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## Vaccines: Their Place in History

*There is nothing new except what has been forgotten.*

—Marie Antoinette (1755–1793)

### Smallpox in history

For the first hundred years or so, the story of vaccination was the story of smallpox. Smallpox first appeared in remote antiquity, perhaps 10 thousand years ago when humankind first embraced settled farming in preference to transhumance. It was, many say, the most feared of all ancient diseases: smallpox killed 20–30% of those who contracted it, disfiguring or blinding those that survived.

It has been suggested, primarily on the basis of extant historical evidence, that virulent smallpox did not appear in Europe until the early modern era – most probably during the seventeenth century – and gradually replaced an endemic and much less virulent form of the disease. This transition seems to have occurred during a series of erratic smallpox outbreaks during the fifteenth and sixteenth centuries. With more certainty we can say that smallpox's case fatality – the proportion of the infected population that dies – escalated over the centuries, peaking during the eighteenth century.

*Homo sapiens* is the only species susceptible to smallpox; there is no known animal reservoir for the disease. Smallpox is contagious – it is transmitted from person to person. The smallpox virus is usually transmitted via the respiratory tract, primarily by inhaling respiratory droplets. While contagious, smallpox is not highly transmissible; dense populations are necessary to maintain transmission. Prolonged

close contact foments infection. After a 10 to 14 day incubation period, infected individuals develop severe symptoms, including fever, malaise and headache. A maculopapular rash then develops on the face, trunk and extremities. Smallpox lesions become deep and pustular over the next 1–2 days, with scabs forming by day 10. Patient infectivity is greatest in week one, when viral shedding is at a peak, with most deaths occurring during the second week.

The discovery of vaccination – though discovery is, as we shall see, altogether too simplistic a term – is most often attributed to the work of Gloucestershire physician Edward Jenner (1749–1823). On 14 May 1796, eight-year-old James Phipps was vaccinated with bovine cowpox; days later Phipps survived deliberate infection with smallpox. Thus Jenner was, for the first time, able to induce protective immunity against the disease of smallpox. Later, in 1881, Louis Pasteur (1822–1895) adopted the word ‘vaccination’ – Jenner’s neologism for his treatment – as a general term for immunization against any disease. In Jenner’s time, vaccination had instead been known as ‘cowpox inoculation’ or ‘vaccine inoculation’. In May 1980, the World Health Organization declared that smallpox had been totally eradicated as the result of a global programme of vaccination. No one has died of naturally occurring smallpox since. Thus vaccination, as a concept and as a practical reality, at least as used against smallpox, would seem to be an unqualified success. Yet, no idea is wholly without precedent; no concept is utterly new; no thought is without inspiration.

Ge Hong was an eminent physician, who is also credited with making important contributions to alchemy and astronomy. He became military adviser to Qi Han, author of *Nanfang caumuzhuang* (*Records of Plants and Trees in the southern region*) and one of the greatest botanists in Ancient China. Ge Hong wrote many books, including the *Baopuzi neipan* which recounts the medicinal properties of many plants and minerals. He described smallpox, and gave the first therapies for it, in the *Zhouhou Jiuzufang* (*Medical Handbook for Emergencies*), a three volume recension written to supplement the 100 volumes of *Jingui yaofang* (*Prescription in the Treasury of Medicine*), which were composed during the Jin Dynasty (266–317).

In India, smallpox was named, and its essential character described, in early Sanskrit medical treatises such as fourth century texts by Caraka and Susruta. Smallpox was called masurika, which means ‘lentil’ or ‘pulse’, since smallpox pustules resemble in shape and colour a local variety of bean. By the twelfth century, Sanskrit texts give other names for the disease, all variants of the word sitala, which means cold or cool.

The first western physician to provide an accurate description of smallpox was Ahrun (610–641), a Greek-speaking Christian Egyptian, who lived in Alexandria. In the tenth century, arguably the best early description of smallpox, and how it differed from measles, was given by one of the most outstanding physicians of the era: Abu Bakr Muhammad ibn-Zakariyya al-Razi, better known to the West as Rhazes. He was born in Rai in Persia in about AD 865. Early on he studied music, physics and alchemy, only becoming interested in medicine aged 30. Much influenced by Hippocrates and Galen, he nonetheless demonstrated independence

and originality, introducing much personal experience into his texts. Of al-Razi's 36 surviving texts, the best known is his treatise on smallpox and measles. In AD 910 he described smallpox in his book *De variolis et morbillis commentaries*, noting the disease was transmitted from person to person. Al-Razi wrongly assumed that both smallpox and measles were manifestations of the disease, yet his descriptions differ only marginally from those in the famous 1892 textbook of Sir William Osler (1849–1919): *Principles and Practice of Medicine*.

## Variolation

Smallpox is a disease which cannot properly be treated but can be prevented. At some now forgotten point, a connection between infection and subsequent acquired immunity was made for smallpox: surviving the disease leads to pock marking and pockmarked individuals rarely, if ever, contracted smallpox again. A similar observation – that smallpox infection which results from a skin scratch has a greatly reduced severity – led, presumably, to the idea of variolation. It is a frustration that we do not know where or when this practice originated, whether it arose once and spread geographically through time or whether it arose independently several times and in several places.

As a prophylactic approach, variolation is something of a paradox, as it caused the disease that it was claiming to prevent. Potential benefits of variolation may have manifested themselves in two ways. Variolation, working at the level of individuals, may have caused a form of the disease much less severe than natural smallpox. At the community level, variolation might abrogate a smallpox epidemic. Moreover, by producing an augmented level of local immunity, variolation could decrease the probability that future outbreaks of smallpox might occur.

Variolation is, or was, the inoculation of uninfected individuals using dried scabs or pustular fluid obtained from smallpox lesions of recovering victims. Eighteenth century writers described the process of variolation as cutaneous inoculation with terms such as insertion, transplantation or engrafting (which has its origin in horticulture, where it refers to inserting a bud into a plant) also in common use. The term *variolation* itself was probably not used until much later: the Oxford English Dictionary, for example, says that it appeared first in 1792, although it was certainly coined earlier. The word variolation derives from the Latin *varus* for pimple, while inoculation comes from the Latin *inoculare*, meaning to graft. The term 'vaccination' has come to mean immunization by vaccine, while 'variolation' now refers only to inoculation of the normal, virulent, pathogenic agent of an infectious disease.

The technique involved first a small scratch of the person being variolated followed by the transfer of infected matter into the wound. In terms of both its underlying (and albeit poorly understood) mechanism of action and associated clinical practice, variolation is a practice quite distinct from vaccination. Postinfection fatality was much reduced for variolation (0.5–2%) when compared to naturally

acquired smallpox (20–30%). Symptoms of the disease were also different, with a decreased general rash and a lessening of permanent pockmarks. Putative explanations for these differences abound. The simplest is also one of the most compelling: when variolated, a patient, who has had adequate preparation, is able to mount a full scale response and ultimately becomes immune to subsequent infection. The fact that overpreparation, and the use of strange purgative regimens, decreases the effectiveness of variolation would support this view. Likewise, another contention is that the transferred virus has been mildly attenuated. Although Pasteur-type attenuation through serial passage is generally performed many, many times, the arm-to-arm transfer seen during variolation may have afforded the opportunity for some kind of selection of less virulent virus. The variolated patient may thus receive less virulent smallpox material and incur a less severe infection compared with naturally transmitted smallpox. Another possibility posits that the physical route of infection into the body was crucial. The argument here runs thus: smallpox spreads with no little celerity through the body when introduced into the lungs; however, when introduced under the skin, as in variolation, progress is rather less rapid and the body, as manifest by the immune system, has the time to mount a proper response. Yet another hypothesis suggests that the transfer of infected material also transfers components of the innate and adaptive immune system already primed to respond to the disease. Such components may include neutralizing antibodies; or immune mediators, such as interferons, which act as natural adjuvants enhancing the immune response to the incipient infection; or Antigen Presenting Cells (APCs), such as Dendritic Cells (DCs), already presenting pathogen derived peptides. Like many complex phenomena, the relative efficacy of variolation is, in all likelihood, a result of the synergistic combination of several such mechanisms of action.

However, because the causative agent used in variolation was not wholly attenuated, or weakened, as subsequent vaccines were, the process had the significant disadvantage that variolated individuals could transmit potentially severe natural smallpox to members of the as-yet-uninfected population. Although it may have protected those wealthy families able to afford it, variolation, practiced on a sporadic basis, as it certainly was in the first half of the eighteenth century, was more a public-health hazard than it was anything else. It certainly came with many problems. Some cases were severe, and even fatal. The lancets used to transfer pustular material were seldom sterilized nor were they wielded by sterilized hands in sterile rooms. Moreover, because many inoculators preferred to take inoculum from more mature pustules, wound infections were quite common. Indeed, variolated individuals were often not isolated, and because they carried the virus yet were sufficiently well to be up and about, they were a risk to non-immunes. Indeed, the last smallpox epidemics in China in 1965, in Afghanistan in 1973, in Pakistan in 1974, and in Ethiopia in 1976 are all thought to have been caused, or at least exacerbated, by variolation. Local practitioners tried to preserve stocks of smallpox virus maintaining them by re-injecting material from consenting individuals, typically friends or family.

Moreover, there are two distinct routes of administration used in variolation: the nasal route, which is considered the more risky, and the cutaneous or skin route, which is thought to be safer. However, opinion differs on this point and it is an issue not easily resolved in the post-eradication era. The variety of variolation used in China was not the arguably safer and more effective cutaneous version, whereby crusts from smallpox pustules were inserted into cuts in the skin, which was in use elsewhere, but one enacted via the nasal route, i.e. via the inhalation, or so-called insufflation or blowing, of powdered material, obtained from dried scabs, directly onto the mucosal lining of the nose. Voltaire likened this practice to taking snuff.

## Variolation in history

It is thought that smallpox itself first entered China in the mid first century AD, coinciding with the beginning of the Eastern Han dynasty (25–220). However, it was not until the fifteenth century, during the Tang and Song Dynasties, that progress in transportation, and concomitant increases in travel, allowed the disease to reach epidemic proportions. Among the first written reports of variolation found in Chinese records are ones that refer to the reign of Jen Tsung (1023–1063). Yu Mao Kun, in *Ke Jin Jing Fu Ji Jie* (*Special Golden Mirror and Solutions*, published in 1727), describes how, in the long Qing period of the Ming dynasty (1567–1572), variolation spread across the whole of China from the Ning Guo district of Anhui.

Many, perhaps rightly, view variolation as a great Chinese innovation, while others favour the notion that the technique had reached China, via Tibet, from India. While variolation was probably practiced in India since antiquity, there are no attested records of the procedure written before the arrival of Europeans in the fifteenth century. Subsequently, and certainly from the early eighteenth century, many settlers and merchants from Europe described the cutaneous form of variolation, which was in widespread use among the resident population. Variolation seems to have been used widely in a number of areas during the eighteenth century, including Bengal, Assam, Bihar, Orissa and Varanasi, and less commonly in parts of the Punjab, Sindh, Rajasthan and Gujarat, and occasionally in isolated regions of central India and Maharashtra. Treatments other than variolation are outlined in texts which date from the fourth century, as well as those from later commentaries, such as the eighth century *Nidana* of Madhava-Kara or that by Dalhana in the eleventh century, all of which belong to the Ayurvedic system. The remedies found in these works comprise both dietary changes and efforts to restore the proper balance between external forces, such as heat and cold. In India, the use of variolation was associated with worship of the goddess Sitalam, who was thought to cause smallpox. The Ayurvedic system concerning the disease and the variolation technique, with its implicit understanding of infection, formed, in thought and deed, a unified and holistic conceptualization of smallpox.

The earliest description of the practice of variolation in India is an account written in 1731 by Robert Coult. As we have said, it remains uncertain when

variola was discovered or introduced into India. Indeed, the Oriya Brahmins, who conducted indigenous variolation in northern India, were themselves unsure when the technique had been conceived or introduced into the subcontinent. In 1767, John Zephania Holwell (1711–1798), who had studied surgery at London's Guy's Hospital and saw service in Bengal from 1732 until 1760, described the Ayurvedic system of inoculation against smallpox to the Royal College of Physicians in London in a tract called *'An account of the manner of Inoculating for the Smallpox in the East Indies. With some observations on the Practice and Mode of Treating that Disease in those parts. Inscribed to the learned, the President and Members of the College of Physicians in London.'*

Arab traders were probably key disseminators of variolation. This was mirrored by the spread of smallpox itself, which occurred in the wake of the rapid territorial gains made by the burgeoning Arabic civilization that emerged in the first 150 years after the founding of Islam. This helped disseminate the disease through North Africa and Europe during the sixth, seventh and eighth centuries. Traders spread knowledge of the practice into South East Asia and, as we shall see below, probably also into Africa and Ottoman Turkey. Perhaps the most compelling evidence, however, comes from Patrick Russell (1727–1805), the noted physician and naturalist, and his brother Alexander (1715–1768). In December 1768, they published an account, in the *Philosophical Transactions of the Royal Society*, which described variolation in Arabia: it summarized the extensive observations that Alexander had made while living in Aleppo in Syria, which suggested that inoculation against smallpox was practiced extensively amongst the Bedouin tribesmen of the Middle East. It seems also to have been in common use in Persia, Georgia and Armenia, among others.

It seems certain that variolation was also widely known throughout many parts of Africa, at least from the late 1600s and, in all probability, much earlier. It is believed, for example, that variolation was introduced into Egypt by the Mameluke Turks during the thirteenth century. In 1738, Englishman Thomas Shaw wrote a discourse on his travels which said that inoculation was well known in North Africa. In 1768, the memoirs of Chais, a protestant priest from Holland, stated that an ambassador from Morocco had said publicly in 1738 that inoculation against smallpox was commonly practiced in North Africa. Also, as we shall see below from the story of Cotton Mather, cutaneous variolation was unquestionably known in West Africa from at least the seventeenth century, and was certainly practiced widely during the nineteenth century.

## Variolation comes to Britain

Despite some evidence in the Anglo-Saxon Chronicles, which may make reference to the disease, it was only in the eleventh and twelfth centuries that returning Crusader Knights, their troops, and civil entourages, coupled to the continuing expansion of trade with the Middle East, brought smallpox to Northern

Europe. The disease had become endemic in Northern Europe by the fifteenth century. By the seventeenth century smallpox had displaced bubonic plague as Europe's most terrifying and fatal disease; and it is during this century that the first accounts emerge of what can be seen as the seeds of variolation in Europe, although its origins are rooted deeply in superstition. Thomas Bartholin (1616–1680), called it 'transplantation of disease', and pronounced it 'a stupendous remedy, by means of which the ailments of this or that person are transferred to a brute animal, or to another person, or to some inanimate thing'. The practice of variolation had even reached Central Europe at this time, probably via the Balkans, where it was being used extensively in Slovakia. Indeed, in 1721, Dr Johann Reiman undertook a well-publicized inoculation against smallpox in Bohemia, now part of the Czech Republic.

By the turn of the eighteenth century, news concerning variolation had even begun to penetrate into England. Throughout much of its history, England was a small, underpopulated, geographically-remote island on the edge of a backward and fractious continent far removed from the centre of civilization. By the end of the seventeenth century this had changed, but not as much as we know it would: within a century England would have gained and lost one Empire and then gained another. The news of variolation that reached England was news in the loosest sense; what was actually circulating was a tiny handful of letters describing the practice.

In 1700, the Royal Society received several reports which described a variety of Chinese intranasal variolation: the first report on Chinese variolation is given in a 1700 account by Dr Clopton Havers (who died in 1702). The Chinese method was also described in an account (dated 5 January 1700) sent by Joseph Lister, an East Indian Company trader stationed in China. This letter, addressed to Dr Martin Lister (1638–1712), reported that:

a method of communicating the smallpox involving opening the pustules of one who has the smallpox ripe upon them and drying the matter with a little cotton and afterwards put it up the nostrils of those they would infect.

Nothing very substantive came of either account; knowledge of the Chinese practice of *sowing the smallpox* by nasal insufflation was not to vanish: witness, for example, the book *De Variis et Morbillis Uber*, written by Richard Mead (1673–1754), where it is mentioned. Moreover, the method is fully described by the Jesuit missionary d'Entrecolles in letters from Jao Tcheon (1715) and Peking (1725), which were published in the *Lettres Edifiantes et Curieuses*.

In the following decade, reports appeared that described cutaneous variolation, as practiced in Turkey. In 1712, Dr Edward Tarry of Enfield, who had returned to England from Pera and Galata, claimed to have observed more than 4000 variolated persons. During late 1712 and early 1713, Richard Waller (1646–1715), secretary to the Royal Society from 1710 to 1714, had initiated a campaign to obtain, on behalf of the Royal Society, more and better information concerning variolation.

In December 1713, Emmanouil Timonis (1665–1741) sent an extensive eye-witness account of variolation, written in Latin from Constantinople, to the Royal Society. On 27 May 1714, this letter was called to the attention of Fellows of the Society by John Woodward (1665–1728). An English translation of the letter was later read out to Fellows of the Society on 3 June 1714, and it was formally discussed on 10 June 1714. Timonis described ‘smallpox by incision’: pustular material was usually only taken from healthy boys with smallpox and applied to persons of all ages, causing them only minor inconvenience. The only required preparation was to abstain from flesh for 20 days.

Despite Woodward’s unpopularity with other Fellows of the Royal Society – he had formerly served on the council of the Royal Society but was expelled in 1710 for insulting Sir Hans Sloane – extracts of the note by Timonis were published in the *Philosophical Transactions of the Royal Society*, during May 1714, as *Timoni E. An account, or history, of the procuring of the smallpox by incision or inoculation, as it has for some time been practised at Constantinople*. Timonis was a physician, as well as an antiquarian and diplomat and, it was said, *a very learned man*. Timonis had in his youth obtained medical degrees from Padua and Oxford, and was later elected a Fellow of the Royal Society in 30 November 1703. At this time, he practiced medicine in Constantinople and served as family physician to various British Ambassadors there, including Sir Robert Sutton and, as we shall see, his successor Edward Wortley Montagu.

The report of Timonis generated some discussion and the Royal Society then commissioned an even more complete investigation, much of which occurred through already established English commercial contacts. In 8 July 1714, Richard Waller wrote to the botanist William Sherard (1659–1728), who had become a Fellow of the Royal Society in 1720, asking if he had access to more information concerning variolation. Sherard was at that time the British Consul at Smyrna (modern Izmir in Turkey), and he afterwards contacted his Venetian equivalent, a man called Iakovos Pylarinos (1659–1718), who also practiced as a physician. Pylarinos later described variolation against smallpox in a Latin pamphlet dedicated to William Sherard, printed in Venice during 1715, which was entitled *Nova et tuta Variolas excitandi per transplantationem methodus nuper inventa, in usum tracta, qua rite per acta immuniaa in posterum praeservatur ab hujus modi contagio corpora* or ‘New and safe method to excite smallpox by inoculation, just invented and put into use, performed routinely, by which the bodies acquire immunity against this infection in later years’. The pamphlet, introduced at the 24 May 1716 meeting of the Society, contained personal observations made by Pylarinos while he practiced at Smyrna and Constantinople. The pamphlet was later summarized in the *Philosophical Transactions*, appearing during 1716 as *Pilarino G. Nova et tuta variolas excitandi per transplantationem methodus, nuper inventa et in usum tracta*.

On 7 March 1716, Sherard sent his brother James Sherard (1666–1738), an apothecary and also a Fellow in the Royal Society, a letter and the printed pamphlet

by Pylarinos. It seems that Pylarinos had undertaken, or at least observed, a series of three successful inoculations in or around 1701. Sherard's letter stated that two sons of Hefferman, Secretary to Sir Robert Sutton, the British Ambassador to Turkey, had been variolated in Constantinople. Pylarinos had been born on Cephalonia, and obtained degrees in law and medicine from the University of Padua and was also, amongst other things, physician to the princes of Serbia and Moldova and, for a time, chief physician to the Russian Tsar Peter the Great (1672–1725).

In 1715, Peter Kennedy, a Scottish surgeon who had visited Constantinople, also published his observations of variolation or, in his words, *engrafting the smallpox*, in a book called *An Essay on External Remedies*. The process he described involved collecting pox fluid on day 12 of the infection, keeping it warm and then introducing it to the patient through a scratch in the skin.

Knowledge of variolation was spreading, but the process of gradual dissemination, which moved with only imperceptible slowness, was haphazard and unsystematic; it came not in a rush but in an uncoordinated dribble. This drip feeding of information continued with intermittent reports of variolation percolating into England. In 1721, Jacob de Castro Sarmiento (1691–1761) was able to publish a pamphlet on variolation called *Dissertatio in Novam, Tutam, ac Utilem Methodum Inoculationis seu Transplantationis Variolorum* or *A dissertation on the method of inoculating the smallpox; with critical remarks on the several authors who have treated of this disease*. His work was published first in London and then translated into German a year later. A supplement followed in 1731. His *dissertation* recommended that smallpox material taken from an inoculated individual should be used in preference to that obtained from someone in whom the disease had occurred naturally.

## Lady Mary Wortley Montagu

However, the kind of small-scale, anecdotal evidence, whether first- or second-hand, as provided by Lister, Pylarinos and Kennedy, or even that provided by Fellows of the Royal Society such as de Castro or Timonis, did little to alter the fixed and cautious opinions that prevailed amongst English surgeons and physicians. They were reluctant to adopt new and untried procedures in a cold northern climate where smallpox manifested itself as such a severe disease. In the opinion of many, these were peculiar foreign medical adventures supported by reportage little better than hearsay; they were seen as virtuoso amusements, as one-off events, as quaint oddities, similar, in many ways, to the cabinets of curiosities, which were so fashionable at the time. What was needed was a strong and persuasive advocate. This variolation received in the form of Lady Mary Wortley Montagu.

Lady Mary, born Lady Mary Pierrepont, was baptized on 26 May 1689 at Covent Garden in London. Lady Mary is, arguably, best known to history for her letters, particularly for her record of her Ottoman experiences, *Turkish Embassy Letters*,

now a notable primary source for historians of the period; but in her own time she was as renowned as a poet as she was as a witty correspondent and letter writer.

Lady Mary was the eldest daughter of Evelyn Pierrepont, afterwards First Duke of Kingston. Her mother, who died while Mary was still a child, was the daughter of William Fielding, Earl of Denbigh. She was cousin to Henry Fielding, the novelist. Lady Mary conducted an animated correspondence with Edward Wortley Montagu, grandson of the first Earl of Sandwich. Lady Mary's father refused to accept Montagu as a son-in-law as he would not entail his estate on a possible heir. When, in 1712, Lady Mary's father insisted his 23-year-old daughter marry a different man, the pair decided to elope. The couple had two children, Mary and Edward. The first few years of Lady Mary's marriage were spent in parsimonious rural seclusion. Edward was elected a Whig Member of Parliament for Westminster in 1715, and shortly afterwards became a Treasury Commissioner. When Lady Mary joined him in London her beauty and her wit rapidly brought her to prominence at court.

It was Lady Mary who is now seen as being ultimately responsible for bringing smallpox variolation to Britain. While she alone was not wholly responsible for introducing the technique *per se*, she was certainly responsible for fomenting its incipient popularity, first in high circles and subsequently amongst the wider population.

Lady Mary was herself no stranger to the effects and lethality of the disease: in 1713, during the first year of her marriage, her beloved 20-year-old brother, already a husband and father, had died from smallpox, his promise yet to be fulfilled. Only 18 months after this vicarious brush with 'the speckled monster', as smallpox was rather quaintly known during the eighteenth century, Lady Mary survived a bout of smallpox; whatever its severity, the bout left her 'previously exquisite' face severely pitted and scarred, and also caused the loss of her 'very fine eyelashes'. The actual extent of her disfigurement and the relative seriousness of her attack remains, however, a point at issue: many have suggested that it was not overly severe, but the tone of her recorded poems of the period suggests otherwise.

We must remember that, for people of the time, death was everywhere: families were large, lives were short. Men, women and children, both those rich and poor, famous or obscure, all were as one before the scourge of contagious disease. Thus the perception of death and personal loss may, for them, have been very different. As Leslie Poles Hartley (1895–1972) says at the start of his most famous book *The Go-Between*: 'The past is another country. They do things differently there.' We cannot guarantee that our own sentimentalized views on personal mortality were necessarily shared by those living in past centuries.

In 1717, a few years after George I (1660–1727) had succeeded Queen Anne (1665–1714) to the British throne, Lady Mary's husband, Edward Wortley Montagu, was appointed ambassador to the Ottoman Empire in Constantinople. Tentative diplomatic relations had first been established between Britain and the Ottoman Empire in 1579 when Queen Elizabeth I (1533–1603) exchanged letters with the then Ottoman ruler Sultan Murad III (1546–1595). Earlier, in 1578, two London

merchants had sent their agent William Harborne to Turkey; his mission was to obtain the right for English merchants to fly their flag in Ottoman waters, a right which had been granted previously only to the French. Later, in 1580, Harborne obtained for British merchants privileges similar to those enjoyed by the French. Subsequently, the Levant Company was established in London. For the next 200 years, Anglo-Turkish relations remained in the hands of the Levant Company: for many years it paid the salaries of English Ambassadors to Turkey; the company remained a power in the eastern Mediterranean until 1821, when it was assimilated by the British Government.

## Variolation and the sublime porte

When Montagu was appointed ambassador to the Ottoman Empire, Lady Mary accompanied him to Vienna and from there to Constantinople, via a 2 month stay in Adrianople. The Wortley Montagu's long and dangerous trans-continental journey, which was undertaken in the dead of winter, was considered something of an achievement at the time. Wortley Montagu and his retinue arrived in Adrianople (present-day Edirne) on 13 March 1717, escorted by some 500 Janissaries. They had come via Sofia and Philippopolis, and would stay for 2 months before moving on to Constantinople, where they arrived towards the end of May 1717. Adrianople had been the Ottoman capital until the fall of Constantinople in 1453 and continued to be much used by the Sultan and the Sublime Porte, as the Ottoman court was known.

Unlike so many western visitors to Turkey and the Orient, Lady Mary sought actively to engage with the upper class Ottoman world. Lady Mary learnt quickly that the Turks inoculated healthy children with a naturally attenuated, postinfection form of smallpox in order to confer immunity against the more virulent, contagious version of the disease. On April Fool's Day 1717, soon after her first arrival in Adrianople, Lady Mary wrote back to her friend in England, Mrs Sarah Chiswell of Nottingham, giving a positive yet very graphic description of the practice of variolation.

How the Ottoman Turks had learned of the practice is once again lost. One suggestion is that it came to them from India, via Arab intermediaries, in the early 1600s. Another is that the practice spread slowly from China along the Silk Road. The first extant report in the Turkish literature reports that in 1679, a man came to Constantinople from Asia Minor and variolated several children. Voltaire relates what is most probably an apocryphal tale: how, in 1670, Circassian traders, from the shores of the Black Sea north of the Caucasus Mountains, first introduced variolation to the Ottoman Court and how women from the Caucasus, who were in great demand in the royal harem because of their legendary beauty were, as children, variolated in those parts of their bodies where scars would not show. However, later travellers in the Caucasus could find nothing to corroborate such tales.

In March 1718, perhaps motivated by the family's impending return to England, and while her husband was absent, Lady Mary had her five-year-old son Edward variolated at Pera, a suburb of Constantinople. The Embassy Chaplain reportedly opposed the procedure, calling variolation an unchristian operation that could succeed only amongst infidels. Lady Mary ignored his querulous objections. Charles Maitland (1668–1748), a Scottish physician who had been retained by the Edward Wortley Montagu as surgeon to the Embassy, oversaw the process. He later wrote an account of this event:

The Ambassador's ingenious Lady, who had been at some pains to satisfy her curiosity in this matter, and had made some useful observations on the practice, was so thoroughly convinced of the safety of it, that she resolved to submit her only son to it, a very hopeful boy of about six years of age: she first of all ordered me to find out a fit subject to take the matter from; and then sent for an old . . . woman, who had practised this way a great many years: after a good deal of trouble and pains, I found a proper subject, and then the good woman went to work; but so awkwardly by the shaking of her Hand, and put the child to so much torture with her blunt and rusty needle, that I pitied his cries, who had ever been of such spirit and courage, that hardly any thing of pain could make him cry before; and therefore inoculated the other arm with my own instrument, and with so little pain to him, that he did not in the least complain of it.

The scars of this variolation later served to identify Edward Wortley Montagu when, as a boarder at Westminster School, he became notorious for absconding without sanction. Advertisements offered a £20 reward for his recovery. These notices described him as possessing 'two marks by which he is easily known; viz. in the back of each arm, about two or three inches above the wrist, a small roundish scar, less than a silver penny, like a large mark of the smallpox.' Edward grew up to be a man who almost eclipsed his mother in his eccentricity and shambolic lifestyle.

In total, the Wortley Montagus' stay in Constantinople lasted no longer than 14 months. Stanyan, Montagu's replacement, had arrived in Adrianople by May 1718, and within a few months the former Ambassador and his wife had left Constantinople, returning to England in July 1718. Within 3 years, London was again gripped by a virulent smallpox epidemic; an epidemic that was to spread to other parts of Britain during the following 2 years. Thus in April 1721 – and, we may presume, strongly motivated by this new epidemic – Lady Mary persuaded a reluctant Charles Maitland to undertake another variolation.

Maitland had by now also returned from Turkey; he had retired to the country and was living in Hertford. The variolation procedure was conducted on Lady Mary's four-year-old daughter, also called Mary. She had been born in January 1718 in Constantinople, and would, in time, become wife to the Scottish aristocrat John Stuart (1713–1792), the Third Earl of Bute; he later succeeded Pitt as Prime Minister in 1763, resigning a year later as a consequence of the Seven Years War.

The variolation of the younger Mary was to be no private event, however; indeed, and importantly, several outside physicians were present. It is unclear if these initial witnesses were there at Maitland's request or, as Lady Mary's granddaughter Lady Louisa Stuart suggests, were representatives of the government or court. Either way Maitland seemed happy to be persuaded. Lady Louisa said also that these witnesses were hostile; so hostile, in fact, that Lady Mary dared not leave her daughter alone with them, in case they should harm her and thus slander the experiment.

However, they were not all hostile. One of them, James Keith, a Scottish physician and old friend of Maitland, described below, was favourably impressed; he had himself lost two sons to smallpox, and asked Maitland to variolate his surviving son, a five-year-old, born 2 months after the death of his brothers. Fortunately, in time, this public demonstration of inoculation proved successful. Little Mary and James Keith's son both did well. Although neither variolation was widely reported, professional circles, and the rather more elevated circles in which Lady Mary moved, became well aware of these events. Shortly afterwards, the venerable Dr Walter Harris, physician to Queen Anne in her lifetime, addressed the Royal College of Physicians on 17 April 1721, subsequently adding an appendix which mentions the variolation of little Mary Wortley Montagu, and does so with a recommending tone, which was published in London in August 1721.

## The royal experiment

Eventually, and in the light of such a demonstration, word of the potential efficacy of variolation spread to members of the royal family, including an erstwhile yet like-minded acquaintance of Lady Mary: the Princess of Wales, Wilhelmina Caroline, daughter of Frederick, Margrave of Brandenburg-Anspach. Caroline was married to the heir apparent George Augustus, later George II. They had eight children, not an uncommon number in an era of high infant mortality and no contraception: Fredrick Louis (future father of George III, Frederick predeceasing George II in 1751), George William, William Augustus, Anne Princess of Orange, Amelia Sophia Eleanora, Caroline Elizabeth, Mary and Louisa. The Princess of Wales was an intelligent and strong-minded woman, with interests that included theology and philosophy; Voltaire described her, somewhat flatteringly perhaps, as a philosopher on the throne.

In order to avoid risking young royal lives, on 9 August 1721 Maitland was granted a royal license to test variolation on prisoners from Newgate Gaol. Six prisoners – three male and three female – were granted the King's favour should they survive the experiment. The variolation of these prisoners was overseen by Sir Hans Sloane and John George Steigerthal. About 25 court physicians, surgeons and apothecaries observed this exercise in experimental variolation. Most of these learned and worthy medical men were members of either, or both, the Royal Society or the College of Physicians. Also in attendance was Claude Amyand, personal surgeon to George I and, later, to George II. Fortunately, all six prisoners survived,

and those challenged with smallpox proved to be immune. In the months that followed, Maitland successfully repeated the experiment on five orphaned children. These forerunners to today's clinical trials, dubiously conducted on orphans and prisoners, raised few, if any, ethical dilemmas at the time.

In the meantime, Princess Caroline consulted Sir Hans Sloane; while he would not advise her to variolate her children, neither would he advise her against it, thus fuelling her intention to act. George I gave permission for the inoculation of his granddaughters, 11-year-old Amelia and nine-year-old Caroline. His grandsons, in contrast, being more likely to succeed to the throne, had to wait for several more years. Thus, on 17 April 1722, the royal surgeon Claude Amyand variolated the two Princesses; he acted under the supervision of Sloan and Steigerthal and was directed by Charles Maitland, who also supplied the infectious material. On the same day, Amyand treated his own two children. A day later he variolated the six children of Lord Bathurst, a friend of Lady Mary. Later the same year, Caroline, Princess of Wales, was inoculated, and in 1724 the King sent Maitland to Hanover to inoculate his grandson Prince Frederick, afterwards Prince of Wales. George I was later inoculated by Amyand and Maitland.

However, on 21 April 1722, within days of these events, news came of the death of the Earl of Sunderland and his recently variolated two-year-old son, William Spencer, who had been treated by Maitland on 2 April. Moreover, one of Lord Bathurst's servants, a 19-year-old footman, who had been variolated by Maitland on 30 April 1722, after being exposed to Bathurst's variolated children on 25 or 26 April, died on 19 May; this may have resulted from natural smallpox infection as there was, after all, an epidemic of the disease underway. Several other prominent deaths followed over time, such as that in 1725 of the niece of Sir John Eyles, sub-governor of the South Sea Company.

Unfortunately for Lady Mary, many of her close friends and family were not persuaded and did not follow her lead where variolation was concerned. When Lady Mary inoculated her daughter, she also invited her sister, Lady Gower, to have her son variolated, but she declined and 2 years later he died of smallpox. Most ironical of all was, perhaps, the death, in 1726, of Sarah Chiswell, the London friend to whom Lady Mary had first written lauding Turkish variolation.

## The Boston connection

Meanwhile, on the other side of the Atlantic Ocean, the city of Boston was also being ravaged by smallpox. On 22 April 1721, HMS Seahorse, commanded by Captain Wentworth Paxon, a British ship out of Barbados, arrived in Boston. It bypassed the harbour hospital, and docked. Within a day, crewmen displayed clear signs of smallpox; soon afterwards cases appeared across Boston. Within days, about 1000 people had left the city. By mid-June, the outbreak had become an epidemic. As the disease became pervasive, panic became endemic, peaking during September to November 1721. This was to be the worst epidemic of smallpox that Boston would

suffer during the eighteenth century, killing 844, of approximately 6000 infected, from a total population of about 11 000. This was the sixth epidemic to overwhelm Boston since it was founded. However, with a fatality rate of 14% of those infected with smallpox, the 1721–1722 outbreak was by far the worst.

The Reverend Cotton Mather (1663–1728) was a remarkable, and eccentric, polymath, now much derided as the archetypal Puritan clergyman: bigoted, harsh, and intransigent. He wrote in his diary on 26 May 1721: ‘The grievous calamity of the smallpox has now entered the town.’ Mather had also been present in Boston during the 1677–1678 and the 1702–1703 smallpox outbreaks, observing for the later epidemic that ‘more than fourscore people were in this black month of December, carried from this town to their long home.’ Three of Mather’s children contracted the disease during the outbreak and fortunately all three survived.

Mather had thought to become a physician but abandoned this for a life as a minister. However, his interest in science persisted; his observations of various American phenomena, which were published in his *Curiosa Americana*, eventually allowed him to become, on 27 July 1713, the first native-born American to be elected a Fellow of the Royal Society.

As was mentioned above, variolation was practised widely within Africa and Mather acquired some knowledge about the practice from his African-born slave Onesimus, given to him in 1706 by some of his parishioners. Mather calls Onesimus a Garamantee or Garamante. A Garamantee is a member of a black African race (as opposed to one with a Berber or Arabic origin) from the Sahara, which is now called the Tabu; they are mostly found in northern Chad, eastern Niger, and southern Libya. However, Garamante can also be a classical reference to denizens of Libya, and Africa more generally, and so this attribution may be erroneous. Mather asked other slaves and slave traders, who corroborated the account of Onesimus. Later, Mather read the account of Timonis in the *Philosophical Transactions*, which described Turkish variolation, and corresponded with John Woodward on 12 July 1716; he enquired why variolation was yet to be introduced into England. Mather also told Woodward that he intended to convince Boston physicians to variolate when smallpox occurred there again.

Thus, on 6 June 1721, during the 1721 epidemic, Mather, perhaps mindful of the response which he might receive, wrote a guarded and conciliatory open letter to the physicians of Boston. The letter, which also contained brief summaries of the articles by Timonis and Pylarinos, advocated that said physicians should undertake a vigorous campaign against smallpox using the method of cutaneous variolation. All this was done quite independently, and without knowledge, of Lady Mary’s activities at the British court. Only one physician responded to Mather’s letter: Zabdiel Boylston. Boylston, who had himself survived smallpox in 1702, was a family friend of Mather; perhaps this personal association was sufficient encouragement in itself, either that or Boylston was too intimidated by the formidable preacher to decline.

Boylston (1679–1766) had been born in Brookline, Massachusetts. Despite receiving no formal medical training, Zabdiel Boylston, like Edward Jenner and many

others, did receive a solid grounding in practical medicine through several apprenticeships. These apprenticeships had been undertaken first with his father, Thomas Boylston, and then as preceptor to the eminent Hiram Cutter; both men were at the time well-known Bostonian physicians. In time, his medical knowledge and surgical skills would gain for Boylston a not inconsiderable reputation as a man of medicine. Nonetheless, he was subsequently alleged by his opponents to be no more than a stone cutter. During the sixteenth and seventeenth centuries, it was common for men to gain what medical expertise they had in this way.

Boylston may have been the first American-born surgeon to undertake a non-trivial surgical procedure in the American colonies, although operations undertaken in North America had previously been performed by English and Spanish surgeons. As reported in the *Boston News-Letter*, on 24 June 1710, Boylston successfully undertook the surgical removal of a large bladder stone from a child named Hill. The child recovered within the month. Boylston had already removed stones from other, unnamed patients prior to this. In the late seventeenth and early eighteenth century, the removal of bladder stones – being ‘cut of the stone’, as Samuel Pepys, another sufferer, famously rendered it – was, like most surgery of any significance, difficult for the surgeon and traumatic for the patient. There was, of course, no anaesthetic. Hygiene, though often better perhaps than we are now apt to credit, was basic. Contemporary manuals record a procedure that begins with lengthy preparation involving bleeding, purges and a series of warm baths. Alcohol was banned, and a fixed diet involving herbal concoctions was prescribed. Patients were counselled to have the operation in the spring when heat and cold could be avoided and there was an abundance of natural light for the surgeon. The operation itself involved two stages: first, passing a metal implement into the bladder via the urethra, and second, cutting a 3 inch incision between the genitals and the anus. The bladder would then be removed with forceps. The wound was not sealed or stitched but bound and left to heal.

After another personal letter from Mather, dated 24 June 1721, Boylston undertook the first in a long sequence of variolations. On 26 June 1721, he wrote: ‘I inoculated my son, Thomas, of about six, my Negro-Man, thirty-six, and Jackey, two and a half Years old.’ Boylston reported, in the *Boston Gazette* on 17 July 1721, the successful variolation of seven more patients. Later, on 12 August, he undertook the variolation of Cotton Mather’s son Samuel. Unfortunately, Samuel Mather almost died, and public disquiet escalated alarmingly.

Boylston was attacked in the street. Professionally, he was opposed by all his colleagues. After a threat of hanging, Boylston was obliged to go into hiding for 2 weeks. Once, in the early hours of the morning, a small bomb was thrown through a window in Mather’s house into a room where his nephew, the Reverend Walter from Roxbury, was recuperating from the after-effects of variolation.

By February 1722, however, Boylston had used variolation on over 247 Bostonians. Two other physicians treated another 39. The danger of death from the procedure and the strongly contagious nature of the variolated patient reduced the number of candidates. Of the 286 individuals variolated, only six had died, and several of

these may have already been infected with naturally acquired smallpox; this equated to a mortality rate of about 2%, compared with over 840 deaths among 5889 cases for naturally occurring smallpox, or a rate of about 15% for the whole epidemic. This clear differential was no small vindication of Mather and Boylston's introduction of smallpox inoculation into North America.

Two years after the epidemic of 1721 had run its course Boylston, his reputation fully rehabilitated, was invited to London; he received honours and lectured to the Royal College of Physicians. Boylston had, perhaps, more direct first-hand knowledge of variolation than anyone in the world. As such, he was invited to write a full account of his experiences, which he duly did. Published initially in London in 1726, Boylston produced a revised, enlarged and corrected version of the book in 1730: *An historical Account of the Small-pox inoculated in New England*.

## Variolation takes hold

By the eighteenth century, with the exception of a few remote places with small populations, smallpox was endemic throughout the world; the annual death rate from smallpox across Europe had by this time reached an estimated 400 000. 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. Thus one might imagine that inoculation, in the form of variolation, would be warmly welcomed, but not so; for there were clearly risks to being variolated. Then, as now, inoculation, whether realized by vaccination or by variolation, was regarded with great scepticism by several sections of society. Initially, variolation had some success amongst the aristocracy, yet this was only a vanishingly-small sliver of the population. The impact on variolation on other sections of society is harder to headline but the widespread use of variolation outside of the court can be seen to have begun early, if sporadically.

Shortly after the *Royal Experiment*, the effectiveness of variolation was investigated by James Jurin (1684–1750), who was both a physician and a skilled mathematician. On the basis of data collected between 1723 and 1727, he concluded that variolation protected against smallpox and that the probability of dying from variolation was much less than that of dying through natural smallpox: the death rate from natural smallpox was 2 in 17, or about 12%, while that in the 1721 epidemic had been in the region of 1 in 5 to 1 in 6, or 17–20%. The risk from variolation ranged from 1 in 60, about 2%, for data collected in Massachusetts during 1726, to 1 in 91, or just over 1%, in England. Subsequently, mortality rates for variolation dropped to around 1 in 500, as the technique was incrementally refined. Based on Jurin's sound statistical analysis, the Royal Society, together with a tranche of well-known London physicians, which included Sir Hans Sloane, John Arbuthnot, John Crawford, Samuel Brady, James Keith and Richard Mead, were happy to endorse publicly the practice of variolation.

However, the revival of variolation in Britain had already begun in the 1740s and, during the 1750s, continued to gain pace. Several factors helped foster the practice. One of the most significant factors fomenting renewed interest in variolation was the nationwide smallpox epidemic visited upon England during 1751–1753. This was, at the time, probably the most pervasive and the most lethal outbreak of the disease that England had seen. It had begun in December 1751 in London, and by the following spring the epidemic had moved out of the capital and across many other parts of England. The disease was virulent, and casualties high: during 1752, it killed over 3500 in London alone, while in Chelmsford in Essex, 95 died out of 290 infected.

Some say that this epidemic was a turning point for the practice of variolation, which went from a minor undertaking enacted on a very small scale, mainly amongst the highest echelons of society – the aristocracy and those associated with it – to a widely practiced medical treatment. Throughout the eighteenth century, much effort was expended on minimizing the inherent dangers and unwanted side effects of variolation. Unfortunately, and particularly so for the patients involved, the relatively simple technique brought to England by Maitland and others was, in time, much modified. Patients were prepared for variolation by an overwhelming succession of highly counterproductive treatments – strict and nonsensical diets, vigorous purgations and rigorous bleedings – that brought little benefit and probably did much harm. The results of this overcomplicated procedure were often disastrous: patients rapidly became exhausted and extremely weak and, as a consequence, many did not retain the strength to fight the virulent viral infection.

## The Suttonian method

The threat of death and disfigurement that came with the 1751–1753 epidemics was responsible for a significant shift in thinking concerning variolation. While opposition remained, the numbers of people who underwent the process increased appreciably. Towns and villages paid for surgeons, physicians and apothecaries to enact the procedure on their residents. The poor were variolated for the first time. Fortunately, with this renewal of interest came beneficial technical enhancements: John Ranby (1703–1773), for example, achieved remarkably low mortality rates amongst his variolated subjects. Ranby had become ‘Surgeon to the Person of the King’ in October 1740, and remained in post until May 1743. He succeeded Claude Amyand, who had held that curiously titled office from 1715 till 1740. The principal reason for Ranby’s success was his use of the arm-to-arm technique. This approach introduced pustular matter into a superficial epidermal incision rather than into a deeper cut in the skin. Ranby, as others would do later, segregated variolated individuals and did away with much of the drastic purgings, extensive bleedings and near starvation which were typical preparations prior to variolation. These innovations were to be perfected, if perfected is not too strong a word, by several physicians, who developed enhancements to the method. However, the technique that achieved

the greatest fame in England was to be the Suttonian System. Robert and Daniel Sutton improved Kirkpatrick's technique and were able to report 2514 cases without a single fatality. The resulting procedure was both less painful and more successful, with a concomitant death rate of about 1 in 2000.

The Sutton family of Suffolk physicians comprised Robert Sutton (1707–1788) and six of his sons. To a large extent, they raised the practice of variolation from a sporadic and idiosyncratic undertaking, popular amongst the aristocracy and those attending them, to the level of a lucrative medical business, which was taken up widely by all stratas of society from the gentry down to the poor. The Suttonian system included a special treatment regime before and after the variolation: abstinence from all animal food and alcohol for 2 weeks before inoculation. Afterwards he had to take exercise in the open air until such time as he developed a fever, which was then treated with cold water, warm tea and thin gruel by mouth. Once the eruption appeared the patient was persuaded to get up and walk about the garden, regular purges were given and the secret remedy was used to try and control the symptoms.

Despite several obvious drawbacks – a still appreciable death rate and the contagious nature of the newly inoculated – variolation was, following the mitigation of its worst effects, becoming better accepted by the general population, at least in Great Britain. However, religious opinions of many remained decidedly against the practice. In 1763 it was prohibited in Paris, as an official investigation showed clearly that a very virulent epidemic was kept up and increased, if not originated, by the practice. In Germany the practice, owing to the opposition of the medical profession, never made good its footing. Goethe says in his *Wahrheit und Dichtung* that 'speculative Englishmen' visited Germany and received handsome fees for the inoculation of the children of persons free from prejudice; the people as a whole, however, would have none of it. However, variolation was beginning to spread back into parts of Europe. Voltaire suggested that in order to stay alive and keep women beautiful the French should adopt the practice. Again, adoption of variolation was greatly influenced by Royal patronage. Physicians from various parts of Europe went to London to study variolation and British inoculators travelled all over the European continent. For example, William Baylies, from Bath, was invited to Berlin in 1775 by Frederick the Great to teach his method of variolation to 14 physicians from the German provinces. However, in terms of the European take up of variolation, three names figure highly: Thomas Dimsdale, Jan Igen-hausz, and Theodore Tronchin.

## Variolation in Europe

Dr Thomas Dimsdale (1712–1800), who held a medical degree from Aberdeen in Scotland, first practiced as a physician in the town of Hertford in 1734. Dimsdale championed variolation during the mid-eighteenth century, and helped to popularize it in England, publishing a book, *The Present Method of Inoculating for Smallpox*, which described variolation in 1767. His disquisition was quickly brought to the

attention of Catherine II, the Great (1729–1796), Empress of Russia, at a time when a smallpox epidemic was sweeping through her country. In order to protect the Russian people, and thus set an example, she volunteered for variolation. Dr Dimsdale, accompanied by his son Nathaniel (1748–1811), was invited to Russia in October 1768 and variolated Catherine the Great and her 14-year-old son, the Grand Duke Paul, later Paul I (1754–1801). It was said that a team of horses was kept in readiness to whisk Dimsdale away should the variolation procedure fail and the Russians seek vengeance against him. Fortunately, things went well. The Empress was most generous, creating Dimsdale a Baron of the Russian Empire, a councillor of state, physician to the Empress, and showering him with gifts of furs and diamonds, together with an emolument of £10 000, £2000 in expenses, and a life-long annual stipend of £500. The Empress later bought houses in Moscow and St Petersburg, which Dimsdale was able to use as vaccination hospitals.

A family tradition holds that Thomas Dimsdale first learnt of variolation from the Suttons, although Dimsdale wrote in 1767 that he had been undertaking the procedure for over 20 years, suggesting his career had begun years before that of Robert Sutton. Initially, Dimsdale had used a method distinct from that of the Suttons: a thread was first drawn through the smallpox pustule and then placed onto an incision in the arm. In his book, *The Present Method of Inoculating for Smallpox*, Dimsdale described another method: ‘a small incision is in skin for no more than an eighth of an inch and this small wound was then stretched between thumb and forefinger, so that pustular material could be smeared around its edges.’

Another prime mover, in terms of European variolation, was Jan Ingen-hausz (1730–1799), now best remembered as a pioneering plant physiologist who, together with Jean Senebier (1742–1809) of Geneva, laid the empirical foundation of what we now understand as photosynthesis. Following the death of his father, Ingen-hausz was invited to London in 1765, where he rapidly became an expert exponent of variolation. In 1768, at the suggestion of her personal physician of 23 years standing Gerard van Swieten (1700–1772), Ingen-hausz was invited to the Austrian capital Vienna by order of the Empress Maria Theresa (1717–1780), in spite of the opposition of the great clinician Anton de Haen (1704–1776). Maria Theresa had given birth to 16 children (10 of whom survived into adulthood), and has thus been called ‘the mother-in-law of Europe’; an accolade – if such it was – that was also to be given, a century or so later, to Queen Victoria. She had her first child at the age of 19. Her sister, Maria-Anna, had died in childbirth. It was for this reason that van Swieten had first been called to Vienna. Maria Theresa instructed Ingen-hausz to variolate her children, including the 13-year-old Marie Antoinette. Ingen-hausz stayed on in Vienna to serve as an Austrian court physician for more than a decade, returning to England in 1779. However, as we shall see below, we are not quite finished with the story of Jan Ingen-hausz.

The great Swiss physician Theodore Tronchin was responsible for introducing variolation into a number of European countries. In 1748, in the Netherlands, Tronchin first used the practice in Amsterdam, immunizing his eldest son after his second son had barely survived a serious attack of the disease. Afterwards, in

1749, Tronchin also introduced variolation to Geneva. Samuel-Auguste A.D. Tissot (1728–1797) introduced variolation to Lausanne, Switzerland in 1754. Gerard van Swieten, also, like Tronchin, an erstwhile pupil of Boerhaave, had the practice introduced into Austria, and Sweden and Denmark took up variolation between 1754 and 1756. Van Doeveren undertook the first variolation in Groningen in 1759, and despite Boerhaave already having claimed that variolation was an effective, safe and reliable prophylactic treatment a heated debate took place resulting in a campaign against Van Doeveren.

In 1756, Tronchin was invited to Paris to treat two children of the Duc d'Orléans, the Duke de Chartres and Mlle de Montpensier, descendents of the brother of Louis XIV, and second in rank only to the King. As a result of this public demonstration and the incipient fame attached to treating royalty, a queue of fine carriages formed outside Tronchin's door: one observer likened it to the chaos seen preceding a performance by the Comédie Française. From then on, Tronchin began to introduce and popularize variolation in France, while continuing to practice it in Geneva despite popular disapproval there.

The use of variolation as a prophylactic disease countermeasure was not limited solely to smallpox however. It was also used against a variety of other diseases including scarlet fever, plague, syphilis, measles and yellow fever. Variolation was also used in animals to address a variety of infectious diseases. These included sheep-pox, cattle pleuropneumonia, rinderpest, ruminant anthrax and bovine plague, amongst others.

Sheep-pox was endemic in many countries. Since the disease had clinical signs somewhat similar to smallpox, variolation was much used to combat the disease. Cattle pleuropneumonia, a bovine lung disease, was causing havoc, decimating cattle throughout Europe. Willems, a young Belgian doctor, developed a technique for variolating at the end of the animal's tail. His method was described and discussed throughout Europe.

## The coming of vaccination

By the end of the eighteenth century, variolation was drawing to the end of its long day. Not that anyone realized at the time. Its demise would come at the hand of yet another eccentric figure; not a fire-and-brimstone Puritan minister nor yet an aristocratic poetess, but instead a quiet country doctor, living in deepest Gloucestershire: Edward Jenner. Most of us are probably well acquainted, in some form or other, with the textbook story of Edward Jenner and the discovery of vaccination: the quaint but compelling account of Sarah Nelmes, Blossom the cow, and eight-year-old James Phipps. However, rather less well known is that in the years following Jenner's work, many came to claim that they had got there first. Arguably, many had. There are many alternative claimants to being the first vaccinator: Fewster (1765), Bose (1769), Jesty (1774), Rabaut-Pommier (1780), Nash (1781), and Platt and Jensen (1791), amongst others.

Despite variolation, smallpox remained a scourge in the mid-eighteenth century. Since the 1720s, many had proselytized and lauded the benefits of inoculation amongst the aristocracy and the gentry, yet the practice remained unpopular amongst the rural and urban poor. Death tolls were high and the effects of the disease were everywhere. In the eighteenth century, for example, very few passed their whole lives without contracting either mild or severe smallpox; indeed, faces so frequently bore smallpox scarring that any woman without such marks was straightway accounted beautiful. It is thought that at this time less than 20% of the European population escaped smallpox altogether.

However, in rural areas of England, Germany, France, Italy, Holland and Mexico, there was a common folk wisdom amongst the dairy farming community: a widespread belief that cowpox conferred immunity against smallpox in humans. Cowpox, a mild, localized disease acquired traditionally when milking infected cows, manifested itself as irregular pustules on cow udders, although cattle showed no other signs of disease except for a slight decrease in milk production. Cowpox was occasionally contracted by humans, particularly dairymaids, who were well known for their flawless complexions. Indeed, the beauty of milkmaids had long been legendary. It had been extolled by the Elizabethan poets, amongst others. This was because few milkmaids exhibited the pockmarks which were so characteristic of other women. Milkmaids and others who contracted cowpox were rendered immune to natural smallpox as well the artificial, variolated version.

In 1765, Jon Fewster, an apothecary from Thornbury in Gloucestershire, sent a report '*Cowpox and Its Ability to Prevent Smallpox*' to the Medical Society of London, although subsequently unpublished it did describe how variolation provoked no response in those who had once had cowpox. Rolph, another physician from Gloucestershire, later expressed the view that no experienced physician was unaware that cowpox induced immunity to smallpox. In 1769, Jobst Böse of Göttingen reported on the protection against smallpox enjoyed by milkmaids.

Of the many who claimed precedence over Jenner as the first to perform vaccination, perhaps the best documented and most reliable case was that presented on behalf of Benjamin Jesty (1737–1816). Jesty was a successful and enlightened tenant farmer who, in 1774, dwelt in a large stone farmhouse called Upbury, situated in the village of Yetminster, near Sherborne in Hampshire. Jesty was prominent in his locality, an overseer of the poor and he attended vestry meetings. He had married Elizabeth, 2 years his junior, in 1770, and they had three children: Robert (born 1771), young Benjamin (born 1772), and young Elizabeth (born 1774). In 1797, Jesty moved his family to Downshay Manor, in Worth Matravers, a village in the Isle of Purbeck, near Swanage. Aged nearly 80, Jesty died on 16 April 1816.

Jesty had contracted cowpox, a mild disease in human beings, when he had worked alongside cattle as a young man. Convinced that cowpox could protect against smallpox, Jesty thought to substitute cowpox material for smallpox as a safer alternative to variolation. He knew, for example, that his two

dairymaids – Anne Notley and Mary Reade – had both been infected with cowpox, yet neither woman had since contracted smallpox, even though they had nursed smallpox victims.

When smallpox visited his locality again, this time in 1774, Jesty resolved to protect his wife and sons. He took the family on a 2 mile walk in order to reach cowpox-infected cattle which were grazing in the vicinity of Chetnole village. Using a stocking needle, of the type used to knit the knee-length stockings worn at the time with breeches, Jesty inserted material from a cowpox lesion into the skin of his wife's arm, just below the elbow. He then repeated the insertion on his sons. The trio of vaccinated Jestys remained free of smallpox, even though they were subsequently exposed to epidemics of the disease. In 1805, Jesty was invited to the Original Vaccine Pock Institute in London, who later honoured him with a pair of gold mounted lancets, a testimonial scroll, 15 guineas expenses and had Jesty's portrait prepared by the painter Michael Sharp.

In 1781, Nash produced another reasonably accurate description of cowpox, which included discussion of how milkers' hands helped to spread cowpox through dairy herds, as well as its protective effect against smallpox. However, this account was not published until 1799, a year or so after the promulgation of Jenner's work.

In 1791 another deliberate cowpox vaccination was made, this time by Peter Plett (born in Klein Rheide in December 1766), a one-time tutor in Schonweide in Holland where he learnt of variolation. He had also learnt from milkmaids that cowpox protected them against smallpox. Later, as a tutor to another family in Hasselburg, Holstein, Plett vaccinated his employer's two daughters and another child with material taken from cows; these children were the only survivors when, 3 years later, a smallpox epidemic ravaged the area. Plett and a physician called Heinze later vaccinated over 1000 children and adults in Probstei. However, the hand of one of the children became severely inflamed and this dissuaded Plett, like Jesty before him, from undertaking further evaluation.

## Edward Jenner

Neither Jesty nor Plett ever strove to publicize their work. Thus their isolated and independent experiments did little or nothing to change medical practice. Instead, it was Edward Jenner who is now generally credited with the discovery of vaccination – perhaps rightly so, perhaps not – and the names of Jesty and Plett, and the names of others like them, have been consigned to the little-read footnotes of history. Jenner was the first to publish on vaccination with cowpox and, through his contacts, to bring it before the scientific establishment and the public.

Edward Jenner was in many ways a remarkable man; in others, he was very much a contradictory – even a paradoxical – figure. There is much in the life of Edward Jenner that his enemies and opponents could find and exploit in order to support their critical assessment of the man and his work. After a brief period of

initial medical training in London, Jenner, a native of Gloucestershire, spent his entire career working as a country doctor. With the possible exception of a trip to Edinburgh, it was said that he never travelled more than 150 miles from his birthplace. Yet, one should not dismiss the man, as many have seemingly done, as no more than a parochial rural doctor. No, indeed not. He was certainly much more than that. Above all, perhaps, Jenner was well connected, making both social contacts and scientific contacts of the first water. He was part of the minor landed-gentry in the area, and he possessed that most useful thing: a modest independent income. His medical status, compounded by his many social connections, guaranteed him clients among both the local gentry and the aristocracy. Contacts made during his brief student days in London numbered many amongst the highest echelons of the British scientific and medical establishments.

Described by some as awkward, Jenner nonetheless possessed the good fortune of being able to build and maintain friendships. Indeed, he seems a fully rounded man. He was, apparently, a respected, kindly and approachable physician; indeed the kind of medical practitioner we would all like to have but seldom find, at least not in the early twenty-first century. He also played his part in the fashionable life of Cheltenham; but again, Jenner was more than well connected and convivial. His work on the cuckoo, for example, or his cataloguing of specimens from Cook's voyages, suggests that he was gifted as well as socially successful.

However, apart from his seminal contribution to vaccination, it was Jenner's ornithological observations of the cuckoo that are, perhaps, the most interesting and significant. Many naturalists dismissed his account, and it remained controversial well into the era of photography. Although in 1921 he was eventually vindicated by photographic evidence supporting his explanation, for over a century, those who opposed vaccination used supposed defects in this study to call his ideas into question. Published at the instigation of John Hunter in 1788, this work led directly to Jenner's election as a Fellow of the Royal Society in 1789.

Edward Jenner was born the fourth son of the Reverend Stephen Jenner (1702–1754), vicar of Berkeley in Gloucestershire, and his wife Sarah (1709–1754), daughter of Henry and Mary Head of Berkeley. Many biographies of Jenner exist: some are hagiographies, some are critical to the point of contumely, while yet others are more measured and analytical. We will only précis them here. Jenner's story begins in the vicarage at Berkeley where he was born. Edward Jenner's early life, of which we know relatively little, seemingly passed without note. Named after a brother who died in April 1749, he was the eighth child of nine. Only five of his eight siblings survived into adulthood. Both of his parents died when he was five years old.

Aged seven, Jenner was sent to Cirencester Grammar School. Here he encountered smallpox for the first time. During the summer of 1757, a smallpox outbreak occurred in Gloucestershire. Pupils at the school, including Edward Jenner, were variolated by a local surgeon. The concomitant trauma, it was said, stayed with him always. The variolations were undertaken by a Mr Holbrook, an apothecary

from Wotten-under-Edge. Long after this event, Jenner recalled that during a 6-week preparation period, he was repeatedly purged, subjected to frequent blood lettings and kept on a diet low in vegetables. The inoculation episode itself nearly killed him. During these travails, and for many weeks after the variolation, Jenner was kept in an inoculation stables.

Jenner's schooling was completed at Reverend Dr Washbourn's school at Cirencester. Here he made a number of lifelong friends, including John Clinch and Caleb H Parry (1755–1822). Clinch was later to bring vaccination to the Americas. Jenner dedicated the first edition of his *Inquiry* to Parry. From an early age, Jenner's family decided that his education should focus on medicine. In 1763, when still only 13, Jenner, as was customary at the time, became apprenticed to Daniel Ludlow, a surgeon apothecary from Chipping Sodbury, near Bristol. Later, in August 1764, Jenner became apprenticed to country surgeon George Hardwicke, also of Chipping Sodbury.

Between 1770 and 1772, Edward Jenner received invaluable medical training as a private pupil of the great John Hunter (1728–1793) at St George's Hospital, London. Moving into Hunter's house on Jermyn Street, Jenner paid him £100 per annum, which included both board and lodging, and hospital fees. Hunter was one of the foremost surgeons of his age, a skilled comparative anatomist, and a physician who insisted that medicine be based upon evidence and sound scientific method rather than unsubstantiated theory persisting from remote antiquity. Hunter was to profoundly influence the life and career of Edward Jenner. Hunter taught Jenner to value observation over received authority. He initiated and fomented many important friendships which Jenner developed during his brief sojourn in London. Amongst the friends and acquaintances that Jenner was to make were such future luminaries as Joseph Banks, later president of the Royal Society, and Henry Cline and Everard Home. Both lodged with Hunter and both later become president of the Royal College of Surgeons.

Even after his return to Berkeley, Hunter continued to mentor Jenner, encouraging his interest in natural history. On his recommendation, Jenner involved himself in cataloguing the varied and various botanical specimens which Joseph Banks had brought back to England from the first expedition made by Captain James Cook to the South Pacific. Jenner discharged his duties with sedulousness and flair, and was even prevailed upon to join Cook's second expedition. He demurred, however, deciding instead to establish a rural practice back in Berkeley.

On 6 March 1788, Jenner married elegant and accomplished Catherine Kingscote (1760–1815) of Kingscote near Berkeley. She was niece to the Countess of Suffolk and possessed a rich father. However, she had contracted tuberculosis and spent most of her life as a valetudinarian, eventually becoming virtually a permanent invalid. Despite this, Edward and Catherine had three children: Edward (1789–1810), Catherine (1794–1833), and Robert Fitzharding (1797–1854). While recovering from typhus in 1794, Jenner established a second medical practice in fashionable Cheltenham.

## Cowpox

Ideas relating to the powerful putative prophylactic powers of cowpox may have come initially to Jenner in 1770 while he was still an apprentice. A dairymaid, treated by Ludlow for a pustular skin infection, was confident that her infection could not be smallpox as she had previously had cowpox. Another pleasing, if probably apocryphal, story relates to a supposed encounter in 1778 when Jenner heard a Bristol milkmaid boast: 'I will never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face.' Certainly, in *The Origin of the Vaccine Inoculation*, Jenner says many of his patients who had contracted cowpox through milking resisted variolation. This was apparently well known among local farmers; as was discussed above, it is certainly true that this relationship was well known in the eighteenth century – witness Jesty, Plett and all the rest. Jenner probably did know of the connection well before he went to London. Certainly, he had begun to explore a link between smallpox and cowpox early in his career.

By the late 1770s Jenner, already an experienced variolator in his own right, was actively gathering data with which he hoped to validate the link between smallpox and cowpox. These data were mostly cases reported retrospectively but also, from 1782, new examples as well. Information accumulated steadily, most deriving from routine variolations done after 1792 by Jenner and his nephew, and assistant, Henry. They collected 28 cases, each representing instances where cowpox had been previously acquired directly from a cow or horse, and where immunity was subsequently measured through variolation or natural exposure to smallpox. These observations seemed consistent with the hypothesis that cowpox lesions were protective against subsequent smallpox infection.

Jenner eventually sought to test these ideas formally. He reasoned that cowpox inoculation should and would be safer than variolation, since cowpox in humans seemed benign. Thus on 14 May 1796, Jenner extracted fluid from the cowpox pustule on the hand of Sarah Nelmes, a dairymaid, and inoculated this fluid, through two half-inch incisions, into the arm of an eight-year-old child. The child, a boy named James Phipps, developed local vesicles and a mild fever from which he soon recovered. About 6 weeks later, on 1 July 1796, Jenner variolated two sites on Phipps's arm; the boy was unaffected and did not develop any of the symptoms of smallpox. Jenner repeated the variolation exercise a few months later; again without effect.

Jenner wanted to publish immediately, but was dissuaded by the Royal Society, who felt more data were needed. How things change. They warned him '... not [to] promulgate such a wild idea if he valued his reputation'. So, instead, he collected more case histories, and undertook a further sequence of vaccinations during March and April 1798. Jenner's work remained controversial. So, based on these 12 vaccinations, together with the 16 additional case histories he had collected between the 1770s and 1790s, Jenner published privately a book of 75 pages in 1798. This book – *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 Cow Pox* – was to become a classic text. Over the next few years, Jenner wrote several more books which sought to develop and expand these ideas, as well as detailing extra experiments and more supporting evidence. The books were: *Further Observations on the Variolae Vaccinae* (1799), *A Continuation of Facts and Observations Relative to Variolae Vaccinae or Cowpox* (1800) and *The Origin of the Vaccine Inoculation* (1801).

Jenner presented evidence that cowpox material could be transferred through four generations and could provide protection against challenge by variolation; ‘These experiments afforded me much satisfaction, they proved that the matter in passing from one human subject to another, through five gradations, lost none of its original properties.’ His assertion ‘that the cow-pox protects the human constitution from the infection of smallpox’ laid the foundation for modern vaccinology.

The *Inquiry* was divided into three sections. The first section explored Jenner’s belief that cowpox was originally a disease of the horse. The second section concerned how cowpox infection protected against smallpox. It contained the key observations and case histories supportive of this view. The third section was a lengthy polemic concerning how Jenner’s results related to smallpox.

In the book, Jenner drew some important conclusions: that inoculation with cowpox conferred lifelong protection against smallpox; that this protection could be propagated, via arm-to-arm inoculations, from person to person; and that inoculated cowpox (unlike inoculated smallpox) never induced fatalities, producing only local lesions (not generalized pustular eruptions) and was not itself infectious. However, vaccinations resisted challenge by smallpox, though this was only assessed after a matter of a few weeks. Notwithstanding this final and important caveat, Jenner felt that vaccination was better and safer than variolation.

Parliament gave Jenner grants of £10 000.00 in 1802 and £20 000.00 in 1807. The first figure equates to over £660 000.00 in 2005 money and the second figure to more than £1 173 000.00. In part, these grants were meant to reward and honour the great man, and partly, it has been suggested, it was intended to compensate him for making his findings freely available. These are not insubstantial sums yet Parliament, dominated then, as now, by politicians as ignorant of science and medicine as they are of the dark side of the moon, remained decidedly ambivalent towards Jenner and vaccination. Despite the grants given to Jenner – and the fact that they abolished the practice of variolation by act of Parliament in 1840 in favour of vaccination – when, in 1858, a statue of Jenner (sculpted by noted nineteenth century artist, Calder Marshall) was erected in London’s Trafalgar Square, Parliament took grave exception: ‘Cowpox was a very good thing in its proper place, but it has no place among the naval and military heroes of the country.’ The statue was taken down as a result and relocated to Kensington Gardens.

## Vaccination vindicated

However, as we know, time was to prove Parliament wrong; vaccination owing to Jenner has raised him, in fact if not in public estimation, far above a Marlborough or a Nelson or a Wellington – indeed far above any other national hero, military or otherwise. Nonetheless Jenner was, in his own time, and despite the views of certain parliamentarians, praised and fêted by gentry and aristocracy alike. He became something of a celebrity in Cheltenham, and a celebrated figure across Europe. Inoculation using the Jennerian method became the cornerstone of burgeoning national health programmes. Governments seized upon mass vaccination as a means to trumpet their desire for healthy citizens and demonstrate their forward-thinking attitudes to science and medicine.

In his later years, Jenner, beset by physical ill health and depression, withdrew slowly from public life, spending his final days back in Berkeley. The mounting sorrows of his life had long oppressed him. In 1810, aged 21, Edward, his eldest son, died of tuberculosis. His sister Mary died the same year; his sister Anne 2 years later. In 1815, his wife also died from tuberculosis. In 1820, Jenner suffered a stroke. He survived and continued his medical practice, albeit intermittently. On January 24, 1823, he visited his last patient, a dying friend. The next morning, Jenner did not appear at breakfast; he had died as the result of a massive stroke – or apoplexy, to use the equivalent terminology of the time. Without regaining consciousness, Jenner died on Sunday, January 26, 1823. Jenner was interred on 3 February in Berkeley parish church beside his wife, son and his parents. An epitaph to Jenner reads: ‘His glory shines in every fresh and healthy face . . . his monument is not in one cathedral but in every home.’

Much of the remaining history of vaccination in the nineteenth century – at least until the time of Pasteur and his successors – was to be characterized by the polarization between opposing views: enthusiastic vaccinators on the one hand and passionate antivaccinators on the other. This mirrors a similar dichotomy between variolators and antivariolators seen in the eighteenth century. The potential loss of a highly remunerative monopoly engendered trenchant opposition from practitioners of variolation. Jan Ingen-hausz, himself a noted variolator, wrote in October 1798 refuting Jenner’s theory that naturally acquired cowpox protected against smallpox.

Within 2 years of the publication of Jenner’s main pamphlets, 100 000 people had been vaccinated across Europe, and vaccination had begun in the United States, spearheaded by Harvard professor Benjamin Waterhouse and President Thomas Jefferson. In 1803, King Charles IV sent the Balmis Expedition to the Americas to begin vaccination in Spain’s colonies. Before disembarking on the so-called Royal Expedition of the Vaccine, Francisco Xavier de Balmis rounded up five orphans from Madrid; they acted as an arm-to-arm transfer chain keeping fresh the vaccine until the expedition reached the Americas. Napoleon Bonaparte had the highest regard for Jenner and vaccination. When Jenner wrote to request the release of an imprisoned British officer, Napoleon’s response was: ‘Anything Jenner wants shall be granted. He has been my most faithful servant in the European campaigns.’

Napoleon had all his troops vaccinated in 1805 and all French civilians a year later. By 1810, cowpox vaccine was widely used throughout Europe, the Middle East, the Americas, India, China and Australia.

## Louis Pasteur

The development of vaccinology stalled somewhat after the ground breaking efforts of Jenner and his forebears. Indeed it was almost another century before the development of the next acknowledged vaccine. However, if we relax the constraining eye of hindsight, this interregnum seems hardly surprising. While in the two centuries that intervene between Jenner and ourselves, a potent and appealing dogma has arisen – what Plotkin is wont to call ‘the doctrine of *for each disease, a vaccine*’ – yet to the minds of late eighteenth century scientists such a persuasive and compelling idea was by no means a foregone conclusion. Jenner’s achievement, and the achievement of those who preceded him, helped, or partly pre-empted him, is all the more remarkable because it was achieved without any knowledge of the underlying immunological basis of disease. This was to change significantly, however, as the intervening years unfolded. A prime force in the mediating of this change was the work of Louis Pasteur and Robert Koch.

Louis Pasteur, a legendary polymath amongst legendary polymaths, was without doubt one of the greatest, and certainly among the most celebrated, scientists of the nineteenth century or, indeed, of any other century. He was born on 27 December 1822, the son of a tanner. Pasteur studied chemistry in Paris at the *École Normale Supérieure* and received his Doctorate in Crystallographic studies in 1847. He was appointed to the post of Professor at Strasbourg in 1849. In 1854, he became Professor of Chemistry at Lille and was simultaneously elected a member of the French Academy of Medicine. In 1857, Pasteur returned to Paris as Director of Scientific Studies at the *École Normale* before moving to become Professor of Chemistry at the Sorbonne in 1867. Later, in 1874, he moved back to the *École Normale* as Director of Physiological Chemistry. Despite suffering a stroke aged 46, which partially paralysed his left side, he continued his research. Pasteur’s last years, from 1888 until his death, were spent as Director of the newly founded Institute Pasteur. In 1887, he suffered a second stroke, which affected his speech significantly. He died on 28 September 1895 at Garches, Seine-et-Oise.

In 1856, while living and working in Lille, Pasteur was asked by brewers and wine manufacturers from Northern France to look at ways to extend the lifetime of their products. Thus he began work on the properties of fermentation; this would ultimately lead Pasteur to make major advances in our understanding of what would later become known as germ theory. During the latter half of the nineteenth century, many physicians and scientists were becoming interested in how diseases of humans and animals might be related to micro-organisms. However, it is clearly wrong to attribute all of the major initial steps in microbiology to the triumvirate of Koch, Pasteur and Lister. Nonetheless these three, together with innumerable if

unenumerated colleagues and coworkers, made large and abiding contributions to the fomentation of the discipline, building it into a major science, opening the way to the acceptance of the germ theory and thus to vaccine development, antiseptics and surgical asepsis.

Pasteur's work on how sugars were fermented by yeast into alcohol indicated that this process was mediated by micro-organisms. Since fermentation displayed several similarities to the observed putrefaction seen in wounds, Pasteur came to believe that other specific ferments, or 'germs', were responsible for specific diseases. He conjectured that these invisible 'germs' travelled about in the air and through physical contact, an idea much deprecated and disparaged by his critics. Pasteur's proof that diseases were caused by air-born 'germs' proved to be an epoch-making discovery.

## Vaccination becomes a science

Perhaps the greatest, and for us the most relevant, of Pasteur's many achievements was his pioneering work in vaccinology. He made vaccinology – if not quite into a science in its own right – into something which at least used scientific methods; this is analogous, perhaps, to the way in which linguistics and archaeology, while not quite sciences in themselves, nonetheless make use of scientific techniques to do the things they do. Pasteur thus made vaccinology into something rather more general, complete and useful than it had been previously. He discovered that one could artificially modify, through various means, the intrinsic virulence of an infectious micro-organism. The process produced attenuated or 'weakened' microbes which were capable of inducing subsequent protection against disease. Chickens, for example, treated with attenuated bacteria survived infection by the virulent form, or sheep, vaccinated with attenuated anthrax bacteria, showed protection versus the virulent strain and hence the disease.

Following on from his work on fermentation, and the ideas of germ theory that they engendered, Pasteur began work on disease in general, and human infections in particular, in or around 1877. His initial studies included some on cholera in chickens. In 1880, a piece of stupendous serendipity came his way. An oversight by a technician had resulted in a stock of cholera bacteria being locked away in a cupboard for several weeks during hot summer weather. This culture had not been exposed to light or air during this period. Emile Roux (1853–1933), one of Pasteur's closest confidants, chanced on this sample and was intrigued by the qualities of this aged culture. He had it injected into healthy chickens, which subsequently developed only mild symptoms which passed away quickly. As a control, he then had a new stock of cholera bacteria prepared, which he again had injected in the same tranche of chickens, who survived this second insult unscathed. Fresh, untreated chickens obtained from a local market succumbed rapidly to the virulent cholera bacteria. Roux and Pasteur reached the conclusion that the attenuated culture offered chickens viable protection against cholera.

At this time, the attention of Pasteur and his colleagues was also directed towards anthrax, a zoonotic disease caused by *Bacillus anthracis*, a spore-forming bacterium. Anthrax affects many animal hosts including sheep, cows and humans. It occurs frequently in grazing herbivores, which become infected either by inhaling or ingesting spores from soil. Humans are infected by contact with anthrax-infected animals or animal products. Hence 'wool sorters disease', a common epithet for anthrax.

Pasteur and their colleagues competed hard with Toussaint, a Professor in the Toulouse veterinary school, to be the first to vaccinate against anthrax. Eventually, Toussaint won, being the first to produce a vaccine. However, it proved near to impossible to industrialize. Meanwhile, Louis Pasteur and his team had developed a live attenuated anthrax vaccine for animals. They found that the virulence of anthrax-infected blood was contingent upon oxygen and temperature. Following Koch's work on anthrax spores, Pasteur's group showed that cultures grown at elevated temperatures had lower virulence. These cultures only induced mild symptoms in sheep. Pasteur's anti-anthrax vaccine was demonstrated successfully in a well-publicized experiment conducted at Pouilly-le-Fort on 5 May 1881. Healthy sheep were protected against anthrax by inoculating them with attenuated bacteria. The egregious level of publicity which this demonstration garnered both nationally and internationally helped open up new possibilities in the immunization against infectious diseases.

Pasteur, and his young colleague Thuillier, were asked to help find a method of protection against swine erysipelas, then a problem in southern France. In March 1882, Thuillier discovered the microbe responsible for the disease: the bacterium *Erysipelothrix rhusiopathiae*. It had been discovered, quite independently, by Detmers in Chicago. Pasteur and Thuillier attempted to reduce the virulence of the erysipelas bacterium by passage through pigeons. These experiments actually increased virulence when tested in pigs and pigeons. However, when they passed the bacteria through rabbits, which were marginally susceptible to the disease, they saw increased virulence in rabbits but a decreased virulence in pigs. The resulting vaccine was the first experimental use of repeated passages through weakly or nonsusceptible species to reduce pathogen virulence in its target species.

## Meister, Pasteur, and rabies

Pasteur's most impressive success, and arguably his best known, was his development of antirabies vaccination. What Pasteur actually created was a rabies antitoxin; it worked as an antidote post-infection primarily because the rabies virus possesses such a long incubation period. However, whatever the vaccine actually was, Pasteur and his colleagues were able to attack a well-known and much feared disease – rabies. The significance of the achievement in itself was matched and reflected in the lead it gave to others. Ideas – and scientific ideas especially – naturally permeate and propagate themselves.

Working with Chamberland, Roux and Thuillier, Pasteur became interested in finding a rabies vaccine. Initially, Pasteur had tried to decrease the virulence of the street rabid virus by serial passages through monkeys. This did not work, and Pasteur was obliged to find another approach. He rejected saliva, the commonest medium for transmitting rabies, as it proved wholly inappropriate and inadequate as a source of virus since it was heavily contaminated with infectious bacteria. Instead, Pasteur and his colleagues decided to use nervous tissues originating in the brain or spinal cord of a rabbit. Material was injected into the brain of other rabbits directly after trepanning under ether anaesthesia. In this way, it proved possible to retain a convenient and uncontaminated supply of virus. Several serial passages later, they generated a strain of rabies that had increased virulence in rabbits: death in 8 days rather than 15 in all vaccinated animals.

Pasteur and his group then changed their choice of experimental animals from rabbits to dogs. They also passed the virus from dog to monkey and then from monkey to monkey and found that the resulting virulence was attenuated at each transmission. If the attenuated virus was inoculated back into dogs, rabbits or guinea pigs, it remained attenuated. However, virulence increased at each passage from rabbit to rabbit or guinea pig to guinea pig.

The precise details of the next stage of this process are hazy, but resulted in the attenuation of rabies virus. Pasteur, Roux and colleagues suspended the spines of rabbits killed by the same laboratory strain of rabies in dry air until they obtained material which lacked all virulence. The greater the duration of the drying process the less virulent the resulting virus. After 14 days of air drying, spinal cord material no longer transmitted rabies to other rabbits. They inoculated the dogs with fragments of infected spinal cord, which had been dried for between 1 and 14 days. Each day of drying decreased virulence: on day 1 the virus was fully virulent but by day 14 it had lost all virulence. The result of all this was the ability to fine-tune the virulence or degree of attenuation. Thus, Pasteur and his coworkers had managed to generate an attenuated rabies vaccine, and with it they successfully immunized 50 dogs. At the end of the treatment, the animals were totally resistant to rabid bites or the inoculation of virulent rabies virus, even intracranially.

On Monday 6 July 1885, a shepherd boy from Alsace called Joseph Meister, then aged nine, was brought to see Pasteur. The child had been badly bitten by a rabid dog 2 days earlier. With some reluctance, Pasteur was persuaded by two experienced physicians Drs Vulpian and Grancher of the Académie de Médecine – to vaccinate the child with emulsion from rabies-infected rabbit spinal cord which had been dried in the air for 2 weeks. The child received another 13 inoculations over 10 days. Each inoculation was with progressively more virulent extracts. After 3 months and 3 days, they could announce that the child was in excellent health.

Meister had become the first person publicly to receive the rabies vaccine. On 20 October, Pasteur successfully treated another patient bitten 6 days earlier by a rabid dog. Fortunately, this second case also ended successfully. By 1886, Pasteur and his

colleagues had treated 350 patients from Europe, Russia and America. After these events, and the ensuing publicity, Pasteur's approach to treating rabid animal bites was widely and rapidly adopted. Thousands of vaccinations were made and few of these inoculated individuals died of rabies. Success indeed and, ultimately, the kind of success everyone is interested in.

Many thus view his work on rabies as Pasteur's most significant and remarkable success. With hindsight, it is easy to agree with such arguments. However, it has subsequently emerged that Pasteur's published account of these events – the one we described above – had been subject to significant redrafting. This obscured the fact that Pasteur had violated prevailing ethical standards for human experimentation; these had been established, in part, by Pasteur himself. Despite the polemics, a skill in which Pasteur was to become well versed, the treatment had not been thoroughly tested on animals before being administered to Meister. Pasteur suggested his vaccine had been tested on a 'large number' of dogs. Pasteur's notebooks indicate something else entirely. They show that Meister had been treated using what was, essentially, a newly devised approach previously untested on animals. The dog was very probably rabid but not certainly. Had the veracity of Pasteur's account been greater, or the experiment ultimately less successful, Pasteur would have been embarrassed, perhaps even disgraced. Instead, his heroic status simply grew.

Moreover, in light of the want of ethics that Pasteur hid from the world, not least his patient, there is a rather melancholy postscript to these events. Later in life, Meister served for many years as commissioner of the Pasteur Institute. During the dark days of the Second World War, 55 years after his first vaccination, the Germans then occupying Paris ordered Meister to open Pasteur's crypt. Rather than acquiesce, Meister is said to have taken his own life.

## A Vaccine for every disease

In the years after Pasteur, scientists continued to work assiduously in pursuit of new or improve vaccines against a plethora of contagious diseases: plague, typhus and yellow fever, cholera, and tuberculosis being prominent among them. Others worked with equal diligence to address diseases of cattle, such as foot-and-mouth disease and bovine pleuropneumonia.

The methods they employed were largely of two kinds. The first set of approaches derived from Pasteur. Pasteur's vaccines were developed in the absence of any proper understanding of the immune system or how it works. Moreover, in the case of rabies, he had no direct evidence – other than that provided by its contagious nature – that a micro-organism was actually involved in mediating the disease. Nonetheless, the use of an attenuated micro-organism was the cornerstone of Pasteur's approach to vaccination. He developed four methods which gave rise to attenuated microbes: ageing in the presence of oxygen, which he used to

develop a vaccine for chicken cholera in or about 1880; prolonged cultivation at higher than normal temperatures, used for anthrax in 1881; passage through different host species, used for swine erysipelas (1883); and lastly drying, used for rabies in 1885.

The second set of methods was based on a wholly different concept. In 1886, Smith and Salmon published their work on a dead hog cholera virus vaccine. At that time, virus meant a pathogen agent rather than a microbe based around infective DNA. The experimental model they used was salmonella killed by heat which, when injected into pigeons, protected these animals against an attack from the same virulent bacteria. The idea implicit in this work did not require the use of a weakened but still living – and thus potentially pathogenic – microbial organism. No, it was based on using some nonliving version or component derived from the original pathogenic organism by some kind of fractionation or chemical inactivation. A paper of Roux and Chamberland, in 1887, described the same phenomenon. Pasteur and the growing clique of vaccinologists were greatly interested by these observations, which had opened the door to a new kind of vaccine that might prove easier to produce and also to quantify. Pasteur was to argue that these observations were first obtained in the Pasteur Institute, which was palpably untrue, as the initial publication had come from North America. These nonliving or ‘dead’ vaccines were chosen on the basis that they still possessed the capacity to be recognized by the immune system and gave rise to protection against the disease mediated by the pathogen in question. Thus these vaccines might comprise immune-active dead pathogens, or their products, or their denatured toxins. Killed bacteria were the first to be explored as tools for potential vaccination.

For either approach, several problems presented themselves. The first was to identify the specific pathogen or set of pathogens which gave rise to the disease in question. A clear limitation to vaccine development in the period following Pasteur was the effective and efficient production of microbial pathogens or their components. To an extent this remains true today. While bacteria were easily grown, viruses needed to be produced either in live animals or in eggs. Moreover, certain viruses could not be grown *in vitro*, while protozoan parasites often had intractably complex life cycles involving one or more host organisms.

## In the time of cholera

In the days before bacteriology, diseases spread by contaminated water supplies – cholera, typhoid and paratyphoid fevers and dysentery – were often confused. However, when microbiology had identified their causative agents, science could begin to identify vaccines effective against them. The first palpable success was cholera. Cholera is an acute disease caused by the bacterium *Vibrio cholerae*. Cholera is often mild and without symptoms, yet in severe cases, particularly during epidemics, symptoms include major disturbances of the gastrointestinal tract, including profuse watery diarrhoea. Other symptoms include vomiting, terrible muscle cramps

and rapid loss of body fluids which, in turn, leads to dehydration and shock. Without treatment, death can occur in hours.

Cholera was another of the great infectious diseases of the nineteenth century: four pandemics swept outward across the world from cholera's endemic centre in northern India. The disease had been endemic along India's Coromandel Coast since at least the 1770s, and probably long before. The Ganges basin was the likely initial reservoir. Progressing by land and sea, the disease propagated itself along trade routes into Russia, then into western Europe, and from Europe it crossed the ocean to North America. The exact dates of these several pandemics remain points at issue, although each was clearly distinct from the other. The first major outbreak of cholera in western records is the Indian epidemic of 1781–1783. Five thousand British soldiers travelling through the Ganjam District were struck by the disease; 1143 were hospitalized, several hundred succumbed.

The first of the four major cholera pandemics lasted from 1817 to 1823. It began in the town of Jessore near Calcutta in Bengal and spread with rapidity across India, entering Sri Lanka in December 1818. Eventually, the pandemic reached as far as China in the east and the Caspian Sea in the west, before receding. The second pandemic lasted from around 1829 till about 1851. It reached Europe during 1832. In London, it was the worst outbreak in the city's history, claiming 14 137 lives. In Paris, 20 000 died from a total population of 650 000; 100 000 died in the whole of France. Cholera first reached North America by sea in 1832. It first entered the United States at New York and entered Canada at Quebec. The New York outbreak lasted for 6 weeks with 3000 fatalities. Health records for April through June 1832 were destroyed to hide the fact that Irish immigrants had brought cholera with them. By June, 300–400 cases per day were being reported in Quebec and Montreal, with a mortality rate running at about 50%. Cholera struck New Orleans in late October; the disease propagated itself through the city with staggering celerity. The outbreak lasted less than a month, yet 5000 died.

The third pandemic (1852–1860) affected Russia most severely, causing a million deaths. An outbreak in Chicago during 1854 killed about 5.5% of its population. The fourth pandemic of 1863–1875 mostly affected Europe and Africa. It arrived in North America in 1866, but was much less severe; a final, and rather limited, cholera outbreak occurred in 1873. Because of rapid advances in public health subsequent pandemics had little affect on Europe, North America and other parts of the developed world. However, Russia was still badly compromised by cholera.

Working in London, John Snow demonstrated the waterborne transmission of cholera in 1854. A cholera epidemic had struck the city then claimed 10 738 lives. Snow made a detailed epidemiologic study of the disease and showed that 73 deaths occurred close to the Broad Street pump. He conjectured that sewage was leaking into the well. A quaint, and probably apocryphal, story has since grown up concerning his removal of the handle from the well pump, thus stopping the epidemic. In fact, reality was slightly different and the epidemic decreased slowly in the face of many other factors.

## Haffkine and cholera

Waldemar Mordecai Wolff Haffkine (1860–1930) was born Vladimir Aronovich Chavkin in Odessa, Russia. He was the third of six children born to Aaron and Rosalie Chavkin, part of a family of Jewish merchants. His mother died before his seventh birthday. In 1872, Haffkine entered the *Gymnasium* at Berdyansk before studying Natural Sciences at Novorossiysk University from 1879 to 1883. In 1886, the Odessa Society of Physicians commissioned him to learn about antirabies vaccination in Pasteur's laboratory. When he returned to Russia Haffkine began the first antirabies clinic outside of France. He also studied cholera, anthrax and pneumonia. A sequence of pogroms induced Haffkine to leave for Geneva. In 1889, he joined Mechnikov at the Institut Pasteur, working as assistant librarian. He enrolled in a course on microbiologic technique run by Emile Roux (1853–1933); in 1890 Haffkine became his assistant when Alexandre Yersin sailed away to Indochina as a ship's physician.

In 1891, Prince Damrouy, the King of Thailand's brother, asked Pasteur to find a cure for cholera. Pasteur turned to Haffkine. During the 3 year period from 1889 to 1892, Haffkine approached the problem systematically and was able to protect various laboratory animals against the disease. At that time, it was thought that live vaccines generated greater immunity than killed ones. Thus, Haffkine used two different live vaccines: an attenuated strain grown at 39°C with aeration, and a passaged strain with augmented pathogenicity. He published a brief paper on this in 1892.

Haffkine vaccinated himself and three politically-likeminded fellow émigrés: Georgi Yaveyn, Georgi Tomamshev and Ivan Vilbouchevich. Haffkine experienced malaise, elevated temperature and pain at the site of injection, but had no intestinal problems. Subsequently, all three volunteers were also vaccinated with both vaccines, and had similarly mild reactions. Haffkine reported his initial trial on 30 July 1892. This brought immediate interest, since France was experiencing a cholera epidemic with a death toll of 4542.

News of Haffkine's work on cholera spread rapidly. Lord Dufferin, a former viceroy of India, who was then British ambassador at Paris, wrote to the secretary of state for India asking that Haffkine be allowed to work in what many saw as the 'home' of the disease. Thus, Haffkine arrived in Calcutta in March 1893. Haffkine carried with him a supply of killed vaccine, as this did not require refrigeration or transfer to fresh culture medium. Haffkine began his vaccination campaign in April. After injecting himself and four Indian doctors, he induced some villagers from the Bengal cholera belt to volunteer for vaccination. His plan was to inoculate where cholera was endemic and then analyse vaccinated populations. The British authorities required all vaccinations to be voluntary, ruling out a comparison between protected and unprotected groups. Buoyed by his early successes, Haffkine travelled through northern India. Thus, from 1893 to 1896, Haffkine's vaccines were tested on a large scale through a substantial part of the subcontinent.

The efficacy of Haffkine's vaccine was far from complete, and its success in mass vaccination trials in India was limited. Modern statistical analysis indicates that only some of his trials were properly efficacious. In Calcutta, during 1894–1896, protection was only seen from day 5 to day 416 post-vaccination. Nor was vaccination an effective treatment of those already infected. Haffkine's vaccine was protective but not therapeutic. Cholera vaccines available today still only provide short-term protection. Cholera is treated by replacing lost fluids and electrolytes, and by administering antibiotics.

Haffkine suffering the debilitating effects of both overwork and malaria contracted while in India. In September 1895, Haffkine returned to recuperate back in France. He arrived back in India in February 1896, and resumed anticholera vaccination. By this time, Haffkine had concluded that his first attenuated vaccine was not necessary. Again, he tested this conjecture on himself, vaccinated with three times the typical dose of virulent vaccine. Since it was 2 years since his last anticholera vaccination, he reasoned that any residual immunity against the disease had long since lapsed. From the summer of 1896, only Haffkine's second vaccine was used on humans. However, in August of the same year, Haffkine was obliged to begin investigating a virulent outbreak of plague. The cholera vaccination programme was now to be managed by the Indian Medical Service.

Cholera is now no longer a significant issue in the developed world. Sanitation has always been vital to the control of cholera. This resulted from the treatment – filtration and chlorination – of the water supply, and an improved understanding of the etiology and transmission of the disease. As with many diseases, such as tuberculosis, there is mounting evidence that cholera is becoming resistant to many antibiotics.

## Bubonic plague

During 1894, Haffkine moved to work on a virulent outbreak of plague which was then affecting India. Bubonic plague is a systemic invasive disease, caused by the gram-negative bacterium *Yersinia pestis*. The plague-causing bacterium has a complex life cycle and is transmitted to humans by flea bite, the fleas living in the coats of animals. Indeed, in excess of 200 different species of mammal have been reported to be naturally infected with *Yersinia pestis*. However, of all potential animal reservoirs of the disease, rodents are by far the most important. Indeed other carriers are of little importance in the long-term survival of *Yersinia pestis*, other than as agents spreading plague between different rodent populations.

The plague pandemic probably began in the Chinese province of Yunnan in around 1855. Moving with war traffic spread the disease to the southern Chinese coast, reaching Hong Kong in 1894 and Bombay in 1898. By 1900 the disease had swept across the globe, reaching every inhabited continent. By 1903, the plague was killing a million Indians year; over 12 million inhabitants of the Indian subcontinent may have died of it from 1898 until the end of the First World War. Improvements

to public health, coupled to the introduction of antibiotics and vaccines, greatly mitigated the potential effects of bubonic plague in the nineteenth and twentieth centuries.

At the height of the Hong Kong plague outbreak, during June 1894, Alexandre Yersin and Shibasaburo Kitasato announced, more or less simultaneously, separate isolations of the microbial source of bubonic plague: *Yersinia pestis*. Haffkine was asked to investigate the plague epidemic which swept across India during the summer of 1896. He set up a plague laboratory at Grant Medical College, Bombay, and there he worked on an antiplague vaccine utilizing principles he had used successfully for his successful cholera vaccine. Haffkine quickly realized that protective immunity could be generated using killed rather than attenuated bacteria. By December 1896 a vaccine was ready. Haffkine's successfully immunized rats against plague, publishing his results in 1897. By January 1897 Haffkine felt able to test his vaccine on himself. In the following few months around 60 people – prison inmates and Indian volunteers – were vaccinated successfully. The vaccine gave substantial, though incomplete, protection, and there seemed to be no major side effects. Haffkine now tested his vaccine on a larger scale: over 42 000 were immunized. His results were valuable, yet the protection afforded by Haffkine's vaccine was short-lived – at most lasting a few months. Sceptics questioned the vaccine's utility and plague vaccination in general. Was it feasible, they asked, to vaccinate the whole of India in time to slow the disease?

Indian hostility to plague vaccination deepened considerably after November 1902 when a tragedy struck the Punjab village of Malkowal, where a cohort of 19 (out of 107 vaccinated) developed tetanus post-vaccination and later died. An Indian Government commission reported that the vaccine had been contaminated before reaching Malkowal. The reaction of many was to blame Haffkine and the staff of his laboratory. This incident left Haffkine something of a broken figure. He left India in 1904 under a cloud of suspicion. Subsequently, no firm evidence against Haffkine or his laboratory could be found, and in 1907 he was asked back. Although he did return, he was a most unhappy figure. Haffkine retired in 1914. He returned to Paris, where he lived until 2 years before his death in 1930.

During the 1910–1911 Manchurian outbreak, Wu recognized that the epidemic was the pneumonic form of plague and instituted the use of protective measures against aerosol spread of the disease. The works of Meyer and associates advanced our understanding of vaccine and antibiotic efficacy, animal models and the pathology of the disease. The studies of M. Baltazard provided early descriptions of the role of resistant or silent enzootic reservoirs in the maintenance and epidemic outbreaks of plague.

Bubonic plague, as opposed to the rather rarer pneumonic and septicemic plagues, is the principal form of the disease. The disease is spread by flea bite or exposure of open wounds. Symptoms of the disease include fever, headache, chills and, within 2 to 6 days post-infection, nausea, vomiting and diarrhoea are also common. However, the single most characteristic symptom is the presence of very

tender, swollen and discoloured lymph nodes – the so-called buboes from which the disease is named. *Yersinia pestis* is now beginning to show worrying signs of multiple drug resistance. Both antibiotics and vaccines have been used to prevent *Y. pestis* infections. Two types of plague vaccine are in current use. The live vaccine derives from an attenuated strain; and the killed vaccine comes from a formalin-fixed virulent strain. Another killed vaccine was developed in the early 1940s to immunize American military personnel.

The current vaccine is manufactured from *Yersinia pestis* 195/P and is injected into muscles as a sequence of three prime doses. Two booster shots are given at 6-month intervals, followed by an additional boost every 1 to 2 years. Antibody-mediated protection wanes quickly, necessitating subsequent immunizations. Vaccines are only administered to those at very high risk. Quoted vaccine effectiveness is based on small numbers of confirmed plague cases in individuals vaccinated during the Second World War and the war in Vietnam. The current vaccine shows adverse reactions in many; these are usually mild, but are occasionally severe.

## The changing face of disease

By the end of the nineteenth century, there were five human vaccines that had been developed: three killed bacterial vaccines (cholera, plague and typhoid) and two live attenuated vaccines (smallpox and rabies). We have traced their story above, but as the story of vaccinology enters the twentieth century, it ceases to be a single tale; it is no longer a continuous, unbroken narrative that can be easily followed as if it were a simple, single plotline. Instead, it begins to split into many concurrent stories moving in parallel through succeeding decades.

Though she may not thank me for saying so, my maternal grandmother was born during the First World War. As we all know, in the 90 years or so since that war, an unprecedented series of technical advances has all but remade the world. The cumulative impact of all these individual changes, each with its own dramatic impact on some particular aspect of our daily existence, has been to engender an unmatched paradigm-shift in the way we live. During those same 90 years, the nature of prevalent disease has also changed dramatically. In 1900, the primary causes of human mortality included influenza, enteritis, diarrhoea and pneumonia, which together accounted for over 30% of deaths. Yet cancer and heart disease were only responsible for 12% of deaths. Compare that with the final quarter of the seventeenth century, when average life expectancy was less than 40 years. The principal cause of death was also then infectious disease: smallpox, tuberculosis, malaria, yellow fever and dysentery, which affected adult and children alike. Plagues and pestilence, epidemics and pandemics, ravaged the population contributing greatly to both morbidity and mortality. Disease struck swiftly, without warning, and seemingly at random. Seemingly little had changed in the intervening 150 years. Today, the picture is radically different, with infectious disease accounting for less than

2% of deaths, and chronic disease now accounting for more than 60% of deaths in developed countries.

Patterns of disease have changed over the past 100 years and will change again in the next 100 years. Some of these changes will be predictable, others not. Nonetheless, many diseases, at least in the western world, have been beaten (or seemingly beaten) or at least subdued and kept in check. This is due to many factors which have militated against the severity and spread of disease; these include improvements to the way that life is lived – precautionary hygiene, nutrition, water quality, reduced overcrowding and improved living conditions – as well as more significant, interventional measures, such as quarantining, antibiotic therapy and, of course, vaccines.

Looking back from the early years of the twentyfirst century we can see how the methodological advances in microbiology, biochemistry and immunology, amongst others, have opened the door to a proliferation of disease-targeting vaccines (see Table 1.1). We will now look at five further diseases: typhoid, tuberculosis, polio, diphtheria and whooping cough. Several vaccines were developed before the Second World War, including tuberculosis and the first trials of a whooping cough vaccine in the 1920s. Yellow fever, for example, was isolated initially in 1927, leading to a vaccine against the French strain of the disease in 1932. A vaccine with fewer side effects, which acted against the 17D strain, soon followed. Two killed vaccines against influenza were developed by 1936. A live and longer-lasting vaccine against the disease followed in 1937. Vaccines against typhus and Q fever appeared in 1937, and were heavily used during the Second World War.

## Almroth wright and typhoid

Enteric fevers, or fevers of the intestines, include typhoid and paratyphoid. Typhoid, or typhoid fever, is a serious acute infection which is transmitted through contamination of water or food by urine and faeces; the causative agent is the bacterium *Salmonella typhi*. Typhoid is a disease characterized by prolonged fever, a bright red rash and intestinal inflammation with ulceration. Paratyphoid is a milder form of enteric fever caused by species of *Salmonella* other than *S. typhi*. Typhoid should not be confused with typhus, or typhus fever, which is another serious infection of high mortality caused by *Rickettsia prowazeki* derived from flea bite. During the nineteenth century, typhoid infection proved to be a public health problem of significant proportions in England and elsewhere.

Soon after the agents which caused both typhoid and paratyphoid were discovered by German bacteriologists, a vaccine against typhoid was developed independently, yet almost simultaneously, by Almroth Wright (1861–1947) and by the German researchers Richard Pfeiffer and Wilhelm Kolle in 1896. In 1867 William Budd had reasoned, by analogy to smallpox, that typhoid (which is characterized by a lesion on the lining of the intestine) must be contagious, and that infective material must be present in the lesion and hence excreted with the

**Table 1.1** Introduction of major vaccines\*

Live attenuated	Killed whole organism	Subunit, toxoid or engineered	Carbohydrate or conjugate	Combination
<b>Eighteenth century</b>				
Smallpox (1798)				
<b>Nineteenth century</b>				
Rabies (1885)				
	Typhoid (1896)	Tetanus (1890)		
	Cholera (1896)			
	Plague (1897)			
<b>Twentieth century</b>				
Tuberculosis (BCG) (1927)	Pertussis (1926)	Diphtheria (1923)	Pneumococcus (1977)	DTP-w (1957)
Yellow fever (1932)	Influenza (1936)	Tetanus (1927)	Meningococcal (1980)	DTPV (1961)
Adenovirus (1957)	Typhus (1938)	Staphylococcus Aureus (1976)	H. influenzae b (1988)	DTPIPV (1966)
Polio (OPV) (1958)	European encephalitis (1939)	Hepatitis B (1981)	Meningitis C (1999)	MMR (1971)
Measles (1963)	Japanese encephalitis (1954)	Pertussis toxin (1981)		DTP-wIPVHib (1993)
Mumps (1967)	Polio (IPV) (1955)	Tick-borne encephalitis (1982)		DTPa (1994)
Rubella (1969)	Hantaan B (1989)	Lyme Disease (1998)		DTP-wHB (1996)
Varicella (1984)	Hepatitis A (1991)			DTPaHib (1997)
Zoster (1994)	E coli (1995)			DTPaIPVHib (1997)
Junin Virus (1996)				
Rotavirus (1998)				
Anthrax (1998)				
<b>Twentyfirst century</b>				
		Pertussis (2005)	Pneumococcus (2001)	DTPaHBIPV (2000)
		Human papilloma virus (2006)		DTPaHBIPVHib (2000)
				DTPaIPV (2004)
				Td/IPV (2004)

List, with dates, of the introduction of major vaccines. Dates of primary introduction vary by country. Those stated equate to the USA or UK.  
 \*Partial list, after Plotkin (1999).

intestinal discharge. This speculation led him to demonstrate the waterborne-nature of typhoid.

A prominent figure in Edwardian medicine, Sir Almroth Edward Wright was known for a variety of achievements of varying provenance: his 1911 work on pneumonia in South Africa; for developing vaccines against enteric tuberculosis; for advancing a therapy based on vaccines prepared from bacteria drawn from the patient's own body; and for his advocacy of scientifically-based medicine. Indeed, he sought yet failed to transform the medical establishment so that diagnosis and prognosis were based not on a physician's whims and fancies but on scientifically-sound, scientifically-based laboratory medicine. As medical opinion turned its figurative back on Wright's vaccine therapy, so it also turned away from his vision of what medicine should be.

Wright was convinced that vaccination against typhoid would save thousands of lives, and determined to fight for its adoption. Wright considered that using a live bacterial vaccine against the disease was unsafe and so instead developed one based on using heat-killed *Salmonella typhi*. He was, in a way, fortunate to be working with a vaccine against typhoid fever. Humans are the only reservoir for the typhoid bacteria; it causes no disease in animals and so there was, practically speaking, little real need for animal testing. Nor were animals needed for production. Wright was not so fortunate when testing his vaccine on humans. Initially, he tried it out on himself and several volunteers. In February 1897, he published a short account of his work in the *British Medical Journal*. Wright now sought an extended trial. After a few months a serious typhoid epidemic in Maidstone in Kent provided him with his chance. There was an outbreak among staff at the Kent County Asylum and Wright was called in. He vaccinated 84 of the 200 staff; none caught typhoid, while four of the unvaccinated cohort did succumb.

During the Boer war in South Africa, Wright took the opportunity to trial his vaccine. Two factors conspired against him. First, his inability (and the inability of those around him) to keep adequate records and, secondly, serious problems in maintaining the viability of stored vaccine. Thereafter the army suspended vaccinations against typhoid. Yet, during the Boer War, Wright's typhoid vaccine was used widely with a mortality of over 16% in nonvaccinated individuals versus 8% in the vaccinated cohort. By the outbreak of the First World War, however, typhoid vaccination had been rehabilitated and the practice was adopted widely in the army and among certain civilian populations. Wright persuaded the British army to prepare 10 million doses of vaccine. At the beginning of the First World War, this made Britain the only country to have soldiers with immunity to typhoid and this proved to be the first war where more British soldiers died in combat than from disease.

Within a decade of its discovery there were several different variants of typhoid vaccine in production. The French and the Germans both developed their own. In Britain, Wright's vaccine was the first to receive extensive testing. Pfeiffer and Kolle also showed that one could vaccinate with dead salmonella. The priority of the discovery was a subject of dispute for a long time.

## Tuberculosis, Koch, and Calmette

At the turn of the last century, among the greatest of all killers was tuberculosis. Tuberculosis (or TB from *Tubercle bacillus*) was, and is, a prevalent bacterial infection caused by *Mycobacterium tuberculosis*. The disease can affect many regions of the body, but is found most often (80% of cases) in the lungs, where it is known as ‘pulmonary tuberculosis’; the TB sufferer develops a persistent ‘dry’ cough, weakness and chest pains. TB also affects the central nervous system, as well as the bones, joints and the circulatory, lymphatic and urogenital systems. Like the 300 or so varieties of the common cold, TB is spread between individuals through droplet infection: sneezing, coughing and spitting.

Without doubt TB was, during recent centuries, amongst the most significant global causes of death and disease. As a disease endemic among the urban poor, TB was a major public health issue during the nineteenth and early twentieth centuries. Considering the prevalence, infection rate and fatalities from the disease, such concern was well founded. Twelve years after his identification of the bacterium that gave rise to anthrax, on 24 March 1882, the great Robert Koch (1843–1910) was able to show that the causative agent of TB was a bacterium: *Mycobacterium tuberculosis*; proving unequivocally that tuberculosis was indeed an infectious disease. He showed that *M. tuberculosis* bacteria were present in tubercular lesions of both human and animals. Using bacteria grown using coagulated bovine or ovine serum, Koch was able to inoculate otherwise healthy animals with live TB bacteria and produce typical tuberculosis. Classical staining did not initially reveal the bacteria, however. Success was later achieved using a serendipitous preparation of methylene blue containing added alkali. When treated with Bismarck brown, only the TB colonies stayed blue: the rest of the slide turning brown. Koch received the 1905 Nobel Prize for Medicine for this and, in the process, became arguably the best remembered bacteriologist of them all.

In 1890, Robert Koch announced a glycerine extract of *M. tuberculosis* culture medium – which he later named *tuberculin* – which he thought might act as a vaccine against TB. It is now known that tuberculin actually produces a cell-mediated delayed-hypersensitivity reaction and, indeed, tuberculin proved ineffective. However, subsequently tuberculin became the basis for a useful skin test for the detection of active presymptomatic tuberculosis. In 1891, Albert Calmette (1863–1933), a former pupil of Louis Pasteur, was appointed to be the founding director of the newly-opened Pasteur Institute in Saigon. As part of his work there, Calmette studied Koch’s tuberculin treatment for tuberculosis and soon found it to be ineffective against TB, although he would subsequently investigate its effectiveness against leprosy, but again without positive result.

In 1893, Calmette was forced by a severe bout of dysentery to return to Paris and the Pasteur Institute. The city of Lille established its own Pasteur Institute 2 years later and Calmette was, at Pasteur’s suggestion, offered the post of director. Among other things, Calmette recognized that endemic TB posed perhaps the greatest risk

to Lille's corporate well-being, since the death rate from TB infection was in the region of 300 per 100 000. Calmette decided that his new institute should, at least in part, focus its endeavours on TB. Over a 30-year period, Calmette's quest to treat TB properly became a veritable obsession. He opened an antiTB dispensary in 1901, the first such clinic in continental Europe, and later founded the first public TB hospital in France during 1905.

## Vaccine BCG

As part of his efforts to address the pressing issue of TB, Calmette returned to the search for a vaccine. He realized that he needed to understand the disease better and, in particular, the route of infection. Prompted by the work of the pioneering German bacteriologist Emil von Behring (1854–1917), Calmette investigated whether pulmonary TB could be acquired through intestinal absorption. He was helped in this, and later work, by the veterinarian and vaccine researcher Camille Guérin. Together, they demonstrated that ingestion of virulent *M. bovis* by goats led to serious lymph node infection followed by secondary infection in the lungs. Moreover, they also found that young cattle, after intestinal absorption of the less virulent human *M. tuberculosis*, developed immunity to a subsequent administration of virulent bovine bacteria. This is how, as smallpox variolation so amply demonstrates, the prophylactic power of virulent agents is invariably compromised on safety grounds. Calmette speculated at the time that heat-modified bacteria might be effective for oral vaccination of neonates. Although, in time, this proved a fruitless avenue of investigation, nonetheless he and his coworkers continued their sedulous search for a live antigenic strain of mycobacteria for use as a vaccine against TB.

Calmette's quest was ultimately to bear fruit in the form of the vaccine BCG (Bacille Calmette-Guérin), which consists of a live attenuated strain of *Mycobacterium bovis*. Today BCG is amongst the most widely used vaccines throughout the world. The vaccine was initially used mainly on the continent of Europe, and it was not until 1956, following much work, that its prophylactic effect was accepted and the vaccine became commonly used elsewhere. During its 80 year history, BCG has been given to more than 3 billion people. Even I have had it. BCG is effective for both animals and humans because bovine and human TB bacteria are sufficiently close genetically that they are cross-protective, to use some immunological jargon. BCG is safe because the live bacteria it contains are poorly virulent. It is still not clear why it works, despite rigorous comparisons of the genome sequence of BCG and virulent *M. Bovis*. Or why it works in some parts of the world and not others. Currently, BCG is produced by over 40 separate manufacturers around the world. However, resistance to BCG use is strong in North America, and it is little used there. Despite its limited use there, it can be beneficial in certain high-risk groups and in those communities where the tuberculosis infection rate is high.

In Calmette's time, bacteria were routinely cultured using glycerinated potato. Using this medium, *M. bovis* became tightly clumped and stubbornly difficult to suspend. However, Calmette and Guérin found that the addition of sterile beef bile greatly improved its ability to form a fine suspension. It may have been the Norwegian physician Kristian Feyer Andvord (1855–1934) who suggested that Calmette might be able to produce successively less virulent tuberculosis bacteria on a medium with added ox bile. After a sustained cultivation on media with ox bile, the bacteria had lost the ability to induce disease in cows. Later, an optimal growth medium was formulated. This consisted of potato slides treated with 5% glycerinated beef bile, a highly alkaline medium rich in lipids. Replanted every 21 days, the culture began to change morphology. Although apparent virulence increased in year 1, subsequent years saw it decrease regularly. Calmette and Guérin began a long and exhaustive series of experiments, involving both continuing passage of the bacterial cultures and animal tests, mostly conducted on cattle, of the attenuated protovaccine. Over a period of 13 years, from 1908 to 1921, Guérin and Calmette produced increasingly avirulent subcultures by repeatedly cultivating *M. tuberculosis*.

During the First World War, Lille was occupied by German forces, and this difficult period, which involved Calmette being suspected of spying and his wife being held hostage by the Germans, rather interrupted ongoing efforts to develop a vaccine. After the eventual cessation of hostilities, Calmette became Sub-Director of the Pasteur Institute, yet he stayed in Lille for several months reforming his teams. After returning to Paris, he and Guérin were joined by L. Neagre and A. Boquet. After 231 serial passages, made between 1908 and 1924, the vaccine finally offered the desired protection in animal models. Calmette and his team believed that they had created an attenuated yet immunogenic variant of *M. bovis*. In 1924, the successful vaccination of infants using BCG began.

The original BCG strain was maintained at the Pasteur Institute in Paris by repeated passage. Before this original BCG strain was lost, however, samples were sent to laboratories in dozens of countries around the world, each of which made its own BCG vaccine, which again they maintained by serial passage. Clinical use of BCG vaccines started during the 1920s. Norwegian tuberculosis experts were anxious to test the vaccine. Its use was supported by 1926 trials conducted by Heimbeck among nursing students at Ullevål in Norway. This demonstrated 80% protection in those vaccinated with BCG when compared with those who did not receive the vaccine. By the 1940s several other clinical studies had confirmed the evidence of protection of BCG vaccines, and it took until then for BCG to receive widespread acceptance in other countries.

After the Second World War, tuberculosis rates increased leading many international health organizations to support BCG vaccination. In the 1960s, the WHO developed recommended routine BCG vaccination. BCG was incorporated into the Expanded Programme on Immunizations infant vaccination programme in 1974 and mass vaccination was undertaken in various countries, including Japan, Russia, China, England, France, Canada and several other countries.

## Poliomyelitis

Another great success for vaccination and public health controls has been the near eradication of polio. The words polio, meaning grey, and myelon, meaning marrow and indicating the spinal cord, are of Greek derivation. It is the effect that poliomyelitis virus has on the spinal cord that generates the classic paralysis characteristic of polio. In the past, many odd ideas had flourished concerning the possible cause of the disease. These included bad smells from sewage, flour which had gone mouldy, poisonous caterpillars, infected milk bottles and, of all things, gooseberries. In 1908, however, the polio virus was finally identified by the Austrian immunologist Karl Landsteiner (1868–1943). He produced a primate model of the disease and showed that observed spinal cord lesions matched those seen in human poliomyelitis. He was later awarded a Nobel Prize, but not for his work on poliomyelitis; he received the 1930 Nobel Prize for Medicine for his contribution to the discovery of human blood groups. By 1912, it had become clear that polio was indeed an infectious viral disease with the capacity to give rise to epidemics. After this, polio became a reportable disease. A major advance, for which they were awarded the 1954 Nobel Prize for Medicine, had come when John Enders (1897–1985), Thomas Weller (1915–) and Frederick Robbins (1916–2003) cultured three polio serotypes in non-neural human tissues.

Two vaccines appeared during the 1930s. Both were highly touted yet at best both proved decidedly ineffective. During 1935, Maurice Brodie and William H. Park of the New York Health Department tried to inactivate poliovirus by treating it with formaldehyde. Using this formalin inactivated vaccine 20 primates were treated; this regime was then extended to include 3000 children. However, results did not prove satisfactory and Brodie's vaccine was never deployed again. John Kolmer of Temple University in Philadelphia later attempted to use live attenuated virus, yet this also proved inefficacious. Indeed, it would later be derided as a 'veritable witches' brew', and was suggested to have induced polio many times.

Before 1900, outbreaks of polio had been rare and sporadic. The first European outbreaks occurred in the early nineteenth century and the first in the United States in 1843. For the next 100 years, polio epidemics of increasing severity were reported from the Northern Hemisphere during the summer and autumn. Before the eighteenth century, polioviruses probably circulated widely. Initial infections occurred in early infancy, when acquired maternal immunity was high. Exposure during life probably provided recurrent immunity, while paralytic infections were probably rare. The disease altered in the late nineteenth century from a mild and endemic form to a variety that was new and virulent. The age of patients with primary infection increased along with disease severity and the number of polio deaths. The size and severity of polio epidemics grew continuously through the first half of the twentieth century.

Polio affected advanced, affluent, hygienic countries disproportionately, and during the early to mid-twentieth century the United States suffered significantly. The first significant polio outbreak in the United States occurred during 1916, when

around 7000 people died and 27 000 were paralysed. In all, it affected 26 states, primarily those in the north west of the country. New York was hit especially hard: 2448 died out of about 9000 reported cases, which equates to an incidence of 28.5 cases per 100 000 people. The average, non-epidemic rate was about a quarter of this figure. Almost all cases were in individuals under the age of 16. The 1916 epidemic began in midsummer and continued until late October, when cooler autumnal weather arrived. The American poliomyelitis epidemic of 1931, which was again centred on the north west, killed a total of 4138 out of around 33 918 reported cases. Later, an extended polio epidemic, which lasted from 1943 to 1953, was also visited upon the United States. It proved to be arguably the most severe epidemic of its kind, eventually peaking during 1952 when over 57 000 cases were reported.

Franklin Delano Roosevelt (1882–1945), when aged 39, was paralysed in both legs following an attack of poliomyelitis on 10 August 1921. In 1938, after Roosevelt had become President, he instigated the formation of the National Foundation for Infantile Paralysis (NFIP) under the directorship of Basil O'Connor. O'Connor was a long-term friend and former law partner of the President. The mission of NFIP was to find a cure for polio, and its aims were to support professional education, patient care and polio prevention, and to foment research into the disease. It acted as a fundraising body, with a tenth of its funds being directed at research. In NFIP's heyday, from 1941 to 1955, the foundation was widely seen as a public institution, and it drew its funding mainly from the middle class. It was said that during the early 1950s, NFIP, which was run solely on donations, spent ten times more fighting polio than did the US National Institutes of Health. It was a grass-roots organization, with 3000 local chapters staffed by 90 000 volunteers, supervised by five regional directors. Another 2 million volunteers collected money during the annual January fund drive. NFIP raised \$1.8 million during its first year; this figure rose to almost \$20 million by 1945; by 1954, NFIP was garnering close to \$68 million. During the period 1938 to 1962, NFIP had received a total of \$630 million in donations. Only the American Red Cross raised more. NFIP spent about half its income caring for polio patients and about \$55 million on research into polio. Eventually, of course, with progress in the development of effective polio vaccines, the work of the foundation was rendered obsolete, and during the 1960s it changed its focus to look at birth defects.

## Salk and Sabin

Following the Second World War, during the late 1940s, the incipient World Health Organization created an Expert Committee on polio, which undertook to adumbrate the main areas needed for research into poliovirus and the disease it caused. Attempts to develop a polio vaccine continued. In 1955, Jonas Salk (1914–1995) developed an inactivated poliovirus vaccine and widespread immunization began. Later, in 1960, a live attenuated oral vaccine was developed by Albert Sabin

(1906–1993). Salk and Sabin have been described as scientists both brilliant and ambitious.

Jonas Salk was born a New Yorker and was an outstanding student. He studied at New York University (NYU) Medical School. Salk's mentor at NYU was bacteriologist Thomas Francis, whom he followed later to the University of Michigan. There, Salk spent a year helping to develop inactivated influenza virus vaccines; experience he would use in developing polio vaccine. Later, Salk set up an NFIP-funded laboratory for poliovirus typing in Pittsburgh in 1948.

Albert Bruce Sabin was born to a Jewish family at Bialystok in what is now Poland. Fleeing racial persecution, his family moved in 1921 to Paterson, New Jersey, in the United States. After graduating in 1928, Sabin spent a year furthering his training in London. In 1935, he joined Rockefeller University before moving to the Cincinnati Children's Hospital in 1939, where he worked on viruses, including polio. Sabin worked for the US army during the Second World War, isolating the virus which caused sandfly fever, studying Japanese encephalitis viruses and helping develop a dengue fever vaccine. After the war, he returned to Cincinnati. Sabin showed that poliovirus first invaded the digestive tract and then the nervous system. He was also among those who identified the three types of poliovirus.

Salk and Sabin took divergent paths towards the ultimate development of safe and effective human polio vaccines, and throughout their separate careers, each kept to his own approach to the development of a vaccine. Salk opted for an approach based on using killed virus, akin to the one he had seen used to combat influenza. Persuaded by the apparent efficacy of vaccines for vaccinia and yellow fever, Sabin had become certain that the best hope for an effective vaccine lay in attenuated live viruses, believing they had a greater chance of being both immunogenic and protective. Thus, he began attempts to attenuate the three polio serotypes.

As we have said, America suffered its worst polio epidemic during 1952. Although both Salk and Sabin had received considerable funding from NFIP, the director, Basil O'Connor, concluded that in light of the pressing need for a vaccine Salk's would likely be available sooner. As a consequence, the NFIP backed Salk's work. When the Salk vaccine became available for field trials, having been first studied in small groups of children, Basil O'Connor recruited Thomas Francis to organize and direct it. By 1954, this vaccine had demonstrated its effectiveness against the three poliovirus serotypes.

During the 1954 trials, in excess of 1.8 million children were randomly assigned to vaccinated or nonvaccinated groups. Vaccination decreased the incidence of polio to below 50%, and when a vaccinated child did contract the disease, it was usually nonparalytic. Results of this extraordinary trial were disclosed with much fanfare during a press conference held on 12 April, 1955, 10 years to the day after the death of President Roosevelt. Salk, perhaps rightly, became an overnight global hero, since the trial had demonstrated rates of protection of about 80% with three doses of vaccine. He further endeared himself to the public at large by refusing to patent or to profit directly from his vaccine.

Salk's inactivated poliovirus vaccine (IPV) was licensed immediately and was used widely until the early 1960s. Soon over 4 million children had received IPV. However, as the general acceptance of Salk's vaccine made it almost impossible for Sabin to conduct large trials in the United States, he chose to collaborate with Soviet investigators and vaccinate children in Eastern Europe with oral poliovirus vaccine (OPV). Later, the WHO sent a group to analyse his studies, which brought back a positive report. The effectiveness was demonstrated in field trials (1958 and 1959).

Eventually, it became clear that Sabin's live attenuated oral vaccine was superior in many respects: it was cheaper and more cost-effective; as an oral vaccine it did not require injection and could be delivered by non-expert personnel in both sporadic and mass vaccination contexts; it provided immunity over a much longer time; the list goes on and on. Arguably, however, the most important factor in its favour, at least in terms of the eradication of polio from the developing world, was that it generated mucosal immunity via the intestine, reducing the spread of wild polio.

In 1961, type 1 and 2 monovalent oral poliovirus vaccine (MOPV) became available in the United States followed, in 1962, by type 3 MOPV. In 1963, trivalent OPV began to displace IPV, becoming the prime polio vaccine against polio in the developed world. Polio vaccination had dramatic effects: reported cases fell from 28 000 in 1955 to 15 000 in 1956. In North America, the prevalence of polio dropped by over 90% in the 5 years of IPV, a decline continued by OPV. In 1960, there were 2525 paralytic cases – by 1965, only 61. The last case of paralytic poliomyelitis caused by endemic wild virus was in 1979, due to an outbreak among Midwest Amish communities. An enhanced-potency IPV was licensed in late 1987, becoming available in 1988. During the 1980s and the 1990s, 144 cases of vaccine-associated paralytic polio caused by live OPV were reported. Since 2000, OPV has been replaced in North America by IPV; OPV is no longer available. No case of polio has been reported since 1999.

## Diphtheria

Let us turn to two other pediatric diseases: diphtheria and whooping cough. Diphtheria is an acute, toxin-mediated infection caused by the bacterium *Corynebacterium diphtheriae*. The disease was named by French physician Pierre Bretonneau in 1826 and derives from the Greek word diphthera, meaning leather hide. Diphtheria was once a major paediatric disease. During the 1920s, 100 000 to 200 000 cases were recorded in the United States, with 13 000 to 15 000 deaths. During the 1930s, in England and Wales, diphtheria was among the top three causes of death for children under 15.

An early yet effective treatment was discovered in the 1880s by physician Joseph O'Dwyer (1841–1898); his tubes could be inserted into the infected throat preventing suffocation. In 1888, Roux and Yersin, working in Paris, purified a heat-labile exotoxin in bacterial filtrate. In the 1890s, Emil von Behring developed a

neutralizing antitoxin which, although not killing the bacteria, did mitigate the disease and its effects. Beginning in 1890, von Behring and Kitasato showed that the resistance of animals immunized against diphtheria toxin could be transferred to other animals. This was used immediately to protect against diphtheria in human patients. Von Behring successfully treated the first patient in 1891 in Berlin. However, the first results were not clear-cut because of the quality and quantity of antisera produced in small animals. For this, and his development of a tetanus antitoxin, von Behring was awarded the first ever Nobel Prize in Medicine in 1901.

Beginning in the early 1900s, prophylaxis was attempted using mixtures of toxin and antitoxin. Glenny and Hopkins prepared diphtheria toxins, using them to vaccinate horses and obtain antidiphtheria serum. They found that keeping toxin in a container sterilized by formalin reduced its toxicity but not its immunogenicity. They called the product 'toxoid'. At the same time, Ramon found that the combined action of heat and formalin reproducibly produced antitoxin. These vaccines were much safer but generated a much reduced immune response.

Toxoid, although developed around 1923, did not come into widespread use until the 1930s; combined with tetanus toxoid and pertussis vaccine it became used routinely during the 1940s. However, antibiotics effective against diphtheria were not developed until after the Second World War. In any case, cases of diphtheria had dwindled in number over time, as a result of improving public health measures, reaching around 19 000 cases in 1945. A more rapid decrease began with the widespread use of toxoid in the late 1940s. From 1970 to 1979, 196 cases per year were, on average, reported in the United States. Diphtheria was frequently seen in lower socioeconomic populations including Native Americans. From 1980 to 2000, 53 cases of diphtheria were recorded in North America and only five cases since 2000.

## Whooping cough

Let us now look at another distressing childhood disease. Pertussis, better known as whooping cough, is an acute infection caused by the bacterium *Bordetella pertussis*. Pertussis epidemics were first recorded in the sixteenth century. In the twentieth century, the disease became one of the great childhood scourges causing the death of many children in developed countries. Before the 1940s, over 200 000 cases were reported each year. From 1940 to 1945, over 1 million cases of pertussis were recorded, averaging 175 000 cases annually. After whooping cough vaccine was introduced in the 1940s, incidence of the disease in the United States dropped gradually, reaching 15 000 cases in 1960. By 1970, there were less than 5000 cases, and during the 1980s there were only 2900 cases per year.

Whole-cell pertussis vaccine is a suspension of *Bordetella pertussis* cells inactivated by formalin. Developed in the 1930s, it was in widespread use by the 1940s. Efforts to develop an inactivated pertussis vaccine began soon after the causative bacterium was first cultured in 1906. In 1925, Danish physician Thorvald Madsen

tested a whole-cell vaccine, controlling an epidemic raging in the Faroe Islands. In 1942, Pearl Kendrick combined pertussis vaccine with antitoxin 'toxoids' against tetanus and diphtheria to create the first combined DTP vaccine. Controlled trials of the 1940s indicated that four doses of whole-cell DTP vaccine were between 70% and 90% effective against whooping cough. Protection dropped with time so that protection disappeared 5 to 10 years after the final dose.

The widespread use of pertussis vaccine has decreased incidence of the disease by over 80%; yet during the 1970s and 1980s, whooping cough vaccination proved controversial. In Great Britain, for example, many feared that whole-cell pertussis vaccine induced brain damage, resulting in levels falling below 30%. This was repeated in Japan and Sweden. Reactions to the vaccine include redness, swelling, pain at the injection site, fever and other mild systemic events. More severe reactions, such as convulsions and hypotonic hyporesponsivity, were uncommon; acute encephalopathy was rare.

It was known that the pertussis component of DTP was responsible for most side effects. Experts disagreed as to whether the vaccine caused brain damage, but did agree that if it did so, it did so very rarely. As a consequence of herd immunity, a dramatic rise in the incidence of whooping cough followed drops in the overall population vaccination level. Two outbreaks of whooping cough in the United Kingdom caused more than 30 deaths, and many of the infected children suffered brain injury. Several published studies have shown no causal link between vaccine and brain damage. However, emotive, highly publicized anecdotal evidence of vaccine-induced disability and death engendered an antiDTP movement, similar to the more recent MMR controversy. In the United States, many manufacturers worried by the economics of litigation stopped producing DTP vaccine during the 1980s. The cost of vaccine escalated dramatically leading to a shortage. Only one American manufacturer remained by the end of 1985.

Safety concerns led to purified acellular pertussis vaccines with a lower incidence of side effects. Yugi Sato developed an acellular pertussis vaccine consisting of pertussis toxin and filamentous haemagglutinin, which were secreted into the culture medium by *Bordetella pertussis*. Sato's vaccine was used in Japan from 1981, and was licensed in the United States in 1992, as part of DTaP. However, whooping cough remains a significant health problem for children of the Third World; an estimated 285 000 deaths resulted from the disease in 2001. Although the whole-cell DTP vaccine is not much used in developed countries, the WHO still purchase and distribute it as it is currently cheaper than the acellular alternative.

## Many diseases, many vaccines

As our story moves through the twentieth century it looses, or starts to loose, the romantic veneer which distance in time affords. Now, instead, it takes on the meaner, fragmented, more disagreeable air of the recent past or present. The apparent medical heroism of Jenner and Pasteur gives way to the anonymous activities of the

corporation and the government laboratory. Apart from Sabin, Salk and Hilleman, few vaccine discoverers active in the second half of the twentieth century have gained any prominence or fame. There is no one now to champion and mythologize the modern day vaccinologist. As it progresses towards the present day, the history of vaccinology and vaccination becomes ever more splintered and concurrent. If we are to deal with it, we must quicken our pace. Table 1.1 is, in effect, an overview of the history of vaccine discovery. A number of technical breakthroughs have driven and directed the course of vaccine development since the Second World War. During the 1940s, tissue culture techniques had a huge impact on vaccine development and production. As we have seen, it led directly to the development of polio vaccines. During the 1960s, vaccines against mumps, measles and Japanese encephalitis appeared followed, in the 1970s, by the appearance of those which acted against German measles and chickenpox.

The RA 27/3 vaccine against German measles or rubella is based on a live attenuated virus. The virus was first isolated in 1965 at the Wistar Institute from infected fetal material. The virus was later attenuated by 25 to 30 passages through human diploid fibroblasts. Chickenpox is an acute infection caused by the *Varicella zoster* virus. In the early 1970s, Takahasi first isolated the virus upon which the initial antichickenpox vaccine was based. Subsequent work led to a live attenuated vaccine in Japan. Chickenpox vaccine was licensed for general use in Japan and South Korea in 1988, and introduced for paediatric and adult use in the United States in 1995.

In the 1980s, Merck and GlaxoSmithKline both developed recombinant vaccines for hepatitis B. The first such vaccine was licensed in the United States in 1986, and was the first produced by recombinant DNA technology. A second, similar vaccine was licensed in 1989. Earlier, a hepatitis B vaccine had been licensed in the United States in 1981 but later removed in 1992. It had been produced from HBsAg particles which had been purified from human plasma. Australia antigen, later known as hepatitis B surface antigen (HBsAg), was first described in 1965 and was, in time, expressed in large amounts, forming the immunogen in several effective vaccines. Although the vaccine was safe and effective it was not taken up.

A polysaccharide-based vaccine against *Haemophilus influenzae* Type b was licensed in 1985, but was not effective in the very young. HbPV was used until 1988, but is no longer licensed in the United States. Hepatitis A vaccines were licensed in 1995 and 1996 and provide long-term protection against the disease. Pediatric pertussis subunit vaccines were licensed in 1991 and 1996.

The first efforts to find pneumococcal vaccines began in 1911, but it was only in the late 1960s, that progress was made to develop a polyvalent vaccine. The first such vaccine was licensed in the United States in 1977; it was composed of capsular polysaccharide antigen from 14 different pneumococcal bacteria. In 1983, a 23-valent polysaccharide vaccine (PPV23) was licensed and replaced the 14-valent vaccine, which is no longer produced. PPV23 consists of polysaccharide antigen from 23 pneumococcal bacteria, which cause 88% of human pneumococcal disease. The first conjugate vaccine appeared in 2000.

The first meningococcal polysaccharide vaccine was licensed in America during 1974. The first monovalent (group C) polysaccharide vaccine was licensed in 1974 and the current quadrivalent polysaccharide vaccine in 1978. Meningococcal conjugate vaccine has been licensed in the United Kingdom since 1999 and has been extremely successful in ameliorating type C meningitis. Menactra, a meningococcal conjugate vaccine from Sanofi Pasteur, was licensed in the United States during 2005; while the first pneumococcal conjugate vaccine was licensed in the United States in 2000, and a quadrivalent conjugate vaccine was first licensed in the United States in 2005.

## Smallpox: Endgame

Let us return briefly to where we began: smallpox. Let us remind ourselves through the perusal of a few statistics what a horror smallpox was. At its height, smallpox killed 10% of Swedish children within their first year. In London, more than 3000 died in a single smallpox epidemic in 1746, and during the period of 1760 to 1770, the city lost another 4% of its population to the disease. By the end of the Second World War, smallpox had receded to the point where it had all but disappeared from the developed world. It remained, however, a very significant problem of the Third World. Even as recently as the late 1960s, there were 10–12 million cases in 31 countries, with 2 million deaths annually. Yet, as we know, the disease is, apart from a few hopefully well-guarded stockpiles, a thing of the past. There have been no cases in the last 25 years. It is the only disease to have been eradicated through the use of vaccination. It was realized in the decades after the Second World War that global eradication of the disease was theoretically possible, though many felt it to be an unattainable goal. Nonetheless, in 1958 the World Health Organization (WHO) made smallpox eradication a key objective. At that time, a programme to eradicate malaria was eating up much of the WHO's time and resources; initially, funds committed to work on smallpox was, by comparison, nugatory. In 1967, however, the WHO committed itself wholeheartedly to eliminating smallpox within a decade. A 10 year effort, costing over \$300 million, eventually succeeded in completely eradicating smallpox. The campaign succeeded, in part, by means of a strategy of containment involving surveillance, isolation and vaccination of contacts. The WHO was eventually able to declare smallpox officially eradicated in 1979.

Smallpox is gone – eradicated. To many, eradication – the reduction of incidence to zero followed by the total elimination of the causative pathogen – has become the ideal; a means to greatly reduce, if not eliminate, the economic and human health costs of disease itself. Indeed, the eventual eradication of disease is a tenet consciously or unconsciously implicit within much of vaccinology. However, there may also be both significant short- and long-term consequences of eradication. As we have seen, this has been achieved for only one disease – smallpox; though the eradication of polio remains tantalizingly close. Time – in the form of 25 long years

since the eradication of smallpox – has greatly dulled our collective recollection of this dread disease. It is now only in the pages of textbooks that we can see terrible images of human suffering brought about by this scourge. The aim of many is to see this repeated for scores of diseases across the world and, in many ways, we are now better placed to see this happen than ever before.

As we shall see in Chapter 2, the current landscape within commercial vaccine development is one characterized by optimism rather than pessimism. While the development pipelines of new small molecule drugs of many pharmaceutical companies both large and small are fast running dry, the vaccine arena is rather more buoyant. Moreover, widespread technical breakthroughs in both pure and applied bioscience and medicine make the prospects of developing a whole tranche of new vaccines seem very positive indeed. Many strands – many techniques of great promise – combine to affect this sea change, not the least of which is immunoinformatics and *in silico* vaccinology.

### Further reading

What the story of vaccinology cries out for is a comprehensive yet accessible text able to draw out all the fascination and excitement implicit in the subject. There are no recently published and wholly satisfying examples, yet all the required hallmarks of popularity are to be found there: drama and danger, eccentricity and character, excitement, importance and controversy. In fact, everything you need to sell books. However, many, many books have been written on the subject of smallpox, none better than that by Hopkins (ISBN 0226351688). Lady Mary Wortley-Montagu is a fascinating topic and several biographies have appeared in the last decade. My recommendation is *Lady Mary Wortley Montagu: Comet of the Enlightenment* by Isobel Grundy (ISBN 0198187653). Peard discourses over much of relevance in his book *Vaccination Rediscovered* (ISBN 0955156106). There are few recent, decent biographies of Pasteur and Haffkine, though Almroth Wright is well served by Dunnill's book *The Plato of Praed Street* (ISBN 9781853154775). *Polio: An American Story* by David Oshinsky covers Salk and Sabine in depth.