

## CHAPTER THIRTEEN

# Canadian Vaccine Research, Production and International Regulation: Connaught Laboratories and Smallpox Vaccines, 1962–1980

Christopher J. Rutty

In the more than two centuries since Edward Jenner identified the effectiveness of vaccine lymph to protect against smallpox, the success of a wide variety of vaccines has demonstrated the power of the human immune system, when precisely stimulated, to protect against the most deadly or debilitating infectious diseases. The development of the immunological science behind the effectiveness of various vaccines has been the focus of some historical attention, as has, to varying degrees, their evaluation, standardization, regulation, delivery and application.<sup>1</sup> However, considerably less historical attention has been focused on the scientific and practical development and large-scale production and quality control of vaccines. This is primarily because of limits placed upon direct access to primary records generated by vaccine manufacturers, most of which, especially in North America, are large private companies that generally do not welcome academic historians into their archival collections – assuming any records have been retained in the first place.

In Canada, there has been one primary producer of vaccines and other public health biological products for most of the twentieth century. Known variously as Connaught Antitoxin Laboratories, Connaught Laboratories and Connaught Medical Research Laboratories while a self-supporting, non-profit part of the University of Toronto from 1914 through 1972,<sup>2</sup> a large and valuable collection of primary records from this period and later have been preserved at what is now the Connaught Campus of Sanofi Pasteur Limited in Toronto.<sup>3</sup>

From 1916 through 1980, and especially after 1962, Connaught Laboratories produced glycerinated and then freeze-dried smallpox vaccines that simultaneously met the increasingly rigorous regulatory standards of Canada, the United States, and the World Health Organization. Indeed, Connaught was a key player in establishing such international standards and it was one of, if not the only, smallpox vaccine producer in the world that had to regularly meet and exceed such domestic and international standards.<sup>4</sup> Satisfying domestic vaccine demands and maximizing profits were the main focus of commercial vaccine producers, particularly in the US. Without the need to satisfy private shareholders, and with a broader, more academic approach to global public health, Connaught developed a tradition of stronger and more open international

connections with governments, regulators, public health organizations like the WHO, as well as other vaccine producers. Moreover, Canadian export regulations allowed Connaught to more easily export vaccines than US manufacturers; Connaught only had to satisfy the regulatory requirements of the importing country, while US commercial producers first had to meet American standards. During the early 1960s, this situation gave Connaught an important advantage, particularly during the early development of Sabin oral polio vaccine (1960–62) as the Labs could export the still experimental vaccine to countries facing major polio epidemics before it was licensed in Canada or the US. Cold war politics and Canadian neutrality also tended to favour Connaught over US and Soviet vaccine producers during this period.<sup>5</sup> Nevertheless, Connaught had always worked closely with American regulators at the National Institutes of Health to ensure their vaccines and other biologicals met US standards to allow for export south of the border, while also working to meet increasingly rigorous Canadian regulatory standards, which were generally based on American standards, but sometimes diverged from them, as was the case with smallpox vaccine. In 1967, Connaught's international reputation and experience with smallpox vaccines were recognized when the WHO designated it one of two Regional Smallpox Vaccine Reference Laboratories, responsible for working with local smallpox vaccine producers in the Western Hemisphere to improve standards and provide testing and consultation services. The National Institute of Public Health in Bilthoven, Netherlands, provided similar services for the Eastern Hemisphere.

Within this context, Dr Paul Fenje oversaw Connaught's smallpox vaccine program from 1962 through 1979, quietly and effectively raising standards, driven by pressures from national and international regulators, academic and commercial interests, and a growing determination to ultimately eradicate 'the speckled monster' from the planet.<sup>6</sup>

The sudden emergence of smallpox after 9/11 as a potential bio-terrorist weapon focused considerable energy on expediting the preparation of renewed supplies of smallpox vaccines around the world.<sup>7</sup> A new Canadian vaccine stockpile has been produced from a series of Vaccinia pulps originally prepared at Connaught in 1979 and then, fortunately, preserved in a deep freeze after smallpox was declared eradicated and vaccine production shut down. Not unlike the frozen Vaccinia pulps, the unique archival record of Connaught's smallpox vaccine development and production activities preserved at the Connaught Campus opens an otherwise closed window on the practical and dynamic world of vaccine development and manufacturing during the twentieth century.

This paper builds upon an earlier article that described Connaught's broader contributions to the global smallpox eradication effort.<sup>8</sup> The main focus here will be on Fenje's smallpox vaccine development and production work and an examination of the scientific and practical advantages and constraints he faced in raising international smallpox vaccine standards, and then consistently meeting and exceeding them in supplying the World Health Organization's smallpox eradication program with what he and others, metaphorically, though not inaccurately, characterized as 'the best dried smallpox vaccine ever made in this galaxy'.<sup>9</sup>

### **Prelude: Smallpox Vaccination in Canada: The Pre-Modern Era, 1797–1916**

Several authors, including Jennifer Keelan in this volume of essays (and in her dissertation), have described and analyzed the pre-modern era of smallpox vaccination,

including the Canadian context.<sup>10</sup> However, the primary focus of this scholarship has been more on the various intersections between vaccination theories, the empirical assessment of its efficacy and political debates surrounding the use and value of the vaccine than on the practical aspects of its production on the various vaccine farms.

The first steps towards more potent and pure smallpox vaccine supplies began with the promotion of a new means of propagating vaccine, which used only 'pure bovine vaccination'. This new approach to selecting and producing good stock vaccine lymph distinguished itself from the mélange of techniques and vaccine lymphs in use. Pure bovine vaccine was made using only spontaneous cowpox as a seed vaccine material, and was propagated in a series solely in the cow. Other more popular means of vaccine production involved a variety of starter materials, which had been propagated serially through a variety of hosts, including humans (see Keelan this volume). The most important improvement in smallpox vaccine production came in 1891 when glycerin was first used to dilute 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 more easily tested in the laboratory, although there were efforts to systematically test lymphs in the lab much earlier (see Keelan and Rusnock this volume). Sterile glass capillary tubes were also introduced at the same time in which the glycerinated vaccine was packaged and distributed. Other antiseptics, including phenol, were later used to ensure purity in vaccine production.<sup>11</sup>

Smallpox vaccine stations overseen by interested physicians and local health boards and supplied with vaccine imported from the United States, or a local supply, facilitated the distribution of smallpox vaccine in Canada through the mid-1880s.<sup>12</sup> In addition, 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 smallpox 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, while in 1899, l'Institut vaccinol de Montréal, a privately funded company, was established in Montreal, although it received some support from the city.<sup>13</sup>

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 smallpox outbreak north of Belleville in 1884, 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.<sup>14</sup>

### **Connaught Laboratories and Smallpox Vaccine, 1916–1962**

Prompted by growing domestic, and particularly military, demand for higher quality, glycerinated smallpox vaccine, in 1916 the Antitoxin Laboratories of the University of Toronto purchased the calves and equipment of the Ontario Vaccine Farm.<sup>15</sup> The Antitoxin Laboratories were founded in 1913 in a small backyard stable in west Toronto by Dr John G. FitzGerald to provide life-saving public health products in Canada, such as diphtheria and tetanus antitoxins, at a price that was within the reach of everyone.



Figure 13.1 Connaught Laboratories' first smallpox vaccine production facility was located in several isolated rooms at the south-east corner of this building (the front corner at the left end of the image). Main laboratory building, c. 1917-18, Connaught Antitoxin Laboratories, Farm Section, University of Toronto. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Acc1180.



Figure 13.2 After packaging bulk smallpox vaccine imported from the New York City Health Department Laboratories for about a year, Connaught Laboratories began to fully prepare its own smallpox vaccine in September 1917. The first step in the production process was shaving and preparing the calf for inoculation. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Acc1954.

Encouraged by his efforts and enthusiasm, and initial antitoxin sales to the Ontario government, on 1 May 1914, the University of Toronto officially established the Antitoxin Laboratories in the basement of the Medical Building.<sup>16</sup>

A severe shortage of tetanus antitoxin during the first year of World War I prompted the donation by Colonel Albert E. Gooderham (Ontario Red Cross Chairman and a University of Toronto Governor) of a large farm property 17 kilometers north of the University campus, along with new laboratory facilities for expanded antitoxin production. In early 1916 these new buildings were almost completed and a corner section of the main laboratory building was renovated for smallpox vaccine production, accommodated and isolated in four separate rooms with an outside entrance.

In the meantime, as was the case when production of diphtheria and tetanus antitoxins was initiated in Toronto in 1914–15, bulk supplies of smallpox vaccine, along with scientific and technical assistance, was sought from the New York City Health Department's Laboratories. Fitzgerald had developed a close relationship with its Director, Dr William H. Park, beginning with his post-graduate studies there in 1910, and was able to negotiate an arrangement for supplies and testing of antitoxins and vaccines at cost. For example, during September and October 1915, a total of 19,760 points of smallpox vaccine were supplied from New York City, the first shipment of 7,500 points immediately forwarded from Toronto to Winnipeg (2,500 points) and Niagara (5,000 points).<sup>17</sup>

The first batch of smallpox vaccine fully produced in the lab in Toronto was harvested from Calf #1 on 12 September 1917, shortly before the official opening of the 'Connaught Antitoxin Laboratories and University Farm'. Connaught's opening took place on 25 October 1917 and was christened by Gooderham after the Duke of Connaught, Canada's Governor General during WWI, and first patron of the Canadian Public Health Association. With the vaccination of the calves and harvesting of the vaccine managed by Albert Double, and after several tests carried out by Frank Scruby, particularly for streptococcus, tetanus and anaerobic bacteria, proved negative and clinical tests showed 'good takes', Connaught's first lot of 6,000 capillary tubes of smallpox vaccine was released on 21 December 1917.<sup>18</sup>

Connaught's smallpox vaccine production then rose sharply under the leadership of the lab's Assistant Director, Dr Robert D. Defries.<sup>19</sup> Defries, Hilda Finegan (secretary, purchasing agent, shipper) and Leila Hanna (laboratory assistant), made several trips to the United States to secure not only an original Vaccinia calf seed virus supply from the New York City Health Department – which, Defries thought was '...an original cowpox strain from England', first brought to New York in the 1850s<sup>20</sup> – but also all the components for smallpox vaccine packaging, including capillary tubes, scarifying needles and rubber bulbs.<sup>21</sup> The greatest demand for smallpox vaccine came from the Canadian military, which had purchased more than 600,000 capillary tubes from Connaught by the end of the war. A large quantity of vaccine was also prepared for provincial health departments and others across Canada, including hospitals and individual physicians.<sup>22</sup>

Not long after the end of the war, domestic demand for Connaught's smallpox vaccine grew sharply when a series of localized smallpox outbreaks struck parts of central Ontario. The Toronto area was struck in 1919 and 1920, and then Ottawa in 1921. A total of 3,046 cases were reported in 1919 in the province, and another 5,129 cases and

33 deaths in 1920. As FitzGerald noted in his Annual Report, 'There was, as a result, an enormous demand for smallpox vaccine and the resources of the Laboratories were greatly strained to meet the need'. Moreover, 'The output of vaccine for each of the months during which the epidemic continued was almost as great as the production for any previous year since the opening of the Laboratories'. In total, sufficient vaccine for 489,270 vaccinations was produced during October 1919 through January 1920, and another 500,000 in 1921.<sup>23</sup>

This level of smallpox vaccine production provided a valuable opportunity for Connaught scientists not only to build up practical experience with vaccine production, but also to study the effectiveness of the vaccine, investigate complications, and to focus on improving its quality. In particular, occasional complaints of vaccine failures from doctors, particularly during the Ontario smallpox epidemic in 1919–20, underscored the importance of how the vaccine was being shipped, stored and administered, and especially how heat could easily destroy its potency. Such complaints also highlighted the limited understanding of vaccination and vaccines among some physicians during this period and the importance of Connaught keeping detailed production records so that individual

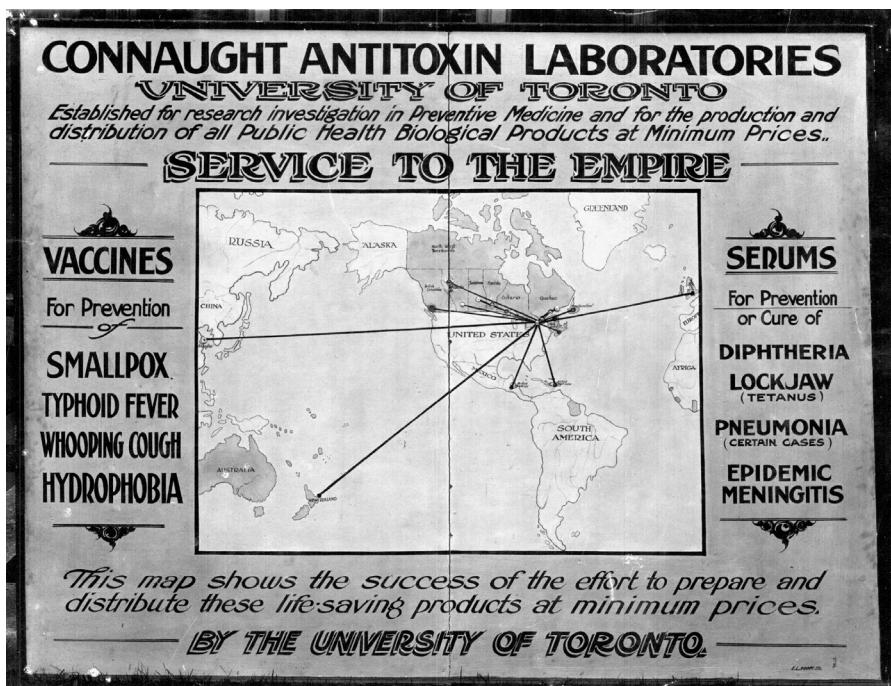


Figure 13.3 During the last years of World War I and expanding into the 1920s, Connaught Laboratories supplied smallpox vaccine, among other vaccines and antitoxins, to all provinces in Canada, as well as to other parts of the British Empire. This promotional map, dating from about 1920–21, was displayed at such public events as the Canadian National Exhibition and highlighted Connaught's mission: 'Established for research investigation in Preventive Medicine and for the production and distribution of all Public Health Biological Products at Minimum Prices'. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Acc0705.

complaints could be investigated.<sup>24</sup> This apparent lack of attention among at least some physicians to the proper storage of smallpox vaccine in the 1920s raises the question of how the vaccine had been stored and handled by nineteenth-century physicians and vaccinators and how this had affected its potency and effectiveness. Moreover, how did such conditions influence the medical and political debate surrounding its use?

In 1921, the first volume of *Studies from the Research Division, Connaught Antitoxin Laboratories* was published and included two original articles on smallpox vaccine that began a tradition of serious scientific research at Connaught into its ongoing improvement. The research was focused on maximizing the stability, potency and purity of the vaccine, particularly through increasingly careful attention paid to how calves were selected, tested, accommodated, washed and handled during and after they were inoculated.<sup>25</sup>

Despite the obvious effectiveness of smallpox vaccine, underscored by the sharp decline in smallpox incidence in Canada, the inherent production problem of bacterial contamination of Vaccinia pulp harvested from calf skin was a constant challenge that Connaught scientists focused intensely on overcoming. Glycerin was effective in sharply reducing bacterial contamination after the Vaccinia pulp was harvested and processed, but during the late 1920s, Connaught scientists focused their attention on further reducing bacterial content by improving how the calves were selected, tested, handled and kept clean before, during and after they were inoculated. More careful attention to the cleanliness of the calf stalls and their handlers made a significant difference, as did increasingly scrupulous measures of washing and rewashing the calves and the vaccinated area of their abdomen, and also the liberal use of 'brilliant green', which was a triphenylmethane dye of the malachite-green series generally used in a 1:500 dilute solution as a topical antiseptic. It was particularly effective against gram-positive microorganisms. The results of such measures in reducing bacterial content were quite clear after a 1927 series of experiments. In a vaccine with a high initial bacterial count of 30,000,000 per cc, a series of phenol-glycerine treatments reduced the count to 300, while in a vaccine with a low initial count of 3,000 per cc, phenol-glycerine treatment reduced the count to an undetectable level.<sup>26</sup> By 1932 an even more intensive routine of washing the calves before and after vaccination and the expanded use of brilliant green, further reduced the bacterial content of Connaught's finished vaccine, ranging from 60 to 60,000 per cc over 45 lots produced during two years of production; 17 lots had counts of less than 1,000 and 14 were between 1,000 and 3,000 per cc.<sup>27</sup>

By the early 1930s a new research program began at Connaught. It was led by Dr James Craigie and focused on Vaccinia and Variola strains and Vaccinia elementary bodies. Utilizing Vaccinia virus cultured in rabbits and other animals, Craigie's interests were focused on the 'flocculation reaction' evident when Vaccinia lymph, or smallpox crusts, were mixed with an appropriate antiserum. Such visible reactions with viral materials were unfamiliar to researchers at the time and had been thought to be bacterial invaders, but Craigie demonstrated that the antigen-antibody floccules in fact contained infectious viral particles, otherwise known as 'elementary bodies'.<sup>28</sup> By the start of World War II, other demands, including an intensive effort to produce typhus fever vaccine for the military, resulted in the slow down of Vaccinia research work at Connaught, although smallpox vaccine production increased significantly.

Interest in improving smallpox vaccines was boosted during World War II and especially through the late 1940s, by the persistent and increasing incidence of smallpox in tropical countries and by the limited effectiveness of glycerinated smallpox vaccine in such environments. Liquid smallpox vaccine was very heat sensitive and under tropical conditions it might not be properly refrigerated. A variety of freeze-dried smallpox vaccines had been produced as early as 1919, particularly in France for use in its African colonies, but it was not until after the end of the war and the establishment of the World Health Organization in 1948 that the usefulness of a freeze-dried smallpox vaccine in tropical countries grew more apparent and research efforts focused on improving production methods to boost the heat stability of dried vaccines.<sup>29</sup>

Dr L.H. Collier of the Lister Institute in England was one of the first to take up this challenge, adapting a centrifugal freeze-drying apparatus developed during the war for blood plasma to smallpox vaccine production. Collier's freeze-drying technique was based upon the preparation of suspensions of Vaccinia virus utilizing a method developed by Craigie in 1932. Collier used a homogeneous strain of Vaccinia first described by Dr Cleeve Russell Amies in 1938, who was then at the Lister Institute. A strain of virus was needed that could be easily purified and which would show uniform characteristics during repeated passages. Collier thus converted the standard Lister strain of vaccinia to a 'homogeneous' strain, the starting material for which was a partially purified elementary bodies suspension prepared from sheep pulp using differential centrifugation, followed by repeated passages on the skin of the rabbit.<sup>30</sup> Twenty years later, Amies himself was to join Connaught. Among other projects, he was to oversee the development of its first generation of freeze-dried smallpox vaccine.

Connaught had experimented with producing a dried smallpox vaccine as early as 1941, however, little more was done in this area until 1958, when a major smallpox epidemic struck what is now Bangladesh, causing more than 100,000 cases. The International Red Cross and the WHO mobilized vaccine from all over the world, including Canada, where stocks were quickly exhausted. The Canadian Red Cross approached Connaught to produce additional vaccine 'with the utmost speed'. Defries, who had retired as Director of Connaught in 1955 after overseeing its 'Herculean' Salk polio vaccine development and production program,<sup>31</sup> stepped in to apply his long experience with smallpox vaccine, and within four weeks Connaught had shipped 1.5 million doses.

The vaccine sent to Bangladesh was regular glycerinated vaccine, but it was clear that a dried vaccine would be more useful in such a tropical environment. After the crisis had passed, Defries stressed to Connaught's Human Antigens Committee the importance of proceeding with developing a dried smallpox vaccine.<sup>32</sup> At the same time, stimulated by the high profile success of the Salk polio vaccine and the beginning of work on an oral polio vaccine, considerable international attention was now focused on improving smallpox vaccines based on tissue culture methods like those being used to produce polio vaccines.

In late 1958, a research program was launched at Connaught under the direction of C.R. Amies, focused on investigating some of the new production ideas, including the development of a freeze-dried smallpox vaccine. By 1960, Amies was able to produce a dried vaccine on a small scale, and by 1962 clinical trials were conducted with the Canadian Armed Forces, as well as in the West Indies and Africa.<sup>33</sup> However, Amies was

more interested in research than vaccine production; he left Connaught in 1962, passing direction of the smallpox program to Dr Paul Fenje, who had worked with him since they both arrived at Connaught in 1958.<sup>34</sup>

### Connaught Laboratories, Paul Fenje and Raising Smallpox Vaccine Standards

The growing global threat of smallpox, particularly through increasing international air travel, and the goal of eradicating this disease required fresh approaches, with energy directed at developing, producing and utilizing the best dried vaccine possible. In early 1962, Paul Fenje assumed this responsibility with a unique blend of research and production skills, enthusiasm and humility, which helped bring the global battle against smallpox to new levels of intensity.

Born in Novi Sad, Yugoslavia, in 1915, and following in the medical paths of his father and grandfather, Fenje received his MD from the University of Zagreb in 1940. He then received a Diploma in Public Health from the Institute of Hygiene in Belgrade and a Specialist in Microbiology certification. Fenje was primarily drawn to microbiology and diagnostics, and, as he later recalled, an interest in 'finding the reason or cause of why things happen' in the laboratory, rather than looking down people's throats as his father as a general practitioner did. He was particularly interested in rabies and influenza. In Yugoslavia under the Communists, Fenje oversaw a viral diagnostic lab and then a general public health laboratory in Sremska Mitrovica.

In 1955, Fenje was appointed Head of the Department for Medical Virology at the Pasteur Institute in Novi Sad, where he served until 1958, when, through some 'conspiratorial work', he and his family escaped from Yugoslavia and moved to Canada. Unsatisfied with a position that increasingly kept him behind a desk at the Pasteur Institute, Fenje accepted an invitation from the University of Edinburgh in Scotland to do some research. At the same time, his wife and children quietly managed to travel to London, where the family reunited and took the opportunity to board a steamship bound for Montreal.

Fenje needed a job quickly and first went to the Institute of Microbiology at the University of Montreal, but they had little to offer him, and neither did McGill University.



Figure 13.4 Dr. Paul Fenje, passport photo taken in 1967. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Aneg67-35.

Fenje and his family next went to Toronto where he arranged to meet the Director of Connaught, Dr J.K.W. Ferguson. At the time, Fenje had heard the Connaught name but knew little about the Labs. Immediately impressed with Fenje's ability to speak six languages, and in need of someone experienced enough with rabies vaccine production to help stem an alarming outbreak of the disease among Eskimo dogs, Ferguson hired Fenje on the spot.<sup>35</sup>

Hired at about the same time as Amies and initially working under his direction, Fenje's primary focus during his first years at Connaught was on preparing and improving rabies vaccine. While he would maintain this interest in rabies throughout his career at Connaught, the development of new smallpox vaccines increasingly consumed his time. As he later recalled, Fenje was immediately overwhelmed by the kindness of his colleagues at Connaught and their readiness to help, and similarly overwhelmed by the availability of money for equipment. Formal budget plans were rarely needed and none of his requests for funds were refused, which was something quite new to him. Fenje's arrival at Connaught coincided with a period of rapid growth in the Labs fueled by large-scale production of Salk polio vaccine and the beginning of development work on the Sabin polio vaccine.<sup>36</sup>

In February 1962, Fenje was invited to a special meeting 'to establish priorities, space and personnel requirements for the continuation of certain projects now underway and to plan for the further development of smallpox vaccines'. There were growing export demands for glycerinated vaccine, but difficulties obtaining enough suitable calves. At this meeting, Robert J. Wilson, an Assistant Director at Connaught, felt that an expanded smallpox vaccine production program was necessary in order to place Connaught 'in the most advantageous position, should shortages develop in other parts of the world as a result of current epidemics, which seem to be gaining ground, particularly in the Congo'.<sup>37</sup>

Top priority, however, was to be given to further development of a dried vaccine. WHO's initial smallpox eradication program, launched in 1955, was stalled after large quantities of vaccine donated by the Soviet Union were found to be contaminated. In response, and in a context of concerns about regulatory lapses that contributed to the 'Cutter Incident' in 1955 when the Salk polio vaccine was first introduced, and then the discovery of extraneous viruses in other vaccines, such as SV40 in the Sabin and Salk polio vaccines in 1960–61, the WHO focused on developing more sophisticated international vaccine standards. Such events, among other factors, helped shape the WHO's recognition that 'biological products are usually highly complex and cannot be assayed for safety and efficacy by examining final material alone'.<sup>38</sup> The new regulatory process would thus involve all starting ingredients, the establishment of reference materials, and the monitoring of all stages of production. This approach contrasted with that of the Standardization Commission of the League of Nations established in 1924, the work of which was primarily focused on using biological methods to define and standardize the chemical purity of final bacterial antisera and antitoxin products (see Mazumdar this volume).

For Connaught, there was no evidence of foreign viruses in its smallpox vaccines during the production process. As noted by key members of Connaught's Human Antigens Committee, the only possible sources for viral contamination would be calves or humans. Indeed, 'such virus contamination is believed to be very unlikely since

a long history of successful vaccine production has indicated no such problem'. The Committee concluded that while a formal testing program would not be needed, there were techniques available that would enable a closer study of vaccinia virus and provide useful data for Connaught to have, including in support of statements 'that our vaccinia virus has been examined for foreign virus and found to be "clean"'.<sup>39</sup>

During the first years of the 1960s, the idea of smallpox eradication was accelerated in light of new epidemics in developing countries and by several alarming outbreaks in Europe sparked by cases imported from endemic areas. Closer to home, in August 1962, North American fears of imported smallpox were realized when a 14-year-old boy returning home to Toronto from Brazil via New York City developed smallpox en route, touching off an international emergency and a mass vaccination campaign on both sides of the border. Fortunately, it was a mild case and there were no secondary infections. Yet, North America's vulnerability to imported smallpox was dramatically exposed.<sup>40</sup>

Picking up where Amies had left Connaught's dried smallpox vaccine development, Fenje initially focused his attention on experimental processing methods. He improved freeze-drying techniques, and standardized methods of testing vaccine potency and stability, beyond the traditional rabbit scarification test.<sup>41</sup> Indeed, the standardization of freeze-dried vaccine was critical to Fenje. As he discussed with Wilson in late May 1962, there did not seem to be any international standard or minimal requirements established regarding the potency of vaccine that was to be freeze dried. Specifically, there needed to be potency standardization based on a specific number of plaque forming units in monkey kidney cells and pock forming units in chick embryos, as well as standardization in drying techniques, moisture content and vaccine stability. As Fenje concluded in a memo, 'These are Dr. Wilson, the most important questions, which if you could discuss with the WHO experts, the resulting information might be of considerable help for the development of our dried smallpox vaccine'.<sup>42</sup>

The pace of Fenje's work accelerated during the latter half of 1962, boosted by the Toronto smallpox scare and by intensified international efforts to develop a dried vaccine that would meet the new WHO standards. As a self-supporting part of the University of Toronto, and in the wake of its pioneering polio vaccine work over the previous decade, Connaught was in a fortunate position to share its progress in the spirit of academic and practical inquiry, and also benefit from the advances made by others. Sharing of experience was from Connaught's perspective, largely unidirectional as they provided critical research capacity to vaccine manufacturers, including the Lister Institute in England, who were interested in obtaining samples of the Vaccinia strains Connaught was using, and the Serum Institute in Copenhagen, who were impressed with the vaccine yields Connaught was obtaining.<sup>43</sup> In addition, Connaught was occasionally asked to test smallpox vaccine batches sent from US manufacturers, particularly to confirm potency or stability test results.

Fenje's relationship with his international colleagues, and his position among them was elevated significantly through an International Smallpox Vaccine Symposium hosted by the Institut Mérieux in Lyon, France, in December 1962. However, Fenje had not yet been granted Canadian citizenship and was nervous about traveling back to Europe for fear of attracting attention in Yugoslavia. He also did not yet feel particularly confident in his position as a smallpox vaccine expert, confiding to Wilson shortly after being invited to the conference, 'It seems the best people in the field of smallpox control

will be present (with my exception). The problems to be discussed are all of practical importance and conclusions will have probably a significant bearing on the future development of the smallpox vaccine'.<sup>44</sup> Nevertheless, Fenje's paper, entitled 'Stability of Dried Smallpox Vaccine at Various Temperatures', was well received, although, as he reported to Wilson, it was scheduled during the last session of the meeting and there was very little time left for discussion.<sup>45</sup>

Following the conference, Fenje spent the next few weeks visiting a variety of European vaccine manufacturers and laboratories, including the Pasteur Institute in Paris, the Lister Institute in England, and the National Institute of Public Health in Bilthoven in the Netherlands. He was particularly impressed by the use of Arcton, a fluorocarbon,<sup>46</sup> at the Lister Institute for purifying calf pulp without high-speed centrifugation, although Fenje recognized that this process did not result in a sterile dried vaccine product. Of more immediate interest was the new Vaccinia unit at Biltoven, which produced low bacterial count pulps and used antibiotic sprays. As Fenje later wrote to the Institute's Director, Dr B. Hoffman, 'We realize now how primitive our way of handling the animals is in comparison with your methods, and we would like to do something about it, to improve it to some extent'. Fenje also asked for Hoffman to send descriptions of the Institute's filling machinery and a simple plan of its animal quarters, although Fenje recognized that, at present, he did not anticipate Connaught would have the means to build new animal quarters.<sup>47</sup>

Fenje's dried smallpox vaccine development work continued through 1963, albeit on a relatively small scale during the first part of the year as the uncertainties of the export market made it difficult for Connaught to commit the necessary resources for large-scale production. The WHO had not yet committed to an expanded eradication program, although, encouraged by a series of clinical trials, the Canadian Armed Forces considered converting to dried vaccine if Connaught could supply it within the next 1–2 years. Nevertheless, as was stressed at a February 1963 meeting of the Human Antigens Committee, 'C.M.R.L. should remain in the forefront of the work leading to the best available smallpox vaccine on a production scale'.<sup>48</sup>

In April 1963, Fenje's leadership of Connaught's smallpox vaccine development and production work was solidified with his invitation to join the Human Antigens Committee.<sup>49</sup> Key priorities for Fenje were preparing an application for a Canadian license for dried smallpox vaccine and also a US license. There was also interest from a US firm known as Panray, to distribute Connaught's smallpox vaccine to take advantage of American efforts to increase smallpox immunization levels.<sup>50</sup>

During his first full year Fenje focused almost totally on dried smallpox vaccines development and production, and was then able to recommend that routine production could begin. By June 1963, as he wrote in his first annual research report, considerable international progress had been made recently in dried vaccine production. However it was clear that there were wide variations in vaccine quality, particularly in the levels of bacterial contamination, and in how much, or how little, producers did about it.

In particular, Fenje noted that vaccine producers in Holland, France, South America, among others, seemed to be doing little to minimize bacterial contamination. They simply homogenized and then freeze-dried calf pulp without any further preparation other than adding a stabilizing agent. The resulting final product contained a relatively high concentration of a bacterial agent that caused a significant loss in potency during freeze-drying and decreased

stability when exposed to higher temperatures. Fenje also noted that 'a huge amount' of dried smallpox vaccine from the USSR donated to the WHO had to be discarded 'since it was so heavily contaminated'. However, 'some producers have sterile products of satisfactory potency, stability, purity and distributed with elaborate means for application', such as the US Army, while others, such as the Lister Institute, 'do not pay any attention to this'.<sup>51</sup>

The rest of Fenje's report detailed the efforts employed at Connaught to control contaminants in the final vaccine, including keeping inoculated calves under the most meticulous sanitary conditions through scrupulous washing, cleansing and scrubbing prior to exsanguination. Contamination control was also reinforced by spraying the inoculated site of each calf with a 1/1000 dilution of brilliant green, while antibiotics, 0.02% Streptomycin and 0.01% Neomycin, were used in the processing and purification of the harvested and homogenized Vaccinia pulp. The pulp was then subjected to a series of differential high-speed centrifugations, after which 10% peptone and 4% phenol solutions were added. Fenje also stressed the adoption of a standard potency of  $10^8$  pock forming units per ml, that would ensure 100% 'takes' in vaccinees and also leave a safety margin to cover potency loss during storage at high temperatures.<sup>52</sup> He noted that it had been 'generally observed that vaccines containing between  $5 \times 10^7$ – $10^8$  infectious units per milliliter will give 100% takes, and those containing approximately  $2 \times 10^8$  infectious units will vaccinate successfully on 50% of susceptible persons'. Nevertheless, it was clear that a positive take will render to the vaccinee a degree of protection which is independent of the potency of the vaccine.<sup>53</sup> Meeting such a standard, and more importantly, meeting it consistently from lot to lot was a significant challenge for smallpox vaccine manufacturers, including Connaught. As his experience grew, however, Fenje was able to maintain and exceed such a standard over time.

Confident in his methods to produce a superior dried vaccine, Fenje faced growing pressure to expand production, particularly as the WHO worked towards intensifying its smallpox eradication program. In January 1964, Fenje was asked whether or not Connaught was prepared to supply 5 million doses of dried vaccine, should the WHO ask for it. The limiting factors he faced were the present production facilities, and an available support staff of only two or three. Calves could be processed weekly and about 44 calves would be needed to prepare the 15,380 grams of pulp required to make 5 million doses of vaccine.<sup>54</sup>



Figure 13.5 Harvesting Vaccinia pulp from calf, Smallpox Vaccine production, 1970s, Connaught Medical Research Laboratories. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, uncatalogued slide.

Fenje's confidence underscored the growing breadth of his intellectual and practical grasp of the broader situation regarding the production of smallpox vaccines around the world. During the early 1960s, he spent considerable time investigating the relative merits of the other, more 'modern', types of smallpox vaccines – that is, various tissue culture-based vaccines, and others based on inactivating the *Vaccinia* virus using various chemical agents or physical methods – that were being developed and promoted widely. He summarized his critical views on the state of the art in a 1964 paper, 'Advances in the Immunoprophylaxis of Smallpox'.<sup>55</sup> Fenje saw the theoretical advantages of some of these new approaches, however, they seemed limited when it came to adapting them to the practicalities of large scale production and quality control demands, and fell short of the immunological response shown with the 'traditional' calf-skin *Vaccinia* pulp-based vaccine. Fenje's progress was also acknowledged in August 1964 with the Canadian licensing of Connaught's dried smallpox vaccine, and in December by the news that it also met WHO's new dried vaccine standards.<sup>56</sup>

By the summer of 1965, the intensity of smallpox vaccine production at Connaught increased after the announcement that the United States government was prepared to sponsor a more sophisticated global smallpox eradication program through the WHO.<sup>57</sup> There were also new inquiries about how much dried vaccine Connaught could supply and how soon. A new smallpox building was under construction to enable larger production, but it would not be ready until late in 1965.<sup>58</sup>

At the same time, the WHO Assembly issued new measures concerning the international control of smallpox, yellow fever and malaria, requiring that all vaccinations for international certification should be made only with a product certified to fulfill WHO vaccine requirements. This meant that, as of 1 January 1967, anyone traveling between countries that required proof of smallpox vaccination or re-vaccination had to present an official vaccination certificate that included information about the origin and batch number of the vaccine they received.<sup>59</sup>

Fenje felt that there were no major differences between the current Canadian and WHO dried vaccine standards, although the WHO was now calling for a more potent vaccine than Canadian regulators required. In September 1965, Fenje stressed to Wilson that Connaught needed to upgrade its present criteria for acceptance in order to meet all of WHO's requirements, which meant increasing the concentration of the vaccine, although this would increase its production cost. At the same time, Connaught had to meet US requirements, which differed substantially from Canadian and WHO regulations with respect to potency testing procedures; American authorities only required the rabbit scarification test, which involved comparing the scratched skin reactions of a series of vaccine samples of varied dilutions. This was also the only test that provided a good indication of the vaccine's effect when applied to human skin. This test required three times as many animals as Connaught's.<sup>60</sup>

In order for Canadian travelers to prove their smallpox vaccination status when they crossed international borders, Canadian regulatory authorities had to certify that Connaught's vaccine met the new WHO standards, and there were concerns that it might not in light of the WHO's reliance on the pock count test, which indicated a vaccine that was perhaps not potent enough, while other tests, and reports from some doctors suggested that it was too potent. It was evident to Fenje, however, that the potency of the vaccine was not related to its potential reactivity; increased reports of

reactions were more related to increased reporting sensitivity than to a more reactive vaccine. The new testing and certification rules proved frustrating to Fenje. As he stressed in a handwritten note to Wilson in response to a letter from R.A. Chapman, Director General of the Canadian Food and Drug Directorate, 'I think it would be entirely impractical from anybody's point of view to deal with 2 kinds of vaccines: 1) one which would be certified and to be used for the International Vaccination Certificate, and 2), another vaccine, non-certified for "non-international" purposes. It seems to me, what we have to do is to prepare the smallpox vaccine so as to meet in every lot their requirements'.<sup>61</sup>

By March 1966, Connaught's smallpox vaccines met all US and WHO requirements, each batch subjected to rabbit scarification and the pock mark tests.<sup>62</sup> Meanwhile, the preparation of a dried vaccine suitable for use with the jet injector would have to meet another set of strict WHO standards, particularly for sterility and consistency in light of the different dosage and delivery system involved. As Dr Donald A. Henderson, Director of the WHO Smallpox Eradication Program, pointed out to Wilson, 'I argued some tolerance in the requirements but it was quite clear the Committee was against bacteria like sin and to advocate some low level of bacterial contamination was akin to arguing the virtues of wine to a group of Methodist clergymen. It's a funny world'.<sup>63</sup> The jet injector for smallpox vaccine was introduced in the early 1960s, initially for use in the US and Canadian military, and involved a special intradermal nozzle designed for use with a hypodermic jet injector apparatus that provided a very rapid method of intradermal injection. When used instead of the traditional multiple pressure method, the vaccine could be diluted 50-fold, thus greatly boosting the efficiency of mass smallpox vaccinations.<sup>64</sup>

Fenje's primary goal was, however, to produce a dried smallpox vaccine that was truly bacteriologically sterile, that is with consistent bacterial counts of 0 in each vaccine lot. By early 1968 Fenje was able to confidently make such a claim. Yet, as early as October 1965, the President of Wyeth Laboratories had personally phoned Connaught's Director, J.K.W. Ferguson, inquiring about the sterility of Connaught's freeze-dried smallpox vaccine. As Wilson reported to Fenje, Wyeth's President had heard a rumour that 'we were producing sterile material for the jet injector', while Wyeth had one contaminated dose for every 200 it produced.<sup>65</sup> 'I don't think we ever claimed that our dried vaccine is sterile', Fenje replied to Wilson, 'although in practice we always tried to achieve this goal. It just happened that the standard tests used for both the glycerinated and for the dried smallpox vaccine did not show any bacterial contamination'. He admitted at the time, however, 'it is quite possible that the vaccine would not pass a rigorous sterility test'.<sup>66</sup> In February 1968, Fenje reported to Connaught's Human Antigen Committee that 9 sterile lots of dried smallpox vaccine had been produced, representing about 1 million doses. In addition, several countries, including Chile, were interested in buying 1.5 million doses of the sterile product.<sup>67</sup> US regulators were also impressed with Connaught's dried smallpox vaccine. In a series of sterility tests in October 1970 at the National Institutes of Health in Washington, they were able to pass at least 1,100 doses of Connaught's dried vaccine through a 0.45 micron pore-size Millipore filter without clogging the filter and with no evidence of contaminants.<sup>68</sup>

The WHO permitted a bacterial count of up to 100 non-pathogenic contaminants per cc of smallpox vaccine. By the late 1960s, Fenje was consistently able to demonstrate

bacterial counts of 0 in virtually every Vaccinia pulp he processed. From January 1970 through February 1976 – which included the period of peak production of some 35 million doses of dried smallpox vaccine primarily for the WHO – only 8 out of 179 fully processed Vaccinia pulps prepared for all vaccine types had bacterial counts that were not 0, and they only occurred sporadically among the first 26 pulps processed between January 1970 and February 1972. The highest bacterial count recorded was 29 per cc (which was the first pulp of the series, but well under the WHO standard of 100 per cc) and the others ranged from 2 to 18; all counts were 0 for each of the remaining 150 Vaccinia pulps processed after February 1972. This smallpox vaccine purification process generally began with initial homogenized Vaccinia pulps with bacterial counts ranging from as low as 6 for pulp #872 (processed in November 1970), up to as high as 50,600,000 for pulp #977 (processed in May 1972), although the average initial count ranged from a low of 1,000 to 100,000 over the 6 years of vaccine production that are well documented.<sup>69</sup>

Fenje's sterile freeze-dried smallpox vaccine took 3 days to prepare, followed by a variety of tests. On the first day one part crude calf pulp was suspended in three parts 0.004 M McIlvaine buffer (with no antibiotics), and then homogenized and centrifuged, resulting in Extraction #1. The supernatant was kept and the sediment used for preparing Extractions 2, 3 and 4, which followed the same process as #1 with the exception that antibiotics were added to the McIlvaine buffer (10 mg% of Neomycin and 20 mg% of Streptomycin). After Extraction #4 the remaining sediment was discarded. The four extractions were then pooled and subjected to three cycles of purification by differential centrifugation, after which the sediment was discarded and the purified pooled extractions stored overnight and then subjected to high-speed centrifugation. The supernatants that contained the antibiotics were then discarded and the final elementary body suspension of Vaccinia virus was prepared from the remaining pellets, which were then re-suspended in the McIlvaine buffer, but without the addition of antibiotics, and then pooled and homogenized. Peptone and phenol solutions were then added and the suspension left at room temperature for 24 hours under constant stirring. The Vaccinia suspension was generally sterile at this point. A peptone solution was then added to decrease the phenol concentration (which lessened the harmful effect of phenol on the Vaccinia virus) and the final suspension stored at 0° C until all bacteriological and potency tests were completed and passed and the filling and freeze-drying process could commence.<sup>70</sup>

Connaught's smallpox production process was not a secret. As noted earlier, there was considerable sharing of information with other smallpox vaccine producers, including Wyeth Laboratories, which was the largest producer of smallpox vaccines in the US. After Fenje sent a copy of Connaught's standard procedure for dried smallpox vaccine, Wyeth prepared a summary document comparing Connaught's and Wyeth's production and testing process. Wyeth's Managing Director, J.H. Brown, felt that 'Apparently there are no great differences between our two laboratories'. Nevertheless, there were interesting differences in the handling of the calf before inoculation: Connaught sprayed the inoculation site with acetone and also injected 40% chloral hydrate as a general anaesthetic, while Wyeth did not use acetone, but rather rinsed the calf with 70% alcohol and did not use any anaesthetic unless the animal was uncontrollable. Connaught used wooden platforms to hold the calves for inoculation to minimize soiled

vaccinated areas, as well as sterile sawdust spread on the floor. At Wyeth, in contrast, sawdust was not used, while the calf was 'held on metal slatted rack but probably too close to floor for maximum effectiveness'. As noted earlier, brilliant green (containing added neomycin and streptomycin) was employed quite liberally at Connaught before and after Vaccinia inoculation, while at Wyeth, brilliant green was not used since 'attempts at using it did not substantially reduce plate counts of the skin swabs or harvested pulp'; also, antibiotic sprays were not used at Wyeth.

During the preparation of the purified Vaccinia suspension, other important differences are evident. At Connaught a total of 4 extractions were made, the homogenate centrifuged at 1200 G for 10 minutes; at Wyeth 3 extractions were made with centrifugation at 1000 G for 15 minutes, with both labs employing neomycin and streptomycin in the buffer. In contrast to the further purification processing at Connaught described earlier, at Wyeth, there was no further purification conducted after the initial low speed centrifugation, but rather treatment with 0.5% phenol and holding for 5 days at 4° C, followed by centrifugation at 5000 G for 2 hours. There were also several differences in the tests that were conducted on the final vaccine. For example, Connaught tested for *Bacillus anthracis*, while at Wyeth no test was done as they felt this would be 'picked up on blood agar'. Also, intratesticular injections of rabbits were done at Connaught with observation for local reaction or generalized infection; at Wyeth no such test was conducted.<sup>71</sup> Wyeth's Managing Director may have felt that these differences were insignificant, but they do highlight important differences between the two labs: in the level of care taken with the handling of the calves, in the level of rigor employed in the processing and purification of Vaccinia pulps, and in the testing of the final vaccine. Connaught had a stronger academic orientation and focused more attention on vaccine development and production. Wyeth, in contrast, had a purely commercial structure; pharmaceuticals were the major product line, and vaccines played only a small part. This different emphasis may explain at least some of the differences.

### Connaught and the Politics of Smallpox Eradication, 1967–1979

Despite the WHO's desperate need for such a high quality vaccine as the global smallpox eradication program began, the Canadian government was unable, or unwilling, to buy the vaccine from Connaught and donate it directly to the WHO. Canadian politics and External Affairs regulations that only permitted general financial support to the WHO was a source of growing frustration for Henderson, Wilson and Fenje. Henderson had earlier suggested to Wilson, '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?'<sup>72</sup> Eight months later, Henderson again stressed to Wilson, 'With your tremendous capacity and good vaccine, I am sorry not to see it more extensively used'.<sup>73</sup>

The most intensive year of Connaught's involvement with the eradication effort was the first, 1967–68, during which Wilson and Fenje, as special consultants to the Pan American Health Organization, visited some 15 labs in 12 countries of Latin America to help improve local vaccine production quality. At Connaught, which was designated

one of two International Smallpox Vaccine Reference Laboratories by the WHO, Fenje also hosted a series of scientists and technicians from Latin American vaccine producers to further instruct them on vaccine production methods. Indeed, it was clear that the quality and purity of locally produced vaccine in Latin American countries, as well as most of the 30 other smallpox endemic countries, was much poorer than expected.<sup>74</sup>

The newly established WHO vaccine production methods and standards, based largely on the initiative of Wilson and Fenje and the experience of Connaught, were codified in 1968 in the WHO's *Methodology of Freeze-dried Smallpox Vaccine Production*.<sup>75</sup> In September 1968, after another trip to South America, Wilson reported to Henderson, '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'. He was 'most gratified 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'.<sup>76</sup>

Meanwhile, a certain level of political and administrative chaos in Canada continued to complicate the WHO's use of Connaught's vaccine. However, some unexpected and somewhat embarrassing press attention in May 1970, featuring 'an eloquent presentation' by Henderson on television of the need for smallpox eradication and for the need for vaccine,<sup>77</sup> finally prompted the Canadian government to donate 7 million doses of Connaught's vaccine to the WHO.<sup>78</sup> According to Henderson and Wilson,



Figure 13.6 Jet injector and smallpox vaccine (dried) vials and needles, Connaught Medical Research Laboratories, 1970s. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, uncatalogued slide.

this TV story had a 'long and colourful' background. Earlier, the Canadian Mission to the United Nations had approached Henderson in support of bilateral donations based on specific requests for aid. Henderson, however, stressed the far greater flexibility of a multilateral donation, directing vaccine to where it was needed most.<sup>79</sup> 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'.<sup>80</sup>

At about the same time, Wilson had a dinner guest of his niece's at his home. Wilson later discovered that he was a television 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'.<sup>81</sup> In June 1970, shortly after this media attention to the issue, the Canadian International Development Agency asked Connaught to provide a quote for 8.5 million doses of smallpox vaccine for the jet injector. Wilson was 'hopeful that the machinery is now grinding'.<sup>82</sup> By August 1970 there were still a few more details to iron out, but it was clear that the Canadian government was now committed to donating \$140,000 to purchase about 7,000,000 doses of dried smallpox vaccine from Connaught.<sup>83</sup> The priority for the first vaccine shipment was Ethiopia and the Congo.

Henderson's main concern in October 1970 was to obtain as much vaccine for the Canadian donation as possible, for use in the jet injector, as well as with the bifurcated needle. As he stressed to Wilson, 'Believe it or not, we are desperately in need of vaccine in quantity for this programme', but hoped Connaught might be able to offer a better price. In particular, Henderson pointed out that 'the costs for [Connaught's] jet injection vaccine, for example, are considerably higher than comparable vaccine from any other source, even Wyeth'. Wilson agreed, but pointed out that 'our process is more costly than other preparations and this is reflected in the very high quality of the vaccine as claimed by NIH. I think we cannot make any short cuts in this processing'.<sup>84</sup>

The bifurcated needle for multiple puncture smallpox vaccination was originally developed at Wyeth Laboratories by B.A. Rubin in 1961. While the jet injector 'marked the peak of complex vaccination technology', historian Derek Baxby has suggested that 'the bifurcated needle marked the peak of simple excellence'.<sup>85</sup> The bifurcated needle was based on a sewing needle with the ends of its loop cut off and then ground to a point, the idea being, as Rubin recalled 'that a pronged needle would retain the capillary activity of a loop and that it might have simultaneous utility in scarification'. Simplicity and economy were the bifurcated needle's main advantages as it could be used by almost anyone after minimal training – although in the hands of an expert made possible 800–900 vaccinations per day per vaccinator – plus the 'capillary action held enough vaccine for one dose between the prongs, a saving of 75% in the volume used for other techniques'. After use the needle could be quickly sterilized, or was cheap enough to be easily discarded. Connaught, however, was unable to utilize the bifurcated needle in its dried smallpox vaccine package due to Wyeth's patent protection. In 1968, in support of the smallpox eradication program, Wyeth waived its patent royalties from the bifurcated needle, shipped them in bulk to Geneva, and allowed the WHO to utilize it freely with all dried vaccines used where smallpox persisted, including Connaught's.<sup>86</sup>

Nevertheless, Henderson remained desperate for vaccine. Indeed, as he stressed to Wilson, 'we are in need of vaccine in fairly large supply and on a continuing basis particularly for the programme in the Congo. Vaccinating as if it was going out of style, consuming vaccine at a prodigious rate – faster by far than we had anticipated earlier'. Henderson preferred to use Connaught's vaccine, 'as it makes it most difficult for the field units to change from one type of vaccine to another – more specifically from the very practical Canadian package to others which are far more cumbersome'.<sup>87</sup>

By February 1971, Henderson's vaccine supply concerns eased when Fenje was pleased to report, 'I have just completed the production of your order. I guess that you will shortly have on hand about 10 million doses of the best dried smallpox vaccine ever made in our Galaxy'.<sup>88</sup> Henderson was 'indeed delighted' and claimed that 'with a continuing flow of this vaccine, I would hope that we would be battling the problem of smallpox in Sudan and Ethiopia (in Africa) by the end of this year'.<sup>89</sup> A few months later, Wilson wrote to Henderson, 'Paul Fenje has recently been asking me whether there have been any reports from the field on his "best vaccine in the galaxy". I think he is rather anxious to know how it is performing although I have few doubts this properly applied will do what is expected of it'.<sup>90</sup> Henderson was very pleased. As he told Fenje, 'Your vaccine, incidentally, is performing magnificently both in the Congo and Ethiopia. The good packaging and ease of reconstitution have both been commented upon. Take rates in primaries have been in the range of 98% to 100%'.<sup>91</sup>

As he stressed in a recent interview, Fenje was quite serious in his claim of galactic supremacy of his dried smallpox vaccine. His ability to consistently prepare a sterile dried vaccine impressed the Canadian and American regulatory authorities as well as the WHO. They were also all similarly impressed with the unique Freon-purified liquid glycerinated vaccine he was also able to regularly produce for Canadian use.<sup>92</sup> Developed in 1969 by Fenje, Connaught's Freon-Purified smallpox vaccine was prepared in the same manner as the standard glycerinated product, but was purified by treatment with Freon (113) to remove proteinaceous cellular debris. The product was thus 'purified' and finished as a 'sterile' vaccine. No antibiotics were used in the preparation, and with the addition of tests for sterility, protein content and residual Freon, the remainder of the testing process was the same as for Connaught's regular glycerinated product. The Freon-purified vaccine was also considerably more stable and hence had a longer expiration dating than the standard product.<sup>93</sup>

By 1971 remarkable progress had been made in the global smallpox eradication program, particularly in Latin America. Smallpox was clearly on the run. However, a 'high emergency' situation in Bangladesh in 1972 reminded everyone about the persistent threat of smallpox. Connaught responded with a commitment of 5 million doses of vaccine. As Fenje said to Wilson, 'D.A. [Henderson] is urging us to cut down the time for our testing to the minimum and to shorten as much as possible the administrative process regarding vaccine delivery'.<sup>94</sup> At about the same time as the Bangladesh epidemic, smallpox was imported into Yugoslavia, sparking a serious outbreak of 170 cases and 40 deaths, further reinforcing the importance, particularly for the Yugoslavian-born Fenje, of establishing national smallpox vaccine stockpiles.<sup>95</sup> After considerable debate over the type of vaccine to be used – glycerinated or dried/jet injection or multiple pressure – how much vaccine to prepare and at what price, by 1974 Connaught had prepared a 1 million dose dried smallpox vaccine stockpile for the Canadian government.<sup>96</sup> By early

1979, however, it was clear to Fenje that a new stockpile would be soon needed.<sup>97</sup> At the same time, the WHO proposed that a 25-million-dose stockpile be prepared and held at Connaught for emergency use in Latin America.<sup>98</sup> Thus, in March 1979, and aware of his forthcoming retirement, Fenje quickly pressed ahead with the preparation of 17 Vaccinia pulps for these new stockpiles.<sup>99</sup>

As is well known, the last stand for smallpox took place in Somalia, the final natural case occurring on 26 October 1977. After two years of careful surveillance for additional cases of smallpox in Somalia or elsewhere, none were found. Smallpox, 'the speckled monster', was vanquished. On 26 October 1979, Africa was officially declared free of smallpox, with global eradication formally declared by the WHO on 9 December 1979.<sup>100</sup>

The timing of the official declaration of global smallpox eradication coincided with Fenje's retirement, prompting reflection by his colleagues on his contributions to this unprecedented effort in medical history. As D.A. Henderson's successor at the WHO, Dr Isao Arita, said of Fenje in a letter to Wilson,

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.<sup>101</sup>

Henderson also recalled, '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?)'.<sup>102</sup> Moreover, he felt that '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'.<sup>103</sup>

With smallpox officially eradicated, Connaught began the process of shutting down its smallpox vaccine production facility, the last lots completed in March 1980 for the new Canadian stockpile.<sup>104</sup> However, the large stockpile the WHO had proposed was abandoned due to lack of Canadian government sponsorship. Thus, in April 1980, 15 Vaccinia pulps remained in deep freeze storage, along with other materials such as seed virus and samples.<sup>105</sup> The shutdown of Connaught's smallpox department was scheduled for July 1980 and included plans for the incineration of the remaining pulps and materials; it was expected that any future smallpox vaccine would be made by using cell culture adapted seed virus.<sup>106</sup>

In September 1980, however, Connaught's Medical Director, E.W. Pearson, strongly recommended that Vaccinia pulps should be kept. As he stressed, 'It surely will not be a great problem to keep the seed virus and pulps for some time to come and at least in this way we might have something to fall back on so as to be able to prepare our licensed product'.<sup>107</sup> These Vaccinia pulps were indeed saved and kept in the deep freeze, undisturbed, for the next 21 years. The terrorist attacks of 9/11 prompted their retrieval, testing and careful processing to expedite the preparation of a new Canadian smallpox vaccine stockpile.

At the first Canadian Conference on Counter Terrorism and Public Health, held in Toronto in late October 2003, a special honour was given to Drs Paul Fenje, R.J. Wilson and D.A. Henderson by the Canadian Public Health Association and Aventis Pasteur Limited (now Sanofi Pasteur Limited). R.J. Wilson had retired from Connaught a year after Fenje, but died suddenly in 1989. His son, Ray Wilson, who also worked at Connaught for many years, accepted the honour on behalf of his father. This honour and rare reunion of the Fenje, Wilson and Henderson team, like the new Canadian smallpox vaccine stockpile, would not have occurred if not for the foresight of Pearson to keep the pulps Fenje had made in 1979, and for the confidence Aventis Pasteur had in their quality that was evident from the extensive archival record Fenje had left of his work. Indeed, my role as a professional historian and my familiarity with this archival record was also significant in a practical way, first in establishing the extensive historical context surrounding the preserved Vaccinia pulps that enabled the new smallpox vaccine stockpile to be prepared with confidence, and, secondly, in providing the wealth of primary documentation from which I was able to assemble this story.

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### Notes

- 1 See for example: C.E. Dolman, 'Landmarks and Pioneers in the Control of Diphtheria: The Donald T. Fraser Memorial Lecture, 1973', *Canadian Journal of Public Health*, **64**, 1973, pp. 317–36; Jane Lewis, 'The Prevention of Diphtheria in Canada and Britain, 1914–1945', *Journal of Social History*, **20**, 1986, pp. 163–76; G.L. Geison, 'Pasteur, Roux, and rabies: scientific versus clinical mentalities', *Journal of the History of Medicine*, **45**, 1990, pp. 341–65; Elizabeth Fee and Evelyn M. Hammonds, 'Science, Politics, and the Art of Persuasion: Promoting the New Scientific Medicine in New York City', in David Rosner (ed.), *Hives of Sickness: Public Health and Epidemics in New York City*, New York: Rutgers University Press, 1995, pp. 155–96; Louis Galambos, *Networks of Innovation: Vaccine development at Merck, Sharp & Dohme, and Mulford, 1895–1995*, Cambridge: Cambridge University Press, 1995; M.R. Hilleman, 'International Biological Standardization in Historic and Contemporary Perspective', in F. Brown, E. Griffiths, F. Horaud, G.C. Schild (eds), 'A Celebration of 50 Years of Progress in Biological Standardization and Control at WHO', *Developments in Biological Standardization*, **100**, 1999, pp. 19–30; M.R. Hilleman, 'Vaccines in historic evolution and perspective: a narrative of vaccine discoveries', *Vaccine*, **18**, 2000, pp. 1436–47; M.L. Meldrum, 'The historical feud over polio vaccine: How could a killed vaccine contain a natural disease?', *Western Journal of Medicine*, **171**, 1999, pp. 271–3; Jean Lindenmann, 'Typhus vaccine development from the First to the Second World War', *History and Philosophy of the Life Sciences*, **24**, 2002, pp. 467–85; Powel Kazanjian, 'Changing Interest among Physicians toward Pneumococcal Vaccination throughout the Twentieth Century', *Journal of the History of Medicine*, **59**, 2004, pp. 555–87;

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- 2 R.D. Defries, *First Forty Years, 1914–1955: Connaught Medical Research Laboratories*, University of Toronto, Toronto: University of Toronto Press, 1968; Paul A. Bator and A.J. Rhodes, *Within Reach of Everyone: A History of the University of Toronto School of Hygiene and the Connaught Laboratories, Vol. I, 1927–1955*, Ottawa: Canadian Public Health Association, 1990, and Paul A. Bator, *Within Reach of Everyone: A History of the University of Toronto School of Hygiene and the Connaught Laboratories, Volume II, 1955–1975, With an Update to 1994*, Ottawa: Canadian Public Health Association, 1995; Christopher J. Rutty, 'Robert Davies Defries (1889–1975)', in L.N. Magner (ed.) *Doctors, Nurses and Medical Practitioners: A Bio-Bibliographical Sourcebook*, Westport, CN.: Greenwood Press, 1997, pp. 62–9; Pierrick Malissard, 'Quand les universitaires se font entrepreneurs: les laboratoires Connaught et l'Institut de Microbiologie et d'hygiène de l'Université de Montréal, 1914–1972', Ph.D. Thesis, Department of History, Université du Québec à Montréal, 1999. In addition to Connaught, Malissard's dissertation focuses on the primarily Quebec-oriented, university-based counterpart to Connaught, originally established in 1935 to produce BCG vaccine.
  - 3 A core, though unorganized, archival document, clippings and image collection was retained in the Connaught Library through the 1970s and early 1980s, assembled rather randomly from the donated or found files of former Directors and leading researchers and staff. By 1983 this primary collection had been more formally organized under the leadership of Dr Robert J. Wilson after he retired from a long career, which included serving as Director and Scientific Director of Connaught from 1972 to 1980. Wilson was also a central figure in Connaught's smallpox vaccine story. Historians have been able to access this collection since the early 1980s with minimal restrictions. Also retained, though not as easily accessed, or as well catalogued, is a vast collection of records stored off-site; the main collection, once kept in the Connaught Library is now stored off-site. I first became familiar with this material in the early 1990s while researching my dissertation on the history of polio in Canada. As a historical consultant for Connaught since 1995, I have utilized these archival collections through many heritage projects at the company and for others, as well as for a variety of more academic, research-oriented projects of my own. The present paper is based primarily on the large off-site archival collection and grew out of both types of projects. See Christopher J. Rutty, 'Do Something! Do Anything! Poliomyelitis in Canada, 1927–1962', Ph.D. Thesis, University of Toronto, 1995. For some personal perspective on how I became familiar with Connaught's archival collection, see Christopher J. Rutty, 'The Canadian Polio Experience: A Personal Journey Through the Past', *Ars Medica*, 1, 2005, pp. 60–73.
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