days each year and to endeavor to vaccinate all children under five years of age. More than 90% of children turned up for the first two vaccination days (SLIDE 21) Everyone sagely informed Brazil that such an event could

not be repeated. After 15 years and a broadening of the immunization activities to include all vaccines, the Brazilian effort continues. As one Brazilian said to me, we celebrate Carnaval every year and no one seems to tire of it. Why can't we successfully celebrate national immunization days every year?

Other countries in Latin America began to conduct their own National Immunization Days. Reporting systems were greatly strengthened. Whereas reports in Latin America were usually received monthly from some 500 hospitals, reports began to be received weekly from more than 20,000 health units. Within three years, it became clear that the principal reservoirs of polio were the slum areas of major cities. Target areas were mapped out and house-to-house vaccination campaigns were conducted in each. The decrease in polio cases accelerated. In August 1991, the last known case of polio in the Americas occurred in a small town east of Lima Peru.

The success in the Americas triggered an international response and, in 1988 polio eradication was declared a global objective. The strategy was adopted from that used in the Americas. As shown in the slide SLIDE 22, the number of countries becoming free of polio is steadily climbing. The most recent dramatic progress has been recorded in China, which has now conducted four national immunization days during each of which more than 85 million children ~~were~~ are being vaccinated. The last documented case in China occurred more than two years ago and in the Philippines more than three years ago. Taiwan, Japan, Korea, Australia and New Zealand are all polio-free. The target is to reach "0" by December 2000.

What can we foresee for the future? First, we need to recognize that we have now an immensely valuable resource--a global system for vaccine delivery. I have been questioned as to how long it would take to vaccinate everyone in Africa, for example, if we had ample quantities of an effective ~~AIDS~~ HIV vaccine. In the late 1960s, there was doubt that it could be done at all; by the late 1970s, it was apparent that two to three years would be needed. Today, I believe, three-fourths of the population could be vaccinated within six months and the total population within a year. This is not because there are more or better roads or significantly better health services in most countries than 20 years ago. The fact is that countries now know how to organize and manage vaccination programs.

Countries throughout the world are beginning to recognize that vaccination is, indeed, the single most cost-beneficial medical procedure in the medical armamentarium--a conclusion strongly endorsed by the World Bank in its 1993 World Development Report. Even the poorest developing countries are beginning to allocate funds in their budgets for the purchase of vaccine--a practice virtually unknown ten years ago.

Meanwhile, we are witnessing a renaissance of interest in vaccine research and development.

A number of important new vaccines have been licensed over the past decade (SLIDE 24). One--hepatitis B--prevents a form of chronic hepatitis which eventually results in liver cancer--one of the most important types of cancer in Asia and Africa. Thus we have our first anti-cancer vaccine. It will not be our last.

More than 150 new vaccines are in various stages of testing in humans and 25 of these are presently in what we call the final or phase III human trials, which measure the degree of protection provided against natural challenge.

Let us suppose that vaccines could be perfected and applied which would protect against malaria, dengue, the more serious acute respiratory infections and diarrheas and, yes, AIDS. Through such immunization alone, mortality rates for children under five years could be reduced even more dramatically over the next 20 years than during the whole of the past generation.

Could such vaccines be developed? Most of those who are knowledgeable of vaccine research and development assert that they could. Several new vaccines that protect against important diarrheal and respiratory illnesses are virtually ready now for general use; a first-generation malaria vaccine has been shown to be effective; and a dengue vaccine is entering phase III trials. At this time, it would appear that a better tuberculosis vaccine and an AIDS vaccine are still a number of years from realization. However, with the exponential growth of knowledge about how organisms cause infections and how the body combats them, vaccine development has been transformed from often "trial and error" experimentation to a true science. Because of this, the question is not if, but when, suitable vaccines can be developed.

But then comes another challenge--the problem of administering large numbers of different vaccines without making pincushions of the vaccinees. And so, a number of new approaches are actively being researched--techniques which combine a large number of vaccines in a single injection; techniques which permit vaccines to be enclosed in

synthetic microcapsules which can be given by mouth; techniques which would permit several vaccine antigens to be combined in a carrier vaccine (such as smallpox vaccine) and administered by mouth.

In 1990, an expert group was convened at National Institutes of Health and an intriguing question was posed. ~~Suppose that we were to identify~~ the 25 to 30 infections which are responsible today for most illness and death. What might be the prospects for developing protective vaccines for ~~each~~, of combining those vaccines into a single dose or in very few doses and of administering all of these by mouth at or soon after birth--in other words, providing protection for life against all of the major infectious agents? It was recognized that this would take an extraordinary investment both in time and resources but that, in principal, it should be possible given the technological tools available to us today. No one considered a Nobel Prize level breakthrough to be essential to the success of that effort. As someone wryly pointed out, such a vaccine product given by mouth would be the ultimate communion wafer.

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Given that countries in almost all parts of the world have now developed programs for vaccine administration that reach 80% or more children, what could thwart the optimistic potential we foresee? There are two significant problems, ~~each posing a formidable challenge~~: 1) vaccine supply; ~~2) vaccine quality~~, and 3) support for research. ~~All are interrelated and potentially soluble. However, neither the solutions nor the necessary commitments to find the solutions are yet apparent.~~

The first ~~one~~ challenge relates to the problem of inexpensively producing adequate quantities of assured high quality vaccine. This is a far more difficult problem

The extraordinary improvements in health due to vaccines truly represent a miracle — or more, this remains one of the best kept secrets in medicine. And yet, so much more is now promised!

than it might appear on the surface. Although the current six EPI vaccines are inexpensive and in plentiful supply, we must recognize that all are new simultaneously in widespread use in the industrialized countries. The revenues from sales in the industrialized world have largely paid for their development costs, as well as much of the capital investment needed to manufacture these vaccines. Prices for the developing country market are established, therefore, at little more than the incremental costs of producing additional amounts of vaccine. Thus, the total cost for all EPI vaccines for one child is less than one pound. Where do we find comparable levels of support for the many important vaccines that have only a limited market in the industrialized world, such as malaria or dengue vaccines? Development and construction of production facilities cost money, which could not now be recovered by sales in the industrialized world.

The second critical issue is vaccine quality assurance even for vaccines now in use. Vaccines purchased by international organizations are not at issue. Such vaccines must meet international standards. However, more than two-thirds of the DPT vaccine is produced in national laboratories and used locally. Only a few of these have satisfactory quality controls. WHO has recently begun an international effort to assure that quality control standards are in place in all laboratories, but limited funds and personnel have been assigned to this task, and progress is slow.

The third critical challenge relates to the need for research support. Recent advances in immunology and biomedicine have opened up all manner of new and exciting avenues pointing toward the development of protective vaccines. The question now is not whether there are potentially productive avenues for research but, rather, which of

They don't perceive a market for most 3rd world vaccines

many options to pursue. However, translating basic concepts into useful products requires substantial resources to cover the needed applied research and development. Industry usually covers such costs but cannot do is unless it expects to recover these from sales. ~~Unfortunately,~~ few national or international assistance agencies view research as an ~~intrinsic~~ part of their agendas and most national authorities support very little medical research which is not of tangible benefit to their own citizens. ~~This is a serious problem.~~

~~I am optimistic, however, that as an international community, we will eventually come to fully understand and support these needs, if not in the interests of furthering child survival, perhaps in the interests of assuring the survival of civilization as we know it.~~ What do I mean? Over the past five years, we have come to appreciate the growing challenge posed by new and emerging infections in an increasingly well-travelled and heavily-populated world. Early detection and identification are the first lines of defense, and here the surveillance systems and laboratory networks developing within the context of EPI ~~could~~ program will be of the greatest value. Viruses are of special concern. Witness current problems with Ebola, Hanta and dengue viruses. ~~None of these have proved catastrophic~~ but suppose that a virus emerged with the pathogenic characteristics of Ebola and the capacity to spread like influenza--an appalling scenario but not an impossible one. Rapid detection and characterization would be critical. Conceivably, effective antiviral compounds might be helpful in treatment identified, but ~~our track record for developing effective antivirals is not a good one.~~ so far, not many developed & very few Almost certainly, we will need vaccines and we will need them quickly.

Substantial additional ~~resources will have to be~~ made available if we are to respond responsibly to these very real microbial threats, ~~at a time when budgets everywhere are constrained. However, if we have our priorities properly ordered, we will~~ must can be

~~The answer must be a partnership~~ One answer and perhaps the only reasonable one, is a unique new partnership of public and private sector interests whose agenda can be succinctly summarized in terms of paving a road from "bench to bush" with basic research, development and field application all part of a single cooperative agenda. This should be possible and is the challenge we are pursuing today.