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## SECOND ANNUAL V.W. SCULLY DISTINGUISHED LECTURE

## "DEATH OF A DISEASE"

by

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It is an honor for me to be asked to deliver the second V.W. Scully Distinguished Lecture. There are all too few forums of this sort which provide an opportunity for those of us in medicine to discuss with the community at large and our medical colleagues, recent developments in medicine. With health increasingly a shared social concern, I particularly welcome the opportunity you afford me this evening. I must warn you, however, of the fact that, for better or worse, your speaker this evening is a renegade Canadian - born in Cleveland of Canadian parents and whose curriculum vitae might well have included Queen's University but for the intervention of World War II.

It was from the ashes of a devastating global war that the United Nations was born little more than 30 years ago. In political-historical age, it is an infant - a disappointment to some who view it as little more than a debating society, but a promising hope to those who remind us of its potential as a mature political adult. That we are interdependent peoples traveling through the Universe on a minute

spaceship is ever more apparent.<sup>1</sup> Our survival depends on our accommodation to each other, on our abilities to work together in the solution of problems. No better example of the United Nation's potential can be cited than in its campaign against smallpox - a program which was beyond the reach of any single government or bilateral assistance agency.

It was on October 22, 1977, in the southern Somalian town of Merka, that a 23-year-old cook, Ali Maalin,<sup>2</sup> developed high fever and headache. By the fifth day, it was apparent that he had smallpox. Field staff discovered that just nine days before he became ill, he had been exposed to two children infected with smallpox - at that time, the world's only known remaining cases. Ali had exposed 161 people. All were identified, vaccinated and kept under surveillance. None developed smallpox.

Since that date, thousands of field staff in previously infected countries have searched village by village and house by house to discover other cases in Afghanistan,<sup>3</sup> Bangladesh,<sup>4</sup> Ethiopia. They show a WHO recognition card<sup>6</sup> and ask, "Have you seen anyone with a rash like this?"<sup>7</sup> "A rash on the face or on the body?" To encourage reporting, the World Health Organization offered a reward of \$1,000 to anyone reporting a case of smallpox.<sup>8</sup> Tens of thousands of persons with rash and fever have been investigated and thousands of specimens examined in WHO Reference Centers in Moscow and Atlanta. I would note that a recent

visitor to Somalia with even a mild case of acne could reasonably expect to have been taken into custody as a suspect case. Reports of cases came from around the world, even from villages in France, from Brussels and from San Antonio. Two further cases of smallpox occurred during 1978 following a tragic laboratory accident in Birmingham, England. But except for these two cases - none have been smallpox. International Commissions have visited each country to verify the results. On October 26, the Director-General of the World Health Organization announced from Nairobi, Kenya:<sup>9</sup> "I am confident in stating that as of today, smallpox has been eradicated throughout the world - that for the first time in history, a disease has been eradicated from the earth. October 26 shall henceforth be known as 'Smallpox Zero Day'."

Variola virus, once the cause of the most feared and devastating disease known to man, is now confined to glass vials in seven laboratories under conditions of high security.

The origin of smallpox antedates written history. The great Ramses V who died 3,000 years ago, in 1160 B.C.<sup>11</sup> is believed to have succumbed to smallpox and the disease was described in China in 1122 B.C. where it was known as "tai-tou." Indian Sanskrit texts suggest that it was known there for as long. Throughout India, even today, there are temples<sup>12</sup> to Sitla Mata or Sitla Devi, as she is variously known. More primitive idols existed in villages.<sup>13</sup> Sitla Mata is believed to possess the power to ward off smallpox and to prevent death among victims of the disease. It was the practice for recovered patients to offer gifts in

gratitude. For our surveillance teams, searching for unreported cases, the temples were important sites for investigation. In other cultures there were also deities consecrated to smallpox - Saponna in Western Africa,<sup>14</sup> Omulu in Brazil and others lost to history.

Deities consecrated to other diseases are all but unknown. But few diseases anywhere were so devastating as smallpox. It occurred in epidemics and killed 20% to 40% of its victims, leaving the others permanently scarred or blinded.<sup>15</sup> It could spread in any climate, in any area. Like measles, essentially everyone eventually contracted the disease. There was and is no treatment.

Smallpox became established in the increasingly populated Europe of the Middle Ages and in the 17th century Lord Macauley wrote: <sup>16</sup>"That disease was then the most terrible of the ministers of death... smallpox was always present filling the churchyard with corpses... and making the eyes and cheeks of the betrothed maiden objects of horror to the lover." Royalty was not exempt. The 29-year-old Elizabeth I developed severe smallpox leaving her bald and her face permanently scarred. In Europe, smallpox killed five reigning monarchs in the 18th century alone; and ended the royal house of Stuart and shifted the Austrian Hapsburg line of succession four times in as many generations.

In 1796, Edward Jenner<sup>17</sup> discovered that inoculation of cowpox material into the arm of a susceptible person prevented smallpox. Folklore of the time attributed the celebrated unblemished complexion of dairymaids

to their acquisition of cowpox,<sup>18</sup> a localized infection on the hand acquired from cows. Jenner deliberately took material from an infection on the hand of the dairymaid Sarah Nelms and inoculated it into the arm of James Phipps.<sup>19</sup> He later showed that Phipps was protected from smallpox and that the material could be transferred from the pustule on the arm of one person to the arm of another. In less than five years, Jenner's cowpox had been carried around the world, a remarkable feat in the era of sailing ships and stage coaches. Jenner in 1801 wrote:<sup>20</sup> "It now becomes too manifest to admit of controversy that the annihilation of the Smallpox, the most dreadful scourge of the human species, must be the result of this practise (of vaccine inoculation)." More than 175 years were to pass before his vision was realized.

Propagation of cowpox, or what later came to be called vaccinia virus, by arm to arm transfer permitted only small numbers to be inoculated at one time. Hepatitis and syphilis were sometimes transferred simultaneously. Extensive vaccination awaited large scale production of vaccine. In the mid to late 1800s, it was found that the virus could be grown in quantity on the flank of a calf. However, such vaccine, if unrefrigerated, became inactive in a matter of days. With increasing use of refrigeration, countries in the more temperate areas began to control smallpox. Even so, as recently as 1926, a Swiss delegate to a League of Nations meeting on quarantine procedures argued:<sup>21</sup> "Smallpox has, in reality, no place in an international convention. It is not a pestilential disease in the proper sense of the term; it is, in effect, a disease that occurs everywhere. There is probably not a single country of which it can be said that there are no cases of smallpox."

The United States recorded 33,000 cases in 1926 and, in fact, 10,000 cases as recently as 1939. Canada recorded 169 cases that year. In developing countries, the disease was all but unchecked.

During the 1940s, vaccination programs in Europe and North America effectively stopped smallpox transmission. In the developing world, where refrigeration was all but unknown, vaccines which were much more heat stable were essential. In the early 1950s, Collier, working at the Lister Institute in England, perfected the technique of freeze-drying of vaccine<sup>22</sup> - much as coffee is preserved today. Vaccine preserved in this manner remains potent for a month or longer at temperatures of 98°F.

Meanwhile, outbreaks of smallpox continued to occur in Europe as travelers brought the disease back from endemic countries.<sup>23</sup> When introduced it was as severe and as frequently fatal as in the developing countries. So frequent were the importations that England and Germany both maintained special smallpox hospitals to be opened and staffed when importations occurred. Vaccination certificates were required of almost all international travelers and national smallpox vaccination programs were routine in most countries, including our own.

Here was a problem of concern to all countries. Why not a global campaign of eradication? In 1959, the World Health Assembly at last decided on just such a course of action:<sup>24</sup>

During the succeeding years, mass vaccination programs were begun in a number of countries but only a few were successful. Countries which succeeded in stopping transmission experienced reinfection from their neighbors. Hoped for contributions of money and vaccine were not forthcoming. Most discouraging was that the strategy itself did not seem to be working. In many areas of the Indian subcontinent, a larger number of vaccinations were performed than there were people - but still smallpox persisted. A WHO Expert Committee was convened in 1964 to consider what should be done. They stated:<sup>25</sup> "The target set by the Organization - namely, that 80% of each segment of the population should be vaccinated - was found in practice to be unsatisfactory... The target must be to cover 100% of the population."

With an obviously foundering program and an increasing sense of frustration, the 1966 World Health Assembly decided to make one further attempt and voted to allocate \$2.5 million from its regular budget for the program. New hope often springs from new buildings and it was in 1966 that WHO occupied its new quarters overlooking Geneva.<sup>26</sup> The sum of \$2.5 million is better seen in perspective when one realizes that support was required for programs in fifty countries. The budget allotted amounted to an average of \$50,000 per country. But it constituted almost 5% of WHO's total budget. Publicly, the delegates were enthusiastic and proposed a 10-year goal for achievement. Privately, it was difficult to identify any who believed eradication to be possible. The skepticism was not unrealistic considering that the program would have to be undertaken in some of the most inhospitable

parts of the world and in some of the least developed countries. The fact that no disease had ever been eradicated and that WHO's only other disease eradication program - that for malaria - was obviously failing did not encourage optimism.

The program commenced on January 1, 1967. The target date for the occurrence of the last case was December 31, 1976.

<sup>27</sup>In 1967 when the program began, smallpox was endemic in 34 countries - nine other countries experienced importations that year. The belief that eradication of smallpox could in theory be achieved was based on a number of characteristics of the disease which, taken together, are unique. Of principal importance is the fact that man is the only host for the virus. There is no animal reservoir as there is in yellow fever, for example.<sup>28</sup> He can transmit infection only from the time when the rash first begins until the last scabs separate. Following recovery he is immune. There are no asymptomatic carriers as there are in malaria or poliomyelitis, for example. Thus, it was possible to know whether or not smallpox was present in an area by searching for patients with a visible rash. <sup>29</sup>The disease spreads in a continuing chain of infection as a result of face-to-face contact between a patient and a susceptible person. Usually, the patient does not infect more than two to five additional persons. <sup>30</sup>Smallpox, when introduced into a remote village, for example, will die out after only a few generations of disease, even if nothing is done. This may also occur over extensive, sparsely populated areas. In Brazil, the smallpox program concentrated



on the heavily populated areas near the coast. When teams then systematically moved up the Amazon, no cases were found. Effectively the same happened in Nepal making it unnecessary to conduct extensive, continuing campaigns in remote Himalayan mountain regions.<sup>31</sup> Finally, there is a heat-stable vaccine which confers long-lasting protection. In endemic areas, for example, we found that 90% or more were protected as long as twenty years after primary vaccination.

We estimated a need for 250 million doses of vaccine each year. Much vaccine was already being used in the endemic countries to control smallpox but was it effective? Connaught laboratories in Toronto and a laboratory in the Netherlands volunteered to test the vaccine. Less than 10% met accepted standards. Some contained no detectable vaccinia virus at all. A plea was made for donations of vaccine. The Soviet Union volunteered 140 million doses during the early years; the United States 40 million; Canada contributed several million doses annually and donations were eventually received from 26 countries.<sup>32</sup> A meeting of vaccine producers was convened and from this came a simplified step-by-step manual describing the production process. Consultants from Connaught Laboratories assisted producers throughout South America and others assisted developing countries in other areas to produce vaccine. By 1970 all vaccine met accepted standards. By 1972, 80% of the vaccine was being produced in the developing countries themselves. Some such as India, Iran, Kenya, Guinea and Argentina contributed vaccine to others. Uniquely, the program grew to become a truly collaborative global effort rather than an assistance program of the rich giving to the poor.

A unique invention, the bifurcated needle,<sup>33</sup> emerged from Wyeth Laboratories in 1968 and immediately we tested a new vaccination technique - multiple puncture vaccination. The needle could be dipped into the vaccine. By capillarity, sufficient vaccine was held between the tines. Fifteen rapid strokes implanted enough vaccine to obtain a take. Only one-fourth as much vaccine was required as had been needed with the older scratch technique. Vaccinators could be quickly trained. The needles were inexpensive and could be sterilized and reused many times.

WHO staff working in Pakistan designed a unique needle holder.<sup>34</sup> Sterilized needles were dispensed from one holder and used needles placed in a second. At the end of the day the heat stable plastic holders could be dropped in boiling water, removed after 20 minutes, shaken once and the vaccinator was prepared for the next day.

A further simplification in vaccination stemmed from English studies which demonstrated that an alcohol or acetone saturated cotton swab did little more than rearrange bacteria on the skin surface. Field tests confirmed that infection rates were not different whether the skin was cleansed or not. Vaccinators were thus instructed only to wipe away caked dirt if present.<sup>35</sup> Thus, with heat stable vaccine, a vaccinator could carry in his pocket all the equipment he needed for a month's work.

Between 1967 and 1969 programs began in most infected and neighboring countries and by 1971, all were in operation. The strategy called for nationwide systematic vaccination programs to be completed over two to three years, during which time reporting systems would be developed. It was expected that by then, smallpox cases would be few in number and the remaining foci could quickly be eliminated. The program had hardly begun, however, when Bill Foege, then working in Eastern Nigeria, demonstrated that even in a developing country which was poorly vaccinated, a sensitive reporting system could be rapidly developed. <sup>36</sup>In early December, 1966, cases were reported from a village called Yache. The patients were isolated and intensive vaccinations conducted in that village, followed by vaccination along the trails leading to the village and in the nearby market. Tracing of cases from the outbreak led to two other villages - Ukelle and Yala. There too, patients were isolated and the villagers vaccinated. In all, 43 cases occurred but the outbreak was stopped in just five weeks. In fact, smallpox transmission throughout Eastern Nigeria was stopped in a matter of months and at a time when less than half the population showed vaccination scars. Similar observations followed in other countries of Western Africa, in Indonesia and in Brazil. The program strategy was changed to give priority to "surveillance - containment," as it was called. A surveillance team of only 2 to 3 persons could cover an area with a population of 2 to 5 million persons. Each health center and hospital was visited and asked to send a report each week as to the number of smallpox cases seen. Schools and weekly markets were visited to ask if any had seen smallpox cases. When cases were reported, the surveillance teams, with local health workers, contained the outbreak.

Progress in most of Africa and in the Americas was rapid. <sup>37</sup>By 1970, the number of endemic countries had decreased from 33 to 17. Programs assisted by the U.S. Center for Disease Control had eliminated smallpox from all but one country in West Africa. <sup>38</sup>By 1973, smallpox was confined to the Indian subcontinent, to Ethiopia whose program did not begin until 1971, and to Botswana which became free of smallpox later that year.

The Indian subcontinent constituted a formidable program. Efforts such as we had made in Africa appeared to have little impact. Nearly 700 million people lived in the most densely crowded areas on earth. Trains and buses traveled everywhere, many carrying smallpox patients who had been infected in cities and were returning to their villages to recover or to die. Many cases and outbreaks were not reported. During the long, hot summer of 1973, a special campaign was planned with Indian colleagues. In essence, the plan called for all health workers during one week each month to visit every village - later every house in India - in search of cases. When cases were discovered, special surveillance teams moved in to contain the outbreaks. The logistics were formidable. The plan called for 120,000 workers to visit over 100 million households. Assessment teams visited a 10% sample of households to verify the work. And special surveillance teams were organized to check the assessment teams, to contain outbreaks and to search for cases at markets and schools during the intervening weeks. More than 8 tons of forms were needed for each search and thousands of vehicles, tens of thousands of bicycles, boats and rickshaws.

The first search took place in October. The results were worse than we had expected. Illustrative were the findings in the Indian State of Uttar Pradesh.<sup>39</sup> Two years of intensive work had already been spent in trying to improve the reporting system. Several hundred cases were being reported each week. During the search, nearly 7,000 cases were found - only later did assessment reveal that the workers had visited only half the villages. However, the outbreaks were now being found. Once found, they could be contained. The quality of the searches steadily improved. Much more rigid containment methods began to be used.<sup>40</sup> House guards were posted round the clock at each house to prevent patients from leaving and to vaccinate all visitors. Vaccination teams, posted to each infected village, searched and vaccinated in a five-mile radius around the infected village. As cases diminished in number,<sup>41</sup> a reward was offered to the villager who reported a case and to the health worker who first investigated it. Techniques employed in India were quickly adapted for use in Pakistan, Nepal and Bangladesh.

The number of cases which were reported continued to rise dramatically. In 1974, the total of reported cases was the highest in 15 years. The newspapers proclaimed "disaster" but by the summer of 1974, the smallpox staff knew that eradication could be achieved even in the ancient home of smallpox. <sup>42</sup>In October 1974, the last case occurred in Pakistan, in May 1975, in Nepal; in June 1975, in India; and, finally, on October 16, 1975, in Bangladesh, Rahima Banu<sup>43</sup> became the last victim of smallpox in Asia.

<sup>44</sup>Only Ethiopia remained to be conquered. Ethiopia, however, was a challenge unto itself. A country of 25 million people scattered across desert and highland plateau<sup>45</sup> in an area larger in size than France, Germany and Denmark - a country where half the population lives more than a day's walk from any accessible road<sup>46</sup> - the definition of "road" being loosely defined<sup>47</sup> - a country where then, as today, insurrection and fighting was widespread. WHO and national staff were periodically kidnapped and fired upon; one of our helicopters was destroyed by a hand grenade and others damaged by bullets. It was a country where vaccination was all but unknown and widely distrusted - a country with only 3,000 health staff, of which only 100 worked for the smallpox program, and those that did worked with difficulty, as paintings by an Ethiopian artist illustrate.<sup>48 49</sup> In 1971, when the program began, 26,000 cases were recorded but the actual number was probably 10 times this figure - or about 250,000 cases. Gradually an intrepid group comprised of national and WHO staff and volunteers from the United States, Japan and Austria succeeded in eliminating the disease from the northern highland areas, leaving localized foci among nomads of the southern Ogaden desert<sup>50</sup> - a scrub desert where it was difficult even to find the nomads - where encampments<sup>51</sup> could be rapidly assembled and as rapidly dismantled and carried 20 or 30 miles in a night. Special funds made available to WHO permitted us to hire and train nomads to search for cases and to vaccinate.<sup>52</sup> Amazingly, these staff would walk 40 miles or more a day and, seemingly by instinct alone, locate nomad bands. Whether or not there was smallpox, they were vaccinated. By containment of outbreaks and by reducing the number of susceptibles,

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smallpox transmission was finally stopped. In this sparsely populated area - the last cases occurred in August, 1976 in this encampment<sup>53</sup> known as Dimo.

There was still to be one last chapter, however. Somali guerrillas then fighting against Ethiopian forces in many areas of the Ogaden desert brought the disease back to Somalia, previously smallpox free. The first cases were discovered in September 1976. For yet another year smallpox campaigns had to be waged throughout Somalia, in neighboring Kenya and Djibouti. More than 3,000 cases were discovered but, at last, the disease had been cornered. <sup>54</sup>Ali Maalin proved to be the last case in a continuing chain of infection extending back at least 3,000 years. Eradication had been achieved - the 10 year time target missed, but only by 9 months and 26 days.

International assistance to the program amounted to an average of only \$8 million per year. The endemic countries spent perhaps twice this amount but few spent much more than what was being spent for ineffectual programs of smallpox control.

For many developing countries, where health budgets are little more than \$1 to \$2 per person, the conquest of smallpox represented the first substantial and tangible achievement of a developing health service. Many issued commemorative stamps to celebrate the victory.<sup>55 56</sup>

With confidence bolstered by achievement, new initiatives were sought. Expensive hospitals and the development of curative services were beyond the scope of the limited funds available. Prevention of disease, however, was possible and so the World Health Assembly decided to begin a global program of immunization to protect the 100 million newborns in developing countries against six destructive diseases<sup>57</sup> for which good vaccines are available - poliomyelitis, measles, diphtheria, whooping cough, tetanus and tuberculosis. The cost - about \$3 per child. Already, more than \$25 million per year is being contributed.

International collaboration and effective management in the health structure were principal ingredients in the success of the campaign. The Expanded Immunization Program demands yet more but these are the same ingredients which are so essential and so fundamental to programs of family planning, sanitation and the control of other diseases in the developing world.

Some 700 international staff from 69 countries served in the field during the smallpox program. More than 150,000 national staff were also engaged. It is they who are now providing a new impetus, renewed vigor and a new sense of mission to an international commitment to better health for peoples throughout the world. It is they whom the Lasker Foundation honored when in 1976 a Special Award was given with these words:



"We salute this historic milestone as one of the most brilliant accomplishments in medical history. We hope that it will provide an example of how, with coordinated international effort many of the other health problems that afflict mankind can be successfully attacked."

The task has begun.