EDWARD JENNER'S VAC

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The first experiment (14 May 1796) was made upon a lad of the name of Phipps, in whose arm a little Vaccine Virus was inserted taken from the hand of a young woman who had been accidentally infected by a cow. Notwithstanding the resemblance which the pustule, thus excited on the boy's arm, bore to variolous inoculation, yet as the indisposition attending it was barely perceptible, I could scarcely persuade myself the patient was secure from the Small Pox. However, on his being inoculated some months afterwards, it proved that he was secure. This case inspired me with confidence; and as soon as I could again furnish myself with Virus from the Cow, I made an arrangement for a series of inoculations.

E. Jenner

The Origin of the Vaccine Inoculation, 1801

CINE

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Nearly two years were to elapse between Dr. Edward Jenner's first vaccination in May 1796 and his subsequent experiments, which began in March 1798. They concluded less than two months later. In all, perhaps 15 persons were vaccinated. Publication of the findings quickly followed. Jenner published at his own expense, in September 1798, his now famous *Inquiry* (shorthand for its proper title, *An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the name of the Cow Pox*).

Not surprisingly, a discovery that promised protection against one of the most serious of diseases was greeted with excitement. The *Inquiry* was widely read. Jane Austen, for example, in a letter to her sister, tells of being at a dinner party after which the host and hostess alternately read "Dr. Jenner's pamphlet" on smallpox. By the summer of 1799, Jenner's observations had been confirmed by a number of practitioners, and upwards of 1000 persons had been given the vaccine. Within three years the practice of cowpox inoculation had spread across Europe to North America and Asia, utilizing material provided initially from England. The rapidity of events between first discovery of a vaccine, the publication of results, and its widespread public use has never been surpassed.

Jenner's discovery is the more remarkable when one recognizes that nearly 90 years were to elapse before Pasteur performed his first experiments with a second human vaccine, namely, rabies. Nearly 180 years were to elapse before Jenner's vision was realized—in his words (1801): "The annihilation of the Small Pox...must be the final result of this practice." The circumstances leading to Jenner's discovery are interesting in themselves but the failure to "annihilate the Small Pox" far sooner than it was bears lessons relevant to today's challenges in vaccine research and development.

Smallpox, Cowpox, and Variolation

Smallpox during the 18th century had been a disease rightly to be feared. Data from Glasgow, a city known historically for the completeness of its statistics, reveal that in the immediate prevaccination era (1783–1800), 50% of children died before 10 years of age and of those deaths, 40% were due to smallpox. Smallpox was then the leading cause of blindness throughout Europe.

The great majority of those who recovered from smallpox bore facial scars, and many were extensively disfigured. However, it was recognized, at least in rural areas, that milkmaids in particular seemed exempt from acquiring smallpox and so retained a fair complexion, which came to be celebrated in literature. Indeed, Jenner cited in his *Inquiry* a number of individuals who had experienced cow-

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pox and who, on subsequent exposure to smallpox, did not acquire infection. According to Jenner in his testimony in Parliament in 1802, "the vague opinion" of the protective value of cowpox had arisen quite recently among farmers.

More definitive proof of the protective effect of cowpox was possible, utilizing a procedure introduced into England in the early years of the 18th century—variolation. Variolation consisted of the inoculation into the skin of a small amount of material taken from a pustule or scab of a smallpox patient. Over the following week a pustular lesion developed at the site of inoculation and often at many other sites as well; however, the disease was generally much milder than smallpox infection acquired by the respiratory route. Death rates of 1% or less were usual, far better odds than the 20% case fatality rates from naturally acquired smallpox.

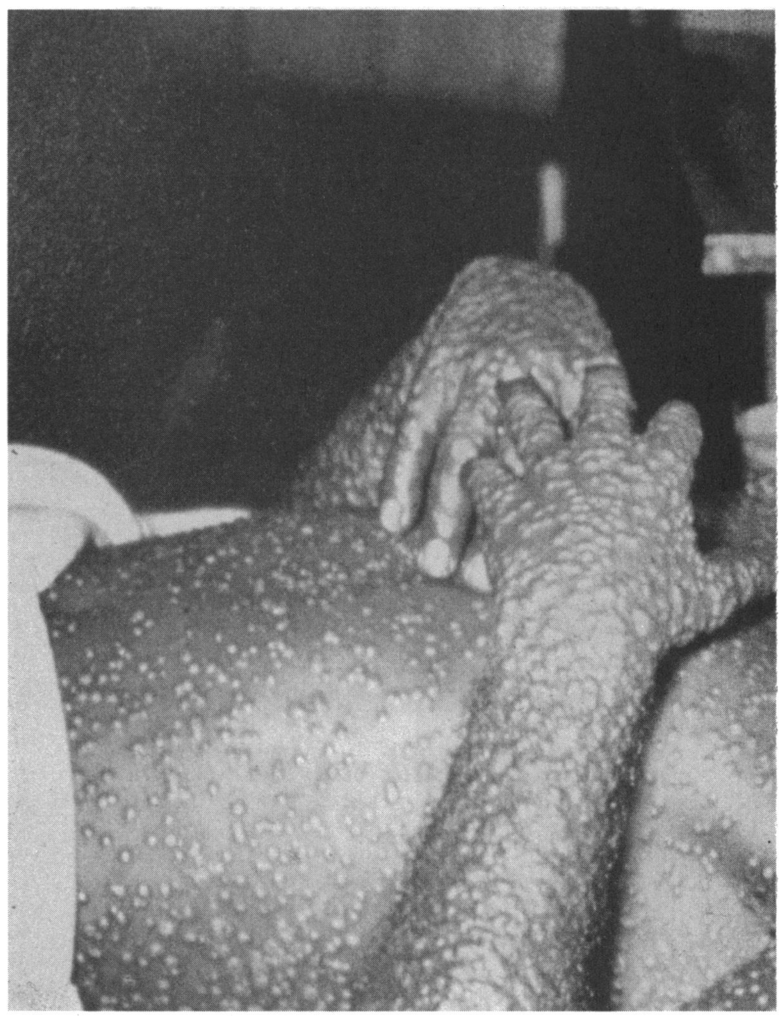
The practice of variolation had long been known in Asia and was introduced into Europe and North America in the early 1700s. However, it was not, at first, widely practiced for two reasons. First, most variolators required the inoculee to undergo an extended period of preparation through diet, bleeding, and purging in an exercise which, it was hoped, would ensure a mild form of the disease. Many had neither the time nor resources to undertake this preparation. Second, the inoculated individual, despite having a milder infection, was fully capable of transmitting infection to others and thus often was the source of outbreaks. Not surprisingly, this resulted in considerable popular resistance to the practice.

In the 1760s, however, Daniel Sutton and Thomas Dimsdale greatly simplified the variolation procedure by requiring little or no preparation of the patient and used a very small incision and amount of inoculum. The resulting illness was customarily milder, often with only one or a few pustules at the inoculation site. Death was said to occur no more frequently than 1 per 3000 to 1 per 8000 inoculations. To thwart the possible subsequent spread of infection, variolation of entire villages was sometimes performed. Thus, in some parts of England, variolation began to be more widely employed. Jenner himself often variolated patients, as did other medical practitioners. As he describes in the *Inquiry*, Jenner was able to show that several who previously had experienced cowpox could not be successfully variolated.

The Vaccine Experiment

Jenner's first experiment with the vaccine, in 1796, was not a radical departure from what was then the accepted practice of variolation. In essence, pustular material from a cowpox lesion was used as the inoculum instead of pustular material from a smallpox lesion. Prudently, Jenner vaccinated only one person, 8-year-old James Phipps, the son of a laborer who often worked for the Jenners. Six weeks later, on July 1, 1796, Phipps was variolated but no infection occurred.

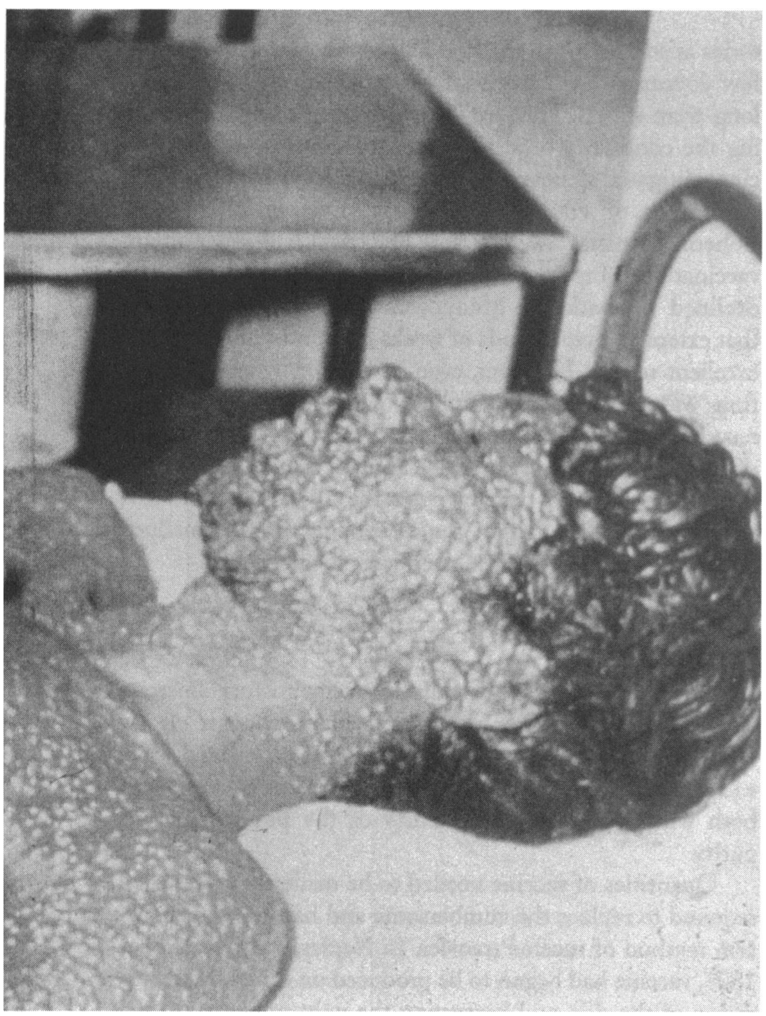
Jenner lost no time in writing up his observations and in September took a copy to London for submission for publication in the *Philosophical Transactions* of the Royal Society. Jenner, by then, had been a member of the Royal Society for some seven years in recognition of his work in the field of natural history. Sir Joseph Banks, the President, decided against publication, advising Jenner that he "ought not to



risk his reputation by presenting to the learned body anything which appeared so much at variance with established knowledge." With only one case to report, experimental proof obviously was too meager even by the English standards of small, elegant studies.

At this time, Jenner was prevented from doing more because of the absence of naturally occurring cases of cowpox. Cowpox occurred only sporadically and unpredictably. Not until February 1798 were additional cases discovered; these involved three farm workers who were believed to have been infected from horses afflicted with an inflammation of the fetlocks called "grease." Cows on the farm also were infected. The disease, "grease," unknown to contemporary veterinary medicine, was believed by Jenner to be related to cowpox. Indeed it was at first his belief that cows only became infected when exposed to farm workers who had acquired the disease from horses. This soon proved not to be the case.

The basis for Jenner's claims for his vaccine derived from some 15 inoculations performed using infectious material from this outbreak. One inoculation was performed using pustular material from one of the farm workers, whereas the remainder involved pustular material taken from the teat of a cow. After the first inoculation, subsequent inoculations were by arm-to-arm transfer of infectious material. In all, four successive transfers of the vaccine were performed, the last proving to be as successful as the first. Surprisingly, Jenner does not make clear how many he vaccinated. Nine vaccinees are named specifically; however, at the second arm-to-arm transfer, he refers simply to the fact that "several" children and adults also were inoculated. Thus, the number 15 is a guess. Only four were challenged by smallpox inoculation and found to be protected; these included both the first and last vaccinees in the series of successive vaccine transfers. Among the group of vaccinees was his son, Robert Jenner, aged 11 months, whose vaccination, ironically, proved unsuccessful.



The *Inquiry* was published on September 17, 1798, less than four months after the final inoculations. Jenner referred to the infectious material as "vaccine," deriving from the Latin *vacca*, meaning cow. The procedure was at first called cowpox inoculation or cowpoxing; however, in 1803, Richard Dunning, a Plymouth surgeon, introduced the terms "vaccination" and "to vaccinate." Many years later, Louis Pasteur was to thoroughly confuse the terminology by insisting that all inoculations designed to protect against a disease should be called vaccination in honor of Jenner. He named his new discovery rabies "vaccine" despite the fact that the cow had nothing whatsoever to do with preparation of the rabies vaccine.

Early Vaccination Practice

Dissemination of news of the discovery and its acceptance occurred rapidly and was aided in substantial part by two prominent London physicians, Dr. George Pearson of St. George's Hospital and William Woodville of the London Smallpox and Inoculation Hospital. They confirmed Jenner's findings, vaccinated substantial numbers, and dispatched vaccine widely. The vaccine material, dried on threads, glass, or ivory points, was dispatched initially to many in Britain and Europe. Within three years the *Inquiry* had been translated into German, French, Dutch, and Latin, and vaccination had begun at various points throughout Europe, Asia, the Middle East, and the Americas. In America, Benjamin Waterhouse performed the first vaccinations in July 1800; one year later, Thomas Jefferson, intrigued by this new procedure, vaccinated some 200 of his Virginia neighbors and arranged to provide vaccine to a

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number of Native American tribes.

The introduction of vaccination was not without its problems. Objections were registered by some religious leaders, who believed it wrong to thwart God's will in preventing a disease. Some rebelled at the idea of inoculating an animal-derived substance and taunted the procedure in cartoons showing vaccinees growing cow horns and tails.

Ensuring an adequate supply of vaccine of good quality was the most difficult problem. The cowpox vaccine could be satisfactorily sustained by arm-to-arm transfer. However, this required that new susceptibles be recruited weekly. Failure of vaccine takes, for whatever reason, could result in loss of the vaccine strain and necessitate obtaining a new supply of material. Although the vaccine could be preserved for some months as a dried product on glass or threads, the likelihood of virus survival was subject to the vagaries of temperature, humidity, and exposure to ultraviolet light. These variables were not well understood at that time; consequently, the virus often was inactivated inadvertently during storage or shipment.

Obtaining new cowpox material for vaccination was likewise a problem. As the disease itself was indigenous only to Europe, the loss of the strain in Asia or America was a serious matter. It required that new dried vaccine material be sent by sailing vessel and, not infrequently, the preparation was not found to be viable on arrival. Even in Europe, cowpox was not present constantly. Moreover, there were several different diseases of cows that resembled cowpox but were caused by different viruses. A number of vaccine failures were attributed to the use of material from pseudo-cowpox infections.

Finally, there were problems with assuring the integrity and quality of the cowpox vaccine itself. One of the earliest problems occurred with material sent to various physicians by Woodville from patients inoculated at the London Smallpox and Inoculation Hospital. The hospital housed smallpox patients and also was used to temporarily isolate individuals prior to and immediately after variolation. Woodville initially vaccinated in this environment. Thus, the pustular material taken from a patient might have several possible sources, and it seems probable that on some occasions smallpox virus was dried and dispatched instead of cowpox virus. Contamination of the vaccine with other organisms also occurred, resulting in cases of erysipelas, hepatitis B, and syphilis. In the early 19th century, most such cases, even though acquired from vaccine, were sufficiently uncommon so as not to be attributed to vaccination. However, the dangers of vaccinal syphilis gradually came to be recognized. The most tragic episode occurred in Italy in 1861. In all, 41 of 63 children vaccinated with material from a child with unrecognized syphilis acquired overt syphilis and some infected their mothers and nurses.

Data as to the total extent of vaccination during the 19th century are sparse. There are reports of vaccination having been introduced into a great many countries and territories at some time in the first half of the century. However, few countries had health structures capable of sustaining long-term efforts. This, coupled with the problems of assuring the continuity of arm-to-arm transmission of the vaccine, mitigated against its sustained use. In Europe, by 1821, a number of countries (Bavaria, Denmark, Norway, Bohemia, Russia, Sweden, and Hanover) had made infant vaccination compulsory, and the numbers of smallpox cases declined dramatically. Many conducted special programs that extended over periods of weeks to months and achieved excellent results. However, even in Europe, where vaccination was most widely applied, pandemics of smallpox recurred in 1824–1829 and 1837–1840. These affected most of Europe, and at least one-half million Europeans died in smallpox pandemics triggered by the 1870–1871 Franco-Prussian war. Throughout the developing world, smallpox in the 19th century continued effectively unchecked.

A Better Vaccine

The first 100 years of smallpox vaccine history illustrate well the limitations of a vaccine which—though clearly effective—was unable to be produced on a commercial scale, was susceptible to destruction by heat, and was often suspect both with respect to the identity of the product and its purity.

Quantities of vaccine needed to be made available when required to replace the cumbersome and hazardous arm-to-arm method of vaccine transfer. In Naples, Italy, as early as 1805, vaccine had begun to be produced on calves by scarification of the skin and harvesting the pulp some five to ten days later. This method, however, remained largely unknown until the Medical Congress of Lyons in 1864, at which vaccination was heatedly criticized because of the risk of transmitting syphilis. This concern had been triggered by the 1861 outbreak in Italy, although there were other vaccine-induced infections as well. An approach was needed to eliminate the arm-to-arm transfer of vaccine. The report of Italian scientists describing their method for vaccine production on calves was enthusiastically received. Soon thereafter, calves (and later sheep and water buffalo) came to be used worldwide in vaccine production.

Having available large quantities of a safer vaccine when needed provided a substantial impetus to smallpox vaccination. Still, two significant problems remained: the inevitable contamination of the vaccine due to the presence of bacteria which proliferated normally on the scarified calf skin and the thermolability of the vaccine. Because of this contamination, staphylococcal and streptococcal infections occurred as well as some cases of tetanus. Moreover when the contamination was great, vaccine efficacy was compromised. The problem was partially solved when, in the 1890s, it was found that glycerol, a bactericidal substance, could be used as a medium for suspension of the pulp. Glycerol had the added advantage of being viscous and thus especially suitable for applying to the skin prior to inoculation using a needle or lancet. The use of glycerol coupled with procedures to keep the animals clean diminished the contamination problems significantly.

Preserving the vaccine, especially in hot climates, was a more difficult challenge. In a few countries, the inoculated calf was led from door to door, the vaccinator taking small amounts of the vaccine matter for each vaccinee. This was not a very practicable approach given the fact that the maturing pustules on one calf provided tens of thousands of doses of vaccine, which had to be harvested over a 5 to 12 day period. Eventually, in the more industrialized countries, refrigeration became widely available, a development which in the United States was explicitly given principal credit for effective control of smallpox during the early 1930s.

For the developing tropical world, there were no evident solutions. In some countries, attempts were made to transport vaccine in kerosene refrigerators moved on mule back—an early more cumbersome version of the World Health Organization's present "cold chain." Dutch and French scientists, during the 1920s and 1930s, were successful in air drying and freeze-drying vaccines, which proved to be stable at 37°C for several weeks or longer. Such vaccines were successfully used in Indonesia and some French colonies of Africa; however, neither method proved suitable for large-scale commercial production of a satisfactory product. Not until the early 1950s was the problem of commercial production of a stable freeze-dried vaccine finally solved. L.H. Collier at the Lister Institute, London, did so, fully describing his methods and making them freely available to all laboratories that sought assistance. And so the stage was finally set for the eradication of smallpox.

The availability of large supplies of an inexpensive, fully potent and pure, heat-stable vaccine was the *sine qua non* for the successful global smallpox eradication program. Although Jenner's discovery of the vaccine is deservedly celebrated, less well-known scientists who engaged themselves in solving the not inconsequential problems of commercial production of a fully satisfactory product deserve special acknowledgment. Without them, Jenner's dream would never have been realized.

Conclusion

Proof of principle that an effective vaccine can be produced is an important first step; however, if it is to realize its promise, considerable additional time, money, and good science are required to make that vaccine available in sufficiently large quantities, at an affordable cost, and as a product whose potency, purity, and stability are ensured.

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Further Reading

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