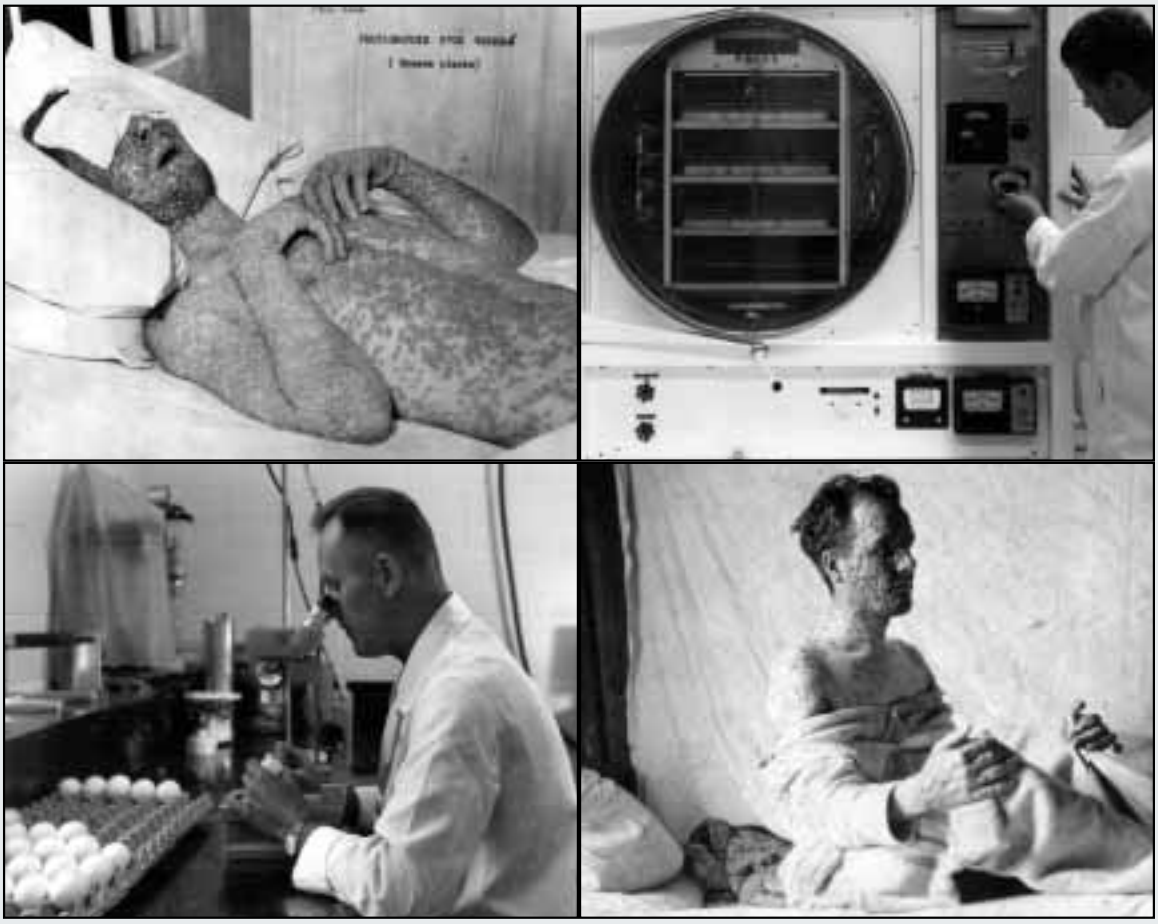

The Speckled Monster

CANADA, SMALLPOX AND ITS ERADICATION

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The Canadian Public Health Association (CPHA) is a national, independent, not-for-profit, voluntary association representing public health in Canada with links to the international public health community. CPHA's members believe in universal and equitable access to the basic conditions which are necessary to achieve health for all Canadians.

CPHA's mission is to constitute a special national resource in Canada that advocates for the improvement and maintenance of personal and community health according to the public health principles of disease prevention, health promotion and protection and healthy public policy.

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The Early Years: 1635-1965

"Directly and indirectly, the ammunition for the [smallpox eradication] campaign bore the indelible stamp – 'made in Canada'. To a once-Canadian, it was always a personal source of pride."

Dr. Donald A. Henderson
Chief, WHO Smallpox Eradication Unit[1]

Introduction

"Today we have no conception of the meaning of the word 'smallpox'." So wrote Dr. John J. Heagerty of Canada's Federal Public Health Service in a 1924 booklet, *Smallpox and Vaccination: A Popular Treatise*, published in the wake of an alarming outbreak in Windsor that year.[2] He went on to stress that, "For us the word has been robbed of its terrors and we discuss the problem of smallpox in the community in a general and academic way." However, in the pre-vaccine days, "the word 'smallpox' blanched the cheek and brought a look of terror to the eyes. Smallpox in those days meant death. Relentless and insatiate the disease would sweep though a community mowing down all those who had not already suffered from it; killing, maiming and leaving its victims blinded or disfigured for life." Moreover, "It played a part of no little importance in the political history of Canada in the early days… When smallpox stepped in and took charge, all activities ceased and as the chronicler says: 'the only meetings were for funerals.' Vaccination has altered all this and forgetful or ignorant of the appalling ravages of the disease in other days, we now scarcely give the subject of smallpox a thought."

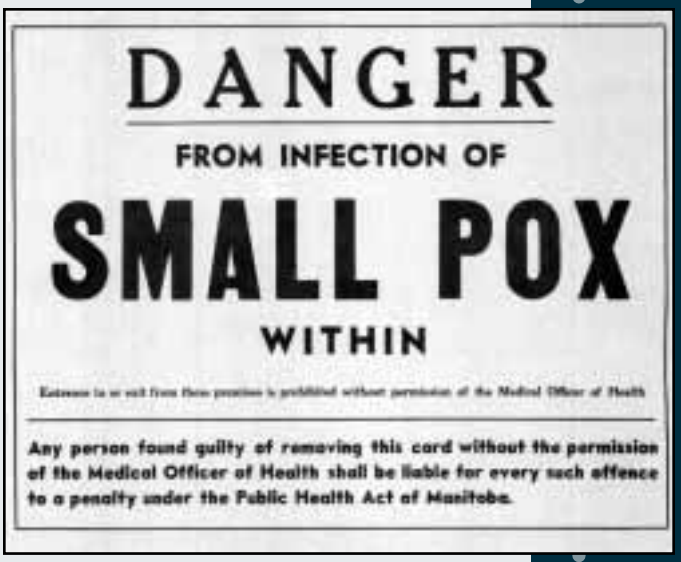
Seventy-eight years later – twenty-two years after smallpox was officially declared eradicated from the Earth in 1980 by the World Health Organization – and in the aftermath of the tragic events of September 11, 2001, the spectre of the "speckled monster" has re-emerged from history. With routine smallpox vaccination in North America stopped in the early 1970s, everyone born since, and perhaps most people on the planet, their immunity faded from earlier vaccinations, are now vulnerable to the smallpox, or variola, virus – this time because of its potential use as a bio-terrorism weapon. Smallpox was the first infectious disease consigned to the pages of history; now, in the face of its possible use as a bio-weapon, one must turn to history to begin the process of reacquainting ourselves with the power of this disease and of re-building an effective defense against it.

Canada's experience with smallpox and smallpox vaccines has been significant. The victim of smallpox's frightening wrath many times since its first appearance here in 1635 and its last in 1962, Canada played an essential role in the development, improvement and delivery of smallpox vaccines and in their utilization in the eradication of the disease. In particular, Connaught Medical Research Laboratories – part of the University of Toronto from 1914 to 1972,[3] and today a key component of the global Aventis Pasteur organization – was the primary hub of Canada's efforts to control and ultimately eradicate smallpox internationally.

"The Speckled Monster" in Canada

Smallpox was first introduced into North America's northern half in about 1635, not long after the first settlers arrived from France. While most of the Old World was well experienced with

this disease, the New World's native population was immunologically innocent of smallpox until the early 17th century arrival of the first Europeans. From the first smallpox epidemic among the Montagnais near Quebec City in 1635, the disease spread rapidly among all natives with great destructive force, by 1670 decimating the Algonquins, Hurons and several other tribes of New France. During the 18th century, as the population of settlers grew, so did the threat of smallpox among them: 3,000 deaths in Quebec City in 1702-03, another 1,800 deaths there thirty years later, and 2,600 dead in 1757. By the early 1780s, the disease had reached into the western plains.[4] In the midst of frequent outbreaks among the European settlers, it is evident that the power of smallpox was harnessed as a bio-weapon against the native population. In the early 1760s, the smallpox virus was deliberately spread among several tribes by the British military using infected blankets given as a "token of good fortune."[5]


DANGER

FROM INFECTION OF

SMALL POX

WITHIN

Any person found guilty of removing this card without the permission of the Medical Officer of Health shall be liable for every such offence to a penalty under the Public Health Act of Manitoba.

Figure 1:
Smallpox public health placard, Manitoba, c. 1930s
(AvP-CA Acc1207)

Over the next century, arm-to-arm variolation, first introduced into Canada in 1768, and then the safer and more effective cow-pox vaccination thirty years later, gradually brought smallpox under control. However, several dramatic epidemics demonstrated what can happen when vaccination lapses through benign neglect, or open defiance by anti-vaccinationists. As Michael Bliss has vividly documented in *Plague: A Story of Smallpox in Montreal*,[6] the great Montreal epidemic of 1885, which left over 3,000 dead, is an example of the latter case; a particularly virulent outbreak in Windsor in 1924 illustrates the former.

Windsor's experience with smallpox in 1924 was both unusual and valuable in terms of its severity and how it clearly demonstrated the protective value of smallpox vaccine. In contrast to Ontario, Michigan did not have compulsory smallpox vaccination at the time, thus the disease was frequently present in the state. In late 1923, a smallpox outbreak in Detroit spread across the border into the Windsor area, affecting mostly adults who had not been vaccinated.

In early February 1924, an especially virulent case of smallpox was reported in a Windsor man. He died a few days later, but soon similarly virulent cases occurred among those who had attended his funeral. In the end, 67 cases were reported and 32 died. Beyond this unusually high death rate, of significance was the fact that all deaths occurred in unvaccinated persons; the mortality rate among the unvaccinated was 71%, while no one vaccinated over the previous 12 years contracted the disease, and no one who had ever been vaccinated died of smallpox. Finally, vaccination of almost the whole population stopped the epidemic abruptly and completely.[7]

There were 4,548 cases and 36 deaths attributed to smallpox across Canada between 1929 and 1933; 291 cases and 14 deaths over the next five-year period; and 247 cases and 1 death between 1939 and 1943. The last indigenous smallpox cases in Canada occurred in 1945-46 with 7 infections reported in Saskatchewan.[8] However, over the next thirty years, the spectre of the speckled monster, if not the virus itself, would periodically remind Canadians of the power and potential threat of this disease, reinforcing the importance of maintaining strong national immunity levels using a potent, pure and stable supply of smallpox vaccines.

The Evolution of Smallpox Vaccines in Canada: 1796-1916

The practice of arm-to-arm smallpox variolation – first used in China and India as early as the 10th century and brought to Europe in 1700 – was introduced into Canada in 1768, when James Latham inoculated the soldiers of his regiment in Quebec City. In many of the 13 British Colonies, there was less interest in variolation. Thus in 1775, when smallpox struck American soldiers on their way to invade Quebec during the Revolutionary war, their greater vulnerability to the disease helped to save Canada for the British Empire.[9]

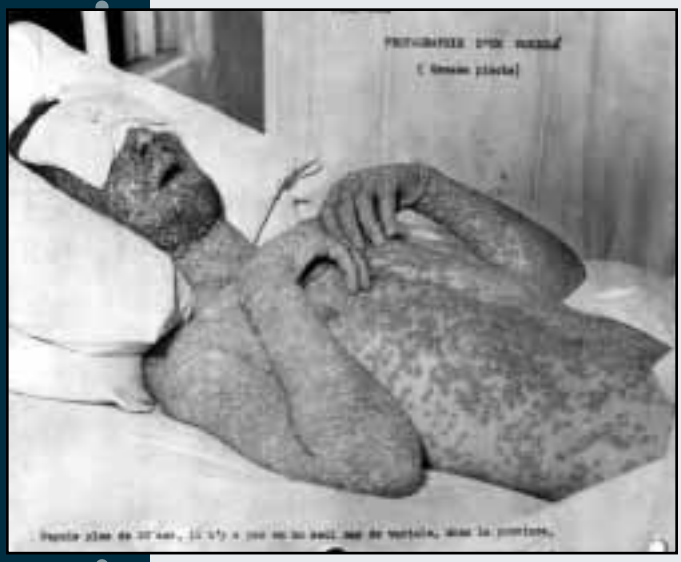


Figure 2:
Smallpox case, Quebec, 1932 (AvP-CA Acc1229)

The earliest records of smallpox, or more properly, cow-pox, or vaccinia virus vaccinations in North America, date from about 1797 in Trinity, Newfoundland. Dr. John Clinch, who had been a classmate of Edward Jenner's in England, had asked him for a supply of his new vaccine in December 1796. The dried vaccinia lymph was sent across the Atlantic in lines of impregnated threads only a few months after Jenner had vaccinated his first subject.[10]

By 1821, as Heagerty notes, with the establishment of Canada's first Bureau of Vaccine, set up in Quebec based on a £1,500 grant to promote Jenner's vaccination system, "the disease lost its terror." There were still cases periodically, particularly imported into the colony via shipping, but as became clear over the rest of the century, serious outbreaks, particularly between 1871 and 1885 in Montreal, were the result of vaccination neglect, or outright hostility against vaccination, based primarily on ignorance and fear. While an improvement over human virus arm-to-arm variolation, Jenner's cow-pox vaccination method depended upon calf-to-arm and then arm-to-arm transfer of vaccine lymph, and thus carried with it a real, though significantly lesser, risk of infection than variolation.[11]

Steps towards a larger, more potent and bacteriologically pure vaccine supply began in 1842 with the transfer of the vaccinia virus from cow-to-cow in series, rather than from human-to-cow. By 1865 a number of countries were producing the vaccine by animal, specifically "bovine" vaccination, although other animals, such as sheep, were sometimes used. The most important improvement in the production of smallpox vaccine came in 1891 when glycerin was first used as a diluent for vaccinia lymph. Not only did glycerin allow for vaccine production on a larger scale, it was also a preservative of the virus, and destroyed extraneous bacteria. The vaccine could now be tested in the laboratory and not released until it was demonstrably potent and free of pathogens. Sterile glass capillary tubes were introduced at the same time and were used in the packaging and distribution of the glycerinated vaccine. Other antiseptics, including phenol, were later used to ensure purity in vaccine production.[12] Progress was also made during the late 19th century to delineate the morphology of the vaccinia virus and the presence of "elementary bodies."[13] Soon, specific diagnostic methods for smallpox were introduced, including a definitive rabbit test developed at Connaught Laboratories in 1928.[14]

Smallpox vaccine stations overseen by interested physicians and local health boards and supplied with imported U.S. vaccine, or a local supply, facilitated the distribution of smallpox vaccine in Canada through the mid-1880s. For example, with support from the Montreal Board of Health, the "Montreal Cow-pox Institute" was established in 1878. Larger scale production

began on a commercial and government-sponsored basis after the great 1885 Montreal epidemic. L'Institut Vaccinogène de Québec was established in 1886 in Sainte-Foy, just outside Quebec City and operated with the support of the Quebec provincial government; in 1899, l'Institut Vaccinol de Montréal was established in Montreal – a privately funded company, although it received some support from the city.[15]

The first smallpox vaccine supply in Ontario commenced in 1885 when the Ontario Vaccine Farm was established in Palmerston. Influenced by the 1885 Montreal epidemic, as well as by a serious 1884 outbreak in the sparsely populated village of Hungerford, north of Belleville, which resulted in 202 cases and 45 deaths, the Provincial Board of Health sponsored the Palmerston Vaccine Farm. Managed single-handedly by Dr. Alexander Stewart, and after his death in 1911 by Dr. Herbert Coleman, the Ontario Vaccine Farm produced vaccinia points, despite increasing imports of higher quality glycerinated vaccine, until 1916. At that time, the Palmerston operation was transferred to and upgraded by the Antitoxin Laboratories of the University of Toronto. On October 25, 1917, these labs would be officially named the "Connaught Antitoxin Laboratories and University Farm."[16]

One of the major U.S. commercial vaccine exporters into Canada at the time was the Pocono Laboratory near Swiftwater, Pennsylvania, founded in 1898 by Dr. Richard Slee.[17] Some 80 years later, the Pocono Labs site would become Connaught Laboratories Incorporated, and today, is the U.S. division of Aventis Pasteur.

The Evolution of Smallpox Vaccines in Canada: 1916-1958

In 1916, when the Antitoxin Laboratories at the University of Toronto assumed responsibility for smallpox vaccine production, new laboratory buildings were near completion at its recently established "Farm" site 22 miles north of the University of Toronto campus. The new buildings were primarily designed to produce tetanus antitoxin, which was desperately needed for the war effort. A corner section of the main laboratory building was quickly redesigned for smallpox vaccine production, which was accommodated and isolated in four separate rooms with an outside entrance. Using a special operating table, the vaccinia virus was inoculated on the belly of calves and the infective vesicles were later harvested and processed into glycerinated vaccine points.[18] (See Figure 3)

Figure 3:
Vaccinia virus inoculation of calf, Connaught Laboratories, 1920s (AvP-CA Acc1125)

Through the efforts of Dr. Robert D. Defries,[19] Connaught's initial smallpox production work, particularly obtaining an original vaccinia virus strain, was greatly assisted by Dr. William H. Park, Director of the New York City Department of Health.
This New York vaccinia strain descended from a strain used by Jenner in England and was first brought to the U.S. in the 1850s. Park's lab began large-scale production with this strain in 1876. Since 1916, and then refreshed every two years after 1927, the New York strain served as the primary seed virus of all smallpox vaccine produced by Connaught.[20]

As was the case for such essential public health biologicals as diphtheria and tetanus antitoxin, Connaught's smallpox vaccine was sold at cost to provincial governments across Canada for free distribution through local health departments. In addition to facilitating routine vaccination

in children at an early age, and re-vaccinations among older groups, Connaught frequently responded to epidemic emergencies in Canada and abroad. Vancouver was struck by a smallpox outbreak in early 1932, with a total of 56 cases and 16 deaths; 6 of the deaths occurred in one family, none of whose members had ever been vaccinated. Connaught sent enough vaccine to the British Columbia Board of Health to vaccinate 80,000 people, packaging it in dry ice for the first time to preserve its potency during the cross-country train trip.[21]

In November 1938, China faced an outbreak of smallpox and made an international appeal for vaccine through the League of Nations to bolster the 12 million dose supply it needed over the winter. The Canadian government turned to Connaught to supply 1,000,000 units.[22] In early 1946, the threat of a smallpox outbreak spreading from Seattle into British Columbia closed the border and created unprecedented demand for vaccine. The province's vaccine supply was exhausted in one day, prompting an appeal to Connaught. Extra staff were employed to boost production and express ship enough vaccine for over 250,000 people.[23]

The Seattle outbreak was sparked by one infected soldier returning home from Japan, and spread into a local hospital and then into the community because of poor isolation procedures and a reluctance to diagnose smallpox cases. The outbreak, and fears of it spreading, effectively paralyzed the North American west coast. A similar experience occurred in the New York City area a year later, after a man got sick on a bus on his way home from Mexico City to New York. Through a complex chain of events starting in late February 1947, 12 smallpox cases and 2 deaths occurred in New York and over the next month more than 6,350,000 people were vaccinated. There had not been a smallpox outbreak in New York City in twenty years, but this experience highlighted the importance of vaccinating everyone in a community as soon as possible after a single case of smallpox was suspected.[24]

The outbreaks in Seattle and New York, along with a similar situation in Glasgow, Scotland in early 1950, when an Indian sailor imported the disease via London, demonstrated the continuing danger of smallpox and how immunization rates had declined in many parts of the world. Canadian public health authorities, particularly Dr. R.D. Defries, who was editor of the *Canadian Journal of Public Health* as well as Director of Connaught Medical Research Laboratories, were confident that Canadians endorsed smallpox vaccination, unlike their counterparts in the United Kingdom. However, the recent outbreaks underscored "that virulent smallpox is still a menace; in fact, air travel makes it possible for the disease to be brought from distant lands where thousands of cases still occur."[25]

New interest in improving smallpox vaccines was also reinforced during the 1950s by a resurgence of smallpox incidence in the developing world, especially since the end of World War II. There were also several post-war advances in vaccine production technologies, especially in tissue culture and freeze-drying methods, and the beginning of efforts by many countries and the World Health Organization to eradicate smallpox. The suggestion that eradicating smallpox was possible was first made in 1953 by the WHO's first Director-General, Dr. Brock Chisholm, who assumed this position after serving as Canada's Deputy Minister of Pensions and National Health for many years. After initially rejecting the idea as impractical, in 1959 the WHO launched a limited smallpox eradication campaign, which was focused on mass vaccinations in several countries, but was very much dependent upon donated funds and vaccine to keep it going.[26]

Connaught, which had played a key role in developing and producing the Salk polio vaccine, and starting in 1957, exporting it internationally,[27] saw a new international market for its smallpox vaccine. There was also a stable but steadily growing domestic market based on an

increasing population, a renewed program of re-vaccinations and expanded use among military personnel. Between 1952 and 1958, Connaught's smallpox vaccine distribution in Canada had grown from about 790,000 to 1,400,000 doses, and by late November 1958, had risen by 15% to 100,000 doses per month.[28] Connaught had no real competition for any of its vaccines within Canada, but it would face several commercial competitors in the global smallpox vaccine market, particularly as several companies, including the Lister Institute in England and Wyeth Laboratories in Philadelphia, had recently begun developing a new freeze-dried type of smallpox vaccine. It was not heat sensitive and could be stored far longer than the traditional glycerinated vaccine.

The Evolution of Smallpox Vaccines in Canada: 1959-1966

During the late 1950s and into the early 1960s, there were several ideas for improving smallpox vaccine, which had not changed significantly for almost a century. The effectiveness of the traditional glycerinated vaccine was not in dispute, but it was clear that it could be improved; specifically, so that it could be more effectively utilized in the developing world where smallpox remained an endemic threat. Inspired by the success of the Salk polio vaccine, researchers began experimenting with an inactivated smallpox vaccine. Later, the Sabin polio vaccine also inspired efforts to develop an attenuated smallpox vaccine. However, neither approach proved particularly successful in stimulating human immunity against smallpox to a level approaching that of the traditional vaccine. They were also more costly to produce and introduced a new range of quality control and regulatory challenges, the importance of which had increased in the wake of the Salk polio vaccine "Cutter" tragedy of 1955.[29]

Beginning in 1959, Connaught's primary focus was on developing a new generation of smallpox vaccines based on lyophilized, or freeze-dried, "elementary body suspensions" (EBS) of the vaccinia virus prepared from the same vaccinia calf skin lymph pulp used for the glycerinated vaccine. The use of EBS enabled a significantly purer vaccine that would be free of extraneous bacteria and viruses. Elementary bodies of vaccinia virus had been identified as early as 1906, but it was now possible to isolate them from the extraneous matter of the dermal pulp at the start of production, rather than more expensively at the end of the process.[30]

Dr. Cleve Russell Amies led Connaught's smallpox vaccine research during the late 1950s and into the early 1960s, producing freeze-dried EBS smallpox vaccine on a pilot scale beginning in the spring of 1959, and also experimenting with an inactivated type at the same time. Within a year it was clear that Connaught's new freeze-dried vaccine, based on L.H. Collier's initial method developed at the Lister Institute in 1948-53, was much more stable and 40 times as potent as traditional glycerinated vaccine. The next step was clinical trials in support of Canadian and U.S. licenses; the Canadian Armed Forces provided an important arena for this step. The U.S. Army was already using a freeze-dried vaccine supplied by Wyeth Laboratories, and the Canadian military had a clear need for smallpox vaccine in light of their involvement in countries where smallpox was endemic. Other possible applications for the new vaccine included emergency stockpiles in Canada, export, and support for the World Health Organization's fledgling smallpox eradication program.[31]

Figure 4:
Vaccinia virus as seen by the electron microscope, 1950s (AvP-CA Acc1231)

By early 1961, Connaught was producing EBS-based freeze-dried and liquid types of smallpox vaccines for trial purposes and possible export. Plans were also proceeding with clinical and other trials, including testing the acceptability, stability and effectiveness of the dried vaccine kit in Africa.[32] The results were encouraging, including discovering, quite by accident, that a vial of dried vaccine left for a month in the heat of the Angola Customs Office still seemed "very potent."[33] By early 1962, trials of freeze-dried vaccine were underway involving infants and school children in the Metropolitan Toronto borough of East York, and among new military recruits in Nova Scotia and Quebec.[34]

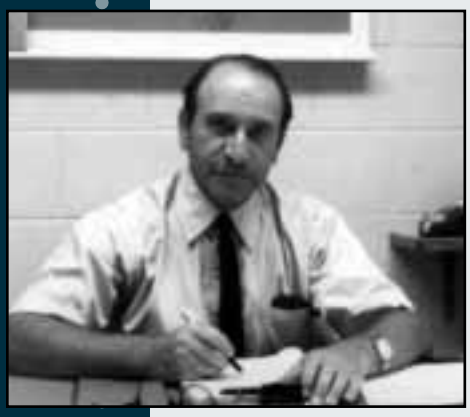


Figure 5:
Dr. Paul Fenje
(photo courtesy of Dr. Fenje)

In early 1962, Dr. Paul Fenje (Figure 5) inherited the leadership of Connaught's smallpox vaccine development work, focussing on accelerating freeze-dried smallpox vaccine development and production, directed primarily towards an improving export market. Vaccine shortages, pressure from the WHO to establish vaccine standards, and new outbreaks in the developing world brought renewed urgency to Connaught's efforts. More immediate attention to the smallpox threat emerged when 62 cases and 24 deaths occurred in England and Wales in 1961-62, originating from a traveler from Karachi. Within the next year, there were also two outbreaks in Germany involving 37 cases and 1 death, an imported case into Sweden leading to 24 cases and 4 deaths, and another into Poland resulting in 110 cases and 7 deaths.[35]

Closer to home, in August 1962, a 14-year-old boy, on returning home to Toronto from Brazil, sparked a major smallpox scare when it became clear shortly after he arrived that he was suffering from smallpox. The boy first arrived with his family by plane in New York City and then, after a six-hour wait in Grand Central Station, proceeded to Toronto by train. Before boarding the flight on August 8, he had general symptoms of fever, nausea and myalgia which persisted by the time he arrived in Toronto on August 12. Five days later he had clear symptoms of smallpox, touching off an international alarm between Toronto and New York City. The boy recovered, an earlier vaccination protecting him from the worst effects of the disease. There were no other cases reported among the possible 2,000 contacts he had during his trip, however vaccination stations were set up in New York for any contacts. Similar emergency clinics were prepared in Ontario, although the Minister of Health stressed that there was no epidemic and no cause for alarm.[36] Nevertheless, as Dr. Donald Henderson, then of the U.S. Centers for Disease Control, later recalled: "it was all but decided to: 1) vaccinate everyone from New York City, the boy's point of entry, to Buffalo; and 2) to close the Canadian border. Fortunately, reason prevailed – although just barely – but these events speak for themselves of the fear which smallpox engendered."[37] This smallpox scare prompted the establishment of a new smallpox surveillance unit at the CDC and fresh enthusiasm among Henderson and his colleagues directed towards doing something about smallpox.[38]

While the Toronto smallpox scare of 1962 reminded Canadians and Americans once again about the potential danger of the "speckled monster," it also provided an opportunity to assess the vaccination status of the public. For example, 1,119 persons were vaccinated at the RCAF unit in Trenton, Ontario in mid-August when it was discovered that there had been a contact with the Toronto boy with smallpox among the group of Air Cadets near the base. The Commanding Officer of the Trenton unit was surprised to discover that approximately 20% of the civilian population had never had the smallpox vaccine before. Moreover, in the Town of

Trenton, where close to 7,000 persons were vaccinated by RCAF medical personnel, at least 25% had never been vaccinated against smallpox.[39]

Despite the urgency of the 1962 Toronto smallpox scare, and the apparent need to reinforce Canadian vaccination levels, larger scale production of freeze-dried smallpox vaccine was still hampered by the lack of a sufficient market to enable Connaught to finance an expanded production facility. Nevertheless, Connaught was clearly committed to being in the forefront of the development work leading to the best available smallpox vaccine. It was evident that the WHO was planning an expanded world-wide smallpox eradication effort, for which it would need vaccine; and the success of the recent clinical trials of the new freeze-dried vaccine pointed to a potential expanded domestic market. Thus, in March 1963, Connaught Director, Dr. J.K.W. Ferguson, authorized the development of freeze-dried smallpox vaccine as a new product, albeit for small-scale production.[40]

Over the next two years, the pace of smallpox vaccine development and production increased at Connaught, prompted by encouraging results from trials of freeze-dried vaccines, both for regular administration and for injection using the new Jet Injector, originally designed in the 1950s by the U.S. military to facilitate mass vaccinations. The Canadian military was interested in the Jet Injector and in early 1965 conducted a series of trials among army inductees using Connaught's freeze-dried vaccine.[41] More significant, however, were events in the U.S. that rejuvenated the WHO's smallpox eradication effort, which had essentially limped along since 1959 without a budget, entirely dependent upon donated vaccine, most of it Russian made.

In June 1965, Connaught's Assistant Director, Dr. Robert J. Wilson (Figure 6), received a phone call from Dr. Donald Henderson of the CDC in Atlanta, informing him of the U.S. government's pledge of considerable aid to the smallpox eradication program.[42] The new interest in smallpox eradication had developed out of preliminary work by Henderson and others at the CDC's smallpox unit, focused on tracking smallpox vaccine complications, working with the jet injector, and preparing staff to handle possible smallpox cases should they be imported into the U.S. At the same time, the U.S. was sponsoring intensive measles vaccination programs in Africa. Measles was a more serious problem in Africa than smallpox and a newly developed attenuated measles vaccine proved very effective. In 1964, as part of International Cooperation Year, U.S. President Johnson pledged to expand such efforts to provide protection against disease on every continent.[43]

Figure 6:
Dr. Robert James Wilson (1915-1989)
(AvP-CA Acc0993)

"Smallpox Alert" was the theme for the WHO's "World Health Day" on April 7, 1965, selected because of the recent imported smallpox cases, especially into Europe in 1962-63. In May 1965, inspired by this anniversary and its theme – and reinforced by a suspected smallpox case in Washington, D.C. – President Johnson made a commitment to eradicating smallpox completely from the earth within the next decade.[44] Echoing an earlier pledge of President Kennedy's, the U.S. delegation to the WHO "reasoned that if one could land a man on the moon in 10 years, surely one could eradicate smallpox from the earth in 10 years." The suspected smallpox case involved a woman from Ghana. The uncertainty surrounding her condition and possible contacts, in addition to the publicity generated, effectively closed down Washington until it was clear, after a more precise diagnostic test than generally used, that she actually had chickenpox. Dr. Henderson, who had only seen 13 cases of smallpox before, including 1 in Toronto in 1962, was "abruptly" dispatched to Geneva to assume the position of global director for smallpox eradication. The

key to Henderson's selling the smallpox eradication idea to the U.S. government was to link it to the African measles control efforts, emphasizing that it would cost very little given that smallpox vaccine was 1/1,000th the cost of measles vaccine.[45] In addition to continuing intensive efforts in Africa, the focus of the U.S. support was to contribute technical personnel and other resources to the Pan American Health Organization and assist in the establishment of laboratory facilities in developing countries in order to help meet vaccine supply requirements. As was immediately clear to Henderson, two monitor laboratories would be appointed for the eastern and western hemispheres, one of which would be Connaught.[46]

The Road to Eradication and Beyond: 1966-2002

By 1965, the Connaught Medical Research Laboratories of the University of Toronto had established itself as a global leader in the development and production of a new generation of freeze-dried and purified smallpox vaccines ideal for the World Health Organization's expanded smallpox eradication program. Connaught's reputation, heightened, in particular, over the previous decade by its key contributions to the development, production and international distribution of the Salk and then Sabin polio vaccines,[47] was well known to Dr. Donald A. Henderson, newly appointed Chief of the WHO's smallpox eradication initiative. Also well known to him, professionally as well as personally, were Connaught's smallpox vaccine specialists, Dr. Paul Fenje and Assistant Director, Dr. Robert J. Wilson. For these three men, the daunting challenge of eradicating the speckled monster from the planet within a decade was as much a personal crusade as a scientific one.

Canada & Smallpox Eradication, 1966-1979

Donald Henderson (Figure 7) was born in Ohio in 1928 to Canadian parents. His family arrived in British North America in 1798, the same year that Jenner discovered smallpox vaccine, and his mother worked as a nurse in Windsor during the intense 1924 smallpox outbreak.[48] Henderson was also quite familiar with Connaught, particularly through close connections that developed between the CDC and Connaught during the introduction of the Salk and then Sabin polio vaccines between 1955 and 1965. Indeed, as he recalled in 1979 on the occasion of Paul Fenje's retirement: "I appreciate only too well how many of the concepts in the execution of the smallpox program saw the first light of day over a glass of beer with Bob [Wilson] and Paul [Fenje]. What I don't recall is whether the ideas stemmed from Wilson or Fenje, so perhaps they are better attributed to Wilje (or should it be Fenson?)."[49]

Figure 7:
Dr. Donald A. Henderson (AvP-CA 88-001-53)

Wilson originally suggested that Connaught assume a regional responsibility for the smallpox eradication effort, focused on Latin America, especially Brazil, where smallpox remained problematic, providing special training of local vaccine production staff. Such training would be done in Toronto, with follow-up visits to local production labs. Connaught would also provide consultation services to overcome production problems and test batches of vaccine as each lab geared up. As Henderson later noted, "In other words, a full service vaccine production back-up for the Americas."[50] Connaught's role

in the eradication effort began along these lines in July 1966 with a request from the Instituto Oswaldo Cruz, of Rio de Janeiro, Brazil.[51] Wilson was asked to visit Rio de Janeiro for 3-4 weeks as a WHO consultant to advise Oswaldo Cruz scientists on the production of smallpox vaccine of high quality and purity.[52] It was clear that the quality and purity of Latin American vaccine was much poorer than expected. In early September 1966, the Pan American Health Organization requested of Dr. Wilson that such a consultancy arrangement with Connaught apply more broadly across the Latin American Region.[53] Through the CDC, Connaught's experience was also applied to improving vaccine quality in Africa.[54]

The formal agreement between the PAHO and Connaught/University of Toronto in support of the smallpox eradication program in Latin America developed during November and December 1966.[55] As Wilson confessed to Henderson, "Dr. Ferguson [Connaught Director] signed the agreement on the 31 January and I suppose we are now launched. I have some misgivings as to how effective our assistance will be in that part of the world but it won't be for want of trying on our part." Henderson seemed more confident. "There is no doubt that you have a bit of a job ahead. I can't tell you how pleased I am however, to know that it is in your hands. The greatest failures to date that we have had with respect to eradication programmes have rested principally upon use of impotent vaccines. This is a real tragedy." Henderson also hoped that the Lister Institute in England would "join us in a parallel enterprise to your own."[56] However, with fewer potential commercial interests involved than had Lister, the National Institute of Public Health in Bilthoven, Netherlands was soon given a parallel role for the Eastern hemisphere.[57] As a non-profit, self-sufficient component of the University of Toronto, Connaught did not have private shareholders to consider and could thus apply its experience with smallpox vaccine production in a more academically open manner. Indeed, as Ferguson noted in Connaught's Annual Report for 1966-67, "This occasion is not the first time that Connaught has assisted laboratories in other countries to develop or to improve their manufacture of biological products of importance to public health. It was done with insulin, with penicillin, and with several vaccines. It might be called a part of the Connaught tradition."[58]

The most intensive year of Connaught's involvement with the smallpox eradication effort was the first, 1967, during which Wilson and Fenje visited some 15 labs in 12 countries of South and Central America, Mexico and Cuba. Their primary focus was Brazil, where almost all of the smallpox cases in the Region occurred. The Instituto Oswaldo Cruz had the third largest production of smallpox vaccine in the world, but its quality was problematic, as were the politics surrounding the way it was used. In April 1968, after a major outbreak revealed these problems, the new Director and the Chief of the Smallpox Unit of the institute visited Connaught for three weeks to study production and testing methods with Fenje in order to meet the WHO's standards. Such methods and standards, based largely on Connaught's experience, and the particular initiative of Wilson and Fenje, were codified in 1968 in the WHO's *Methodology of Freeze-dried Smallpox Vaccine Production*.[59] In September 1968, after another trip to South America, Wilson reported to Henderson that "The WHO 'Methodology' was received with great enthusiasm and everyone agreed that it was a most useful document even though they do not all follow the precise procedures." By this time, five labs in South America were meeting, or almost meeting, the standards of adequate potency, stability and bacteriological sterility. "I am most gratified," Wilson noted to Henderson, "to see such progress in about one year, (since my last visit) and the enthusiasm [with which] these people have attacked the problem in spite of economic, political and administrative chaos."[60]

At about the same time, a certain level of political and administrative chaos in Canada was complicating progress of the larger eradication effort. Early in 1967, Wilson looked to the

Figure 8:
Administering smallpox vaccine with the Jet Injector, c. 1967 (AvP-CA Acc1241)

Canadian government for a donation toward the WHO's global vaccine supply. Henderson had made it clear to Wilson that "A donation to the Organization of perhaps 5 to 10 million doses of vaccine for jet injection (100 dose vials) would really be a Godsend. The [limited] availability of vaccine for jet injection is going to put us in a real bind before long. Any hope?"[61] The prospects did not look good for a simple donation, as far as Wilson could tell through his discussions with Department of National Health and Welfare officials, although individual countries could make a specific request directly to Ottawa through the Canadian International Development Agency (CIDA).[62] Despite continued pressure, it was clear by September 1967 that the Canadian government was not able to make a direct donation to the WHO because of present policy, which seemed impractical, slow and cumbersome in the context of the smallpox program. Henderson noted to Wilson that "We shall certainly do our best to encourage some sort of bilateral contribution. With your tremendous capacity and good vaccine, I am sorry not to see it more extensively used."[63] However, a poor economy and uncertain politics in Ottawa in early 1968, precipitated by a Liberal leadership race, made it difficult for the government to make a donation, despite direct appeals by Ferguson to the Secretary of State for External Affairs, and Liberal leadership candidate, Paul Martin.[64] Despite Martin's close experience with and respect for Connaught during the Salk vaccine introduction in 1955, his hands were tied by policy and party politics. Martin explained to Ferguson that Canada supported the WHO based on an assessed share of its global budget, which was 2.7%, or about $80,000 per year of the smallpox budget. Martin's loss of the Liberal leadership to Pierre Trudeau, his move to the Senate and the subsequent changes in the government during the spring of 1968, and then a federal election in June 1968, won by the Liberals, complicated the process.

However, some unexpected press attention in late May 1970, featuring "an eloquent presentation" by Henderson on television about the need for smallpox eradication and for vaccine,[65] finally prompted the Canadian government to donate 7 million doses of Connaught's vaccine to the WHO.[66] According to Henderson and Wilson, this TV story had "long and colourful" background. Henderson had been approached by the Canadian Mission to the UN, which supported the idea of bilateral donations based on specific requests for aid. He stressed the idea's impracticality and the far greater flexibility of a multilateral donation, directing vaccine to where it was needed most.[67] As Henderson recalled, "The man at the Mission seemed a bit troubled by this (for reasons I do not know) but when informed that the approximate cost of the vaccine would be in the range of one cent per dose and that we were talking of only 85,000 dollars, he rather snorted at the various proposed restrictions, etc. suggested by CIDA."[68]

At about the same time, Wilson entertained his niece and a dinner guest of hers, who he later discovered was a TV producer. "At her prompting, I told him about some of the problems related to the smallpox process, amongst these was the stupidity of the Canadian government over a donation of smallpox vaccine."[69] In June 1970, shortly after this media attention to the issue, CIDA asked Connaught to quote on 8.5 million doses of smallpox vaccine for the jet injector. Wilson was "hopeful that the machinery is now grinding."[70] By August there were still a

few more details to iron out, but it was clear that the Canadian government was committed to donating $140,000 dedicated to purchasing about 7,000,000 doses of smallpox vaccine from Connaught.[71]

By this time, Connaught's work in South America had wound down successfully, the last Brazilian case occurring in 1971. The main focus of the eradication effort then shifted to Africa (particularly east Africa) and Asia. The Canadian government's donation was given over five years, totaling 35,000,000 doses between 1970 and 1974, much of it directed to African countries, although during 1972-74 it was used in 24 countries, including Bangladesh, India, Iran and Pakistan.[72] With this broader application of Connaught's vaccine, in August 1971, Wilson noted to Henderson that "Paul Fenje has recently been asking me whether there have been any reports from the field on his 'best smallpox vaccine in this galaxy.' I think he is rather anxious to know how it is performing although I have few doubts that if properly applied it will do what is expected of it."[73]

Whether Fenje's smallpox vaccine really was the best in the galaxy is hard to know. Connaught was not resting on its laurels, however, but continued research efforts to improve its smallpox vaccines, gaining Canadian and U.S. licenses for freeze-dried vaccine made for both multiple pressure and jet injector application. Moreover, as Wilson told Henderson in September 1969, just as Connaught received the new U.S. license, "Since all of our dried vaccine, including that for multiple pressure is sterile, it is going to put a little pressure on American manufacturers, which may be a good thing."[74] By January 1970, Connaught was working on a new glycerinated EBS vaccine, which seemed more stable than the traditional glycerinated lymph vaccine. "Physicians will continue to require the single dose glycerinated preparation," Wilson noted to Henderson, "so we decided to clean it up and improve it." The National Institutes of Health in the U.S. were "fascinated that we can produce a sterile glycerinated product on a regular basis."[75] Henderson, too, was surprised to hear about the new sterile vaccine.[76] By the end of 1970, new research was planned at Connaught aimed at either an inactivated or attenuated smallpox vaccine, or something different based on another substrate. However, as had been the case since the late 1950s, regulatory authorities remained concerned about extraneous agents contaminating these types of vaccines, but welcomed any ideas that would eliminate them.[77]

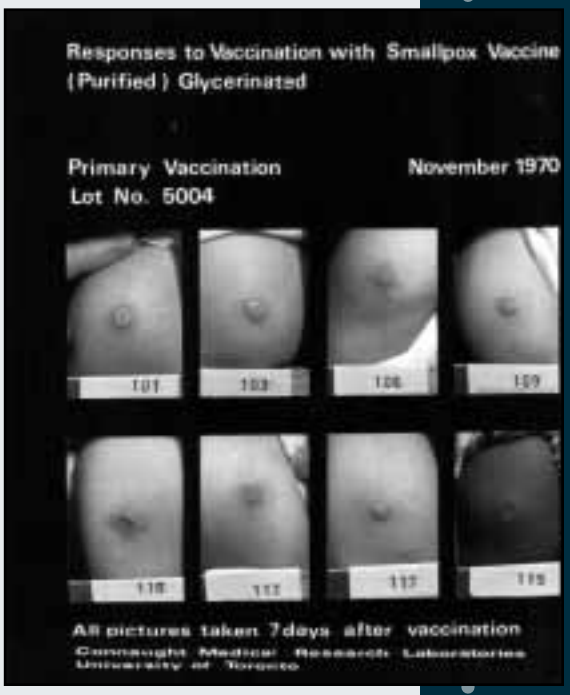


Figure 9:
Clinical testing of Connaught's purified glycerinated smallpox vaccine, 1970
(AvP-CA Acc1240)

The success of the eradication effort during the early 1970s and the ending of routine smallpox immunizations in Canada and the U.S. in 1972, however, undermined efforts to develop new types of smallpox vaccine. Indeed, Connaught's Director, in his 1970-71 Annual Report, recognized that he would soon have to find other work for the staff involved with smallpox. There was considerable debate over the issue of stopping smallpox vaccination programs in North America, complicated by another alarming smallpox outbreak caused by a traveler. The outbreak occurred in Yugoslavia in March-April 1972 when a pilgrim returned from Mecca and brought the smallpox virus with him to his village, resulting in 170 cases and 40 deaths. There were many hemorragic cases, reminding Wilson and Henderson of the 1924 Windsor outbreak.[78] The Yugoslavia outbreak underscored the continuing danger of smallpox, raising

concerns about how well prepared Canada was against the potential threat of immigrants from countries where smallpox has been reported.[79] Such concerns were exaggerated as Canada had, in early 1972, reverted to a policy of vaccinating all persons arriving from abroad, while federal and provincial authorities had set up a new smallpox surveillance and containment mechanism and vaccine depots across the country.[80]

Ensuring that there was sufficient vaccine for the depots and a stockpile secured were issues that grew in importance in Canada during the mid 1970s, as well as in many other countries as the final goal of global smallpox eradication approached. Shortly after the Yugoslavian scare, Henderson wondered whether the Canadian government would underwrite the costs of a smallpox vaccine stockpile. As he suggested to Wilson, "It would seem to me a prudent thing for the Government to do. The U.S. is looking at this matter and perhaps some kind of international cooperation might even emerge. Just an idea."[81] By 1977, little had developed along these lines, although Connaught had a contract with the Canadian government for a stockpile of one million doses. However, Wilson thought that the contract should be re-negotiated and the stockpile replaced in the near future. He was not sure if it was available to the WHO or other nations in the event of a smallpox emergency.[82] It seemed to Henderson that each country managed their stockpile individually, with no real plans for international co-ordination. He knew that the Soviet Union had sufficient vaccine to vaccinate its entire population and the U.S. had about 20 million doses on hand.[83]

Such was the state of the smallpox security in North America in late 1977, just as the smallpox virus' last stand took place in east Africa. The last natural smallpox case was contracted on October 26, 1977 in a 23-year-old Somalian man. For Wilson and Henderson, while this event was of great significance, it marked the end of a period of transition and of frustration. Since the Yugoslavia smallpox scare, Connaught had been transformed into a profit-oriented biotech company after the University of Toronto sold Connaught in June 1972 to the federally-owned Canadian Development Corporation, Wilson serving as transitional Director, then as Scientific Chairman under the new commercial structure. As Wilson told Henderson, "It may well be a whole new ball game but we will face the future with fortitude." More personally, the situation was a "mixed blessing." "It will change my life-style to some degree but not to the extent that I will relinquish my interest and activity in 'our operation.'"[84]

By the early 1970s, with Connaught's successful role in eradicating smallpox in Latin America, Wilson and Henderson were hopeful that the momentum gained during the smallpox campaign could be directed towards the control of other diseases in the developing world for which good vaccines existed but were less accessible. Such vaccines included diphtheria, pertussis, tetanus and polio vaccines, as well as typhoid and BCG vaccines. Not unlike the situation with smallpox vaccines, a local supply of high quality vaccine was critical, but producing these types of antigens was more complex and costly than smallpox vaccine. Wilson's idea was for Connaught to produce each vaccine in bulk and then ship them to various countries, where they could be processed and filled locally and then distributed at minimal cost.[85] While Henderson was excited by the idea,[86] there was insufficient financial or political support in Canada and the WHO to proceed.[87] Henderson felt that it was "all very tragic as there could be no more opportune moment to launch the immunization scheme."[88] Within the next two years, however, progress was made in this area, including by UNICEF and Connaught, that evolved into the WHO's Expanded Program on Immunization (EPI), the success of which has been significant.[89] In the meantime, Wilson felt frustrated by the loss of momentum, and by such distractions as the 1976 Swine Flu episode, when the U.S. and Canadian governments poured enormous resources into preparing for a major influenza epidemic that did not happen. Connaught was supplying

10-12 million doses of influenza vaccine to the Canadian government, but as Wilson confessed to Henderson, "It's a noble effort but I wish we could be directing these energies towards the extended immunization programme!"[90]

By this time, it was clear the smallpox eradication campaign was coming to a successful conclusion, clear evidence of which was presented to Wilson and Fenje in the form of their being included in the "Order of the Bifurcated Needle." The bifurcated needle was developed by Wyeth Laboratories in the mid-1960s for administering smallpox vaccine in a very economical way. Beginning in 1970, this small, sharpened fork-like instrument, which held a dose of vaccine between its forks, was used in smallpox eradication programs throughout the world.[91] The "Order of the Bifurcated Needle," a certificate and pin, fashioned from a bifurcated needle bent into an "O" to symbolize "Target Zero", was given by the WHO to staff involved in the smallpox eradication effort.[92] Upon receiving the "Order" in October 1976, Wilson wrote to Henderson that, "The Certificate, when appropriately framed, and the symbol will ever be a reminder of the confidence, courage and even audacity with which many of us embarked upon our respective commitments towards the common goal of 'Smallpox Zero.' In terms of World War II, 'The impossible we do immediately: The miraculous takes a little longer.'"[93]

While the last smallpox case in Somalia marked the end of the natural disease, the smallpox threat was not yet fully vanquished, as was dramatically demonstrated in England in late August 1978. A medical photographer, working in the Birmingham University Medical School, was infected by the smallpox virus, which had escaped from a nearby laboratory and circulated through an air vent. The photographer was immediately placed in hospital and 200 of her contacts were put into isolation. The professor in charge of the lab with the variola virus, upon hearing the news, cut his own throat. The photographer also died, smallpox's last victim, but the incident and its timing, so soon after smallpox seemed to be eradicated, raised several alarms, particularly about the storage of variola virus in laboratories around the world. What security measures were in place to prevent the accidental, and perhaps deliberate, release of the smallpox virus into a lab and/or community? At the time, the Birmingham lab was 1 of 13 around the world storing the virus. The WHO wanted only 4 labs to keep smallpox virus for archival and research purposes: 1 each in London, Moscow, Japan and the CDC in Atlanta.[94] After this incident, and much deliberation, ultimately only 2 labs retained the smallpox virus, 1 in Siberia and 1 at the CDC.

Just before the Birmingham incident, the possibility of biological warfare using smallpox virus became prominent when one lab resisted destroying their smallpox virus stock. The U.S. Army Medical Research Institute of Infectious Diseases wanted to keep its stock of variola virus for fear of biological warfare, or bio-terrorists. Their rationale was that the virus might be needed for diagnostic purposes should rapid identification of smallpox cases be necessary.[95]

For Wilson and Henderson, the discussion about possible biological warfare using smallpox was disturbing, particularly because of the timing. In August 1978, the WHO had published its program for winding up the eradication campaign by December 1979, which, according to Wilson, brought "the realization of ultimate accomplishment very close indeed." As he noted to Henderson, "May 'whomever' has been watching over us up until now not lose interest yet!"[96] Henderson was hopeful that the Birmingham incident and the biological terrorism question would lead to all remaining stocks of variola virus being destroyed.[97] Connaught was not retaining any variola virus but, as Wilson outlined to Henderson in March 1979, "We have never had (touch wood) a similar type of situation with any 'Dangerous Pathogen' with the exception of B virus in monkeys where we had two deaths and two recovered, but almost vegetables. But at that time [1957-58] we did not know what security precautions to take."[98]

After two years of careful surveillance for additional cases of smallpox in Somalia or elsewhere, none were found. Smallpox, "the speckled monster," was dead. On October 26, 1979, Africa was officially declared free of smallpox, with global eradication formally declared by the WHO on December 9, 1979.

Figure 10:
WHO button commemorating eradication of smallpox, 1980 (courtesy of Dr. Paul Fenje)

October 1979 also marked Connaught's 65th anniversary, and the retirement of Paul Fenje. Wilson asked Henderson, and his successor at the WHO, Dr. Isao Arita, to sum up Fenje's contributions to the eradication effort.[99] Said Arita: "As you will remember, at the beginning of the programme in 1967, the quality of many vaccines was not good. In three years, the quality had been rapidly improved and since then the eradication programme has employed potent and stable vaccine. You have been the principal scientist in the WHO Collaborating Centre for this excellent development. Your contribution was considerable. The supply of quality vaccine has, in fact, been one of the major elements which led to the successful eradication of the disease."[100] As Henderson stressed, "Directly and indirectly, the ammunition for the campaign bore the indelible stamp – 'made in Canada'. To a once-Canadian, it was always a personal source of pride."[101]

Bob Wilson marked "Smallpox Target Zero" day by recalling to his long-time friend and colleague, Paul Fenje, that "This day brings to a successful conclusion one of the greatest feats in medical history – the complete eradication of a disease from the world. No single chronicle has ever, or will be able to, document the wanton destruction of life, the misery and disfigurement visited upon countless millions over the centuries or the changes in the course of history caused by the loathsome disease, Smallpox. It is no more." He also pointed out that "'Future nations will know by history that the loathsome Smallpox has existed.' So wrote Thomas Jefferson to Edward Jenner in 1806. This prophecy has been realized after some 173 years."[102]

Smallpox Still Scares

From the perspective of 2002, and particularly from the so-called post "9/11" world in North America, the Canadian smallpox story clearly underscores an extensive history of experience with, and a progressive approach to, the development, production and application of smallpox vaccines by Connaught Laboratories, now Aventis Pasteur. Driven by the rather heady and hitherto unprecedented goal of eradicating a disease from the planet, especially such an historically devastating disease as smallpox, Wilson and Fenje dedicated themselves to improving smallpox vaccines to a point where they would no longer be needed. Despite the concerns expressed in 1978 about the security of the remaining smallpox virus stocks, the eradication of smallpox as a natural disease quickly allowed vaccinations to stop around the world, perhaps prematurely. The primary goal of the eradication effort was to prevent the disease, disability and death caused by smallpox and the high human and financial costs involved, especially in the developing world. Less important was saving the actual costs of producing and delivering smallpox vaccine. By the time smallpox was eradicated, smallpox vaccines were very inexpensive to produce. In contrast, the current polio eradication effort is driven more significantly by the goal of saving the costs involved in supplying polio vaccines, which are far higher than smallpox vaccine. The problem is that an almost complete global immunological vacuum has been created over the 30 years since smallpox was eradicated and vaccinations stopped.

The North American and European experience, particularly from the mid-1940s to early 1960s, highlights the potential for disaster when even a single, and perhaps inapparent, smallpox case innocently enters an area where familiarity with the disease has declined and the immunity status of the public is uncertain. Fortunately, enough smallpox vaccine was readily available at the time and mass vaccination efforts were conducted, the objective being as much to quell public fears of smallpox as to stop its potential spread. The same cannot be said today about a ready vaccine supply, or about the public's immunity levels, although fears of the disease may be less today due to a lack of public memory of its power. While one might debate whether or not the remaining variola virus stocks should have been destroyed, one could never be absolutely certain that everyone who held the virus complied. Such uncertainties about how much variola virus remained and who had it in their labs, officially and unofficially, increased during the 1990s. By then it was clear that the Soviet Union had been using the smallpox virus as part of its biological weapons program during the 1980s. The dismantling of the Soviet Union in 1989 and questions about the fate of their smallpox virus stock complicated the situation. Has some variola virus gotten into the hands of international terrorists? One can never really be certain one way or the other.

Canada's smallpox experience clearly demonstrates the value of smallpox vaccination, including of the traditional glycerinated vaccine produced by Connaught beginning in 1916. The traditional vaccine was responsible for eradicating the natural disease from Canada by 1946, with high immunity levels maintained by routine vaccination vigilance. Over the 30 years since routine vaccinations stopped, smallpox immunity has all but disappeared among the majority of the Canadian population. While focused efforts are required to vaccinate health care workers and emergency personnel as quickly as possible using existing vaccine stocks, the broader smallpox immunity vacuum must be addressed as soon as possible. Mass smallpox vaccinations are one option, albeit a risky one due to the known complication risks of the existing vaccine administered in a context of little to no natural immunity. However, based on the extensive experience with smallpox vaccine development at Connaught – now Aventis Pasteur's Connaught Campus in Toronto – and subsequent advances in vaccinology since smallpox eradication, a different approach could also be taken to develop safer vaccines. While smallpox vaccine given on its own should be modernized, a less problematic inactivated or attenuated smallpox vaccine needs to be developed that will be available as a response strategy to control cases that may result from a bio-terrorist attack, and only if necessary, for mass vaccinations. Should the need arise, immunization against smallpox may in fact have to become routine once again. This would begin the process of rebuilding a base level of smallpox immunity defense among children and gradually reduce the immunity vacuum that now leaves Canadians, along with the rest of the world's population, so vulnerable to the mercy of terrorists armed with the speckled monster.

"Never would I have thought 30 years ago that we would need to digitize the [smallpox eradication] training materials and set up a Web site for a disease we worked so hard to eradicate…."

David Heymann,
Head, Communicable Disease Section, WHO
November 5, 2001

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