It is important to emphasize that although variolation was a useful public health intervention at the time, it was not without risks. Early variolation procedures led to death in approximately 1% to 2% of the immunized subjects. This was considered an acceptable risk in view of the much higher likelihood of a fatal outcome if smallpox (a common disease at the time) were to be acquired by the natural mode of transmission. The other major drawback was that variolated subjects could themselves spread the smallpox virus to susceptible contacts. So it was clear that the control of smallpox needed a better preventive intervention.

THE ORIGIN OF VACCINATION

During the last decades of the 18th century, smallpox was rampant in Europe, despite the increasing use of variolation as a preventive measure. Among rural folk during this period, it was increasingly appreciated that milkmaids were selectively spared the ravages of smallpox and that this was somehow related to the mild pox infection they often acquired from the cows they milked (2,4). Although several scholars and physicians in the period 1765 to 1791 acknowledged this association and some, like the farmer Benjamin Jesty, even inoculated family members with cowpox (2), appropriate credit must be given to Edward Jenner for his pioneer achievements (Fig. 1). In 1796, Jenner undertook to test rigorously the putative protective effect of a prior cowpox infection against smallpox by actively immunizing an eight-year-old boy with cowpox and later challenging the child with smallpox (i.e., by variolation). Other vaccinations (or *inoculation of the cowpox*) of additional subjects, followed by smallpox challenge (variolation), were carried out thereafter. Jenner had the foresight and perseverance to publish his results and, for the rest of his professional life, promulgated the practice of ''vaccine inoculation'' (10,11).

During the 19th century, smallpox vaccination became increasingly popular and accepted in other areas, including Europe and North America (4). A remarkable and often forgotten global public health campaign was the Royal Philanthropic Expedition of the Vaccine commissioned by King Charles IV of Spain and directed by the physicians Francisco Xavier de Balmis and José Salvany, that between 1802 and 1806 took the smallpox vaccine to Spain's territories in the Americas and the Philippines (12,13). It is fitting that smallpox became the first (and so far the only) communicable disease to be actively eradicated, an accomplishment achieved in the decade 1967 to 1977. An enigma that remains unresolved after the eradication of smallpox concerns the origin of vaccinia, the smallpox vaccine virus. Whatever its origin, vaccinia is a separate species within *Orthopoxvirus* genetically distinct from both cowpox and variola viruses. Cowpox is in fact a rodent virus that occasionally infects other mammalian hosts (14). Hypotheses that have been promulgated include that it represents a hybrid between cowpox and variola virus, that it derives from cowpox virus, or that it is a descendant of a virus (perhaps of equine hosts) that

Figure 1 Edward Jenner (1749–1823), the father of vaccinology. An 1800 pastel portrait of Edward Jenner by J. R. Smith. *Source*: Photo courtesy of The Wellcome Institute Library, London, U.K.

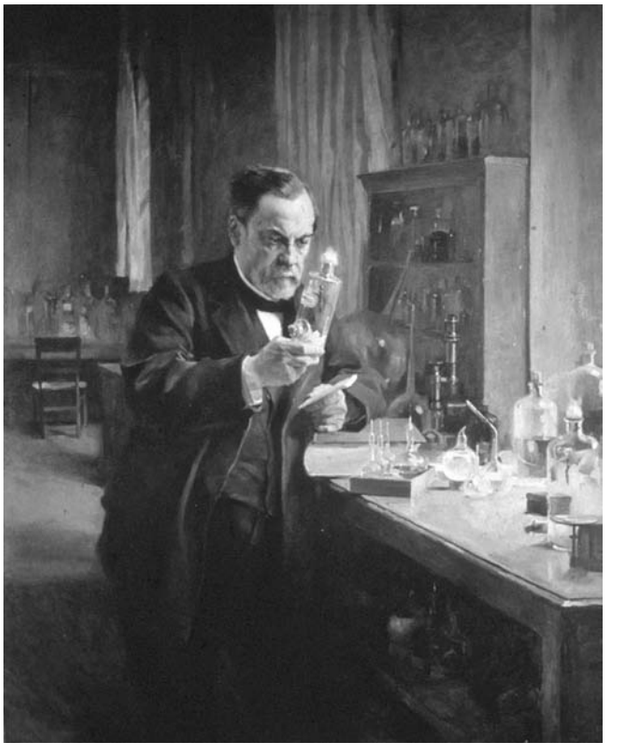

Figure 2 Louis Pasteur (1822–1895), a 19th century pioneer of vaccinology. *Source*: Photo courtesy of Institute Pasteur, Paris, France.