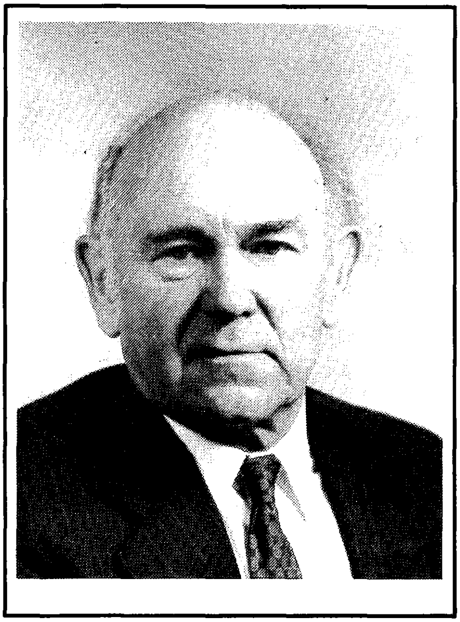


THE EARLY YEARS OF VACCINOLOGY: PROPHYLACTIC IMMUNIZATION IN THE EIGHTEENTH AND NINETEENTH CENTURIES

C. Huygelen

About three centuries ago Europe started experimenting with a procedure that would become one of the most successful chapters in the history of medicine : prophylactic immunization against infectious diseases. The principle was of Asian origin and the Chinese experience with it was recently summarized by Ki-Che Leung (1996); I would like to limit this presentation to the Western world and to the history based on written documents which are accessible to us.

In the eighteenth and nineteenth centuries four important basic approaches were developed in the field of immunization; they can be summarized as follows :

- inoculation of homotypic natural virus : this procedure started in the beginning of the eighteenth century with variolation;
- use of heterotypic natural virus : this was an application of the discovery of vaccinia by Jenner in 1796 (Jenner, 1798);
- artificial attenuation of pathogenic agents : this phenomenon was demonstrated scientifically for the first time by Pasteur with fowl cholera in 1880;
- use of killed antigens starting with the work of Salmon and Smith on Salmonella cholerae suis in 1886 (Salmon & Smith, 1886).

These basic approaches were all known before 1900. The discoveries in the twentieth century were predominantly refinements of these techniques, like the use of toxoids and subunits; virus vaccines enjoyed a significant expansion in the middle of this century as a result of the discovery of new cultivation techniques.

Immunization against infectious diseases is based on two sciences, i.e. microbiology and immunology, both of which were inexistent in the beginning of the eighteenth century; it lasted until the latter part of the nineteenth century before they started developing. The term "virus" had been in common use for a long time, but it referred to undefined poisons. The contagionists saw these poisons as being contagious, but others attributed epidemics to so-called miasmatic phenomena; the discussions between these two opposing groups continued for several decades in the nineteenth century. In his description of the cholera epidemics Rosenberg emphasized that few physicians thought it was a contagious disease, they were of the opinion that the cause had to be sought in atmospheric changes (Silverstein, 1989). Ferguson in England (Wilkinson, 1992) and Clot-Bey (1840), a French plague specialist, working in the Middle-East in the first half of the nineteenth century, denied the contagiousness of plague and wanted to abolish quarantine measures. The Metropolitan Sanitary Commission in London stated in its 1848 report that cholera was not contagious (Winslow, 1943).

On the immunological side knowledge stood if possible, at an even lower level. The most widely accepted concepts were based on the so-called depletion theories : a first invasion by a pathogen was thought to expulse an undefined "principle" from the body, so that on subsequent exposure the same agent could not encounter this principle any more in the body and thus became unable to cause illness. According to Thomas Fuller's depletion theory, all human beings were born with a kind of ovula, which were specific for e.g. smallpox or measles, they had no effect as long as they were not fertilized by a male element (afflatus genitalis) coming from outside; once fertilized and germinated, these ovula disappeared from the body for ever and, on a new exposure, the external male elements fell on sterile ground (Fuller, 1730). The lack of progress in immunology during the nineteenth century is illustrated by the thesis Pasteur developed in 1880 : he thought that the nutrients which microbes needed for their multiplication in the body, were exhausted by a first infection, so that on a second invasion by the same microbes, the latter were unable to find the nutrients required for their multiplication

(Pasteur et al, 1880).

While on the one hand the theoretical knowledge was completely lacking in those days, practical experience gathered over the centuries, had nevertheless taught a few important lessons : it was commonly accepted that one attack of smallpox led to immunity and during a plague epidemic those persons who had recovered from the disease were employed preferentially to take care of the sick. The same practical experience had shown the specificity of the resistance to infections : smallpox protected only against itself and not against other diseases.

In the period before Pasteur the following approaches to immunization were explored :

- inoculation of the causal agent via a non-natural route of infection : this was applied to smallpox, rinderpest, measles, sheeppox and contagious bovine pleuropneumonia;
- the use of heterotypic virus : the only application was vaccinia virus against smallpox;
- attempts to attenuate homotypic virus by serial passage via a non-natural route of infection : this approach was explored in sheep pox.

Smallpox

The first publication on smallpox inoculation appeared as a letter from Constantinople, written in December 1713 by a Greek named Timonis or Timonius who had studied in Oxford. It was addressed to the Royal Society of which Timonis was a member; the letter was published in the Philosophical Transactions of the Society (Timonius, 1714). Timonis reported in the letter that the Circassians had introduced the inoculation method against smallpox in Constantinople about forty years earlier. This novelty had understandably been looked upon with suspicion in the beginning, but had become more popular with time. The inoculation was done through an incision in the skin, mostly of the arm, with material from a smallpox patient. Timonis had had the opportunity to observe about fifty inoculated patients himself, of whom none had died.

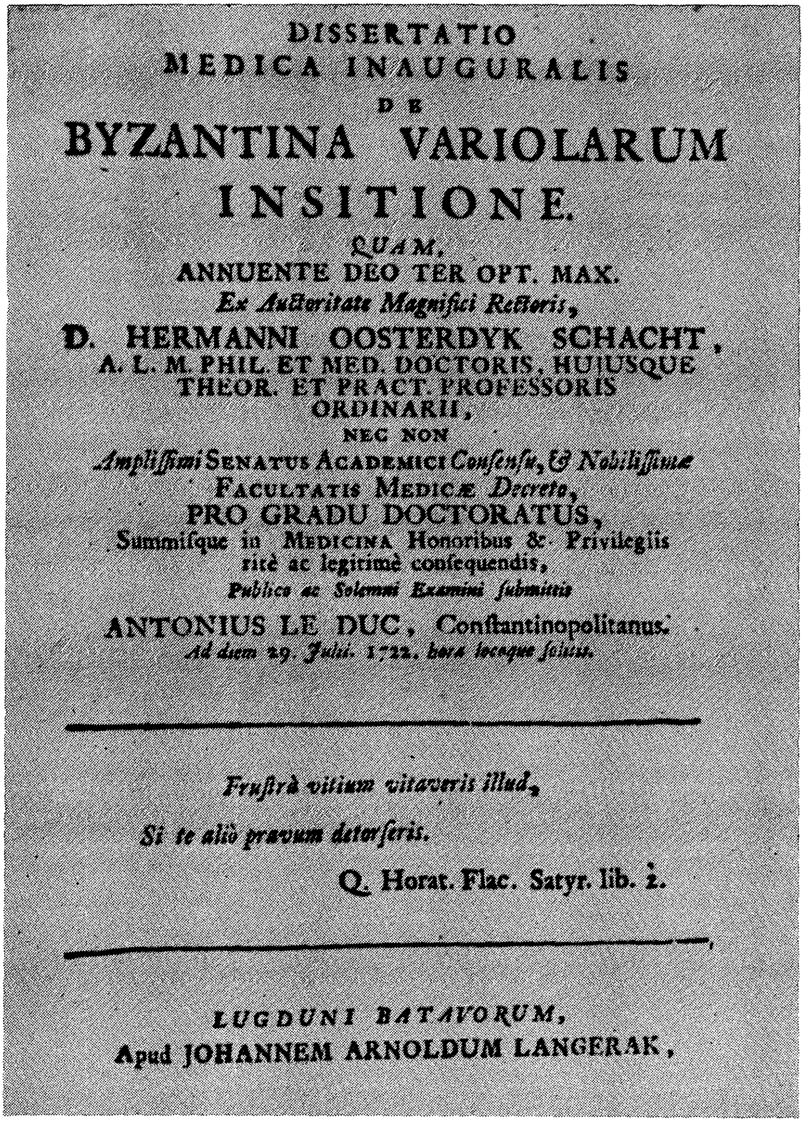
In the same volume of the Philosophical Transactions a letter was published from a Venetian physician, Jacob Pylarini, working in Smyrna. He reported that a Greek friend of his had discussed this novelty with him back in 1701 and wanted his own children to be variolated. A Greek woman explained the procedure to Pylarini, who had the opportunity to follow up the results. He then started to apply it himself in several Greek families in Smyrna and described in detail the symptoms and the course of the illness after inoculation (Pylarinus, 1716).

Around the same time Lady Mary Wortley Montagu was staying in Turkey. She was the wife of the British ambassador and showed a great interest in local habits and events. She used to describe them in her many letters, which were later published in book form (Wortley Montagu, 1800). In a letter from 1717 she reported how an old woman came every year in September to inoculate smallpox with a needle in four or five sites of the body. Each time thousands underwent this operation, apparently without much risk. In the same letter she announced that she wanted her son to be inoculated and that she would like to propagate the procedure in England. She feared, however, that she would not succeed because the physicians would lose a major part of their income and would not collaborate. Smallpox infected almost everybody in those days and the mortality was about 1 in 14, but sometimes it was much higher. Lady Mary, one of the female stars at the English court, had had smallpox herself; it had ruined her beauty and this explained her hatred and contempt for the medical profession. She had her son inoculated on 19 March 1718 (Parish, 1965).

After a trial on six prisoners sentenced to the death penalty and on a group of orphans, the Prince and Princess of Wales also had their children inoculated in April 1722 and, not surprisingly, this royal example did much to propagate the procedure in England (Miller, 1981). In the meantime the first inoculations had also been initiated in the British colonies in America (Kahn, 1963). Compared to the natural disease, the results were generally favourable, but there were also some failures resulting in death of the patients. A bitter struggle started between advocates and opponents of inoculation (Miller, 1957). The mortality after inoculation was 1 in 60 or lower versus a death rate after natural smallpox that varied at the time between 7 and 19 percent.

Meanwhile the procedure had also received attention on the continent. The Greek Antonios Doucas or Le Duc (1722) defended a thesis in Leiden on 29 July 1722 on "de Byzantina variolarum insitione". (Fig. 1) In the beginning the influence of the publications on variolation remained restricted to the small groups of learned men who had contacts with the Royal Society or with similar organisations, open to new scientific discoveries. The masses remained suspicious and this suspicion was kept alive by groups of physicians, theologians and others who were opposed to the novelty for a variety of reasons. On the continent the great debate started several years after that in England. In France de la Condamine and Voltaire became the best known defenders of inoculation. Voltaire had known Lady Montagu during his stay in London between 1726 and 1729 and he shared her enthusiasm (Rowbotham, 1935). All these discussions and publications lifted inoculation out of the sphere of mystery and darkness. Variolation had many imperfections and was attended by relatively high risks but it allowed man to decide rationally for himself whether to take that risk in order to acquire a lifelong immunity against one of the most terrifying diseases. This concept fitted well the thinking of the Enlightenment and enlightened monarchs such as Catherine II of Russia and Joseph II af Austria strongly supported variolation.

Kirkpatrick, Sutton and Dimsdale introduced smaller scarifications and more adequate care for the inoculated in specialized hospitals and made inoculation more popular (Klebs, 1913; Leikind, 1942; Kahn, 1963). According to Miller (1957) this increased popularity was mainly attributable to the activity of more promotionally oriented inoculators like the three mentioned above. Interest in inoculation also went up and down as the risk of epidemics increased or decreased. Mortality post inoculation had been reduced to 1 in 400 or lower and the debate between proponents and opponents evolved in favour of the former. In the Austrian Netherlands intense discussions were held between F.C. Cremers of the University of Louvain as a violent opponent, and P.C. de Brabant from Ghent, member of the Paris medical association, as an advocate of variolation (Cremers, 1778, 1781; de Brabant, 1777, 1778). From the



DISSERTATIO
MEDICA INAUGURALIS
DE
BYZANTINA VARIOLARUM
INSITIONE.
QUAM,
ANNUENTE DEO TER OPT. MAX.
Ex Auctoritate Magnifici Rectoris,
D. HERMANNI OOSTERDYK SCHACHT,
A. L. M. PHIL. ET MED. DOCTORIS, HUJUSQUE
THEOR. ET PRACT. PROFESSORIS
ORDINARII,
NEC NON
Ampliſſimi SENATUS ACADEMICI *Conſenſu, & Nobiliſſimæ*
FACULTATIS MEDICÆ *Decreto,*
PRO GRADU DOCTORATUS,
Summiſque in MEDICINA Honoribus & Privilegiis
ritè ac legitimè conſequendis,
Publico ac Solemni Examini ſubmittit
ANTONIUS LE DUC, Conſtantinopolitanus.
Ad diem 29. Julii. 1722. hora locoque ſolitis.

Fruſtrà vitium vitaveris illud,
Si te aliò pravum detorſeris.
Q. Horat. Flac. Satyr. lib. 2.

LUGDUNI BATAVORUM,
Apud JOHANNEM ARNOLDUM LANGERAK,

Figure 1 : Title page of a thesis by Antonius Le Duc (or Doucas) (Leiden, 1722)

years 1760 onwards began the heyday of variolation, under the influence of Gatti (1764) and others. It would last until Jenner's publication of his results with vaccinia.

The basic principle of variolation rested on the inoculation of infectious material by a route which was different from the natural portal of entry. In natural infection by the respiratory route vital organs such as the lungs were affected in the primary stage and the skin exanthem was secondary. Morbidity and mortality were determined above all by the involvement of the internal organs. In artificial infection through the skin the cutaneous process became the primary one and the pathogenesis was modified so that the illness took a more benign course. This was the generally accepted theory in the eighteenth century, which was confirmed by the results in practice.

Rinderpest

Rinderpest is caused by a morbillivirus closely related to that of measles and canine distemper. The disease has been eradicated in Europe, but in the eighteenth century it caused the death of 200 million cattle and had a catastrophic impact on the rural economy (Scott, 1990). Many contemporary medical opinion leaders had an active involvement in the disease, in part out of scientific interest, in part because their assistance was requested by the governments in several countries. The rinderpest epizootics contributed considerably to the creation of the first veterinary schools in the latter part of the eighteenth century.

Rinderpest was considered to be a kind of pox disease in those days and application of the inoculation principle appeared therefore to be a logical step to combat it. After initial trials in England in 1754, most later inoculations took place in the Netherlands, North-Germany and Denmark. The history of these inoculations is described in more detail elsewhere (Huygelen, 1997 a). The operation consisted of making an incision in the skin and infecting it with nasal or conjunctival discharge of affected animals. (Fig. 2) The most enthusiastic proponents of smallpox inoculation in man, like Pieter Camper in the Netherlands, were

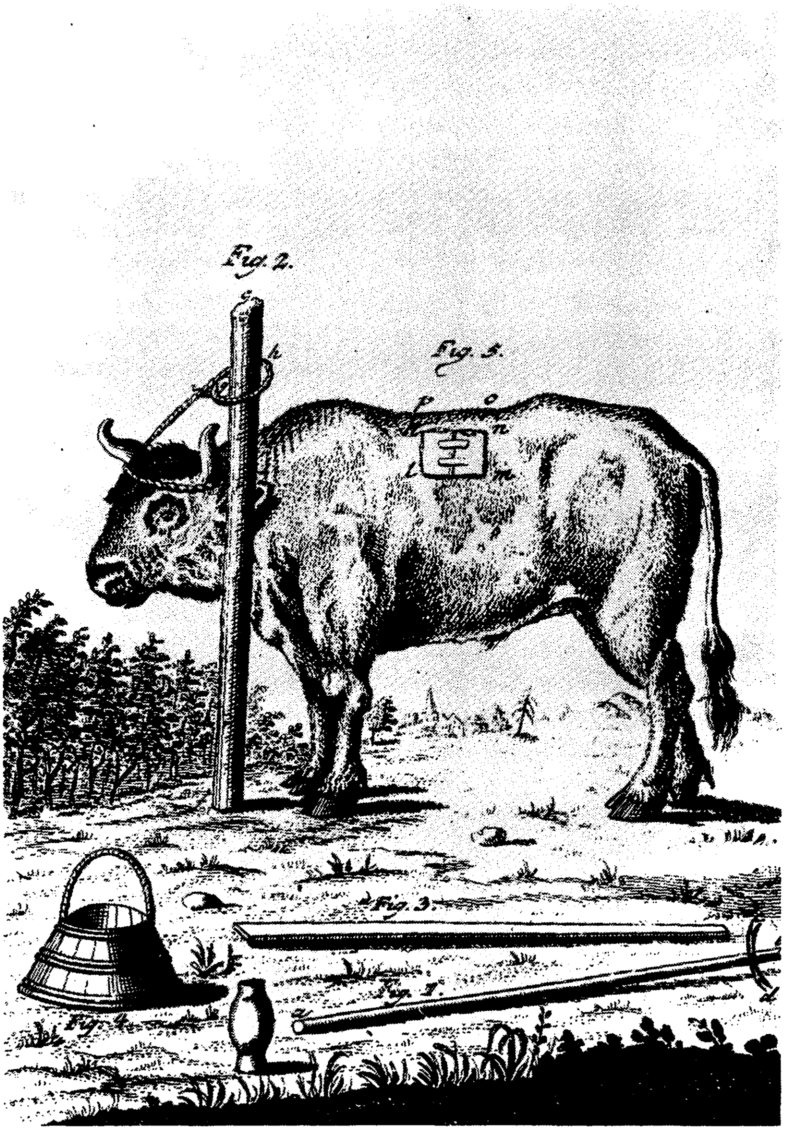


Figure 2 : Inoculation against rinderpest (W. Schumacher : "Die sichersten Mittel wider die Gefahr beym Eintritte der Rindviehseuche, Berlin, 1793)

also those who were most active in the promotion of rinderpest inoculation, at least in the initial stages. Mortality after inoculation turned out to be very high however; attempts to spare the internal organs by producing a primarily cutaneous infection like in smallpox failed. Therefore the interest in the procedure soon declined. Two approaches, however, led to better results and were also of interest from the viewpoint of the history of vaccinology.

In the Netherlands, Geert Reinders, a farmer in the province of Groningen and self-taught man, had observed that calves from cows, which had recovered from the disease, were immune against it. He saw that this phenomenon was not of hereditary origin, since the resistance of the calf was determined only by the status of the dam and not by that of the father. Reinders also noticed that a few months after birth these calves became as susceptible to rinderpest as calves from non-immune cows and that the age at which they became susceptible, varied widely from calf to calf. He then took advantage of this maternally derived resistance to develop an inoculation scheme. The calves were born in the first months of the year and received a first inoculation when they were a few weeks old and were still kept indoors; a second inoculation was given when they had been out in the pastures for some time and, finally, a third inoculation was performed towards the end of the summer, in August-September. By means of this threefold operation Reinders increased the chances of inoculating at a time when the calf had lost enough of its maternal antibody to allow virus replication, but when the antibody titre was still high enough to provide a certain degree of protection against severe illness. This method led to a marked reduction of the mortality post inoculation and was applied with relative success. In 1778 a society was founded which organized the inoculation of calves under strict conditions. The owner paid for the operation and received his animals back from the inoculation stables after recovery. It is noteworthy that the same procedure, i.e. administration of virulent rinderpest virus to calves with maternally derived immunity, was "rediscovered" one and a half centuries later by Doutresoulle (1924) in Africa. The principle was also applied to measles by Herrman (1915) in the United States in infants from immune mothers.

In Mecklenburg in the 1770's milder rinderpest strains were circulating alongside the more virulent ones. These "benign" strains were used to inoculate non-immune cattle and this resulted in a reduction of the mortality after inoculation to ten to fifteen percent, as compared to an average of around fifty percent after inoculation with more virulent strains. Isolated inoculation "institutes" (Impfanstalten) were created in which 15 to 40 animals could be inoculated at the same time through an incision in the skin using nasal discharge from animals with a benign form of rinderpest. The cattle were kept in the stables until they had completely recovered and were then returned to their owners. Towards the end of the 1770's insurance systems were in operation : the owner estimated the value of his calf; if it died after inoculation he received this amount as compensation; if it survived he had to pay half of the estimated value to get his calf back (von Oertzen, 1779).

Towards the end of the eighteenth century rinderpest inoculation was abandoned in Europe. It had become obvious that this approach perpetuated the infection and that epizootics could be better prevented by slaughtering the infected animals and by applying strict sanitary measures. The experience gathered from the rinderpest inoculation trials, however, was interesting in many respects :

- it proved that immunization against smallpox was not a unique phenomenon and that the inoculation procedure could also provide protection against other diseases;
- it was presumably the first time that maternally derived immunity was observed and used to reduce the losses post inoculation; and
- another novelty was the systematic use of naturally attenuated virus strains transferred between cattle in isolated inoculation stables.

Measles

The publication of the first results of rinderpest inoculation lead Weszprémi, a Hungarian physician then living in England, to promote the idea of extending the approach to other diseases like measles and plague (Weszprémi; 1755). Measles was causing the death of about ten percent of all children in those days. The first inoculation trials with measles were done in 1758 by Francis Home (1759) in Edinburgh with encouraging results. During the next two hundred years isolated trials were carried out in several countries, but measles immunization has never received wide acceptance before the 1960's because the results were too unpredictable (Huygelen, 1996 a).

Canine distemper

I have not found any references to immunization attempts against canine distemper in the eighteenth century literature. The interest in the disease increased in the beginning of the nineteenth century and Jenner, the discoverer of "cowpox" inoculation, published a good description of it (Jenner, 1809). Some attempts were made to apply the variolation principle by inoculating nasal discharge from affected dogs into healthy animals but data are scarce. In 1844 Karle, a veterinarian in Besigheim, rubbed the inoculum on the lips and gingival mucosa. He even proposed a trade name for his "vaccine" : Kyonin (Karle, 1844). However, even more so than for measles, inoculation against distemper remained limited to a few small trials. According to Johann Emanuel Keith the disease after inoculation was as severe as in natural infection (Veith, 1831).

The principle of cutaneous inoculation with natural homotypic virus failed to produce acceptable results in the case of rinderpest, measles and distemper. As mentioned above, in poxvirus diseases it was possible to induce a localized cutaneous reaction by inoculation whereby the internal organs were less involved; this was not the case in morbillivirus diseases. For these three diseases the attempts in the late 19th and the first half of the 20th centuries, ran a strikingly parallel course, but reliable live attenuated virus vaccines did not become available before the second half of this century (Huygelen, 1997 b).

Sheep pox

Sheep pox is caused by a capripoxvirus and is by far the post severe kind of pox disease in domestic animals. It shows many points of analogy with smallpox and is also transmitted aerogenically. Mortality varies considerably, but can reach fifty percent. The disease has now been eradicated in most European countries, but in the eighteenth century it was causing great losses in many places; the mortality averaged about 1 in 8. Sheep breeding had become economically more important and Merino sheep had been imported from Spain into the more northern countries in order to improve production. These Merino sheep, however, were more susceptible to pox than the indigenous breeds (Hutyra & Marek, 1909). Because of the analogy between sheeppox and smallpox, application of the inoculation procedure to sheep pox came as a logical step. This approach was recommended in France by Bourgelat in 1765 and in Germany by Erxleben in 1770 (Hurtrel d'Arboval, 1874; Kitt, 1886). Trials were initiated in several places; exudate from pocks, scabs or sometimes blood or nasal discharge were used as inoculum and applied through an incision in the skin of the legs or the ventral side of the tail (Sick, 1803). Later the procedure was made less traumatic by the use of special inoculation needles. (Fig. 3) As was the case in smallpox, the reactions after sheep pox inoculation were much milder than after infection by the natural portal of entry and mortality was about fourty times lower (Müller, 1837). The results remained to some extent unpredictable, however, and sometimes unusually high morbidity and mortality were observed, especially in animals in weak condition for a variety of reasons.

Sheep pox inoculation was used only sparingly in the eighteenth century, but became more widespread in the beginning of the nineteenth century as an indirect result of the growing popularity of Jenner's vaccination in man. In the early years after Jenner's discovery attempts were made to use vaccinia as a vaccine against sheep pox, but these trials inevitably failed because of the lack of cross immunity between the two affections. Thereupon attempts were started to attenuate the sheeppox virus itself by serial transfer from sheep to sheep by skin inoculation. This was done mainly in the countries under the rule of the Austrian monarchy. The early history of these attenuation trials was described in detail by Liebbald (1815) in Hungary. The pioneering work was done by Pessina and by Waldinger, both of them professors at the Veterinary

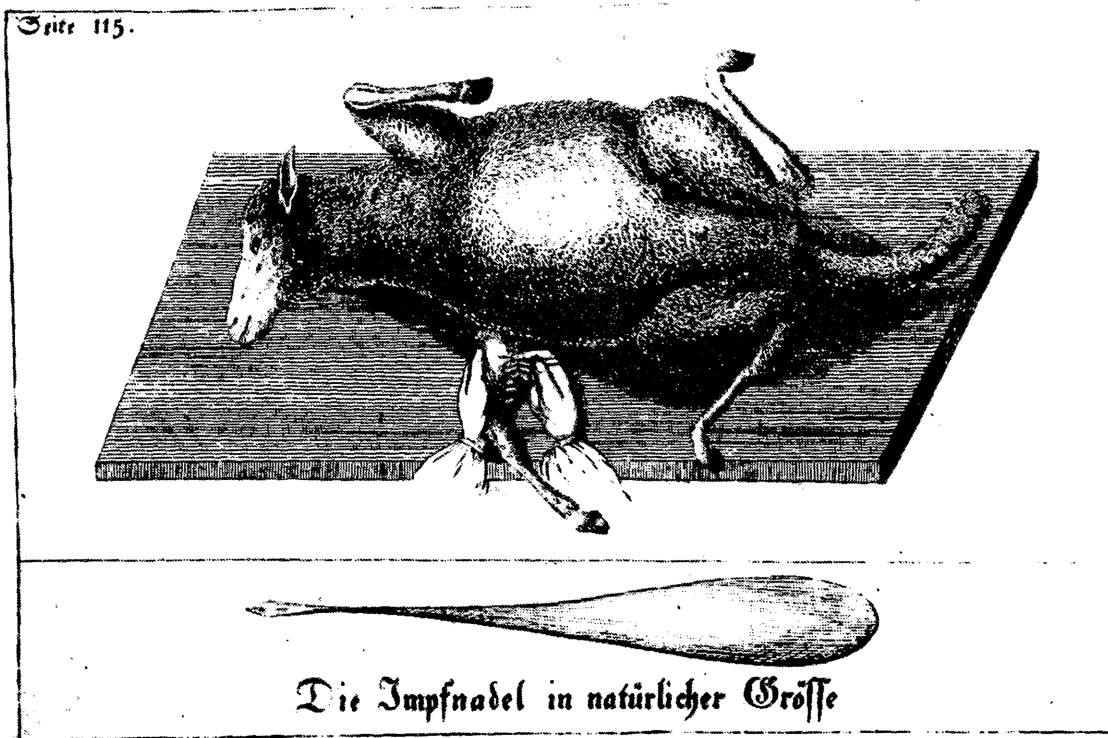


Figure 3 : Inoculation against sheep pox (G.F. Sick : "Ueber die Schafpokken und deren Einimpfung", Berlin, 1803)

Institute in Vienna. Pessina recommended inoculation of material from benign cases of sheep pox to a group of sheep, followed by selection of pocks from the mildest cases in the inoculated group and transfer of this material to the next group of sheep. He advised to continue this serial passage until only one pock would be induced at the inoculation site. In several parts of the Austrian empire pox production was organized in isolated stables which were usually established on large sheep farms. The sheep destined for inoculum production were kept under sanitary surveillance and isolated from other sheep. They also had a special attendant who was not allowed to come into contact with other sheep and they had their own pastures. Every fortnight two or more animals were inoculated with material from a previous passage and the pocks were harvested in the second week, i.e. about seven days after the beginning of the reaction at the inoculation site.

The inoculum obtained by serial transfer from skin to skin, was called "kultivirter Impfstoff". In the beginning of the nineteenth century most inoculators preferred it over the use of material from natural cases. The number of passages was increased systematically with the clear objective of attenuating the virus; in some cases a hundred or more transfers were carried out. This cultivated "vaccine" has been the subject of many years of controversy in the first half of the century (Huygelen, 1996 b). The proponents claimed to find marked differences in reactogenicity between cultivated and natural virus; they also claimed that the virus had lost its contagiousness, so that inoculated sheep could be put in contact with non-inoculated non-immune sheep without risk. The opponents saw no advantage in the use of cultivated material. It is very difficult to reach a conclusion in retrospect, because the literature data from that period were mostly incomplete and the interpretation of the results given by the authors often lacked critical judgement. In addition, the basic knowledge in the field of isolation, aseptic working conditions, sterilisation techniques etc. was not available. It was therefore impossible to isolate sheep destined for the production of the inoculum in such a way that they were adequately protected against infection with natural virus or with virus from a lower passage level. As time went by, more and more critical voices were being heard, also against sheep pox inoculation as such, because it perpetuated the infection in herds by transmission of the virus from inoculated to non-inoculated animals. Consequently the procedure was forbidden in most countries around 1880, except in herds in which the disease had already made its appearance.

From the scientific viewpoint the trials with cultivated inoculum are of great interest, because it was the first attempt to attenuate a virus by systematic serial transfer under artificial conditions. The concept of artificial attenuation thus existed long before Pasteur carried out his pioneering experimental work on the attenuation of bacteria and viruses. Serial passage of viruses under artificial conditions would be used extensively in the twentieth century and most live attenuated vaccines in use today have been developed by this technique.

Plague

As mentioned above Weszprémi had proposed in 1755 to extend the inoculation procedure to measles and plague, but he limited himself to theoretical considerations. Oehme in his thesis in 1771 also defended plague inoculation in areas where the disease was endemic (Oehme, 1771). In the second half of the eighteenth century plague was not a problem any more in Western Europe, but it continued to rage in Russia. Samoilowitz, a physician who had been actively involved in the 1771 epidemic in Moscow, proposed to start inoculating against the disease in 1782. He wanted to perform first a trial in prisoners sentenced to death and described the conditions, under which the experiment should be carried out (Samoilowitz, 1782). He was unable, however, to obtain the required permission from the authorities.

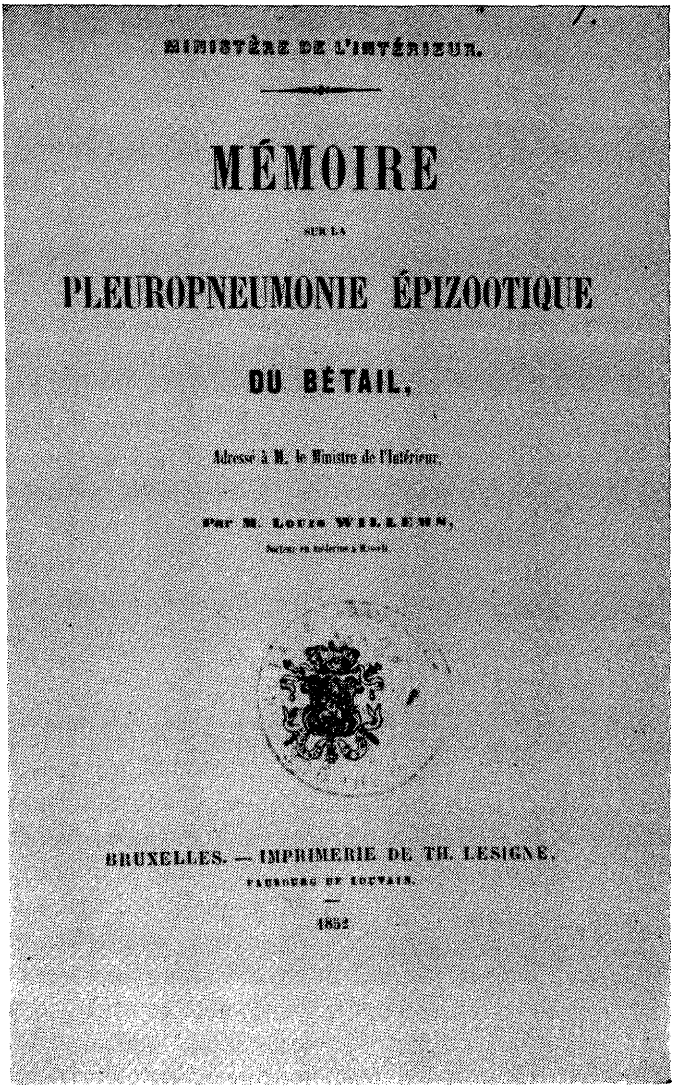
At the start of the nineteenth century several trials were performed in the Middle East where plague was still rampant. The English physician Whyte, inoculated himself and four assistants in 1802 with pus from a bubo; all five died a week later (McGregor, 1804; di Wolmar, 1827). A few other trials had less dramatic consequences, but most of them were inconclusive, because no plague symptoms appeared, probably because no plague bacilli were present in the inocula. Thereupon the interest in plague inoculation disappeared until the discovery of the causal agent at the end of the nineteeth century.

Contagious bovine pleuropneumonia

Contagious bovine pleuropneumonia is a mostly subacute or chronic affection, characterized by extensive oedema of the interlobular and alveolar lung tissues and by a sero-fibrinous pleurisy. It is caused by Mycoplasma mycoides subspecies mycoides, the prototype of the Mycoplasmata, which for many years were known as pleuropneumonia-like organisms or P.P.L.O. The incubation time is usually three to six weeks and epizootics follow a slow course. Cattle who recover, often remain contagious for a very long time.

In our countries the disease has been completely eradicated, but in the past century it caused enormous damage to the cattle population. It was presumably present in the beginning of the eighteenth century in some parts of Central Europe and from there it invaded the rest of Europe. Around the middle of the nineteenth century the whole continent had been contaminated. At the end of the eighteenth century it was still often confused with rinderpest (Semmer, 1889; Leclainche, 1955; von den Driesch, 1989). The struggle against the disease was hampered considerably by the debate between contagionists and non-contagionists. The latter were the advocates of the miasma-theory and did not believe in the contagiousness of pleuropneumonia.

In the middle of the nineteenth century the Limburg physician, Louis Willems, played a pioneer role in the inoculation against pleuropneumonia. Impressed by the severe losses in the cattle population in the region, he decided to attempt inoculation and started his trials in his father's herd. He used serous fluid from the lungs of affected freshly slaughtered animals and inoculated this material at the tip of the tail of healthy cattle. In 1852 he published his results in a report, which he sent to the then Minister of the Interior, Charles Rogier (Willems, 1852). (Fig. 4) His results were very encouraging and the minister appointed a commission consisting of professors, civil servants and practitioners to evaluate the procedure further. The publication also aroused much interest



MINISTÈRE DE L'INTÉRIEUR.

MÉMOIRE

SUR LA

PLEUROPNEUMONIE ÉPIZOOTIQUE

DU BÉTAIL,

Adressé à M. le Ministre de l'Intérieur,

Par M. Louis WILLEMS,

BRUXELLES. — IMPRIMERIE DE TH. LESIGNE,

FAUBOURG DE LOUVAIN.

1852

Figure 4 : Title page of Willems' first publication on inoculation against contagious bovine pleuropneumonia

abroad and in the Netherlands and in France and other countries similar commisions were created. These commissions had an extremely difficult task. The highly critical and negative reports of the Belgian commission led to a heated debate between Willems on the one hand and some commission members on the other hand. On both sides bitter reproaches were used and the medical and agricultural circles in the country were split in two camps, both of them defending their position with the utmost vigour (Rapports, 1858).

What was with hindsight the merit of the inoculation against bovine pleuropneumonia and the pros and cons in terms of reactogenicity, contagiousness and immunogenicity ?

At the inoculation site in the tail a painful swelling developed which was accompanied by fever; these symptoms usually subsided in one or two weeks, but in less favourable cases the swelling increased with suppuration and necrosis. About 7 to 9 % of inoculated animals lost part of their tail. The mortality after inoculation usually ranged between 1 and 3 %. The figures reported in the literature varied strongly from one country to another (Semmer, 1889). This variation was most probably related to the inoculation method used and to the titre and the degree of contamination of the inoculum with other bacteria.

The opponents of inoculation pretended that it did not provide immunity, but this claim was mostly based on the fact that the inoculation had been performed on already infected animals; inoculation had no effect in the incubation period and the animals often developed the disease in the weeks after the inoculation. Later trials in the nineteenth and twentieth centuries have provided overwhelming proof that inoculation induced protection in the large majority of animals, even when they were vaccinated with attenuated cultures of mycoplasma. Inoculation is stil being used in several countries in Africa and, until recently, in Australia (Henning, 1956; Radostits, 1994; Newton, 1992).

The risk of transmission from inoculated to other non-immune animals was relatively small according to most reports, but inoculation was nevertheless seen as a source of perpetuation of the presence of the causal agent in a herd. This aspect has contributed significantly to its the abandonment in Europe later in the nineteenth century.

Vaccinia and the use of a heterotypic virus

On 14 May 1796, now two hundred years ago, Edward Jenner inoculated James Phipps on his arm with pock material from Sarah Nelmes. Sarah had been infected by milking the cow Blossom who had pocks on her teats. (Fig. 5) Although some inoculations with such material had already been performed previously i.a. by Jesty, a local farmer, it was Jenner who approached the phenomenon from a more scientific standpoint. He thus initiated a new era by using a heterotypic virus that had enough in common with the infection against which it was used, to produce immunity and was yet sufficiently different so as not to cause severe illness. This approach has made it possible to eradicate one of the major scourges of mankind : in 1979 the world was officially declared smallpox free. The virus with which this victory was achieved, was vaccinia, but it was usually called cowpox. Vaccinia differs significantly, however, from cowpox. Its origin has never been completely elucidated and several theories have been developed about it; the most likely explanation is that it originated from horse pox, a disease which does not exist any more today (Baxby, 1981). Cowpox itself is probably an infection of rodents, from where the virus occasionally invades other species, like cattle, cats, man, etc. (Baxby, 1977).

The number of heterotypic viruses used as vaccines has remained very limited, because there are very few viruses which are close enough to the causal agent of a disease to be still immunogenic and yet different enough to be apathogenic. The big step forward taken by vaccinology as a result of Jenner's discovery, can therefore be largely attributed to luck. All together only half a dozen such vaccines have been used, almost exclusively in the veterinary field : in fowl pox, Marek's disease, canine distemper and parvovirus infection in dogs.

The Jennerian procedure was introduced extremely fast in many countries in spite of the Napoleonic wars. It lead to a significant expansion of the knowledge in vaccinology in the three quarters of a

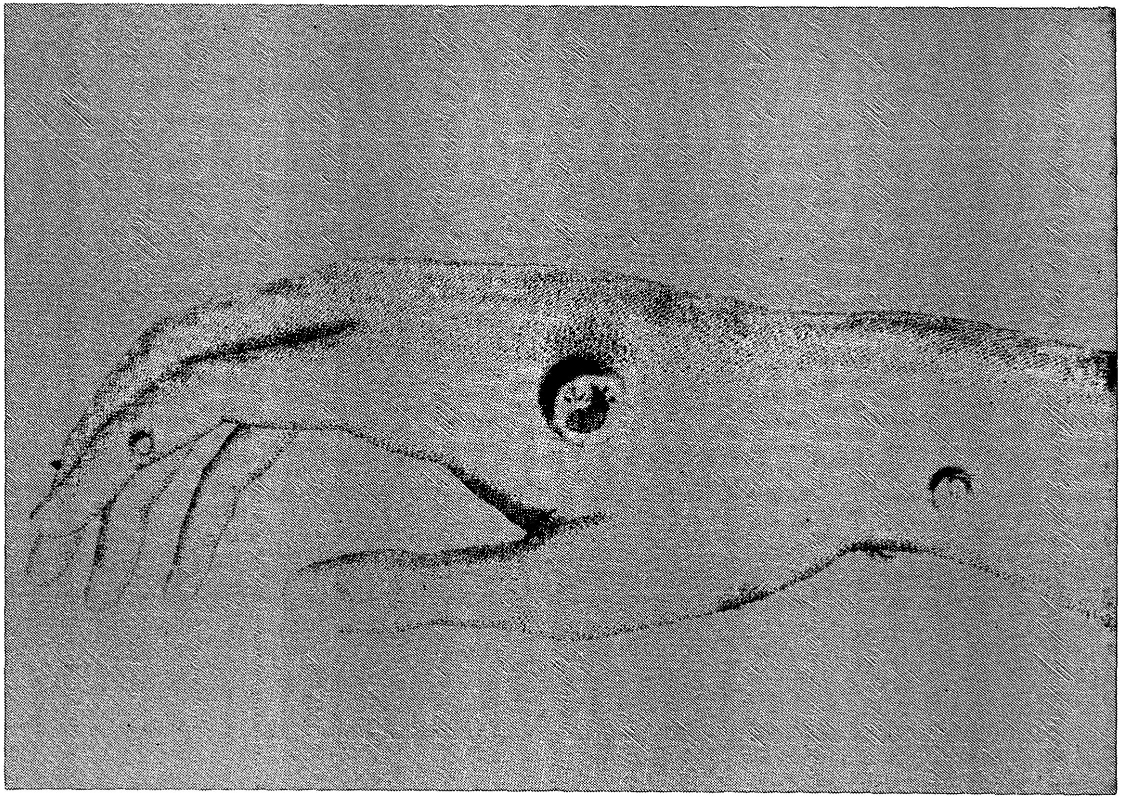


Figure 5 : Pocks on the hand of Sarah Nelmes

century that elapsed between the discoveries of Jenner and Pasteur. A more detailed description of this evolution can be found elsewhere (Huygelen, 1996 c).

For most of the nineteenth century vaccinia, wrongly called cowpox, was inoculated from arm to arm. The reasons for using this method can be summarized as follows :

- the procedure had been applied for several decades for variolation and, hence, was well introduced;
- many had an irrational fear of "bestialisation" as a result of inoculating substances of animal origin; this fear was kept alive and stimulated by the antivaccinists and by some caricaturists; (Fig. 6)
- genuine cowpox (or vaccinia) was rare in most countries and could therefore not be used as a direct source of vaccine; furthermore it was very difficult to differentiate between genuine cowpox (or vaccinia) and the many other lesions which were found on the bovine udder and which were called spurious cowpox in the nineteenth century. Today they are known to be caused by pseudocowpox, bovine papular stomatitis, herpes mammilitis, papillomatosis, bacterial infections or even insect bites;
- the reactions were less severe than after inoculation with material obtained directly from the cow; two factors may have been responsible for this phenomenon: genuine cowpox is more reactogenic in man than vaccinia (Baxby, 1994); the second reason was presumably that material from the cow was more heavily contaminated with bacteria;
- several investigators experienced difficulties when they tried to inoculate cows with material that had been passed for a long time from man to man;
- storage and transportation problems were avoided by using inoculated children for transportation of the virus; for intercontinental shipments a few dozen children were put on a ship and each week some of them were inoculated;
- the risk of transmitting human pathogens by the arm-to-arm procedure was strongly underestimated.

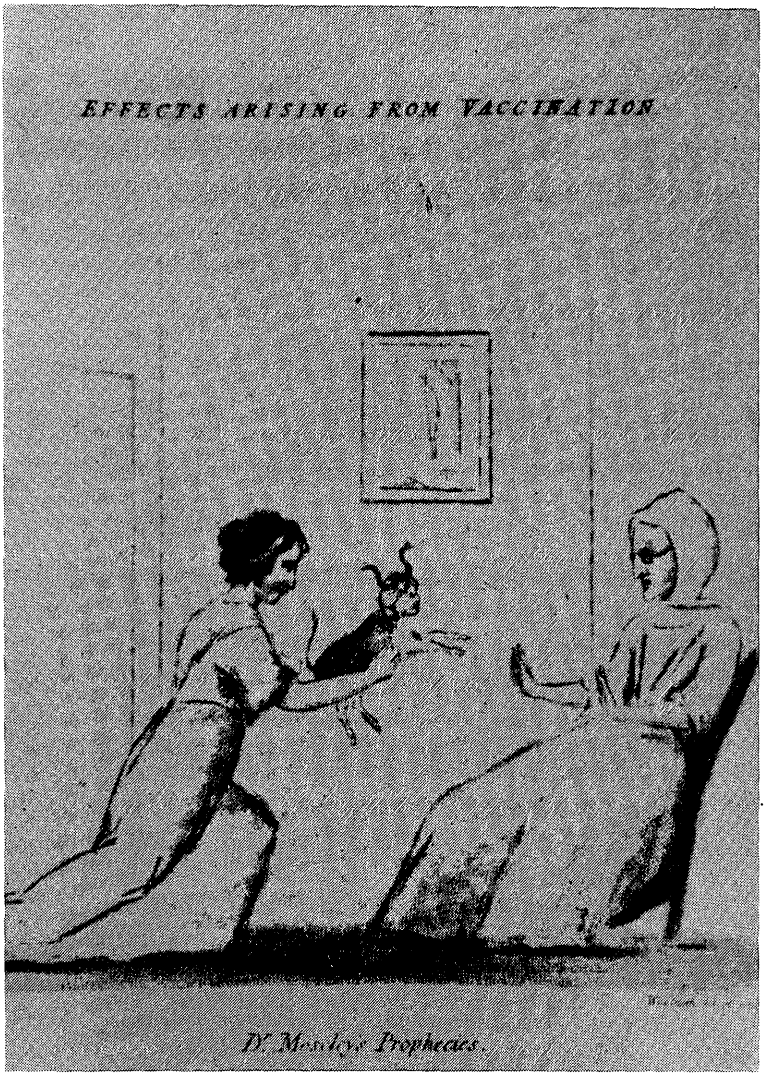


Figure 6 : "Effects arising from vaccination" From a caricature, 1806

What were the main lessons drawn from the widespread use of smallpox vaccination during the first three quarters of the nineteenth century ?

Contamination of the vaccine

In the beginning of the century most vaccinators believed that two different diseases could not be present at the same time in the same organism. This theory had been propagated by John Hunter (1788). This assumption was one of the main reasons why so little attention was being paid to the possible risk of the vaccine becoming contaminated with other agents. The most striking examples of such contaminations in the nineteenth century were those with smallpox, syphilis, hepatitis and with several bacterial agents.

Contamination with smallpox occurred in the very beginning of the vaccination era, because the vaccination was often carried out in smallpox hospitals. The problem was soon identified and resolved. Syphilis contaminations were reported in several countries from 1814 onwards and they led to animated debates which lasted for several decades. The available reports were critically reviewed by Viennois (1860), who reached the conclusion that syphilis could indeed be transmitted by vaccination when the person from whom the vaccine was taken was syphilitic. His conclusion was not accepted by many opinion leaders on the theoretical grounds mentioned above. In the end so many concrete proofs were gathered of syphilis transmission, that the arm-to-arm method was gradually replaced by vaccine production on the skin of calves. Our country played an important role in this switch under the influence of Warlomont (1875). Before the end of the century the arm-to-arm method was forbidden in most countries. Overall, the known cases of secundary infections remained relatively rare, but were used extensively by the antivaccinists as a propaganda weapon to create fear among the population. The risk of transmitting syphilis, hepatitis and other specific human infections disappeared after the switch to bovine vaccine, but this was not so for bacterial infections such as those caused by staphylococci and streptococci.

Immunity failures

Another problem identified in the early period of vaccination, was that of the duration of the immunity. It would also lead to long and heated discussions. Jenner himself and other pioneers of vaccination believed that the administration of vaccinia would provide the same lifelong immunity as that observed after variolation. This thinking was supported by the depletion theories which were widely accepted in those days. As we know today, immunity after vaccinia administration lasts only five years on average.

Immunity breakdowns were already observed from 1805 onwards, but they became more frequent as time advanced and the interval between vaccination and infection increased. They created enormous confusion among the general population and the medical community. This confusion was further aggravated by the atypical nature of the smallpox symptoms in those who had previously been vaccinated: the incubation time and the course of the disease were shorter, there was a lower tendency to confluence of the pocks and a much reduced mortality; this atypical smallpox was called varioloid. Many different explanations were put forward :

- in the beginning many blamed faulty vaccination due to the use of "spurious cowpox" or an inoculum harvested too late;
- many others attributed the symptoms to varicella;
- some saw varioloid as a new disease completely different from smallpox;
- another widespread opinion was that vaccinia had been overattenuated by the repeated arm-to-arm transfers and had lost its immunogenicity;
- finally, but much too late, the most obvious explanation was accepted, i.e. that the resistance to smallpox provided by vaccination was limited in time; it took several decades before this explanation was generally accepted.

Depending on the explanation given to the immunity breakdowns, several different solutions were proposed:

- some advocated resuming variolation or a combination of vaccination followed by variolation;
- many thought that the solution was to be found in going back to fresh "cowpox" and in several countries active searches were organized for pocks on the udder of cows; in some countries potential finders were promised a financial reward;
- many others were in favour of the so-called regeneration of vaccinia by making a few transfers in bovines
- only after tens of years of debate was revaccination adopted as the most appropriate means to avoid varioloid. Germany started much earlier with revaccination than e.g. France and the consequences were enormous : during the French-Prussian war of 1870-71 the Prussian army which was revaccinated every seven years counted only 316 deaths by smallpox as compared to 23,400 in the badly vaccinated French forces.

Conclusions

The inventory of the knowledge in the field of "vaccinology" at the time Pasteur initiated his vaccine trials, can be summarized as follows :

- a human subject or an animal that has gone through an attack of a disease, is, generally speaking, resistant against a reinfection by the same agent;
- this resistance is specific for a given disease;
- this resistance can be provided as well by a mild form of the disease as by a severe attack;
- administration of an agent through a non-natural portal of entry, results in some diseases in a relatively benign reaction and produces nevertheless a strong immunity; this approach was applied succesfully to pox diseases and to bovine pleuropneumonia, but it largely failed in morbillivirus diseases like measles and rinderpest;
- in some cases a heterotypic virus can also provide immunity;
- immunity can be lifelong or, as in vaccinia, restricted in time;
- immunity can be transferred from a mother to her offspring and this phenomenon is not attributable to hereditary factors; this maternally

derived immunity disappears after some time and its duration varies strongly from one individual to another;
- the concept of virus attenuation by serial transfers under artificial conditions was known but there is no experimental evidence that it was ever proven in practice;
- an adventitious agent can contaminate a vaccine and be transferred simultaneously with the immunizing agent;

In conclusion a significant amount of experience had been accumulated at the time when microbiology made its first steps and when the theoretical knowledge in the immunological field was still inexistent. The experience in active immunization was based above all on observation, experience and pragmatism. The traditional dogmas and theories of the eighteenth and nineteenth centuries e.g. those about miasmata, depletion, "unicity" of infectious agents, etc. have often been a hindrance rather than a help in the development of vaccinology.

References

Baxby D., (1977). Is cowpox misnamed ? Brit. Med. J., *i*, 1379.

Baxby D., (1981). Jenner's smallpox vaccine. The riddle of the origin of vaccinia virus. Heineman, London.

Baxby D., Bennett M. & Getty B. (1994). Human cowpox 1969-93 : a review based on 54 cases. Brit. J. Dermatol., *131* : 598-607.

Brabant P.C.J. de, (1777). Antwoorde op het gerucht van wedergekomene pokken naar de inentinge. J. Begyn, Gend.

Brabant P.C.J. de, (1788): Ad Expert. D. Ferdinandum Henricum Cremers epistola. J. Begyn, Gandavi.

Clot-Bey A.B., (1840). De la peste observée en Egypte. Recherches et considérations sur cette maladie. Fortin, Masson, Paris.

Cremers F.H., (1778). Ostentationes excusationesque inoculatorum super varioles simul cum velsianis refutatae. Van Overbeke, Lovanii.

Cremers F.H., (1781). Epitome seu additamentum ad ostentationes, excusationesque inoculatorum. Van Overbeke, Lovanii.

Doutresoulle, (1924). Rapport sur la recherche d'une méthode d'immunisation active des veaux non sevrés, provenant de mères réfractaires à la peste bovine. Rec. Méd. vét., *100*: 464-468.

Driesch A. von den, (1989). Geschichte der Tiermedizin. Callwey, München.

Fuller T., (1730). Exanthematologia: or, an attempt to give a rational account of eruptive fevers, London. (quoted by Silverstein).

Gatti, (1764). Réflexions sur les préjugés qui s'opposent aux progrès et à la perfection de l'inoculation. Musier, Bruxelles.

Henning M.W., (1956). Animal diseases in South Africa. Central News Agency, South Africa.

Herrman C., (1915). Immunization against measles. Arch. Pediatr., 32, 503-507.

Home F., (1759). Medical facts and experiments. Millar, London.

Huygelen C., (1996 a). The long prehistory of modern measles vaccination. In: Vaccinia, Vaccination and Vaccinology: Jenner, Pasteur and their successors. (S. Plotkin, B. Fantini, eds). Elsevier, Paris, 257-263.

Huygelen C., (1996 b). The concept of virus attenuation in the eighteenth and early nineteenth centuries. Biologicals (in the press).

Huygelen C., (1996 c). Jenners koepokentstof in het licht van de moderne vaccinologie. Verhand. Kon. Acad. Geneesk. Belg. (in the press).

Huygelen C., (1997 a). Immunization against rinderpest in eighteenth century Europe. Med. Hist. (in the press).

Huygelen C., (1997 b). De vroege geschiedenis van de immunisatie tegen drie morbillivirusziekten: mazelen, runderpest en hondenziekte. Argos, (in the press).

Hunter J., (1788). A treatise on the venereal disease 2nd ed., London.

Hurtrel d'Arboval L.M.J., (1874). Dictionnaire de médecine, de chirurgie et d'hygiène vétérinaires. (revu par A. Zundel). Baillière, Paris.

Hutyra F. & Marek J., (1909). Spezielle Pathologie und Therapie der Haustiere. Fischer, Jena.

Jenner E., (1798). 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 the cowpox. London.

Jenner E., (1809). Observations on the distemper in dogs. Medico-chirurg. Trans., 1, 263-268.

Jurin J., (1722). A letter from the learned Dr. Caleb Cotelworth, containing a comparison between the danger of the natural smallpox, and that given by inoculation. Philos. Trans., 22,213.

Kahn C., (1963). History of smallpox and its prevention. Amer. J. Dis. Childr., 106, 597-609.

Karle, (1844). Ueber Impfung der Hundeseuche oder Staupe. Magaz. f. die gesammte Thierheilk., 10, 450-451.

Ki-Che Leung A., (1996). Variolation and vaccination in late imperial China.: in: Vaccinia, Vaccination, Vaccinology (S. Plotkin & B. Fantini, eds) Elsevier, Paris, 65-71).

Kitt Th., (1886). Wert und Unwert der Schutzimpfungen gegen Tierseuchen. P. Parey. Berlin.

Klebs A.C., (1913). The historic evolution of variolation. Bull. Johns Hopkins Hosp., 24, 69-83.

Leclainche E., (1955). Histoire illustrée de la médecine vétérinaire. A. Michel, Paris.

Le Duc A., (1722). Dissertatio medica inauguralis de Byzantina variolarum insitione. J.A. Langerak, Lugduni Batavorum.

Leikind M.C., (1942). Variolation in Europe and America. Ciba Symposia, 3, 1090-1101.

Liebbald J., (1815). Ueber die zweckgemässeste Methode die Schafe von den Blattern zu sichern und die allmählige Tilgung dieser Krankheitsform zu bewirken. Keszthely.

McGregor J. (1804). Medical sketches of the expedition to Egypt from India. J. Murray, London.

Mammerickx M., (1967). Histoire de la médecine vétérinaire belge. Mémoire de l'Acad. roy. Méd. Belg. IIe sér. in 8°, 5: 267-708.

Miller G., (1957). The adoption of inoculation of smallpox in England and France. Univ. Pennsyl. Press, Philadelphia.

Miller G., (1981). Putting Lady Mary in her place: a discussion of historical causation. Bull. Hist. Med., 55, 2-16.

Müller F., (1837). Ueber die Schaafpockenimpfung. In : Preisschriften über die Schaafpockenimpfung. Königliche märkisch-ökonomische Gesellschaft zu Potsdam. Horvath, Potsdam.

Nettleton, (1722). Part of a letter from Dr. Nettleton to Dr. Jurin R.S. Secr. Concerning the inoculation of the smallpox and the mortality of that distemper in the natural way. Philos. Trans., 22, 209.

Newton L.G., (1992). Contagious bovine pleuropneumonia in Australia: some historic highlights from entry to eradication. Austral. vet. J., 69, 306-317.

Oehme J.F.A., (1771). Dissertatio inauguralis medica de peste in qua simul questio movetur, an pestis inoculatio sub certis conditionibus rationi sit consentanea. Nonnius, Erfordiae.

Oertzen C. von, (1779). Oeffentliche Bekanntmachung der nunmehr sattsam erprobten und in Mecklenburg allgemein gewordenen Inoculation der Rindviehseuche. C.W. Meyn, Hamburg.

Parish H.J., (1965). A history of immunization. Edinburgh & London.

Pasteur L., Chamberland C. & Roux E., (1880). C.R. Acad. Sci., 90, 239, quoted by Silverstein (1989).

Pasteur L., (1880). De l'atténuation du virus du choléra des poules. C.R. Acad. Sci., 91: 673-680.

Pylarinus J., (1716). Nova et tuta variolas excitandi per transplantationem methodus, nuper inventa et in usum tracta. Philos. Trans, 29, 393-399.

Radostits O.M., Blood D.C. and Gay C.C., (1994). Veterinary Medicine, Baillière Tindall, London.

Rapports et documents officiels relatifs à l'inoculation de la pleuropneumonie exsudative d'après le procédé de M. le Docteur Willems (5e Rapport de la Commission instituée près du Ministère de l'Intérieur), (1858). Lesigne, Bruxelles.

Rowbotham A.H., (1935). The "philosophers" and the propaganda for inoculation of smallpox in eighteenth-century France. Univ. Calif. Publ. modern Philology, 18,265-290.

Salmon D.E. & Smith T., (1886). On a new method of producing immunity from contagious diseases. Amer.Vet. Rev., 10: 63-69.

Samoïlowitz D., (1782). Mémoire sur l'inoculation de la peste, avec la description de trois poudres fumigatives antipestilentielles. Lorenz & Schouler, Strasbourg.

Semmer, (1889). Lungenseuche, in: A. Koch. Encyclopädie der gesammten Thierheilkunde und Thierzucht. Moritz, Wien/Leipzig.

Sick G.F., (1803). Ueber die Schafpocken und deren Einimpfung. Dieterici, Berlin.

Silverstein A.M., (1989). A history of immunology. Acad. Press., San Diego.

Scott G.R., (1990). Rinderpest virus in: Virus infections of ruminants (Z. Dinter and B. Morein, Editors), Elsevier, Amsterdam.

Timonius E., (1714). An account, or history, of the procuring of the smallpox by incision, or inoculation, as it has for some time been practised at Constantinople. Philos. Trans., 29, 72-82.

Veith J.E., (1831). Handbuch der Veterinärkunde. 3. Aufl., Strauss, Wien.

Viennois A., (1860). De la transmission de la syphilis par la vaccination. Arch. gén. Méd., 5e sér., 15i, 641-671; 15ii, 32-48 en 15 ii, 297-323.

Warlomont, (1875). Institut Vaccinal de l'Etat à Bruxelles (Vaccination animale). Extrait du Compte-Rendu du Congrès périodique international des Sciences médicales, 4e session, Bruxelles.

Weszprémi S., (1755). Tentamen de inoculanda peste. Tuach, Londini.

Wilkinson L. (1992). Animals and disease. An introduction to the history of comparative medicine. Cambridge University Press, Cambridge.

Willems L., (1852). Mémoire sur la pleuropneumonia épizootique du bétail. Th. Lesigne,Bruxelles.

Winslow C.E.A., (1943). The conquest of epidemic disease. Princeton Univ. Pr., 1943. Reprinted by Univ. of Wisconsin Press, Madison, 1980.

Wolmar E. di, (1827). Abhandlung über die Pest. Voss, Berlin.

Wortley Montagu Mary (1800). Letters written during her travels in Europe, Asia and Africa. Didot, Paris.