In celebration of the 200th anniversary of Edward Jenner's *Inquiry into the causes and effects of the variolae vaccinae*

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This review commemorates the 200th anniversary of Edward Jenner's development of a vaccine for variola, the cause of smallpox, and the 20th anniversary of its eradication. Jenner's original 23 case reports are briefly revisited within the context of earlier attempts to prevent this dreaded disease and in light of the current understanding of vaccinology and immunology. In addition, with molecular biological information available about many pox viruses and detailed sequence knowledge of some, it is now possible to appreciate Jenner's prescient accomplishments more fully.

Key Words: *Edward Jenner, Pox viruses, Smallpox virus, Variolla, Vaccination*

Pour célébrer le 200e anniversaire de *Inquiry into the causes and effects of the variolae vaccinae* de Edward Jenner

RÉSUMÉ : Le présent article de synthèse commémore le 200e anniversaire de la mise au point du vaccin contre la variole par Edward Jenner, la cause de la petite vérole et le 20e anniversaire de son éradication. Les 23 rapports des cas originaux de Jenner sont brièvement revus dans le contexte des premières tentatives pour prévenir cette maladie redoutable et à la lumière des données actuelles sur les vaccins et l'immunologie. De plus, avec les informations apportées par la biologie moléculaire sur de nombreux poxvirus et les connaissances détaillées sur la séquence de certains d'entre eux, il est désormais possible d'apprécier pleinement les réalisations prescientes de Jenner.

Pure and simple, vaccines have proven to be an unexpectedly elegant solution to controlling and eradicating the question of the cause in many acute contagious infectious diseases which have dogged humankind. Many such diseases resulted from the development of dense human settlements that followed the domestication of plants and animals more than 10,000 years ago. Chief among these infections was smallpox. It produced epidemic disease approximately every decade and persisted at endemic levels in almost all populations.

Creighton's classic analysis of the history of epidemics in Britain (1) provides insight into the impact that infectious diseases had in the era before modern medicine. His review of the mortality bills for London during the 17th and 18th centuries are morbidly compelling and show that smallpox accounted for about 10% of all deaths at that time, except for epidemic periods when it accounted for an even larger proportion of deaths.

Clearly, smallpox was a frequent threat to human health, and great efforts to avoid the disease were often made. Early observations indicated that survivors of smallpox had lifelong

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resistance to reinfection. Therefore, it became a common practice to inoculate people deliberately with material taken from active cases of smallpox by the 11th century in China and 18th century in Europe (2). This process, called variolation, resulted in a milder case of smallpox that protected against natural smallpox. However, in about 0.5% to 2% of variolated persons, severe smallpox developed which often proved (3). At a time when the risk of wild type smallpox was substantial and its mortality rate was greater than 20%, the risks associated with variolation seemed acceptable.

It is against this background that a country doctor (and accomplished naturalist), Edward Jenner (lived between 1749 to 1823) attempted to find a safer way to protect against smallpox. Two hundred years ago (1798), he published at his own expense observations and interpretations based on 23 case reports (4). His *Inquiry into the causes and effects of the variolae vaccinae* changed the course of history and ultimately resulted in the global elimination of a heretofore constant pestilential companion of humanity. Arguably, his contribution to biomedical research stands first among the great contributions. He founded the fields of immunology and vaccinology, and shed light on the dark and frightening face of epidemic infectious disease. Pasteur honoured Jenner's achievements by bestowing the name 'vaccination' on all immunization approaches, including Pasteur's own developments of inactivated rabies and *Pasteurella multocida* (fowl cholera) vaccines. On the 200th anniversary of Jenner's publication, it is appropriate to recall the results and interpretation of his 23 case reports. His publication, despite an intervening 200 years of biomedical progress, is characterized by a remarkably modern view of infectious disease biology and by a surprising clarity of results.

The 23 cases can be considered in blocks of four. Jenner

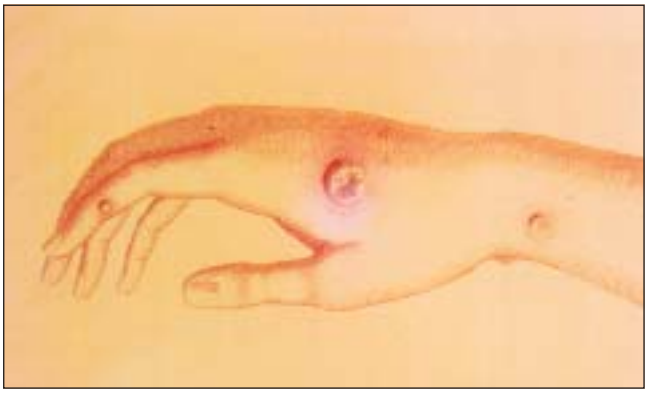

Figure 1) *Plate 1 from Jenner's* Inquiry *showing the cowpox lesions on the hand of Sarah Nelmes, one lesion of which was the source of material used to immunize James Phipps against smallpox. Thus began one of public health's greatest triumphs, vaccination*

had become convinced that cowpox prevented subsequent smallpox illness, whether it was variolation-induced or a natural infection. Cases 1 through 12 were presented to make this point. They consisted of adults who, one to 40 years previously, had cowpox infections, but, despite Jenner's attempts, resisted cutaneous variolation. Several of these adults also had documented histories of exposure to natural smallpox when caring for ill family members or neighbours, but none had acquired wild type smallpox. Jenner interpreted these findings to suggest that cowpox infection conferred long-lived resistance to smallpox. He also noted that cowpox produced a much milder infectious disease in humans than did smallpox.

Jenner believed that cowpox infection was related to a similar pustular infection of horse's hooves, called grease, and that this infection was directly transferable to humans and

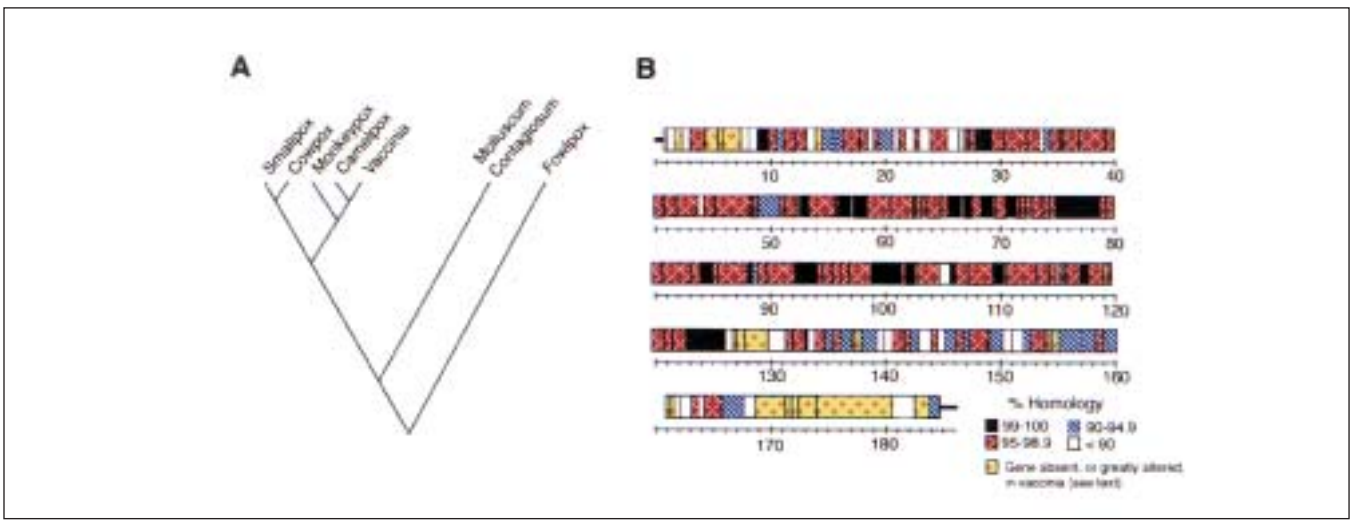

Figure 2) *Genetic relatedness of selected poxviruses.* **Left** *'Low-resolution' diagrammatic representation of relatedness of indicated viruses, based upon restriction fragment analyses (6,7) and partial sequence comparisons (8). Line lengths are arbitrary*. **Right** *Schematic comparisons of amino acid identity between vaccinia virus (10) and smallpox virus (11). The smallpox sequence is presented, and percentage homology of each predicted protein to the corresponding protein in vaccinia is indicated (11). Intervening noncoding regions are not shown. The scale line under the sequence indicates kilobases. Regions in the central portion of the smallpox genome share very high sequence homology (90% to 100%) to similar genes in vaccinia; however, regions present near both smallpox genomic termini share very little homology, are greatly altered or are absent from the vaccinia genome*

could produce an infection similar to cowpox. However, he was uncertain about whether infection originating from horses provided as much protection against smallpox as did cowpox originating directly from cows. Cases 13 to 15 are presented to investigate this concern and consist of three adults, each with a history of horsepox. Two of the adults were resistant to smallpox variolation. However, the third case, that Jenner did not challenge, had a history of natural smallpox despite prior horsepox infection. Because of this exception, Jenner concluded that horsepox may not protect as well against smallpox as cowpox virus infection, and to test this conjecture, took material from the pox lesion of a human case with horsepox and inoculated it into the arm of a five-year-old boy (case 18). However, Jenner was unable to test if this child remained susceptible or became resistant to smallpox variolation because the child became seriously ill (and died) after acquiring a contagious fever while employed in a workhouse.

Jenner abandoned this line of inquiry and began to study the clinical and immunizing effect of cowpox vaccination directly. Cases 16 and 17 are the most famous in his case series. Case 16 is of a mild cowpox infection in a young milkmaid, Sarah Nelmes, who acquired her infection in May 1796. Figure 1 represents the cowpox lesions on her hand and is one of the four splendid plates that Jenner included in his publication that illustrate the appearance of pox lesions. On May 14, 1796, material from one of her lesions was used to inoculate an eight-year-old boy named James Phipps. Two superficial incisions, each about 12 mm long, were made into the skin of his upper arm. He developed a mild cowpox virus infection eight days later, with the pustular lesions on his arm that quickly resolved. Six weeks later, on July 1, 1796, James Phipps was challenged with smallpox variolation that he completely resisted, thus directly establishing that cowpox infection conferred resistance to smallpox. Jenner ensured that the smallpox inoculum used to challenge James Phipps was infectious by successfully challenging several other family members who had not received cowpox; they developed the usual modified smallpox illness that routinely followed variolation.

The last five cases (cases 19 to 23) were meant to determine whether cowpox could be successfully passed from person to person while maintaining its immunizing effectiveness. Five children, ages five to seven years, were serially immunized with cowpox, with the first case (case 19) inoculated with material obtained directly from a cow. Jenner appears to have chosen children for these experiments because he wanted to ensure that he tested individuals who were immunologically naive with respect to pox virus infection. Successful transfers occurred and all children developed mild cowpox infection, which spontaneously resolved. He challenged the first two and the last case with smallpox variolation, and all resisted challenge. Jenner concluded that "these experiments afforded me much satisfaction, they proved that the matter passing from one human subject to another through five gradations lost none of its original properties, J. Barge being the fifth who received the infection successively from William Summons, the boy whom it was communicated from the cow." (4)

With the hindsight of two centuries of research, including recent molecular biological data, Jenner's achievement can be evaluated and appreciated. The remarkable protective effect of cowpox against smallpox may reflect the origin of human smallpox from cowpox itself several thousand years ago during the early period of animal domestication in the Middle East and/or western Asia (5). In fact, partial genomic analyses show that smallpox is more closely related to cowpox than to other animal pox viruses (6-8) (Figure 2, left). Surprisingly, the contemporary vaccinia virus is only distantly related to smallpox and cowpox (6-8). The origin of vaccinia is traceable to about a century ago, and its natural host source still remains obscure. Somewhat ironically, given Jenner's ambivalence about horsepox, one theory has suggested that vaccinia may be descended from the now extinct horsepox (9). Despite this uncertainty, no doubt exists about vaccinia's ability to immunize against smallpox because this was the virus used in the smallpox global eradication program. Detailed comparisons of the smallpox and vaccinia genomes, whose complete sequences are known (10,11), reveal that many of the genes within the central region of the genomes share more than 95% amino acid identity (Figure 2, right). The genes in this region primarily encode major structural and enzymatic proteins. Such high similarity could explain the effectiveness of vaccinia in providing immunity against smallpox. In contrast to the high similarity in the central regions of the two genomes, there is much greater variability in the sequences in the terminal regions. This variability includes genes present in one virus, and absent, greatly truncated or elongated in the other. The flanking regions contain genes involved in host range, viral virulence factors and immune evasion factors (12), and variation in these regions could explain the differences in pathogenicity between vaccinia and smallpox virus.

The world has remained free from smallpox for over two decades now, and smallpox vaccination itself ceased over 15 years ago. It remains uncertain whether the niche emptied of human smallpox by vaccination will remain that way in an era when smallpox vaccination has ended. For instance, in central Zaire, outbreaks of monkeypox virus infection in human populations have been documented, primarily occurring among non-immunized children (13). Whether monkeypox can achieve the ecological success of human smallpox in human populations is unclear at this point, but for this and other reasons, much research interest remains centred on vaccinia and the other pox viruses. Their potential use as recombinant vaccine vectors may prove useful not only to vaccinate against other infectious diseases but also to prevent the re-emergence of humanpox virus infection.

Jenner believed he had developed a safer way to vaccinate against smallpox – and indeed he had. In concluding his *Inquiry*, Jenner stated that he was "encouraged by the hope of its [the vaccination procedure] becoming essentially beneficial to mankind". This thought proved amazingly prophetic, although it took 175 years to achieve the full potential of his approach. We now live in an age free from smallpox thanks to his astute observations, and stand on the threshold of an era when we can contemplate the elimination of several other

acute infectious diseases through the principle of vaccination that he so compellingly demonstrated. We have much to honour in the achievements of Edward Jenner.

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