

2018

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Recommended Citation

Morabia, Alfredo. "Edward Jenner's 1798 Report of Challenge Experiments Demonstrating the Protective Effects of Cowpox against Smallpox." *Journal of the Royal Society of Medicine*, vol. 111, no. 7, 2018, pp. 255-257. doi: 10.1177/0141076818783658 . Post-print reprinted in CUNY Academic Works.

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Edward Jenner's 1798 report of challenge experiments demonstrating the protective effects of cowpox against smallpox

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Variolation

Variolation, that is, the inoculation of smallpox material in people who have not experienced natural smallpox, appears to have been a prophylactic used for centuries in much of Asia and North Africa.¹ It was introduced to England in 1721 by Lady Mary Wortley Montagu, the wife of the British ambassador to Constantinople. Although variolation was believed to be safer than naturally acquired smallpox, it was not without danger. In 1722 and 1723, respectively, the English physicians John Arbuthnot (1665–1735) and James Jurin (1684–1750) used the bills of mortality in London in an attempt to compare mortality from natural smallpox with mortality due to variolation.² In 1722, Thomas Nettleton, a physician inoculator in Halifax, reported that about one in five patients with smallpox in parts of Yorkshire and neighbouring counties had died, while there had been no deaths among the 61 people that he had inoculated.³ Comparisons based on larger numbers in England and New England were subsequently published.^{4,5} These confirmed that variolation was a less risky option when the risk of contracting natural smallpox was increased, but confirmed that the former was not innocuous.^{1,2,6}

Vaccination

The application and evaluation of variolation during the 18th century represented a major public health advance. However, it had been recognised in south west England that natural infection with cowpox (*Variolæ Vaccinæ*) also protected against subsequent infection with smallpox. Furthermore, in 1774, during an outbreak of smallpox at Yetminster, Benjamin Jesty (a farmer), 'reasoning upon the nature of the affection among cows, and from knowing its effects in the casual way among men', deliberately infected his wife and two sons with

cowpox to protect them against smallpox.⁷ It was not until 31 years later, however, that Jesty's 'vaccination' (as it came to be called), the continuing good health of his family and the resistance of his son to deliberate attempts to infect him with smallpox were eventually recorded in a medical journal.⁷

A few years earlier, Edward Jenner (1749–1823) had provided the first systematic account of smallpox challenge experiments following infection (natural and deliberate) with cowpox.⁸ Jenner was a general practitioner in Gloucestershire, and he was aware of the claimed protective effects of natural infection with cowpox. In his published account of his observations and experiments, Jenner first focused on the *long-term* protection against subsequent exposure to smallpox conferred by *natural* cowpox infection. He described 15 cases of people who had had cowpox years before being exposed to smallpox, and who had subsequently not developed clinical smallpox. Case I, for example, was a servant who had contracted cowpox in 1770. Twenty-five years later, in April 1795, he and his family underwent smallpox inoculation. Not only did the servant not develop smallpox, but: '*during the whole time that his family had the smallpox, one of whom had it very full, he remained in the house with them, but received no injury from exposure to the contagion*' (Jenner,⁸ p.10)

Having satisfied himself from these 15 case histories that natural infection from cowpox was protective, Jenner assessed whether intracutaneous injection of cowpox material (vaccination) had the same effect. Case XVI was a dairymaid, Sarah Nelmes, who had become infected with cowpox naturally in May 1796. Case XVII was an eight-year old boy, James Phipps, whom Jenner selected to receive an inoculum of cowpox from a pustule on the hand of Sarah Nelmes on 14 May. Phipps suffered from fever and some uneasiness but no great illness. When, six weeks later, Jenner repeatedly injected Phipps with variolous material, the boy developed neither

a pustule at the inoculation site nor the symptoms generally associated with variolation.⁹ At this stage, Jenner still lacked the evidence needed to convince his peers that the only possible interpretation for the absence of clinical smallpox in James Phipps after vaccination followed by variolation was that the vaccine had been protective. Indeed, the Royal Society rejected a paper on the topic he submitted in 1797.¹⁰

Transfer of effective inoculum from one vaccinated child to another

Jenner resumed his observations and experiments in March 1798, when cowpox broke out again. In Cases XVIII and XIX, he describes inoculating two five-year old boys on the same day: John Baker, with material from a pustule on the hand of a servant who had contracted the disease from the heel of an infected horse; and William Summers, with matter taken from the nipples of an infected cow. In his accounts of Cases XX to XXIII, Jenner showed that vaccination could ‘take’ with material transferred from one child to another after serial transfers through four generations.

The pustules which arose in consequence so much resembled, on the twelfth day, those appearing from the infection of variolous matter, that an experienced inoculator would scarcely have discovered a shade of difference at that period. Experience now tells me that almost the only variation which follows consists in the pustulous fluids remaining limpid nearly to the time of its total disappearance; and not, as in the direct smallpox, becoming purulent. (Jenner,⁸ p. 815 /id, Case XXI)

These ‘cross-vaccinations’ demonstrated that ‘the [cowpox] matter on passing from one subject to another lost nothing of its original properties’ (Jenner,⁸ p. 44). Furthermore, Jenner showed that immunity had resulted in William Summers (Case XIX) and William Pead (Case XXI) by inoculating them with variolous material.

The impact of Jenner’s report

Jenner did not resubmit an amended text to the Royal Society. In 1798, he published his *Inquiry* privately, claiming that: ‘I presume it may be unnecessary to produce further testimony in support of my assertion that the cow-pox protects the human constitution from the infection of the smallpox’ (Jenner,⁸ p. 45).

We will never know whether the Royal Society would have accepted a further submission, but

others were ready for it. Publication was followed by campaigns of mass vaccination in the 19th century and these had a dramatic impact on population mortality from smallpox. For example, Figure 99 in William Osler’s¹¹ book *The Evolution of Modern Medicine* presents the data available from the Prussian army, showing that mortality from smallpox nearly vanished a few years after the introduction of vaccination in 1834, and did so after 1865 when vaccination became compulsory by law. One hundred and two years after Jenner’s publication, mass vaccination led to the eradication of smallpox (<http://en.wikipedia.org/wiki/Smallpox#Eradication>).

Declarations

Competing Interests: ■■ [AQ2]

Funding: ■■

Ethics approval: ■■

Guarantor: AM.

Contributorship: Sole authorship.

Provenance: Invited article from the James Lind Library.

Acknowledgements: I am grateful to Arthur Boylston for comments on earlier drafts of this commentary.

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