SPEECH FILE

"The Eradication of Smallpox"
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On the occasion of the presentation of the John Scott Medal to Ben Rubin for Eradication of Smallpox

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On 8 May 1980, the 33rd World Health Assembly, in a specially convened plenary session passed unanimously a resolution which:

1 o "Declares solemnly that the world and all its peoples have won freedom from smallpox, which has been a most devastating disease ... since earliest times, leaving death, blindness and disfigurement in its wake and whch only a decade ago was rampant in Africa, Asia and South America;

2 o "Calls this unprecedented achievement in the history of public health to the attention of all nations, which by their collective action have freed mankind of this ancient scourge and, in so doing, have demonstrated how nations working together in a common cause may further human progress."

The Assembly recommended that:[2]

3 o "Smallpox vaccination should be discontinued in every country except for investigators at special risk" and

o "No country should now require vaccination certificates from international travelers."

4 Four years have now elapsed since October, 1977, when a 23-year-old hospital cook in Merka, Somalia, became ill with smallpox. He represented the last known case in a continuing human-to-human chain of infection extending back more than 3,000 years. Two additional smallpox cases were recorded in 1978 in Birmingham, England,

the result of a tragic laboratory accident.[4] However, intensive search throughout recently infected areas and the investigation of countless rumors stimulated by the offer of a substantial reward, have revealed no other cases.

Beginning in 1978, a Global Commission on Smallpox Eradication, convened by the World Health Organization, carefully reviewed all documentary evidence. It requested and undertook additional corroborative studies of its own. Finally, in 1980, the Commission reported to the WHO Executive Board and the World Health Assembly that it was completely satisfied that smallpox eradication had been achieved. The Assembly concurred. So concluded a chapter in medical history the first successful campaign to eradicate a disease.

Even today, however, there are some, scientists and laymen alike, who remain skeptical that this disease, so long of concern and fear to countries throughout the world, could at last be eliminated. Understandably most skeptical are those who have lived or worked in Asia, in Africa, or in the vast Amazon region of South America and who appreciate well the immense geographical expanse of these areas, the extent of the inaccessible regions and their still primitive state. Indeed, it is difficult to forget that as recently as seven years ago, headline news stories from India proclaimed "History's worst smallpox epidemic." To quote from a 1974 Associated Press dispatch: "A virulent smallpox epidemic, described as India's worst of the century, has killed an estimated 30,000 persons this year. The outbreak has surged from village to village despite an intensive detection and vaccination drive launched last October."

In light of this, how can one be so confident of eradication as to cease vaccination and to abandon such security as was afforded by international certificates of vaccination? At the same time, a younger generation queries as to why there is so much interest and concern as to whether or not a disease of the distant tropics has been eradicated. Let me first, therefore, recount briefly the history of smallpox and its impact on mankind before describing the development of the global campaign and, finally, the evidence upon which the World Health Assembly reached its decision that smallpox has been eradicated.

Smallpox had no animal reservoir and, in man, there was no human carrier state. Therefore, the virus, to persist, had to infect person after person in a continuing chain of transmission. Its origins are thus assumed to date back no more than 10,000 years,[6] to the time of the first agricultural settlements, to a time where there was a sufficient concentration of population to permit a chain of infection to be sustained. A mutant of one of the large family of animal poxviruses was presumably its source. The earliest evidence of its presence dates back more than 3,000 years. The mummy of Ramses V, who died in 1160 B.C. and which was examined most recently only two years ago, bears unmistakable, characteristic lesions of smallpox.[7] An Indian Sanskrit text, also dating from about this period, vividly describes the disease.[8]

Throughout history, few diseases have been so devastating as variola major. In recent centuries, both during major epidemics and in its endemic form, case-fatality rates of 20% to 40% or more have been the rule with most of those surviving, permanently scarred and some blind. The disease could spread in any climate, in any area. Like measles, essentially everyone contracted the disease. There was and is no treatment. Over recent centuries, variola major ~~appeared to~~ changed little in virulence and thus it seems reasonable to suppose that the disease 20 to 30 centuries ago was comparable in virulence. The fact that deities consecrated specifically to smallpox have long been known in many cultures would support this view. Throughout India, even today, there are temples to Shitala mata ~~or Devi mata, as she is variously known~~.[8] More primitive idols existed in villages. Shitala was believed to possess the power to ward off smallpox and to prevent death among victims of the disease. In other cultures, there were also deities consecrated to smallpox, such as Shapona in Western Africa and Omulu in Brazil.

From India or perhaps Egypt, smallpox spread across Asia and Africa, becoming endemic over an ever-wider area as population densities increased.

It became established in the increasingly populated Europe of the Middle Ages. In the 17th century Lord Macauley wrote: "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. During the 18th century alone, smallpox killed five reigning monarchs, ended the Royal House of Stuart and shifted the Hapsburg line of succession four times in as many generations.[3]

In the Americas, it was smallpox which precipitated the collapse of both the Incan and Aztec civilizations as the disease swept through a virgin population. Settlers in the New World experienced few problems with the native Indian population not because they were so welcome but because so few Indians remained after smallpox had taken its toll.

Edward Jenner's demonstration in 1796 that an infection induced with cowpox virus could prevent smallpox[10] was understandably hailed as one of history's most important advances. Folklore of the time attributed the celebrated unblemished complexion of dairymaids to their acquisition of cowpox, a localized infection on the hand acquired from cows. Jenner was cognizant of this folklore and deliberately took material from an infection on the hand of the dairymaid Sarah Nelms and inoculated it into the arm of James Phipps. He later showed that Phipps was protected from smallpox and that material could be taken from the pustule which developed on the arm of the inoculee and successfully transferred to the arm of another person. In less than five years, Jenner's cowpox had been carried around the world, its survival assured by arm-to-arm transfer.[11] This was a remarkable feat in the era of sailing ships and stage coaches. Jenner in 1801 wrote: "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)."[12] More than 175 years were to pass before his vision was realized.

Propagation of cowpox, or ~~what probably~~ was its (probable) derivative, vaccinia virus, by arm to arm transfer permitted only small numbers to be inoculated at one time. When vaccination ~~was unsuccessful~~ failed, a new strain had

to be sought. Extensive vaccination awaited large scale production of the virus. In 1840, ~~Negri of Naples~~ found that the virus could be grown in quantity on the flank of a calf and this method of propagation of vaccinia gradually came into use throughout Europe and North America ~~over the next 30 years~~.[13] However, such vaccine, after harvest, 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:- "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." As recently as 1938, the United States recorded 15,000 cases.

During the 1940s, vaccination programs in Europe and North America effectively stopped smallpox transmission. In the developing world, where there was little refrigeration, vaccines which were much more heat stable were essential. In the 1950s, Collier, working at the Lister Institute, perfected a commercially applicable method for freeze-drying vaccine. Vaccine preserved in this manner remained potent for a month or longer at temperatures of 37°C.[16] For smallpox control in the tropical developing countries, this was a development of signal importance.

Meanwhile, outbreaks of smallpox continued to occur in Europe as travelers brought the disease back from endemic countries. When introduced it was as severe and as frequently fatal as in the developing countries. Vaccination certificates were required of all international travelers and national smallpox vaccination programs were routine. Here was a problem of concern to all countries, ~~a health problem which would appear to be an obvious one for the World Health Organization to address~~.

In 1958 Professor Victor Zhdanov, then Vice-Minister of Health of the Soviet Union, proposed to the World Health Assembly that the global eradication of smallpox be undertaken.[18] And the following year it was adopted. The Soviet Union with its long common border with many

then-endemic countries, was troubled by frequent importations. Moreover, smallpox eradication seemed more feasible than did malaria eradication, then just beginning. At the same time, this represented a Soviet initiative which neatly balanced the heavily U.S.-supported malaria eradication effort.

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. New Delhi, India, reported that 120% of the population had been vaccinated and later that year experienced its largest epidemic in a decade. A WHO Expert Committee was convened in 1964 to consider what should be done. They stated:[19] "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.[20] The budget provided an average of less than $75,000 for each endemic country. Nevertheless, 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 foundering did not encourage optimism.

The program commenced on January 1, 1967. Thirty-four countries were then endemic and 9 others experienced importations that year. The target date for the occurrence of the last case was December 31, 1976.

The belief that eradication of smallpox could in theory be achieved was based on a number of characteristics of the disease which, when taken together, are unique. Of principal importance is the fact that man was the only host for the virus. There is no animal reservoir. A person with smallpox could transmit infection only from the time when the rash first appeared until the last scabs separated. Following recovery he was immune. There were no asymptomatic carriers as there are in malaria, 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. Moreover, the characteristic residual facial scars of smallpox permitted one to determine the past history of smallpox in that area. The disease spread in a continuing chain of infection almost always as a result of face-to-face contact. By tracing the source of infection of the victim and by identifying his contacts, other cases in the chain of transmission could be identified and outbreaks contained. Usually, the patient did not infect more than two to five additional close contacts. Outbreaks thus tended to cluster among acquaintances of the victim within localized areas of a city or in particular sections of a country. This tendency toward a concentration of cases permitted a comparatively few teams engaged in outbreak containment to deal with problems over an extensive area. Moreover, smallpox, when introduced into remote villages, soon depleted the susceptible population and often died out after only a few generations of disease, even if nothing was done. This could and did occur even over extensive, sparsely populated areas. In Brazil, for example, the smallpox program initially 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 continuing campaigns in remote Himalayan mountain regions. Finally, the heat-stable vaccine conferred much longer lasting protection than had been thought possible. In endemic areas, for example, we found vaccine-efficacy levels of 90% or more as long as twenty years after primary vaccination.

As the program began in 1967, we faced immediately two critical problems. We needed a technique for vaccination which assured high take rates and we needed vaccine in large quantity - approximately 250 million doses each year. Purchase of vaccine was out of the question. Even at a cost of one cent per dose, $2.5 million would have been needed - and this represented our total budget. Most countries were then using quantities of vaccine in control programs and we hoped this vaccine might meet perhaps half of our needs. Two laboratories volunteered to test the vaccines in use in the endemic countries. The results were appalling. Less than 10% of the vaccine then in use met accepted standards and many samples contained no detectable ~~living~~ vaccinia virus at all. We sent an appeal to all governments for help. The Soviet Union responded with 140 million doses per year; the USA gave us 40 million doses of jet injection vaccine which was produced by Wyeth; and a few other countries offered contributions of 500,000 to 100,000 doses. It was still far short of what we needed.

The jet injector appeared to offer ~~some relief~~ help. In studies conducted collaboratively by CDC, Wyeth Laboratories and the U.S. Army during the mid-60's, we had found that a greatly diluted vaccine suspension could be administred intradermally by ~~the~~ jet injection with take rates as high or higher than those obtained by any other technique. ~~More than this~~, as many as 1,000 persons per hour could be vaccinated. The injectors were introduced for use in West Africa, ~~in a USAID-CDC program~~, in Brazil and in Zaire in Central Africa. When the injectors worked, they worked well but they required skilled maintainance, a commodity in short supply, and a never-ending flow of spare parts. Their capacity was remarkable but rarely was it possible to assemble anywhere near 1,000 persons and to move them past a single point in one hour. In fact, in well-directed programs, an average of 1,000 to 1,500 vaccinations per day was the rule.

We had established a central vaccine store in Geneva in order to respond quickly to requests from countries but, in fact, the demand for vaccine was so great that we ~~were~~ customarily ~~receiving~~ vaccine by one air flight and ~~sending~~ it off the same day. For several countries, including several

in Asia, we simply had to advise that they continue to use the vaccine they were producing; however inferior it was.

We convened a meeting of vaccine producers which traveled from Geneva to Moscow to Marietta, Pennsylvania, and, in the process developed a simplified manual for production. Following this, consultants visited vaccine production centers in the developing countries to assist them in their efforts. At best, we ~~assumed~~ it would ~~take~~ five years before we had sufficient, high-quality vaccine.

Meanwhile in most countries, vaccinators continued their time-honored technique of dipping a glass rod or pipette into a vaccine suspension, placing a drop on the skin and with a needle or small scalpel, making two or three scratches through the drop. With an ampoule of 0.25 ml, 15 to 25 vaccinations could be performed.

It was a memorable day indeed when in late 1967, Ben Rubin showed me his ingeneous and eloquently simple bifurcated needle. The results which he and his colleague, Mal Bierly, had obtained with the needle in multiple pressure vaccination were impressive. Most important, the amount of vaccine required for vaccination was one-fourth or less than was required ~~for~~ traditional methods. Even so, we were concerned that multiple pressure vaccination ~~might still~~ be too difficult to teach illiterate vaccinators and so, in the course of a brief conversation that day in Marietta, we decided to try a multiple puncture technique. The technique called for the needle to be dipped into the vaccine. By capillarity, sufficient vaccine was held between the tines and 15 rapid strokes could be made with the needle held perpendicular to the skin. By early January, 1968, we had already completed studies in Kenya, Liberia and Egypt. (Table) (Table)

So little vaccine was taken up by the needle that even our field staff doubted the results and so a special study was done in which vaccination was performed on one arm as prescribed and on the other arm, a full drop of vaccine was first applied and then multiple puncture vaccination was performed. (Table). The results were indistinguishable.

Concern was expressed that slight bleeding which often occurred at the vaccination site might "wash out" the virus. This was conventional medical wisdom at that time. So, deliberately, vaccination was vigorously performed on an entire group of children, inducing moderate bleeding in each case. The results were unchanged. All had takes.

Vaccinators could be taught the technique in a matter of minutes and the vial of vaccine which previously vaccinated no more than 25 now could readily vaccinate 100 or more. And with the needle, vaccination could be rapidly performed. The average vaccinator in Africa normally performed an average of 500 per day and in one country, they averaged over 1,200 per day (although they did request that we supply thimbles, as their fingers got sore.) The vaccine shortage was all but solved. Even so, simple as the needle was, vaccinators periodically wound up reversing the needle and vaccinating their own fingers. Nothing is accident-proof!

Wyeth generously agreed to waive all patent costs and we immediately negotiated with a metalurgical firm to make a somewhat harder but non-rusting needle which could be reused many times. And, with a budget as slim as we had, we shortened the needle from 6.5 cm. to 5.0 cms to save money. Within 12 months, the needle was in use throughout the world and, in all, more than 60 million were distributed. It was still Ben Rubin's needle and it was an invention which I frequently likened to the safety-pin which, in its day, was eloquently revolutionary.

(33)

WHO staff working in Pakistan next designed a unique needle holder borrowed in concept from Wyeth. Sterilized needles were dispensed from one holder and used needles placed in a second. At the end of the day the thermostable 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 stemmed from English studies[24] which demonstrated that an alcohol or acetone saturated cotton swab did little more than rearrange bacteria on the skin surface. Field tests confirmed that

the frequency of bacterial sepsis following vaccination was no different whether the skin was cleansed or not. Vaccinators were thus instructed only to wipe away caked dirt if present. 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 initially called for nationwide systematic vaccination programs to be completed over two to three years, during which time reporting systems would be developed.[25] It was expected that by then, smallpox cases would be few in number, an effective reporting system would have become well-established and the remaining foci could quickly be eliminated. The program had hardly begun, however, when in Eastern Nigeria, serendipity prevailed. Awaiting the arrival of transport and supplies for a mass vaccination campaign and lacking more than a limited supply of vaccine, Bill Foege decided simply to contain those outbreaks he could find. A mission radio network cooperated in reporting cases. Using such transport as could be found, Foege with a small group of Nigerians undertook to vaccinate intensively in those villages where cases were reported, to trace the origins of the outbreaks and to repeat the process when new outbreaks were discovered. When supplies arrived months later, he began a systematic vaccination program, but no smallpox could be found. A vaccination scar survey revealed that less than half the population had ever been vaccinated. The observation that it was possible to rapidly develop a reporting system and to interrupt transmission even in a densely populated developing country less than half the population possessed any immunity came as a great surprise. Similar observations soon 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 decision that the strategy should be changed and changing it, however, proved to be, quite different matters. Mass vaccination was traditional and well understood. Moreover, the formidable logistics of a systematic vaccination program permitted little

time for other activities. To give emphasis to surveillance-containment, we eventually stated bluntly that mass vaccination was not really required, only surveillance-containment. Gradually, the strategy changed. In Africa and South America, we found that a surveillance team of only 2 to 3 persons could effectively cope with an area inhabited by 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 persons 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. By 1970, the number of endemic countries had decreased from 33 to 17. 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, however, proved to be a more formidable challenge. Efforts such as we had made in Africa appeared to have little impact. In endemic Asian areas, nearly 700 million people lived in the most densely populated areas on earth. An extensive network of train and bus service facilitated extensive travel. Many smallpox patients, infected in cities, returned to their villages to recover or to die. The disease spread rapidly and widely. Numerous cases and outbreaks were not reported, some deliberately. There were many then who knowingly assured us that eradication in Africa or South America was one thing but in Asia, the traditional, ancient home of smallpox, the task could not be done. More than once, we wondered if they might not be right.

During the summer of 1973, a special campaign was planned.[27] In essence, the plan called for all health workers during one week each month to visit every village in India - later every house - 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 sur-

veillance 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, as well as tens of thousands of bicycles, boats and rickshaws.

The first search took place in October. The results were astonishing. Illustrative were the findings in the northern Indian State of Uttar Pradesh. Two years of intensive work had already been spent in efforts to improve the reporting system in this populous state. Several hundred cases were then being reported each week. During the one-week search, nearly 7,000 unreported active cases were found. Only later did assessment reveal that the workers had visited only half the villages and that there must have been at least 15,000 active, unreported cases at that time. However, because of the search program, a higher proportion of outbreaks were being found and more rapidly than before. Once found, they could be contained. The quality of the searches steadily improved. Much more rigid containment methods began to be used. House guards were posted at each infected house on a 24-hour schedule to prevent patients from leaving and to vaccinate all visitors. Vaccination teams, posted to each infected village, searched and vaccinated in an increasingly wider radius around the infected village. As cases diminished in number, a reward was offered to the villager who reported a case and to the health worker who first investigated it. As the cases diminished in number, the reward was gradually increased. Techniques employed in India were soon adapted for use in Pakistan, Nepal and Bangladesh.[28]

The number of cases which were reported continued to rise dramatically. In 1974, the total of reported cases from the Indian subcontinent was the highest in 15 years. The newspapers proclaimed a "disaster" but by the summer of 1974, the smallpox staff knew that eradication could be achieved even in the ancient home of smallpox. In October 1974, the last case occurred in Pakistan; in May 1975, in Nepal; in June 1975, in India; and, finally, on 16 October, 1975, in Bangladesh. A three-year-old girl, Rahima Banu, became the last victim of smallpox in Asia.

Only Ethiopia remained to be conquered. Ethiopia, however, was a formidable challenge ~~unto itself~~. It is a country of 25 million people scattered across desert and highland plateau in an area larger in size than all the states on the eastern seaboard combined. It is a country where half the population is said to live more than a day's walk from any accessible road, the definition of "road" being loosely defined. ~~It is a country where then, as today,~~ insurrection and fighting were 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. Health staff were few in number and less than 100 could be employed for the smallpox program. In 1971, during the first year of the program, 26,000 cases were recorded but the actual number was probably 10 times this figure.[29] 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. This left infected foci only among nomads of the vast southern Ogaden desert. However, in this scrub desert it was difficult even to find the nomads, ~~who~~ lived in portable encampments which could be rapidly built and as rapidly dismanteled and carried 20 or 30 miles in a night. ~~Special funds permitted us to~~ hire and train nomads to help search for cases and to vaccinate. By containing outbreaks and by reducing the number of susceptibles, smallpox transmission was finally stopped. Finally, in August 1976, ~~in an encampment known as Dimo~~, the last cases were discovered and the last outbreak contained. We celebrated.

But there was still one last chapter. 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 reported in September 1976.[30] For yet another year a smallpox campaign had to be waged throughout Somalia, as well as in adjacent areas of Kenya and Djibouti. More than 3,000 cases were discovered but, at last, the final chains of transmission were severed. Ali Maalin.

the 23-year-old cook in Merka, Somalia, proved to be the last case in a continuing chain of infection extending back at least 3,000 years. Eradication appeared to have been achieved. The 10 year time target had been missed, but only by 9 months and 26 days.

Two major questions remained, ~~questions which had been of concern to us since the earliest days of the program~~: (1) How could could we be certain that eradication had been achieved and; (2) Even if ~~smallpox program staff~~ were confident ~~of eradication~~, how could national authorities ~~gain a comparable level of confidence~~, sufficient to permit them to stop vaccination and the requirements for international vaccination certificates?

As pointed out, smallpox, to persist, must continue to be transmitted from person to person. We reasoned that evidence of persistent transmission should be increasingly evident with the passage of time, either through detection of one of an ever increasing number of active cases or through detection of residual facial scars caused by the disease. We believed that two years of continuing surveillance should detect cases if present and this became a working standard. If no cases were found, during this period, it was decided that natural transmission could be considered to have been interrupted.[31] Experience supported this presumption. During the course of the program, we discovered just six instances in which smallpox transmission continued in a country for periods of 6 to 36 weeks after we thought transmission had been interrupted. The prescribed 104-week period of surveillance was almost three times longer than the longest interval of time ~~during the program~~ when smallpox persisted in a country unknown to national health authorities. Notably, all of these episodes occurred prior to 1974 when we ~~increasingly~~ began to publicize that a reward would be given to anyone who reported a case ~~which could be~~ confirmed as smallpox. The ~~expectation of a substantial~~ cash award quickly brought to light many cases which otherwise might have been hidden. In additon to offering a reward, the program of surveillance became increasingly rigorous, ~~as time progressed~~.[32] Special teams conducted repeated house to house searches to discover cases, to detect facial pockmarks and to document when they occurred. Specimens

were collected from cases with rash and fever and dispatched to WHO Laboratories in Atlanta and Moscow for examination. Many other measures were employed as well, so many, in fact, that it was our belief that from 1973 onwards, eradication could have been reliably certified in a country one year or even less after the last known case. Nevertheless, the two-year surveillance standard was retained.

To provide assurance to the international community that eradication had been achieved, it was decided to appoint international commissions to visit each of the previously endemic countries after at least two years had elapsed since the last case.[3] For the commissions, knowledgeable and critical individuals from many different countries were selected. ~~whom it was felt would be especially critical~~. Prior to the commission's visit, each country prepared reports detailing ~~the nature of~~ its program and of the surveillance activities undertaken during the proceeding two years or more. After reviewing the reports, members of the commission decided on the areas in each country which they wished to visit to verify the work. Each usually spent two to three weeks in direct field observation, usually in those areas where documentation appeared questionable or in areas considered to be at greatest risk of harboring smallpox.

In all, 10 different International Commissions visited 48 different countries, including all of those which had experienced endemic smallpox since 1967 and others which were bordering them. Special visits were also made by WHO staff and consultants to an additional 28 countries to review programs and to obtain further documentation. Because numerous respected scientists and public health workers from many different countries participated in these Commissions, knowledge of the nature of the smallpox program and the rigorous evidence required to certify eradication became ever more widely known.

Finally, in 1978, the Director-General appointed a WHO Global Commission comprised of 21 persons from 19 different countries and charged them with the responsibility of reviewing existing documentation and identifying additional measures which they considered needed to be undertaken to satisfy themselves that global eradication had been achieved. In January,

1980, after two years' work, the Chairman of the Global Commission was able to report to the WHO ~~Executive Board and~~ Assembly that the Commission was fully satisfied that eradication had been achieved.[3] Confidence in the achievement was manifest quickly in the prompt action of countries to terminate their requirements for international vaccination certificates. Routine programs of smallpox vaccination have now been stopped in almost all countries.

Variola virus is now known to exist only in five laboratories, all of which have been inspected by international teams. The risk of accidental escape from any was considered ~~by the WHO Global Commission~~ to approach nil.

The possibility that there might be an animal or natural reservoir of the virus had been of concern from the beginning of the program. Recalling the unexpected discovery of a natural reservoir of yellow fever virus long after eradication of that disease had commenced, we undertook and supported from the beginning ~~of the eradication program~~, a wide-ranging series of studies in an effort to discover such a reservoir. None was found. The best evidence that there is no reservoir comes from the epidemiological evidence that all smallpox outbreaks detected in otherwise smallpox-free areas during the past 12 years were able to be traced to known human cases. If there were an animal reservoir or if the virus were able to persist in nature in crusts or other material, apparently "spontaneous" outbreaks should have been discovered. None were identified.

A surprising discovery in 1970 was the identification in Africa of human illness caused by monkeypox virus.[33] Clinically, the disease was essentially indistinguishable from smallpox. Some 55 cases have so far been identified, all of which have occurred in the tropical rain forest belt, mostly in remote, small villages. Person-to-person transmission may have occurred in six instances but it is apparent that the virus can be transmitted only with difficulty even when susceptible persons are in close contact. Genome maps of this and other animal poxviruses are still being constructed but, the differences between variola and other poxviruses so far studied are many and occur at many different locations

on the genome, suggesting that a spontaneous mutation to variola is extremely unlikely.[34 35]

The recurrence of smallpox due to deliberate release of the virus as an act of terrorism cannot be ruled out despite an international Convention which bans the use of biological weapons. However, as the Global Commission pointed out, the potential hazard of such an act should not be exaggerated.[3] Smallpox does not spread rapidly, as does measles or influenza, and between each generation of cases, there is an interval of two weeks or more. Intensive vaccinaton programs thus should readily be able to contain a terrorist-propagated outbreak within two to three generations of the disease, or roughly within a four to six week period. Moreover, it should be noted that if an agency decided to employ biological weapons, there are other agents for which there are no effective vaccines and whose combined characteristics of ease of spread and virulence are superior to those of variola virus.

As insurance against presently unforeseen events, the WHO has established vaccine storage reserves containing some 200 million doses of vaccine and additional stocks are being retained by national governments. Since vaccine has been shown to be fully potent even after 17 years of storage at -20°C, it is believed these stocks can be retained indefinitely.

Thus, barring improbable circumstances, a human case of smallpox will never again be seen.

Savings to be realized annually because of the cessation of vaccination are estimated to be $1 to $2 billion per year dollars. In contrast, 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.

What program logically should follow that of smallpox eradication? Many have proposed that another disease should be targeted for eradication and another global campaign launched. In my opinion, there is no other

disease which possesses so many characteristics favorable to an eradication effort or for which we now have available, effective, simple and inexpensive measures for prevention or treatment. Although smallpox eradication may now seem to have been comparatively straightforward, I recall well innumerable instances in which the program balanced on a knife edge between success and disaster, decided by such as an unexpected change in government, a cessation of hostilities or an heroic exhibition of dedication, courage and leadership by WHO and national staff or by the discovery of a bifurcated needle. There were a multitude of miraculous and timely events and to relate them all would require a book. Even with these, eradication just barely succeeded.

More than 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 to an international commitment to better health for peoples throughout the world in WHO's Expanded Program of Immunization. It is they whom the Lasker Foundation honored by a Special Award which was given with this citation:

> "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."

A first step has been taken in a long and difficult journey but in taking that step, we have obtained renewed confidence that other successes are possible.