CHAPTER 6

EARLY EFFORTS AT CONTROL: VARIOLATION, VACCINATION, AND ISOLATION AND QUARANTINE

Contents

INTRODUCTION

Besides killing many of those who were infected, an attack of smallpox left most of its survivors pockmarked, and it was realized in ancient times that pockmarked persons never caught smallpox again. By accident, it was found that persons who were infected with smallpox via a scratch on the skin suffered a much less severe form of the disease.

Long ago, in places in which smallpox had become endemic, a connection must have been made between these observations, and attempts to ameliorate the severity of smallpox were initiated by administering the pustular fluid or the dried scabs to persons who had not had smallpox. The disease which followed such artificial infection was like smallpox, but usually much milder. In some such way, the practice arose of inoculation with smallpox pus or scabs—or "variolation" as it was eventually called, to distinguish it from vaccination. It may have developed independently in China and India, because different routes of inoculation, nasal and cutaneous respectively, were used in these countries. It was said to have been introduced into Egypt by the Mamelukes in the 13th century, and was known in North and western Africa, at least from the late 17th century. It is impossible to know whether it was indigenous in Africa or spread to that

Clinical Differences between Smallpox after Variolation by the Cutaneous Route and "Natural" Smallpox

Variolation would never have been adopted so widely if it had not caused a less severe disease, and been less likely to kill or cause permanent pockmarks, than naturally acquired smallpox. The difference in mortality varied, but commonly the case-fatality rate was 0.5–2% after variolation, compared with 20–30% after natural smallpox. The symptomatology was also different. A primary lesion appeared at the inoculation site on about the 3rd day (see Chapter 3, Fig. 3.1) and commonly there were satellite pustules around the site of inoculation (see Plate 6.2), but usually a much less severe generalized rash occurred than in ordinary-type smallpox. The reasons for the difference in severity are not known; possible explanations are given in Chapter 3. In any event the virus was not attenuated and one of the major disadvantages of variolation was that it could spread to susceptible contacts to produce severe natural smallpox.

continent along with smallpox itself, possibly with Arab traders who had themselves learned of the practice in India.

Early in the 18th century, variolation spread through the Balkans into central Europe and from Turkey to Great Britain and subsequently to other countries of Europe. It became popular and widely used in some countries, especially in Great Britain and its colonies in America. Then, at the end of the 18th century, Edward Jenner showed by experiment that inoculation with cowpox virus would protect people against smallpox, with very much less constitutional disturbance and danger, to themselves and others, than was the case with variolation. The new procedure rapidly became popular and was adopted all over the world, although in some countries variolation continued to be practised as well for many years.

This chapter traces the discovery, spread and popularization of variolation and subsequently of vaccination, and then outlines the way in which, in parallel with preventive inoculation, concepts of contagion led to the notions of isolation and quarantine. Table 6.1 presents a summary of the important historical events in these fields, from the 10th to the 19th century. Development of the vaccine during the first half of the 20th century is described in Chapter 7 and its use to eliminate smallpox from most of the industrialized countries during that period is outlined in Chapter 8. Chapter 11 describes later developments in vaccine production and vaccination procedures that occurred during the Intensified Smallpox Eradication Programme.

VARIOLATION

Called smallpox inoculation, insertion, engrafting, or transplantation by 18th century authors—terms derived from the horticultural procedures for inserting a bud into a plant—the practice of cutaneous inoculation of material from smallpox pustules later came to be called "variolation", to distinguish it from the practice of vaccination with material from cowpox lesions, introduced in 1798 by Edward Jenner (Plate 6.4).

Variolation and Vaccination Performed with Different Viruses

It is important to emphasize that different species of *Orthopoxvirus* were used for variolation and for vaccination. The active agent in variolation was variola virus, the agent that caused smallpox in man, and after a successful cutaneous inoculation there was always a severe local lesion, usually with many satellite pustules (Plates 6.1–6.3), and a generalized rash customarily occurred that was sometimes quite extensive. Severe constitutional symptoms were common and sometimes subjects died of smallpox produced by variolation. Inoculation of variola virus by insufflation (the Chinese method), if successful, also produced a generalized rash and usually more severe symptoms than those produced by cutaneous variolation. Unlike the viruses later used for most other live virus vaccines, the agents used for vaccination

Table 6.1. Important events in the history of smallpox control, from ancient times to 1900

Variolation	Vaccination	Isolation and quarantine
10th century		
Variolation first reported in China, by insufflation, as a secret rite. Probably also practised in India at this time, by cutaneous inoculation.		Hospitals for smallpox established in Japan (*Ishinho*, 982).
13th century		
Variolation by cutaneous route introduced into Egypt by Mamelukes.		
17th century		
Variolation more widely used in China. K'ang Hsi (1661–1722) variolated his soldiers and his children.		Quarantine introduced to control entry of smallpox into North American ports (Boston, New York, Philadelphia; 1650s). Mandatory isolation of smallpox cases at home (Virginia, 1667).
18th century		
Papers on variolation published by Royal Society of London (Chinese method, 1700; Turkish method: Timoni, 1714; Pylarini, 1716). Cotton Mather told of variolation by his African slaves (Boston, 1706). Variolation by cutaneous route carried out in Great Britain (Sloane, 1721), Bohemia (Reiman, 1721) and Boston, USA (Boylston, 1721). Variolation popularized in England by the Suttons (1726). Dimsdale variolates Catherine the Great and variolation accepted in Russia (1768). Louis XV dies of smallpox and variolation accepted in France (1774). Washington orders variolation of the Continental army (1777).	Publication of Jenner's *Inquiry* (1798).	London Small-Pox and Inoculation Hospital established (1746). Eradication of smallpox by systematic variolation of population and isolation of cases suggested by Haygarth (1793) and Carl (1799).
19th century		
Variolation banned in Russia (1805), Prussia (1835), Great Britain (1840) and British India (1870), but still widely practised in Afghanistan, China and many parts of Africa.	*Inquiry* translated into several European languages (1800–1802). Vaccination adopted in most European countries and in the USA (1800–1803). Vaccine sent successfully to Bombay (de Carro, 1802) and to South and Central America, the Philippines and Macao (Balmis-Salvany Expedition, 1803–1806). Primary vaccination of infants made compulsory in Bavaria (1807), Denmark (1810), Norway (1811), Bohemia and Russia (1812), Sweden (1816), Hanover (1821) and Great Britain (1853). Revaccination introduced into Württemberg (1829). Vaccination compulsory in Prussian army (1833). Vaccine produced in calves (Italy, 1805, 1810). Vaccine passaged in calves for production (Negri, 1840). Production in calves adopted in France (1864), Belgium (1865), Great Britain (1881) and Germany (1884). Use of glycerol as diluent introduced in Italy (Negri, 1840s). Glycerolated vaccine popularized by Copeman (1892). Jenner's arm-to-arm vaccination banned in Great Britain (1898).	Control of smallpox by isolation of cases and quarantine of contacts ("Leicester method", 1870); reinforced by vaccination of contacts (Millard, 1914).

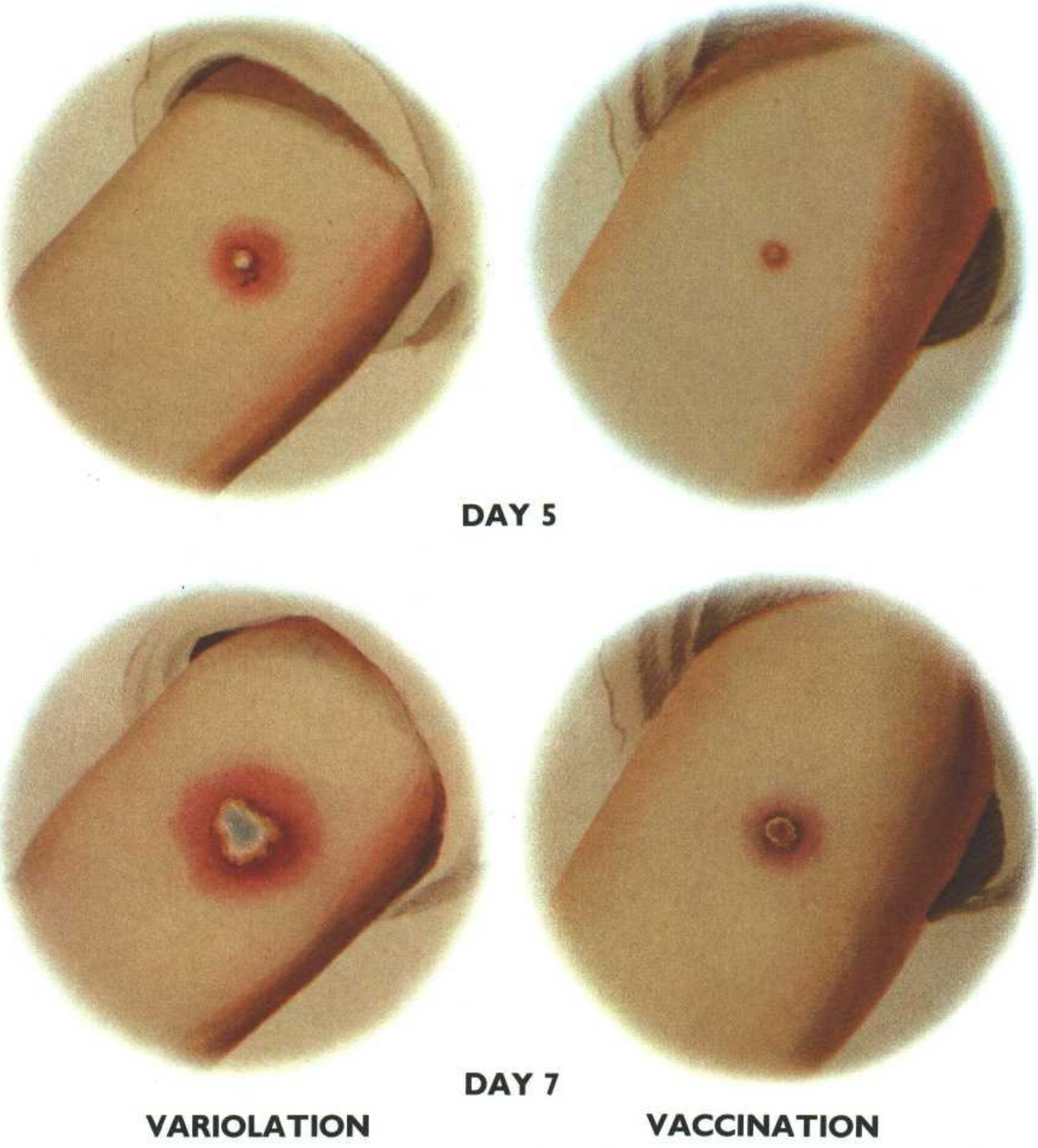

Plate 6.1. Engravings by George Kirtland of coloured drawings made in 1801 by Captain C. Gold, showing the appearance of the local lesions at various times after variolation and vaccination. They were published by Kirtland in 1806 and independently reproduced from the original drawings in the Jenner Centenary Number of the *British medical journal*, published on 23 May 1896. Variolation and vaccination are represented on the 5th and 7th days after inoculation.

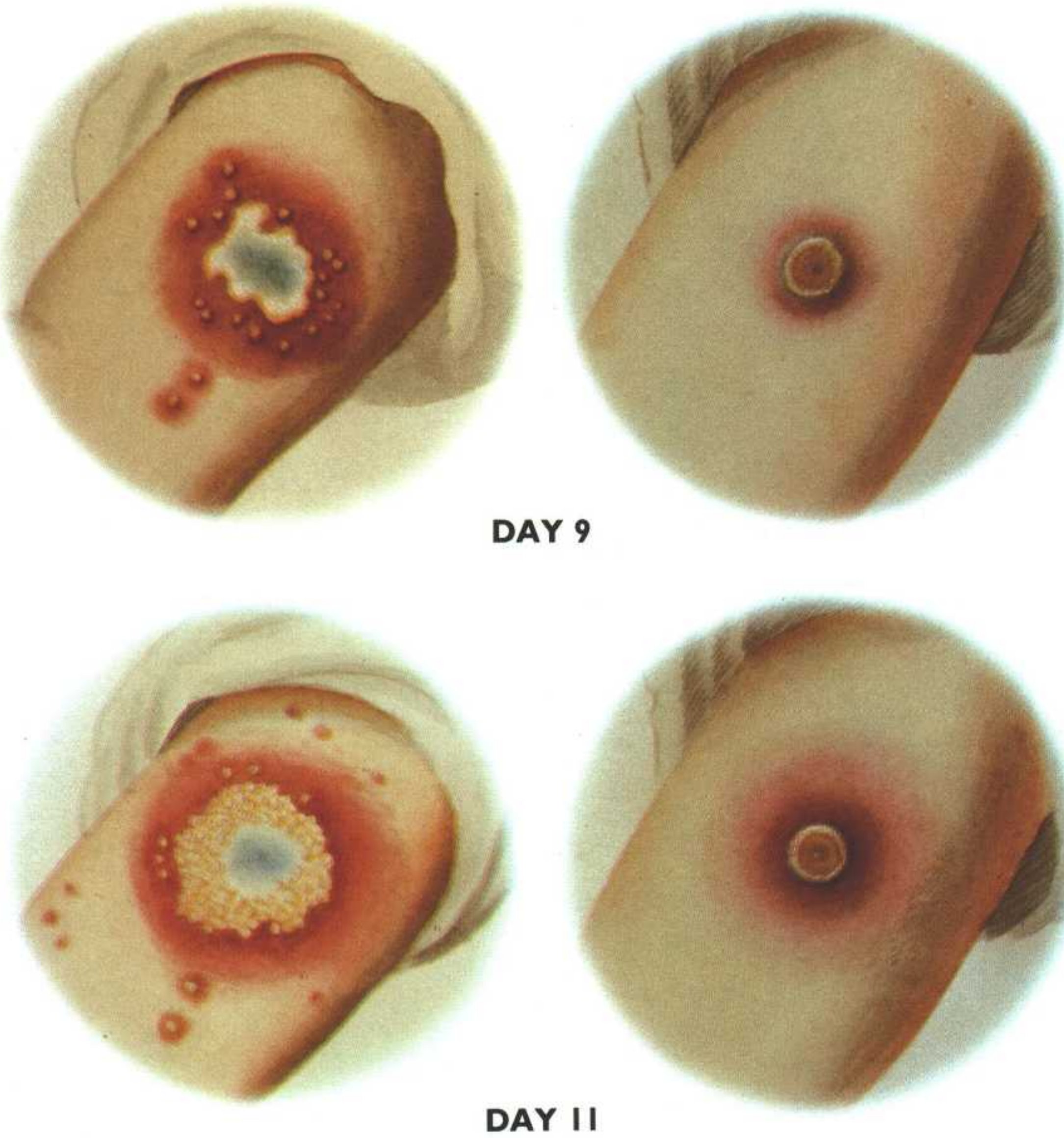

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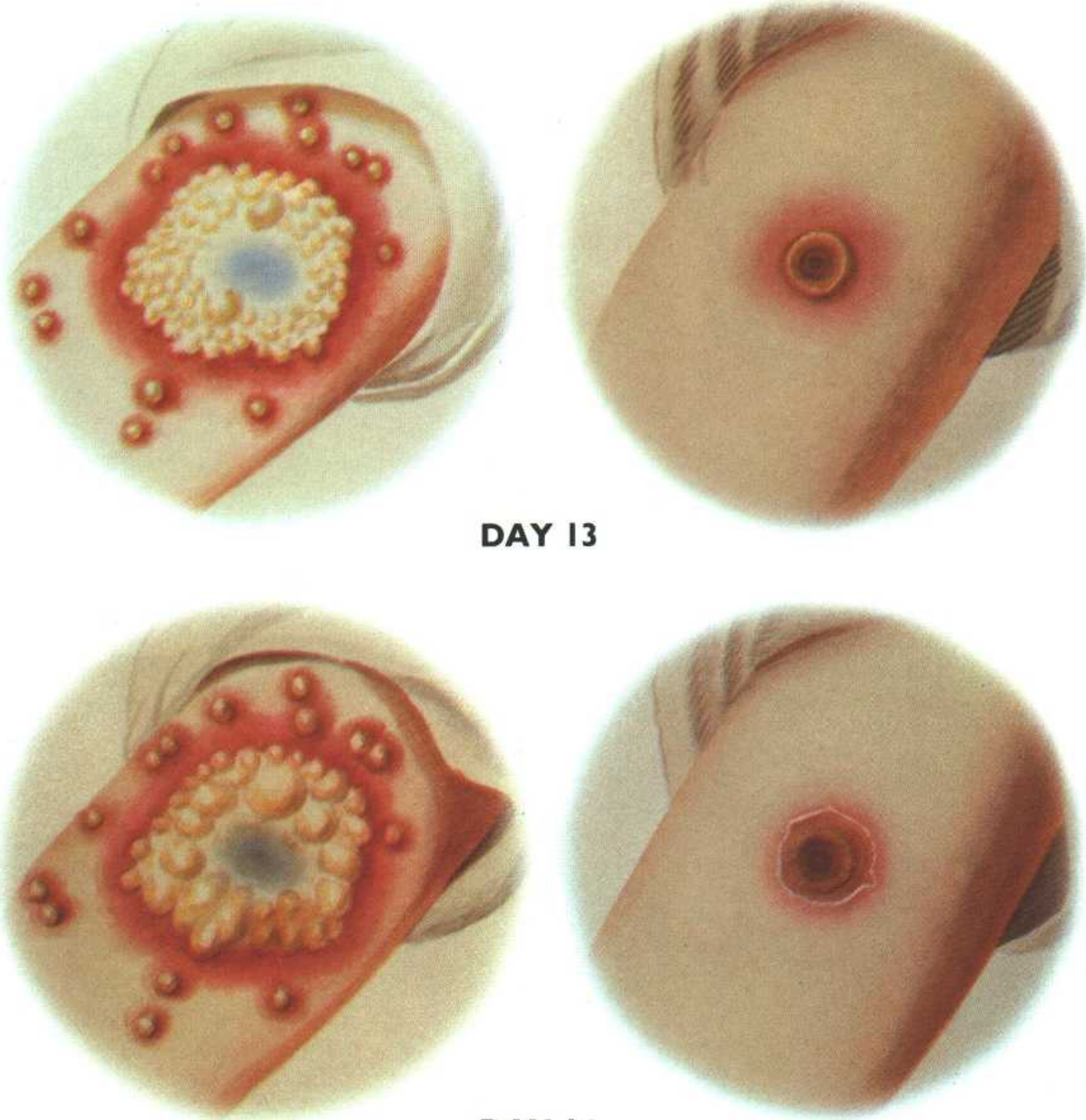
Plate 6.2. The Gold-Kirtland drawings. Variolation and vaccination on the 9th and 11th days after inoculation.



DAY 13

DAY 14

VARIOLATION

VACCINATION

Plate 6.3. The Gold-Kirtland drawings. Variolation and vaccination on the 13th and 14th days after inoculation.

Plate 6.4. Edward Jenner. (1749-1823). Pastel portrait by J. R. Smith in 1800.

The Art of Variolation in China

"... the art was first taught by a nun in the reign of Jen Tsung (A.D. 1023–63). That reign was signalised by a famous premier, Wang Tan, a great statesman and scholar. Small-pox had deprived him of all his children, and when in old age a son was born to him he was most solicitous to secure for that child a safe attack of the fell disorder ... An officer at the capital, a native of Szechwan, hearing of the circumstances, obtained an introduction to the minister and gave him the following information. A young woman of Kiangsu vowed to quit the world, and, rejecting marriage, devoted herself to the worship of Buddha, but refused submission to the tonsure, preferring to retain her hair. She wandered to Omei Mountain (sacred to Sakyamuni, contiguous to Thibet), and on its summit lived in a reed hut. The women of all that region became her disciples, fasting, reciting prayers and doing good. Recently she told her followers that she had been inspired to impart instruction in implanting smallpox, which consisted in selecting scabs from cases that had had but few pustules, and these pointed, round, red and glossy, full of greenish-yellow pus that became thick. The scabs to be used when a month old, or in hot weather those that had fallen only 15 or 20 days might be used, while winter ones should be 40 or 50 days old before using, which may be in spring or autumn. Take 8 grains of the desiccated scabs and 2 grains of *Uvularia grandiflora*; pound the two together in a clean earthen mortar. Select lucky and eschew unlucky days for implanting. Employ for the operation a silver tube curved at the point; blow the prepared matter into the right nostril in the case of a boy, and into the left in girls; six days after there is slight fever, which on the following day increases greatly; in two or three days more an eruption appears, charged with matter, and then scabs. Not one in 10, not one in 100, that does not recover. All the inhabitants of the region adjacent to Omei Mountain adopted the practice, praying her to perform the operation. On hearing this the minister sent for the venerable recluse, who came to the capital and operated successfully ... She returned to the sacred mountain, and some years later informed her followers that she was not uterine born, but was an incarnation of the Goddess of Mercy, and had come to preserve the lives of children by implanting small-pox, 'which,' said she, 'I have taught you, that you should impart the art to others.' On hearing this announcement the women all worshipped her, lauding her righteousness, asking by what title they should invoke her. She answered, 'As Your Ladyship the Celestial Mother,' adding 'whenever anyone shall offer incense and prayers to me, invoking my intervention, I will from heaven manifest myself by turning malignant into benignant cases'; whereon she was transformed, that is, she died. Every official temple has a shrine to this 'Goddess of Smallpox' and many cities have temples for her exclusive worship. Evidently inoculation had been taught at Omei Mountain by some Thibetan monk, who had acquired his art in India, where it appears to have been known in high antiquity." (Macgowan, 1884.)

against smallpox were not attenuated strains of the virus that caused smallpox (variola virus), but a totally different species of *Orthopoxvirus*, initially cowpox virus and subsequently vaccinia virus. Both these viruses produced a localized lesion at the site of cutaneous inoculation, without satellite or generalized lesions except in very rare cases, and they were only very rarely transmissible to other persons. Neither cowpox nor vaccinia virus can be "transformed" into variola virus, nor is the reverse possible (see Chapter 2); both provided a high degree of protection against smallpox, for at least several years.

Variolation in China

The early practice of variolation is better documented in Chinese literature (Needham, 1980) than in Indian. It appears to have begun as a secret procedure about AD 1000, and did not become public knowledge until about AD 1500, when writings about it appeared in Chinese medical books. The mode of inoculation was by the intranasal insufflation of powdered scab material (see Plate 6.14B). Descriptions of the method of preparing the inoculum show a realization that its activity persisted for longer in winter than in summer

Method of Variolation in India

"The operation of inoculation called by the natives *tikah* has been known in the kingdom of Bengall as near as I can learn, about 150 years . . . Their method of performing this operation is by taking a little pus (when the small-pox are come to maturity and are of a good kind) and dipping these in the point of a pretty large sharp needle. Therewith [they] make severall punctures in the hollow under the deltoid muscle and sometimes in the forehead, after which they cover the part with a little paste made of boiled rice." (Coult, 1731.)

and that it was sensitive to sunlight and excessive heat. Fresh scab material was supposed to be stored "on the person" (i.e., at about 37 °C) for up to a month, a prescription that ensured that it contained little active virus, but consisted in large part of inactivated virus. Intranasal insufflation was still employed as a method of variolation in some parts of China in the 20th century (Tao, 1935). Cutaneous inoculation with variola virus appears not to have been practised there until after vaccination by the same route had been introduced in 1805 (Jiang Yutu, personal communication, 1982). Surprisingly, the Japanese were ignorant of variolation until about the mid-18th century, when the practice was introduced from China.

Variolation in India and South-western Asia

Hopkins (1983a) suggests that variolation had been practised in India for centuries, an opinion with which we agree, although there is no documented evidence of its use before Europeans settled there in the 16th century. From then onwards there are several references to inoculation against smallpox, usually by the cutaneous route, in the writings of European visitors. Variolation was made illegal in British India in 1870, but it continued to be practised on a reduced scale, particularly in the princely states, until recent times. It was common in Afghanistan and parts of Pakistan up to the 1970s, occasionally accompanied by a high case-fatality rate (see Chapter 14).

From India the practice spread to various countries in south-western Asia and thence into central Europe via the Balkans, and probably with Arab slave traders to eastern and western Africa. However, nowhere in Asia was variolation used as a systematic large-scale effort to prevent smallpox, in the way it was developed by some of its practitioners in Great Britain during the latter part of the 18th century.

Detailed European knowledge of variolation came via two routes: through the Balkans to central Europe, where it was extensively practised in Slovakia very early in the 18th century (Dubay, 1972), and from the Turks in Constantinople, where it is said to have been introduced during the 17th century, probably from India. The Ottoman Empire was then a powerful independent state, the nearest place to Europe in which the "exotic practices" of the Orient could be seen at close hand, and a succession of descriptions of the procedure of inoculation were made by European visitors to Turkey.

Introduction of Variolation into Europe

In contrast to the paucity of published information on variolation elsewhere, there is a large literature on its introduction and spread in Europe (Miller, 1957) and North America. Variolation was important in Europe not only because it was practised on a scale that far exceeded that attained elsewhere, and probably influenced the incidence of smallpox in some European countries (Razzell, 1977b), but also because it set the stage for Jenner's discovery of vaccination and its rapid acceptance. Of all the European countries, Great Britain was the most important, as far as variolation was concerned, and the Royal Society of London played a critical role as the focus for reports on the practice elsewhere in the world.

There were apparently folk practices in several parts of Europe in the latter part of the 17th century of "buying the smallpox", which involved sending children to homes in which a patient was recovering from smallpox to buy

Plate 6.5. Lady Mary Wortley Montagu (1689–1742). Suffered from smallpox in 1715 and was left severely pockmarked. Learned of variolation in Constantinople. Her daughter was the first person to be professionally inoculated in Great Britain, in 1721.

some crusts for a penny or two. Also, children were sometimes deliberately exposed to mild cases, or "bedded" with other children who had mild smallpox, so that they might get the disease in favourable circumstances (Miller, 1957).

But, as Samuel Johnson remarked, during the 18th century there was a great passion for innovation, and for innovation from lands foreign to European traditions and knowledge. Thus in the year 1700 two independent reports were made to the Royal Society of London describing the Chinese method of variolation by intranasal insufflation. Then in 1714 and 1716 accounts of the Turkish method of cutaneous inoculation were independently communicated to the Royal Society by the physicians Emanuele Timoni and Jacob Pylarini. However, British doctors were too conservative to follow up these suggestions immediately, in spite of the severity of smallpox at that time.

Lady Mary Wortley Montagu (Plate 6.5) is widely credited with having introduced variolation into Great Britain in 1721, as the funeral monument erected in 1789 in Lichfield Cathedral, 27 years after her death in 1762, attests:

"Sacred to the memory of the right honourable Lady Mary Wortley Montagu, who happily introduced, from Turkey, into this country, the salutary art of inoculating the small pox. Convinced of its efficacy, she first tried it with success on her own children, and then recommended the practice of it to her fellow-citizens. Thus, by her advice, we have softened the virulence, and escaped the danger of this malignant disease."

Miller (1981) suggests that this is too simple an explanation, and argues that the introduction of variolation into Western medicine is a classic example of how innovation in medical practice occurs. The process includes the urgent need for a method of prevention or cure, a promising solution, a strongly supported programme of experimentation and study and prominent examples of the effectiveness of the new procedure if it is to gain acceptance. With inoculation against smallpox, the first component was obvious and the second provided by the succession of reports and discussions at the Royal Society of London on inoculation as practised in China and Turkey. The major force in study and experimentation was Sir Hans Sloane, who was the king's physician and President of the Royal Society. Through his influence, when the time was ripe, royal sanction was given to experiments on prisoners, and then prominent examples of its use were provided when in April 1722 two royal princesses, Amelia and Caroline, were inoculated, under Sloane's supervision. By the end of the century, Woodville (1796), in his comprehensive history of variolation, extolled Lady Mary's virtues and concluded: "It is therefore highly probable, had it not been for the uncommon fortitude of Lady Mary Wortley Montague . . . that the era of the commencement of inoculation in this country would have been much later than here stated." Miller attributes the credit given to Lady Mary Wortley Montagu to her vivacity and prominence in British society, her considerable skill with the pen, the common knowledge that her daughter was the first person in Great Britain to be inoculated, and the advertisement of her activities, especially by Voltaire.

In the same year as this highly publicized operation, Dr Johann Adam Reiman carried out smallpox inoculations in Bohemia, following earlier articles (see, for example, Reiman, 1721) discussing the rationale of the practice. The 250th anniversary of Reiman's performance of the first variolation in continental Europe was celebrated by a scientific conference in Prešov, Czechoslovakia, in 1972 (Dubay, 1972). Clearly, smallpox was then so severe in Europe, and contacts with the East were sufficiently numerous, that the time was ripe for the introduction of the only palliative measure known.

The practice spread in Great Britain, although not without opposition, which was based partly on theological grounds and partly on its association with some mortality and with the spread of smallpox to uninoculated contacts. But it was clear from early statistical studies by Jurin (1722) that there was much less of a risk of dying from inoculated smallpox than from naturally acquired smallpox. James Jurin, who was then Secretary of the Royal Society, requested information from inoculators about details of all their inoculations, including a complete description of any fatal cases. The response was excellent, and the Royal Society files contain numerous letters from inoculators and from laymen interested in the practice (Miller, 1981). Jurin produced a series of annual reports between 1723 and 1727 which demonstrated that variolation conferred immunity, since by 1727 there would have been ample opportunity for inoculated subjects to have acquired the natural infection. The death rate for natural smallpox remained constant, at 1 death in every 6 cases; the death rate for inoculated smallpox varied from 1 in 48 to 1 in 60 cases.

Thus, beginning in the 1720s, variolation became an acceptable medical practice in Great Britain, for a combination of reasons that did not operate at the time in other countries of Europe. Opposition was particularly strong in France (Miller, 1957), until it was overcome by the mathematician and geographer, Charles de La Condamine, who began a campaign in 1754 by suggesting that nearly a million deaths could have been averted in France if the country had followed the British precedent in 1722.

The further history of variolation in Europe, especially in France and Great Britain, is developed at length in books by Miller (1957) and Razzell (1977b). The practice having once been accepted by the medical profession of the day, the practitioners of inoculation developed elaborate and expensive regimens to "prepare" children for inoculation and treat them during the ensuing illness, and the incision for inoculation itself became much deeper than previously. Its popularity waxed and waned, depending on a variety of factors: the severity of smallpox at the time, the occurrence of cases and especially deaths among members of Europe's royal families, and encouragement from across the Atlantic. In 1746 the London Small-Pox and Inoculation Hospital was established, and together with the Foundling Hospital it offered variolation free. Further advances occurred in Great Britain in the

"Preparation" for Variolation

In contrast to the way variolation was performed in Turkey, members of the medical profession in Europe made a deep incision, and, influenced by a belief in the humoral pathology of smallpox, prescribed an elaborate procedure of preparation before carrying out the operation. This was designed to "weaken" constitutions that were too "high", a condition thought to occur in robust and active individuals and accentuated by meat-eating. Preparation therefore took the form of purging, bleeding and restriction to a light diet, which were the measures then used by the medical profession for the treatment of natural smallpox. For example, the regimen was said to include emetics, purgatives and sometimes bleeding, and an abstention from animal food and strong liquors. The period of preparation was lengthened, and for Edward Jenner, when he was variolated as a boy in 1756, the preparation lasted 6 weeks. "He was bled, to ascertain whether his blood was fine; was purged repeatedly till he became emaciated and feeble; was kept on a very low diet, small in quantity, and dosed with a diet-drink to sweeten the blood." Subsequently the procedure was simplified, but not greatly shortened until the late 1760s, when the Suttons' advocacy of a short preparation and a shallow incision popularized variolation in Great Britain. (Based on Razzell, 1977b.)

1760s, when Robert Sutton perfected a much simpler technique of inoculation and, with his six sons, practised it on a large scale. The Suttonian method was in many ways a return to the practice in Constantinople, where the British had learned of variolation: a short period of preparation, or none at all in the face of an epidemic of smallpox, a shallow incision, fresh pustule fluid and no dressing. However, Thomas Dimsdale (1781) criticized the Suttons for allowing their patients to move freely in the community, a practice which produced many cases of smallpox among uninoculated contacts.

The simplified Suttonian method commended itself to physicians elsewhere in Europe, but not before an unprecedented number of royal personages had contracted smallpox, with devastating political effects when one death followed another (Hopkins, 1983a). Other notable events included the inoculation of the Tsarina of Russia, Catherine II, in 1768, by Dimsdale and, eventually, the acceptance of variolation by the French, which was precipitated by the quite unexpected death of Louis XV from smallpox on 19 May 1774.

In Great Britain, variolation by the Suttonian method was practised on a wide scale (Razzell, 1977b), but tended to be neglected in the large towns and cities, in which the risk of dying of smallpox actually increased towards the end of the 18th century.

As well as advocating the Suttonian method, Dimsdale (1767, 1781) recommended measures to prevent spread from inoculated subjects, including "general inoculation" of all the inhabitants of a village at one time, with isolation of those not well enough to be inoculated, since "more lives are now lost in London than before inoculation commenced and the community at large sustains a greater loss". Eventually, in 1793, John Haygarth (Plate 6.6) published "a sketch of a plan to exterminate the casual small-pox from Great Britain" (Haygarth, 1785, 1793; Downie, 1965b) which included "systematic inoculation throughout the country, isolation of patients, decontamination of potentially contaminated fomites, supervised inspectors responsible for specific districts, rewards for observance of rules for isolation by poor persons, fines for transgression of those rules, inspection of vessels at ports, and prayers every Sunday" (Hopkins, 1983a). Carl (1799), then Director of the Inoculation Institute in Brno (Bohemia), made a similar proposal.

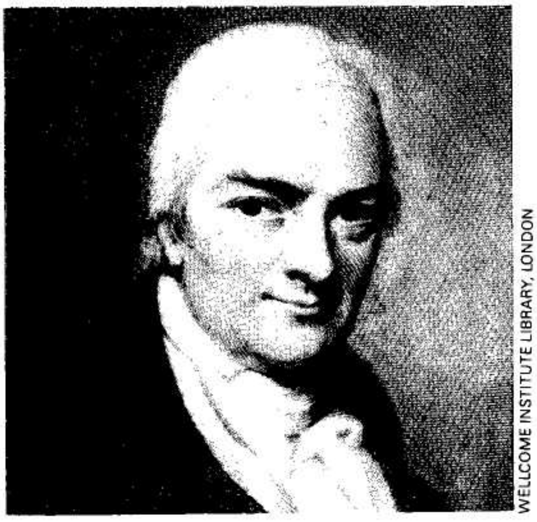

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Plate 6.6. John Haygarth (1740–1827). Published excellent disease statistics for the city of Chester and developed a plan for the extermination of smallpox from Great Britain by general variolation and the isolation of cases.

The way was prepared for Edward Jenner, who had himself been inoculated as a boy and had practised variolation as a physician, to substitute cowpox virus for variola virus and thus do away with variolation—a development that would ultimately vanquish smallpox forever.

Introduction of Variolation into the Americas

Roman Catholic missionaries from Portugal introduced variolation into Brazil in 1728, but it was not much used there. Spain had been very slow to accept variolation, and it was not introduced into the colonies of New Spain until the latter part of the 18th century: Chile in 1765, Venezuela in 1769, Argentina in 1777, Peru in 1778, Mexico in 1779 and Guatemala in 1780.

The situation was very different in the British colonies in North America. Stimulated by the occurrence of a severe epidemic of smallpox in Boston in 1721, the Reverend Cotton Mather (Plate 6.7) persuaded a local physician, Dr Zabdiel Boylston, to try variolation as a method of controlling the disease (Blake, 1959). Mather had first learned of the practice from his African slaves in 1706 and had subsequently read the articles

Table 6.2. The use of variolation for the control of natural smallpox in Boston[a,b]

Year	Population	Had smallpox before	Presumed susceptible	Natural smallpox: Number of cases	Natural smallpox: Case-fatality rate (%)	Inoculation smallpox: Number of cases	Inoculation smallpox: Case-fatality rate (%)	Percentage of smallpox cases due to variolation	Left town	Escaped disease
1721	11 000	..	..	5 759	14.6	287	2.1	2	..	..
1730	13 000	..	..	3 600	13.9	400	3.0	10	..	..
1752	15 684	5 998	9 686	5 545	9.7	2 124	1.4	28	1 843	174
1764	15 700	ca. 8 370	ca. 7 330	699	17.7	4 977	0.9	87	1 537	519[c]
1776	..	..	..	304	9.5	4 988	0.6	90	..	..
1778	..	..	..	122	32.8	2 121	0.9	95	..	..
1792	19 300	ca. 10 300	ca. 9 000	232	29.8	9 152[d]	2.0	97	262	221

[a] Based on Blake (1953).
[b] .. = data not recorded.
[c] Most of these were out of town during the epidemic.
[d] Including 1038 non-residents inoculated in Boston.

by Timoni and Pylarini in the Philosophical Transactions of the Royal Society of London. Variolation at first provoked a violent controversy, but the results of its limited use in the Boston epidemic—6 deaths among 244 inoculated persons (2.5%), compared with 844 deaths among 5980 people who had contracted "natural" smallpox (14.1%)—led to its wider adoption in the colonies, especially in Philadelphia. Nevertheless, there was continued concern about the risk of inoculated persons spreading smallpox; this made the citizens of the colony receptive to Jenner's proposal to use cowpox vaccine, which did not carry this danger. However, even before the era of vaccination, Boston and other towns in Massachusetts achieved a measure of control of smallpox (Table 6.2) by combining widespread variolation under careful supervision, including inoculation of the poor, with strict policies of quarantine and isolation.

So great was the disruption of his military plans by smallpox that George Washington, after considerable hesitation, ordered the compulsory variolation of new recruits to the Continental army early in 1777.

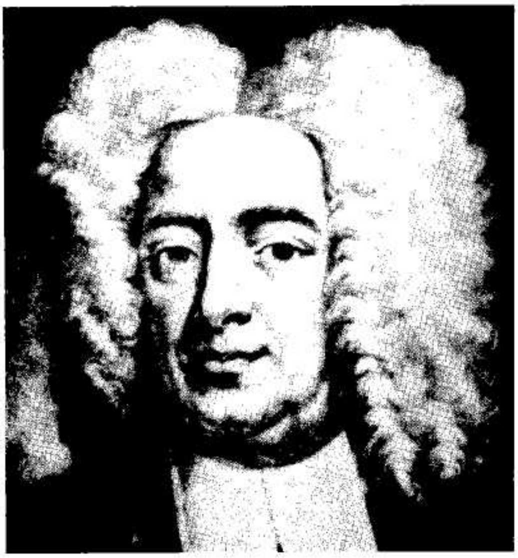

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Plate 6.7. Reverend Cotton Mather (1663–1728). Had learned about variolation from his African slaves in 1706 and arranged for Dr Zabdiel Boylston to carry out the first variolations in North America in 1721. Portrait by Peter Pelham.

Variolation in Africa

The earliest reference to the existence of variolation in Africa was the discussion between Cotton Mather and his slaves in 1706, which indicated that cutaneous inoculation was a common practice before that time in some parts of western Africa. Later references from European travellers, traders and explorers, summarized by Herbert (1975), show that variolation was widespread in Africa throughout the 19th century. Smallpox was introduced into central Africa late in its history, probably during the early years of the 19th century (see Chapter 5); variolation appears to have been introduced soon afterwards, probably via Arab-led caravans. It was rarely practised on a scale that had an appreciable influence on the overall incidence of smallpox. In some places variolation of all those who had not yet had the disease was carried out when the first cases of smallpox occurred in a village, using material from these cases. Elsewhere—in Ethiopia, for example—the head of a house would obtain material when there were reports of cases in the vicinity and variolate the members of his extended family.

The site of inoculation varied from place to place—for example: the forehead, the arm, the leg and the "anatomist's snuff-box" (on the dorsum of the hand at the base of the metacarpal of the thumb) in different parts of Africa; the forearm and the anatomist's snuff-box in Afghanistan and Persia. At the turn of the century the French authorities were concerned about the growing popularity of variolation (in preference to vaccination) in Algeria, and it was suggested that the practice "ought to be sternly suppressed in all French colonies" (*Lancet*, 1901). However, variolation continued to be practised up to modern times and was encountered during the eradication programmes in western, eastern and southern Africa (see Chapters 17, 19, 20 and 21).

THE DISCOVERY OF VACCINATION

The second half of the 18th century saw smallpox at its most destructive stage in Europe, and by this time the practice of variolation was well established as a preventive measure, although it was recognized that occasionally inoculated subjects died and perhaps more often they conveyed severe disease ("natural" smallpox) to their susceptible contacts. There was also the observation among country folk in several parts of Europe that milkmaids were rarely pockmarked, and the local belief was that they were protected because of an infection acquired from cows. As Jenner testified to the House of Commons in 1802, the "vague opinion" of the protective value of cowpox had arisen quite recently among farmers and was probably connected with the observation of the insusceptibility of milkmaids to variolation, practised much more widely during the late 18th century because of Sutton's improved method.

A few educated men took up this story and when they found a case of cowpox they inoculated material from it into their children. After Edward Jenner had demonstrated by challenge inoculation with variola virus that subjects inoculated previously with cowpox were indeed resistant to smallpox, claims for priority were made by several of these people: Fewster in 1765, Bose in 1769, Jesty in 1774, Nash in 1781 and Platt and Jensen in 1791 (Dixon, 1962; Baxby, 1981). However, without denying that each of these claimants may have made an inoculation with cowpox to protect against smallpox, the principal credit must go to Edward Jenner, who demonstrated its protective effect by subsequent challenge inoculation with smallpox virus, published his results (Jenner, 1798), and for the rest of his life actively promoted the cause of vaccine inoculation (Baron, 1838; LeFanu, 1951). Subsequently, to honour Jenner, Pasteur (1881) generalized the use of the term "vaccination" to include preventive inoculation with all kinds of infectious agents.

Jenner's Observations and Experiments

We cannot do better than Jenner himself in summarizing how he came to carry out the famous experiments on James Phipps on 14 May 1796 (Plate 6.8; Jenner, 1801).

"My inquiry into the nature of the Cow Pox commenced upwards of twenty-five years ago. My attention to this singular disease was first excited by observing, that among those whom in the country I was frequently called upon to inoculate, many resisted every effort to give them the Small Pox. These patients I found had undergone a disease they called the Cow Pox, contracted by milking Cows affected with a peculiar eruption on their teats. On inquiry, it appeared that it had been known among the dairies from time immemorial, and that a vague opinion prevailed that it was a preventive of the Small Pox. This opinion I found was, comparatively, new among them; for all the older farmers declared they had no such idea in their early days—a circumstance that seemed easily to be accounted for, from my knowing that the common people were very rarely inoculated for the Small Pox, till that practice was rendered general by the improved method introduced by the Suttons: so that the working people in the dairies were seldom put to the test of the preventive powers of the Cow Pox.

"In the course of the investigation of this subject, which, like all others of a complex and intricate nature, presented many difficulties, I found that some of those *who seemed to have undergone the Cow Pox*, nevertheless, on inoculation with the Small Pox, felt its influence just the same as if no disease had been communicated to them by the Cow. This occurrence led me to inquire among the medical practitioners in the country around me, THE

ORIGIN

OF THE

VACCINE INOCULATION.

By EDWARD JENNER, M.D. F.R.S. &c.

London:

PRINTED BY D. N. SHURY, BERWICK STREET, SOHO.

1801.

it now becomes too manifeſt to admit of controverſy, that the annihilation of the Small Pox, the moſt dreadful ſcourge of the human ſpecies, muſt be the final reſult of this practice.

Plate 6.8. Jenner's forecast of smallpox eradication. The full text of this paper is reproduced in this chapter.

who all agreed in this sentiment, that the Cow Pox was not to be relied upon as a certain preventive of the Small Pox. This for a while damped, but did not extinguish, my ardour; for as I proceeded, I had the satisfaction to learn that the Cow was subject to some varieties of spontaneous eruptions upon her teats; that they were all capable of communicating sores to the hands of the milkers; and that whatever sore was derived from the animal, was called in the dairy the Cow Pox. Thus I surmounted a great obstacle, and, in consequence, was led to form a distinction between these diseases, one of which only I have denominated the *true*, the others the *spurious*, Cow Pox, as they possess no specific power over the constitution. This impediment to my progress was not long removed, before another, of far greater magnitude in its appearances, started up. There were not wanting instances to prove that, when the true Cow Pox broke out among the cattle at a dairy, a person who had milked an infected animal, and had thereby apparently gone through the disease in common with others, was liable to receive the Small Pox afterwards. This, like the former obstacle, gave a painful check to my fond and aspiring hopes: but reflecting that the operations of Nature are generally uniform, and that it was not probable the human constitution (having undergone the Cow Pox) should in some instances be perfectly shielded from the Small Pox, and in many others remain unprotected, I resumed my labours with redoubled ardour. The result was fortunate; for I now discovered that the Virus of Cow Pox was liable to undergo progressive changes, from the same causes precisely as that of Small Pox; and that when it was applied to the human skin in its degenerated state, it would produce the ulcerative effects in as great a degree as when it was not decomposed, and sometimes far greater; but having lost *its specific properties*, it was incapable of producing that change upon the human frame which is requisite to render it unsusceptible of the variolous contagion ...

"During the investigation of the casual Cow Pox, I was struck with the idea that it might be practicable to propagate the disease by inoculation, after the manner of the Small Pox, first from the Cow, and finally from one human being to another. I anxiously waited some time for an opportunity of putting this theory to the test. At length the period arrived. The first experiment was made upon a lad of the name of Phipps, in whose arm a little Vaccine Virus was inserted, taken from the hand of a young woman who had been accidentally infected by a cow [Sarah Nelmes; Plate 6.9]. Notwithstanding the resemblance which the pustule, thus excited on the boy's arm, bore to variolous inoculation, yet as the indisposition attending it was barely perceptible, I could scarcely persuade myself the patient was secure from the Small Pox. However, on his being inoculated some months afterwards, it proved that he was secure.* This case inspired me with confidence; and as soon as I could again furnish myself with Virus from the Cow, I made an arrangement for a series of inoculations. A number of children were inoculated in succession, one

"* This boy was inoculated nearly at the expiration of five years afterwards with variolous matter, but no other effect was produced beyond a local inflammation around the punctured part of the arm."

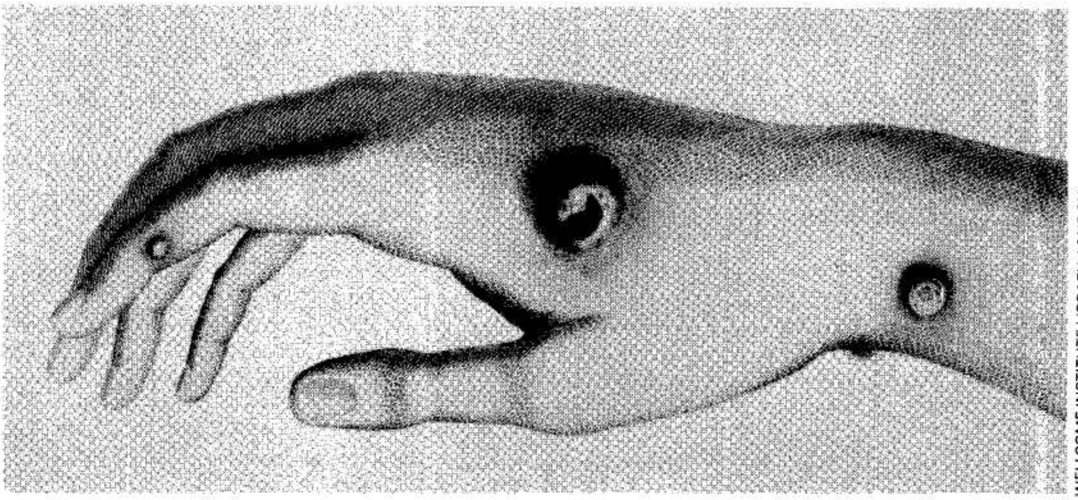


Plate 6.9. Accidental cowpox lesions on the hand of Sarah Nelmes (case XVI in Jenner's *Inquiry*) from which material was taken for the vaccination of James Phipps in 1796.

from the other; and after several months had elapsed, they were exposed to the infection of the Small Pox; some by Inoculation, others by variolous effluvia, and some in both ways; but they all resisted it. The result of these trials gradually led me into a wider field of experiment, which I went over not only with great attention, but with painful solicitude. This became universally known through a Treatise published in June 1798. The result of my further experience was also brought forward in subsequent publications in the two succeeding years, 1799 and 1800. The distrust and scepticism which naturally arose in the minds of medical men, on my first announcing so unexpected a discovery, has now nearly disappeared. Many hundreds of them, from actual experience, have given their attestations that the inoculated Cow Pox proves a perfect security against the Small Pox; and I shall probably be within compass if I say, thousands are ready to follow their example; for the scope that this inoculation has now taken is immense. An hundred thousand persons, upon the smallest computation, have been inoculated in these realms. The numbers who have partaken of its benefits throughout Europe and others parts of the Globe are incalculable: and it now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice."

Jenner's home in Berkeley, Gloucestershire (Plate 6.10), has been purchased by the Jenner Trust. It has been developed as a museum which commemorates not only Jenner but also the application of his discovery to the global eradication of smallpox, achieved 181 years after his experiments on Phipps.

The World-wide Acceptance of Vaccination

At the beginning of the 19th century the educated public was receptive to Jenner's idea. Unlike many other diseases that were common at the time, smallpox struck at all levels of society and was the object of much dread. Variolation had by then been widely accepted; Jenner's vaccine was a way of providing the advantages of variolation without the risks either to the person inoculated or to his fellows (Miller, 1957). And there was no doubt that cowpox produced a much less severe disease than did variolation (Plates 6.1–6.3).

Vaccination was taken up with remarkable speed all over Europe and in the newly independent United States of America. It was, wrote Edward Edwardes (1902), "as if an Angel's trumpet had sounded over the earth".

S. WOOLNOUGH

Plate 6.10. The Jenner Museum. Edward Jenner bought The Chantry in Berkeley, Gloucestershire, in 1785 and lived in it until he died in 1823. The original cottage dates from 1384 at the latest. Purchased by the Jenner Trust in 1983, the building has been completely restored. The museum was opened on 10 May 1985 and commemorates Jenner, the development of the science of immunology, and the eradication of smallpox.

Effects of Introduction of Vaccination on Life Expectancy

Vaccination was the only public health measure of any importance that was newly and widely applied during the first quarter of the 19th century. It was enthusiastically accepted in France, where Napoleon gave it strong support, and in Sweden (see Fig. 6.1), two countries for which there were reasonably good vital statistics at that time.

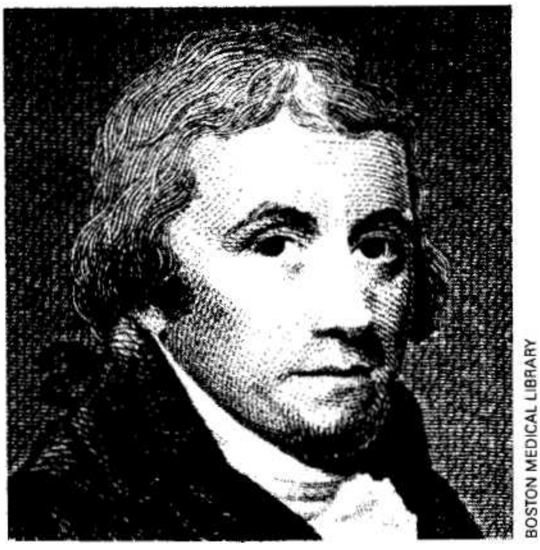
During the early 19th century there was a vigorous controversy as to whether the human life span was fixed (a view supported by Thomas Malthus) or could be extended by public health measures, as the statistician Duvillard maintained (Westergaard, 1932). Data for life expectancy at birth before and after the introduction of vaccination supported Duvillard's view and illustrate what must be primarily the effect of vaccination on life expectancy.

Average Life Expectancy at Birth (in years)[a]

	France		*Sweden*	
	1795	*1817-1831*	*1791-1815*	*1816-1840*
Male	23	38	35	40
Female	27	41	38	44

[a] From Hishinuma (1976), rounded to nearest whole number.

Within 3 years of its publication in London, Jenner's *Inquiry* had been translated into German, French, Dutch, Italian and Latin (LeFanu, 1951). Jennerian vaccination was adopted much more rapidly and widely in Europe than variolation had been, and quickly spread around the world, gradually supplanting variolation where that had been practised. In London it was taken up immediately by William Woodville, Director of the London Small-Pox and Inoculation Hospital, and his colleague George Pearson, who in 1799 sent the vaccine, dried on threads, to some 200 physicians in England and to physicians in Paris, Berlin, Vienna, Geneva, Hanover, Portugal and North America. By 1800 vaccination was being practised in Constantinople, Paris and North America, and by 1801 in Moscow and Berlin; by 1802 viable vaccine had been shipped from Vienna to Bombay (Bowers, 1981). Additional challenge inoculations with smallpox, carried out in many places, confirmed Jenner's hypothesis that inoculation with cowpox virus provided protection against smallpox. In Boston, Benjamin Waterhouse (Plate 6.11) demonstrated protection in 7 persons in July 1800 (Blake, 1957) and in 1803, out of 17 000 vaccinations done in Germany, over 8000 had been tested by subsequent variolation (Dixon, 1962). In



BOSTON MEDICAL LIBRARY

Plate 6.11. Benjamin Waterhouse (1754–1846). The first professor of medicine in the United States of America, he carried out vaccinations in Boston in 1800 and interested President Jefferson in promoting vaccination. Portrait by Gilbert Stuart.

the USA, Waterhouse interested the then Vice-President, Thomas Jefferson, in the potential value of vaccination, and Jefferson immediately responded and enlisted the in-

Early Methods of Distributing Vaccine

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, in which 20 orphans were carried on the ship to provide a succession of susceptible subjects for vaccination. However, more convenient methods were clearly needed.

Initially the commonest method was to impregnate threads with vaccine, much as thread impregnated with material from smallpox pustules had been used for variolation. Many of the early shipments between countries were made with such material. Another method was to spread the lymph on a glass slide and, when it was perfectly dry, cover it with a thin coat of mucilage of gum arabic (Paytherus, 1801). Silver or ivory lancets or points were also used, on which vaccine was allowed to dry; sometimes the liquid lymph on the ivory point was enclosed within a wax ball (Baron, 1838). 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 1898.

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.

terest of laymen and the medical profession in Virginia, Washington, Philadelphia and other places. In December 1801 he arranged for the vaccination of members of an American Indian delegation, supplying them with vaccine and with instructions from Waterhouse about its use (Halsey, 1936).

Perhaps the most dramatic demonstration of the readiness of the world for vaccination was the Balmis-Salvany Expedition commissioned by King Charles IV of Spain, which in 1803–1805 carried vaccine by the arm-to-arm vaccination of orphan children from Spain to the Spanish colonies in the New World, China and the Philippines (Fernández del Castillo, 1960; Smith, 1974; Bowers, 1981).

Early Problems with Vaccination

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 complete and lifelong protection against smallpox.

Contamination of cowpox material with variola virus

The first evidence of this kind of contamination came very early, from Woodville and Pearson, who had embarked on vaccination at the London Small-Pox and Inoculation Hospital. In January 1799 cowpox was discovered at a dairy at Gray's Inn Lane, and Woodville collected lymph from lesions on one of the milkmaids. With this he vaccinated cases at the Small-Pox and Inoculation Hospital and about two-thirds of some 500 subjects had a generalized eruption. Subsequently Woodville (1800) realized that this was due to cross-infection or contamination with material from smallpox cases, and noted that a generalized eruption did not occur when persons were vaccinated in private houses. Material from some of the hospital patients was widely distributed by Pearson (Baxby, 1981), and Razzell (1977a) has suggested that it consisted of attenuated strains of variola virus which constituted the source of vaccinia virus. This hypothesis is not supported by biological evidence (see Chapter 2), but the origin of vaccinia virus, the agent used for smallpox vaccine throughout the latter part of the 20th century, is still uncertain (Baxby, 1981).

Viral contamination has been a recurrent, usually unrecognized, problem. During the latter part of the 19th century it was often decided that vaccine produced by repeated arm-to-arm transfer or maintained in cows needed to be enhanced in potency. As well as "humanized lymph" being passed from man back to the cow ("retrovaccination"), cows were inoculated with variola virus from cases of smallpox. Many of the best-known strains of vaccinia virus were purported to have been derived from smallpox cases in this way (see Copeman (1899) and Chapter 11). However, the environment of vaccine lymph institutes was heavily contaminated with vaccinia virus, as Kelsch et al. (1909) showed, when cows in such an institute which had been inoculated in the scarified skin with glycerol on its own developed a few vaccinial vesicles a few days later. Carefully performed experiments in modern times have failed to "transform" variola to vaccinia virus (Nelson, 1943; Herrlich et al., 1963; Dumbell & Bedson, 1966).

Contamination of human lymph

With the separation of vaccine maintenance and preparation from the smallpox hospitals, the problem of contamination with variola virus was overcome, but other kinds of contamination posed problems. While arm-to-arm vaccination provided a simple means of maintaining a source of virus, it introduced the possibility of the transfer of other human diseases, especially erysipelas and syphilis and, although usually unrecognized, hepatitis B. The etiology and epidemiology of the last-named disease were quite unknown at that time, but in a remarkably percipient paper Lürman (1885) concluded that an epidemic of 191 cases of jaundice among some 1200 employees in a factory in Bremen, Germany, in 1883–1884 was probably associated with the mass vaccination of the staff with a particular batch of humanized glycerolated lymph.

The danger of vaccinal syphilis was recognized in Italy as early as 1814, and soon after that in other countries. Particularly dramatic was an episode at Rivalta, Italy, in 1861, in which 44 out of 63 children

Jenner's Critics

Jenner was not without faults or without critics. His principal biographer, Baron (1838), was adulatory in his attitude; Creighton (1887, 1889) was violently condemnatory and Crookshank (1889) mildly critical. More recently, Razzell (1977a) entered the controversy with a book entitled *Edward Jenner's Cowpox Vaccine: the History of a Medical Myth*, to which Baxby (1981) has produced a rejoinder.

Many of the specific comments made by these and other critics have some substance. Both Creighton and Crookshank were particularly critical of Jenner's adoption (in the published paper of 1798 but not in the draft submitted earlier to the Royal Society) of the term "variolae vaccinae"—cow smallpox—which they held was a false name, designed to mislead. Creighton could see no value in Jenner's contribution, except in so far as it led to Woodville's vaccine, and could discern many disadvantages, especially the danger of transmitting syphilis by arm-to-arm vaccination. Razzell holds that the material used for vaccination, at least after Jenner's original experiments, was not derived from cowpox but was an attenuated strain of variola virus and thus vaccination was really an extension of variolation.

This is not the place to adjudicate on these controversies; Baxby (1981) discusses them at length. It seems to the present authors that, whatever its shortcomings and Jenner's failings, publication of the *Inquiry* and the subsequent energetic promulgation by Jenner of the idea of vaccination with a virus other than variola virus constituted a watershed in the control of smallpox, for which he more than anyone else deserves the credit.

vaccinated with material from a child with unrecognized syphilis acquired overt syphilis; several died and some infected their mothers and nurses. Grön (1928) lists several other episodes, and Creighton (1887), a particularly bitter critic of Jenner, even suggested that "the real affinity of cowpox is not to the small-pox but to the great pox".

Shortages of cowpox virus

For reasons which have only recently become apparent (see Chapter 29), cowpox, as a disease of cows, was a sporadic disease, as Ceely (1842; quoted in Crookshank, 1889) accurately described. It was very rare in certain parts of Great Britain and some other countries of Europe, and its occurrence from year to year varied unpredictably. Thus it was not always easy to have access to a cow with lesions at the right stage for the direct vaccination of man. Jenner recognized this problem and sought to overcome it by using arm-to-arm vaccination, a method that was widely adopted (see Plate 6.14A). Arm-to-arm vaccination continued to be practised in England until 1898, when it was banned, as far as public vaccinations were concerned. But it was not always possible to maintain a chain of infection in children, so that recourse to animal sources was still necessary. Further, the potential problem of vaccinal syphilis was still present, if human sources were used for vaccination. Another problem was that vaccine was thought to lose effectiveness after having been maintained for a prolonged time by arm-to-arm vaccination (Ballard, 1868).

One alternative source recommended by Jenner was material from the lesions of horses suffering from a disease called "grease". This is an inflammation of the fetlocks and is caused by a variety of agents, a rare one being horsepox virus, which usually produces lesions on other parts of the body (face, vulva) as well (Crookshank, 1889; see Chapter 2, Plate 2.15). Loy (1801) demonstrated that virus obtained from lesions on the hand of a man who had been treating horses suffering from grease, and material obtained directly "from a sore in the heel of a horse with the Grease", produced typical vaccine lesions in children and lesions like cowpox on the teats of inoculated cows. He showed that children inoculated with this material resisted variolation.

In 1817, equine virus supplied to the National Vaccine Establishment was widely distributed in Great Britain (Baron, 1838), and horsepox was also used as a source of vaccine in continental Europe. Chaveau (1866) believed that in any case horsepox was caused by the same virus as cowpox, although it was an even less common disease.

Production of vaccine in calves

For some time "retrovaccination" was practised, a procedure that consisted in taking the virus from human lesions back to the cow, which was then used as a source for further arm-to-arm vaccination. This was done primarily to maintain the potency of the vaccine, rather than providing a source of vaccine for distribution and use. The use of animals as a method of vaccine production on a large scale, which overcame problems of vaccinal syphilis and of the loss of vaccine sources, was developed in Italy, which had long shown an interest in vaccination. As early as 1805 Troia

Horsepox as a Source of Vaccine Lymph

In 1817 Jenner appears to have replaced vaccination by "equination" and stocks of virus from cases of horsepox were supplied to the National Vaccine Establishment and widely diffused. Crookshank (1889) concludes a long commentary on horsepox as follows: "In this country, it is more than probable that some of Jenner's stocks of equine lymph are still in use; but equination is not wittingly practised, for it is commonly supposed that all the lymph employed for the purposes of vaccination has been derived from Cow Pox. In France, on the other hand, it is extensively employed. M. Larget informed me that at the Animal Vaccine Station at Bordeaux the lymph which gave most satisfaction was derived from the horse, and that he had been able on two occasions to renew his stock from equine sources."

Plate 6.12. Wood engraving from *Harper's weekly*, 23 April 1870, showing a general vaccination day at the Paris Academy of Medicine. Arm-to-arm vaccination had been superseded by vaccination from the cow after the discussions of the Medical Congress of Lyons in 1864.

in Naples was employing calves as a source of human vaccine, and Galbiati (1810) continued the practice. Then in 1840 Negri in Naples carried the virus continuously in calves.

Use of the calf as a source of vaccine appears to have been confined to Italy until the Medical Congress of Lyons in 1864, when there was heated criticism of vaccination on the grounds that the method of maintenance and production of vaccine then practised in France—namely arm-to-arm vaccination—carried a serious risk of transmitting syphilis. In this discussion, Dr Viennois and Professor Palasciano spoke about the calf as a source of virus, as practised in Italy (Congrès Médical de Lyon, 1864). Dr Chambon and Dr Lanoix immediately arranged for the delivery of a calf incubating vaccinia to be sent to Paris from the Neapolitan Institute and henceforth the use of calf vaccine gradually extended through France (Depaul, 1867). Belgium adopted it in 1865, and by 1884 the German Royal Commission on Vaccination recommended it in Germany (Hime, 1896). The Netherlands and many states of the USA followed suit. Great Britain was one of the last countries to adopt the practice. Its use there was initiated in 1881, but arm-to-arm vaccination continued to be popular until it was finally banned in 1898 (Table 6.3; Dudgeon, 1963). As late as 1896 Hime felt obliged to devote considerable effort to justifying the practice of "animal vaccination".

The manner of inoculation consisted in making multiple insertions on a shaved area

Table 6.3. Record of vaccine lymph issued by the National Vaccine Establishment, Great Britain[a]

	1881	1882	1898	1899 (to March)
Human lymph:[b]				
Ivory points	10 260	8 193	0	0
Glass slides	440	40	0	0
Capillary tubes	21 118	25 572	3 739	0
Calf lymph:[b]				
Ivory points	470	975	20 317	0
Capillary tubes	30	95	105	125 038

[a] Based on Dudgeon (1963).
[b] For an explanation of the methods of distribution, see box earlier in this chapter.

on the skin of a calf (Plate 6.13), vaccine being reaped from the separate pocks found at each insertion site on the 5th day after inoculation by expressing the fluid and, as Hime (1896) recommended, scraping the surface of the pock. The material expressed was ground in a mortar and suspended in glycerol, a practice embarked on empirically in Italy in Negri's day, and supported by Koch in Germany. In Great Britain considerable credit was given to Copeman (1899; see also McNalty, 1968), who demonstrated that glycerol was not only a convenient fluid for suspending vaccine, in terms of its clarity and its viscosity, but was also bactericidal though not virucidal (Copeman, 1892).

An important feature of the first hundred years of vaccination was that vaccine production was conducted without any sort of state control. "Vaccine parks" were established by all and sundry, individual physicians maintained their own stocks of "humanized" vaccine by arm-to-arm inoculations, and Hime (1896) complained "The country [Great Britain] is flooded with cheap stuff 'made in Germany' and elsewhere, of unknown nature or origin. It is cheap and therefore sells." In Great Britain the labours of the Royal Commission on Vaccination (Great Britain, 1898) resulted in the Vaccination Act of 1898, which prohibited arm-to-arm vaccination by public vaccinators and undertook to supply them with glycerolated calf lymph. However, it was not until 1925 that regulation of the quality of vaccine was firmly established with the promulgation of the Therapeutic Substances Act (Hutchinson, 1946).

Plate 6.13. Production of vaccine in calf, 5 days after inoculation. (From Depaul, 1867.)

Theological and philosophical objections

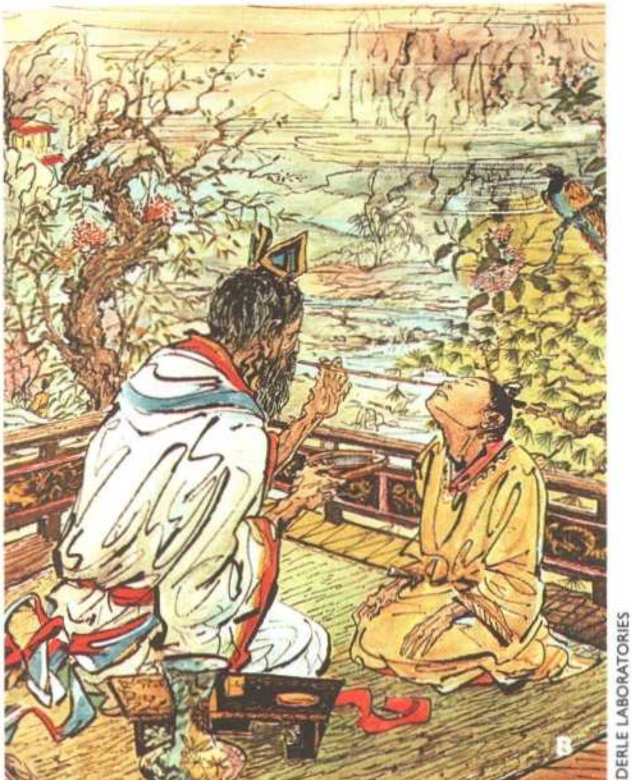
Some churchmen had taken strong positions in controversies about variolation, both for and against. It was much the same with vaccination. In Italy, priests led processions of people to vaccination sites to be vaccinated; in Bohemia village priests reminded parents of their responsibility not to neglect the vaccination of their children, and in Germany, Great Britain and Switzerland some clergymen vaccinated people themselves. Vaccination was endorsed by the Pope during an epidemic of smallpox in Rome in 1814.

On the other hand, some members of the Church raised objections that vaccination was interfering with the will of God and that smallpox was sent to chasten the population. There were objections to the inoculation of humans with a disease of animals, and popular cartoons depicted people growing horns or tails after being vaccinated (Plate 6.15B).

More serious philosophical objections emerged from the mid-19th century onwards, especially in Great Britain, when efforts to make vaccination compulsory conflicted with growing sentiments favouring personal freedom of choice. Before the era of bacteriology, there was no generally accepted scientific basis for the theory of infection by contagion. Anticontagionists and antivaccinationists tended to be liberal re-

MUSÉE DE LA CHARTREUSE

Plate 6.14. A: Arm-to-arm vaccination, as practised in Europe. Painting by Charles Desbordes, "La Vaccine", 1822. **B:** Insufflation of powdered smallpox scabs by the intranasal route, as practised with variola virus in China.



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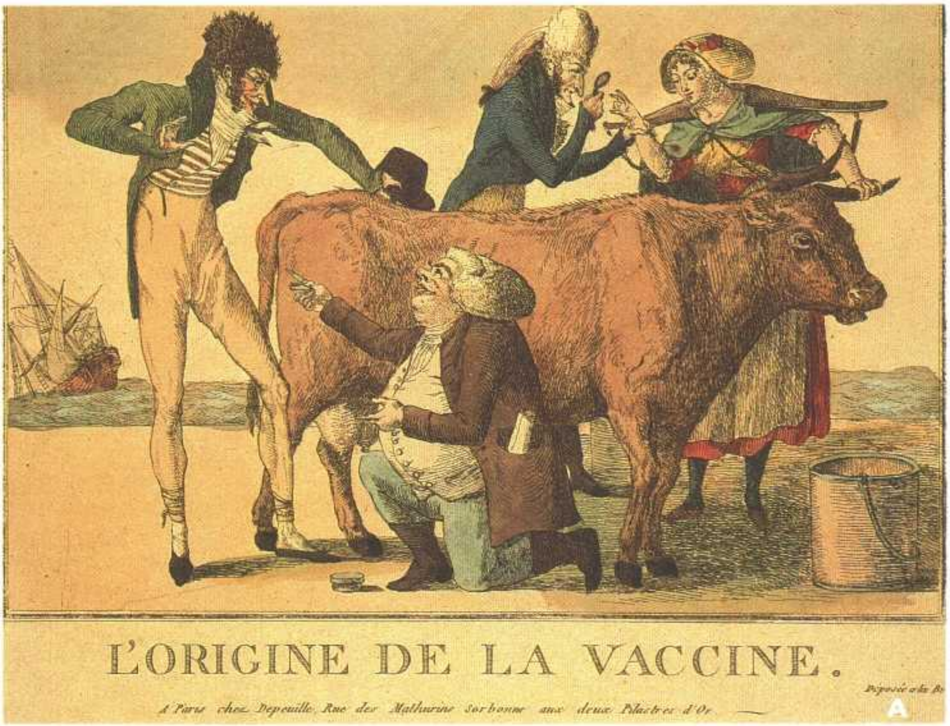

Plate 6.15. **A:** French engraving, c. 1800, depicting the newly discovered process of vaccination. **B:** English engraving by James Gillray, 1802, reflects the scepticism with which vaccination was received initially in some quarters.

formers who fought for individual freedom against what they saw as despotism and reaction; both quarantine and vaccination were equated with the restrictions of unheeding officialdom.

Although Parliament in Great Britain was slow to introduce legislation on vaccination, possibly because of the belief that it was important that the poor should not be protected at public expense (Chase, 1982), and because of liberal antivaccinationist sentiment, firm action was taken quite early in several other European countries. Vaccination was made compulsory in Bavaria in 1807,

Resistance to Compulsory Vaccination in Great Britain

"The Vaccination Acts of 1840, 1841 and 1853 ... made [vaccination] successively universal, free, non-pauperising and, finally, compulsory. The Acts of 1861, 1867 and 1871 made vaccination enforceable by the appointment of Vaccination Officers, and finally compelled enforcement by making such appointments mandatory ... the Act of 1867 permitted parents to be fined repeatedly until the child was vaccinated ... the Act of 1871 ... made negligent parents liable both for non-compliance with the Act and for disobedience of a court order. In default of fines and costs, parents were sometimes committed to gaol and household goods were distrained for sale. As incidents of bona fide opposition to vaccination arose, the severity with which the law was enforced and the weight it laid upon the poorer classes attracted more attention. Gradually, individuals found organised means of expressing their discontent. Such opposition merged with the rising tide of working-class opinion and with the efforts of radical reformers who saw in the vaccination question the embodiment of impersonal and uncompromising governmental intervention in the daily life of the individual ... Sanitary reformers of the era were largely united in the belief that enforced 'cleanliness' was a prerequisite to social 'godliness' and a sufficient defence against disease and while many accepted vaccination as a useful, ancillary instrument of prevention, they could not agree with the implicit assumption of 'specificity', and were reluctant to see it impede or replace the elimination of foul air, overcrowding and filthy streets.

"The [subsequent] development of the antivaccinationist movement can be seen in five distinct phases. First, sporadic Radical outbursts in London and the North led during the seventies to the formation of the Society for the Suppression of Compulsory Vaccination in London ... The second phase of activity, under the Cheltenham National Anti-Compulsory Vaccination League, extended the movement to the rural population and the agricultural middle classes. When League intrapolitics and its limited programme failed to make an impact on national opinion, a more extensive campaign was begun. This came about in the third phase, with the establishment of a new London Society for the Abolition of Compulsory Vaccination. The highly co-ordinated pressure group tactics of this Society unified support and helped to secure Government inquiry into the vaccination question. The actions of this group in the period 1880–89 prepared the ground for the fourth phase which emerged in the nineties, when the London Society, using the Report of the Royal Commission on Vaccination as a manifesto, amalgamated antivaccinationists into a new National Anti-Vaccination League, and pressed for remedial legislation. The fifth phase, beginning in reaction to administration abuse of the conscientious objection provision of the 1898 Act, receded with the League's decline after 1907, when its final objectives were essentially achieved.

"In retrospect, the movement was part of a wider public reaction against the advance of 'new science' and scientific medicine. Fear, distrust and the human tendency to cherish 'natural' methods of treatment and 'sanitary' methods of prevention could be overcome only by educational means. This required the active co-operation of physicians and lawyers in supervising the administration of compulsory law which had, historically, been accepted naively by Parliament. This co-operation was noticeably absent at this critical interface of law, medicine and public opinion." (MacLeod, 1967.)

in Denmark in 1810, in Bohemia in 1812, and in Sweden in 1816.

Duration of immunity following vaccination

Jenner is regarded as the father of immunology, but it would be a mistake to believe that he interpreted the resistance to smallpox conferred by vaccination as an immunological phenomenon, as now understood. Rather he saw it as a change in the constitution that rendered an individual resistant to smallpox forever. Jenner maintained this belief until he died in 1823, and explained the increasing number of cases that occurred as time passed since vaccination as being due to "imperfect" vaccination with "spurious cowpox", or for some other reason. Jenner was right in noting that pock-like lesions on the teats of cows could be due to agents other than cowpox (see Chapter 29) but wrong in believing that immunity to smallpox was absolute and lifelong. Jenner's fallibility on this issue was exploited by antivaccinationists opposed to all vaccination, until revaccination provided the solution.

Recognition of the need for revaccination came much earlier in continental Europe than in Great Britain, where the official attitude throughout the 19th century was that vaccination in infancy gave lifelong protection. Thus, in Great Britain the 1840 legislation providing for infant vaccination, and subsequent Acts providing for compulsory infant vaccination, were founded on the false Jennerian concept that infant vaccination produced lifelong immunity, so that revaccination was unnecessary. As late as 1898 the Royal Commission on Vaccination (Great Britain, 1898) stated that only in very exceptional circumstances did infant vaccination not give lifelong protection.

On the continent of Europe and particularly in Germany, the need for revaccination was recognized early, with dramatic results in countries in which revaccination was compulsory (see Table 6.4).

Evidence for the Efficacy of Vaccination

The initial response to the idea of vaccination was based on an optimistic extrapolation of Jenner's meagre experimental results, its close resemblance to variolation, in principle and in the production of a local lesion, and the deeply felt need to find something better than variolation, which usually brought on a severe disease and could cause outbreaks of smallpox in uninoculated contacts. This is well expressed in a letter dated 2 August 1798 from Cline, who performed the first vaccination in London, in July 1798, to Jenner (Baron, 1838):

> "I think the substituting of cow-pox poison for the small-pox promises to be one of the greatest improvements that has ever been made in medicine: for it is not only so safe in itself, but also does not endanger others by contagion, in which way the small-pox has done infinite mischief. The more I think on the subject the more I am impressed with its importance."

After Jenner's initial publication in 1798, Woodville and Pearson in London and others in Germany, Italy and the USA lost no time in carrying out challenge inoculations that far exceeded in number those that Jenner had performed. Then followed growing experience of the immunity of vaccinated persons to natural smallpox. Because of its very obvious advantages, and because it built on the practice of variolation, established in Europe and the Americas for some 80 years, vaccination was adopted throughout the world—and very rapidly. For example, Jenner stated that by 1801 over 100 000 persons had been vaccinated in Great Britain, whereas by 1730, 8 years after the introduction of variolation, less than 1000 people had been variolated in Great Britain and North America.

As more and more people were vaccinated, smallpox mortality declined dramatically and for some decades remained low. Such epidemics as did occur were less severe and less frequent than in the 18th century. Where good statistics were kept, as in Geneva (Perrenoud, 1980) and Denmark and Sweden (Moore, 1817), it was seen that the numbers of reported deaths from smallpox fell to unprecedently low levels. Not only did the morbidity and mortality decline dramatically, but the cases that did occur were almost always in unvaccinated persons. There was no logical explanation for this change except the introduction of vaccination.

Faced with this evidence, the governments of several countries decided that protection against smallpox was not something that could be left to individual choice. First, variolation, as a potential source of smallpox, was banned in Russia in 1805, in Prussia in 1835 and in Great Britain in 1840 (Edwardes, 1902). Then vaccination, usually of infants, was made legally compulsory in Bavaria (1807), Denmark (1810), Norway (1811), Bohemia and Russia (1812), Sweden (1816) and Hanover (1821). Great Britain and France were to follow much later, in 1853 and 1902 respectively. Of course, having a law on the statute books and enforcing it were two different matters, especially as the problem of the large-scale production and distribution of vaccine was not solved until the latter half of the 19th century. Nevertheless, the evidence for the efficacy of vaccination, provided by countries in which it was compulsory and in which the law was enforced, was compelling. Edwardes (1902) summarized much of this evidence in his excellent little monograph.

The figures for Sweden, which has some of the earliest reliable statistics, are shown in Fig. 6.1. Vaccination began in Sweden late in 1801 and was made compulsory in 1816. From about 1802 onwards there was a dramatic change in the 18th century pattern of major epidemics (3000–7000 smallpox deaths per million population) every 5 years or so, against a background of high endemicity (600–800 smallpox deaths per million population). The epidemic waves subsided and from about 1810, as vaccination became more widespread, the figures fell to unprecedently low levels. Six years after the institution of compulsory vaccination the ratio of smallpox deaths per million population reached a single figure—over a hundredfold reduction from the previous endemic level. After that, in spite of the maintenance of a reasonably high level of infant vaccination, the death rate rose again and epidemics recurred, although at a tenth the amplitude and at longer intervals than in the 18th century.

This pattern occurred elsewhere in Europe, wherever vaccination coverage was reasonably good. After a period of freedom for some 20 years, smallpox began to recur in pandemics affecting most of Europe in 1824–1829 and 1837–1840, with mortalities that were low by 18th century standards but much higher than the general public or the health workers of the time regarded as tolerable. Further, the pattern of the epidemics had changed. During the 18th century the high level of endemicity had ensured that most adults living in cities were immune as a result of childhood infection or perhaps of variolation; urban epidemics occurred primarily in children. Now, where

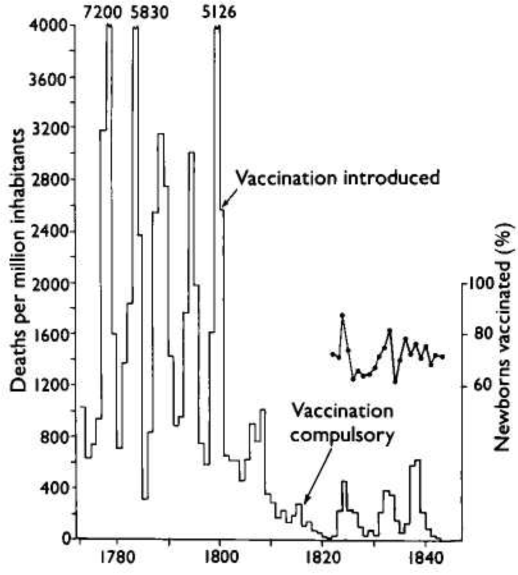

Fig. 6.1. Smallpox deaths per million population in Sweden between 1722 and 1843, showing from 1820 onwards the proportion of newborn children who were vaccinated in infancy. (Based on Edwardes, 1902.)

infant vaccination was widespread, there was a higher rate of illness in adults than in children. And even more than in the past, smallpox deaths occurred among the lower classes of society, who had less access to vaccination.

It was clear that Jenner's belief that one inoculation with cowpox gave permanent protection against smallpox was wrong. An increasing number of cases occurred in vaccinated adults, but with a much lower case-fatality rate than before, and a different and milder symptomatology, which caused difficulties in diagnosis (Monro, 1818). One suggested answer, in Great Britain, was to revive variolation (Creighton, 1894). A safer, more sensible, solution was to recommend revaccination. The German states took the lead, and revaccination was introduced in Württemberg in 1829; other states, beginning in 1833, instituted the compulsory vaccination of military recruits. In the Prussian army, the number of deaths from smallpox, which had averaged 88 per year in 1831–1834, dropped to single figures and averaged less than 2 per year for the next 30 years.

The great European epidemic of 1870–1871 (see Chapter 5) provided a salutary lesson that smallpox was not yet under control, but the very much lower incidence in the Prussian than in the French army demonstrated the value of vaccination and revaccination. Germany took these lessons to heart and in 1874 promulgated a vaccination law requiring that every child should be vaccinated during the 2nd year of life and that every schoolchild should be revaccinated during the 12th year, unless an attack of smallpox, or a successful vaccination, had occurred within the previous 5 years. The results, when compared with the prevailing situation in Austria, in which general conditions were similar but revaccination had not been introduced, were dramatic (Table 6.4) and hardly require comment.

A hundred years after Jenner's experiment with James Phipps, the *British medical journal* (1896) published a Jenner memorial number and medical journals in many other countries published special articles on Jenner and vaccination (Pfeiffer, 1896; *Index medicus*, 1897). Russian translations of all of Jenner's publications on vaccination were also produced in 1896 (LeFanu, 1951).

A few years later Edwardes (1902) published his compendium of statistics. All investigations illustrated that the practice of vaccination and revaccination, properly conducted, was a brilliant success; Jenner's prediction (see Plate 6.8) that smallpox could be eradicated by vaccination was correct. Almost 80 years were to elapse, however, before *global* eradication was achieved, and practices additional to mass vaccination, which in an elementary form had antedated the concepts of variolation and vaccination, had to be invoked—namely, isolation and containment.

CONTROL BY ISOLATION AND QUARANTINE

One other method of control began even before variolation and, combined with vaccination, furnished the ultimate method for the control of smallpox—namely, isolation and, for travellers by sea, its equivalent, quarantine. It was believed from early times, first with leprosy and then with plague, that it might be possible to avoid certain diseases by ensuring that no contact occurred between

Table 6.4. A comparison between the number of smallpox deaths per million population in German states before and after the German vaccination law of 1874 (compulsory vaccination and revaccination) and in Austria (in which only primary vaccination was practised), during the same period[a]

Year	Prussia	Bavaria	Württemberg	Austria
1866	620	120	133	368
1867	432	250	63	484
1868	188	190	19	370
1869	194	101	74	374
1870	175	75	293	293
1871	2 432	1 045	1 130	383
1872	2 624	611	737	1 866
1873	356	176	30	3 094
1874	95	47	3	1 725
1875	36	17	3	576
1876	31	13	1	406
1877	3.4	17	2	555
1878	7.1	13	0	631
1879	12.6	5	0	534
1880	26	12	5.6	674
1881	36.2	15	3.6	807
1882	36.4	12	6.6	947
1883	19.6	6	35.2	596
1884	14.4	1	11.6	530
1885	14	3	0	600
1886	4.9	1	1	400
1887	5	1.8	0	417
1888	2.9	3.8	0.5	615
1889	5.4	5.2	0	537
1890	1.2	1.5	0	249
1891	1.2	1.2	0	287
1892	3.0	0.5	0	256
1893	4.4	0.7	1	244
1894	2.5	0.3	0	105
1895	0.8	0.2	0	49
1896	0.2	0.2	0	36
1897	0.2	0	0	61

[a] Based on Edwardes (1902).

diseased and healthy persons. The practice of designating huts or villages in which severe infectious diseases such as plague or smallpox were present, as an indication that they were to be avoided, appears to have arisen independently among several different peoples in Africa, Asia and Europe. It was difficult to achieve the efficient isolation of cases where diseases were endemic, but relatively easy when they were present on ships that approached disease-free ports. Thus the quarantine of ships developed earlier and more effectively than did effective isolation of smallpox patients on land.

The scientific underpinning of the concepts of isolation and quarantine had to await the enunciation of the germ theory of infectious diseases by Pasteur and Koch, in the latter half of the 19th century, but long before this a belief had developed that such diseases were spread by contagion. The best-known early European exponent of this view, for smallpox and measles, was Girolamo Fracastoro of Verona (1478–1553). In a classic book (Fracastoro, 1546) he attributed these diseases to specific seeds, or seminaria, which were spread by direct contact from person to person, by intermediate objects, or fomites, or perhaps at a distance, through the air.

Quarantine for Shipping

At the time of the Black Death, in the 14th century, the Venetians and other trading nations of the Mediterranean recognized that ships sometimes brought plague to their cities, and instituted the practice of isolating travellers and ships suspected of carrying plague for a period that became, after some adjustments, 40 days—hence the word quarantine (Gerlitt, 1940).

The idea of using quarantine to prevent the entry of smallpox came most readily to European colonists in places previously free of smallpox, notably North America and Australia. Smallpox was endemic in Great Britain when North America was being settled in the early part of the 17th century, and smallpox occurred on several ships during the Atlantic crossing. Later, epidemics of smallpox occurred in Boston, the major seaport at the time, in 1636, 1659, 1666, 1677–1678, 1689–1690 and 1697–1698. Between these times the disease disappeared; the introductions followed the arrival of ships carrying new settlers or slaves with smallpox.

Although the early North American settlers believed no less than their British contemporaries in the notion of pestilence as divine punishment, they were pragmatic enough to invoke quarantine to prevent the entry of smallpox from overseas. By 1647, vessels arriving in Boston from the West Indies with infected passengers or crew were quarantined in the harbour, initially probably for yellow fever (Blake, 1953, 1959), and similar measures were subsequently adopted in New York and other port cities (Tandy, 1923).

Eventually, as the European settlements in North America increased in size, smallpox became endemic and quarantine was no longer relevant. Variolation and subsequently vaccination became more important ways of controlling smallpox. But in Australia and New Zealand, much more sparsely populated and situated much further from other centres of population than North America, smallpox never became endemic and quarantine remained an important method of excluding the disease throughout the 19th and 20th centuries (Cumpston, 1914; see also Chapter 8).

Isolation of Cases

The isolation of patients on land was more difficult to put into effect than preventing the landing of infected persons from ships. Nevertheless, the colonists in North America attempted this as early as 1662, when an order was issued at East Hampton, Long Island, to prevent the spread of smallpox from local Indians to the town's population (Tandy, 1923). In 1667 the colony of Virginia legislated for the mandatory isolation of victims of smallpox at home.

The idea of isolation to control the spread of smallpox received a considerable stimulus with the popularization of variolation, since it was early recognized that one of the risks of this practice was the spread of smallpox to uninoculated contacts. It therefore became customary to variolate children in groups and keep them in isolation, tended by persons who had already had smallpox, until the scabs fell off. Jenner himself had this experience in 1757, at the age of 8 (Baron, 1838).

By the end of the 18th century some writers had already conceived the idea of controlling smallpox by a combination of variolation on a wide scale and the isolation of smallpox patients. Haygarth (1793) developed a comprehensive plan involving the periodic variolation of the general public, the isolation of cases, the disinfection of fomites, etc.; a few years later Carl (1799), then Director of the Inoculation Institute in Bohemia, proposed a similar procedure. By 1803 the government of Bohemia required the compulsory notification of cases of smallpox, the isolation of cases and the sterilization or destruction of bed-linen, toys, etc., of smallpox patients (Carl, 1802; Raška, 1976).

Impressed by the example of the "stamping out" of the devastating cattle plague, rinderpest, in Great Britain a few years earlier, Sir James Simpson, famous for his introduction of chloroform for anaesthesia, wrote an article for the *Medical times and gazette* in 1868 (Simpson, 1868), which aroused considerable interest and discussion. In it he developed a proposal for eradicating smallpox and other infectious diseases, such as scarlet fever, measles and whooping-cough, by the isolation of cases. He recognized that his proposals could be most readily achieved with smallpox, because vaccination provided a means of protection for nurses and others who had to remain in contact with patients. His proposed "Regulations" were as follows:

"1st. The earliest possible notification of the disease after it has broken out upon any individual or individuals.

"2nd. The seclusion, at home or in hospital, of those affected, during the whole progress of the disease, as well as during the convalescence from it, or until all power of infecting others is past.

"3rd. The surrounding of the sick with nurses and attendants who are themselves non-conductors or incapable of being affected, inasmuch as they are known to be protected against the disease by having already passed through cow-pox or small-pox.

"4th. The due purification, during and after the disease, by water, chlorine, carbolic acid, sulphurous acid, etc., of the rooms, beds, clothes, etc., used by the sick and their attendants, and the disinfection of their own persons."

Perhaps the most vigorous advocacy of isolation as a method of controlling smallpox was developed in the city of Leicester, in England, largely as a result of the strength of the local antivaccinationist movement (Fraser, 1980). The essentials were the prompt notification of cases of smallpox, the isolation of cases in the town's Fever and Smallpox Hospital, and the quarantine of all immediate contacts, with compensation for loss of time from work. Vaccination was not mentioned, and in Leicester there was strong disapproval of compulsory vaccination, and especially of the prosecution of those who refused vaccination on grounds of conscientious objection, until the turn of the century. The system was developed during the 1870s and achieved notoriety in the 1890s. Subsequently, the vaccination or revaccination of contacts was added to the routine procedure (Millard, 1914). This procedure, the "Leicester method" plus vaccination, like the proposals of Haygarth and Carl long before, anticipated the surveillance and containment strategy of the World Health Organization's Intensified Smallpox Eradication Programme.

The Establishment of Smallpox Hospitals

Dixon (1962) devotes a chapter of his book to the smallpox hospital and traces the history of such hospitals in Great Britain, as well as outlining his views on basic requirements. The notion that a special infectious diseases or smallpox hospital or ward should be an integral part of the control of smallpox arose as recently as the 20th century, except for a

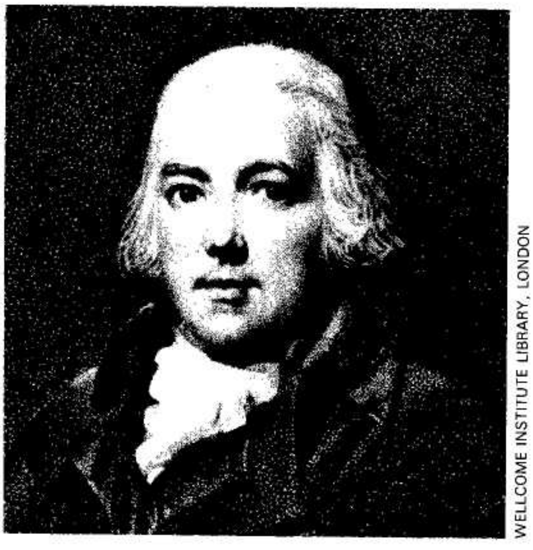

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Plate 6.16. William Woodville (1752–1805). Director of the London Small-Pox and Inoculation Hospital at the time of publication of Jenner's *Inquiry*. Many of his early vaccinations, carried out in the presence of cases of smallpox, were associated with generalized rashes, a source of confusion until they were recognized as being caused by variola virus.

few places, such as Leicester (see above), in which such institutions already existed. Prior to that, hospitals were sometimes established in response to epidemics, often of smallpox, as in Quebec in 1639 (Hôtel Dieu) and on frequent occasions in towns in Great Britain. But in general smallpox patients were not admitted to hospitals.

In England, the London Small-Pox and Inoculation Hospital was founded in 1746, initially for the treatment of poor persons with smallpox but soon afterwards mainly as a hospital for subjects undergoing variolation. An Inoculation Institute was established in Brno (Bohemia) at about the same time. Subsequently small private "inoculation hospitals" were set up in most places in which variolation was practised extensively, to prevent the spread of smallpox to susceptible contacts. The London Small-Pox and Inoculation Hospital played an important role in the early days of vaccination, for Woodville worked there (Plate 6.16) (Woodville, 1796, 1799, 1800).

Long before this, the Japanese book *Ishinho*, produced in AD 982, mentioned the establishment of special hospitals for smallpox cases, but it is difficult to interpret their significance. The use of infectious diseases hospitals as part of the machinery for controlling smallpox required an efficient system of notification, which was easier for smallpox than for most other diseases. Notification formed the core of the "Leicester method" and was a most important factor in limiting the spread of smallpox after importations into Europe and North America during the 20th century (see Chapter 23). However, national notification of cases of infectious diseases was not introduced into Great Britain, for example, until 1899, and even an imperfect system of notification required a public health service far more effective than anything that existed during the 19th century. Even in the industrial countries of Europe, therefore, elimination of smallpox was not achieved until well into the 20th century (see Chapter 8).