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Translational Mini-Review Series on Vaccines: The Edward Jenner Museum and the history of vaccination

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Summary

Edward Jenner's discovery of vaccination must rank as one of the most important medical advances of all time and is a prominent example of the power of rational enquiry being brought to bear during the Age of Enlightenment in 18th century Europe. In the modern era many millions of lives are saved each year by vaccines that work essentially on the same principles that were established by Edward Jenner more than 200 years ago. His country home in Berkeley, Gloucestershire, is where he carried out his work and where he spent most of his life. The building is now a museum in which the life and times of Jenner are commemorated including not only the discovery of smallpox vaccination but also his other important scientific contributions to natural history and medicine. The trustees of the Edward Jenner museum are committed to promoting the museum as a real and "virtual" educational centre that is both entertaining and informative.

Introduction

It is more than 200 years since Edward Jenner vaccinated James Phipps in 1796 with cowpox obtained from a pustule on the hand of the milkmaid, Sarah Nelmes. The circumstances that led up to this momentous event and its consequences have been examined exhaustively elsewhere [1–6], and it is probably true that what can be said about Edward Jenner has already been said. Nevertheless, it being the 50th anniversary of the British Society for Immunology (BSI), it is not only timely, in this short paper, to comment briefly on the life and work of Jenner but to also draw attention to the existence of the Edward Jenner Museum. The museum is Jenner's former country house (Fig. 1) in Berkeley, Gloucestershire in the United Kingdom.

Many would consider Louis Pasteur to be the first immunologist [7], while others would say that Edward Jenner (Fig. 2) should be given this honour because he carried out the first rational vaccination experiments [8]. In fact, Pasteur paid tribute to Jenner by first coining the word 'vaccine' in the context of the anthrax and rabies treatments he had developed. Perhaps the Dorset farmer, Benjamin Jesty, should also be mentioned, as he vaccinated his own family as early as 1774 using cowpox taken directly from a cow [9,10]. The Chinese were conducting a form of vaccination 700 years before this and the Ancient Greeks should not be forgotten as they, according to Thucydides in 430 BC, were aware of the resistance to plague shown by survivors of previous epidemics. Immunity to disease has been in the human consciousness for a long time, although immunology as a discrete entity, distinct from microbiology and in the form we recognize today, really only began in the early- to mid-20th century.

Of course, Edward Jenner (1749–1823) is an iconic figure for immunologists everywhere and the many millions of lives that have been saved as a result of his bold vaccination experiments more than justify this. It is said that Jenner was no Isaac Newton, no great theoretician [11], but he was a talented country gentleman who had trained in medicine, such as it was then, and satisfied his intellectual curiosity in the study of natural history [12]. The late 18th century in Europe is often referred to as the Age of Enlightenment, when the scientific study of the natural world first began. Jenner is an interesting figure in terms of both the social and scientific history of this period, in many ways epitomized by his life and work.

In Jenner's day it has been estimated that up to 10% of the population of Europe died of smallpox each year and, of those who survived, many would suffer permanent facial

Fig. 1. The Chantry as it is today – the former Queen Anne country residence of Edward Jenner located in his home town of Berkeley. He lived here from 1785 until his death in 1823. The museum is dedicated to the life, work and legacy of Dr Edward Jenner. The original Chantry was built as the residence of Berkeley Chantry priests and used as such between 1384 and ca. 1547. The present Chantry was rebuilt ca. 1702–1707 and bought by Dr Jenner in 1785 for £600. It became the new Berkeley Vicarage in 1885 and was acquired in 1980–84 by the Jenner Appeal Trust and is now the Edward Jenner Museum.

disfigurement and blindness. Several million smallpox deaths occurred per annum worldwide in the mid-20th century, of which about 250 000 cases were in India. There were 43 000 cases of smallpox in the USA as recently as 1930. The last death from smallpox in the United Kingdom was in Birmingham in 1978, in a laboratory accident. During the 20th century more than 300 million deaths were attributable to the smallpox [13]. Despite these appalling statistics, the human collective memory of infectious diseases, in the West at least, has been somewhat patchy and short-lived. The global spread of HIV/AIDS, the recent SARS outbreak in 2003 and the threatened bird flu pandemic have brought the benefits of vaccination into sharp focus once again.

Variolation and the discovery of vaccination

Vaccination was one of the greatest practical advances ever made in medicine, and many others apart from Jenner played a role in the early days. Variolation, the practice of inhalation of, or scarification with, dried and powdered smallpox pustules, had been in use since AD 1000 in China, later in the Middle East, and made popular in Europe in Jenner's day by Lady Mary Wortley Montague (1689–1762), the wife of the British ambassador to Turkey. Lady Mary was a glamorous aristocrat with royal connections and a woman of independent mind. She had arranged for her own children to be variolated according to practice common in Turkey at that time. Variolation, or inoculation as it became known, received official approval from the Royal College of Physicians in 1754. Lady Mary can take some credit for making variolation fashionable in a fashion-conscious age [1]. The power of celebrity is nothing new. Fatalities due to variolation were significant by today's standards and occurred in about 2% of subjects but provided 80% protection. The many that chose variolation had made the simple calculation that their chances of dying of smallpox were likely to be greater if they remained untreated, there being a fatality rate of about 30% on actually catching the virus.

Variolation had become common practice by the late 1700s, and Jenner would have been entirely familiar with the procedure. He knew that variolation was effective and also that those who survived smallpox would never contract the disease again. Jenner was well aware that milkmaids who had suffered the cowpox would not contract smallpox. Whether this view was arrived at through knowledge of the activities of Benjamin Jesty some 20 years earlier, when he vaccinated his family with cowpox taken from a local cow [9,10], his own observations of milkmaids or simply as a matter of folklore is not known. It seems that he spent some time considering how he could, and even if he should, test his idea of vaccination but was encouraged by his former mentor and renowned London surgeon, John Hunter. The argument has always been made that the discovery of vaccination should

Fig. 2. Jenner's portrait. 'Dr Edward Jenner – discoverer of vaccination against smallpox. An oil-on-canvas painting by William Pearce, being a contemporary copy of a portrait by John Raphael Smith. Smith's portrait was exhibited at the Royal Academy, London, in 1800 and both portraits later influenced many other artists. The portrait currently hangs in the Jenner's former dining room in the Edward Jenner Museum and shows Berkeley Castle in the background. Reproduced by kind permission of the Jenner Museum.

be attributed to Jenner, because his conclusions were reached on a scientific basis where he had carried out an experiment to test a hypothesis. Most importantly, he succeeded in publishing his results so that they could be scrutinized by others [8].

James Phipps and the first experimental vaccination

Jenner's vaccination of the young James Phipps involved the removal of fluid from a cowpox lesion on the hand of Sarah Nelmes. The fluid was inserted into two superficial incisions in the skin of Phipps' arm. After 7 days the young boy became slightly unwell, but soon recovered. After 6 weeks several punctures and incisions were made in the boy's arms and freshly removed smallpox pustule material was inoculated into the new incisions. This was much riskier than variolation as one would suspect that, in the absence of drying and storage at ambient temperature, the smallpox virus would not be in the slightest bit attenuated. However, no disease ensued and the smallpox challenge was repeated several months later with no adverse consequences. Jenner initially submitted a manuscript describing his findings to the Royal Society in London, but it was rejected. The then President of the Royal Society, Joseph Banks, replied politely saying that Jenner should be concerned for his reputation and esteem among his colleagues. Jenner promptly published his results in a book at his own expense [8].

Jenner's method of vaccination had spread to most European countries within 2 years and the first vaccination in North America took place in 1800. George Washington's successor, John Adams, had already been inoculated in 1764 and was made aware of the new vaccination in 1799 by a Dr Benjamin Waterhouse, of the Harvard Medical Institution, who had not only obtained Jenner's publications but also some cowpox from Jenner himself [1]. Vaccination became compulsory in 1853 in England and, again, most other countries followed suit soon after. Thus smallpox vaccination took hold, ultimately ridding the world of the disease some 150 years later in 1977 following the World Health Organization (WHO) eradication programme [13,14]. It remains a mystery to this day as to what connection, if any, existed between the cowpox virus used in Jenner's time and the vaccine viruses used in the eradication campaign in the 20th century [15]. Jenner was fortunate that it was the smallpox virus he was vaccinating against. The virus has only one stable serotype and infects only humans, there being no secondary animal hosts. The virus is infectious only after a relatively long incubation period, is not a persistent infection and subclinical infections are not a source of spread. The disease is diagnosed easily and infection confers long-term immunity. Last but not least, an animal homologue with a sufficiently attenuated infectivity in humans was conveniently to hand in the form of cowpox virus.

One aspect which remains controversial is the question of the ethics of Jenner's vaccination of James Phipps. Did Jenner consider that if his hypothesis was wrong James Phipps might die of the smallpox? Would he have carried out this first experiment on his own children or children from the higher social echelons of society? On the other hand, when would a smallpox vaccine have been created and how many people would have died had he not conducted the experiment? The social perspective in those days was rather different to the present, in that any family that had five children would not expect more than three of them to reach young adulthood. Given that variolation was practised commonly on children, Jenner's experiment on James Phipps was perhaps less ethically outrageous than it seems from our perspective. Nevertheless, his experiment raised eyebrows in the medical establishment and elsewhere, and not just because they doubted the science. No record exists of any views that may have been expressed by James Phipps before or after he was vaccinated by Jenner.

Jenner's world

It is probably worth being reminded of what was happening in Jenner's world in the late 18th century. Captain Cook had been exploring the Pacific Ocean in his ship the *Endeavour*. Edward Jenner was involved briefly in the cataloguing of the numerous specimens brought back by the famous botanist, Joseph Banks, in 1771 on Cook's voyage in the *Endeavour*. It was the same Joseph Banks who, as president of the Royal Society decades later, would reject Jenner's manuscript describing his first vaccination experiments. Jenner was even invited to be the resident naturalist on Cook's next voyage but declined the offer. The American Declaration of Independence had taken place in 1776 and George Washington was succeeded by John Adams as President of the United States in 1798. In the same year Thomas Malthus published his famous essay on 'The Principle of Population'. William Pitt the Younger was the British prime minister from 1783 to 1801 and the 'mad' King George III was on the throne. The French Revolution took its course between 1789 and 1799, and 1796 marked the beginning of the Napoleonic wars during which, ironically, Jenner was awarded a Napoleonic medal [1,16]. Jenner was held in such high esteem by Napoleon that he was able to negotiate the release of a number of important British prisoners of war. The year 1798 also saw the invention of the battery by Volta and the publication of Lavoisier's list of 'elements', but the works of Charles Darwin and Louis Pasteur were not to emerge for several more decades.

Jenner the man

Jenner was a country doctor who, despite the unusual distinction of having trained for 2 years with the famous London surgeon John Hunter in the 1770s, spent almost his whole life in the small market town of Berkeley, about 15 miles north of Bristol. He never travelled abroad and it is

unlikely that he even went up to St Andrew's University in Scotland to receive his medical diploma, which was not awarded until 1792. He was eventually given an honorary MD by Oxford University in 1813. He certainly had professional friends in the Georgian spa city of Bath, 20 miles to the south, and travelled there from time to time on horseback. Edward Jenner was something of a renaissance man, in that he had been interested in a wide range of things including hydrogen balloons, the behaviour and anatomy of cuckoos, geology and heart disease. Indeed, it was his discoveries on the secret life of the cuckoo which gained him a fellowship of the Royal Society.

The Edward Jenner Museum

The Edward Jenner Museum is located in Berkeley and is a fascinating place to visit, currently attracting over 4000 visitors per annum. Berkeley is an historic town with not only a retired magnox nuclear plant but also an important 12th-century castle where Edward II was imprisoned and murdered in 1327. The museum offers an impressive collection, combining the life and legacy of Edward Jenner with that of an 18th-century country house of modest size. The house, known as The Chantry, was Edward Jenner's home. Jenner was born in Berkeley and came to live in this house in 1785, where he remained until his death in 1823. It was here that Jenner carried out his first experimental vaccination against smallpox in 1796.

The museum was founded originally in 1968 and housed first in James Phipps' old cottage, Berkeley. The collections were moved to The Chantry in 1982 and responsibility for them transferred to the newly constituted Jenner Appeal Trust. The museum reopened in 1985 and is currently celebrating its 21st anniversary. The Chantry is a Grade 2* listed building and stands in about 1 acre of garden (Fig. 1). Within the gardens are three other historic buildings associated with Edward Jenner; the Temple of Vaccinia (also a Grade 2* listed building) (Fig. 3), and the Vinery in which grape vines, originally from Hampton Court Palace in London, were planted by Jenner in 1818. The Sasakawa Conference Centre, a former coachman's house in the grounds of The Chantry, now provides a venue for meetings, courses, educational and cultural activities. The Temple of Vaccinia is where Dr Jenner vaccinated the local poor of Berkeley free of charge. The museum expanded further in 1996 during the bicentenary of Jenner's first vaccination, with the addition of a multimedia exhibition on immunology.

The museum, the gardens and the collections are managed by the Trustees with income from an endowment fund, museum admission, sales of publications and other goods, conference facilities and charitable donations. In 1985 the American Friends of the Museum was established providing regular small donations. Ultimately, it is intended to establish a worldwide Friends of the Jenner Museum organization. The aim of the trustees of the museum is to maintain the historic buildings, museum, objects, library, historical documents and memorabilia associated with the life and achievements of Edward Jenner. The museum collections reflect personal and domestic aspects of the Jenner family living at The Chantry, such as Jenner's spectacles, a lock of his hair and family christening robes. Jenner's study (Fig. 4) has been recreated in the Museum based on an inventory of contents at The Chantry made by Jenner's executors on his death in 1823. His great friend and mentor, John Hunter, wrote to him after the birth of his first child in 1789, saying 'Jenner I wish you Joy, it never rains but it pours. Rather than the brat should not be a Christian, I will stand godfather. I hope Mrs Jenner is well and you begin to look grave now you are a father'. Also not to be missed are hair and horns from Blossom, the cow from which Sarah Nelmes apparently caught cowpox, Jenner's much-used apothecary scales, a second edition of Jenner's *An Inquiry into the Curses and Effects of the Variolae Vaccine*, and fascinating smallpox casebooks from the Smallpox and Vaccination Hospital in St Pancras, London, in the early 1820s. The detailed notes chart the progress of male sufferers from diagnosis to recovery or their demise with date and cause of death.

Fig. 3. 'The Temple of Vaccinia' – a thatched summerhouse where Dr Edward Jenner vaccinated the poor of Berkeley against smallpox free of charge. On certain days there were long queues winding across the lawn and back towards the town.

In particular, the trustees aim to provide an educational resource for the public about the history of vaccination and its enormous impact in the world, not least being the eradication of smallpox. It could be said that Jenner's vaccinations in the late 18th century were the first examples of the science of immunology. The museum houses a substantial interactive display section illustrating the fundamentals of immunology and vaccination. This display was designed and presented by the BSI. The museum has a large archive relating to the social history of smallpox and medicine and a new website for the museum has been constructed, which can be found at http://www.jennermuseum.com.

The Edward Jenner Museum

Fig. 4. Jenner's study – a recreation of Jenner's former study at his home, The Chantry. The study is based on an inventory of contents at The Chantry made by Jenner's executors on his death in 1823. It reflects the varied influences and interests in Jenner's life with fine pieces of furniture, scientific instruments and natural history specimens.

A number of other institutions and bodies have an interest in the life and work of Edward Jenner and hence in the Edward Jenner Museum. These include the modern-day vaccine research laboratories at the Edward Jenner Institute for Vaccine Research, The Wellcome Library, which houses the largest collection of Jenner-related manuscripts, the BSI and the WHO. Many other national and international museums and institutions have Jenner memorabilia: for example, the Science Museum in London.

Given the profound impact of vaccination on world health, the present Jenner Museum is a modest establishment with a status and public recognition disproportionately small when set against the epoch-making discoveries it was designed to commemorate. The Edward Jenner Museum has the potential to become a coordinating and facilitative centre of information on the life and work of Edward Jenner. The trustees' ambition is for the museum to be the first point of contact, physically or virtually, for anyone interested in Jenner, whether it is for general, professional, academic, historical, genealogical or local interest. The trustees aim to enhance the status of the museum as a major tourist venue and attract more visitors, to help preserve the memory of Edward Jenner, to promote further the use of the museum as an educational centre for the study of Jenner's life and scientific achievements, to organize activities and exhibitions reflecting the diverse cultural aspects of Jenner's legacy and to develop the museum website, so that 'virtual' visitors can benefit from the work of the museum. In particular, we wish to increase educational activity to support school science at all key stages. The Jenner story in modern education is a powerful tale of science and rationality prevailing over a wide variety of unfounded but strongly held prejudices.

Vaccination today

While it is true that vaccination against a range of diseases has had a huge impact on public health, the vaccines used have been 'conventional' in that the simple principles demonstrated by Jenner were exploited. However, the detailed immunology of successful conventional vaccines is still poorly understood. For example, what are the immunological details of the protective immune responses induced by smallpox vaccination? What are the relative contributions made by antibody and cell-mediated immune responses in protective immunity against measles? What are the relative contributions made by $CD4^+$ and $CD8^+$ T cells in protective immunity against chickenpox? In fact, the immunological correlates of protective immunity against most infections are not at all clearly understood. If a vaccine works, then perhaps we are less interested in how it works and want to focus on why other vaccines do not work. New science, new technology and an ever more sophisticated understanding of immunology have yet to make a significant impact on world vaccination. Vaccination was to have been revolutionized by the advent of synthetic peptides, DNA technology, DNA vaccines, recombinant live virus and bacterial vectors as each of these new technologies emerged. With the notable exceptions of the recombinant S antigen hepatitis B vaccine [17] and recent human papillomavirus vaccines [18] [also see paper later in this review series], the world is still waiting patiently for these technological and scientific advances to have an impact.

What would Jenner have made of the papers that are presented within this vaccine review series in *Clinical & Experimental Immunology*? He would certainly be able to appreciate the development of vaccines to combat tuberculosis, although the technologies used would be difficult for him to grasp. While he would not, of course, have been aware of the cause of tuberculosis, the disease of 'consumption' would have been very familiar to him in his daily practice as a country general practitioner. Whether he had any idea of what cancer was is another matter. The novel and exciting approaches to cancer vaccines reviewed later in this

series, while beyond Jenner's comprehension, will still be based on the principle he first established, namely, the strengthening or induction of immune responses using materials or agents that have a degree of immunological identity with the pathogen or cancer in question. In some senses we have moved on a long way since Jenner, but in others perhaps we have not.

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