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Smallpox: The Triumph over the Most Terrible of the Ministers of Death

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More than 200 years ago, Edward Jenner performed an experiment that laid the foundation for the eradication of smallpox and transformed humankind's fight against disease. Smallpox afflicted humankind as no other disease had done; its persistence and diffusion were without parallel. The disease brought down at least three empires. Generations watched helplessly as their children succumbed to the disease or were disfigured or blinded by it. Attempts were made to contain smallpox by isolating its sufferers and, later, by using variolation with varying degrees of success. However, the definitive solution was not found until Jenner's work was done at the end of the 18th century. Milkmaids who had developed cowpox from contact with cow udders informed Jenner that they were protected from the human form of the disease; he listened to their folk wisdom and raised it to the status of scientific fact. Jenner did not discover vaccination, but he was the first to demonstrate that this technique offered a reliable defense against smallpox. It was also a reliable defense against other illnesses, such as poliomyelitis, measles, and neonatal tetanus, although this was not known in Jenner's lifetime.

"Smallpox was always present, filling the churchyard with corpses, tormenting with constant fear all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover [1]."

Smallpox has been one of humankind's greatest scourges since time immemorial. Even illnesses as terrible as the plague, cholera, and yellow fever have not had such a universal and persistent impact. Smallpox is believed to have appeared at the time of the first agricultural settlements in northeastern Africa, around 10 000 BC [2]. It probably spread from Africa to India by means of Egyptian merchants in the last millennium BC [3]. The earliest evidence of skin lesions resembling those of smallpox is found on the faces of mummies from the time of the 18th and 20th Egyptian Dynasties (1570 to 1085 BC) and in the well-preserved mummy of Ramses V, who died as a young man in 1157 BC [4-6].

The first recorded smallpox epidemic occurred in 1350 BC during the Egyptian-Hittite war. The illness was passed to the Hittite population by Egyptian prisoners and affected soldiers and civilians alike. The Hittite King Suppiluliumas I and his heir, Arnuwandas, were victims; their civilization fell into sharp decline [2].

During the epidemic in Athens in 430 BC, Thucydides noted that those who survived the disease were later immune to it [7]. These observations were reiterated by Rhazes (Abu Bakr Muhammad Ibn Zakariya al-Razi), to whom we owe the first medical description of smallpox, De variolis et morbillis commentarius, which was written in about AD 910. Rhazes also noted that the illness was transmitted from person to person [8]. His explanation of

why survivors of smallpox do not develop the disease a second time is the first theory of acquired immunity.

The Fall of Empires: Variola Rex and the Course of History

Smallpox greatly affected the development of western civilization. The first stages of the decline of the Roman Empire, around AD 180, coincided with a large-scale epidemic: the plague of Antonine, which killed between 3.5 and 7 million persons [9, 10]. The Arab expansion, the Crusades, and the discovery of the West Indies all contributed to the spread of the illness. Unknown in the New World, smallpox was introduced by Spanish and Portuguese conquistadors. It decimated the local population and was instrumental in the fall of the empires of the Aztecs and the Incas. When the Spanish arrived in 1518, Mexico had about 25 million inhabitants; by 1620, this number had diminished to 1.6 million [11]. A similar decrease occurred on the eastern coast of what became the United States, where the advent of smallpox had disastrous consequences for the native population [12], and the disease continued to be spread through the relentless process of European colonization [13]. The devastating effect of smallpox gave rise to one of the first examples of biological warfare. In a letter written to Colonel Henry Bouquet in 1763, Sir Jeffrey Amherst, commander-in-chief of British forces in North America, suggested grinding the scabs of smallpox pustules into blankets that were to be distributed among disaffected tribes of Indians [14, 15]. The slave trade also contributed to the introduction of the illness in the Americas because many slaves came from regions of Africa in which smallpox was endemic [16].

Princes and Peasants

Smallpox made no distinctions. It affected all ages and socioeconomic classes. It killed Marcus Aurelius in AD 180; the first Abbasid caliph, Abbul al-Abbas al-Saffah ("the blood shedder"), in 754; King Thadominbya of Burma in 1368; the Aztec emperor Ciutlahuac in 1520; King Boramaraja IV of Siam in 1534; the King and Queen of Ceylon and all of their sons in 1582; Prince Baltasar Carlos, heir to the Spanish throne, in 1646; William II of Orange and his wife, Henrietta, in 1650; Emperor Ferdinand IV of Austria in 1654; Emperor Gokomyo of Japan in 1654; Emperor Fu-lin of China in 1661; Queen Mary II of England in 1694; King Nagassi of Ethiopia in 1700; Emperor Higashiyama of Japan in 1709; Emperor Joseph I of Austria in 1711; King Louis I of Spain in 1724; Tsar Peter II of Russia in 1730; Ulrika Eleanora, Queen of Sweden, in 1741; and King Louis XV of France in 1774. During the 18th century, four reigning European monarchs died of the disease, and the Habsburg line of succession to the throne changed four times in four generations because of the deaths of heirs [2]. Citizens were equally at the mercy of the illness. In the late 18th century in Europe, 400 000 people died of smallpox each year and one third of the survivors went blind [3].

The word variola (smallpox) was used for the first time by Bishop Marius of Avenches (near Lausanne, Switzerland) in AD 570. It came from the Latin word varius, meaning "stained," or from varus, meaning "mark on the skin" [17]. In England, the term small pockes (pocke meaning sac) was first used at the end of the 15th century to distinguish the illness from syphilis, which was then known as great pockes [18]. The dread that smallpox inspired is graphically described by Macaulay [1]: "that disease ... was the most terrible of all the ministers of death."

The Speckled Monster

The symptoms of smallpox-or the speckled monster, as it was known in 18th-century England-appeared suddenly and included high fever, chills or rigors, cephalagia, characteristic dorsal-lumbar pain, myalgias, and prostration. Nausea and vomiting were also common. After 2 to 4 days, the fever relented and a rash appeared on the face and inside the eyes; the rash would subsequently cover the whole body. These maculopapular skin lesions evolved into vesicles and pustules and finally dried into scabs that fell off after 3 or 4 weeks [19]. This sequence of events was characteristic for variola major.

Other clinical forms of the disease existed. Persons with fulminating smallpox (purpura variolosa) had mucocutaneous hemorrhages that preceded the appearance of the characteristic skin lesions [19, 20]. In malignant smallpox, the rash had a slow evolution characterized by pseudocropping,

subconjunctival hemorrhages, and death when lesions on the face and limbs were confluent. In benign smallpox, the evolution of the rash differed from that of the malignant variety; this form was also less extensive [19, 20]. Modified smallpox (varioloid) occurred in persons who were partially protected by vaccination and was usually benign. Variola sine eruptione was smallpox without a rash and occurred predominantly in vaccinated persons [19, 20]. Variola minor (alastrim, Kaffir-pox) was a mild form of smallpox caused by a less virulent strain of the virus and was endemic in Africa and South America [19].

The case-fatality rate associated with smallpox varied between 20% and 60% and left most survivors with disfiguring scars [21, 22]. Many persons went blind as a result of corneal infection. The case-fatality rate in the infant population was even higher; among children younger than 5 years of age in the 18th century, 80% of those in London and 98% of those in Berlin who developed the disease died [23]. The case-fatality rate also varied according to the nature of the attack-it ranged from almost 100% in fulminating smallpox to 0.5% to 2% in variola minor [24]. The ravages of smallpox were apparent in 18th-century Europe, with case-fatality rates ranging from 20 to 400 per 100 000 per year, and it is said that smallpox was responsible for 10% of deaths in Europe during that century [25]. The incidence rate varied greatly, but during epidemics it was as high as 37.5% in Boston in 1752 [26], 43.1% in Hastings in 1730 and 1731, and 92.7% in Chester in 1775 [25]. In Copenhagen between 1750 and 1800, the annual incidence rate ranged from 875 to 1750 per 100 000; in London between 1685 and 1801, it ranged from 313 to 2355 per 100 000; and in Sweden between 1774 and 1798, it ranged from 341 to 1024 per 100 000 [25]. The incidence rate was so high that the disease was regarded as universal or almost universal, and many authorities believed that everyone would eventually develop it [8, 25, 27]. As recently as 30 years ago, smallpox was endemic in 31 countries, between 10 and 15 million persons developed smallpox yearly, and more than 2 million persons died of smallpox each year [3].

The Art of Variolation

That survivors of smallpox became immune to the disease was common knowledge. As a result, physicians and others intentionally infected healthy persons with smallpox organisms in the hope that the resulting infection would be less severe than the naturally occurring illness and would create immunity. Children were exposed to organisms from persons with mild cases of smallpox, and various forms of material from persons with smallpox were administered to healthy adults in different ways. This method of immunization was named variolation and involved taking samples (vesicles, pus from pustules, or ground scabs) from patients in whom the disease had been benign and introducing this material into other persons through the nose or skin [28]. In China, powdered scabs of smallpox pustules were blown into the nostrils of healthy persons through a tube [29]. In India, variolation took several forms, the most common of which was the application of scabs or pus from a person with smallpox to the intact or scarified skin of a healthy person [30]. In China, 100 years before Edward Jenner, healthy persons took pills made from the fleas of cows to prevent smallpox; this is the first recorded example of oral vaccination [31]. The technique of variolation was spread by the caravaners (merchants traveling by caravan to sell their wares); for these persons, protection against smallpox was obviously a great advantage.

Variolation was known and practiced frequently in the Ottoman Empire, where it had been introduced by Circassian traders around 1670. Women from the Caucasus, who were in great demand in the Turkish sultan's harem in Istanbul because of their legendary beauty, were inoculated in childhood in parts of the body where scars would not be seen. These women must also have brought variolation to the court of the Sublime Porte [32].

Variolation came to Europe at the beginning of the 18th century with the arrival of travelers returning from Istanbul. The Royal Society of London received a communication in 1714 from Emanuele Timoni [33] and another in 1716 from Giacomo Pilarino [34]. These reports described the Turkish method of cutaneous inoculation; however, they did not change the ways of conservative English physicians, despite the rate at which smallpox was ravaging the country at that time.

Lady Montague

The English aristocrat Lady Mary Wortley Montague was responsible for the introduction of variolation into England. She had an episode of smallpox in 1715 that disfigured her beautiful face, and her 20-year-old brother had died of the illness 18 months earlier [35].

In 1717, Lady Montague's husband, Edward Wortley Montague, was appointed Ambassador to the Sublime Porte; the family left for Istanbul on 15 March. Two weeks after her arrival, Lady Montague wrote to her friend Sarah Chiswell (who died of smallpox 9 years later) and described the method of variolation used at the Ottoman court. She called it "ingrafting"; it was a procedure done by old women, who made four or five scratches or a slight puncture on the arm and introduced material taken from smallpox pustules from patients who had mild cases of the disease [19]. Lady Montague was so determined to prevent the ravages of smallpox and so impressed by the Turkish method that she ordered the Embassy surgeon, Charles Maitland, to inoculate her 5-year-old son in March 1718. On returning to London in April 1721, she had Maitland inoculate her 4-year-old daughter in the presence of the physicians of the court. Among these physicians was Sir Hans Sloane, President of the Royal Society and the king's physician [36]. This was the first professional variolation performed in England [37]. Word of these practices spread and reached the Princess of Wales and other members of the Royal Family. Charles Maitland was granted royal license to perform a trial of variolation on six prisoners at Newgate on 9 August 1721; these prisoners were promised a full pardon if they submitted to the so-called Royal Experiment [38]. The trial was observed by the court physicians and 25 members of the Royal Society and the College of Physicians. All of the prisoners survived and were released. One was exposed to two children with the illness and proved to be immune [17]. Maitland later variolated six charity children in London and successfully treated the two daughters of the Princess of Wales on 17 April 1722. Not surprisingly, the procedure gained general acceptance after this last success [32].

Two to three percent of variolated persons died of smallpox; became the source of a new epidemic; or developed other illnesses from the lymph of the donor, such as tuberculosis or syphilis [39]. Nonetheless, case-fatality rates were 10 times lower than those associated with naturally occurring smallpox, and artificial inoculation was widely practiced until Jenner's discovery; indeed, Jenner himself was variolated at 8 years of age. The primary side effect of the procedure was the appearance of smallpox itself; however, in 1722, in one of the first applications of statistics to a medical and social problem, James Jurin [40] observed that the smallpox-associated case-fatality rate was 1:14 in noninoculated children and 1:91 in inoculated children. With new improvements that reduced the likelihood of serious infection, the technique became widespread in England and reached towns and rural communities by the 1740s [32, 37]. In 1745, the London Smallpox and Inoculation Hospital was founded; this center was dedicated exclusively to the treatment and prevention of smallpox [41].

The Spread of Variolation

In Europe (although not elsewhere), the medical profession was relatively organized and the new methods of variolation became known among physicians, who inoculated on a mass scale according to the demand for protection. In the 1750s, more young princes of Europe died of smallpox, giving further impetus for the use of variolation [2]. Empress Marie-Therese of Austria and her children and grandchildren, Frederick II of Prussia (who also inoculated his soldiers), King Louis XVI of France and his children [16], and Catherine II of Russia and her son were all variolated [42].

Variolation soon reached the New World, and in 1721, Reverend Cotton Mather persuaded Dr. Zabdiel Boylston to use the technique to stop the smallpox epidemic in Boston [43-45]. Six of the 244 inoculated inhabitants (2.5%) compared with 844 of 5980 persons (14%) who developed the disease naturally died of the disease [46]. In the Boston epidemic of 1753 and 1754, Benjamin Franklin (whose son had died of smallpox in 1736) carried out a statistical study for William Heberden to assess the effectiveness of variolation and became one of its most enthusiastic supporters [47]. Variolation became widespread in the colonies of New England and especially in the city of Philadelphia, and it contributed to the notable growth in population in the second half of the 18th century. In 1766, American soldiers under George Washington were unable to take Quebec from the English, apparently because of a smallpox epidemic that reduced the number of healthy troops by half; the British troops had been inoculated [48, 49]. Smallpox was apparently one of the main causes of the preservation of Canada in the British Empire. The General of the Continental Army, who survived smallpox at 19 years of age (as evidenced by his pockmarked face) [50], proclaimed smallpox to be his "most dangerous enemy" [51]. By 1777, Washington had learned his lesson and had all his soldiers variolated before beginning new military operations [52]. He ordered new recruits to be variolated "as fast as they arrived" [51].

Cows, Milkmaids, and the Pox

In rural areas of England, Germany, France, Italy, Holland, and Mexico, it was well known that milkmaids became immune to smallpox after developing cowpox. Cowpox was characterized by the appearance of irregular pustules on cows' udders; however, the cows showed no signs of disease except for a slight decrease in milk production. In 1765, Dr. Fewster of Thornbury, Gloucestershire, wrote to the Medical Society of London to report that variolation induced no reaction in persons who had had cowpox [25]. Dr. Rolph, another Gloucestershire physician, stated that all experienced physicians of the time were aware of this [53]. In 1769, Jobst Bose in Gottingen reported the protection enjoyed by milkmaids [54].

In 1774, a farmer from Yetminster in Dorset named Benjamin Jesty vaccinated his wife, Elizabeth, and his sons, Robert and Benjamin, with material taken from the udders of cows that had cowpox. Years before, Ann Notley and Mary Read, two servants on Jesty's farm who had previously had cowpox, cared for two boys who had smallpox in the knowledge that they were immune. Because neither woman developed the disease, Jesty decided to vaccinate his family [55]. None of the Jestys developed smallpox during later epidemics, and variolation done in them several years later induced no reaction. Jesty himself was immune to human smallpox because he had had cowpox. Nonetheless, his technique did not catch on. His wife nearly lost the arm in which she had been vaccinated because of severe inflammation, and Jesty was reproached by his neighbors as an "inhuman brute" for daring to perform experiments on his own family [55].

A schoolmaster named Peter Plett performed vaccinations in 1791. Plett, who had been a tutor in Schonweide, Holland, knew of the variolation technique and had been told by milkmaids that cowpox protected against the human disease. Later, as a tutor for another family in Hasselburg, Holstein, Plett vaccinated his employer's two daughters and another child with material taken from cows; these children were the only survivors of a smallpox epidemic in Holstein 3 years later [56]. However, the hand of one of the children became severely inflamed and this dissuaded Plett, like Jesty, from performing further trials [25].

Edward Jenner

Edward Jenner (1749 to 1823) (Figure 1) was the third child of Reverend Stephen Jenner, vicar of Berkeley, Gloucestershire. At 13 years of age, he became an apprentice to Daniel Ludlow, an eminent surgeon in Sodbury, near Bristol. It was there that Jenner heard a dairymaid say "I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face" [57]. This belief was part of common lore. At 21 years of age, Jenner was apprenticed to John Hunter in London. With Hunter, Jenner learned surgical techniques and, more important, use of the scientific method, which his instructor summarized as follows [58]: "Why think-why not try the experiment?" Jenner was also interested in natural science; he classified a species that Captain Cook brought back from his first voyage. In 1772, Jenner declined Cook's offer to take part in the second voyage and returned to Gloucestershire. At Hunter's suggestion, Jenner wrote several scientific studies; the most important of these was "Observations on the natural history of the cuckoo," published in 1788 [59]. For that work, Jenner was named Fellow of the Royal Society [60].

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Figure 1. **Portrait of Edward Jenner (1749-1823) painted by James Northcote in 1803.** (Courtesy of the National Portrait Gallery, London.).

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Regardless of Jenner's other successes, the connection between cowpox and smallpox continued to intrigue him, as his comments to Edward Gardner in 1780 reveal. By 1788, Jenner was convinced of the truth of the popular belief that cowpox protected against the human disease. He drew sketches of a milkmaid's hand that showed the characteristic cowpox marks and showed them to Hunter and other experts [61]. By that time, Jenner must have been planning to test his hypothesis by inoculating persons with material from cowpox lesions and was waiting for an opportunity. The moment came in May 1796, when a milkmaid named Sarah Nelmes developed cowpox through contact with a cow. On 14 May, Jenner extracted fluid from a pustule on Nelmes's hand and used it to inoculate a healthy 8-year-old boy named James Phipps through two half-inch incisions on the surface of the arm. Six weeks later, Jenner variolated the child but produced no reaction. He performed the procedure again some months later with the same result [62].

Despite this breakthrough and the "redoubled ardour" that Jenner promised in a letter to his friend Gardner, he was not able to resume his experiments until the spring of 1798 because no new cases of cowpox were recorded in the vicinity [25]. At the end of 1796, Jenner sent an article to the Royal Society describing 13 persons who had previously had cowpox in whom variolation had induced no reaction. It also described the experiment with James Phipps. However, Sir Joseph Banks, the President of the Royal Society, and Sir Everard Home rejected the manuscript for publication in Philosophical Transactions of the Royal Society. The Council of the Royal Society repulsed Jenner because he was "in variance with established knowledge" and "incredible." Jenner was further warned: "He had better not promulgate such a wild idea if he valued his reputation" [58]. Jenner added new material to his manuscript and revised it substantially. On the advice of friends, he decided to finance its publication himself. It finally appeared under the title "An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the cow pox." The word vaccinae was from the Latin vaca, meaning "cow." Jenner described 10 cases of vaccination and 13 persons who had had cowpox in whom variolation was unsuccessful [63].

The Controversy Surrounding "Inquiry"

The reaction to Jenner's "Inquiry" was initially unfavorable, and his work was subjected to fierce criticism. Some physicians were skeptical; others had a financial interest in variolation. Shortly after publication of the article, Jenner went to London in search of volunteers for vaccination; however, after 3 months, he had found none. In the capital, vaccination was made popular by other physicians, such as the surgeon Henry Cline (to whom Jenner had given material for use in vaccination); George Pearson, from St. George's Hospital; and William Woodville, from London's Smallpox and Inoculation Hospital [64]. Jenner's findings were confirmed by Pearson, who began vaccinating in 1799; Jenner conducted a nationwide survey in search of proof of resistance to smallpox or to variolation among persons who had had cowpox. The results of this survey confirmed Jenner's theory [58]. Woodville vaccinated about 600 persons in the first 6 months of 1799 [65]; many of these persons developed generalized rashes that differed considerably from those found by Jenner. Jenner attributed this to the use of lancets contaminated with the smallpox virus [55]. It is probable that mistakes were made during the development of the vaccine; on many occasions, smallpox rashes were confused with cowpox rashes, presumably leading to the use of smallpox material for vaccination. Another possible source of error was the contamination of the pustule fluid with the smallpox virus. This was always a danger because the same lancets were used for variolation and for vaccination.

The Era of Vaccination

Vaccination done by using pustule fluid spread rapidly. By 1800, it had reached most European countries and about 100 000 persons had been vaccinated worldwide. In July of that year, only 2 years after the publication of Jenner's "Inquiry," Benjamin Waterhouse, professor of the "Theory and Practice of Physic" at Harvard Medical School, vaccinated his 5-year-old son and six servants with vaccine from England [66]. These were the first vaccinations done in the United States [67, 68]. The practice soon spread from Boston to Philadelphia, New York, and Baltimore [69].

President Thomas Jefferson had 18 members of his family, some of their neighbors, and the last Mohican vaccinated. In December 1801, Chief Little

Turtle and several of his warriors were vaccinated while on a visit to Washington, D.C., after Jefferson explained that "the Great Spirit had made a gift to the white men in showing them how to preserve themselves from the smallpox" [57, 70, 71]. The President himself vaccinated many persons [72]. Waterhouse received great support from Jefferson, who appointed him Vaccine Agent in the National Vaccine Institute, an organization set up to establish vaccination in the United States [67].

King Charles IV of Spain sent vaccine from Spain to his dominions in North and South America and Asia through the Expedicion de la Vacuna (the Balmis-Salvany Expedition) in 1803 through 1806; this was the first official program of mass vaccination overseas. The vaccine was maintained during the voyage by sequentially vaccinating, arm-to-arm, 22 susceptible orphan children brought along specifically to constitute a living chain [73, 74]. Before the expedition left Spain, a report by one of the king's physicians declared smallpox to be the "first and principal cause of the depopulation of America." The governor of the Council of the Indies noted that depopulation would mean a decrease in income from taxes that the Spanish received from the colonies and in commerce and farming. The economic benefits of such a mission would, in his view, justify paying for it from the royal treasury [2].

The impact of Jenner's work was so great that, in 1805, Napoleon himself insisted that all his troops who had not had smallpox should be vaccinated with the "Jennerian vaccine." He ordered the vaccination of French civilians 1 year later [2]. The first smallpox vaccination law was passed in the Grand Duchy of Hesse in 1807; vaccination was declared obligatory in Bavaria in the same year and in Denmark in 1810 [39].

The extraordinary value of vaccination was also acknowledged in England. In 1802, the British Parliament granted Jenner the sum of £10 000, which was worth $44 150 in 1802 and more than half a million dollars in today's currency [75]. Five years later, parliament awarded him £20 000 more [62, 76]. Jenner received honors from the universities of Harvard, Oxford, and Cambridge, and numerous scientific societies made him an honorary member. However, he was never knighted. In 1803, the Royal Jennerian Institute was founded to provide lymph for vaccination; Jenner was its first president [60]. Jenner's prestige was so great that Napoleon released English prisoners after his mediation. In 1813, Napoleon was reluctant to pardon Captain Millman, a relative of Jenner's who had fallen captive. When told who had made the request for the soldier's release, Napoleon exclaimed, "Ah, c'est Jenner, je ne puis rien refuser a Jenner!" [Ah, it is Jenner, I cannot refuse Jenner anything!] [77]. The Emperor of Austria and the King of Spain also freed English prisoners after Jenner intervened [58].

Jenner's work represented the first scientific attempt to control an infectious illness by the deliberate use of vaccination. Strictly speaking, he did not discover vaccination but was the first person to confer scientific status on the procedure and was the instigator of its popularization [41]. Jenner had been trained in the scientific method by Hunter and, in his studies on vaccination, was able to confirm his hypotheses by means of experimentation and observation. Jenner's experiments on the transmission of cowpox from human to human (not from cows to humans) were extraordinarily important because they meant that prophylaxis could be given even in the absence of the natural illness. His great merit, indeed his genius, lay in the fact that he performed exceptional experimental work on the basis of popular beliefs in the England of his times. Jenner demonstrated that the folk medicine tradition could be scientifically verified. Jenner's work established the practice of vaccination, although the term would not become widely accepted until it was adopted by Pasteur 80 years later [57].

Jenner himself showed that he was aware of the far-reaching consequences of his work when he stated that the universal application of the vaccine would lead to the eradication of smallpox. In 1802, he wrote "... 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 his practice" [78]. In 1806, Thomas Jefferson congratulated Jenner: "Future generations," he wrote, "will know by history only that the loathsome smallpox existed and by you has been extirpated" [39]. Both of Jefferson's predictions proved to be true; less than 200 years after the vaccination of James Phipps, the penultimate act of the smallpox drama was played out in a small Somali village called Merka. Ali Maow Maalin, a cook, developed the characteristic smallpox rash on 26 October 1977 and was the last person to acquire the illness as a result of direct contact with another human being. The final act was the official declaration that the illness had been wiped off the face of the earth. This occurred on 8 May 1980, when the 33rd Assembly of the World Health Organization (WHO) accepted the Final Report of the Global Commission for the Certification of Smallpox Eradication [79].

The Deadline

In 1978, injudicious manipulation of the smallpox virus in the Medical School of the University of Birmingham led to the death of Janet Parker, a medical photographer, and the subsequent suicide of Professor Henry S. Bedson, head of the Department of Medical Microbiology. This episode emphasized the need for close supervision of smallpox virus stocks in laboratories [3].

The epilogue in the history of smallpox will be the destruction of all strains of smallpox virus presently stored in the high-security facilities at the Centers for Disease Control and Prevention in Atlanta, Georgia, and at the Institute for Viral Preparations in Moscow. The virus has thus far gained two reprieves; its sentence was initially postponed to 31 December 1993 and later to 30 June 1995. In both instances, its destruction was delayed because of lack of consensus among the members of the WHO's executive board [80]. The two main arguments against destruction of the virus are that it will eliminate the possibility of future studies on the virus and that destruction of the virus in the two known repositories may not guarantee complete eradication [81-83]. The main arguments for destruction are that escape of the virus from the laboratories would be a serious risk because an increasing proportion of the global population lacks immunity to the disease and that the sequence information and the availability of cloned DNA fragments of the full genome of several strains of the virus will allow most scientific questions about the properties of the viral genes and proteins to be resolved. Finally, the decision to eradicate smallpox was a collective decision of the world community made on the basis of public health considerations; all possible measures should be taken to ensure that smallpox does not again afflict mankind [84-86].

The 97th session of the WHO's executive board that met in Geneva in January 1996 recommended to the 49th World Health Assembly that the last stocks of smallpox virus be destroyed [87]. There have also been proposals to retain 500 000 doses of smallpox vaccine and to keep the Lister Elstree strain of vaccinia virus as seed virus stock of the smallpox vaccine. The destruction would affect all stocks of smallpox virus, including variola minor, clinical specimens, and other material containing infectious smallpox virus or viral genomic DNA [87]. Genomic DNA of the smallpox virus should be destroyed in all laboratories holding such material. The current deadline for variola virus is 31 June 1999. This would represent the first deliberate elimination of a biological species from this planet but also the extinction of an old enemy that humankind will not miss.

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