

PERSPECTIVES ON VACCINATION

Helsinki, Finland

January 9, 1996

I welcome the opportunity to share with you this morning something of my sense of the miracles wrought by a simple innocuous medical procedure called vaccination and the challenges it poses. 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 few decades. I will recount this in four brief capsules beginning with the dramatic discovery of vaccination just 200 years ago; then a brief description of its first global application in the eradication of smallpox; next, I will touch on 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 accepted for granted--and not so long ago. I like this quotation from Rousseau, dated 1762, which conveys something of the perceptions of the time (**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."

On May 14, 1796, however, there occurred in the annals of medicine a truly momentous event which was to alter this--the first vaccination. On that day, Edward Jenner (**SLIDE 2**) took some pustular material from a cowpox lesion on the hand of a milkmaid--named Sarah Nelms (**SLIDE 3**), and inoculated it into the arm of an eight-year-old boy, James Phipps (**SLIDE 4**).

Some six weeks later he inoculated the boy with smallpox virus but no infection occurred.

Bear in mind that this event occurred at a time when cholera and malaria and yellow fever were thought to arise in the malodorous air of swamps. It was a time when throughout Europe--indeed the world--everyone could expect to acquire smallpox at some time in their lives. Commonly, between 20 and 25% died. Macauley in his history of England wrote at the time (SLIDE 5):

"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 6) and as shown here in a more recent victim in Asia, it often caused blindness (SLIDE 7).

But, as folklore held, there was one group of persons who were spared the smallpox--whose complexion was unblemished and often written about in literature. These were the milkmaids who became infected with cowpox and were subsequently protected from smallpox and the facial scarring it caused. Thus, Jenner's use of cowpox.

For the first time, there was a method to protect against mankind's most feared disease. Within four years, the cowpox had been sent by sailing vessel to countries on

every continent. Even by today's standards, this was an incredibly rapid dispersion of technology.

Over the 150 years following Jenner's discovery, vaccination prevented many cases of smallpox but it failed to achieve its promise. The virus had to be 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 8**) and Asia (**SLIDE 9**). Eventually, it was discovered that the virus could be grown in large amounts on 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 the developing world. All tried to control the disease but resources were limited. The vaccine quality was poor and readily destroyed by heat. Smallpox-free countries feared importations of smallpox and continued to vaccinate everyone; all travellers had to carry yellow vaccination certificates stating that successful vaccination had been performed within the preceding three years.

In 1966, a landmark decision was taken by delegates to the World Health Assembly (**SLIDE 10**). They decided that the World Health Organization should undertake a global program for the eradication of smallpox. They suggested that this be done within ten year times. At the time, some 43 countries recorded cases of smallpox; an estimated 10 to 15 million cases were occurring annually with two million deaths. The

entire budget allotted for the effort was \$2.4 million or roughly \$50,000 per country per year.

I will touch on only a few highlights of the program--those which were important to what subsequently developed in immunization programs globally. The strategy can be briefly summarized as comprising two parts (**SLIDE 11**): a) A vaccination campaign in each endemic country to assure that at least 80% of all persons had been vaccinated and 2) The development of a surveillance-containment system.

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 not a lack of health staff but rather, large numbers of underemployed, unsupervised staff who responded eagerly to a challenge given even modest direction. Many workers, 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. Where staff had usually vaccinated 20 to 50 persons per day, productivity increased to as many as 500 to 1200 vaccinations per day per vaccinator. And some of these areas were unbelievably difficult to reach (**SLIDES 12 & 13**). Special quality control measures were put in place to assure that vaccine was potent; to assure that vaccination teams reached at least 80% of all persons; and to assure that all health units reported cases weekly.

A second surprise was the discovery that community leaders and groups were eager to help in publicizing the program, in organizing vaccination sites, in searching for

cases, and in vaccinating. The results of their involvement was dramatic and vaccination coverage of at least 90% came to be accepted as a standard.

We were astonished by how rapidly progress was made (**SLIDES 14, 15, 16, 17**). Finally, on 26 October 1977, the last case occurred--in Somalia (**SLIDE 18**). 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. Vaccination everywhere ceased in 1980.

The fact of eradication was notable but how the victory was achieved and what was required proved catalytic for future programs. The program was incredibly inexpensive. International assistance of all types for all countries amounted to only \$8 million per year over a 12-year period--not enough to sustain one clinical department of one modest-sized medical school. The endemic countries spent little more than what they were spending already for ineffective control programs. Nor were there armies of smallpox staff working in the field. The international staff never numbered more than 100 persons at any one time and our total headquarters staff in Geneva numbered only six professionals.

Another surprise for us during the smallpox campaign had been to discover in virtually every hospital, whole wards filled with children with tetanus, polio, measles and whooping cough--all diseases which were and are wholly preventable with inexpensive vaccines which are widely used throughout the industrialized world. Almost none of the countries, however, provided vaccines other than for smallpox and some for tuberculosis. In fact, surveys showed in 1975, just 20 years ago, that less than 5% of children in

developing countries were being given DPT, polio or measles vaccines--all vaccines which had been available for more than ten years.

In 1974, therefore, we proposed to the World Health Assembly that a next stage in immunization be launched--called the Expanded Program of Immunization, i.e., to expand on the smallpox vaccination activity to include five additional antigens.

At first, progress was slow. By 1983, coverage rates scarcely exceeded 20% (SLIDE 19). But about that time, two organizations stepped forward to play critical roles. UNICEF incorporated 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. In fact, more than \$300 million was eventually made available. And Rotary members themselves participated in vaccination campaigns in countries around the world. About this time, bilateral assistance programs also joined the effort. 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 the effort. Indeed, as the late Jim Grant, the former director of UNICEF pointed out, this has proved to be the most extensive organized social mobilization and prevention program in all history. What has this meant in more quantitative terms (SLIDE 20)?

Note -- a time when GNP in most developing countries was growing slowly or falling.

As immunization rates climbed, the incidence of the vaccine-preventable diseases plummeted, 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 but the results were poor. Vaccination levels hovered around 60%. So Brazil decided to hold two National Immunization Days each year and to vaccinate all children under five years. 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 Brazilians continue to perform--just like the Energizer Bunny.

Other countries began to conduct National Immunization Days. Reporting systems were greatly strengthened. Where once reports in Latin America were received from some 500 hospitals once each month, the numbers increased to more than 20,000 units reporting each week. 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.

In 1988 polio eradication was declared a global objective--the strategy being the same as in the Americas. As shown in the slide (**SLIDE 22**), the number of countries becoming free of polio is steadily climbing. The situation as of 1994 is, if anything rather better than this slide (**SLIDE 23**) would suggest. The most dramatic progress has been recorded in China, which itself has now conducted four national immunization days

during each of which 85 million children were vaccinated. The last documented case in China occurred 18 months ago and in the Philippines some two years ago. The target is to reach "0" by December 2000.

So where does this take us for the coming century? First of all we have now in place a global system for vaccine delivery. I have been asked as to how long it would take to vaccinate all in Africa, for example, if we had ample quantities of an AIDS 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 sufficient. Today, I believe, three-fourths of the population could be vaccinated within six months and the total population within a year.

Countries throughout the world are beginning to recognize that vaccination is, indeed, the single most cost-beneficial medical procedure in our entire 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 have witnessed a renaissance of interest in vaccine research and development. Ten to fifteen years ago, a conference on vaccines would have attracted hundreds; today special conferences dealing only with respiratory vaccines, for example, will draw thousands.

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.

However, there is still some distance to go before the truly high priority vaccines will see routine use (**SLIDE 25**). Vaccines against these diseases would prevent between seven and eight million deaths annually--or twice the number of deaths currently prevented under the WHO global program. There are specific research projects dealing with each, but resources for this effort are still very scarce. National governments are investing very little--and pharmaceutical companies understandably are not willing to invest substantial resources unless they can expect to recoup expenditures through sales. And sales of sufficient magnitude for vaccines almost solely for developing country use are not foreseen as likely.

Another challenge is that of administering large numbers of different vaccines without making pincushions of the vaccinees. And so, a number of new approaches are being pursued actively.

combined vaccines

microencapsulation/sustained release

Recombinants --- "the old smallpox vaccine"

Much more could be said about these and many other significant developments, but I shall forego doing so given the fact that the new 1995 NIH Jordan report has just

been issued and gives a more comprehensive review of work in progress than I could probably do.

In 1990, an expert group was convened and an intriguing question was posed. What might the prospects be for developing protective vaccines against 25 to 30 of the most important diseases, of combining those vaccines into one or a few doses and of administering all of these by mouth at or soon after birth? The conclusion was that, in principal, this would take time but that it should be possible given essentially the tools available. There clearly are technical problems to be solved but a Nobel Prize level breakthrough was not considered essential to the success of that effort.

As someone wryly pointed out this indeed would be the ultimate communion wafer. Thus, two centuries after Jenner's first vaccination, we are moving into a new century in which we may celebrate prevention through vaccines as the most cost-beneficial and most critical of all medical procedures. The most difficult problem today is not that of identifying new approaches but of deciding which should be selected for applied research and development. Wisdom and leadership is needed to define a practical future which would serve to provide focus to the research enterprise.

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