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> On 14 May 1796, Jenner inoculated 8-year-old James Phipps with cowpox lesion material from milkmaid Sarah Nelms.

MILESTONE 2

Putting smallpox out to pasture

Although smallpox variolation dramatically reduced infection-induced fatality rates, it still carried significant risks, including the potential to trigger new smallpox outbreaks. In addition, it relied upon a constant supply of smallpox-infected individuals as a source of inoculation material. As variolation became more widely practised in the 18th century, an ostensibly simple observation started to gain more attention, with profound consequences for not only smallpox, but also many other infectious diseases.

In stark contrast to most individuals, dairy workers were generally protected from serious disease following smallpox exposure and lacked the permanent scars that often afflicted their non-dairy compatriots. Dairy farmers and milkmaids were in close and frequent proximity to cows, who sometimes developed pustules on their udders, symptoms of a zoonotic disease known as cowpox. In humans, cowpox generally manifested with pustules on the hands and arms, but was otherwise mild. Multiple reports of the protection afforded against smallpox by prior cowpox infection, in England and elsewhere, circulated in the 1760s. Although the relationship between the two diseases was unknown at the time, cowpox virus is a member of the *Orthopoxvirus* genus, which also includes variola virus, the causative agent of smallpox.

In 1774, Benjamin Jesty, an English farmer, leveraged this observation and inoculated his wife and two sons using pustule material from cowpox-infected cows. They remained healthy during subsequent smallpox epidemics, but he did not publish or further test his approach. Other reports of similar inoculations were made, but none appears to have received much attention and it is not clear whether Edward Jenner, an English physician, was aware of these reports prior to his own more famous test. On 14 May 1796, Jenner inoculated 8-year-old James Phipps with cowpox lesion material from milkmaid Sarah Nelms. Phipps fell mildly ill, but recovered, and in July of that same year, Jenner formally tested the hypothesis that prior cowpox infection could prevent smallpox by variolating Phipps with smallpox lesion material. Phipps did not develop disease. Jenner's approach was eventually described as 'vaccination', a nod to its bovine heritage (*vacca* is the Latin word for cow). After his initial report of these findings was rejected by the Royal Society, Jenner self-published a longer monograph in 1798, documenting Phipps and an additional 22 cases that proved that cowpox, either through vaccination or natural infection, could protect against disease following smallpox variolation.

Jenner's results were met with some scepticism, but by 1800, vaccination had spread beyond England to other European countries and the United States. Since its initial iteration, the smallpox vaccine has itself evolved. In the 1800s, both cowpox and horsepox, which can also infect cows and humans, were used in parallel for immunizations. The exact virus in Jenner's original vaccine remains unknown. The modern smallpox vaccine contains vaccinia virus, which is related to, but genetically distinct from, cowpox virus. In spite of its popularization, the mechanisms that contributed to the vaccine's protectiveness remained unclear until the 20th century. Studies in the 1970s suggested that pre-existing neutralizing titres were predictive of protection, pointing to a key role for antibodies in vaccine-elicited immune responses. In 2003, an analysis of individuals vaccinated 25–75 years earlier showed that 90% exhibited highly stable serum antibody titres and had vaccinia-specific T cells. Importantly, serum antibody titres correlated with neutralizing titres, and approximately 50% of those individuals still had antibody levels thought to be sufficient for protection against smallpox. Together with other studies, these data suggested that antiviral immunity following a single injection of the replicating vaccine was robust and potentially long-lived.

Jenner's initial arm-to-arm vaccination approach, which was more akin to the practice of variolation, remained common for some time. As vaccination spread globally, procedures for producing the vaccine were increasingly standardized, with serial passage of vaccine lymph in calves becoming the dominant approach after 1860. Variolation was formally outlawed as part of the Vaccination Act of 1840, and the Vaccination Act of 1853 made smallpox vaccination compulsory for all children born in England. Parents who chose not to vaccinate their children were subject to fines. This instigated the first anti-vaccination movement, which gained sufficient attention in Great Britain that a commission was appointed in 1896 to evaluate its concerns versus the benefits of vaccination. Although the commission concluded that smallpox vaccination was protective against disease, it also recommended against levying financial penalties, and a subsequent Vaccination Act in 1898 allowed parents to obtain a certificate of conscientious objection, a harbinger of things to come.

Following his first tests, Jenner continued to perform and promote smallpox vaccinations, presciently predicting that it could lead to the 'annihilation' of the disease, which had killed and afflicted so many. Less than two centuries after his first vaccination, Jenner was proved right and smallpox was declared eradicated by the World Health Organization in 1980.

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