

VACCINATION AND WORLD HEALTH IN THE NEXT CENTURY

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This evening I welcome the opportunity to share with you something of my sense of the miracles wrought by a simple innocuous medical procedure called vaccination. The incredible difference this has made to health throughout the world is surprisingly little known--and, no less its potential for 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 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**):

On May 14, 1796, however, there occurred in the annals of medicine a truly momentous event--the first vaccination. On that day, Edward Jenner (**SLIDE 2**), an English country physician, 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 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 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, usually as a child. Commonly, between 20 and 25% died although death rates as high as 50% were recorded during some epidemics. In some parts of Central Europe, it was customary to delay naming a child until after he had recovered from smallpox. Indeed, the population of England remained essentially static

until two events occurred--vaccination against smallpox and the Industrial Revolution. 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. In 1798, Jenner published his observations on vaccination. The report documented just 12 vaccinations.

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. The usual method for transport of the new vaccine was to take a group of young orphans--those who had not had smallpox, and to place them on a vessel. As one developed the cowpox lesion, usually 7 to 10 days after inoculation, material was taken from his arm and the next child was inoculated. Arm to arm inoculation it was called. In this way vaccination came to Africa, Asia and the Americas. However, little was said as to what became of the orphans.

II Smallpox

Over the following 150 years, vaccination prevented many cases of smallpox but it failed to achieve its initial promise. The arm to arm technique for maintaining the virus remained in use until the late 1800s. Regularly, the virus died out when vaccination

proved unsuccessful--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 the skin of a calf and methods were subsequently discovered to purify the product, to package it and to preserve it by refrigeration.

Through the 1950s and 1960s, smallpox remained a major problem throughout most developing countries. All tried to control the disease but resources were limited and the vaccine quality was poor and readily destroyed by heat. The United States and all other smallpox-free countries feared importations of smallpox and continued to vaccinate; 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.

Finally, 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 to promote and direct a global program for the eradication of smallpox. They suggested a ten-year time frame. At the time, some 43 countries recorded cases of smallpox; an estimated 10 to 15 million cases were occurring annually with between 2 and 2.5 million deaths. The entire budget allotted for the effort was \$2.4 million or roughly \$50,000 per country per year.

I want only to touch on a few highlights and findings of the program, particularly those which were so 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 which was intended 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 management. 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, for the first time ever, were visited in the field for supervision and training by WHO advisers and senior national staff and they responded with enthusiasm to the leadership. Where staff had usually 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 tough (**SLIDES 12 & 13**). Quality control measures began 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 regularly. Implementing such controls proved remarkably easy.

A second surprise was the discovery that community leaders and groups were very responsive and 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 could cease--and it did, in 1980.

The fact of eradication was notable but how the victory was achieved and what was required proved to be catalytic for future programs. First, 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--barely enough, I suspect, to sustain one small clinical department of your 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 contingent

in Geneva numbered only six professionals. Special national field staff numbered, for example 40 in Kenya, 14 in Rwanda and 25 in Ethiopia.

III EPI

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 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.

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 this time, two organizations, in particular, 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. The Rotarians amazed themselves and indeed the world by raising the \$100 million, not over 20 years as they anticipated, but more like 20 months! Eventually, more than \$300 million will have been expended by Rotary in support of the program. And Rotary members themselves began to participate in vaccination campaigns in countries around the world. About this time, USAID and other countries 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 the effort. As Jim Grant, the former director of UNICEF pointed out, this is the most extensive organized social mobilization and prevention program in history. He pointed this out once to the

President of Pakistan and wondered aloud if indeed it might not rival the postal service in the extent of its outreach. To which Pakistan's President replied, "Mr. Grant, this program extends far beyond the frontiers of the postal service."

The success of the program relies substantially on the principles which made smallpox eradication possible--planning, field leadership and community outreach to involve community groups and leadership.

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

Note -- a time when GNP in most countries is falling.

As immunization rates climbed, 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 but the results were poor. Vaccination levels hovered around 60%. As is the case with sickness care centers, i.e., health clinics and hospitals, in many countries, including our own, vaccination and preventive services are not generally of high priority. So Brazil decided to hold two National Immunization Days and vaccinate all children under five years. The Brazilian capability to organize and publicize an event should never be underestimated. 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 activates 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 monthly from some 500 hospitals, the numbers have increased to more than 20,000 each of which reports weekly. Within three years, it became clear that the principal reservoirs of polio were the slum areas of major cities. Target areas were mapped out, comprising roughly 10% of Latin American residents and house to house vaccination campaigns were conducted in each. For these, as with the Immunization Days, volunteer groups,

community leaders, Rotarians and others played major roles. The decrease in polio cases accelerated. In August 1991, the last known case of polio in the Americas became ill 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. Taiwan, Japan, Korea, Australia, New Zealand are all polio-free. The target is to reach "0" by December 2000. And while there are still many hurdles, expectations are high.

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 ample. 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 in most countries than 20 years ago. In many countries, they are worse. However, the countries now know how to organize and manage vaccination programs.

Thus, we have a delivery system such as never before in history. Now, countries throughout the world are beginning to recognize that vaccination is, indeed, the single most cost-beneficial medical procedure in the entire medical armamentarium--a conclusion strongly endorsed by the World Bank in its 1993 World Development Report. Even some of the poorest developing countries are beginning to allocate funds in their budgets for the purpose of buying vaccine--a practice which was virtually unknown ten years ago.

Meanwhile, we have begun to witness during the 1980s and 1990s, 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. But there are specific research projects dealing with each and progress is being made.

But then comes the next challenge--the problem of administering large numbers of different vaccines without making pincushions out of the vaccinees. And so, a number of new approaches are actively being researched.

(**SLIDE 26**) --- combined vaccines

(**SLIDE 27**) --- microencapsulation

Vectors --- "the old smallpox vaccine" ---
and work at Florida

In 1990, an expert group was convened at NIH 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 the prospects be for developing protective vaccines for each, of combining those vaccines into a single dose and of administering all or these by mouth at or soon after birth--in other word, providing protection for life against all of the major infectious agents? The conclusion was that, in principal, this would take time but that it should be possible given essentially the technological tools

available to us today. There clearly were technical problems to be solved but a Nobel Prize level breakthrough was not 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 which will celebrate vaccine prevention as one of the most important medical advances and medical procedures.