

## The Smallpox Story: Life and Death of an Old Disease†

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### INTRODUCTION

Smallpox, a disease of antiquity, was one of the greatest scourges of mankind. In endemic form and in waves of epidemics, it killed and

† Dedicated to Ray, Allen, and Bitá, who, unlike their father, recollect smallpox only in connection with a childhood vaccination.

disfigured innumerable millions of people throughout the world. Variolation, the immunization of susceptible individuals with material taken from smallpox lesions, was practiced in Asia and Africa for many centuries; it was introduced into Britain by Lady Mary Wortley Montagu in 1721. As variolation was not a safe

protective measure, Dr. Edward Jenner introduced vaccination (using cowpox virus instead of smallpox virus) into Britain in 1796. As a result of widespread vaccination, smallpox declined steadily in Europe and North America. Elsewhere, however, death from smallpox prevailed. In January 1967, The World Health Organization (WHO) initiated a program for the global eradication of smallpox. This was achieved in October 1977 when the last person to acquire naturally occurring smallpox in the world recovered from this disease in Somalia, Africa. Currently, there is concern about the emergence of naturally occurring animal poxviruses (e.g., monkeypox virus, which also infects humans) as possible widespread agents of human poxvirus disease.

I became well familiar with the ravages of smallpox during my childhood in Persia and have ever since been anxiously following the progress of global efforts to eliminate this disease from the entire world. Now that smallpox is dead, it is therefore with a great sense of relief and much joy that I recount the fascinating story of the long fight with this dreadful scourge.

## THE EARLY PERIOD

### Antiquity of the Disease

Descriptions of smallpox appear in the earliest Egyptian, Indian, and Chinese writings. The mummy of Pharaoh Ramses V (Fig. 1) (discovered in 1898 and currently at the Cairo Museum, Egypt), who reportedly died of an acute illness at the age of 40 years in 1157 B.C., shows a striking rash of yellowish blisters or pustules which closely resembles that of smallpox. The pustules measure 1 to 5 mm in diameter and are found on the lower face, neck, shoulders, arms, and the lower part of the abdomen and scrotum. No rash is manifest on the chest and upper part of the abdomen. The palms and soles have not been examined. Donald R. Hopkins, Assistant Director for International Health at the Centers for Disease Control, Atlanta, Ga., was allowed on 8 November 1979 by special permission of the late President Mohammad Anwar Al-Sadat to collect and examine specimens from this mummy to scientifically determine whether Pharaoh Ramses V had died of smallpox. Electron microscopic and other immunological and virological studies of tiny pieces of skin on the shroud, which appeared to be normal, intervening skin rather than directly affected skin, did not reveal evidence of poxvirus. However, since obtaining a piece of the mummy's skin containing one or more of the visible lesions was not permitted, the negative results do not preclude death by smallpox (53).

The disease was present in India for many

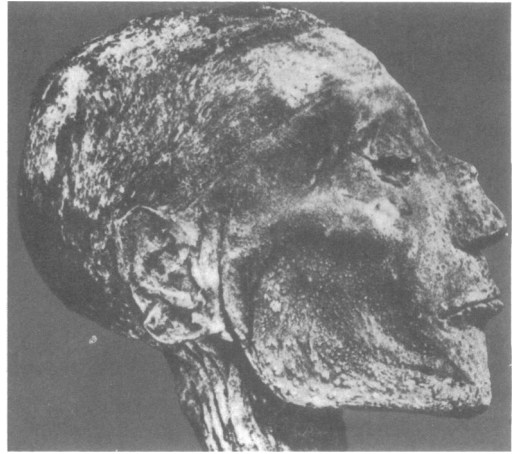


FIG. 1. Pharaoh Ramses V (died 1157 B.C.) (courtesy of the WHO, Geneva, Switzerland).

thousands of years; evidence of the preventive measure of variolation is found in the Sanskrit text "Sacteya," attributed to Dhanwantari. A special god, Kakurani, was recognized for smallpox in the Brahmin mythologies. In China, smallpox was known since 1122 B.C. during the Chou (Tcheou) dynasty (1122 to 255 B.C.), and the nasal route of variolation was practiced during the Sung dynasty (960 to 1280 A.D.) (29). Thucydides, the Athenian chronicler, described an outbreak of a disease with certain similarity to smallpox which occurred in Athens around 430 B.C. He further stated that the plague started in Ethiopia, spread to Egypt and Libya, and later was introduced into Athens by a ship coming from North Africa and docking at Piraeus (the port of Athens) (95, 101). However, medical historians have speculated endlessly about the nature of the aforementioned plague. It is striking that smallpox is mentioned neither in the Old and New Testaments nor in the classical Greek (including the Hippocratic writings) and Roman literatures. The disease described by Eusebius as occurring in 302 A.D. in Syria appears most likely to be smallpox. Marius, the Bishop of Avenches, first used the word variola in his "Chronicle" of 570 A.D., but it is not certain that he was describing smallpox since no clinical description was given. However, it is possible that the disease described by Gregory of Tours in 580 A.D., which fits the description of smallpox well, was the same as that described by Marius 10 years earlier (29).

### Smallpox During the Middle Ages

The Persian physician Rhazes (Fig. 2), who in 910 A.D. wrote the first differential and graphic description of symptoms of smallpox and measles in his classic monograph *A Treatise on*



FIG. 2. Rhazes (Abu Bakr Mohammad Ibn Zakariya Al-Razi) (865 to 925 A.D.) (courtesy of Parke, Davis and Co., Detroit Mich.), Chief Physician at Baghdad Hospital, was considered the greatest physician of the Islamic world. He was also a celebrated alchemist and Moslem philosopher. He regarded himself as the new Islamic version of Hippocrates in medicine. His two most important medical books are *Kitab Al-Mansouri* (or the Mansouri book) which he composed for the Persian ruler of Ray (a city near Tehran, Iran, where Rhazes was born and returned to in his later years to die), Mansour Ibn Ishaq Samani (this work became popular in the west through Gerard of Cremona's twelfth century Latin Translation), and *Kitab Alhawi* (or the comprehensive book—composed by his students from his notes after his death at the request of Abol-Fazl Mohammad Ibn Al-Amid, Grand Vizier of the Buyids, Persian rulers of west Persia and Iraq between 945 and 1055) in which he surveyed Greek, Syrian, Indian, and early Islamic medicine. This work was translated into Latin by Ferragut ben Salem in 1279. Throughout his medical writings, Rhazes added his own considered judgment as well as his own wide-ranging clinical experience as detailed rational commentaries. The scholarly Rhazes was a very compassionate physician who gave away his fortune to the poor. He refused treatment for his cataract, which blinded him toward the end of his life, saying "I have seen enough of this world." (Al-Razi or The Razi, which was latinized to Rhazes, means "of or from the city of Ray.")

*Smallpox and Measles*, stated that smallpox was described by Galen in the second century (90). However, it is generally believed that although smallpox was prevalent in China and India some 1,000 years before the advent of Christianity, the first recorded epidemic of this disease further west occurred in Arabia during the sixth century. In 570, an Abyssinian (Ethiopian) army provided with war elephants, under the command of the Christian zealot Abraha Ashram, set forth from Yemen (then occupied by the Abyssinians) and attacked Mecca (now in Saudi Arabia) to destroy the Kaaba in that city. Kaaba was the sacred shrine of the Arabs, who were then heathen and kept their idols in it. According to Moslem tradition, this shrine was built by Abraham, the father of Isaac and Ishmael, whose descendents are the Jews and the Arabs, respectively. As stated in the Koran, the holy book of

the Moslems, God sent flocks of birds which showered the attacking army with stones producing sores and pustules that spread like a pestilence among the troops. Consequently, the Abyssinian army was decimated, and Abraha died from the disease; thus, the Kaaba was saved from destruction. The year 570 A.D., which is also the birth year of Mohammad, the prophet of Islam, was designated by the Mecsans as the year of the elephant (52). Medical historians have interpreted the above pestilence as an outbreak of smallpox which introduced this disease to Arabia from Africa.

Smallpox was subsequently disseminated to North Africa and Europe during the sixth, seventh, and eighth centuries by the Arab invaders. The disease first appeared in Egypt around 570 A.D. as recorded by Aaron of Alexandria. He was a contemporary of the Prophet Mohammad,

and his writings were quoted by Rhazes some 300 years later. The Arabs captured Tripoli in 647, and in 710, Spain was invaded by the Moslem Moors of northwest Africa. The Moors then crossed the Pyrenees and invaded France in 731. In his translation of Arabic medical books into Latin, Constantinus Africanus (1020 to 1087) used the term *variola* for the disease described by Rhazes in 910.

Smallpox was reintroduced more extensively into Europe by the Crusaders returning from wars in the Levant for the recapture of the Holy Land from the Moslems (1096 to 1291). Early in the sixteenth century, the disease appeared in Britain. In October 1562, Queen Elizabeth I of England, at the age of 29 years, survived a smallpox attack which left her bald with permanent disfiguring facial scars. Meanwhile, slave ships from Africa spread smallpox to the West Indies in 1507 and then to Central America, and subsequently the native Mexicans suffered heavily from this scourge. It is believed that during the smallpox epidemic of 1520 to 1522, which followed the conquest of Mexico by the Spanish Conquistador Hernando Cortes (who took the reigning Aztec Emperor Montezuma as a hostage), some 3.5 million Aztec Indians died of the newly introduced disease. Cortes invaded Mexico with 500 men and 23 cannons, introducing the disease from Cuba through an infected Negro slave owned by one of his rivals. About 5 years later, the Peruvian Empire, some 2,000 miles to the south, was devastated by smallpox. The disease first appeared in Brazil in 1563 and caused the extermination of whole tribes (29, 110).

#### Smallpox During the Seventeenth and Eighteenth Centuries

During the seventeenth and eighteenth centuries, smallpox caused deadly endemics and epidemics in Britain; at times and in certain cities, the smallpox mortality was not less than one-sixth of the birth rate. Queen Mary II of England died of smallpox in 1694 at the age of 32 years. Moreover, the disease was present in most of the major cities of Europe during the eighteenth century, and epidemic years occurred from time to time throughout the European continent. It is estimated that smallpox killed 400,000 people each year and caused more than one-third of all the blindness in Europe at the end of the eighteenth century. Five European reigning monarchs (Joseph I of Germany, Peter II of Russia, Louis XV of France, William II of Orange, and the last Elector of Bavaria) succumbed to this disease during the eighteenth century. The disease appeared in southern Africa in 1713 after its introduction into Capetown from India. Smallpox reached Australia in 1789; however, New

Zealand was spared until April 1913, when the disease was introduced to Auckland by a Mormon missionary from Utah. Hawaii was invaded by smallpox around the middle of the nineteenth century. Smallpox was introduced before the eighth century into Japan from China concurrently with the introduction of Buddhism (29, 110).

In the United States, smallpox epidemics, involving occasionally one-third of the population, occurred frequently during the eighteenth century. In contrast to Britain, where 90% of all cases occurred in children younger than 10 years, Americans of all ages were afflicted. For example, during a smallpox epidemic which occurred in Boston between April 1721 and February 1722, 5,889 cases with 855 deaths were recorded among 10,700 citizens of that city.

Smallpox, however, continued to be a great scourge among the Europeans even decades after the introduction of the Jennerian vaccination. A violent epidemic of this disease occurred during and after the Franco-Prussian War of 1870 to 1871. It involved mostly the French, who did not believe in the necessity of revaccination for continued protection. While the French army lost 23,400 soldiers to smallpox, the German army had only 278 dead from the disease. All in all, this great scourge of mankind was best described by the British historian Lord Thomas B. Macaulay (1800 to 1859) as "the most terrible of all the ministers of death." Indeed, no other disease of the past or present times has come close to smallpox in wreaking such havoc on the world population (110).

#### INTRODUCTION OF VARIOLATION INTO BRITAIN

##### Variolation in Asia and Africa

In China, India, Persia, and Africa, immunization against smallpox was initiated hundreds of years ago by variolation. According to Voltaire, the ancient Chinese inhaled dried powder of smallpox crusts through the nose in a manner similar to taking snuff. Variolation apparently spread from China across Asia to Persia and Turkey. The Persians were reported to have used a similar method by taking the powder of dried pocks "inwardly" (i.e., swallowed). In Greece, Turkey, Arabia, North Africa, and the Caspian Sea region, a modified method of variolation, namely, removing some of the thick liquid from a smallpox pustule and rubbing it into a small scratch made with a needle on the arm of a child, was widely used as an empirical folk practice. It is reported that in 1679, a man came to Constantinople from Anatolia and variolated a number of children; this is the first mention of variolation in Turkish literature. Vol-

taire also wrote that the Circassians (inhabitants of a region north of the Caucasus Mountains on the shores of the Black Sea) practiced variolation as a preventive measure against death and disfigurement of their daughters from smallpox. These people were poor and sold their beautiful daughters to the Sultans of the Ottoman Empire and the Shahs of Persia. However, travellers in the Caucasus could not confirm Voltaire's story at a later date. The physician and naturalist Patrick Russell (1727 to 1805) wrote in 1767 that variolation was commonly practiced by the Bedouins of the Middle East, including Iraq (29, 55).

Around the turn of the seventeenth century, a considerable number of the British (as well as the French, Italians, and Germans), including reputable physicians, became aware of variolation as practiced outside of Europe for protection against smallpox. As smallpox was a universal and often fatal disease in western Europe, any information about its control aroused considerable interest. The Royal Society of London (established in 1660 for the promotion of learning) was informed of the Chinese practice on 14 February 1700 by Dr. Clopton Havers (died 1702). This method of variolation was also described in a report dated 5 January 1700 from Joseph Lister, an East Indian Co. trader stationed in China, to Dr. Martin Lister (1638 to 1712), a member of the Royal Society. Later in 1712, Dr. Edward Tarry of Enfield, who had returned to Britain from Pera and Galata, claimed to have observed more than 4,000 variolated persons. Moreover, the Scottish surgeon Dr. Peter Kennedy described variolation in his book published in 1715 (29).

#### Role of the Royal Society of London

In late 1712 and early 1713, Richard Waller, Secretary of the Royal Society, started a campaign to better inform Society members of the practice of variolation by soliciting correspondents in foreign countries and the British colonies. Subsequently, on 27 May 1714, Dr. John Woodward (1665 to 1728), who formerly served on the council of the Royal Society but was expelled in 1710 for insulting Sir Hans Sloane (see below), communicated a letter in Latin from Dr. Emanuel Timoni, dated December 1713 at Constantinople, to the Royal Society. A translation of this letter was read to the Society on 3 June 1714 and was discussed by the members on 10 June 1714. Dr. Timoni (born in Chios, Greece of Italian parents) had medical degrees from Padua and from Oxford and was elected Fellow of the Royal Society in 1703. At that time, Timoni practiced medicine in Constantinople and served as the family physician to the British Ambassadors to Turkey (Sir Robert Sutton and later his successor, Edward Wortley Montagu).

His letter described the art of variolation, as observed and practiced by him, in great detail. It was published as *An Account or History of the Procuring of the Smallpox by Incision or Inoculation; As Has for Some Time Been Practiced at Constantinople* in the *Philosophical Transactions* of the Royal Society for April, May, and June 1714. It is believed that Timoni first wrote an unsigned account of variolation in 1713 for the exiled Swedish King Charles XII, who spent the summer of that year near Adrianople, Turkey, where variolation was widely practiced. The King paid Timoni 100 ducats for the unsigned Latin manuscript and sent it to Stockholm. Moreover, copies of a signed, slightly different version of the account were also sent to the Caesar-Leopoldine Academy in Nuremberg, the French Regent's Council, and scientists in Leipzig.

More information and confirmation of Timoni's account, however, was asked by Society members. Consequently, Secretary Waller on 8 July 1714 wrote to botanist Dr. William Sherard (1659 to 1728), the British Consul at Smyrna (now called Izmir in Turkey), for more information. On 7 March 1716, Dr. Sherard sent to his brother James (1666 to 1738), an apothecary and a Fellow in the Royal Society, a letter along with a printed pamphlet (published at Venice in 1715 and dedicated to Dr. William Sherard) by Dr. Jacob Pylarini. Pylarini was a native of Cephalonia and a graduate of Padua in both law and medicine and had served as Venetian Consul at Smyrna. He had previously resided in Constantinople, where he had observed the practice of variolation since 1701. Sherard's letter stated that two sons of Mr. Hefferman, the Secretary to Sir Robert Sutton, the British Ambassador to Turkey, who had been variolated in Constantinople, were sent to London in February and that the variolation marks they were bearing could be viewed by interested persons. The pamphlet, introduced at the 24 May 1716 meeting of the Society, confirmed Timoni's account of the practice of variolation and contained Pylarini's personal observations made while practicing in Smyrna and Constantinople. It was promptly printed in the *Philosophical Transactions* of January to March 1717. In the same year, an inaugural thesis on variolation was written by J. N. B. Boyer of Montpellier (later Dean of the Medical Faculty in Paris), who had travelled as a young man in the Orient and had become familiar with the practice. Moreover, it is probable that actual variolation was practiced around that time in Paris by a Greek physician named Carazan and an apprentice named J. Th. Eller of Anhalt, Germany.

Both Timoni and Pylarini described the practice as opening the pustules of a child with



FIG. 3. Lady Mary Wortley Montagu (1689 to 1762) (courtesy of the Wellcome Institute for the History of Medicine, London). Lady Mary, the eldest daughter of Evelyn Pierrepont, the first Duke of Kingston, was born on 26 May 1689 in London and received a good education at home. She married Edward Wortley Montagu, M.P. for Huntingdon, and later Ambassador to Turkey, in 1712 after a long bickering courtship. Faced with an increasingly unhappy marriage in the 1720s (her husband became insensitive and a miser), she looked elsewhere for emotional satisfaction. As she was gifted with an active intellect and a wide-ranging curiosity, she quickly emerged as a prominent and widely admired letter writer, staunch advocate of variolation, moral and political reformer, and feminist. However, her intense romantic attachment at the age of 47 years to the handsome and highly cultured but effeminate Venetian Count Francesco Algarotti (who was half her age) led to her retirement to Italy in 1739 where she lived away from her husband (although still on friendly terms with him) and children for more than 20 years (the twosome were together only in Turin for about 2 months in 1741). However, in this love affair, Lady Mary had a rival in Lord John Hervey of Ickworth who met the Venetian Count first through an introduction letter from Voltaire and made the initial introduction of the Count to Lady Mary in the spring of 1736. In parallel to Lady Mary, Lord Hervey continued to express his affection for the Count and exchanged romantic letters with him. In January 1762, after her husband's death, Lady Mary returned to London where she died in her daughter's house on 21 August 1762 at the age of 73 years from breast cancer. Lady Mary was an extraordinary woman and a lively, adventuresome mother with a very gifted pen, going beyond the boundaries of her time and class. In her feuds and eccentricities, she acquired a great number of admirers as well as many opponents; notable among

uncomplicated smallpox on day 12 or 13 of illness with a needle and pressing the pus into a clean glass vessel which was then stoppered tightly. The pus was kept warm on the bosom or in the armpit while being transported to the person to be variolated. Several small cuts were made on any fleshy part of the body by tearing up the skin with a needle or lancet which would result in minimal bleeding. However, the muscles of the upper forearm were preferred by Timoni as the site of variolation. The pus was then mixed with the blood, and the site was covered with one-half of a walnut shell or with some other object for a few hours, after which the covering was removed. Symptoms of inoculated smallpox, i.e., fever and pustules, usually appeared after 7 days. As regards the variolation of other Europeans, it is reported that the children of the French Consul in Aleppo, Syria were inoculated in 1713 and that Timoni's daughter was variolated in 1717 in Constantinople. Undoubtedly, other Europeans residing in the Near East were also variolated during this period. Both Timoni and Pylarini, however, stated that the procedure originated in Greek folk medicine but was refined in medical hands (29, 45, 78, 79, 96, 99).

The above two scientific articles, however, aroused little interest in Britain because they, as later stated by Dr. William Douglass of Boston (see below), were regarded as virtuoso amusements. London physicians of the early eighteenth century were very cautious and reluctant to risk their reputations by adopting this novel procedure in a cold northern climate where smallpox was such a severe and often fatal disease.

#### Role of Lady Mary Wortley Montagu

The awareness of the British people of the practice of variolation in foreign lands through traders, ambassadors, missionaries, sailors, etc., and the two scientific communications mentioned above apparently needed a third element for the introduction of variolation into Britain. This was seemingly provided by the unconventional and forward Lady Mary Wortley Montagu (Fig. 3), the wife of Lord Edward Wortley Montagu, the British Ambassador Extraordinary, who was sent in 1716 on a mission of reconciliation to the Ottoman Empire, which was on the brink of war with Austria. The

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the latter were poet Alexander Pope (1688 to 1744) who first adored her but after being repulsed by her in 1722 presented her as Sappho in his *The Dunciad* and other satires, and author Horace Walpole, Lord Orford (1717 to 1797), who described her as a dissolute, profligate, heartless woman (46).

Montagu with surgeon Charles Maitland and other staff members travelled overland by way of Vienna and reached Turkey on 16 February 1717. There they lived in Adrianople and Constantinople until June 1718.

Lady Mary had been stricken as a young wife of 26 years of age with smallpox in December 1715 and had suffered deeply pockmarked skin and loss of eyelashes, which gave a fierceness to her eyes. Moreover, her brother had died of this disease. While in Turkey, she became enthusiastically interested in the practice of variolation as a preventive measure against smallpox. On 1 April 1717, she wrote from Adrianople to her friend Sarah Chiswell of Nottingham: "The smallpox so fatal and so general among us, is here entirely harmless by the invention of ingrafting (i.e., inoculation) which is the term they give it." She described the operation as she saw it practiced: "by scratching open a vein in the patient and putting into it as much of smallpox venom as could lie on the head of a needle." She further wrote that she was so much satisfied with the safety of variolation that she intended to try it on her dear little son and that she was patriotic enough to take pains to bring this useful invention into fashion in Britain. Lady Mary's statement that the vaccine was inoculated into the vein is in error as it contrasts all other accounts of variolation recorded at that time.

On 18 March 1718, Lady Mary, without her husband's knowledge, who was then at the Grand Vizier's camp in Sophia, had her 6-year-old son Edward Jr. (Fig. 4) variolated (reportedly despite the opposition of the Embassy Chaplain, who called variolation an unchristian operation that could succeed only in the infidels). Her 1-month-old daughter Mary, however, was not variolated at that time because, as Lady Mary wrote to her husband, the infant's nurse had not had smallpox. This indicates that Lady Mary was aware of the infectiousness of inoculated smallpox, which apparently had not been recognized by Dr. Maitland (see below) even in 1721, when he wrote an account of variolation in Britain. The variolation of the boy was most likely suggested or approved by Dr. Emanuel Timoni, who was engaged by Lady Mary's husband Edward as the family physician, and was performed at Pera, near Constantinople, with the supervision and participation of the Scottish Embassy surgeon Dr. Charles Maitland (1668 to 1748). An old Greek woman inoculated one arm very painfully with her blunt rusty needle, and then Dr. Maitland inoculated the other with his own instrument (a lancet). Lady Mary was also influential in the variolation of the three children of the Marquis de Chateauf, Secretary to the French Embassy, which was performed at about the same time. The



FIG. 4. Edward Wortley Montagu, Jr. (1713 to 1776) (courtesy of the Wellcome Institute for the History of Medicine, London). In contrast to his younger sister Mary (see the text), Edward grew up to become a rascal and a constant embarrassment to his parents. After a number of boyhood escapades, he was sent to the West Indies and France for education with private tutors and later studied Oriental languages at the University of Leyden, Holland. He became involved in an affair of gambling and robbery in Paris and was imprisoned in The Chatelet for 11 days. Subsequently, he joined the English army and was captured and released by the French. In 1747, through the favor of his cousin, Lord Sandwich, he was elected Member of Parliament for Huntingdon. However, Lady Mary, who was repeatedly anguished by his follies, succinctly remarked that her son would never amount to anything (46).

immunization of young Edward was successful, and after her return to London by sea in 1719, she informed her friend Caroline of Anspach, the Princess of Wales (who later became the Queen of King George II) of her experience with this practice (29, 45).

In the spring of 1721, a deadly smallpox epidemic, which involved both children and adults of the aristocracy and the poor, broke out in London. Consequently, in April 1721, Lady Mary sent for Dr. Maitland (who had retired to Hertford, a small town near London) and requested him to variolate her 3-year-old daughter Mary (1718 to 1794), the future Countess of Bute, who became the very conventional and conservative wife (unlike her mother) of Prime

Minister Lord Bute. Maitland initially hesitated but later agreed on the condition that two outside physicians be called in as credibility witnesses, to which Lady Mary agreed after her initial refusal. The girl was variolated in late April, without any preliminary preparation, in both arms, and when the pocks appeared, she was examined separately under the watchful eyes of her mother (see below) by three members of the Royal College of Physicians. One member, Dr. James Keith, was so favorably impressed that he requested Dr. Maitland to variolate his remaining 6-year-old son, who had survived all of his siblings who had died from smallpox. The boy was deemed to have a warm and sanguine complexion; hence he was bled 5 ounces and variolated 10 days later on 11 May 1721. Although the above two variolations were not reported in the newspapers, the professional circles became well aware of them.

The Montagu variolation, being the first performed in Britain, is generally considered of signal importance since variolation had been hitherto regarded by the medical profession as a virtuoso amusement until Lady Mary sponsored it by having her own daughter variolated. Indeed, the private action of Lady Mary provided the needed impetus for variolation and aroused considerable interest among the medical practitioners in Britain. In July 1721, the first English treatise on variolation, written by a visiting young Portuguese physician, Jacob de Castro Sarmiento, was published in London. Shortly after, an address by the venerable Dr. Walter Harris, physician to Queen Anne, delivered before the Royal College of Physicians on 17 April 1721, with a subsequently added appendix mentioning the Montagu variolation recommending, was also published in London in August 1721.

Lady Mary is believed to have gained support for variolation from her friends, the intellectually and scientifically oriented Princess of Wales (described by Voltaire as a philosopher on the throne) and her husband. Moreover, the royal couple was also convincingly influenced in favor of variolation by the royal physicians and hence agreed to sponsor a number of human experiments. Consequently, the royal couple requested that six condemned criminals at the Newgate Prison in London be allowed to volunteer under the arrangement of the royal physicians for variolation, with freedom as their reward should they survive. Arrangements with the Newgate authorities for the selection and sequestration of the six prisoners were made in late July 1721 by the royal physicians Sir Hans Sloane and Dr. John George Steigherthal and the royal apothecary. At the request of Sloane (1660-1753), then also President of the Royal College of Physicians

of London, Dr. Maitland variolated the prisoners (three males and three females ranging in age from 19 to 36 years) on 9 August 1721. The variolation of these prisoners was supervised by Sloane and Steigherthal and was also witnessed by about 25 physicians, surgeons, and apothecaries, most of whom were members of the College of Physicians or the Royal Society or both. Sloane had previously corresponded with Dr. Edward Tarry (see above) on 29 July 1721 and had obtained more information about variolation. The convicts were inoculated on the arms and right legs; however, the inoculation was repeated on 12 August 1721 in five convicts whose inoculation sites were not sufficiently inflamed. Five of these convicts developed a mild smallpox on 13 August; one other did not because he had had smallpox the previous September. All were released on 6 September 1721. These experiments were reported in detail in the newspapers.

The protective effect of variolation was tested by sending one of these three women, Elizabeth Harrison, aged 19 years, at the expense of Sloane and Steigherthal and under the supervision of Maitland, to Hertford, where a severe smallpox epidemic was occurring. She nursed a smallpox patient at Christ's Hospital and then had close contact (i.e., lying every night in the same bed) with a 10-year-old boy with smallpox for 6 weeks without acquiring the disease. Shortly after the above experiment, Dr. Richard Mead was permitted to variolate a young woman prisoner intranasally with material obtained from a favorable smallpox patient. The woman developed smallpox symptoms promptly and more pronouncedly than those variolated by Maitland but recovered fully. Although the newspapers did not criticize the royal experiment, they were critical of Mead's experiment, alleging that the smallpox material was placed in the woman's nostrils while she was asleep. Later, Maitland variolated a few children privately in Hertford; one of them, named Mary Batt, developed about 15 pustules and transmitted the disease to six servants in the household, resulting in one death. Subsequently, on 23 February 1722, six adults, followed in March by five orphan children from St. James' Parish, Westminster, were also successfully variolated publicly in London by Maitland. Furthermore, Maitland performed the first variolation with material taken from a variolated person, instead of from a person with naturally occurring smallpox, on a child during 1722. In the same year, Maitland published an account of variolation which he dedicated to the Prince and Princess of Wales. A few years later, he went to Hanover (then belonging to the English Crown) and variolated Prince Frederick and others. In the meantime, Dr. Thomas Nett-



leton of Halifax, Yorkshire started variolation independently in December 1721 and inoculated 40 persons, who had requested to be variolated, by the end of March 1722.

The above London variolations which were publicly sponsored by the Princess and her husband and were supervised by the royal physicians were followed by the much-publicized variolation of two of the Princess's daughters, 11-year-old Amelia and 9-year-old Caroline. They were variolated by the royal surgeon Claude Amyand under the supervision of Sloan and Steigerthal and the direction of Maitland (who also supplied the inoculum) on 17 April 1722. Amyand variolated his own two children on the same day, and on the next day he variolated the six children of Lord Bathurst, who was a friend of Lady Mary (29, 45, 46, 78, 79, 80, 96, 99).

On 21 April 1722, however, the 2-year-old son of the Earl of Sunderland, who had been variolated by Maitland on 2 April, died, most likely from variolous bronchopneumonia. Moreover, one of Lord Bathurst's servants, a 19-year-old footman, who had been variolated by Maitland on 30 April, after being exposed to Bathurst's variolated children on 25 or 26 April, also died on 19 May. This latter death, however, is believed to have been due to natural smallpox (acquired at the time of exposure) and not the inoculated disease. It should be pointed out here that despite early warnings contained in Timoni's communication and also contrary to what was known to and expressed by Lady Mary in a letter to her husband in regard to the desirability of protecting susceptible individuals from exposure to inoculated smallpox (see above), both Maitland and Amyand did not realize the adverse effects of such exposures.

Much publicity and some opposition by the clergy and the medical profession followed. The Reverend Mr. Edmund Massey in a sermon entitled "The Dangerous and Sinful Practice of Inoculation," which was delivered on 8 July 1722 from the pulpit of the Parish Church of St. Andrew's Holborn, referred to variolation as "a diabolic operation which usurps an authority founded neither in the laws of nature or religion and which tends to anticipate and banish Providence out of the world and promotes the increase of vice and immorality." The surgeon Legard Sparham in a pamphlet entitled *Reasons against the Practice of Inoculating the Smallpox*, which was published in 1722, argued against inserting poisons into wounds and bartering health for diseases (96). However, in defense of variolation, Lady Mary, who had very strong feelings against the medical profession and distrusted and despised physicians, published an anonymous essay entitled *A Plain*

*Account of the Inoculation of the Smallpox by a Turkey Merchant* in a popular London newspaper (*The Flying Post*, or *Post-Master*, 11 to 13 September 1722). In this essay, she described the simple natural method of variolation as practiced in Constantinople. As Lady Mary was too much the aristocrat to become personally involved in the controversy and, at the same time, too forward in her thinking to remain passive when she felt so strongly in favor of variolation, the above essay represented her only public appearance as a proponent of this practice (79).

Lady Mary subsequently became commonly regarded in Britain and elsewhere (e.g., France, mainly due to letter 11 of the *Letters Concerning the English Nation* by Voltaire, who met Lady Mary in London in 1727) as the introducer and popularizer of variolation. Her granddaughter, Lady Louisa Stuart, wrote in 1837 what her mother, Lady Bute (see above), had told her about Lady Mary taking her variolated daughter to houses with smallpox patients to demonstrate her daughter's immunity. She also related how certain parents, nurses, and servants showed their disapproval of Lady Mary's pro-variolation activities.

#### Endorsement and Practice of Variolation in Britain

The Royal Society and many prominent London physicians, especially Sir Hans Sloane and Dr. James Jurin and certain others (e.g., Dr. John Arbuthnot, Dr. John Crawford, Dr. Samuel Brady, Dr. James Keith, and Dr. Richard Mead), after evaluating the collected statistical data, publicly endorsed the practice. This endorsement was based largely on the investigation conducted by Dr. James Jurin (1684 to 1750), the Secretary (later the President) of the Royal Society, who was also an accomplished mathematician. As suggested by Dr. Nettleton of Halifax, Dr. Jurin requested all inoculators to send him pertinent data (e.g., age, method of inoculation, number of days of sickness, number and kind of pustules, as well as the final result) on all of their variolated individuals. Jurin examined these data carefully to assess first whether variolation protected against natural smallpox and second whether it had a smaller risk than that of the natural disease, which was then assumed to be inevitable during one's lifetime. He concluded from the data collected between 1723 and 1727 that variolation did protect against natural smallpox and that the death rate from variolation ranged from 1 in 48 to 1 in 60 cases, whereas the death rate from the natural disease remained about 1 in 6 cases (29).

The practice of variolation, however, did not become widely accepted in Britain as it entailed

some risk to the inoculated individuals and their contacts. However, in spite of opposition, at least 182 individuals (mostly children of the nobility and high government officials and their servants) were variolated by 15 different inoculators by the end of 1722. As practiced in Britain, variolation was performed by taking pus from the lesions of a favorable smallpox patient and introducing it into the skin of the vaccinee by incision or puncture. During the early years of variolation, the inoculum was frequently inserted through a deep incision in the skin (as recommended by Nettleton) directly into the blood stream to facilitate the expulsion of the innate disease-causing agents by allowing the morbid humors to escape. This procedure was based on the classical humoral theory (expressed by Rhazes in the tenth century), which placed the seat of infection in the blood. According to this theory, every person was born with disease-causing agents (referred to as ferments, seeds, contagions, etc.), which at a certain period of life must be expelled through the skin. This explained why virtually every person developed smallpox at one age or another and also gave the reason for the milder disease in children, who at their tender age had not yet acquired blood-corrupting materials (79). In contrast to the above procedure, however, the variolators in Turkey made light needle scratches for inoculation. Subsequently, the British variolators realized that a light scratch was sufficient and produced the best results. In this connection, however, it should be pointed out that, in the early years, the very costly procedures of elaborate preparation and surgical deep-incision operation were advocated by a number of physicians, surgeons, and apothecaries solely on the basis of mercenary calculation. Thus, this costly practice maintained its vogue among the wealthy, who generally constituted influential protectors for the medical practitioners.

The variolation produced a local lesion, a fever starting on day 7 or 8, and a general eruption on day 9 or 10. For a number of years, prior bleeding, purgation, and a special diet for the removal of impurities were recommended by most practitioners of variolation. Although the inoculated smallpox had a shorter incubation period and was milder in most vaccinees than was natural smallpox, 17 of 897 variolated persons (2%) in the British Isles, America, and Hanover died during the first 8 years of this practice (1721 to 1729). Moreover, the danger of variolated persons spreading the disease to their contacts became well recognized. Hence, during the 1730s, since no threatening epidemics occurred in Britain, variolation was not widely practiced; however, it continued at a reduced scale and without publicity in Britain.

### Role of the Reverend Cotton Mather in Colonial America

In Colonial America, the Reverend Cotton Mather of Boston (Fig. 5) acquired some knowledge about the practice of variolation in Africa from his African slave Onesimus, given to him in 1706 by some of his parishioners. Onesimus was a Garamante (a Negro-Berber race) who had originally come from the Fezzan region (southwestern Libya) in North Africa. The curious Mather inquired about variolation from other blacks and slave traders, who confirmed the practice of variolation in Africa. Subsequently, Mather read Timoni's letter in the *Philosophical Transactions* (which he borrowed from Dr. William Douglass [see below]) in 1716 and corresponded with Dr. John Woodward (see above) in London on 12 July 1716, asking him why variolation had not been introduced into Britain. He also indicated to Woodward that he planned to persuade Boston physicians to practice variolation when smallpox recurred in that city. Moreover, the Reverend Benjamin Colman of Boston also disclosed at a later date that a "poor Negro" had informed him of the protective practice of variolation in Africa. Later, in the spring of 1721, an outbreak of smallpox was initiated in Boston (almost simultaneously with that in London) by the arrival of HMS *Seahorse*, commanded by Captain Wentworth Paxon, from the West Indies, and the outbreak became a full-blown epidemic by mid-June of that year. On 6 June 1721, Mather independently and without any knowledge of Lady Mary's pro-variolation activities in London wrote a cautious and appealing letter which contained abstracts of the Timoni and Pylarini articles and which urged Boston physicians to practice variolation. Initially, only Zabdiel Boylston (1679 to 1766) of Brookline, Mass. was persuaded, after receiving another personal letter dated 24 June 1721 from Mather. On 26 June 1721, Boylston variolated his 6-year-old son Thomas, his 36-year-old slave Jack, and Jack's 2.5-year-old son Jacky. Boylston, who had had smallpox in 1702, reported in the Boston Gazette of 17 July the successful variolation of seven more persons.

Boylston, who was the son of a physician but who had not had any formal medical training (he was alleged by some of his opponents to be a cutter of stone), was promptly opposed by all of his colleagues, including the eminent Dr. William Douglass (1691 to 1752), a graduate of the University of Edinburgh, who was the only holder of a Doctor of Medicine degree in Boston. He was also opposed by many lay townspeople who, on several occasions, assaulted him in the street. Douglass was reportedly aggrieved by not being consulted about the letter that



FIG. 5. The Reverend Cotton Mather (1663 to 1728) (reprinted, with permission, from *Cotton Mather* [11], Johns Hopkins University Press, Baltimore, Md.). Cotton Mather, American congregational minister (at North Church in Boston) and author (444 separately published works), son of the Reverend Increase Mather (President of Harvard College) and grandson of the Reverend Richard Mather (who sailed from England and settled at Dorchester, Mass. in 1636) and of the Reverend John Cotton, once considered becoming a physician but abandoned the idea after overcoming a speech impediment and returned to his religious studies. He is now generally considered as the archetype of the intolerant and severe Puritan clergymen, who fought unsuccessfully to maintain the old order of ruling clergy. However, his deep and sustained interest in science made him the first native-born American to become a Fellow of the Royal Society in 1713. Although he and his father believed in witches (as did most other people at that time) and hence did not publicly condemn the trial of witches, their strong opposition to the admission of "spectral evidence" against accused witches in the courts eventually put an end to the notorious witchcraft trials of their time (e.g., the Salem trials of 1692). His steadfast leadership in introducing variolation into Boston in 1721 was met with widespread disapproval of the Bostonians, and when he variolated his own son, Samuel, who almost died from it, the whole community was filled with wrath. A hand grenade was hurled at 3 a.m. one morning through the window of one of the rooms in Mather's house where the variolated Reverend Mr. Walter of Roxbury was recuperating. The grenade, whose fuse became detached and hence did not explode, had an attached scurrilous note to Cotton Mather. Ironically, however, it has been said that the history of preventive medicine in the United States began with the unpopular preaching of Cotton Mather and the antiestablishment practice of Zabdiel Boylston (11).

Mather sent out to Boston physicians, which contained medical information derived from books borrowed from him. Consequently, on July 24, he entered a statement opposing variolation in the *News-Letter*. However, six of the most prominent clergymen, including the Reverends Increase Mather and Benjamin Colman, replied to Douglass in the 31 July issue of the *Gazette* and defended Boylston and the righteousness of his experiments. Moreover, a number of prominent Boston citizens also supported Boylston. Later, on 16 November 1721, at a meeting of the Royal Society in London, Douglass spoke strongly against variolation. He stated that of about 1,000 persons with smallpox, 60 had been variolated, and some had had severe attacks or died. Boylston subsequently reported that by February 1722 he had variolated 242 individuals from Boston and its suburbs, of whom 6 died, which gave a mortality rate of 2.5% as compared with 15% among persons with naturally occurring smallpox during the same epidemic period (849 deaths among 5,889 cases). However, in May 1722, Boston authorities (the Selectmen) placed the practice of variolation under official control, and Boylston promised not to variolate any person without prior approval. The widespread opposition in Boston was centered around the then familiar theme that variolation was a deliberate infection of healthy persons with a serious disease and was considered a serious offense against God and mankind. It should be noted here that, ironically, in both Britain and America, variolation was introduced by two nonmedical persons, namely, an adventuresome mother, Lady Mary, and a pragmatic pastor, the Reverend Cotton Mather (11, 40).

A modification of the procedure first tried in Britain by Maitland on a child in 1722 was introduced into Charleston, S.C. by a Mr. Mowbray (a surgeon of a British man-of-war then anchored in the harbor) and Dr. James Kirkpatrick (a Scottish physician who was initially known as Killpatrick) at the time of a severe smallpox epidemic in that city from June to August 1738. The disease was imported from Guinea, Africa by the slave ship *London Frigate*, which reached the harbor on 13 April 1738. The first three persons variolated in Charleston on 21 May 1738 were the two daughters of a Mrs. Sarah Blakeway and a Miss Baker. Mowbray later used material from the pustules of a variolated person (instead of from a person with smallpox) for inoculation and repeated the process up to six times without any loss of infectivity. The above modification, as reported by Kirkpatrick, reduced the risk of generalized disease significantly, i.e., eight deaths among 800 variolated individuals (40, 104).

Kirkpatrick, whose son Thomas died of smallpox early during the epidemic, subsequently went to London and in 1743 published a revised essay (first published in Charleston in 1738) on his experience with variolation in South Carolina. He later helped in the establishment of the Smallpox and Inoculation Hospital in London (see below) in 1746 and was invited to Paris in 1756 to inoculate members of the French nobility. Kirkpatrick claimed that he was responsible for the revival of variolation in Britain. However, contrary to this claim, the resumption of large-scale variolation in Britain had already begun in the 1740s and 1750s, when smallpox epidemics recurred and the demand for protection by variolation increased. Thus, the smallpox epidemic of 1746 in London led to the establishment of the Smallpox and Inoculation Hospital, which provided free care for smallpox patients and made variolation readily available for those who wanted protection. Moreover, from the late 1750s onwards, a number of well-known variolators, e.g., Robert Sutton (an apothecary), his son Daniel (a physician who kept his method secret and amassed a considerable fortune from variolation through questionable means, such as flamboyant advertising), Thomas Dimsdale (1712 to 1800), and John Ranby (1703 to 1773), who became the royal surgeon after Amyand, achieved remarkably low mortality rates among their variolated subjects. This success was mainly due to the arm-to-arm technique, the introduction of the vaccine into a superficial (epidermis) rather than a deep (dermis) incision of the skin, the isolation of the variolated individuals, or the elimination of prevariolation medication (drastic purgation and bleeding). Dimsdale, a physician, was subsequently invited to Russia in 1768 by Catherine the Great, as a result of Voltaire's far-reaching influence, to variolate the royal family and was rewarded by a title of nobility, i.e., Baron of the Russian Empire, and 20,000 pounds in cash and annuities. The so-called Suttonian method which, in a trial experiment in 1767 on 74 children at the Foundling Hospital in London, produced an average of 20 pustules per person, consisted essentially of no preliminary preparation, using matter from an unripe, crude, or watery early-stage pustule and introducing it through a slight scratch. However, the majority of variolators did not obtain such favorable results (78, 79).

#### Variolation in Continental Europe and Colonial America

Other western European nations started to practice variolation around the middle of the eighteenth century after a number of physicians from various parts of Europe went to London to

study variolation and British inoculators travelled all over the European continent. Variolation was first practiced in Amsterdam, Holland in 1748 by Theodore Tronchin, a Genevese who also introduced the practice to Geneva in 1749. S. A. A. D. Tissot introduced variolation to Lausanne, Switzerland in 1754, and Sweden and Denmark received variolation during 1754 to 1756. Variolation was publicly performed by Tronchin in Paris in 1756 on two children, the Duke de Chartres and Mlle de Montpensier. The Empress Maria Theresa invited Dr. John Ingenhauz to Vienna to variolate two archdukes and one archduchess in 1767. Dr. William Baylies of Bath was invited to Berlin in 1775 by Frederick the Great to teach his method of variolation to 14 physicians from the provinces (29).

In the United States, variolation was widely practiced both before and during the Revolutionary War. Washington's troops were variolated in 1775 during the siege of Boston. However, concern about the possibility of variolated individuals transmitting the disease to others caused several of the 13 colonies at one time or another to pass laws against variolation or at least against its practice outside of very strictly controlled variolation hospitals or private institutions. Hence, by 1776, a number of cities were officially antivariolation. Consequently, it has been suggested that the reason for the severe outbreaks of smallpox among the colonial troops was that, in contrast to the British soldiers, only a small percentage of the American soldiers had been variolated. The severity of the smallpox outbreak among the colonial troops is vividly illustrated by the following two statements from eyewitnesses. Governor Jonathan Trumbull of Connecticut, who visited the retreating American troops in July 1775 after the failure of the assault on Quebec, stated: "I did not look into a tent or hut in which I did not find either a dead or dying man." Lewis Beebe, a young physician who attended these troops, said: "I wept till I had no more power to weep." Indeed, smallpox saved Canada for the British Empire (21).

#### JENNER SUBSTITUTES VACCINATION FOR VARIOLATION

##### Edward Jenner and his Innovation

Dr. Edward Jenner (Fig. 6) was born on 17 May 1749 in Berkeley near Bristol in southwestern England. He was the youngest of three sons and the sixth and last child of the Reverend Stephen Jenner, the Vicar of Berkeley. He lost both parents within a few weeks of each other at the age of 5 years; thus, his elder brother Stephen, who replaced his father as Vicar, directed Jenner's early years. When 7 years old, Edward Jenner was sent to the Grammar School at



FIG. 6. Dr. Edward Jenner (1749 to 1823) (courtesy of the Wellcome Institute for the History of Medicine, London).

Cirencester. In the summer of 1757, a smallpox epidemic broke out in Gloucestershire, and Jenner at the age of 8 years was variolated by an apothecary of Wooten-Under-Edge named Mr. Holbrow. During a 6-week preparation period, as Jenner told his biographer, Dr. John Baron, he was bled till his blood was thin, purged repeatedly till his body was wasted to a skeleton, and kept on a low-vegetable diet in an inoculation stable owned by the variolator. After the inoculation, from which he nearly died, he was kept at the stable for several weeks, and after being released, the enfeebled Jenner went to a small school in Wooten-Under-Edge kept by the Reverend Mr. Clissold.

When he was 13 years old, his family decided on a medical profession for the young Jenner. He was apprenticed, as was customary for medical education at that time, for 7 years to a surgeon apothecary named Daniel Ludlow in Sodbury, near Bristol, who had an extensive practice. After this apprenticeship, Jenner spent more than 2 years (1770 to 1773) with one of the giants of the age, the great surgeon and innovator of contemporary medicine, Dr. John Hunter (1729 to 1793) in London. Hunter, then 41 years old, took Jenner, then 20 years his junior, as one of his resident house pupils (as with Everard Home and Henry Cline [see below]) for 100 pounds per year, which included board, lodging, and hospital fees. Jenner moved to Hunter's house on Jermyn Street and worked at the newly

established St. George's Hospital in London. During these 2 years, Jenner acquired much experience at the most up-to-date medical school of his time and began a lifelong friendship with the great innovator. In addition to his medical practice, Hunter was a great naturalist; thus, the young Jenner, being a keen naturalist himself, followed the guidance of his mentor and later worked enthusiastically for about 20 years on such special studies as the habits of the cuckoo, the body temperatures of hibernating hedgehogs, and bird migration; these studies resulted in several scientific publications.

At the completion of his residency at St. George's Hospital in 1773, Jenner, then 24 years old, had the opportunity for a lucrative medical practice in London. However, he opted to be a country doctor and spent the rest of his life, except for brief visits to London, in Berkeley and, from 1795 onwards during the summer months, in Cheltenham. Later, he declined a partnership offered to him by Hunter in 1775. Moreover, he did not even attempt to take the compulsory examination in classics to become a member of the Royal College of Physicians. However, he became a Fellow of the Royal Society in 1788 after the publication of his celebrated article *Natural History of the Cuckoo*. In this article, Jenner indicated that the newly hatched cuckoo was responsible for the ejection of the eggs or newborn nestlings of its foster parents from the nest. This ejection was achieved by a peculiar depression between the scapulae of the young cuckoo which disappeared in about 12 days.

Jenner married the elegant and accomplished Catherine Kingscote on 6 March 1788 after being crossed in love 10 years earlier. The couple then settled in their favorite home, The Chantry, in Berkeley, which Jenner had bought earlier in the same year. Catherine (1761 to 1815) was the niece of the Countess of Suffolk and had a rich father. However, she was a sickly girl who later became virtually a permanent invalid (respiratory illness). Although her disability handicapped Jenner's social life, the couple had 27 years of a happy married life and parented three children (Edward, who died in 1809 from pulmonary consumption at the age of 20 years, Catherine, and Robert). The Jenners owned another house in Cheltenham which was a fashionable health resort, and the family spent the summer months ("the season") from 1795 onwards there since the climate was beneficial to Catherine's frail health (37, 93).

As a practicing surgeon and physician, Jenner studied various disease processes enthusiastically and performed postmortem examinations. He introduced a new method for preparing emetic tartar (antimony potassium tartarate), described

the endocardial results of acute rheumatism, studied angina pectoris, and formulated a mercurial ointment for ophthalmia later called the "Golden Eye Ointment." Moreover, he recognized the cause of Hunter's long-standing illness, i.e., angina pectoris, but abstained from publishing his findings (acute coronary insufficiency due to atherosclerosis of the coronary arteries) lest he should upset his mentor. For his significant contributions to medicine, the University of St. Andrews in Scotland, upon the recommendations of two Scottish friends of Jenner's, Dr. John Hicks of Gloucester and Dr. Caleb H. Parry (1755 to 1822) of Bath, granted him the degree of Doctor of Medicine on 8 July 1792. During two serious illnesses, namely, typhus (1794) and severe frostbite, he recorded his own signs, symptoms, and progress with remarkable clarity and clinical detachment.

The notion of cowpox protecting against smallpox was given to Jenner in 1770 while he was an apprentice to Dr. Ludlow in Sodbury by a dairymaid who was being treated by Ludlow for a pustular skin infection. She expressed confidence that her infection was not smallpox because she had had cowpox. This notion was apparently well known among the regional farmers. In *The Origin of the Vaccine Inoculation*, published in 1801, Jenner indicated that many of his patients who had contracted cowpox by milking cows with cowpox lesions on their teats resisted variolation. Moreover, as reported by Dr. Edgar M. Crookshank (see below), Fewester wrote a paper entitled *Cow Pox and its Ability to Prevent Smallpox* in 1765 and submitted it to the Medical Society of London; however, the Society did not publish it. In 1769, Jobst Bose in Germany pointed out the protection against smallpox acquired by milkmaids. Crookshank also reported that in 1781, a fairly accurate account of the natural history of cowpox, including its mode of spread in the herd through the milkers' hands and its protective effects against smallpox, was written by Mr. Nash. However, this information was not published until 1799. It is also well established that during an outbreak of smallpox in the spring of 1774, a farmer and cattle breeder of Yetminster in Dorsetshire named Benjamin Jesty (Fig. 7) vaccinated his wife, Elizabeth, and his two sons, Robert and Benjamin, aged 3 and 2 years, respectively, with material taken directly from the cowpox lesion of the udder of a cow in the herd of his neighbor Mr. Elford.

Jesty had had cowpox in his youth and was aware of the protective effect of this disease against smallpox. Moreover, he had observed that two of his servant girls, Ann Notley and Mary Read, who had had cowpox showed a solid resistance to smallpox upon repeated expo-



FIG. 7. Farmer Benjamin Jesty (1736 to 1815) (courtesy of the Wellcome Institute for the History of Medicine, London).

sure to this disease. He used a "stocking needle" and inoculated his wife on the forearm (because of her dress) and his sons on the upper arm. However, his wife developed a septic infection in addition to cowpox and he had to call the local doctor (Mr. Meech or Dr. Trowbridge of Cern) for consultation. Jesty was reproached severely (pelted with mud and stones and pursued with hoots and jeers by his neighbors) for this vaccination. He did not inoculate any other person. The two boys, however, were variolated by Dr. Trowbridge of Cern about 15 years later along with other persons in the same region because of a local smallpox outbreak. Jesty's inoculation, however, was brought to light in 1802 or 1803 by the Reverend Dr. Bell after he was informed of it by Jesty himself (see below).

Most probably, other laymen performed similar prophylactic measures, using materials obtained directly from infected cows. However, as later indicated by Jenner himself and confirmed by others (e.g., Dr. J. B. Estlin and Dr. R. Ceely), inoculation of humans with material from primary cowpox in cattle was frequently unsuccessful. There is no evidence to indicate that Jenner was acquainted with either Fewester or Nash or that he was aware of any cowpox inoculations by Jesty or others when he initiated his experimentation.

The Sodbury dairymaid's remark about the protective effect of cowpox against smallpox

had apparently left an indelible impression on Jenner. He mentioned the Sodbury incident to Hunter, who, as usual, suggested more experimentation and less speculation to prove the notion. Subsequently, a smallpox epidemic in 1778 rekindled Jenner's interest in cowpox, and he started to investigate the validity of this country lore. As mentioned above, Jenner himself was variolated as a boy in 1756 and nearly died of the combined effects of the preparation and inoculated smallpox. Before his introduction of vaccination, Jenner practiced variolation with increasing uneasiness and never showed any enthusiasm for it. Thus, the search for a safe and effective measure against smallpox was of immense importance to him.

In 1787, Jenner became familiar with a disease called grease (or greasy heels) of horses, which he then thought to be the source of cowpox. Grease was observed in horses kept in wet and muddy conditions; however, relocation to dry paddocks usually lead to their recovery. The disease became extinct at the beginning of the current century. Later, after observing cases of cowpox, Jenner went to London in 1788 with a drawing which showed the hand of a milker with cowpox and presented it to Dr. John Hunter and Dr. Everard Home (1756 to 1832), who was a member of the Royal Society, and other practitioners of medicine, including Dr. Richard Worthington and Dr. Henry Cline (see below). He discussed his ideas about the protective effect of cowpox against smallpox with his peers. Hunter again strongly suggested experimentation instead of speculation.

In 1789, when the nurse of his 10-month-old son Edward contracted what was then called swinepox (also called pigpox and occasionally cowpox), Jenner, with the cooperation of Dr. Henry Hicks, inoculated infant Edward and two young female servants of a neighboring family with material taken from the nurse's pustules. The infant developed a mild pustular disease. Subsequently, on 12 January 1790, Jenner variolated his son and the nurse; he observed a solid immunity in both. Moreover, for about 10 years, Jenner carefully studied and recorded individuals who became refractory to variolation or natural smallpox after being infected with the cowpox virus. He requested that his medical colleagues in western counties of England help him investigate the notion that cowpox protects against smallpox; however, they emphatically expressed to him that the notion was nonsense and merely an old wives' tale. Jenner nonetheless continued his investigations, personally examined cows and humans with cowpox, and acquired expertise in distinguishing true cowpox from spurious kinds. However, Jenner also observed in 1791 that under certain circumstances

infection with cowpox contracted from infected cows (as for milkers) did not always protect against smallpox. He asked an artist, Mr. Cuff, to draw pictures of cowpox in both cows and humans. These extended investigations convinced him of the protective effect of cowpox against smallpox under appropriate conditions. Consequently, he decided to use material from a typical human cowpox lesion as the inoculum for immunizing susceptible humans. He also decided to transfer cowpox from person to person without resorting to the bovine disease material for inoculum because he believed that there was more than one type of cowpox.

On 14 May 1796, Jenner immunized 8-year-old James Phipps of Berkeley (after obtaining his parents' permission) with material taken from a typical cowpox lesion on the hand of a milkmaid named Sarah Nelmes, who lived near Berkeley. The lesion had appeared on a part of her hand, previously injured by a scratch from a thorn, after milking an infected Gloucestershire cow called Blossom. The immunization of the boy produced a relatively mild vesiculating lesion which healed within 2 weeks. Phipps, who had never had smallpox, was challenged (variolated on both arms) with material from a real smallpox lesion on 1 July 1796; he showed a solid immunity. Although Phipps was believed to have a tuberculous hip or spine, he lived to a ripe old age and was variolated some 20 times to demonstrate his immunity to smallpox. As a sign of gratitude, Jenner built for him in 1818 a house in Berkeley, planting the roses in the garden with his own hands, which still stands today.

Jenner prepared a paper describing the details of the Phipps experiment along with the case histories of 13 other individuals who had had either grease or cowpox before either being exposed to natural smallpox or being variolated. Three of these involved naturally acquired grease. In the first case, subsequent variolation produced minimal effect; in the second, the normal expected effect was observed; and in the third, natural smallpox developed. The other 10 individuals had casual cowpox, and all subsequently exhibited resistance to natural smallpox or variolation. Jenner submitted this paper to the Royal Society on 10 July 1797 through his friend and council member Sir Everard Home. The manuscript was reviewed by Sir Joseph Banks (1743 to 1820), President of the Society, and Lord Somerville, President of the Board of Agriculture, who decided that it did not merit publication because of insufficient data. It was simply returned to Jenner without being read to the Society. Two copies of this manuscript still exist, the first in the Royal College of Surgeons and the second in the Wellcome Medical History Museum in London.

Jenner, however, was undaunted. He planned to collect further evidence and repeat his procedure as soon as possible. However, no cowpox material became available until the end of February 1798, when a mare developed horsepox (grease), and the cows on the same farm followed with cowpox. Thus, on 16 March 1798, he inoculated 5-year-old John Baker with material taken from the hand of Thomas Virgoe, who apparently had been infected with grease or greasy heels of the mare, and 5.5-year-old William Summers with material taken from the nipples of a cowpox-infected cow. Jenner initially proposed that grease of horses (now an extinct disease) was the origin of cowpox; however, he later abandoned this idea and stated that only vaccines derived from cowpox-infected cows were reliable. Baker subsequently died of a fever unrelated to the inoculum, which was most probably erysipelas caused by contaminating bacteria at a parish workhouse. Summers developed typical cowpox lesions and provided material for the vaccination of William Pead on 28 March 1798. Pead, in turn, on 5 April, was the source of vaccine for several persons, one of whom was 7-year-old Hannah Excell. This girl then provided the material for the vaccination of four more children, one of whom was Jenner's 11-month-old son Robert, in whom the vaccine did not take. The other three, J. Macklove, M. James, and Mary Pead, developed cowpox, and material from Mary Pead was used to vaccinate a 7-year-old boy, J. Barge, the fourth person who had been successively vaccinated with material obtained from William Summers by the arm-to-arm transfer (a total of five successful serial passages). In the meantime, Summers was challenged by Jenner with smallpox inoculum and showed a solid immunity. Jenner used quills to store lymph from person to person and observed that the inoculum remained viable for days or even weeks.

In June 1798, when he was 49 years old, Jenner published, using his own meager resources, a 64-page monograph with four colored plates printed by Sampson Low of London. It was entitled *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 "Cowpox"*. Jenner dedicated the work to his friend Dr. Caleb H. Parry of Bath. Subsequently, Jenner published three more books: *Further Observations on the Variolae Vaccinae* (1799), *A Continuation of Facts and Observations Relative to Variolae Vaccinae or Cowpox* (1800), and *The Origin of the Vaccine Inoculation* (1801). The second edition of *An Inquiry* with added data and a dedication to the King was presented to His Majesty by

Jenner in person on 7 March 1800. The third edition, which was later translated into many languages, was published in 1801. A total of 23 cases, of which 7 involved cowpox virus inoculation, with 4 of these being subsequently challenged (James Phipps and William Summers by himself, and William Pead and J. Barge by his nephew, Dr. Henry Jenner) with the smallpox virus, were reported by Jenner in *An Inquiry*. In this monograph, Jenner concluded that cowpox confers lifelong protection against smallpox (see below) and that his immunization procedure (vaccination) was safer than variolation.

The term *variolae vaccinae*, which means smallpox of the cow, was coined by Jenner, and from it the term vaccination was derived and used by surgeon Richard Dunning of Plymouth in his pamphlet *Some Observations on Vaccination*, published in London in 1800. Later, when Pasteur developed his anthrax vaccine, he adopted the term vaccination in 1881 as a tribute to Jenner, for any protective inoculation. Jenner, however, was bitterly attacked about a century later by his archenemy Dr. Charles Creighton (see below) for coining this Latin phrase because he (Jenner) had not taken the examination on classics. Furthermore, Creighton believed, as did Dr. Benjamin Mosely, one of the contemporary critics of Jenner, that cowpox was not related to smallpox and that it was really modified syphilis. Some of Jenner's contemporary opponents called his innovation cowpoxing.

Jenner's proposal, which was based on conclusive, although limited, evidence, was initially met with indifference and later, when it appeared successful, with violent opposition from most of his medical colleagues. He went to London with a supply of his vaccine and stayed there from 26 April to 14 July 1798 (during which time *An Inquiry* was published) trying, in vain, to convince his colleagues of the validity of his immunization procedure. He hoped that somebody would use his vaccine and repeat his experiment. However, to his utter disappointment, his innovation was characterized by his opponents as unnatural and dangerous.

A fortnight after returning to Cheltenham from the above disappointing trip, however, Jenner received a very encouraging letter from Dr. Henry Cline (1750 to 1827) (one of Hunter's old students and then a surgeon and lecturer in anatomy at St. Thomas' Hospital) informing him of the efficacy of his vaccine. In July 1798, Jenner had inadvertently left a quill containing vaccine derived from Hannah Excell (see above) with Cline who subsequently used it (then stored in the quill for about 3 months) as a counterirritant in a boy with an inflamed hip joint to induce a discharge from the joint. However, Cline was later informed by his colleague Dr. Lister (for-



merly a physician at the Smallpox Hospital) that the boy had been rendered immune to inoculated smallpox. This observation communicated by Cline and Lister to their colleagues produced a blaze of publicity and helped greatly in the popularization of Jenner's vaccination in Britain. Cline also inoculated three other individuals with the same vaccine; however, no take was observed in these vaccinees (5, 9, 29, 37, 75, 93, 95).

#### Jenner's Opponents and Supporters

Jenner, however, was subsequently confronted with cartoons showing vaccinated babies growing cow-horns or cows erupting from inoculation sites (e.g., James Gillray's 1802 notorious cartoon captioned *The Cow Pock or the Wonderful Effects of the New Inoculation* [Fig. 8]), disreputable books ascribing strange results to vaccination, and mere vicious abuse by certain anti-vaccination people. Moreover, a number of London physicians tried to take the title of "Discoverer of Vaccination" away from him and subsequently in 1805 invited old Benjamin Jesty and his son Robert to London (at the expense of the Original Vaccine Pock Institution set up in Golden Square by the self-promoting Dr. George Pearson [see below]) in an attempt to prove that Jenner was a fraud. The guest of honor, Jesty, was presented with two gold-mounted lancets (which he had never used) and a testimonial stating that he had afforded decisive evidence of having vaccinated Mrs. Jesty and the two boys in 1774. Jesty had previously

met with the Reverend Dr. Andrew Bell, the Vicar of Swanage, while the latter was engaged in the vaccination of the people in his rectory during 1802 and 1803. He had expressed the desire to declare himself as the discoverer of vaccination. However, Dr. Bell advised him that it was too late for such a declaration. Jenner understandably was immensely hurt by the deeds of the above group whose motivation was solely a spiteful jealousy.

Jenner's opponents were a formidable group of prominent London physicians. They included Dr. William Woodville (1752 to 1805) (a Quaker from Cumberland and the Director of the Smallpox and Inoculation Hospital in London near St. Pancras which was founded in 1746 [Fig. 9]) and the aggressive and very dynamic Dr. George Pearson (1751 to 1828) (physician, chemist, and teacher at St. George's Hospital and a member of the College of Physicians [Fig. 10]). The two ironically had adopted the Jennerian innovation and, using their own cow-derived vaccines, inoculated thousands of people, unequivocally confirming Jenner's claim.

The vaccines initially used by Woodville and Pearson were obtained in January 1799 from Mr. Harrison's dairy farm in Gray's Inn Lane near London. Woodville took Mr. Thomas Tanner, an authority on veterinary surgery and a friend of Jenner, to this farm for inspection of the infected cows, and Tanner made a diagnosis of cowpox. Woodville then obtained material from the pustules on the udder and used it to inoculate seven persons (including 17-year-old Jane Col-



FIG. 8. *The Cow Pock* by James Gilbray (1757 to 1815), (courtesy of the History of Medicine Library, The University of Kansas Medical Center, Kansas City).



FIG. 9. Dr. William Woodville (1752 to 1805) (courtesy of the Wellcome Institute for the History of Medicine, London).

lingridge [see below]) on 21 January 1799 at the Smallpox Hospital; however, the inoculated persons were not isolated from the smallpox patients. On 24 January, he returned to the farm and obtained material from one of the infected milkers, Sarah Rice, and used it to inoculate five additional persons at the same hospital, again without any isolation measure. As several of these vaccinees were exposed to natural smallpox within 1 week, Woodville variolated them, for prophylactic purposes, shortly after vaccination. These patients were under the care of an apothecary named Mr. Wachsels who kept no records of them. In a conference attended by Sir Joseph Banks, Lord Somerville, Dr. William Watson (one of the King's physicians), Dr. Robert Willan (1757 to 1812) (the renowned dermatologist), Woodville, and Pearson, which was held at the dairy farm, the pustules on the infected cows and milkers were compared with the pictures drawn by Mr. Cuff in *An Inquiry*; it was concluded that both the cows and milkers at the farm had typical cowpox. At this time, Pearson obtained some pus and used it to start his vaccination program in collaboration with Woodville.

Pearson, however, had previously met Jenner during the latter's visit to London in 1798 but showed no interest in vaccination until Cline's successful use of Jenner's vaccine was publicized. He then perceived the possibilities of

fame and fortune for himself and thus lost no time in his vigorous attempts to attain them. From answers to his inquiries to various medical practitioners, some of whom were cognizant of the protective effects of cowpox, he quickly prepared a pamphlet entitled *An Inquiry Concerning the History of Cowpox Principally with a View to Supersede and Extinguish the Smallpox*, which strongly supported Jenner's findings, and published it in November 1798. Pearson then wanted to duplicate Jenner's experiments but could not find an active case of cowpox; he failed when he tried to vaccinate eight volunteers with material from an almost healed cowpox. However, he reported in his pamphlet that although three men who had had cowpox showed immunity to variolation, two other volunteer controls who had never had smallpox developed inoculated smallpox after variolation. It should be noted here that Pearson never made any significant original contribution, and his published work is based on the results of others with commentaries supporting his own self-promoting views.

Jenner came to London on 21 March 1799 and had a friendly meeting with Woodville; however, he expressed his strong objection to the lack of isolation between vaccinated people and smallpox patients at the Smallpox and Inoculation Hospital. Woodville published his first *Reports* on vaccination of about 600 persons in



FIG. 10. Dr. George Pearson (1751 to 1828) (courtesy of the Wellcome Institute for the History of Medicine, London).

May 1799; there was a high rate of general eruption, typical of smallpox, among his vaccinees. However, in June 1799, after his recognition of the importance of isolation, he reported 110 additional cases of vaccination, among which only 7 had general eruption. Woodville later published another report when the number of his vaccinated persons reached 3,001. Moreover, Woodville showed that cowpox virus passed from Sarah Rice to a vaccinee named James Crouch, could be passed back to a cow at the Veterinary College and from it, in turn, to humans. By 1802, the number of Woodville's vaccinees reached 7,500; about one-half of these were subsequently variolated without any untoward effects. Altogether, at least 100,000 persons were vaccinated by various vaccinators in Britain by 1801.

Woodville and Pearson, who were involved in most of the vaccination programs, consequently acquired the large-scale vaccination experience which Jenner never obtained throughout his medical practice in Berkeley and Cheltenham. However, they first disagreed with Jenner over the cause of generalized eruptions, which occurred in about two-thirds of their early vaccinees. Jenner contended that contaminating variolous virus in their vaccines was responsible for the eruptions and emphasized the extreme importance of medical care after vaccination. He also indicated the existence of true and spurious cowpox in nature, the latter producing atypical lesions in humans and not protecting against smallpox. Woodville and Pearson were not willing to accept Jenner's explanations. In this connection, it should be pointed that the teats of cows can be infected with a variety of bacteria and viruses, and even today, differential diagnosis usually requires laboratory work. Woodville believed that the generalized eruption in his vaccinees was due to airborne infection with smallpox virus, whereas Jenner held the view that certain batches of the vaccine itself were contaminated. Dr. John Ring (1752 to 1821), the influential London physician, described Woodville's Smallpox Hospital as the most unfit place for vaccination. However, when people were privately vaccinated at their homes, no generalized eruption was observed. Furthermore, Woodville and Pearson refused to acknowledge that Jenner was the innovator of vaccination. Later, Pearson, with utterly selfish motives and contrary to Woodville's inclinations, gave evidence against Jenner's petition to the House of Commons (which was presented by Mr. Mildmay, M.P., on 17 March 1802) for official recognition of his introduction of vaccination. In the meantime, Pearson unjustifiably pressed his own claims for recognition in the introduction of vaccination. However, despite Pearson's testi-

mony, Parliament awarded Jenner 10,000 pounds in 1802 and again an additional 20,000 pounds in 1807 to support his experiments.

The British political economist the Reverend Thomas Robert Malthus (1766 to 1834), who considered catastrophes like wars, famines, and epidemic diseases like smallpox to be divinely established checks on the reckless breeding of the underserving poor, also opposed the Jennerian vaccination. He emphatically expressed the opinion that if smallpox was eradicated by vaccination, the mortality of other diseases would necessarily increase.

The first significant opposition from the European continent came to Jenner in October 1798 in a letter from Dr. John Ingenhausz, a Dutch former student of Dr. Thomas Dimsdale (see above) and physician to the Emperor of Austria, in which he stated that his investigation indicated that cowpox does not protect against smallpox. This and subsequent communications both surprised and embarrassed Jenner.

As Jenner had ethical standards far ahead of his time and believed in actions rather than words, he did not have the slightest interest in personally meeting, arguing, or dealing in any way with his opponents. There were several attempts to place Jenner in a position where he could be personally insulted or subjected to mob action. As recently expressed by Dr. Derrick Baxby, Jenner was a dogmatic person who made certain mistakes and did not document some of his experiences adequately. Moreover, it has been stated that Jenner did not have a pleasing personality and was not easy to work with. However, it should be realized that, after the introduction of vaccination, Jenner was confronted with very unpleasant circumstances most of which involved his medical colleagues who maliciously tried to deprive him of his well-deserved credit. Many of these opponents were indeed self-promoters and characteristically mercenary. Jenner, apparently at a time when he was greatly anguished by his opponents, described Woodville and Pearson as "snarling fellows and so ignorant withal that they know no more of the disease they write about than the animals which generate it."

On the other hand, Dr. John Baron (1786 to 1851), Jenner's close friend and contemporary biographer, presented him as a man of genius. The prominent physician and anatomist Dr. Matthew Baillie (1761 to 1828), who reported to the parliamentary commission considering the matter of awarding a cash grant to Jenner, described the Jennerian innovation as "the most important discovery ever made in medicine." Moreover, Dr. William Buchan (1729 to 1805), the famous author of the popular *Domestic Medicine*, stopped variolation and switched to



FIG. 11. *Vaccination Against Smallpox*, a caricature by George Cruikshank (1792 to 1878) depicting Jenner driving out spreaders of death and devastation (courtesy of the History of Medicine Library, The University of Kansas Medical Center, Kansas City).

vaccination immediately after the publication of Jenner's *An Inquiry* in 1798. Sir John Simon (1816 to 1904), the first Medical Officer of Health for London, in his report on vaccination prepared in 1857 for the Board of Health (which was presented to Parliament), regarded Jenner as a saint who could do nothing wrong (Fig. 11).

The opposition to Jenner and his medical innovation continued to be a most curious phenomenon far beyond any logical period. About a century later, two influential and vociferous critics of Jenner, namely, Dr. Edgar M. Crookshank (Fig. 12) (Professor of Comparative Pathology and Bacteriology at King's College who was a dresser with Lord Joseph Lister [1827 to 1912] and studied with Louis Pasteur [1822 to 1895] and Robert Koch [1843 to 1910]) and Jenner's archenemy Dr. Charles Creighton (Fig. 13) unjustifiably called Jenner a cunning charlatan. Crookshank, in an obvious gesture against Jenner, used Benjamin Jesty's portrait as the frontispiece for his book *History and Pathology of Vaccination*, published in 1889. George Bernard Shaw (1856 to 1950) regarded the Jennerian vaccination as a semisavage rite.

More recently, an attack on Jenner by Dr. Peter E. Razzell ironically appeared when his innovation had eradicated one of the most dreadful scourges of mankind. In 1977, Razzell, a sociologist and demographer from Bedford College, London, published two books entitled

*The Conquest of Smallpox and Edward Jenner's Cowpox Vaccine*. In these books, the author argues that variolation was remarkably safe and effective and that smallpox would have been eliminated whether or not the Jennerian innovation had ever been introduced. He states that the practice of variolation which caused a significant decline in smallpox mortality was directly related to the increase of England's population during the latter part of the eighteenth century. He further states that Jenner's vaccine used by most vaccinators during the first 40 years of the nineteenth century contained an attenuated smallpox virus emerging from arm-to-arm passage (following E. M. Crookshank's view at the end of the nineteenth century) and not the cowpox virus. The British author accuses Jenner of deliberate distortion of evidence and self-deception. Interested readers are referred to the above two books published by Caliban Books, Firle, Sussex, England.

Jenner pursued his medical practice in Berkeley and Cheltenham and vaccinated many poor people (at a summerhouse in The Chantry garden called The Temple of Vaccinia) who came to him for this purpose. He initially used a locally obtained vaccine in November 1798 (Stonehouse strain, obtained from a farm at the village of Stonehouse in Gloucestershire) which he used to successfully vaccinate two people (out of six inoculated) on 2 December 1798. He supplied



FIG. 12. Dr. Edgar M. Crookshank (1858 to 1928) (courtesy of the Wellcome Institute for the History of Medicine, London).

this vaccine to a neighboring surgeon, Dr. Darke, who used it to vaccinate the Reverend Colborne's two children and three other individuals in Stroud, Gloucestershire on 13 December. However, these vaccinations gave unsatisfactory results; a significant number of these vaccinees developed sore and inflamed arms.

Jenner subsequently used mainly the so-called Ann Bumpus strain of Woodville's vaccine sent to him, as lymph dried on a thread, by Pearson on 15 February 1799. Pearson distributed various strains of vaccine (as impregnated threads) widely to medical men and clergymen in Britain and to more than 100 physicians in Europe. Ann Bumpus, aged 20 years, who developed 310 pustular eruptions, was vaccinated on 6 February 1799 with material taken from Sarah Butcher who did not develop pustular eruptions after being vaccinated on 30 January 1799 with material taken from Jane Collingridge. Collingridge, aged 17 years, in turn received the initial inoculation from the cow in Gray's Inn Lane (see above) in the left arm on 21 January; she was variolated in the right arm on 26 January, 1799 and subsequently developed 170 pustular eruptions. Jenner vaccinated some 20 children, including his nephew, 3.5-year-old Stephen Jenner, in the Berkeley area with the Ann Bumpus vaccine; however, he observed a few red spots or slight eruptions in some of his vaccinees.

Jenner gave the Ann Bumpus strain of vaccine to his friend and colleague, Dr. Joseph H. Marshall of Eastington, Gloucestershire, who vaccinated 296 persons with it by September 1799 without observing any generalized eruptions. Jenner received another supply of vaccine in late April 1799, which was obtained by Thomas Tanner from a cow at Mr. Clark's farm in Kentish Town, London. He sent this vaccine to Dr. Marshall, who used it to vaccinate 127 people, with only 1 developing an additional pustule. Jenner obtained this vaccine back from Marshall at a later date; he and his nephew Dr. Henry Jenner used it to vaccinate more than 100 individuals without observing generalized eruptions. Jenner's erroneous lifelong belief that vaccination confers permanent immunity was



FIG. 13. Dr. Charles Creighton (1847 to 1927) (courtesy of the Wellcome Institute for the History of Medicine, London). Creighton was a graduate in both arts and medicine and spoke most European languages. The noted medical historian Dr. William Bulloch described him as "the most learned medical scholar of the nineteenth century" but with a character defect which made him "totally unfitted" for medical practice. He thus spent more than 30 years studying history of medicine at the British Museum and wrote the 2-volume *A History of Epidemics in Britain*, which posthumously gave him the distinction of being regarded as "Father of Modern British Epidemiology." However, because of a paradoxical twist in his mentality, he regrettably spoiled a brilliant career by his blind opposition to vaccination and his vicious attacks on Jenner. Consequently, he was ostracized by his colleagues and died a poor, lonely, and forsaken man.

subsequently recognized by the vaccinators first on the European continent and decades later in Britain (5, 8, 9, 23, 29, 92).

#### Initiation of Vaccination Programs in Europe and Worldwide Acclaim of Jenner's Innovation

The Jennerian vaccination was introduced in 1800 to the Mediterranean basin by Dr. Joseph H. Marshall and Dr. John Walker, with Jenner's sanction. They sailed on HMS *Endymion* from Portsmouth on 1 July, introducing vaccination to Minorca in September, Gibraltar in October, and Malta in December. Later, under the patronage of the Catholic Church, vaccination was introduced to Naples and Palermo. Vaccination was also introduced to France in 1800 when Dr. Woodville and Dr. Aubert (a French physician who went to London to be trained by Woodville) took a supply of vaccine to Boulogne and successfully vaccinated a number of children. As Woodville's vaccine became inactive when they reached Paris, the Boulogne children provided the vaccine for the capital city. In Russia, under the leadership of Empress Dowager Marie Feodorovna, a supply of vaccine was received in Moscow from Breslau, Prussia on 1 October 1801 and was used successfully on the same day to vaccinate a boy at the Moscow Foundling Home. The Empress renamed the boy Vacinoff and awarded him a dacha and a lifetime dowry. A newly vaccinated girl from the above home was sent to the St. Petersburg Foundling Home at the end of October and provided vaccine for all orphans above the age of 7 days at that home. The Empress's continued patronage led to the extension of vaccination to other regions of the country (29).

To provide viable vaccine to India, Jenner was consulted by the Secretary of State, Lord Hobart. Jenner proposed the concept of using relays of vaccinated individuals who would be vaccinated successively at 8-day intervals aboard ship. When Lord Hobart rejected this project, Jenner suggested to his influential Tortuga-born Quaker friend and supporter Dr. John Coakley Lettson (1744 to 1815) that a similar project should be financed by public subscription and offered 1,000 guineas toward it. However, Jenner's initial efforts to send his vaccine to Bombay, India on commercial vessels of the East India Co., which went around the Cape of Good Hope (a voyage of 10,500 nautical miles), were unsuccessful.

Jenner's vaccine was maintained by arm-to-arm passage during the first half of the 19th century. However, fresh material from an active case of bovine cowpox was introduced occasionally. In the mid 1840s, Dr. Negri of Naples propagated the vaccine virus in cows, initially using humanized lymph, and thereafter the bovine lymph (obtained from vesicular lesions of

the skin) from inoculated cows was used for human vaccination and propagation of virus in cows. In 1850, Dr. Cheyne of Britain mixed the bovine lymph with glycerol, which prevented the decomposition of the vaccine and allowed its prolonged storage. The above method of preparation was introduced to France by Lanois in 1864 and subsequently to most of Europe. In the United States, calf lymph was first distributed by Dr. H. A. Martin of Boston in 1870, the original lymph (Beaugency strain) being obtained from France. In Britain, however, calf lymph vaccine was introduced in the 1880s, and the Vaccination Act of 1898 finally prohibited the arm-to-arm vaccination. The technique of scarifying the entire flank of a cow and producing a large quantity of vaccine was eventually introduced. During the latter part of the nineteenth century, physicians in the United States sometimes brought cowpox-inoculated calves into their offices, scraped vaccine from their flanks, and used it directly to vaccinate their patients (Fig. 14). This method was used until the early years of this century in certain localities in India, where an inoculated cow was lead from door to door, and a bit of matter was scraped off for the vaccination of residents at each door.

Jenner received many honors and awards from emperors and kings and from various groups and organizations throughout the world. He gave a royal command performance in 1800 when he personally vaccinated the 85th Regi-



FIG. 14. Vaccination in New York City, circa 1870 (courtesy of the Bettmann Archive, New York).

ment of Foot in London. To promote universal vaccination, Jenner's friends formed a Jennerian Institution which, after the King's consent, was called the Royal Jennerian Society with the Queen as its patron. Jenner and Dr. John Walker became its first President and Resident Vaccinator, respectively, on 3 February 1803. After leaving the above position, Walker founded the London Vaccine Institute, which also promoted free vaccination. However, in 1808, the British Government created the National Vaccine Establishment (whose plan was submitted by Jenner) for the purpose of evaluating the benefits and dangers, if any, of vaccination, with Jenner as its Director and his loyal friend, Dr. James Moore, as Assistant Director. The activities of this establishment eventually overshadowed all other private institutions concerned with smallpox. However, Jenner resigned from his directorship position over disputes with members of the Board, and Moore was appointed the Director.

When requested by Jenner to release English prisoners of war or to permit English citizens to return home, Napoleon, who was at war with Britain, remarked that he could not refuse anything to such a great benefactor of mankind. In a congratulatory letter to Jenner, President Jefferson praised him for erasing "from the calendar of human afflictions one of its greatest." A wampum belt with a letter of thanks sent to him in 1807 by the chiefs of the Five Nations of the North American Indians (among whom smallpox, which was on occasions introduced deliberately by contaminated blankets, had killed hundreds of thousands) was especially valued by Jenner, who wore the belt with pride on ceremonial occasions. The letter said: "Brother: Our Father has delivered to us the book you sent to instruct us how to use the discovery which the Great Spirit made to you whereby the smallpox that fatal enemy of our tribe may be driven from the earth. We send with this a belt and a string of wampum in token of our acceptance of your precious gift." However, in his homeland, appropriate official recognition came quite belatedly as he was appointed Physician Extraordinary to His Majesty King George IV on 16 March 1821, 2 years before his death.

Jenner was a blond, blue-eyed, robust man of middle height who wore his own hair instead of wigs, which were the fashion of his time. He enjoyed company and was a good judge of wine and food. He played both the flute and the fiddle and had a good voice. He composed poetry; two of his poems with a country flavor entitled the *Address to a Robin* and the *Signs of Rain* are of considerable lyricism and have great merit. Although normally calm and of good humor, he felt depressed when tired, irritated, or frustrated. At age 50, Jenner was introduced to freemasonry

by his cousin Dr. Henry Jenner, who practiced in Bristol. He found new companionship and relaxation in masonry and founded an ancillary lodge of science. As its permanent chairman, he attracted notable speakers and subsequently became the Master of the Berkeley lodge in 1812. In his medical practice, Jenner met the Prince Regent (the future King George IV) at Berkeley Castle in 1820. As the Prince was Grand Master of England, he conferred the title "Royal" on the Berkeley lodge when he visited it at the invitation of Jenner. Being a compassionate and generous man, Jenner was never wealthy, nor was he ever poor. After his wife's death on 13 September 1815, Jenner confined himself to a quiet life at the Chantry but kept up his correspondence and his medical work.

Jenner had a minor stroke in 1821 and died from a major attack on 26 January 1823 at the age of 73 years. He was buried in the vault of Berkeley Church beside his beloved wife Catherine on 3 February 1823. The delay was due to a futile attempt by Sir Gilbert Blane to arrange for a state funeral at Westminster Abbey, which was not to be, because the government of the British empire refused to bear the cost. However, Dr. Jenner was indeed the most universally honored person of his era (29, 37, 75).

#### Eastward and Westward Odysseys of Vaccination

After Jenner's unsuccessful efforts (see above), two physicians became prominent in the global odyssey of smallpox vaccination. Dr. Jean de Carro (Fig. 15) a Swiss who studied medicine at the Universities of Geneva and Edinburgh and resided in Vienna, and Dr. Francis Xavier de Balmis (1753 to 1819) Physician Extraordinary to King Charles IV of Spain, were the sovereigns of the eastward (Middle East, India, and Ceylon) and westward (South America, The Philippines, and China) odysseys, respectively.

Immediately after learning of Jenner's innovation, Carro wrote to his Genevan classmate at the University of Edinburgh, Dr. Alexander G. Marcet (1770 to 1822), who was then at Guy's Hospital in London, requesting a supply of vaccine. He received and used the vaccine on 29 and 30 August 1799 to perform the first vaccination in Vienna, Austria-Hungary in a physician's son. He then introduced vaccination to many European countries, e.g., large sections of Germany, Poland, Hungary, and Russia. Moreover, at the request of Thomas Bruce (Lord Elgin), the British Ambassador to Turkey, Carro sent, in the latter part of 1800, a supply of vaccine to Constantinople which the Ambassador used to vaccinate his son, and from his inoculated arm many other children were also vaccinated.



FIG. 15. Dr. Jean de Carro (1770 to 1856) (courtesy of the Wellcome Institute for the History of Medicine, London).

The vaccine used by Carro in the eastward odyssey was most likely the one he received in early 1801 from Dr. Luigi Sacco (1769 to 1836) of Milan, a physician and the Director of Vaccination in Lombardy. Sacco, who is regarded as the Jenner of Italy, later became a target for Creighton's vicious attacks as did Jenner himself (see above). He obtained this vaccine from local infected horses (or Swiss cows, according to another report) in the autumn of 1800. He vaccinated 8,000 persons by October 1801 and sent some of this vaccine to Jenner (who in turn gave it to Dr. Ring) and Woodville; it was subsequently used widely in Britain. Sacco in return received some of Jenner's vaccine.

Carro started the eastward odyssey by sending Sacco's vaccine to Baghdad (at the request of its Resident British Commissioner, Hartford Jones), where it was received on 31 March 1802; after a series of passages, it was sent to Basra. From here, under the supervision of Dr. Milne of the British consulate, the vaccine was taken by Captain of the *Recovery*, in late May, to Bombay, where it was received after 3 weeks. The first successful vaccination in India was performed by Dr. Helenus Scott on 14 June 1802 in Anna Dusthal (Anne Dulthels), the 3-year-old daughter of an Anglo-Indian servant of Captain Hardie, a British army officer in Bombay. Nineteen other people including three of his own children were also vaccinated by Scott, but all

these were unsuccessful. The vaccination program assigned to Dr. George Keir was subsequently extended to many parts of India, e.g., Hyderabad, Mysore, Malabar, Kanara, Bengal, and Madras, by the arm-to-arm transfer. Shortly after, vaccination was introduced to Ceylon and the French colonies of Ile de France and Reunion.

In the westward odyssey, Dr. Balmis used a vaccine (probably of the Sacco stock) sent to the Spanish Royal Palace as a gift in 1800 by an Italian physician. The 50-year-old Balmis, appointed on 28 June 1803 as the Director of the Real Expedicion Maritima de la Vacuna, his deputy Dr. Don José Salvany, their medical and nursing staff, and 22 orphan boys (aged 3 to 9 years) sailed on the 160-ton corvette *Maria Pita*, commanded by Lieutenant Pedro del Barco, from La Coruna, Spain on 30 November 1803. The expedition was sponsored by the Bourbon King Charles IV (whose daughter had been stricken with smallpox in 1798) at the request of the ruling council of Santa Fe de Bogota. The use of the orphan children was suggested by Jose Felipe de Flores, who had previously variolated Indians in Guatemala in 1780. The boys were vaccinated in pairs at 9- to 10-day intervals during the voyage across the Atlantic. The expedition established many vaccination centers in Spanish America, the Philippines, and China during its 3-year voyage. It called first at Tenerife in the Canary Islands and on 9 February 1804 reached San Juan, Puerto Rico. Here, to Balmis' disappointment and anger, vaccination had already been introduced in November 1803 from the Danish island of St. Thomas by Dr. Francisco Oller (1758 to 1831) with the vaccination of his son, Jose. The number of vaccinees had reached 1,500 by 9 February 1804, when Balmis arrived. The egotistical Balmis antagonized the Governor of Puerto Rico, Ramon de Castro, by denouncing Oller's work; the Governor, in turn, refused to provide him with a fresh group of boys as vaccine carriers. The expedition then sailed to Puerto Cabello on the northwestern coast of Venezuela and from there to La Guaira, the principal seaport of Caracas, Venezuela, which was reached on 20 March 1804. From here, Salvany sailed to Bogota, Colombia; Quito, Ecuador; and Lima, Peru, where he died in December 1804 from tuberculosis; however, in January 1808 his deputy, Manuel Granates, led the expedition to Valparaiso, Chile.

In the meantime, Balmis sailed from La Guaira on 8 May 1804 to Havana, Cuba and thence to Mexico City, Mexico in June 1804; however, again to Balmis' disappointment, vaccination had been already introduced to both of these locations. On 8 February 1805, Balmis, with 26 Mexican boys, sailed on the *Magellanes* from



Acapulco (Mexico) across the Pacific Ocean for Manila Bay, which he reached on 14 April 1805. He immediately introduced vaccination to Manila, The Philippines; later, he sailed across the China Sea with three Filipino boys as vaccine carriers and docked at Macao, Macao Island on 10 September 1805. After establishing a vaccination center in Canton, China (2 December 1805) with the help of the British, Balmis sailed back to Spain. On his return voyage, Balmis lastly introduced vaccination to the British island of St. Helena in the South Atlantic Ocean and was received by King Charles IV at the royal court in Madrid on 7 September 1806. During this period, vaccination was also successfully introduced to Brazil in 1804 by a group of slave children who were sent by Felisberto C. B. Pontes from Bahia to Lisbon, and had arm-to-arm transfer of vaccine on their return voyage. Uruguay probably received the vaccine through the same slave ship which brought the children back to Bahia (17).

In North America, John Clinch, a local practitioner and cleric in Newfoundland (and a friend of Jenner from his student days in England), vaccinated his own family, including a nephew who showed no ill effect after intentional exposure to smallpox, in early 1800. He used vaccine sent to him by Jenner's nephew, the Reverend George Jenner, who had previously served as rector at Harbor Grace in Newfoundland but had since returned to England to assist in Jenner's vaccination program.

#### **Role of Benjamin Waterhouse and James Smith in the Introduction of Vaccination to the United States**

Dr. Benjamin Waterhouse (Fig. 16) is credited with the popularization of vaccination in the United States. Early in 1799, Waterhouse received Jenner's book along with the pamphlet on the history of cowpox published in 1798 by Pearson (see above) and one of Woodville's reports on vaccination results published in 1799 from Dr. John C. Lettsom. He published on 12 March 1799 an article entitled *Something Curious in the Medical Line* in Boston's newspaper *Columbian Centinel*, describing the Jennerian innovation. Later, he made a presentation of Jenner's discovery and showed Jenner's book at a meeting of the American Academy of Arts and Sciences (whose President was the President of the United States, John Adams) held in the Philosophy Chamber of Harvard Hall. Waterhouse corresponded with Jenner and received a supply of live vaccine in June 1800 from Dr. John Haygarth (1740 to 1827) of Bath, who had obtained it from the young surgeon Thomas Creaser, also of Bath, who in turn had received it from Jenner (probably either the Ann Bumpus strain or the strain from Kentish Town).

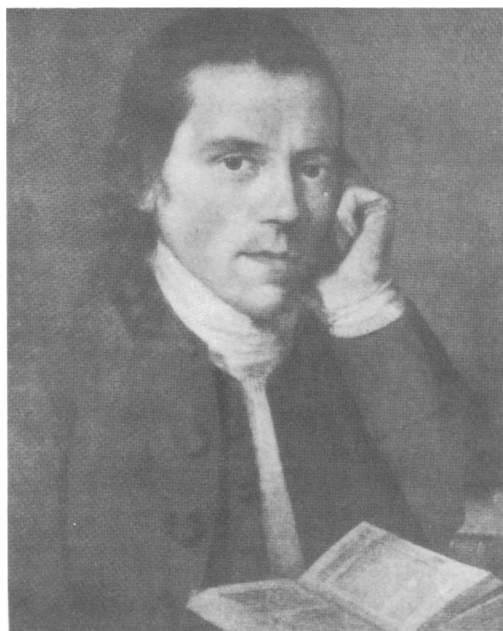


FIG. 16. Dr. Benjamin Waterhouse (1754 to 1846) (courtesy of the Redwood Library and Athenaeum, Newport, R.I.). Waterhouse was born in Newport, R.I. on 4 March 1754. Being a Quaker and an objector to war, he escaped to Britain in the early part of 1775 on what is said to have been the last ship leaving Boston. He first spent 9 months at the University of Edinburgh studying medicine, which was followed by about 3 years in London living with his mother's cousin Dr. John Fothergill, the famous London Quaker physician, and attending lectures at various London hospitals. He then studied medicine for 4 years at Leyden, Holland, where he graduated in April 1781. After graduation, he remained at that University for one additional session and attended lectures on topics not included in the University curriculum. Here, he lived for a time with John Adams, the American minister, and his two sons and became a student of the Free Republican American Federated States. He returned to Newport in June 1782, perhaps as the best-educated physician in America. In 1783, at the age of 29 years, he was appointed to the newly founded Chair of Theory and Practice of Physic at the new Harvard Medical School. However, he was deprived of his Chair in 1812 after nearly 30 years of service (see text); Dr. James Jackson succeeded Waterhouse to the vacated Chair. He died in Cambridge, Mass. on 2 October 1846 at the age of 92 years (15, 26).

On 8 July 1800, Waterhouse started his vaccination program, beginning with his 5-year-old son Daniel. From his lymph, he vaccinated his 3-year-old son Benjamin, Jr., followed by two more of his children, Mary and Elizabeth, aged 1 and 7 years, respectively, as well as a nursery maid, a 12-year-old servant, and two domestics. At the request of Waterhouse, young Daniel was

chosen from the eight vaccinees by Dr. William Aspinwall, physician at the Brookline Smallpox Hospital, for challenge. The boy was variolated at that hospital and was kept there in bed alongside a smallpox patient for 12 days without developing smallpox.

Waterhouse wrote a pamphlet entitled "A Prospect of Extinguishing the Smallpox," which he first sent to President John Adams and later, on 1 December 1800, to Vice President Thomas Jefferson who in a letter dated 25 December 1800 expressed great interest in vaccination. Later, as President, Jefferson played a valiant role in the introduction of the Jennerian innovation into the United States (see below).

During the latter part of 1800, Dr. Elisha Story vaccinated a number of adults and children (including his own daughter) in Marblehead (a port located 16 miles from Boston) with material obtained by his seafaring son from the arm of a sailor vaccinated in London. The vaccine was believed to contain cowpox virus but in reality contained smallpox virus; thus, an outbreak of smallpox with 68 fatalities ensued. At about the same time, Waterhouse had vaccinated, at his home in Cambridge, the son (8 or 9 years of age) of Dr. John Drury of Marblehead. By using material from the arm of his son, Dr. Drury vaccinated some 40 people in Marblehead; all but 1 of these developed smallpox. Much opposition to the practice of vaccination followed the above outbreak of smallpox.

Waterhouse, however, received a new supply of vaccine from Britain in March 1801 and was subsequently permitted by the Boston Board of Health on 31 May 1802 to engage six Board-appointed physicians (James Lloyd, Samuel Danforth, Isaac Rand, Charles Jarvis, John Jeffries, and John Warren) for the vaccination of a rather statistically significant number of children from the poorhouse, who would later be challenged with the smallpox virus. Thus, 19 volunteer boys were vaccinated on 16 August 1802 at the health office without any untoward effects. Subsequently, on 9 November 1802, 12 of them along with another boy, George Bartlett, who had received the vaccine 2 years earlier, were variolated at a special hospital on Noddle's Island near Long Wharf in Boston. No smallpox developed in these 13 boys, whereas 2 boys who had had neither natural smallpox nor vaccine and who were likewise variolated with the same material developed inoculated smallpox. Moreover, Waterhouse rechallenged the above 13 boys with material obtained from the latter 2 boys and again observed a solid immunity. Waterhouse's thoroughness in this early human experimentation is indeed remarkable.

In the meantime, Waterhouse, being the active promoter of vaccination and the only person

who had the vaccine in the United States, set himself up in the franchise business of vaccine distribution. During the late summer and fall of 1800, he restricted the distribution of the vaccine and issued it only to those who obtained exclusive rights from him and agreed to share at least one-fourth of the profits with him. Furthermore, Waterhouse frequently made deceitful statements in his attempts to protect his monopoly on the vaccine and continued for about 1 year to charge his colleagues for vaccine until his monopoly was broken through the efforts of Dr. James Jackson (1777 to 1867) of Boston and Dr. Thomas Manning of Ipswich. Jackson brought a supply of vaccine in September 1800 from Britain which, when used in Boston, proved inactive. However, another supply sent to Manning by his brother in London proved active, and he supplied the vaccine without charge to Jackson and other vaccinators. Boston physicians regarded Waterhouse with suspicion and hostility. Furthermore, being a Quaker, an educated controversialist, a religious dissenter, and a Jeffersonian republican did not endear him to his medical colleagues.

Waterhouse wrote to President Thomas Jefferson (who then was also President of the American Philosophical Society in Philadelphia) on 8 June 1801 and requested him to sponsor the distribution of the vaccine to the southern States. Jefferson subsequently received a number of shipments of vaccine from Waterhouse, the first of which he gave to the Reverend Dr. Edward Gantt (1741 to 1837), a respected physician in Washington and Chaplain of the Senate, to initiate a public vaccination program which did not succeed because the vaccine proved inactive. Another shipment was successfully used by Dr. Wardlaw of Monticello, Va. to vaccinate Jefferson's entire family and his neighbors (some 200 people) in Monticello. Jefferson himself had been variolated at the age of 23 years by Dr. Richard Shippen of Philadelphia. Materials from the Monticello vaccinees were taken by Dr. John Vaughn to Washington, D.C. The same vaccine was also received by Dr. John Redman Coxe of Philadelphia for large-scale vaccination programs which he started on 9 November 1801. Moreover, many Indians, including Chief Little Turtle, were vaccinated in Washington with materials from the same source by Dr. Gantt under the sponsorship of Jefferson (15, 26, 95).

President James Madison was authorized by Congress on 27 February 1813 to appoint a Federal Vaccine Agent for the preservation of the genuine vaccine matter and its distribution to all U.S. citizens. Madison appointed Dr. James Smith of Baltimore (Fig. 17) a student of Dr. Benjamin Rush at the University of Pennsylva-



FIG. 17. Dr. James Smith (courtesy of The Baltimore Museum of Art, Baltimore, Md.; bequest of Elise Agnus Daingerfield).

nia, who had started his vaccination program with vaccine received from a Mr. Taylor, who in turn had received it from his brother in London. Smith first vaccinated 7-year-old Nancy Malcum in the Baltimore Almshouse on 1 May 1801. He later organized the first Vaccine Institute in the United States in Baltimore in 1802 and pursued his vaccination program very enthusiastically. He subsequently became the main source for vaccine and had some 20 subagents throughout the United States supplying the vaccine postage free to both the civilians and the military as well as certain foreign countries in this hemisphere. Smith's usual price for vaccine was \$5.00, which he was authorized to retain for himself; however, he sent out large quantities of vaccine with no charge whatsoever. Contrary to Smith's expectation, however, no official smallpox agency was approved by Congress, and, hence, Smith established a private foundation named The National Vaccine Institute, with a projected federal charter in Washington, D.C. Again, the Senate did not approve Smith's request for a federal charter.

Smith saved many lives by his enthusiastically pursued vaccination programs. However, the above two disappointments and two subsequent setbacks in his vaccination endeavors anguished him to the limits of his endurance. In a smallpox epidemic imported to Baltimore from Liverpool,

England in the summer of 1822, a girl who had been previously vaccinated as a child by Smith himself died from smallpox. Smith, reversing his repeatedly declared opinion, expressed that vaccination did not confer complete protection and when one of his medical colleagues rightfully suggested that perhaps revaccination was needed for continued protection, the anguished Smith ironically proposed a return to variolation. At that juncture, the staunch advocate of vaccination had apparently lost his faith in a practice he had enthusiastically pursued for more than 20 years. This caused much confusion about the efficacy of vaccination in the United States and consequently delayed its widespread practice. The other setback, which occurred earlier, involved the vaccine sent by Smith on 1 November 1821 along with a letter to Dr. John F. Ward, the National Vaccine Institution's subagent in Tarborough, N.C. However, instead of vaccine, Ward received a supply of smallpox scabs labeled "varioli" with no accompanying letter. When this material was unknowingly used, a smallpox epidemic with several deaths occurred in Tarborough. Smith initially attempted to explain away the epidemic scientifically, and when the mixup in the vaccine delivery was discovered, he wrote to the Speaker of the House of Representatives explaining what had occurred. However, politics entered the vaccination issue, and the result was the repeal of Smith's mandate. Shortly after, the Institute's funds were exhausted, and Smith's ultimate goal of establishing a national vaccination center in the United States was not realized during the remainder of his life. He died in 1841 (95). Both Waterhouse and Smith have been considered by different medical historians as the Jenners of America.

The Jennerian innovation was adopted by almost the whole world as described above within 10 years of its inception. Japan was the last major country in the world to receive vaccination. The vaccine was successfully carried on a ship to Nagasaki in August 1849 by Dr. Bosch, the medical officer of The Netherlands East Indies, through the efforts of Dr. Otto G. J. Mohnike, a German physician serving with the Dutch in a trading post on islands in Nagasaki Bay. In 1860, the government sponsored vaccination, and the practice became compulsory after the extensive epidemic of 1870 and 1871.

Variolation, however, continued to be practiced in Britain until stopped by an act of Parliament in 1840; it was practiced at the Smallpox Hospital in London until 1822. Subsequently, the Act of 1853 provided for the compulsory vaccination of the entire population of England, Scotland, and Wales; however, it was not effectively enforced.

## SMALLPOX AFTER THE JENNERIAN INNOVATION

### Worldwide Prevalence

After the introduction of vaccination in 1796 by Dr. Edward Jenner, the incidence of smallpox declined steadily in Europe and North America during the nineteenth century. Vaccination became legally compulsory in Bavaria, Denmark, Hanover, Norway, and Sweden by 1821. Other European countries instituted compulsory vaccination programs soon after. During the first three decades of the twentieth century, with the exception of a few epidemic years (e.g., about 49,000 cases and 173 deaths recorded in 1930 in the United States and about 14,900 cases and 47 deaths recorded in 1927 in Britain), smallpox became of lesser importance as a cause of death among children than measles and scarlet fever in Europe and North America. However, even in 1939, 9,875 cases of smallpox were reported by physicians in the United States.

The worldwide incidence of smallpox between 1924 and 1947 was published by the WHO in June 1947. The disease was reported from most countries of the world (including those of Europe and North America) at the beginning of this period. However, between 1926 and 1941, the number of countries where smallpox occurred decreased from 79 to 69 mainly because fewer European countries (with a temperate climate and advanced health delivery systems) reported the disease. Variola minor (see below), however, continued to occur in Canada and the United States, but the number of cases became much fewer. On the other hand, in most countries of Asia, Africa, and South America, large outbreaks of smallpox continued to occur throughout this period.

The elimination of smallpox from most countries of Europe, North America, and Oceania was not achieved until the 1940s, when more widespread vaccination programs and intensive efforts to stop outbreaks wherever they occurred were initiated. This delay has been attributed to the fortunate or unfortunate replacement of the virulent variola major virus (mortality rate up to 45%) by the much less virulent variola minor virus (mortality rate about 1%) in Europe and the Americas around the turn of the century. The variola minor virus apparently originated in South Africa and spread only to other parts of Africa and the two above-mentioned continents; in the rest of the world, however, variola major virus retained its dominance.

A sharp deterioration in the control of smallpox was caused by World War II (1939 to 1945), and the number of countries where this disease occurred increased from 69 in 1941 to 87 in 1946. Large epidemics were reported from North Afri-

ca and Asia during the first half of the current century until the global eradication was initiated and became effective in late 1960s and early 1970s. Moreover, many cases of smallpox, which were often followed by epidemic transmission, were imported from the above regions into most west European countries. As examples of the large epidemics of this period in the endemic areas, India had probably more than 1,000,000 cases, with 230,849 deaths in 1944; 157,322 cases with 14,092 deaths were officially reported in 1950. These numbers, however, are believed to be much lower than the actual numbers.

The WHO, at its first meeting (with Dr. Brock Chisholm of Canada as Director General) in July 1948, decided on the creation of a joint study group on smallpox to be appointed by the Expert Committee of International Epidemiology and Quarantine. Later in February 1953, Director General Dr. Marcolino G. Candau of Brazil was requested to explore ways of implementing a campaign against smallpox which would be included as an integral part of the national public health programs throughout the endemic areas of the world. In May 1954, further studies on the most effective methods of smallpox control along with provision of assistance to various countries which requested it were approved by the Seventh World Health Assembly. The Eleventh World Health Assembly, however, noted in 1958 that smallpox still remained widespread, with endemic foci in many regions of the world which constituted a permanent threat of exporting the disease to nonendemic countries. In that year, 63 countries officially reported some 280,000 cases of this disease. In the same year, the U.S.S.R. delegation at the World Health Assembly introduced a motion for the worldwide elimination of smallpox (110). Further involvement of the WHO in the global eradication of this disease is discussed below.

### The Disease

The causative agent of smallpox is now classified as a member of Poxviridae family, which comprises the largest viruses, measuring 230 by 400 nm. They are brick shaped or ellipsoid, with an outer lipoprotein membrane (envelope) and a core of linear double-stranded DNA enclosed in a thick membrane. The virus contains several enzymes and about 100 polypeptides and has about 20 different antigens. However, all poxviruses share a common nucleoprotein antigen located in the inner core. The family includes two subfamilies, namely, Chordopoxvirinae and Entomopoxvirinae. The first includes the genus *Orthopoxvirus*, in which all of the poxviruses mentioned in this monograph are included. Biological and serological tests indicate extensive antigenic interrelationships among orthopoxvi-

ruses. These have been classified into the following three intra- and interrelated groups: (group A) vaccinia, variola major, variola minor, whitepox, and Lenny pox viruses; (group B) buffalopox, camelpox, mousepox (ectromelia), and MK-10 pox viruses; and (group C) cowpox, monkeypox, and elephantpox viruses (7). However, more work on these viruses is needed for a universally acceptable classification.

In regard to the pathogenesis of this infection as it occurred throughout the world in recent years, smallpox has been classified as two related diseases, namely, variola major (classic or Asian smallpox) and variola minor (alastrim or African smallpox), caused by two poxviruses with distinctive characteristics. In contrast to variola minor, which has a negligible fatality rate, variola major has an overall fatality rate of 15 to 45%. Moreover, the occurrence of smallpox of intermediate virulence with a fatality rate of 10 to 15% was recognized in 1970s in sub-Saharan Africa. Accordingly, various human strains of smallpox virus isolated recently in Asia, Africa, and South America (where the fatality rates of this disease ranged from highest to lowest) have been classified into A, B, and C subgroups, respectively, on the basis of hemadsorption tests performed on human diploid cell cultures infected with these viruses and maintained at 40°C. The WHO, however, recognizes six types of variola major with different fatality rates: (i) ordinary discrete, <10%; (ii) ordinary semiconfluent, 25 to 50%; (iii) ordinary confluent, 50 to 75%; (iv) flat, >90%; (v) hemorrhagic, almost 100%; and (vi) modified (altered by previous vaccination), <10%. Variola sine eruptione, observed in well-vaccinated persons, is a febrile disease which occurs after the usual incubation period has elapsed. The virus is rarely isolated from these cases; however, clinical diagnosis is confirmed by serological tests. The relationship between the clinical severity of the disease and the virulence of the causative variola virus strain has been clearly established (94).

The virus enters the susceptible host through the mucous membrane of the upper respiratory tract and, after local multiplication, is drained by the lymphatics to the regional lymph nodes. Here, further multiplication occurs, and the virus then enters the blood stream causing the primary viremia. This is followed by the invasion of the reticuloendothelial system and extensive multiplication of the virus leading to the secondary viremia. The virus then invades the epidermis, causing the skin eruptions. The patient is not infectious during the incubation period and the first 1 to 2 days of the preeruptive phase. As the rash appears, which usually coincides with the development of oropharyngeal lesions, the patient becomes infectious, espe-

cially during week 1 of this phase. Oropharyngeal secretions are the main source for contaminating the face, the body, the clothes, and the beddings of the patient. Direct face-to-face contact with a patient via infected droplets and physical contact with a patient or the contaminated articles are usually responsible for the transmission of the disease.

Clinically, after an incubation period of about 12 days, the preeruptive symptoms of headache, fever, malaise, prostration, pain in the back and limbs, and vomiting may appear suddenly or gradually. The skin eruptions usually develop after 3 to 5 days; they appear as one crop of macules which successively change to papules, vesicles, and pustules. The pustules start to scab toward the end of week 2 and the crusts fall off in about 1 week, leaving pink scars (pockmarks) which gradually fade in color. The distribution of the skin lesions is typically centrifugal, showing the greatest concentration on the face, forearms, wrists, palms, soles of the feet, mouth, and throat. The chest, abdomen, thighs, and the upper arms are relatively spared. The skin eruptions coincide with a fall in temperature (presumably due to the appearance of antibodies) which is followed by a rise in temperature (presumably due to absorption of toxic products of necrotic cells) and the pustulation of the vesicles. Conjunctivitis is manifested in some patients during the first 8 days of illness. Bacteria, especially staphylococci, may contaminate the pustules, leading to a variety of complications such as abscesses, septic joints, osteomyelitis, and corneal ulcers which may cause blindness. The cause of death is not well understood; general toxemia, septic shock, and disseminated intravascular coagulation (in the hemorrhagic type) have been suggested (Fig. 18, 19, and 20).

The four principal types of variola major are ordinary (discrete, semiconfluent, and confluent), flat, hemorrhagic, and modified. The ordinary type is seen in the majority of vaccinated and revaccinated persons whose immunity has waned and corresponds to the classical smallpox described above. The lesions are sharply raised and tend to be tense and firm to the touch. The severity of the clinical features generally parallels the extent of the rash.

In the flat type, the preeruptive phase is severe, with fever persisting to the end of the eruptive phase. The lesions mature slowly, and the vesicles, which are soft and velvety to the touch, tend to be flat and project little from the surrounding skin. In some cases, there is hemorrhage into the bases of the lesions which renders them not readily distinguishable from those of late hemorrhagic cases.

In the hemorrhagic type, the preeruptive phase, which may be prolonged, is marked by



FIG. 18. Classical smallpox (pustular stage) in an unvaccinated child (reprinted, with permission, from *Viral and Rickettsial Infections of Man*, 4th ed., J. B. Lippincott Co., Philadelphia, Pa.).

fever (with little or no remission throughout the illness), intense headache and backache, restlessness, a dusky flush or sometimes pallor of the face, extreme prostration, and toxicity. In fulminating cases, hemorrhagic manifestations appear on day 2 or 3 as subconjunctival bleeding, bleeding from the mouth or gums, petechiae in the skin, epistaxis, hematuria, and, in women, bleeding from the vagina. The patient often dies suddenly between days 5 and 7 of illness, when only a few insignificant maculopapular cutaneous lesions are manifested. When the patient survives for 8 to 10 days, the hemorrhages develop early in the eruptive phase, with flat lesions which do not progress beyond the vesicular stage.

The modified type occurs in vaccinated persons and is modified as to the character of the eruption and the rapidity of its development. The preeruptive phase is less severe than that of the ordinary type, and the evolution of the lesions may not be accompanied by secondary fever. The skin lesions are usually few and more superficial; they evolve more rapidly. Moreover, they may not exhibit the uniformity which is characteristic of typical smallpox lesions.

Variola minor (alastrim) has a pathogenesis similar to that of variola major, but the clinical features are much milder. The skin lesions generally are fewer, smaller, and not as deep as those in smallpox; they remain discrete and evolve quickly (Fig. 23). The general condition of the patient is usually good, and convalescence is rapid. Bacterial contamination and complications are very rare (13, 61, 110).

One of the WHO global eradication program workers, a 21-year-old male vaccinator from Bihar, India, developed an occupationally acquired smallpox on 8 October 1974. The disease was atypical in that there were two distinctly separate "crops" of skin lesions; the first appeared on 14 October, and the second appeared 2 days later. The victim had previously received

several successful vaccinations (the last less than 1 month before the onset of the disease). He was found to have a very low level of immunoglobulin M (IgM) but adequate levels of circulating antibodies against vaccinia and variola viruses. A deficiency in cellular immunity and absence of immunological memory in this patient were believed to be responsible for the atypical smallpox. The patient recovered within 1 month; however, he died from unrelated causes on 17 February 1976 (20).

Vaccinia immune globulin was used for the treatment of smallpox. This globulin is also used for eczema vaccinatum and accidental infection



FIG. 19. Facial scars carried by a smallpox survivor for the rest of her life (courtesy of the WHO, Geneva, Switzerland).

of the eye with vaccinia virus (56). In three field trials, methisazone (Marboran) was used as an effective prophylactic drug (48). Moreover, human leukocyte and fibroblast interferons have been effectively used for the prevention of vaccinia lesions in monkeys (106). Adenine arabinoside and cytosine arabinoside proved ineffective in the treatment of variola major (62, 82).

Histopathologically, the skin lesions start with the proliferation of the prickle cells due to viral invasion. Dilatation of capillaries in the corium with swelling of the endothelial lining and infiltration of mononuclear cells especially around the vessels are also present. The malpighian cells then become edematous and undergo ballooning degeneration. The cell walls of the affected cells break down to form vesicles between the horny layer (as roof) and corium (as floor). Small vesicles coalesce with their neighboring ones, forming larger vesicles which become filled with tissue debris and white cells. Similar lesions also occur at the same time in the mouth and esophagus. Due to the absence of a horny layer in the mucous membrane, the mucosal vesicles rupture early in the disease and shed virus into the secretion before the skin lesions become infectious. The infected epithelial cells of the skin and mucous membrane lesions show the typical intracytoplasmic eosinophilic Guarnieri inclusions (13). Permanent facial pockmarks (normally more than five) are observed in about 75 and 7% of patients recovering from variola major and variola minor, respectively (58).

As indicated above, smallpox is generally transmitted by direct contact; however, indirect transmission such as that which may occur with laundry workers through infected bed clothes has also been observed. Certain poorly documented reports relate that in Britain during the eighteenth century, smallpox was transmitted to unsuspecting individuals after contact with cadavers in graveyards. The disease, however, is less contagious than influenza or measles and spreads relatively slowly through a community. Close contact between individuals is required for the transmission of the disease from infected persons to susceptible contacts; an infected person rarely transmits the disease to more than two or three additional persons even at the height of the transmission phase. The virus can survive in the dry state for months as evidenced by outbreaks of this disease in England which were traced to infected cotton shipped from Egypt. The distinct and constant seasonal patterns of smallpox in many parts of the world were not well understood; effects of humidity and temperature on the virus, effects of wet and dry periods on the activities, movements of various populations, and merely a reduction in

case reporting were advanced to explain the above patterns.

Immunity after clinical smallpox, which has no carrier state, is believed to be permanent. The disease may occur in persons vaccinated many years earlier; however, it is milder, with less virus shedding and less transmission efficiency. Previously uninfected or unvaccinated persons of all ages were equally susceptible; however, as the ratio of the vaccinated to the unvaccinated persons in a population increased with age, the disease was most commonly observed in children.

Laboratory diagnosis of smallpox and other poxvirus infections is now made mainly by electron microscopy, using scrapings from vesicular or pustular lesions or suspensions prepared from crusts. Typical poxvirus particles are readily distinguished from all other human pathogenic viruses because of their characteristic shape and size as described above. Moreover, these viruses can be grown on the chorioallantoic membranes of 10- to 12-day-old chicken embryos; they produce characteristic lesions (pocks) at different ceiling temperatures which distinguish the various members of this group from one another.

The pocks of variola virus are white, small, circular, and dome shaped, with no necrosis or hemorrhage; those of cowpox virus are deep red and hemorrhagic; and those of vaccinia virus are large and flat, with central depressions due to necrosis. The pocks of monkeypox virus are similar to those of cowpox virus. The white pock variants of cowpox virus, which fail to produce necrosis and hemorrhage in either chicken embryo chorioallantois or rabbit skin, lack an antigen, designated d, which is present in the wild type (91). Moreover, white variants of cowpox virus have been generated in chicken embryo fibroblasts maintained in an arginine-deprived culture medium (108). In regard to their ceiling temperatures, no pocks are produced by variola minor (alastrum) virus at or above 38°C, whereas variola major virus produces pocks at up to 38.5°C, and vaccinia virus produces pocks at 39 to 40°C. The effect of temperature on the growth of the international reference strains of variola major virus (Harvey) and variola minor virus (Butler) in human embryonic skin-muscle cell cultures was recently shown to be mainly on virus release and hemagglutinin; the latter was much more sensitive than the former. This may have relevance to the clinical manifestations of the two diseases in humans (33). Moreover, variola virus is infectious only for humans and monkeys (never rabbits or mice), whereas vaccinia virus can be passed serially in rabbits by skin-to-skin transfer. Another unrelated virus, i.e., herpes simplex, also produces pocks on the

chicken chorioallantois; however, its pocks are smaller (1 to 2 mm in diameter) than those of variola virus and appear dense, superficial, and round or oval, with occasional taillike structures.

Primary monkey kidney and human embryonic lung cell cultures can also be used for the isolation of these viruses. Serological tests (complement fixation, hemagglutination inhibition, radioimmunoassay, and serum neutralization), the fluorescent antibody technique, agar gel precipitation with antigens derived from vesicular or pustular lesions or from crusts, and enzymatic procedures are also used for the diagnosis of poxvirus infections (12, 14, 85, 100, 103).

#### Recent Importations of Smallpox to the United States and Europe

The last indigenous documented case of smallpox in the United States occurred in 1934. In Britain, smallpox ceased to be endemic after 1935. However, the disease continued to be imported into the United States and was last observed early in 1949, when eight cases with one death occurred in the lower Rio Grande Valley in Texas. The outbreak began on 17 February 1949, when a worker in a citrus juice processing plant became ill and later transmitted the disease to his hospitalized wife, who in turn developed smallpox shortly after dismissal and died on 12 March. He also infected his 10-year-old son (Fig. 20), an oil field worker, and his visiting physician. The virus was isolated from the index case and these three secondary cases. The other three cases, including a county commissioner, were recognized during February and March 1949. The source of this outbreak could not be determined, and since chickenpox was prevalent at that time on both sides of the border (United States and Mexico), it is believed that some cases of smallpox were missed. Approximately 239,000 people were vaccinated in three adjoining counties within about 1 week (57).

Some 2 years before the above outbreak, a 47-year-old American businessman, Eugene Le Bar, travelled with his wife by bus from Mexico City after living there for 6 years and arrived in New York City (passing through Dallas, Tex.; St. Louis, Mo.; Cincinnati, Ohio; and Pittsburgh, Pa.) on 1 March 1947, when he developed smallpox and died at Willard Parker Hospital (the communicable disease hospital in Manhattan) on 10 March 1947. Initially, he was hospitalized at Bellevue Hospital on 5 March and remained there until 8 March, when he developed a rash and was therefore transferred to Willard Parker Hospital. However, a diagnosis of smallpox was made about 2 weeks after his death, when the two contact people developed the



FIG. 20. The son of the index patient of the smallpox outbreak in the Rio Grande valley, Tex., February to March 1949: day 10 (courtesy of Mrs. J. V. Irons, Austin, Tex.).

classical disease. These individuals were a 27-year-old man with mumps and a 22-month-old girl with croup, who were hospitalized at Willard Parker Hospital at the same time as was Mr. Le Bar. A 2.5-year-old boy hospitalized there for whooping cough at the same time also developed the disease. The fourth infection acquired by contact at Willard Parker Hospital was of a 4-year-old boy, who was discharged on 10 March and went to a convalescent home in Milbrook, N.Y., where he later developed smallpox and transmitted it to three other persons at the home. The above-mentioned 27-year-old man, who transmitted the disease to his wife (the second fatal case) was first admitted to Bellevue Hospital, where he also transmitted the disease to three male patients before being transferred to Willard Parker Hospital. Altogether, the outbreak, which was effectively contained, involved 12 persons: 9 in New York City with two deaths and 3 in Milbrook, N.Y. Some 6,350,000 people were vaccinated in less than 1 month during an emergency mass vaccination program.

Le Bar had been successfully vaccinated in childhood and subsequently had only one unsuccessful vaccination about 1 year before he left Mexico. His wife, who visited him at Willard Parker Hospital, had been successfully vaccinated earlier and remained in good health. An investigation of places he contacted on the bus



route from Mexico City to New York City revealed no case of smallpox traceable to Le Bar. Of the 12 smallpox patients, only 3 had been vaccinated more than 40 years previously (107). In both of the above-described outbreaks, failure to make an early diagnosis was largely responsible for the spread of the disease from the index patient.

A similar smallpox (*variola major*) outbreak was initiated in Glasgow, U.K. by a 32-year-old lascar patient with clinical and radiological evidence of lobar pneumonia, who was admitted to an open ward of a Glasgow hospital on 10 March 1950. However, the patient developed a rash 4 days later; and 17 secondary smallpox infections of contacts (12 of them female), ranging in age from 11 months to 84 years, ensued, with five deaths. These cases occurred among hospital staff, patients, and visitors, all known to be contacts of the index patient (1). The protective effect of previous vaccination and the importance of early diagnosis were again clearly demonstrated in this outbreak.

More recently, at least 50 importations of smallpox from the Indian subcontinent, Africa, and the Middle East to Europe, resulting in 1,113 cases with 107 deaths (all among *variola major* patients) in 10 different countries occurred between 1950 and 1973. Data from the last 27 importations which involved 568 cases and occurred between 1961 and 1973 indicate that 10 originated from India, 9 from Pakistan, 2 from Zaire, and 1 each from Gabon, Liberia, Afghanistan, Iraq, and an unknown country in Asia. Twenty-four of the index patients travelled by air, two travelled by sea, and 1 travelled by land. About one-half of these cases occurred by nosocomial transmission among hospital personnel and their contacts, hospital patients, and visitors. In two of these outbreaks, airborne transmission occurred at considerable distances in a closed hospital setting. The index patient in both airborne outbreaks had a severe cough which presumably increased the number of airborne viral particles shed by the patient in oral secretions. In the first outbreak, persons in an adjoining ward down a corridor from the smallpox patient were infected; in the second, persons in rooms located either on the same floor or on the two floors above the patient were infected (74, 110).

The second outbreak, which involved 20 smallpox cases and was investigated with considerable interest, occurred during January and February 1970 in Meschede, near Dusseldorf, Federal Republic of Germany. The index patient, a 20-year-old West German male, had returned by air from Pakistan on 31 December 1969. He developed a fever 10 days later and was admitted on 10 January to a private room in

the infectious isolation ward located on the ground floor of the three-story Meschede Hospital. The patient developed a rash on 14 January, and a diagnosis of smallpox was made on 16 January, at which time he was transferred to Wimbern Smallpox Hospital. During the period of 13 to 16 January, while the patient was still in the Meschede Hospital, the disease was transmitted to 17 persons. These were 13 patients (3 on the ground floor and 5 on each of the first and second floors), one nurse on the first floor, two nurses on the second floor, and one visitor. The visitor came to the hospital on 13 January and spoke for no longer than 15 min with a physician in an outer corridor of the ground floor. The 17 second-generation patients developed smallpox during 22 to 31 January, a time span which is within the limits of one incubation period. Two additional smallpox cases representing the third generation of transmission, occurred during 13 to 17 February in two roommates of the second-generation patients. The four patients who died in this outbreak were three elderly persons (one of them in the third generation) with severe underlying illness and a 17-year-old healthy nurse who worked on the second floor and had never been vaccinated.

The airborne route in the transmission of smallpox in this outbreak was demonstrated by a smoke-generating device which was released in the index person's room on 10 April, when meteorological conditions (warm and dry) in the hospital were similar to those of January. The patterns of air currents, as shown by the smoke within and without the building corresponded very well with the locations of second-generation patients in this hospital (42).

More recently, smallpox was introduced into Yugoslavia, where no case had occurred since 1946, on 15 February 1972 by a Moslem native named Ibrahim Hoti, who resided in the village of Danjani in southern Yugoslavia. He returned by bus with 25 others from a pilgrimage to Mecca, Saudi Arabia via Baghdad, Iraq, where smallpox reportedly existed at the time. Hoti (last vaccinated, most likely unsuccessfully, on 19 December 1971) manifested only a mild fever and a few lesions on his face shortly after arrival and was not confined to bed; however, serological tests were indicative of smallpox virus infection. The extensive outbreak (during February to April 1972) which followed involved 175 cases through three generations of transmission, with 35 deaths. Eleven cases, one of them hemorrhagic, developed among the pilgrim's many contacts. The disease in one victim (the hemorrhagic case), who was severely ill and attended four hospitals in five days, remained undiagnosed until several days after his death, when the victim's infected brother developed classical

smallpox. However, by then the victim had infected 48 other persons, of whom 42 were hospital personnel or hospital contacts, and had also introduced smallpox to Belgrade. In a mass vaccination program, which brought the epidemic under control, 8,160,000 persons were vaccinated in a population of 8,437,000. Meanwhile, in the United States, over 1,000 travellers from Yugoslavia were placed under surveillance by state and local health officials. Seventeen of the travellers developed rashes or other signs of illness requiring clinical, epidemiological, and laboratory studies; however, no smallpox was detected (95; Centers for Disease Control, *Morbidity and Mortality Weekly Report*, 21:136, 1972).

#### Laboratory-Associated Infection in London

Laboratory-associated infections have also caused outbreaks; one such outbreak at the London School of Hygiene and Tropical Medicine in March 1973 caused two deaths. Ironically, the index person, 23-year-old Ann Algeo, was vaccinated by her general practitioner in Northern Ireland in June 1972 and worked at a mycology laboratory. However, she was apparently exposed to smallpox virus (the Harvey strain of variola major virus) on 28 February while using equipment in the old-fashioned and crowded poxvirus laboratory (headed by Dr. Charles J. M. Rundle) of that school, where infected eggs were being harvested on the open bench. She became ill on 11 March and manifested atypical smallpox symptoms (headache, vomiting, pyrexia, and a sparse rash provisionally labeled as pyrexia of unknown origin and later changed to glandular fever) and hence was initially hospitalized on 16 March in a general ward at the Harrow Road branch of St. Mary's Hospital in Paddington. However, she was transferred to the Isolation Hospital on 20 March and recovered from the infection. The two fatal cases, husband and wife Thomas and Margaret Hurley (aged 34 and 29 years, respectively), acquired infection during the period of 16 to 20 March by visiting Mr. Hurley's ill mother, Mrs. Norah Hurley, whose bed was next to that of Miss Algeo. Margaret and Thomas became ill during 29 and 30 March and were initially admitted to West Hendon Isolation Hospital on 2 April. They were transferred on 4 April to Long Reach Isolation Hospital in Dartford, Kent, where they died of smallpox on 6 and 15 April 1973, respectively. Mrs. Norah Hurley, however, was not infected and was released from the hospital on 20 March (65, 66, 95).

#### Vaccines and Method of Inoculation

The vaccines used worldwide since the 1960s were produced from three basic strains: the

Lister Institute or the Elstree strain (United Kingdom), the Wyeth or the New York Board strain (United States) and the EM63 strain (USSR). The Lister strain is said to have originated from a Prussian soldier with smallpox during the Franco-Prussian War in 1870 and was introduced to Britain as calf lymph from Cologne in 1907. The Wyeth strain was started in 1876 from an unidentified vaccine imported from Britain in the 1850s. The EM63 strain was derived from a commercial vaccine of unknown origin obtained from Ecuador. The vaccine contains 40% glycerol and 0.4% phenol for destroying bacteria and preventing it from freezing at its storage temperature of  $-10^{\circ}\text{C}$ . In accordance with WHO standards, the vaccine should have a potency of not less than  $10^8$  pock-forming units on chicken embryo chorioallantois per ml.

The vaccine virus is now called vaccinia, which is, in its present form, different from both the original cowpox virus and the smallpox virus. Cowpox, which is found only in Britain and western Europe, is a rare disease, and its agent is isolated from cattle and farm workers dealing with these animals. However, human cowpox may occur without any contact with bovine cowpox. Rodents were recently shown to serve as natural reservoirs for the cowpox virus, which is pathogenic for a wide range of animals, including the cat family, in which the virus causes a fatal fulminating pulmonary infection (76). Certain strains of vaccinia virus proliferate in nervous tissue; however, the types of cells involved have not been delineated. A recent study of the neurovirulence of this virus for weanling mouse brains by light and electron microscopy indicated that the virus replicates in meningeal cells, adventitial cells of meningeal arterioles, and small nonneuronal cells. No replication in the neurons was observed (16).

Dr. Keith R. Dumbell and Dr. Henry S. Bedson proposed in 1967 that vaccinia virus represents a hybrid which arose from the inadvertent mixing of the cowpox and smallpox viruses during the early vaccination programs. More recently, Dr. Derrick Baxby has proposed that the current strains of vaccinia virus probably represent an extinct horsepox (grease) virus. This view is based on the fact that during the nineteenth century, strains of vaccine derived from horsepox were established in Britain and other European countries. Dr. Peter E. Razzell believes that most of the vaccine used by Jenner, Woodville, Pearson, and their contemporaries was accidentally developed from an attenuated strain of smallpox virus (89). It appears that at present the origin of vaccinia virus cannot be definitely determined. In genetic relationship, however, vaccinia virus is more closely related to smallpox virus than to cowpox virus (24).

Nonetheless, vaccinia virus (of which many strains with different laboratory characteristics and levels of human pathogenicity exist) is relatively avirulent for humans and produces an effective immunity against smallpox (9).

The vaccinia virus was recently used to produce a potential live vaccine against hepatitis B virus infection. The coding sequence for hepatitis B surface antigen was inserted into the vaccinia virus genome; cells infected with such vaccinia virus recombinants synthesized and excreted antibodies to the surface antigen (98). Moreover, genes from herpes simplex and other human pathogenic viruses are now being incorporated into the genome of this virus; these recombinants have proved effective in the immunization of experimental animals.

The smallpox vaccines last used in the United States were mainly glycerinated lymph from infected skins of calves or sheep; lyophilized lymph was also used. Moreover, vaccines derived from infected chorioallantoic membranes of embryonated eggs and, more recently, cell culture-grown vaccines were also available.

Most recently, vaccination has been generally performed by the multiple pressure technique, using a Wyeth bifurcated needle. After cleansing the skin (arm or thigh) with acetone, ether, or soap and water and allowing the site to dry, 1 drop of vaccine is placed on the skin, and the side of the needle is pressed firmly (at least five times) through the vaccine drop into the superficial layers of the skin (only intradermal inoculation). No blood should be drawn by the point of the needle. Excess vaccine is then removed from the skin with sterile dry gauze, and no dressing is applied. A primary take in the fully susceptible individual is manifested by the appearance of a papule surrounded by hyperemia on day 3 or 4. This papule increases in size and is followed by the appearance of vesiculation on day 5 or 6. The vesicle is at its maximum size by day 9, when it becomes pustular, usually coinciding with some tenderness of the axillary nodes when the arm is used. This is followed by desiccation, which is complete in approximately 2 weeks, leaving a depressed pink scar which eventually turns white. Observation of the vaccination result is usually made on day 7; if the above-described reaction is not seen, vaccination is repeated with another vaccine lot until the expected reaction is observed.

Revaccination, when successful, results in the appearance of a vesicular or pustular lesion or an area of palpable induration surrounding a central lesion (a crust or ulcer) in 6 to 8 days. Only the above reaction is indicative of a successful revaccination. Equivocal reactions in revaccinations may indicate immunity but also may be due to an allergic reaction to an inacti-

vated vaccine. In such cases, revaccination is repeated until the desired reactions are obtained. Revaccination was routinely performed at 3- to 7-year intervals. No resistance to infection is manifested 20 years after vaccination.

#### **Discontinuation of Vaccination in the United States**

As the risk of acquiring smallpox in the United States became essentially zero in late 1960s, routine vaccination of children was discontinued in 1971. In 1976, routine smallpox vaccination of U.S. hospital employees was likewise discontinued. The above policy was recommended by U.S. Public Health Service officials because, first, vaccination was no longer needed; and second, there is a finite number of complications associated with this immunization. The second reason for discontinuation was first emphasized in the early 1960s by Dr. C. Henry Kempe of the University of Colorado (60, 72, 87, 88). However, currently active-duty personnel of the U.S. Army, Navy, Air Force, Marine Corps, the National Guard, and the Reserves are routinely vaccinated when they enter the service and are revaccinated at 5-year intervals. The reserve personnel are vaccinated at the beginning of their 2-week annual training at the same intervals. This involves the vaccination of about 1,000,000 military personnel each year. In the United Kingdom and Finland, however, vaccination of army recruits was discontinued in 1981.

#### **Adverse Reactions to Vaccination**

It has been estimated that after primary vaccination, the risk of death is about 1 per 1,000,000; that of hospitalization with encephalitis, eczema vaccinatum, or progressive vaccinia is about 10 per 1,000,000; and that of a serious complication including eczema vaccinatum, accidental implantation of vaccinia on the eye, or superinfection of a variety of skin conditions approaches 1,000 per 1,000,000. On the whole, however, the frequency of complications varied with the type of vaccine virus used, the age of the vaccinee, and his or her state of health. More specifically, among 14,168,000 vaccinated individuals (5,594,000 primary vaccinations and 8,574,000 revaccinations) during 1968 in the United States, 510 serious reactions including eight deaths were documented. Four deaths were due to postvaccinal encephalitis among 16 individuals, of which 3 were infants who received primary vaccination in the first year of life. The other four deaths were due to vaccinia necrosum among 11 individuals, of which two were revaccinated and two were initially vaccinated. Eczema vaccinatum occurred in 64 individuals. Moreover, 60 additional cases of eczema vaccin-

atum (one fatality) occurred in contacts of the vaccinated individuals. In France between 1968 and 1977 there were 4,113,109 primary vaccinations. Thirty deaths occurred among these vaccinees, whereas no death occurred among the revaccinated individuals. Moreover, the risk of death was three to four times greater in children under the age of 1 year (34, 43, 73).

## GLOBAL ERADICATION OF SMALLPOX

### Concept of Eradicating Smallpox

The concept of eradicating smallpox was conceived by Jenner himself, who wrote in his book entitled *The Origin of the Vaccine Inoculation* (published in 1801): "It now becomes too manifest to admit of controversy that the annihilation of the smallpox, the most dreadful scourge of the human species, must be the result of this practice (vaccination)." Subsequently, data collected in recent years from extensive worldwide investigations on smallpox and its patterns of transmission indicated that the global eradication of this disease was an attainable objective. This concept was based on the findings that, first, smallpox is a specifically human disease with no known animal reservoir; second, in unvaccinated individuals, the disease occurs only as an acute seasonable infection in which infectivity regularly coincides with rash, and the infected person either dies or recovers (with or without sequelae) with lifelong immunity and without recrudescence; and third, there exists a very effective vaccine for extended protection against this disease which is caused by only one stable serotype. Moreover, the disease was not associated with any stigma as in leprosy or venereal diseases and thus the detection of cases presented no cultural barriers.

Jenner's original hope for eradicating smallpox in the human species, however, remained virtually ignored until 1950 when Dr. Fred L. Soper (1893 to 1977), Director of the Pan American Sanitary Bureau (1947 to 1959), proposed at the Third World Health Assembly of the WHO a program for smallpox eradication in a defined geographic area, i.e., throughout the Americas. Soper had developed a deep interest in disease eradication programs while working with the Rockefeller Foundation Yellow Fever Commission. By using mass vaccination strategy, the WHO-approved eradication program began in 1950 in the Americas; within 8 years, smallpox transmission was interrupted in the Caribbean, Central America, and a number of South American countries. However, on the global scene, during the following years, beyond passing pious resolutions in the annual meetings of the WHO, little progress in the eradication of smallpox from endemic areas was made (50).

### Preparations for Global Eradication

In 1958 at the Eleventh World Health Assembly, Dr. V. M. Zhdanov, Vice Minister of Health of the USSR, boldly proposed the adoption of the principle of global smallpox eradication as a policy. This was adopted as a matter of urgency by the Assembly in 1959, and a program of vaccinating or revaccinating 80% of the population within 5 years to eradicate the disease from endemic areas was conceived. This mass vaccination was believed to produce herd immunity in the involved population that would result in the cessation of virus transmission. Moreover, it was envisaged that sufficient stocks of vaccine could be produced in 2 years which was to be followed by 3 years of intensive globally coordinated vaccination programs. However, preoccupation of many member states with malaria eradication, unavailability of sufficient suitable vaccine doses, and insufficient budget (an average of less than \$100,000 per year in cash and in kind) hindered the progress of the program.

Although a number of countries soon embarked on mass vaccination programs after the WHO adoption of the global eradication policy, the results were disappointing. Moreover, there were those who called attention to the failures in the eradication of yellow fever and its vector *Aedes aegypti* in the Americas and the unsuccessful global malaria eradication program. They argued that, similarly, the eradication of smallpox could not be achieved because of the inadequacy of the tools and the likely existence of the causative agent in yet unknown animal reservoirs from which the virus could not be eliminated. Others implied that the removal of a pathogen would offer the vacated niche to another equally noxious agent. Still others argued that the eradication of a pathogen entails some breach of ethical principle and also worsens human fate by enhancing the population explosion. In addition, those with vested interest in the maintenance of the disease saw the continuation of their jobs threatened by a successful eradication program. More importantly, the involved health authorities became discouraged and pessimistic when it was subsequently realized that the disease still persisted in 80% vaccinated populations. Later, the serious setbacks in the eradication programs in Bangladesh and Ethiopia (see below) revived the skepticism in certain circles even as late as 1975.

In 1965 at the Eighteenth World Health Assembly, the member states took a much stronger position. Thus, a more realistic budget (about \$2.5 million) was provided by the Assembly in 1966. This sum was to provide for the overall program coordination and for assistance to some 50 countries, with a total population of over 1 billion people, which required it; however, it

represented about 5% of the WHO total budget for 1966. In the period between 1966 and 1968, three essential elements of the eradication program, namely, availability of a stable vaccine of good quality, a more efficient vaccination method, and a more effective strategic approach, were worked out by the WHO experts (35, 36, 49-51, 105).

In regard to the vaccine, some 200 million doses were needed annually. As inhabitants of remote areas of tropical regions were also to be vaccinated, the use of a stable freeze-dried vaccine became essential. The technology for mass production of such a vaccine (which is stable at temperatures of 37°C or higher for 1 month or longer) had already been developed in 1954 by Dr. L. H. Collier and applied at the Lister Institute in London; this was then made freely available to various manufacturers (27). The Lister strain of vaccinia virus, which causes less severe reactions than those of most other strains (some 15 different strains) was eventually used by two-thirds of the producers of vaccine by 1972. In 1967, 64 laboratories (9 in Africa, 9 in the Americas, 19 in Asia, and 27 in Europe) were producing the freeze-dried vaccine.

Donations of such vaccine were initially made by the USSR (140 million doses annually), the United States (40 million doses annually), and subsequently by 24 other countries. In later years (by 1973), 80% of the needed vaccine was produced by the endemic countries themselves, some of them supplying vaccine to others. The WHO, therefore, incurred no expenditure for the vaccine used in the eradication program. Two selected international reference centers (WHO Collaborating Centers at Connaught Laboratories in Toronto, Canada and the Rijks Institute in Bilthoven, The Netherlands) were officially designated in 1969 for testing the donated vaccines for potency, stability, and purity in accordance with the WHO standards. It is estimated that 2,400 million doses of vaccine were used in the global program.

As to the method of vaccine administration, the jet injector was introduced at the start of the program in 1967; however, a highly efficient device developed in 1966 by Wyeth Laboratories in Philadelphia, Pa., which consists of a bifurcated needle for the multiple pressure technique, was adopted for the program late in 1968. The vaccine is introduced between the prongs of the needle, and, thus, considerable economies in the amount of vaccine used (0.0025 ml per dose, which is one-fourth the dose previously required) are achieved. The needle is so simple to use that an untrained person can learn how to use it properly in about 1 h and consequently can vaccinate up to 1,500 persons per day. Moreover, the needles are easily sterilized and, unlike

jet injectors, need no maintenance (92). The WHO supplied over 40 million of these needles to the program.

The third element, namely, the strategy, also had to be worked out. The concept of mass immunization, originally proposed to include 80% or more of the population in each country to achieve herd immunity, proved ineffective as virus transmission did not cease, and smallpox persisted in such immunized or even ostensibly over-immunized populations. A carefully designed sample survey conducted in 1969 among the 23 million people of Central Java, where more than 95% of the involved population bore scars of vaccination, detected some 1,700 cases in that year principally among the unvaccinated individuals who constituted less than 5% of the total population. Logistic problems and costs of vaccinating such small percentages of unvaccinated individuals in remote areas of endemic countries have repeatedly proved prohibitive. Later, the most extensive epidemic of smallpox in New Delhi, India in a decade occurred in the 1960s after this city reported the vaccination of 120% [sic] of its citizens. In 1967, an outbreak of smallpox occurred in the state of Alagoas, Brazil 3 months after a vaccination team reported that the involved population was 100% vaccinated. The team was discharged when it was found that in reality only one-half of the population had been vaccinated (83). Moreover, during the earlier years of the eradication program, the so-called sporadic outbreaks and cases of smallpox were often not appreciably associated with the essential principle that this disease spreads in an identifiable continuous chain with one infected individual transmitting the disease to other susceptible ones.

The experience gained in eastern Nigeria during 1967 to 1968 under the innovative supervision of Dr. William H. Foege (now Director of the Centers for Disease Control, Atlanta, Ga.), where the initiation of an effective reporting system and an intensive containment vaccination in areas reporting smallpox resulted in the interruption of transmission, clearly established that such an interruption could be achieved by the vaccination of no more than one-half of the involved population. It was noticed that the disease spread slowly, and even in densely populated areas, the infected person rarely transmitted the disease to more than three or four additional persons. Moreover, it was recognized that even a single dose of vaccination conferred effective protection for 10 or more years; thus, revaccination was recommended only in outbreak containments (39). Although subclinical infections may occur in formerly vaccinated persons, such patients as well as those with *variola sine eruptione* (see above) are unlikely to

transmit the disease to susceptible persons. The same observations were made by Dr. J. Michael Lane, who supervised a similar program in Sierra Leone and Guinea. These observations were later confirmed by other studies in other parts of Africa and Brazil. As vaccination of 100% of the population proved to be virtually impossible to achieve, a shift in strategy which deliberately over-emphasized the epidemiological surveillance (active case hunting) and vigorous containment of outbreaks, both to be introduced and coordinated at the inception of all eradication programs, was adopted in 1969. The above three modifications were, as evidenced by the results, quite effective.

In January 1967, the intensified global smallpox eradication program with a central headquarters office in Geneva, Switzerland was started (under the able direction of Dr. Donald A. Henderson) as one of the WHO major objectives but with less than universal enthusiasm. The disease was then reported from 46 countries, of which 33 were considered endemic areas (the latter in Asia, Africa, and South America, involving a population of more than 1.2 billion). However, in 1967, smallpox had been eradicated (and stayed eradicated) in a number of countries (some with primitive health services) through vaccination and, in certain areas, active surveillance. These countries were Cambodia, Laos, The Philippines, Vietnam, the Caribbean, Central America, and most of South America. Thus, the feasibility of smallpox eradication in both developed and developing countries had been clearly demonstrated. However, as late as 1967, case reporting in many endemic areas was so inadequate that only about 1% of cases in these countries were reported. Officially, 131,697 cases of smallpox were reported in that year but it is believed that the actual number of cases was as many as 10 to 15 million with some 2 million deaths (110).

#### Problems and Setbacks

The aim of the program, which emphasized systemic vaccination in accordance with the WHO *Field Handbook* (published in July 1967), was to eradicate smallpox from the entire world in 10 years. After the change in strategy (see above), the eradication goal became achievable as the incidence of this disease declined rapidly, and the last naturally occurring incidence of smallpox (variola minor) was in a Somalian named Ali Maow Maalin (see Fig. 23), who developed the rash of the disease on 26 October 1977. Moreover, the last historic case of variola major was that of a 3-year-old girl name Rahima Banu (see Fig. 22), who happily survived, on Bholia Island, Bangladesh. This case was report-

ed on 16 October 1975. The main obstacles encountered in the global eradication were as follows.

India, Pakistan, and Bangladesh, with a combined population of over 700 million, posed special problems to the surveillance-containment strategy since comparable efforts which proved successful elsewhere did not succeed on the Indian subcontinent. Large numbers of poor people, frequently unvaccinated and sometimes with active smallpox, travelled frequently and far from rural villages to urban centers and back in these densely populated countries because of the availability of a relatively extensive network of railroads and bus lines. As population densities were far greater here than elsewhere, vaccination immunity levels were also remarkably low. In addition, a great number of religious festivals regularly attracted and mixed hundreds of thousands to millions of vaccinated, unvaccinated, and infected people in certain geographic areas. Moreover, among the Hindus, Shitala Mata (Fig. 21) has been worshiped for centuries as the goddess of smallpox, whose blessing of a person was believed to result in the acquisition of this disease. Relatives and friends of a smallpox patient would travel long distances to pay homage. The goddess's annual visits during the



FIG. 21. Shitala Mata (goddess of smallpox in India) (courtesy of the WHO, Geneva, Switzerland).

spring were so integrated into the life of the Hindus that they frequently called smallpox "the spring disease." Hence, vaccination against the goddess's generosity especially with a vaccine derived from the sacred cow was utterly unacceptable to the devotees (22).

Villagers frequently became agitated when vaccinators arrived, and as vaccination got under way, violence followed. They claimed that their children had died from vaccination; however, this was due to rubbing cow dung on the vaccination site which resulted in tetanus. Others sucked out the vaccine immediately after inoculation. The vaccinators often vaccinated themselves in full view of the entire community to prove that vaccination was not harmful. In the Indian state of Bihar, the so-called dawn raids proved highly effective in overcoming the resistance of the villagers to vaccination. Large vaccination teams descended at 4:30 a.m. on the sleeping villagers and vaccinated them quickly. The vaccinators then surprisingly enjoyed a convivial breakfast with the village elders who, although defeated in their attempted efforts to resist vaccination, were nonetheless traditionally bound to show their hospitality. On one occasion, when all earlier efforts failed and the vaccinators were repeatedly driven off by spears and arrows, the supervising epidemiologist engaged himself in a long and futile discussion with the well-armed Chief and his villagers in regard to whether his or the Chief's powers were greater. In the end, the epidemiologist, looking at his watch, raised his hand, and an airplane appeared, dived on the village, and dropped hundreds of picture cards of smallpox and vaccination. The previously arranged "miracle" with the local flying club worked, and the amazed chief consented to the vaccination of his villagers. However, in later years, opposition faded away when the protective effect of vaccination was realized by the villagers: consequently, the vaccinators were welcomed in most communities (49).

The above problems necessitated changes in the strategy pursued in the Indian subcontinent which were initiated in June 1973. In India (later in the adjacent countries as well), more rapid and complete case hunting was achieved by mobilizing some 100,000 health workers for monthly week-long village-by-village and later house-by-house searches for smallpox cases. Fire-fighting teams were mobilized and trained as surveillance-containment teams for dealing with newly discovered outbreaks. Four watch guards were assigned to each infected dwelling, and local teams vaccinated all visitors to such dwellings. Moreover, a reward was offered to persons reporting new cases. Consequently,

transmission of smallpox was interrupted on the Indian subcontinent within about 2 years (see below).

The practice of variolation, which continued in certain Asian and African countries (e.g., Afghanistan, Pakistan, Benin [Nigeria], Malawi, and Ethiopia) up to the latter part of 1970s was also of concern to the program directors since it provided a mechanism for both persistence and reintroduction of the smallpox virus. The last known variolation was performed in Bale Province in southern Ethiopia in August 1976 during the last smallpox outbreak in that country. However, of 45 scab specimens obtained from variolators in Afghanistan, Ethiopia, and Pakistan, only 4 (all from Afghanistan) contained live variola virus. Moreover, no positive isolation was made from specimens collected 9 months before testing. Thus, the practice of variolation, although impossible to stop, proved to be amenable to control and consequently did not adversely affect the global eradication program (3).

The nomads who roam the vast Ogaden desert in the eastern Horn of Africa were the last population in the world to be rid of smallpox. These nomads, who move erratically from one location to another, harbored an exceptionally mild form of this disease (fatality rate of less than 0.5%) which did not hinder the remarkable mobility of even acutely ill individuals among them. Moreover, as there was a direct correlation between the severity of disease and the ease of spread, transmission among small groups of these nomads persisted for the unusually long period of 4 to 6 months, with only one or two cases in each generation. This indicated a remarkable equilibrium between the virus and the Ogaden nomads (41). Here again, for the last time, techniques of intensified case detection and containment prevailed, and the last case was diagnosed on 26 October 1977.

In parallel to the above problems, political aspects inherently involved in any global eradication efforts often presented additional formidable problems. In the 18 countries included in the West Africa eradication program (see below), there were 23 changes of government which frequently caused policy and personnel changes in various state undertakings, including the national smallpox eradication programs. As Dr. Donald A. Henderson (now Dean of the School of Hygiene and Public Health at Johns Hopkins University, Baltimore, Md.) has recently reflected, had the eradication program in a number of countries begun a year earlier or later, it might have failed. The Zaire program could not have succeeded if it had been started after 1975; Uganda achieved eradication just as Idi Amin came to power; the current conditions

in Iran are not conducive to a national smallpox eradication program (2, 49–51, 67, 102).

### The 10-Year Program for Global Eradication

The period between 1967 and 1977, during which the global eradication was achieved by intensified efforts, has been divided into three phases.

**Phase I.** During phase I (1967 to 1972), eradication was achieved in South America, Indonesia, and most of the African countries by similar approaches.

Mass vaccination programs coordinated by the Pan American Health Organization and carried out between 1950 and 1957 eliminated the disease from all countries of South America except Brazil, which exported smallpox for the last time to Argentina in 1970. However, the last known case in Brazil occurred on 19 April 1971.

In Indonesia, smallpox was eradicated in the late 1930s by a systemic vaccination emphasizing primary vaccination of infants. However, the disease was reintroduced after World War II, and 490,348 cases were reported in 1949. The WHO program started in May 1968 with mass vaccination being pursued initially but later being replaced by active surveillance and rapid containment. The last case was recorded on 23 January 1972. The Indonesian workers first conceived the idea of showing pictures of a child with smallpox in their surveillance work. Consequently, all WHO workers used such recognition cards very successfully in their worldwide surveillances.

In West and Central Africa, an eradication program involving 20 countries (Benin, Chad, Central African Republic, Congo, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Togo, United Republic of Cameroon, and Upper Volta) assisted by the U.S. Center for Disease Control and financed by the U.S. Agency for International Development and the WHO was started in 1967. The program aimed at (i) vaccinating 80% or more of the involved population and (ii) developing an effective reporting surveillance system which could be successfully used for the rapid eradication of the disease in other areas. The program was staffed by international advisors who worked closely with national counterparts and was well provided with transport and other logistic support. The disease was widespread in this region, and, in one of the countries (Nigeria), the Yorubas worshipped the smallpox god *Sopona* who was believed to be very stubborn and unappeasable.

Jet injectors were used for vaccination mostly at collection points. Children aged 9 months to 4 years were also simultaneously given the mea-

sles vaccine. The selective surveillance containment strategy (see above) was developed during this program. Eradication was achieved in about 3 years; the last case occurred in Nigeria in June 1970. Three other central African countries, i.e., Burundi, Rwanda, and Zaire, also reported smallpox in 1967 or thereafter. Well-organized mass vaccinations at collection points in Burundi and Rwanda were hampered by a slow and inadequate reporting system; however, intensified surveillance during 1969 and 1970 bore fruit, and the last cases in both countries were reported in October 1970. In Zaire, a vast country with 18 million people, a carefully planned 3-year program of mass vaccination, using Ped-O-Jet injectors, followed by active surveillance and prompt and thorough containment by mobile teams produced the most remarkable results. The last case was reported in August 1971.

In Southeastern Africa, two countries (Malawi and the United Republic of Tanzania and Zambia) participated in the WHO program; the other two (Mozambique and Botswana) conducted their eradication programs independently. The disease in this region was widespread and comparable in severity to that seen in West Africa. In Malawi, Tanzania, and Zambia, systemic vaccination, using mobile teams, involved a large proportion of the population. Subsequently, a maintenance phase which was aimed at maintaining high immunity levels followed by surveillance containment proved successful. In Zambia, the last two cases, which were imported from Zaire, occurred in April 1970; in Tanzania, no case was reported after September 1970. The last case in Malawi was reported in February 1971. Variolation was practiced in both Malawi and Tanzania but had been stopped before 1967. In Mozambique, a 3-year mass vaccination program with locally produced freeze-dried vaccine followed by a maintenance phase resulted in interruption; the last case was reported in February 1969. In Botswana, small-scale vaccination with liquid vaccine had been carried out for many years, which resulted in interruption in 1965. However, the disease was imported from South Africa in 1971 and spread widely throughout the country. A massive containment-vaccination program finally brought the disease under control, and the last case occurred in December 1973.

In Sudan and Uganda, the intensified WHO-assisted program in Sudan was started in 1969 with mass vaccination which gradually changed during 1971 to 1972 to surveillance and containment. The last indigenous case occurred in November 1972; however, there was a single imported case in December 1972 from Ethiopia. In Uganda, an intensified WHO-assisted 6-month-long mass vaccination program with six large



mobile teams (using freeze-dried vaccines and bifurcated needles) was started in 1969. Surveillance by a network of health units and small mobile teams reported the last indigenous case in 1970. However, importations from Sudan into Uganda continued until December 1972, when transmission ceased, and eradication was achieved in Sudan.

In countries of the Arabian Peninsula, the last case of endemic smallpox was reported by Yemen in 1969. No endemic case was reported from the other seven countries (Bahrain, Democratic Yemen, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates) after 1962. The last importation into this region occurred in 1972 during the annual pilgrimage to holy places (Mecca and Medina) in Saudi Arabia.

**Phase II.** During phase II (1973 to 1975), major efforts were made to develop several new approaches to cope with a number of formidable and special problems encountered in the eradication of smallpox from the Indian subcontinent.

In Burma, an eradication program based on mass vaccination was started in 1963; however, a focus of smallpox persisted in Karen State until 1966, when endemic transmission ceased. Subsequently, importations from East Pakistan (now Bangladesh) occurred in 1968 and 1969, the last case being reported in June 1969.

In Afghanistan, smallpox was endemic in all parts of Afghanistan (a country with difficult terrain and climate, a large nomadic population, and scarce health personnel) when the eradication program was started in 1969. Moreover, variolation was widely practiced by traditional mobile variolators who left numerous outbreaks in their wake. Mass vaccination combined with highly effective surveillance-containment programs and cessation of variolation resulted in the termination of endemic transmission before the end of 1972. However, in 1973, there were three importations from Pakistan, the last case occurring in July 1973.

In Pakistan, the intensified eradication program was started in 1970 with somewhat different plans of rapid mass vaccination for the four provinces of Baluchistan, the North-West Frontier, the Punjab, and Sind, and for Azad Kashmir. These areas have different population densities, climates, terrains, languages, customs, and statuses of health services. Later, active surveillance and vigorous containment, especially in the mountainous areas and among nomadic populations and where variolation was still practiced, were emphasized. Moreover, extensive publicity and educational campaigns to eliminate resistance to vaccination helped terminate endemic transmission; the last case was reported in October 1974.

In Bhutan, mass vaccination with freeze-dried

vaccine was started in 1966. However, smallpox was finally eradicated in 1974, the last case occurring in March of that year.

Nepal is bordered on the south by Bihar and Uttar Pradesh, then two of the most heavily infected Indian states. The eradication program based mainly on mass vaccination was started in 1967. The strategy was changed to intensified surveillance and containment in 1971. However, transmission in Nepal was interrupted only when the disease was brought under control in the two neighboring Indian states. The last case occurred on 6 April 1975.

India, with a population of about 600 million and a long history of severe and extensive smallpox outbreaks, presented a formidable challenge to the various eradication programs (see above). The government, using 450 million doses of freeze-dried vaccine provided by the U.S.S.R., implemented a nationwide eradication program during 1962 and 1963. However, the number of reported cases in 1967 was as high as that of 1962. A new plan of smallpox eradication coordinated by the government and the WHO was started in 1970 with liquid vaccine and bifurcated needles. The strategy was gradually changed to active surveillance with epidemiological investigation of outbreaks and rapid containment. Subsequently, most of the southern states where eradication had been achieved or nearly achieved were classified as nonendemic, and most of the northern states where smallpox still occurred and surveillance-containment was ongoing were classified as endemic.

Little progress, however, was made in the endemic areas until 1973, when an intensified campaign program with special emphasis on four major endemic states of Bihar, Madhya Pradesh, Uttar Pradesh, and West Bengal was launched to detect outbreaks in the urban areas in July and August and throughout the country from September to December. Over 60,000 health workers, both national and international, visited every village in the above-mentioned states in search of outbreaks during a period of 1 week. This resulted in the discovery of an unexpected and unprecedented number of outbreaks. Later, special house-to-house searches were conducted every month in the endemic states and at longer intervals in the nonendemic states. However, exportation of infected individuals from endemic to nonendemic areas of India, to neighboring countries, and also overseas was frequently documented.

The eradication program was further intensified in 1974 with additional funds provided by the government, the Swedish International Development Authority, the WHO, and Tata Industries Ltd. Some 100 national and international epidemiologists became engaged in field work

at any one time. Consequently, the number of outbreaks decreased gradually, and the containment measures were intensified. To overcome the problem of concealment of infected persons, which often led to the continuous spread of the disease, an effective program which sought information, with the aid of smallpox recognition cards, from all sectors of the public in schools, markets, and places of gathering was introduced. Reporting of smallpox became commendable with a financial reward rather than reprimand or discipline. Consequently, the last indigenous case occurred in Bihar on 17 May 1975; the last imported case from Bangladesh was reported on 24 May 1975 in a 30-year-old woman, Saiban Bibi, at Karimganj railway station in Cachar district of the eastern state of Assam.

In Bangladesh, an intensified eradication program based on mass vaccination was started in 1967; its effectiveness was later increased by the administration of freeze-dried vaccine with the bifurcated needle. The strategy of surveillance and containment was introduced in 1969, and in

August of 1970, transmission was interrupted. However, when Bangladesh (then called East Pakistan) became independent of Pakistan (then called West Pakistan), smallpox was reintroduced and was spread widely in February 1972 by thousands of infected persons returning from a refugee camp near Calcutta, India after liberation. Early detection through active surveillance and immediate local containment proved successful; however, mass migration caused by devastating rains and floods toward the end of 1974 again spread the disease to many parts of the country. In February 1975, intensified surveillance through house-to-house searches, rapid containment, and financial rewards for case reporting, which were all coordinated by national and WHO epidemiologists, bore fruit, and the last case was reported on 16 October 1975 (see above).

**Phase III.** During phase III (1975 to 1977), other different and difficult problems requiring further changes in strategy were encountered in the final eradication of smallpox from the Horn of Africa.

In Djibouti, importations from Ethiopia after 1959 resulted in four epidemics. The last occurred in April 1974 and was followed by a vaccination program. In October 1977, Djibouti was included in the accelerated surveillance program for smallpox in the Horn of Africa. No case was detected by five nationwide searches among the nomads and refugees and in places where people assembled (caravan gathering centers, military border posts, schools, etc).

The large and mainly mountainous country of Ethiopia with 28 million people (90% in rural areas) and poor communications in most areas (many areas could be reached only by four-wheel-drive vehicles, by mule, or on foot), a rudimentary health system, few health personnel, and a widespread practice of variolation presented all known difficult obstacles to the eradication program. The program started in 1971 with emphasis on surveillance, an improved reporting system, and active containment of outbreaks. Outbreaks were detected, defined as to their extent, and immediately contained by two-man teams which consisted of a sanitarian and a U.S. Peace Corps volunteer located in regional capitals. The surveillance teams numbered only 19 at the start; however, after the arrival of additional volunteer workers from Austria and Japan in 1972, the number rose to 65. A radio network which connected the mobile units to headquarters was established. Moreover, additional vehicles and four helicopters funded by the WHO and the U.S. Public Health Service, respectively, as well as coordination with the eradication programs in neighboring Kenya, Somalia, and Sudan, rendered



FIG. 22. Rahima Banu of Bangladesh (the last case of variola major in the world, reported on 16 October 1975) (courtesy of the WHO, Geneva, Switzerland).

some regions of this country smallpox free by 1973.

After the 1974 revolution, farmers' associations were organized, and many students became temporary containment workers throughout the country. WHO support increased greatly in 1975, when the rest of the world became smallpox free. House-to-house searches and containment were intensified in the remaining few foci, and the last case occurred in the Ogaden region on 9 August 1976.

In Kenya, the intensified eradication program based on mass vaccination with freeze-dried vaccine started in 1968, and the last endemic case occurred in 1969. However, importation from neighboring Ethiopia and Somalia to the Mandera district continued until December 1977; the last importation from Somalia was reported in February 1977.

In Somalia, the initial intensified WHO-assisted program, started in January 1969 and aimed at vaccinating 100% of the country's 3.5 million people within 3 years, proved unfeasible because a large percentage of the Somalians were nomadic, and many resisted or were indifferent to vaccination. The strategy was therefore changed, and a reporting system, particularly in the border area with Ethiopia, was developed during 1971 to 1976. However, importation continued, especially in 1975, when a very severe drought caused extensive population movements across the Somalia-Ethiopia frontier. Numerous outbreaks continued to occur until March 1977, when the government declared a national emergency and appealed for help, through the WHO, to the office of the United Nations Disaster Relief Coordinator.

Generous aid in equipment and personnel was promptly received, and in June the eradication program became fully operational with more than 3,000 hired workers. A weekly reporting system from villages and nomad encampments, with house-to-house and locality-to-locality searches, accompanied with wide publicity for financial reward given to those who reported cases as well as rapid containment by secure isolation of patients and vaccination of all residents in the vicinity, resulted in the interruption of transmission within a few months. Thus, the last case of smallpox in the entire world was diagnosed on 26 October 1977 (see below).

In addition to the countries involved in the three phases of the WHO global eradication program, there were a number of other countries which did not have WHO-assisted eradication programs. These consisted of countries which had importation between 1967 and 1977 and others which were considered to be at high risk due to the presence of endemic smallpox in their neighboring countries. These countries were

Madagascar, Namibia, southern Rhodesia, Angola, Lesotho, Swaziland, and South Africa in Africa; Iran, Iraq, and the Syrian Arab Republic in the Middle East; Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates in the Arabian Peninsula; and China, Democratic Kampuchea, Lao People's Democratic Republic, Thailand, and Viet Nam in Asia.

South Africa, where variola minor had prevailed for many years, was invaded by variola major imported by the crews of the mule ships of World War II who had been infected in India or Burma. The disease then spread rapidly throughout the country and caused severe cases with high mortality rates; some fully vaccinated soldiers developed variola major, and a few died. The intensive vaccination program which followed eliminated the newly imported disease. The same kind of increase in the virulence of the disease was observed elsewhere, e.g., Sudan, when native patients unexpectedly started to die from smallpox. Here again, the vaccination program eliminated the newly introduced variola major while the locally prevalent variola minor persisted into the 1970s.

In China, where vaccination was introduced on a limited scale in 1803, smallpox prevailed until 1951. When the People's Republic was established in 1949, facilities for large-scale vaccine production were soon set up, and the government announced in October 1951 its goal of eradicating the disease from the entire country. This was achieved in the early 1960s. Surveillance-containment was needed only in the border regions of Yunnan and Tibet; elsewhere, mass vaccination, using a liquid vaccine, resulted in the interruption of transmission. Currently, vaccination is provided for newborn children whose mothers request it (54).

All of the above countries, however, were visited by the WHO consultants, who explained the required steps for formal certification by an International Commission. Moreover, the WHO consultants helped in the preparation of appropriate programs and in the training of the needed health personnel. Forms for uniform recording of the necessary information, which were the same as those used in recently endemic countries, were also supplied by the WHO consultants. Certification by the Global Commission was based on both the data provided by these countries and the information obtained by the WHO consultants (including members of the Global Commission) who personally visited the involved countries.

Publicity campaigns about detecting and reporting smallpox cases were vigorously pursued in endemic areas by the national and international health workers until the issuance of formal certification. Radio, newspapers, and television

were used in large urban centers; leaflets and posters showing pictures of smallpox patients were used in villages and remote areas. During 1978 and 1979, a special WHO multilanguage poster, which was distributed widely, announced a \$1,000 reward for the first person who reported a confirmed case of smallpox acquired by person-to-person spread (110).

#### Certification of the Global Eradication

The certification of smallpox eradication by the WHO in various countries and eventually in the entire world started in August 1973 with South America and ended in October 1979 with Somalia in the Horn of Africa. The establishment of the Global Commission was recommended by a group of international experts to the Director General of the WHO in October 1977. This procedure was endorsed by the Executive Board and then the 31st World Health Assembly in January and May 1978, respectively. The first meeting of the Global Commission was held in December 1978 to review the program and advise on subsequent activities as described below.

The certification of smallpox eradication in a country required that at least 2 years had to elapse after the last detected case and that the surveillance system had to be adequate for the detection of cases throughout the country. The surveillance system in each country was always evaluated by the WHO before the time of certification by an International Commission.

The first International Commission visited Brazil in August 1973 and certified the 13 South American countries on 25 August of that year. Indonesia was certified on 25 April 1974. Other International Commissions certified the rest of the countries of the world (see above) in the following order: 15 countries in West and Central Africa on 15 April 1976; Afghanistan and Pakistan on 30 November and 18 December 1976, respectively; Nepal on 13 April and Bhutan and India on 23 April 1977; 9 central African countries on 30 June 1977; Burma and Bangladesh on 30 November and 14 December 1977, respectively; Malawi, Mozambique, and the United Republic of Tanzania and Zambia on 29 March 1978; Uganda and Sudan on 27 October and 29 November 1978, respectively; 6 countries of the Arabian Peninsula, Iran, Syrian Arab Republic, Namibia, Southern Rhodesia, Thailand, Lao People's Democratic Republic, and Viet Nam on 3 December 1978; Angola in February 1979; Botswana, Lesotho, and Swaziland on 23 March 1979; Iraq and South Africa on 17 April 1979; Democratic Yemen and Yemen on 10 June 1979; Madagascar on 29 June 1979; Djibouti, Ethiopia, Kenya, and Somalia on 26 October 1979; and lastly China and Democratic

Kampuchea on 9 December 1979. Altogether, 21 International Commissions for the Certification of Smallpox Eradication visited 61 countries successively during the period of 1973 to 1979.

At the request of the Global Commission, all other countries submitted formal statements declaring that they were free of smallpox and indicating the years when the last cases had occurred. Such statements from 121 countries of the world were reviewed by the Global Commission to issue the certification of global eradication.

On 26 October 1979 in a ceremony in Nairobi, Kenya, Dr. Halfdan T. Mahler, the Danish Director General of the WHO, declared that smallpox had been eradicated from the entire world and that this disease could now be consigned to history. This represented the first disease ever eradicated by human efforts. He further proposed that the date of 26 October 1979 be henceforth designated as Smallpox Zero day. This day occurred just 12 years, 9 months, and 26 days after the WHO had embarked on the global eradication program on 1 January 1967 and 178 years after Dr. Edward Jenner foresaw in 1801 the possibility of global eradication of this disease by vaccination. Subsequently, in December 1979 the Global Commission for Certification of Smallpox Eradication consisting of an independent body of 21 experts from 19 nations chaired by Frank Fenner of Australia declared that the world was now in the post-smallpox era and that no one, except investigators at special risk, should be vaccinated. These investigators were defined as: (i) those who are engaged in research at highly secured laboratories on variola virus and other orthopoxviruses pathogenic for humans; (ii) those who handle vaccinia virus for vaccine production; and (iii) those who investigate monkeypox cases directly. The Commission further declared that requirements for smallpox vaccination certificates at national frontiers throughout the world should be abolished. The commission consisted of the following members: J. Aashi (Saudi Arabia), J. Azurin (Philippines), R. N. Basu (India), P. N. Burgasov (USSR), A. Deria (Somalia), K. R. Dumbell (United Kingdom), F. Fenner (Australia), D. A. Henderson (United States), K. Ruti (Zaire), W. K. Karuga (Kenya), J. Kostrzewski (Poland), H. Lunbeck (Sweden), S. S. Marennikova (USSR), J. S. Moeti (Botswana), C. Mofidi (Iran), I. Tagaya (Japan), P. F. Wehrle (United States), Z. Yi-hao (China), R. Netter (France), B. A. Rodrigues (Brazil), and P. N. Shrestha (Nepal).

The Commission finished its 4 days of intensive work on 9 December 1979 by witnessing the signature, by all members except the prominent epidemiologist Chamsoddin Mofidi, who was

unable to leave Iran, of a document bearing the following sentence in six languages: "We, the members of the Global Commission for the Certification of Smallpox Eradication, certify that smallpox has been eradicated from the world." A 122-page final report by the Commission on the global smallpox eradication and its certification was issued by the WHO in 1980. However, as a form of insurance against the likelihood (which is now considered to be negligible) of reintroduction of smallpox from poxvirus laboratories or from natural or animal reservoirs, the Commission recommended that freeze-dried vaccine stocks for the vaccination of about 300 million people, be stored at  $-20^{\circ}\text{C}$  together with stocks of bifurcated needles for emergency use (in Geneva, Toronto, and New Delhi) by the WHO indefinitely. Moreover, many countries have stockpiled their own national reserves of smallpox vaccine. Later, at the 33rd World Health Assembly of the WHO, victory over smallpox was officially marked by solemn ceremonies at the Palais des Nations in Geneva, Switzerland on 8 May 1980. A resolution passed by the 34th World Health Assembly in 1981 amended the International Health Regulations to remove smallpox from the list of internationally quarantinable diseases effective 1 January 1982. Hence, the legal basis for requirement of smallpox vaccination of international travellers was eliminated (3, 18, 110).

The eradication of this disease is indeed a unique event in the history of mankind and represents a signal achievement by the WHO. The credit for this phenomenal feat deservedly belongs to the thoughtful and dedicated field workers, both national and international, who worked out remarkable solutions to many very difficult problems with due understanding and consideration of the local customs and circumstances. The work of these individuals was mostly arduous and tedious, requiring days of walking, fording rivers, riding on camels, mules, and occasionally elephants, as well as bouncing over rough roads by bicycles, motorcycles, or landrovers. Moreover, the field workers lived under the most difficult of field conditions and survived, as best they could, on the locally available food; those serving in India and Bangladesh usually lost 4 to 10 kg (8.8 to 22 lbs) during a 3-month period of service.

The following individuals are some of these dedicated workers to whom mankind is greatly indebted for the global eradication of smallpox: D. A. Henderson, W. H. Foege, J. G. Breman, L. B. Brilliant, J. M. Lane, S. O. Foster, L. K. Altman, R. H. Henderson, J. D. Millar, E. W. Brink, G. Meiklejohn, P. F. Wehrle, and A. Schnur (United States); I. D. Ladnyi, V. A. Moukhopad, and S. Selinonov (USSR); N. C.

Grasset and P. Ziegler (France); I. Arita (Japan); M. I. D. Sharma, R. N. Basu, M. Singh, R. P. Singhal, R. S. Bajpai, M. Dutta, R. R. Arora, C. K. Rao, N. K. Gupta, and B. Singh (India); Z. Jezek and V. Zikmund (Czechoslovakia); A. Monnier (Mexico); and many others. Dr. Donald H. Henderson directed the global eradication program with much zeal and vision from 1967 to 1976 when Dr. Isao Arita, who had been responsible for vaccine production, became Director and supervised the eradication in the Horn of Africa and certification of global eradication. Both men were extensively involved in field work which was most important in the successful execution of the program. Moreover, two highly skilled and devoted research-oriented laboratory workers have been prominent among many who were involved in the laboratory aspects of this program. They are J. H. Nakano, Director of Viral Exanthems Branch at the Centers for Disease Control, Atlanta, Ga. and S. S. Marennikova, Director of the Smallpox Prophylaxis Laboratory of the Research Institute of Virus Preparations, Moscow, USSR. The laboratories of these two investigators have been officially designated as WHO centers for the diagnosis of suspected human smallpox, monkeypox, and other poxvirus infections.

The total WHO cash input during the last 13 years of the eradication program (1967 to 1979) was only \$112 million, with 687 WHO workers from 73 countries being involved in the eradication program. In addition, the endemic countries themselves provided more than \$200 million and some 200,000 workers. As a direct result of the global eradication of smallpox, over \$1 billion is being saved annually in global health expenditure. In the United States alone, the cost of vaccination and quarantine measures amounted to about \$150 million each year. Moreover, as an example of the cost of one importation of this disease, the smallpox epidemic introduced into Britain by a Pakistani traveller in 1961 involved 67 cases and required the vaccination of 5.5 million people, costing the British government \$3.6 million.

The Somalian case is believed to be the last naturally occurring smallpox in the world. The disease, diagnosed as variola minor, occurred in an unvaccinated 23-year-old male hospital cook named Ali Maow Maalin (Fig. 23) from Merka near Mogadishu, the capital of Somalia, who apparently acquired the disease during the evening of 12 October 1977. On that evening, he served as the guide in a vehicle which was transporting two persons with smallpox (i.e., a 6-year-old girl named Habiba Nur Ali who had severe smallpox and her 1.5-year-old brother who was then in the papular stage of rash, both detected in the vicinity of Kurtunawarey settle-



FIG. 23. Ali Maow Maalin of Somalia, last case of smallpox (*variola minor*) in the world, reported in October 1977 (courtesy of the WHO, Geneva, Switzerland).

ment) from his hospital to the home of the local smallpox surveillance team leader (total contact time during that ride was less than 15 min). The victim developed high fever and headache on 22 October and was hospitalized and treated for malaria; however, his symptoms persisted and a rash appeared 4 days later. At this stage, chickenpox was suspected, and the patient was discharged from the hospital to recuperate at home. Within 5 days, the clinical symptoms indicated smallpox, which was later confirmed by laboratory tests. The patient recovered uneventfully without transmitting the disease to anyone else. However, before his isolation, he had exposed 161 persons of whom 41 were unprotected; all were identified and kept under surveillance with no indication of transmission. As Maalin did not report himself to his hospital officials because of his reluctance to go to the isolation camp, a male nurse friend reported him to the Regional Health Superintendent on 30 October and collected a reward (28, 95).

#### Use of Vaccine After the Global Eradication

About 1.5 years after the detection of the last case of naturally occurring smallpox in the entire

world, the U.S. Centers for Disease Control (CDC) reported on 15 June 1979 that during 1978 more than 4.4 million doses of smallpox vaccine were distributed in the United States (*Morbid. Mortal. Weekly Rep.* 28:266, 1979). In 1980, more than 2.8 million doses were distributed, of which about 500,000 were given to the civilian population. In 1981 and 1982, it is estimated that the number of vaccinated civilians fell to about 250,000 and 50,000, respectively. The adverse reactions which may follow vaccination were described above.

The vaccine has been needlessly administered to international travellers. Currently, only Chad in Africa requires a smallpox vaccination certificate for entry. The government of the Democratic Kampuchea (Cambodia) has recently advised that a certificate is no longer required. However, some local authorities may require proof of vaccination. Because of the risk of complications of vaccination to both the vaccinees and their contacts, the WHO recommends that waiver letters stating that vaccination is medically contraindicated be given by physicians to international travellers. However, WHO reported that a 5-month-old boy in Kuwait who was vaccinated against smallpox on 24 April 1979 died on 15 July of ulcerative lesions on the entire inoculated arm and of coalesced lesions forming large destructive ulcers on the trunk, perineum, and buttocks despite intensive care (*Morbid. Mortal. Weekly Rep.* 28:536, 1979).

The vaccine has also been used without any demonstrable benefit for the treatment of herpetic infections and warts. Many serious and even fatal reactions to such smallpox vaccinations (see below) have been reported by the CDC. In January 1983, the CDC Immunization Practices Advisory Committee recommended that smallpox vaccine be taken off the commercial market for civilian use. Subsequently, in May 1983, Wyeth Laboratories, Inc. (the only active licensed producer of smallpox vaccine in the United States) discontinued general distribution of smallpox vaccine. However, Wyeth continues to produce the vaccine for the Department of Defense.

A recent fatal case in the United States involved a 7-month-old male infant in California who was vaccinated in mid-June 1979 because of a 3-month history of recurrent mouth ulcers suspected of being caused by herpes simplex virus. The vaccination site in the child, who had a severe combined immune deficiency, never healed, and satellite lesions developed 2 weeks later and spread rapidly. Vaccinia virus was isolated from the skin lesions. He was treated with intravenous vaccinia immune globulin, methisazone (Marboran), topical adenine arabinoside, gentian violet, and rifampin. Moreover, a thymic transplant was attempted, and transfer

factor was administered. However, the infant developed a severe pulmonary infection with *Pneumocystis carinii* which was treated with pentamidine, trimethoprim, and sulfamethoxazole. Respiratory failure requiring ventilatory support followed, and the child died on 31 August 1979 (CDC, Morbid. Mortal. Weekly Rep. 29:117, 1980).

More recently, during the latter part of 1981, smallpox vaccine was administered by a physician in California to a 53-year-old man with chronic lymphocytic leukemia for the treatment of recurrent herpes labialis. The patient developed severe vaccinia necrosum, and the California Board of Medical Quality Assurance revoked the physician's medical license and placed him on probation for 5 years (CDC, Morbid. Mortal. Weekly Rep. 31:159, 1982). Another recent report described a young man with recurrent genital herpes infection who received seven smallpox vaccinations (administered by two physicians) in the deltoid region. These vaccinations not only failed to control the genital herpes but in fact caused recurrent herpes at the vaccination site (most likely by autoinoculation) (81).

The last case reported by CDC involved a 61-year-old woman with a 2-year history of severe genital herpes who was vaccinated in her left arm on 1 April 1982. The patient, who apparently had an underlying immunosuppression or immunodeficiency, developed vaccinia necrosum (gradually enlarging to approximately 8 by 7 cm) at the site of vaccination and later on the left thigh (increasing to approximately 2.5 cm) as well. Both the left arm and the left thigh ulcers repeatedly yielded the vaccinia virus. However, the herpetic perineal ulcers cleared after the intravenous administration of acyclovir during the first hospitalization and became negative on virus culture. She was hospitalized three times during May to July 1982 and was treated with vaccinia immune globulin (three times), oral methisazone (three times), intravenous acyclovir (once), interferon (twice), as well as transfer factor (four doses) (CDC, Morbid. Mortal. Weekly Rep. 31:501, 1982). At last reporting (November 1982), the extensive treatment has not been effective against her vaccinia necrosum either at the vaccination site or on the thigh.

A vaccinated person may also serve as a source of vaccinia virus infection among his or her contacts. CDC reported (Morbid. Mortal. Weekly Rep. 30:453, 1981) that an 18-year-old female military recruit developed satellite lesions on her lower lip, abdomen, and left thigh after smallpox vaccination on 12 December 1980 at Canadian Forces Base Cornwallis, Nova Scotia. Subsequently, six cases of contact vaccinia, four transmitted from the index person and two from one of the first contacts, were reported

during January 1981 in Western Newfoundland. None of these six contact persons had been previously vaccinated. Elsewhere, nine cases of contact vaccinia were reported in Britain during 1980; two of them were transmitted by military personnel. More recently, CDC reported (Morbid. Mortal. Weekly Rep. 31:683, 1982) that a 19-year-old male student at the University of Tennessee in Knoxville who was vaccinated on the right arm for the first time at an Air National Guard meeting on 3 October 1982 developed multiple pustules on both cheeks in areas of active acne (probably by autoinoculation) on 9 October after he returned to the University. The patient became acutely ill with chills, fever (38.7°C), a swollen and erythematous right upper arm, and tender right axillary nodes. On the evening of 12 October, 25 ml of vaccinia immune globulin (one-half the indicated dose) was injected intramuscularly, and the following morning the patient became afebrile and appeared much improved. He returned to class on 18 October; however, no contact case was reported from this vaccinee. The last cases of contact vaccinia infection reported by the CDC (Morbid. Mortal. Weekly Rep. 28:536, 1983) involved an 11-year-old military dependent girl who was mistakenly vaccinated on 14 April 1983 in Nevada. She had a primary reaction and transmitted the infection to seven other girls during a slumber party on 17 April. The girls developed widely distributed lesions; however, the illnesses were mild. They were quarantined at their homes for 2 weeks, during which their lesions resolved. No additional contact case occurred. In this connection, however, as amply illustrated above, the relative ease with which vaccinia is transmitted from a recently vaccinated individual to unvaccinated contacts should be emphasized.

#### POXVIRUS DISEASE AFTER THE GLOBAL ERADICATION OF SMALLPOX

After the global eradication of smallpox, two potential sources of poxvirus infection of humans still remain. The first is accidental infection with laboratory smallpox virus stocks, and the second is infection with animal poxviruses. The recent laboratory-associated infection in 1978 at Birmingham University Medical School in Birmingham, England is a vivid example of the first type.

#### Laboratory-Associated Infection at Birmingham University

Janet Parker, a 40-year-old medical photographer in the Department of Anatomy worked in a darkroom located on the floor above a research laboratory where a comparative study of smallpox and whitepox viruses was being performed by 48-year-old virologist Dr. Henry S. Bedson

(the son of the late Sir Samuel P. Bedson) of the Department of Medical Microbiology. On 25 July 1978, Mrs. Parker spent most of the day on the phone in an office next to her darkroom ordering photographic supplies before the end of the financial year on 31 July 1978. While telephoning, she would have been close to an ill-fitting inspection panel of the service duct linking this office to Dr. Bedson's animal poxviruses laboratory on the lower floor. The inspection panel of the service duct in this laboratory was also ill fitting. Connected to the animal poxviruses laboratory was a small research laboratory where intensified work on, among other poxviruses, the Abid strain of variola major virus (isolated in 1970 from a 3-year-old boy in Pakistan and named after him) was proceeding. Very large quantities of virus were being handled in this laboratory.

Bedson's laboratory was due to close at the end of 1978 as it had not been approved by the WHO as one of the few laboratories to continue work with smallpox virus after the global eradication. In May 1978, a three-man WHO team (including Dr. J. H. Richardson, Director of the Office of Biosafety at the CDC) inspected Dr. Bedson's laboratory and found that the physical facilities and laboratory procedures were far from satisfactory and clearly below the WHO standards; the team strongly recommended either upgrading or closure at the earliest possible date. However, Bedson was regarded as a conscientious and experienced virologist of considerable worldwide repute; thus, no peer pressure was brought on him to immediately abide by the WHO recommendation. In the meantime, intensified work with the smallpox virus was being pursued by Bedson and his two assistants in an attempt to complete the research by the end of 1978.

Mrs. Parker, last vaccinated in 1966, became ill on 11 August, developed a rash 2 days later, and was admitted to East Birmingham Hospital on 24 August. Her illness was diagnosed by electron microscopy as smallpox on 25 August (ironically by Dr. Bedson himself), and she was immediately transferred to the Catherine De Barnes Isolation Hospital near Birmingham. On 27 August, the Abid strain of variola major virus was isolated from Mrs. Parker, and she died of smallpox (renal failure and bacteremia) on 11 September 1978. As the other part of this double tragedy, Dr. Bedson, who became depressed and blamed himself for the escape of the virus, had already died of self-inflicted throat wounds (discovered by his wife when she returned home from a trip) on 6 September 1978. His death occurred after switching off the machine that had been sustaining him when it was determined that he had suffered brain death. A suicide note said: "I am sorry to have misplaced the trust

which so many of my friends and colleagues have placed in me and my work." Mrs. Parker's mother and close contact, Mrs. Helen Witcomb, was prophylactically vaccinated on 25 August and was administered vaccinia immune globulin and methisazone. However, she developed a mild modified smallpox on 8 September and recovered uneventfully. Mr. Frederick Witcomb (Mrs. Parker's father) developed fever on 1 September and was admitted to the Smallpox Hospital on 3 September as a precaution; however, he died suddenly on 5 September from a heart attack.

Three-hundred forty-one close and casual contacts of Mrs. Parker and her mother were promptly identified and either vaccinated or placed under surveillance. One of these, a 20-year-old British woman (Mrs. Parker's co-worker, who was vaccinated in 1973) traveled to a North Dakota farm on 18 August 1978. Daily surveillance revealed no infection in this and other contacts.

The British Department of Health and Social Security appointed a team, headed by Reginald A. Shooter, Chairman of the Dangerous Pathogens Advisory Group (formed after the inquiry into the outbreak of smallpox in London in 1973) and Professor of Microbiology at St. Bartholomew's Hospital in London, to investigate this laboratory-associated smallpox at Birmingham. The investigation resulted in the preparation of the Shooter report, which was released by Clive Jenkins, General Secretary of the Association of Technical and Managerial Staffs, the trade union to which Mrs. Parker belonged. Considering the physical and procedural circumstances described above, the report indicated that Mrs. Parker (who had never been in the Department of Medical Microbiology) was probably infected with the Abid strain of smallpox virus while telephoning on 25 August 1978. The virus apparently escaped from the small research laboratory into the animal poxviruses laboratory and from there to the service duct through the ill-fitting inspection panel and finally reached Mrs. Parker as she was talking on the phone (the virus here again coming out of the common service duct through the ill-fitting inspection panel).

A safety cabinet (hood) equipped with filter and extraction fan routinely utilized in the research laboratory to prevent the smallpox virus from escaping into the adjacent animal poxviruses laboratory was later shown to be unable to do so under all conditions. Ironically, the outbreak of smallpox (variola minor) which affected 73 people with one death in the Birmingham region from February to May 1966 started from the same source, with the first victim being a male photographer who became ill on 18 February and held exactly the same position as Mrs. Parker (44). Previously, a hospital outbreak in



Meschede, Federal Republic of Germany, was associated with the ability of smallpox virus to travel from one floor to another via external air currents (see above).

The Health and Safety Executive issued a summons against the University of Birmingham for failing to protect the health of its employees. However, the Birmingham Magistrates dismissed the charges largely on the basis that a number of internationally prominent smallpox experts (e.g., Alan W. Downie, Keith R. Dumbell, and Kevin McCarthy) challenged the thesis presented by the Shooter report and discounted the likelihood of airborne spread of the virus from Dr. Bedson's smallpox laboratory. The experts believed that the normal working conditions in Bedson's laboratory were unlikely to generate sufficient amounts of airborne virus to produce Mrs. Parker's infection. The University of Birmingham has also issued its account challenging the Shooter report.

Experiments and calculations performed by experts indicated that: (i) 1 particle among 480 million aspirated by laboratory workers had found its way into the air (according to Kevin McCarthy); (ii) 11,812 gallons of virus fluid would have had to have been aspirated for 1 particle to reach the telephone room (according to O. M. Lidwell); and (iii) it would take 20,000 years for 1 particle to escape to the telephone room at the rate the virus was aspirated (according to Alexander Buchan). However, Dr. Shooter and members of his team (Dr. C. C. Booth, Sir David Evans, Dr. J. R. MacDonald, Dr. David A. J. Tyrell, and Sir Robert Williams) indicated that the procedures employed by workers at the Birmingham laboratory were far from satisfactory and that smallpox virus could have become airborne. At this writing, the mode of transmission has not yet been unequivocally delineated (47, 68-71, 86).

Currently, global efforts are being made to restrict all remaining smallpox virus stocks to only two WHO Collaborating Centers, where adequate containment facilities are available and storage is secure in accordance with WHO specifications. These are the CDC in Atlanta, Ga. and the Research Institute of Viral Preparations in Moscow, USSR. However, the National Institute of Virology, Sandringham, South Africa, has so far refused to relinquish its smallpox virus stocks. The virus may still be unofficially retained by certain other laboratories. It is claimed that the virus is stored for only archival purposes. Historically, during the 25 years preceding the global eradication of smallpox, there were some 600 laboratories worldwide that, at one time or another, dealt with variola virus. However, in 1976 there were only 76 laboratories throughout the world that officially kept stocks of smallpox virus. By mid-1978, 62 of the

76 laboratories had either destroyed or transferred their virus stocks, and in 1980, the number was reduced to only 6 laboratories.

As smallpox is now eradicated from the entire world, it is often asked, why keep the causative agent and take the risk of laboratory-associated infections? The answer lies in the fact that there exist in various parts of the world a number of animal poxviruses (e.g., monkeypox and cowpox viruses) that closely resemble smallpox virus and can produce human infections (see below). Other new poxviruses may yet be discovered. The natural histories of these viruses have not yet been delineated, and it is not known whether these agents can someday replace the eradicated smallpox virus as widespread human pathogenic agents. It is therefore necessary to conduct comparative studies on these animal poxviruses along with the smallpox virus to construct a catalog for these various viruses, map their viral DNAs, and define the antigenic nature of each strain by certain sophisticated biochemical procedures. Such studies will undoubtedly result in a greater understanding of the genetic relations among these viruses and will hopefully provide a basis for better prediction of their disease potential (38).

#### Human Infections with Animal Poxviruses

The second source of human infections, namely, animal poxviruses, has become of considerable concern in recent years. As smallpox virus is highly species specific; it can only infect humans and certain subhuman primates. However, infection in the latter cannot be serially passed by contact transmission. Thus, it is believed that there is no simian reservoir for the smallpox virus. However, two other poxviruses of mammals, namely, the monkeypox and the so-called whitepox viruses, are capable or potentially capable of infecting humans.

**Monkeypox virus.** The monkeypox virus was first isolated in 1958 by Dr. Preben von Magnus and his colleagues at the Statens Serum Institut in Copenhagen, Denmark from cynomolgus monkeys (shipped from Singapore) with a generalized vesicular eruptive disease. Later, several outbreaks of monkeypox occurred both in Europe and the United States among monkeys imported from Asia and Africa. However, infection among these animals in the wild has not been observed; thus, it has been suggested that monkeys (like humans) are accidental hosts and do not serve as natural reservoirs. In an attempt to establish a specific natural reservoir for this virus, a WHO-Zaire joint team collected liver, spleen, and kidney specimens from 1,372 wild animals representing some 98 species (nonhuman primates, rodents, squirrels, pangolins, etc.) in the Equateur Region of Zaire and tested them for poxvirus; no poxvirus was isolated.

However, specific monkeypox virus antibody was detected in a few wild monkeys captured in West Africa.

Human infection with the monkeypox virus, which is clinically indistinguishable from smallpox and shows a fatality rate of about 15%, was first recognized in a 9-month-old boy in Equateur Province, Zaire (then called the Congo), who developed fever on 22 August 1970 and a rash 2 days later. This human case was recognized 9 months after the last case of smallpox was recorded in that region. The child was admitted to Basankusu Hospital on 1 September, and on examination, hemorrhagic lesions with centrifugal distribution, typical of that of smallpox, were observed. The patient, who had not been vaccinated, recovered from monkeypox; however, on 23 October, he developed measles and died on 29 October. The monkeypox virus, which has been generally considered nonpathogenic for humans, was isolated from this case at the WHO Collaborating Center in Moscow, USSR (63). The disease is a rare zoonosis which remained unrecognized until smallpox was eradicated from the involved areas. Most cases of human monkeypox have certain characteristic clinical and epidemiological features. A 2-day prodrome is followed by typical smallpox-like rash which evolves over 2 to 4 weeks. The lymphadenopathy is more prominent than that in smallpox cases (Fig. 24). Moreover, about 13% of cases have been mild or very atypical, which suggests the possible occurrence of unrecognized cases. The interhuman transmission rate is much less than that of smallpox. During the 1970 to 1979, 63 cases (the majority in children with only 7 in individuals over 15 years of age) with eight deaths were documented in six countries of equatorial rain forest areas in West and Central Africa, namely, Cameroon (2 cases), Ivory Coast (2 cases), Liberia (4 cases), Nigeria (3 cases), Sierra Leone (1 case), and Zaire (51 cases). Seroepidemiological surveys suggest that forest-dwelling monkeys, squirrels, porcupines, or pangolins may be involved in the natural cycle of transmission. However, the mode of transmission to humans has not been delineated (19, 25).

One case diagnosed at the WHO Collaborating Center at the CDC by isolating monkeypox virus on 27 December 1978, involved a 35-year-old male traditional herbalist of the People's Republic of Benin, who travelled to Omifounfoun Village, Oyo State, western Nigeria, and stayed with his family for 2 months. He developed fever and rash there on 24 November 1978 and returned to Benin to be hospitalized in Parakou, Borgou Province, on 5 December. Thirty-six close contacts, four of whom had never been vaccinated, were investigated; no



FIG. 24. Human monkeypox (courtesy of the WHO, Geneva, Switzerland).

secondary case was detected (CDC, *Morbidity and Mortality Weekly Report* 28:135-136, 1979). A more recent case occurred in a 3-year-old unvaccinated girl in Cameroon who developed a rash on 14 September 1979. Only 5 of the above 63 monkeypox patients had been vaccinated, and only in 6 was the possibility of human-to-human transmission indicated. Moreover, tertiary transmission of human monkeypox has not been reported. Thus, little epidemiological significance is currently given to this virus. However, as stated above, epidemiological surveys have suggested that certain wild monkeys and rodents of the region, which show serological evidence of infection with an orthopoxvirus, may serve as the reservoir of this virus and thus constitute a potential source of human infection. At this writing, the total number of reported human monkeypox cases has reached 79. The most recent one occurred in a 6-month-old girl who had a close contact, for no more than 2 h, with a wild chimpanzee on 30 May 1982 in Kivu, Zaire. This latest case provides evidence that wild

nonhuman primates can be the source of human infections (84).

Currently, the WHO is continuing its special surveillance program on monkeypox in West and Central Africa. The virus is readily differentiated from the smallpox virus. However, certain white-pock variants or whitepox viruses (producing no hemorrhage on the chorioallantoic membranes of chicken embryos and breeding true upon passage through hamsters, thus resembling smallpox virus) have been isolated from monkeypox virus preparations and have been considered as ominous mutants of monkeypox virus. Some studies suggested that these variants arose most likely by genetic interaction in mixtures of monkeypox and smallpox viruses. Other follow-up studies, carried out in certain WHO Collaborating Centers, have failed to verify the above findings (19). In this connection, serological differentiation of smallpox, vaccinia, and human monkeypox virus infections by an adsorption radioimmunoassay test was recently reported (103).

**Whitepox virus.** The first two of the so-called whitepox viruses were isolated in October 1964 from monkey kidney cell cultures prepared at the Rijks Institute in Bilthoven, The Netherlands from two healthy cynomolgus monkeys imported from Malaysia and which had been in contact with African monkeys during transportation. The viruses, designated 64/7255 and 64/7275, were distinguishable from animal poxviruses but resembled the smallpox virus very closely. However, a recent laboratory investigation of these two viruses has indicated that they represent laboratory contamination. Two variola viruses designated 64/7124 and 64/7125 were isolated in September and October 1964 at the same laboratory from specimens obtained from smallpox patients in Vellore, India. A detailed comparison of certain biological markers of these four viruses and their DNAs showed that the two whitepox viruses were identical to the Vellore virus designated 64/7124.

Four more viruses with the same properties were subsequently isolated by the WHO Collaborating Center for Poxvirus Infections in Moscow from the kidney tissues of a chimpanzee (designated Chimp-9), a sala monkey (designated MK-7-73), and two African rodents, namely, a *Mastomys* (designated RZ-10-74) (the common native rat in Zaire) and a squirrel-like rodent (designated RZ-38-75). All of these animals were obtained in the wild between 1971 and 1975 in Zaire, which had been free of smallpox for several years. Sera from three of these animals contained orthopoxvirus antibodies, and the virus was reisolated from the tissues of two animals. In contrast to monkeypox virus, these four viruses as well as the two described

above produce white pocks on the chorioallantoic membrane of the developing chicken embryo and have hence been named whitepox viruses. Experimentally, they cause a generalized disease with rash in *Cercopithecus* monkeys. As these viruses are indistinguishable from the smallpox virus by the currently available laboratory procedures, they, especially the last four, remain as both a threat and a puzzle. However, so far no human infection has been reported from the areas inhabited by the animals yielding these viruses. Moreover, the possibility that the latter four whitepox viruses may also represent laboratory contamination has not been unequivocally excluded since smallpox virus was handled in the Moscow laboratory when these four whitepox viruses were isolated (4, 31, 32, 76).

Various strains of variola virus and whitepox viruses can be differentiated from one another by the pattern of hemadsorption in infected human diploid cell cultures and the relative abilities of these strains to grow in a continuous rabbit kidney cell cultures (RK-13) as measured by the hemagglutination test. Variola and whitepox viruses, on the other hand, can be differentiated from other poxviruses by a laboratory procedure which tests the sensitivity of thymidine kinase, which is produced by all these viruses, to inhibition by thymidine triphosphate (12).

Another poxvirus, called Lenny virus, was isolated by the WHO Collaborating Center in London in 1969 from a woman with severe vesicular disease and fever resembling those of smallpox, who died in eastern Nigeria. The virus, which most closely resembles vaccinia virus, was characterized as a hybrid of smallpox and vaccinia viruses and possibly emerged from a double infection. No transmission of this virus among the natives of the region was detected (4).

**Other animal poxviruses.** Currently, certain WHO Collaborating Centers are also conducting surveillance and research on a number of other poxviruses, namely, camelpox, gerbilpox, tanapox, ratpox, raccoonpox, and certain others closely related to cowpox, which have been isolated from cats and cheetahs. As regards the cowpox virus (see above), it is now generally believed that both cows and humans are only sporadic indicator hosts of this virus and that they acquire infection from a hitherto unrecognized reservoir. An outbreak of cowpox in three cheetahs, two of which died, occurred at Whipsnade Park in London, England in February 1977. Administration of immune globulin did not change the course of the disease, and smallpox vaccine did not take in the uninfected cheetahs. The isolated cowpox virus, however, could not be virologically or serologically traced to either captive or wild animals of the area (4, 10).

Moreover, spontaneous cowpox infections in humans and various exotic animal species (such as large felines kept in zoos located in Moscow, USSR and the United Kingdom and most recently a young tiger in Stockholm, Sweden) with no contact with cows have been documented. A poxvirus designated Turkmenia virus, which is closely related to cowpox virus, was recently isolated from the great gerbils in the Turkmen Republic of the Soviet Union. It is thus postulated that the natural reservoir of the cowpox virus in the United Kingdom and western Europe might most likely be in small wild rodents.

The camelpox virus was isolated by the WHO Collaborating Center at the CDC from camels with rash observed in Somalia during 1977 to 1979. Moreover, camelpox has posed a serious problem in Iran; its etiological agent was isolated in the early 1970s by Dr. H. Mirchamsy and Dr. H. Ramyar in Tehran. The virus produces pocks on the chicken embryo chorioallantois which closely resemble those of variola virus but which are easily distinguished from the latter by other characteristics. No infection with this virus was detected in the nomads who had close contact with the infected animals (6). Gerbilpox virus (taterapox) was isolated from a wild gerbil obtained in 1968 in northern Dahomey, Africa. It, too, resembles variola virus but has distinctive characteristics. Tanapox virus (named after the Tana River in Kenya, which is of unknown reservoir, can produce one or a few skin nodules in humans; more than 163 cases were observed in Zaire during 1978 to 1981. The virus is not a member of the orthopoxvirus group and is readily distinguished from the latter. Another similar virus has caused epizootic outbreaks in primate centers in California, Oregon, and Texas (4).

#### Smallpox Scares

More than 170 smallpox scares (15 of them within the last 12 months) have been rumored in 60 countries and reported to the WHO since 26 October 1977. National health authorities or joint national/WHO teams from the international smallpox rumor register in Geneva have investigated all of these scares; all have proved false. They turned out to be chickenpox, measles, monkeypox, herpes simplex, or other skin diseases or were due to typographic errors, mistakes in recording, or otherwise unfounded reports. Some 9,170 specimens were collected from suspected cases in the Horn of Africa and other regions of the world during 1978 and 1979; none contained the smallpox virus. However, certain Nigerian traditional healers (including Chief J. O. Lambo, President of the Nigerian Association of Medical Herbalists) have claimed that despite the WHO reward of \$1,000 for reporting a confirmed case of smallpox in 1978,

the disease still occurred in Nigeria in 1980 (97). An official of the WHO (Dr. T. A. Lambo, brother of the above-mentioned Chief Lambo) indicated in 1981 that the last case of smallpox in Nigeria was recorded in 1970 and that the Nigerian herbalists were dealing with cases of chickenpox and possibly human monkeypox (64).

The last scare, which made worldwide headlines, concerned a 32-year-old Italian engineer, Umberto Moretti (most recently vaccinated in 1970), who developed smallpox-like symptoms (fever and a vesicular skin rash) in Brescia (60 miles east of Milan) on 12 April 1980, 5 days after returning from a business trip to Japan, Indonesia, and Singapore. New skin lesions in different stages of development (more numerous on the trunk than on the extremities, with few on the palms and fingers) appeared during the following 3 days. Although his illness was diagnosed clinically as chickenpox, electron microscopic study at a Lombardy regional laboratory reported poxvirus-like particles (resembling those of Orf) in the patient's skin lesions. However, further examination of the skin lesion material by electron microscopy, chicken embryo inoculation, as well as complement fixation tests at the National Laboratory of the French Ministry of Health in Paris and at the CDC indicated the involvement of the chickenpox virus. The patient had been previously vaccinated several times (the most recent in 1970) and had a visible vaccination scar; however, he had not had chickenpox. Moretti's wife and father were also hospitalized as a precaution. Health authorities disinfected the six-story building where the Morettis lived and asked 22 resident families to take gamma globulin (CDC, *Morbidity and Mortality Weekly Report* 29:193, 1980). Similarly the suspected smallpox outbreak in Nigeria during November 1982 to January 1983 and the suspected smallpox in a 12-year-old girl in India in June 1983 (both investigated by the CDC) also proved to be chickenpox (CDC, *Morbidity and Mortality Weekly Report* 32:490-491, 1983).

Facial pockmark surveys, particularly among children born since the last recognized case, have been recently used by the WHO for confirming the absence of smallpox. However, 2.4% of individuals recovering from varicella in Somalia had five or more residual facial scars indistinguishable from those of smallpox (59).

At this writing, in 153 of the 159 WHO member states and associated members, smallpox vaccination is no longer obligatory. In regard to the other six countries, primary vaccination continues but revaccination has been stopped in Egypt, and primary vaccination has been stopped but revaccination continues in France. The current official status of vaccination policy in Albania, Bhutan, Chad, and the Democratic

People's Republic of Korea is being awaited by the WHO.

### Certain Unanswered Questions

Finally, there still remain certain unanswered questions which have been recently raised by some concerned physicians in regard to the wisdom of adopting the universal cessation of antismallpox vaccination on the basis of the belief that smallpox has definitely disappeared from the face of the earth. Are there still hidden foci of smallpox or a smallpox-like diseases in isolated or remote populations? Can such infected inanimate objects as bed clothes and fragments of smallpox scabs left inside houses after recovery or death of past smallpox patients serve as potential sources of future human infections? Are there hitherto unknown animal reservoirs of smallpox or smallpox-like viruses? Can another orthopoxvirus be transformed to smallpox virus? Are we absolutely certain that laboratory infections such as that which occurred very recently in Birmingham, England (see above) will not recur? Will animal poxviruses (e.g., monkeypox) eventually replace the eradicated smallpox virus as widespread human pathogens? Lastly, could biological warfare with the smallpox virus be waged in the future when no immunological protection is afforded by the victims as the result of the gradual loss of smallpox immunity in the world population (30)?

Providing definitive answers to all of the above questions is impossible at this time. However, in an attempt to give partial answers, it could be pointed out that smallpox has not reappeared in any of the WHO-certified smallpox-free countries. During the 11 years of the global eradication program, it was established that smallpox never persisted in any area for more than 8 months without being discovered (i.e., the experience in Indonesia during 1971 and 1972). Thus, the condition of 2 years of smallpox-free period, established by the WHO, for certification of any country, was three times longer and quite adequate. Moreover, the virus does not survive for more than 1 month in the tropical countries where infected inanimate objects may have been most likely left after recovery or death of smallpox patients. However, in a temperate zone, viable virus was isolated in 1967 from scabs collected in March 1954 (from three patients with variola minor in The Hague, The Netherlands) and kept for 13 years in unsealed envelopes at a Leiden laboratory at temperatures ranging from 15 to 30°C and relative humidity ranging from 35 to 98% (109). Moreover, all outbreaks of smallpox which occurred during the last 12 years in tropical areas of Africa, Asia, and South America were shown by WHO epidemiologists to have been initiated solely by

known persons or well-documented laboratory sources. In addition, as there are substantial genetic differences between smallpox virus and other orthopoxviruses, mutation of the latter viruses to the former virus is believed to be quite unlikely.

As regards the possibility of animal poxviruses filling the ecological niche vacated by the smallpox virus and the unthinkable possibility of biological warfare with this virus, only the future will provide the answers. In this connection, however, it should be kept in mind that vigilance is continuously exercised by the WHO in regard to animal poxviruses in various areas of the world as a potential danger to humans. Moreover, as a protective measure against some of the above possibilities, vaccine stocks and bifurcated needles for vaccination of about 300 million people are maintained indefinitely by the WHO in Geneva, Switzerland; Toronto, Canada; and New Delhi, India.

Lastly, in regard to the WHO's declaration of global eradication of smallpox on 26 October 1979, the noted medical historian Erwin H. Ackerknecht writes in *A Short History of Medicine* (published in 1982): "This announcement might be premature in view of the unreliability of statistics in underdeveloped countries." This author does not agree with Professor Ackerknecht's pessimistic statement and objects to the use of the words "unreliability" and "underdeveloped" for obvious reasons.

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