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Pioneers and Milestones

Prometheus in Gloucestershire: Edward Jenner, 1749-1823

*Thou shalt not be afraid for the pestilence that walketh in darkness nor for the destruction that wasteth at noon day.*¹

Edward Jenner (Fig 1) is renowned throughout the world as the originator of vaccination against smallpox. His work is widely regarded as the foundation of immunology—this despite the fact that he was neither the first to suggest that infection with cowpox conferred specific immunity to smallpox nor the first to attempt cowpox inoculation for this purpose. However, his reputation is entirely justified. He was the first to demonstrate by experiment that naturally acquired cowpox did indeed protect against smallpox. He distinguished between “true” cowpox and unrelated conditions with similar symptoms, as well as inactivated cowpox, which provided no protection (“spurious cowpox”). He transformed the protective power of cowpox from folk belief and medical curiosity into widely available prophylaxis. He established the efficacy of this method by experiment. When there was (at the very least) a good living to be made by keeping his discoveries secret, he published his findings. Last, but not least, he had the vision to see that cowpox inoculation had the potential to eradicate smallpox.

The origins of smallpox are lost in prehistory. Jenner believed it to have arisen as a consequence of the domestication of animals.² This might not be far from the truth.³ By the eighteenth century, with the exception of a few remote places with small populations, smallpox was endemic throughout the world. It was among the most feared diseases. In Europe, few people did not have it at some time during their lives. It killed between 12% and 20% of its victims; this equates to between 7% and 12% of deaths from all causes. Young children were particularly at risk. Smallpox might have accounted for 30% of child mortality.⁴

Edward was the eighth child of Sarah and the Reverend Stephen Jenner, vicar of Berkeley, in the English county of Gloucestershire. He was born in May 1749 and was orphaned when he was 5 years old. At the



Fig 1. Edward Jenner (circa 1800), by William Pearce.

age of 8, he was sent as a boarding pupil to Wotton-under-Edge Grammar School. It was here that smallpox first entered his life. He and other pupils were inoculated with the disease by a local surgeon. It is said that the trauma affected him for the rest of his life.⁵

The practice of deliberately infecting healthy individuals with smallpox (later referred to as *variolation*, to distinguish it from vaccination, as cowpox inoculation came to be called) is presumed to have arisen from the observation that survivors rarely got the disease again. Smallpox inoculation was introduced into Britain from Turkey in 1721. In the same year, it was first used by North American colonists in Boston, on the basis of information from African slaves and reports of Turkish practice.⁶ Material from either a smallpox pustule or an inoculation vesicle was used.⁷ The latter method provided a prototype for Jenner’s “arm-to-arm” vaccination. Reported death rates of 1 in 50 were a considerable improvement on mortality from naturally acquired smallpox.⁸ By the late eighteenth century, some practitioners were achieving much lower mortality rates.⁹ Nevertheless, inoculated smallpox retained all of the drawbacks of the natural disease, including the risk of death. The patient risked permanent disfigurement and blindness. Inoculated smallpox was as infectious as the naturally acquired disease. Unless isolation was strictly enforced, variolation propagated the disease.

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Edward Jenner's childhood did include happier interludes. He explored the countryside, collecting fossils and the nests of dormice.¹⁰ He completed his schooling at Cirencester Grammar School, where he made some lifelong friendships, most notably with Caleb Parry (to whom Jenner later dedicated the first edition of his "Inquiry into the Causes and Effects of the Variolae Vaccinae") and John Clinch (possibly the first person to vaccinate in the New World).^{11,11a} On leaving school, Jenner served an apprenticeship with George Hardwick, an apothecary, and Daniel Ludlow, a surgeon, of Chipping Sodbury, near Bristol. It is said that he first heard of cowpox and its apparent prophylactic properties during this time.¹²

Beginning in 1770, Jenner spent 2 years in London as a boarding pupil of John Hunter, surgeon at St George's Hospital. Hunter was among the foremost surgeons, comparative anatomists, and medical scientists of his age. From Hunter, Jenner learned to privilege observation over received authority. Teacher and pupil formed a friendship that endured until the death of Hunter in 1793.

In 1771, Captain James Cook returned from his first voyage to the Pacific; it is said that on John Hunter's recommendation Jenner was employed to classify the natural history specimens that had been collected by Joseph Banks during that voyage. Some involvement is plausible, but the suggestion that Jenner was offered the post of naturalist on Cook's second voyage is probably an embellishment.¹³

At the end of 1772, Jenner returned to Berkeley to establish his own medical practice. He does not appear to have been short of other career opportunities. A German university offered him a medical degree as an inducement to join their medical faculty. An incident at a dinner party resulted in the offer of a medical post in India.¹⁴ In 1775, Hunter gave Jenner the chance to buy a partnership in his School of Anatomy and Surgery. The letter in which Hunter acknowledges Jenner's refusal also contains an oft-quoted injunction from mentor to former pupil: "... why think, why not trie [sic] the Experiment?"¹⁵

For 13 years Jenner lived with his brother Stephen. Relatively little is known about his life or general practice during this period. He was disappointed in love; learning of this setback, Hunter, in typical down-to-earth fashion, wrote, "'... let her go never mind her.' I shall employ you with Hedge Hogs."¹⁶ He was as good as his word, providing Jenner with thermometers and directing him in a study of hibernation. Hunter bombarded Jenner with requests for all manner of natural history specimens, which Jenner did his best to supply.

By his own account, Jenner began to investigate the relationship between cowpox and smallpox early in his career.¹⁷ He became a member of an informal medical society that met at the Ship Inn, Alveston (approximately 10 miles from his home in Berkeley).

Here he so often raised the subject of the supposed ability of cowpox to prevent smallpox that "at length it became so distasteful to his companions . . . that they threatened to expel him if he continued to harass them with so unprofitable subject."¹⁸

He occupied himself with many other matters. He studied geology¹⁹; he carried out experiments on the use of human blood as plant food; he devised an improved method for preparing the medicine known as *tartar emetic* (potassium antimony tartrate); he wrote a treatise (now lost) on ophthalmia.²⁰ In 1784, after public demonstrations of hot air and hydrogen balloons in France during the preceding year, Jenner built and twice launched his own (unpiloted) hydrogen balloon. On each flight it traveled approximately 12 miles.

At Hunter's suggestion, Jenner made a particular study of the cuckoo. The final version of Jenner's paper includes the original observations that it is the cuckoo hatchling that evicts the eggs and chicks of the foster parents from the nest and that for the first 12 days of life it has a physiological adaptation to enable it to do so. The final version of this paper was read to the Royal Society of London in 1788 and resulted in Jenner's election as a Fellow the following year. Many naturalists dismissed his work. For more than a century, anti-vaccinationists used the supposed defects of the cuckoo study to cast doubt on Jenner's other work. He was vindicated in 1921, when photography confirmed his observations.²¹

In 1785, Jenner purchased The Chantry, which was to be his home and principal residence for the remaining 38 years of his life. In March 1788 he married Catherine Kingscote. Despite her poor health, they had 3 children.

In May 1788, Jenner became a founding member of another medical society, which met at The Fleece, an inn at Rodborough (approximately 15 miles from Berkeley). This was a serious-minded affair. His contributions included original observations on rheumatic heart disease and the cause of angina pectoris.²²

It was only in 1792 that Jenner became a doctor. A payment of £15.00 and a letter of recommendation from 2 medical friends were sufficient to secure the degree of Doctor of Medicine from St Andrews University in Scotland. This too later became grist to the anti-vaccination mill.²³

In 1794, Jenner contracted typhus. While convalescing he established a second medical practice in the fashionable spa town of Cheltenham and drew together his "Observations on the Migration of Birds." In this paper (published posthumously) he offered original evidence to disprove the widely held belief that many birds pass the winter in hibernation and demonstrated that the main purpose of their spring migration was to breed in the most favorable environment.

An accumulation of case histories over many years convinced Jenner that cowpox was indeed preventive of

smallpox. In some cases, people who had had cowpox subsequently resisted natural smallpox infection; in other cases, such individuals resisted smallpox by inoculation. In the spring of 1796, Sarah Nelmes, a dairy-maid at a farm near Berkeley, contracted cowpox. This gave Jenner the opportunity to perform a critical experiment. On May 14, 1796, he inoculated James Phipps, an 8-year old boy, with material from a sore on the hand of Sarah Nelmes. James was somewhat unwell between the seventh and ninth days after inoculation. On July 1, Jenner inoculated him with smallpox, "but no disease followed."²⁴ The challenge was repeated a few months later with the same result. Jenner had demonstrated both that cowpox could be passed from person to person by inoculation and that inoculated cowpox retained the ability to protect against smallpox. Jenner wrote a paper summarizing his research. If, as was later suggested, he hoped that it would be published by the Royal Society, he was disappointed.²⁵

In the spring of 1798, another local outbreak of cowpox allowed him to carry out more experiments. In one series, cowpox inoculated from a cow to a person was then passed by arm-to-arm inoculation through a series of 4 more people; the last person in the series later resisted smallpox by inoculation. Jenner incorporated this additional evidence into his paper and published it privately in June 1798. "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" made some important claims. Jenner asserted that (a) inoculation with "true" cowpox conferred lifelong protection against smallpox; (b) the protective factor could be propagated by inoculation from person to person; and (c) inoculated cowpox (unlike inoculated smallpox) did not cause fatalities, produced only local lesions (not generalized pustular eruptions), and was not infectious. He also speculated that cowpox was derived from an equine disease called "grease" that attained its protective properties by passage through a cow.

Reactions to the "Inquiry" were many and varied, both critical and favorable. Jenner soon became embroiled in controversies that dominated the rest of his life. Dr John Ingenhousz, physician to the Emperor of Austria, wrote to Jenner in October 1798 rejecting the idea that naturally acquired cowpox protected against smallpox. In correspondence with medical journals, other practitioners expressed similar views and also contradicted Jenner's opinion that cowpox in humans was a mild condition.²⁶ As cowpox inoculation became established, these critics were joined by others, who published alleged cases of vaccination failure and of patients who developed bovine characteristics after vaccination. Religious and Malthusian objections to vaccination were also advanced, but these had little impact.²⁷

In January 1799, cowpox was discovered in a London dairy. Over the next 4 months Dr William Woodville, physician to the London Smallpox and Inoculation Hospital, assisted by Dr George Pearson, carried out large-scale trials using inoculant from this source. The conclusions of this study were broadly favorable to the new practice but contradicted several of Jenner's claims. Approximately 60% of patients developed generalized pustular eruptions. It was thought that these patients were infectious. Worse was to follow. At Petworth, in Sussex, children inoculated with vaccine from London developed an illness that was indistinguishable from smallpox. Jenner argued that Woodville and Pearson's vaccines had become contaminated with smallpox. Woodville ultimately accepted that this was the case, but by then the damage had been done.²⁸ Toward the end of 1799, Pearson founded the Vaccine-Pock Institution; to this Jenner refused his support. Two years later he did endorse the foundation of a rival organization, the Royal Jennerian Society for the Extermination of the Smallpox by the Extension of Vaccination. After some initial success, this body was riven with internal dissent and became moribund for a number of years. It is little wonder that John Baron, Jenner's friend and biographer, concluded that "the progress of vaccination was . . . more impeded by the misjudging zeal and mistakes of its professed supporters than by all the efforts of its most determined opposers."²⁹

In correspondence and in pamphlets, Jenner responded to his critics, clarified his views, and modified his position in the light of experience. "Further Observations on the Variolae Vaccinae or Cow Pox" (1799), "A Continuation of Facts and Observations Relative to the Variolae Vaccinae, or Cow Pox" (1800), "The Origin of the Vaccine Inoculation" (1801), and "Instructions for Vaccine Inoculation" (circa 1802) were followed by "Facts, for the most part unobserved, or not duly noticed, respecting Variolous Contagion" (1808). Neither the "grease" theory for the origin of cowpox nor the hypothesis of lifetime immunity was correct, but neither was central to Jenner's thesis. The former was quietly dropped. However, in public, at least, Jenner and his closest supporters continued to maintain that a single inoculation provided lifelong protection against smallpox.

Despite the calumnies of the sceptics and confusion among its supporters, cowpox inoculation spread remarkably quickly in Britain, in the rest of Europe, and in other parts of the world. Vaccine was distributed dried onto threads, ivory points, or lancets and sometimes between glass slides sealed in wax. Although sometimes embarrassed by a lack of supply, Jenner sent vaccine to his medical acquaintances and to anyone else who requested it. Toward the end of 1798, he sent some with a copy of the "Inquiry" to John Clinch, his former school friend, now at Trinity, Newfoundland. Beginning with his own family, Clinch performed



Fig 2. Center: Edward Jenner inoculating 8-year-old James Phipps with cowpox. Clockwise from upper left: Jenner's home, The Chantry, in Berkeley, United Kingdom (now the Edward Jenner Museum); lesions of cowpox on the hand of Sarah Nelmes, a dairymaid; Blossom, the cow that was a source of cowpox; Jenner's manuscript, "An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England—Particularly Gloucestershire—and Known by the Name of the Cow Pox"; the "Temple of Vaccinia," where Jenner provided free vaccination to the people of Berkeley; vaccinia lesions after inoculation.

approximately 700 inoculations.³⁰ After introducing cowpox inoculation in their own districts, many recipients passed vaccine onto others. Dr John Haygarth (of Bath, Somerset) received vaccine from Jenner and in 1800 sent some of this strain to Benjamin Waterhouse, Professor of Physic at Harvard University. Waterhouse introduced cowpox inoculation in New England and then persuaded Thomas Jefferson to try it in Virginia. Jefferson, in turn, introduced the practice among some Native American tribes.^{31,31a} In March 1799, George Pearson circulated vaccine dried on threads to 200 correspondents, both in Britain and on the European mainland. In the same year, cowpox inoculation secured royal patronage; George III agreed that the second edition of the "Inquiry" should bear the dedication "To the King." In the following year, the practice was adopted by the Royal Navy. Two doctors were dispatched on a medical expedition to inoculate British garrisons in Gibraltar and the Mediterranean.³² A Latin translation of the "Inquiry" appeared in 1799; by 1803, the work had been published in all of the principal European languages.³³ In some places, local sources of cowpox (and other animal pox diseases) provided new vaccine strains. After failed attempts to send dried vaccine to India, Jenner proposed to recruit 20 people who had not had smallpox for serial inoculation during the sea voyage from England. Before this plan could be put into action, news reached him that vaccine from Vienna had

reached Bombay overland, by way of Constantinople, Damascus, and Baghdad.³⁴ Serial inoculation was adopted by the Spanish in an extraordinary round-the-world expedition that set sail in November 1803 and brought vaccine to the Canary Islands, Puerto Rico, the Spanish colonies in central and south America, the Philippines, Macao, and Canton.³⁵

As early as 1801 Jenner had claimed that

[a]n hundred thousand persons, upon the smallest computation, have been inoculated in these realms. The numbers who have partaken of its benefits throughout Europe and other parts of the Globe are incalculable: and it now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice.³⁶

By 1802, he felt confident enough to petition Parliament for a grant from the public purse. Rewards for inventions of public benefit were unusual but not unprecedented. A committee heard testimony for more than a month. The originality of Jenner's work was challenged. One prior claim was found to have some substance. But the evidence confirmed that apart from Jenner, no one had systematically investigated the relationship between cowpox and smallpox or

devised a means of propagating the protective factor. Jenner received his reward from a grateful nation—£10,000 in 1802 and an additional £20,000 in 1807.

In 1808, the British parliament instituted a National Vaccine Establishment, under the control of the Royal Colleges of Physicians and Surgeons. Although many things about this were not to Jenner's liking, vaccination in Britain was now on a more secure footing. After a decade of being honored and reviled in more or less equal measure, he gradually withdrew from public life. Sorrows crowded in on him. In 1810, at the age of 21, his eldest son (also Edward) died of tuberculosis. His sister Mary died in the same year and his sister Anne 2 years later. In 1815, his wife Catherine died of tuberculosis. In 1820, Jenner had a stroke, from which he recovered. On January 24, 1823, he visited his last patient, a dying friend. Jenner failed to appear for breakfast the following morning and was found in his study; he had had a massive stroke. He died during the early morning of Sunday, January 26, 1823, without regaining consciousness. He was laid to rest with his parents, his wife, and his son near the altar of the Berkeley church.

Scientific advances in the 2 centuries since Jenner published his findings have proved him to have been more right than wrong. The germ theory of disease, the discovery and study of viruses, and the understanding of the immune system have tended to support his main conclusions. Vaccination enabled the eradication of smallpox: this is Edward Jenner's ultimate vindication and memorial (Fig 2).

The Chantry, Jenner's former home, is now a museum celebrating his life and work. The museum is owned and managed by The Jenner Appeal Trust. The Jenner Museum and Conference Centre are located in Berkeley, Gloucestershire, United Kingdom (www.jennermuseum.com).

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