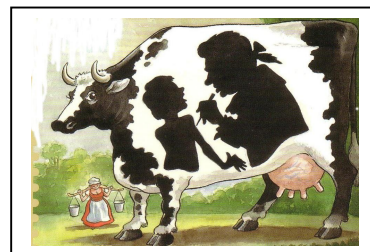


COW BELLS AND COLD CHAINS

THE SPREAD OF SMALLPOX VACCINE AND VACCINATION BEFORE REFRIGERATION



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INTRODUCTION

The histories of transmissible diseases that have afflicted mankind and their containment do not have the happy ending that we can attribute to the history of Smallpox, and this is what makes it unique.

When I first started my career in Pharmacy in the 1950s, the concept of a “Cold Chain” for all perishable medicinal products hadn’t really been thought of.

One exception however was the recognition of the special arrangements required to handle Smallpox Vaccine, as the Commonwealth Serum Laboratories in Australia insisted that to preserve potency, the vaccine had to be stored in the frozen state, at as lower a temperature as possible.¹

Wholesalers despatched the boxed capillary tubes wrapped in layers of newspaper and the parcel was kept apart from other goods in an insulated box in the delivery van.

In those days a dispensary refrigerator was a rarity, and most pharmacies stored this vaccine in the freezer of a neighbouring butcher’s shop or ice cream parlour.

With such specific storage directions for Smallpox Vaccine, I began to wonder how this product was transported around the world in the days before refrigeration, and on voyages through the tropics often lasting over 3 or 4 months.

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With such specific storage directions for the Smallpox Vaccine, I began to wonder how this product was transported around the world in the days before refrigeration and so the idea for this research was germinated.

Smallpox was the first disease to which an artificial immunity was created by deliberate inoculation with the causative organism, obtained from the skin blisters of mild cases, This was known as **Variolation**, a process which originated in Asia in ancient times, and by this deliberate inoculation of smallpox material into a human arm it was hoped that a mild form of smallpox would develop to give immunity in the patient.

Variolation was at best unpleasant, and at worst very dangerous. The strength of the attack was unpredictable and could sometimes be fatal

In ancient China, a lucky day was chosen and crusts from the skin of a smallpox sufferer were blown into the patient's nose through a tube or quill, or in India, children were sometimes wrapped in infected clothing

Variolation was first introduced into Britain by Lady Mary Wortley Montagu, the wife of the British Ambassador to Turkey, who had learned of it in Constantinople and had her son variolated there in 1717. On her return to England she had her daughter variolated in 1721 and so introduced the practice to London society.

Country people in some areas of Europe were well aware that a person who caught the milder disease, cowpox, would not catch smallpox. The medical establishment, however, remained ignorant of this important fact, perhaps because few 18th-century doctors had much contact with cows.

Doctor Edward Jenner was the first to prove scientifically that vaccination with cowpox gave protection from smallpox (the word vaccination derives from the Latin word for cow = Vacca). He also demonstrated that cowpox could be transmitted artificially from one human to another, so vaccination was not dependent on the existence of cowpox in a community.

Jenner first communicated his observations in 1797 to the Royal Society in London, about the use of cowpox materiel (Variolae Vaccinae) taken from a lesion on the hand of the West Country milkmaid Sarah Nelmes, to produce an immune response to the Smallpox Virus in an eight-year-old boy, James Phipps.

In 18th-century England, scarred and pockmarked survivors of the disease were common sights. Advertisements for servants sometimes specified that they must have already had smallpox. It has been estimated that the disease killed 60 million people around the world during the 18th century and in the fifty years following Jenner's first inoculation in 1796, the number of deaths from smallpox in England fell from about 23 000 to 5000 a year.²

THE SPREAD OF VACCINE AND VACCINATION

Although Jenner's publications and ideas were spread relatively quickly, there were some difficulties in exporting the vaccine. Initially, there was a natural desire to obtain material from, or approved by, Jenner himself although vaccines made by other workers were also exported.

Also, if and when indigenous cowpox was found abroad, it could then be compared with the authentic product.

In Naples in the early 1800s, the production of vaccinia on the flank of a cow began and this permitted much larger quantities to be produced.

In some villages it was not uncommon for the cow to be led around from door to door with small aliquots being taken off for vaccination³

TRANSPORTING THE VACCINE

Although Jenner's publications and ideas were spread relatively quickly, there were some difficulties in exporting the vaccine even over short distances or in cool climates.⁴

The commonest methods used in the 19th century included

(1) Drying the vaccine on points.

Lancets made of silver; gold or ivory. Sometimes the liquid lymph on the ivory point was enclosed within a wax ball, and in some Eastern countries, the dried thorns of a bush were used instead of ivory points.

(2) Drying the vaccine and sealing it between small glass plates. A pool of Vaccine was dried on a glass plate and when it was perfectly dry a thin coat of mucilage of Gum Arabic was applied. Alternatively another glass plate was placed over the dried vaccine and the edges sealed with wax

(3) Using lengths of thread to soak up the vaccine, which were then dried.

Initially this was the commonest method, and it was similar to the variolation process using threads or clothing impregnated with material soaked up from smallpox pustules. Again the dried threads were sometimes sealed between two glass plates, or sealed in tubes with wax

(4) Dried crusts or scabs. Edinburgh surgeon James Bryce, discovered in 1809 that the crust or scabs which form at the vaccination site also contain viable vaccine virus.⁵

In 1813 Dr Russell, of Calcutta, sent some dried scabs from pustules of cowpox to Dr D'Arcy Wentworth in Sydney, and he cautioned that these had to be reconstituted with cold water. He also despatched ivory lancets that had been moistened with the vaccine but in his view the desiccated form would better withstand the rigours of transport from India to Australia.⁶

By these methods vaccine was soon distributed throughout Britain and to North America, southern and central Europe and the Mediterranean basin by 1800, and by 1801 to Scandinavia and Russia

Jenner's early attempts to get vaccine to India were foiled by shipwreck. However, Sacco's dried vaccine reached Constantinople by 1800 and Baghdad early in 1802. After being revived in human trials it was then sent in dried form to India.

For longer distances, particularly in warmer climates, a different method was used. Weekly arm-to-arm transfer through volunteers or children maintained the vaccine. This had the advantage that the immune population could be increased at the same time, and in this way vaccination was spread through the British forces in India.⁷

The direct contact of arm-to-arm vaccination, which was the favoured, if not the only method of vaccination through most of the nineteenth century. A group of children (and sometimes adults) would be vaccinated and were to return to the vaccinator usually on the seventh or eighth day, firstly so that the local reaction could be measured and assessed as successful or unsuccessful, and secondly in order that one or more of the children could be chosen to perpetuate the vaccine. A new batch of children would be infected with lymph from the arm of the original child or children. That group would return a week later, and another arm-to-arm process

would take place. Thus, it was intended that the vaccine would be kept in circulation in an exponential way. While the use of stored lymph from calves became more common at the very end of the nineteenth century, most experts in the mid to late nineteenth century thought that the arm-to-arm method was preferable, that this process kept the lymph 'alive' and effective in a population of children.⁸

From the earliest days of the development of vaccination it was clear that the most certain way of assuring that the vaccine was potent was to take material directly from a pustule, hence the importance of Jenner's demonstration that vaccine could be maintained by the arm-to-arm vaccination of children. The most famous exploitation of this procedure for the long-distance carriage of vaccine, was the Balmis-Salvany Expedition, commissioned by King Charles IV of Spain, in 1803-1805 Vaccine was carried by the arm-to-arm vaccination of 20 orphan children from Spain were carried on the ship to provide a succession of susceptible subjects for vaccination to the Spanish colonies in the New World, China and the Philippines. However, more convenient methods were clearly needed⁹

In Great Britain the National Vaccine Establishment took over the responsibility for maintaining serial arm-to-arm transfers in 1808, and distributed several thousand preparations to physicians each year on ivory points or glass slides. Later, capillary tubes filled with glycerolated vaccine were used, but ivory points were still being employed in Great Britain as late as 1898¹⁰

A French researcher, M.Bretonneau of Tours, described a method of using fine glass tubes with a small expansion in the middle to collect and store drops of fluid from a punctured vesicle.

The Vaccinator of the Public Dispensary in Edinburgh, Dr. William Husband, published another method of preserving lymph in capillary tubes in July 1851. He demonstrated the method of filling and sealing fine tubes of glass containing lymph, which had a long shelf life and could be carried in a Doctor's bag without refrigeration.

Husband advocated strongly the keeping of exact records of the source of the vaccine as well as the success or failure of the vaccination.

With most species of virus all methods of transport except by direct transfer from pustule to arm would have been unsuccessful. However, the poxviruses are relatively so resistant to inactivation that these air-dried or wet preparations, maintained without refrigeration, often contained enough viable virus to produce a pustule in the vaccinated person. Nevertheless, failures did occur in the long-distance shipment of vaccine, as in Jenner's attempts to send material to India via the Cape, in several of the shipments from Great Britain to North America and in many shipments from Batavia to Japan. This is why he recommended that calf-to-arm vaccination should continue

In spite of this remarkable record of acceptance, a variety of problems arose. Some of these were due to contamination of the cowpox material, some to shortage of material owing to the absence of infected cows and failure to maintain the virus in human subjects, some to theological and philosophical objections and some to Jenner's insistence that primary vaccination gave a lifelong protection against smallpox.¹¹

SMALLPOX AND VACCINE IN AUSTRALIA

The surgeons of the First Fleet that was sent from England in 1788 to establish the Colony of New South Wales and a new convict settlement, are said to have brought out " variolous matter " with them. Exactly what "variolous" matter means is not clear, but in any case there is no record of their ever having made use of it

In May 1803, the Governor of New South Wales, addressed a letter to the Secretary of State, in London, suggesting that " vaccine matter " should be sent to the colony. In this letter he states, " every search has been made on the teats of our cows (for cow-pox) but nothing of the kind can be found." In response to the Governor's letter, a supply of vaccine lymph, obtained from the Royal Jennerian Society, was despatched in the transport ship *Coromandel*, which arrived in May 1804. A second packet of lymph also arrived on the same vessel, addressed to Assistant Surgeon John Savage, which was " put up in a different way from that sent by the Royal Jennerian Society."

On receipt of the lymph, the principal surgeon, Dr. Thomas Jamison immediately vaccinated three children at the 'Orphan Asylum' and some other persons were vaccinated by Mr. Savage.

Their efforts were successful, for a notice which appeared on 3rd June, 1804, in the *Sydney Gazette* stated that " the cow-pox is now fully established in the Colony," and invited parents to have their children vaccinated.

In July 1804 Governor King wrote, "that vaccination had succeeded so well in New South Wales that most of the children in the Colony have received the inoculation." In New South Wales which was strongly governed from its inception as a penal colony in 1788, production and administration of vaccine was very early the business of government.

In the 1880s, the New South Wales Government received regular despatches of Calf Lymph from Bombay. It also sought and received from the Government in Bombay detailed information and instruction about the methods of obtaining lymph from the calf.¹¹

The colony had a constant though small supply, derived from England until 1881, and since that time from Victoria and New Zealand, both of which colonies had established vaccine stations. No lymph was cultivated in New South Wales, though the necessity for it has been frequently urged, and the disastrous effects of such unprepared-ness, which may be expected should an epidemic occur, had been pointed out time after time.¹²

In the colony of Western Australia, which was founded in 1829, advertisements frequently appeared in the local newspaper "The Inquirer", announcing the arrival of a quantity of vaccine lymph from interstate and the Colonial Surgeon would issue a constant reminder that the head of every family should have his children vaccinated. Ship's captains were also usually acknowledged in these advertisements, as they were a vital part in the links between the western and eastern seaboard settlements.¹³

By the middle of the nineteenth century, the Surgeons Superintendent on board the convict ships were given written instructions as to their duties whilst at sea, which in part read "you are to keep such a succession of vaccinated cases as may enable you to convey fresh virus to the colony and to obtain an acknowledgement from the

medical officer of the Colony, stating whether you have delivered to him any recent virus consequent upon vaccination of individuals during the voyage.”¹⁴

Shortly after the settlement at Sydney Cove had been established The disease was seen on a large scale among the indigenous population and it had wreaked havoc among the unprotected tribes.

Governor Phillip thought it had been brought by the French rather than by his own fleet.

By the 1820s, the most serious problem was the failure of imported smallpox vaccine as several people who had been vaccinated in New South Wales contracted smallpox on their return to Europe.

The possibility of a failure of this type had been realised, earlier. In 1813 Dr Russell, of Calcutta, sent 'Recent dried scabs from perfect pustules' of cowpox to Dr D'arcy Wentworth in Sydney. Russell cautioned that these had to be reconstituted with 'Cold' water. He also despatched ivory lancets that had been moistened with the vaccine but in his view the desiccated form would better withstand the rigours of transport from India to Australia.¹⁵

SOME OTHER EARLY METHODS OF DISTRIBUTING VACCINE

Dr.Sydney Monckton Copeman F.R.S. stated that glycerine had first been used as a preservative for lymph as early as 1850. In 1869 Muller in Berlin showed that Glycerine could be added to lymph without loss of potency, a finding of great practical importance as it extended the supply of lymph.

Vaccines were also developed from horsepox and were widely used in the 19th century, and it was not necessary for horsepox to be passaged through a cow.

In Britain, up until the 1914-18 war, glycerinated calf lymph was the only form of smallpox vaccine used. Due to the wartime shortage of calves, sheep were introduced as vaccinifers by the Lister Institute and eventually in 1946, when the Lister Institute took over the responsibility of vaccine production; a complete change was made from calves to sheep as vaccinifers

In later years vaccines were prepared in fertile eggs and in tissue culture. The development of a freeze-dried vaccine at the Lister Institute for use in tropical areas was a major step forward, and recently the development of a killed vaccine was announced from the same institute (Kaplan, 1962). Against this background of modern technical development the achievements of the early pioneers of smallpox prophylaxis in the eighteenth and nineteenth centuries are even more remarkable when it is remembered that their work was accomplished before the cause of the disease was known.¹⁶

In Australia in 1881, Graeme Mitchell, a veterinarian, first produced calf lymph for smallpox vaccination privately on the site occupied by the present day Commonwealth Serum Laboratories However, strict regulations were then in force to prevent anyone but a qualified medical practitioner giving vaccinations. This was in response to the extravagant claims of the quacks and bogus doctors who flourished in 19th-century Victoria.

The original wooden building and stables for the calves, known initially as the “Calf Lymph Depot” and later as the “Vaccine Depot”, was taken over by the Victorian Government in 1883 and then by the Commonwealth in October 1911¹⁷

In 1881, an epidemic of Smallpox broke out in Sydney and there was a quarantining measure established at the border between the colonies of New South Wales & Victoria. Passengers on the Sydney-Melbourne train would be examined at the border town, and only those with certificates of vaccination and a viable vaccination scar were permitted to cross the State border.

In 1913, Smallpox again appeared in Sydney and the new Commonwealth Government declared all of Sydney a quarantined space with roadblocks established in a circumference of 15 miles (24km) from the City Post Office. Again people were permitted in both directions only if they could display a viable vaccination scar. In later years such a proviso applied to all persons leaving and entering Australia from overseas, who were required to hold a “vaccination passport”.

In 1967, teams of health care workers organised by the World Health Organisation using vaccination, surveillance and containment strategies carried out the first intentional eradication of a biological species.

However there were some technological advances made during the eradication programme that made its success possible, the most important being the development of a freeze-dried vaccine which was more potent and stable than the original vaccine, allowing easier transport and it reduced the cost of bringing large amounts of vaccine to remote areas.

The two other developments dealt with the need for a reliable and efficient technique to introduce the vaccine to the skin that required little training to use. A hydraulic powered jet injector was developed by the US National Communicable Disease Centre that was suitable for use in developed countries as it worked very fast. However it was too expensive for use for house-to-house vaccination in densely populated developing areas. Benjamin Rubin of Wyeth Laboratories found another cheaper solution: He developed the bifurcated needle a needle with a prolonged fork, and a piece of wire suspended between the prongs. The piece of wire held the required amount of vaccine by capillarity and the two prongs would scratch the skin. Therefore the scratch and the delivery of the vaccine could be done in one action.¹⁸

Routine smallpox immunisation in Australia came to an end in the 1970's, but the Commonwealth Serum Laboratories kept it on its inventory right through until the early 1990's when the decision was finally made to discontinue the product. Smallpox was eradicated from the planet in 1979 and this was regarded as one of the great triumphs of modern science. Today Smallpox virus officially resides in the Centres for Disease Control in Atlanta USA and in at a Russian Virology Institute called “Vector”, in Siberia.

Since the scare of the “Anthrax Letters” in America which followed the September 11 2001 disaster in New York the possibility of a genetically engineered super smallpox virus, resistant to vaccines is being examined very seriously.¹⁹

Despite this recognition that smallpox is an agent that could be used in germ warfare. the outlay required to develop a modern production process, along with the clinical trials and Regulatory requirements could not be justified commercially, and the Australian government would rely on an overseas supplier, should vaccination against

smallpox ever become necessary.”²⁰

This paper has visited many areas connected with the Smallpox story, which has fascinated whole nations as well as individual researchers for centuries.

Technological advances that we now take for granted such as refrigerators, air-conditioners and microwave ovens, have not only improved the quality of life even in third world countries, but have also made possible the control and treatment of many of the health threats we have to face.

The histories of transmissible diseases that have afflicted mankind and their containment do not have the happy ending that we can attribute to the history of Smallpox, and this is what makes it unique.

The spread over time and space of the technologies of vaccination, of infected/immune individuals and populations, and of both the vaccinia and the variola viruses, implicates smallpox and vaccination in a modern history of travel and colonisation. The movement of the vaccinia virus in stored vials or cloth, or in the pustules of children's arms traced the global lines of Empire in the Victorian period. These were also the lines of knowledge, as the technique was disseminated with the matter and the disease itself. This is the colonial history of vaccination.²¹

The successful circumnavigation of the globe with vaccine in the era before refrigeration, freeze-dried vaccines and jet aircraft, ultimately rested upon a singular medium - little boys.²²

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FOOT NOTES

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