

The birth of virology

Marian C. Horzinek

Head, Virology Unit, Dept. Inf. Dis. & Immunol. Director, Institute of Veterinary Research, Veterinary Faculty, Utrecht University, Yalelaan 1, de Uithof, 3584 CL Utrecht, The Netherlands

*Si quis sit ea immanitatae naturae ut congressus
haminum fugit atque oderit, tamen id pati non
poterit ut non anquirat aliquem apud quem
evomat virus acerbitatis suae*

Introduction

This quote is from Cicero's 'De Amicitia' (23, 87) — I happen to remember it from my days at school, and it comes in conveniently to start a talk on the birth of virology, my occupation since three decades. In Cicero's quote it is said of an intransigent person that she '...still cannot be without somebody where to spit out the venom of one's own bitterness' (Horzinek 1995). Throughout antiquity 'virus' was a common, general term to designate anything unpleasant and dangerous, from snake and scorpion poison to disease agents, viscous fluids from plants and animals, semen, the salty taste of sea water, even bad odour or stench (Klotz 1857). The word probably originated in Sanskrit and is related to German 'Wiesel', English 'weasel', French 'vison', all names for an animal that — as mustellids do — sprays a strong smelling fluid from its peri-anal glands when threatened.

In this Centennial's programme it will be my task to illustrate the role Martinus Willem Beijerinck has played in defining the nature of a group of novel disease agents, of 'contagia', as he used to call them. He thereby indeed gave birth to a new discipline. Virology keeps attracting young scientists, with World Congresses of some 2000 participants every 3 years and an estimated tenfold number working in academia, in hospitals, diagnostic laboratories, in industry. Virology has played a pivotal role in addressing public health issues, in solving animal and plant production problems and in the biological sciences in general. Of the Nobel Prizes between 1950 and 1980 in physiology/medicine, 13 were awarded to virologists, and several more to scientists that used viruses as tools (Table 1).

Consequently, virology should occupy quite a prominent position in microbiological thinking, and it does world-wide. However, in paraphrasing the biblical 'A prophet is not without honour, save in his own country' (New Testament; St. Matthew Chapter 13, Verse 57) - concerning the hero we celebrate today it should read: '..., not even in his own country'. Beijerinck's importance for virology was barely mentioned by the 'NRC Handelsblad', a leading Dutch newspaper which ran a 1 $\frac{1}{2}$ page article on him (November 30, 1995) at the occasion of this Centennial. Our Calvinist heritage still shows. I have the privilege of compensating for this omission.

Any centenary is welcomed as an opportunity to look back and celebrate. With respect to virology, the ambiguity of this approach becomes obvious when reviewing recent and not-so-recent commemorations:

- in 1982 a two-day symposium '100 Years of Virology in Wageningen' was organized in honour of Adolf Mayer's first publication on the transmissibility of tobacco mosaic disease;
- in 1992 a meeting in St.Petersburg celebrated 100 years after Dmitri Ivanovsky had published his results of the filterability of the agent causing tobacco mosaic;
- the present Beijerinck Centennial highlights 100 years of the Delft School of Microbiology and its lasting influence on the study of microbial biochemistry, biodiversity and biotechnology;
- for 1998 plans are being developed to honour Friedrich Löffler and Paul Frosch with a symposium on the Baltic Sea island Riems for their work on the etiology of foot-and-mouth disease, and finally

Table 1. Nobel Prizes in Physiology or Medicine connected with virology

| | | |
|------|----------------------------|--------------------------------------------|
| 1951 | Theiler | yellow fever discoveries |
| 1954 | Enders, Weller, Robbins | growth of poliovirus in cell culture |
| 1966 | Huggins/Rous | virus as a cause of sarcoma |
| 1969 | Delbrück, Hershey, Luria | viruses & viral diseases |
| 1975 | Dulbecco, Temin, Baltimore | tumour viruses, reverse transcription |
| 1976 | Blumberg, Gajdusek | hepatitis, kuru |
| 1978 | Nathans, Smith, Arber | restriction endonucleases (bacteriophages) |
| 1993 | Roberts, Sharp | gene splicing (adenovirus) |

* the Virology Division of the International Union of Microbiological Societies is considering a similar event in the same year.

However, as Dmitri K. Lvov proclaimed in his opening statement to the St. Petersburg meeting (Lvov 1993), ‘...the birth of virology occurred neither in a day nor in a year...’. In the following account therefore I shall rather try to capture the atmosphere around the turn of the century, to emphasize the relative merits of the personalities involved, but also to look at the period of pregnancy preceding the happy parturition, the birth of virology.

Prehistory of virology

Let us therefore start some 300 years earlier. In 1576, Carolus Clusius (Charles de l'Ecluse, born in Arras 1526, died in Leiden 1606), Professor of Botany at Leiden University, the Netherlands, published a booklet entitled *Rariorum aliquot stirpium per Hispanias observatorium Historia* (The history of strange stripes observed in Spain). He described conspicuous colour changes on the petals of tulips - white streaks and flame patterns — which immensely increased their appeal to buyers. The popularity of these varieties is not only reflected by the punctilious plant portraits in still lives of Flemish and Dutch painters from the beginning of the 17th century, but also by commercial documents: for one bulb of the ‘Viceroy’ tulip a price equivalent to US\$ 30.000 was payed in Holland. The ‘bulb madness’ had reached its climax around 1635 when the trade finally collapsed. As early as 1637, Dutch tulip growers knew that the desired stripe pattern could be transferred to the petals of monochrome tulips by grafting bulbs to those of the streaked variety. Some 250 years later it was shown that the ‘breaking’ of tulip

petals is caused by a virus infection. Using advanced techniques in phytopathology, the infection has been controlled, and presently available tulip bulbs are virus-free — the flame patterns today having a genetic rather than an infectious origin. The detailed grafting instructions published in 1675 by Blagrave are probably the first publication of an infection experiment in virology.

We find more elements of estheticism in early microbiology, and it may be more than chance that its cradle stands in this country. The visual arts have culminated in the Netherlands of the Golden Age, with painters reaching global fame that none of our composers, architects or poets has ever matched. Microbiology owes much to this Dutch passion for the visible, I think, of which the invisible is just the coin’s other face. A monumental figure in the exploration of the microcosmos is Antoni van Leeuwenhoek, born in 1632 in the same city of Delft that domiciled Beijerinck some 200 years later. Antoni had no university education and still became a Fellow of the Royal Society in London (1680), a peer to contemporary scientists and famous already during life. Using his self-made microscopes, he examined microorganisms and tissue samples and gave the first descriptions of bacteria, protozoa and spermatozoa. His burial monument can be found in Delft’s Old Church, and its custodian assured me that it is visited almost weekly by some scientist. Beijerinck was a great admirer of his countryman and found out about his priority in cultivating and observing anaerobic bacteria - on October 9, 1676 (Beijerinck 1913).

While Leeuwenhoek has become a household name, so to speak, in microbiology, another figure in the virology, immunology, vaccinology triangle has been almost completely forgotten. Only three months ago, however, during his veterinary immunology inaugural lecture in Utrecht, Prof. Willem van Eden drew the audience’s attention to another self-taught Dutchman, a miller and farmer, whose observations and

relentless vaccination efforts were focused on a highly lethal disease of cattle, rinderpest. His name was Geert Reinders (1737–1815). After the 1768 epidemic he concluded

- that cattle which had experienced the natural illness were protected from disease after another infection,
- that the same was true for animals with only light symptoms e.g. after vaccination, and
- that the mode of inoculation and supportive therapy had no influence on the outcome of infection. He also discovered what we today would call ‘maternal immunity’, transferred from an immune cow to its calf through colostral antibodies.

Geert Reinders published his observations in 1776 — Edward Jenner’s variola-vaccinia protection experiments appeared 22 years later. It cannot be excluded that Jenner knew about these results (Eden 1995), but the citation ethics apparently were poor even then.

The beginnings of plant and animal virology

The history of plant virology starts one generation after Reinders’ death, in 1876, when Adolf Mayer (1843–1942), an agricultural chemist from Heidelberg University, Germany, was appointed Director of the Agricultural Experimental Station in Wageningen. One of his study objects in the Netherlands was a disease of the tobacco plant that affected its leaves: they showed an irregular pattern of dark and light green patches. As a man with a classical education Mayer was probably reminded of Pompeian mosaics when he proposed the name ‘mosaic disease’ in 1886. He showed that the condition was infectious by performing a key experiment: he triturated diseased leaves with water, aspirated the green suspension into thin glass capillaries and used these to inject minute quantities of the sap into the veins of healthy tobacco plants; after some time, 9 out of the 10 inoculated plants had developed the same mosaic. The importance of these experiments was not overlooked. A cartoon from 1904 shows Adolf Mayer as Dr. Faust from Goethe’s drama with the evil Mephistopheles peeking over his shoulder; Mayer/Faust holds a bottle in which a homunculus can be discerned. The cartoonist, Louis Raemaekers, then arts teacher at the Wageningen Agricultural School wanted to express the potential danger of meddling with phenomena at the threshold of life (Bos 1995a). Not much has changed in the public’s attitude in this respect.

During this period no attempts were made to elucidate the character of the infectious principle. Again the

disease symptoms were described in terms emphasizing their visual appeal — break, flame, streak, mosaic. Euphemisms are only left when man himself falls victim to an infectious disease — its sinister quality is then also reflected verbally. But the use of the term ‘virus’ for agents of killer diseases in animals and man certainly does not suffice to identify the first scientists that had a conception of its uniqueness. The microbiologists at the turn of the century seem to have been largely unaware of the fact that these uncultivable agents might be very different from the bacteria causing anthrax, tuberculosis and diphtheria, although Pasteur, working in the 1880’s on rabies, did conceive of the agent as being an ‘micro-organism infinitesimally small’ (Pasteur et al. 1884). As so often in the history of science, the availability of a new method heralded the beginning of a new era. In the case in point, filtration - once it had been introduced by Ivanovsky and interpreted by Beijerinck - was quickly adopted to show the uniqueness of the agents of foot-and-mouth disease, rabbit myxomatosis, African horse sickness and fowl plague in the years between 1898 and 1901. Actually the filters were first used in bacteriology, e.g. by Edwin Klebs, who indicated that the cause of anthrax is a non-filterable bacterium: the filtrate would not produce the disease (1871). The earliest industrial and consumer application of filter candles compacted of porous diatomite (Kieselguhr) came from Germany, the ‘Berckefeld filters’ named after the owner of mines near Hanover, Lower Saxony. Their widespread use started in 1884 after a paper entitled ‘A filter permitting to obtain physiologically pure water’ had been published by Charles Chamberland, a trusted collaborator of Pasteur (Chamberland 1884).

In 1898, Friedrich Löffler and Paul Frosch in Germany published a report on foot-and-mouth disease of cattle with the observation that its causative agent would pass through such a bacteriological filter. Löffler was already famous for his discovery of the etiology of diphtheria, Frosch — a former assistant of Robert Koch — was Professor of Bacteriology at the Berlin Veterinary School. Together they expressed the opinions of a commission that had been established to investigate the possibility of vaccinating against foot-and-mouth disease (Löffler & Frosch 1897). In these articles the authors speculate about the nature of the agent and write ‘...either 1. an unusually effective toxin was dissolved in the lymph or 2. the filtrate contained a previously undiscovered disease agent so small as to pass through the pores of a filter capable of retaining the smallest known bacteria. If it were a soluble poison

it must have been amazingly active. An amount of filtrate corresponding to 1/30 cc of lymph, could, in two days, produce disease in calves weighing 200 kg.' The authors calculated the highest effective dilution of the infectious material and came up with a figure of 1:3,750,000 for the 'toxin' of foot-and-mouth disease; and they continue '...therefore one cannot exclude the possibility that the activity of the lymph is due to an agent that can multiply... The smallest known bacterium is Pfeiffer's influenza bacillus which is 0.5 to 1.0 microns in length. If the hypothetical agent of foot-and-mouth disease was 1/10 or even 1/5 this size, it would be beyond the resolving power of our microscopes, even with the best immersion systems. This simple consideration would explain our failure to demonstrate the agent in the lymph under the microscope'. We know today that their estimate was only one order of magnitude off the mark — foot-and-mouth disease virus has a diameter of 30nm.

Already in 1890 Robert Koch had deplored the fact that a number of infectious diseases was still etiologically undefined; it was at the occasion of the 10th International Congress of Medicine in Berlin that he proclaimed '... I tend to believe that the diseases mentioned (he referred to influenza, pertussis, trachoma, yellow fever, rinderpest, pleuropneumonia) are not caused by bacteria but by structured disease agents that belong to quite different groups of micro-organisms'.

This statement was not far from the mark. It was the method of passing infectious material through bacteria-retaining filters that the 'quite different group of micro-organisms' has been identified and referred to as filterable viruses for a long time.

The optimistic atmosphere at the turn of the century, the enthusiasm about discovering more — perhaps even all — human and animal pathogens is reflected in the minutes of the 7th International Veterinary Congress, Baden-Baden, 7–12 August 1899. It was held under the protectorate of His Royal Highness the Grand-Duke Frederick of Baden, and this is how the protocol reads for Tuesday, August 8th (original translation):

'...The microscopical examination of coloured and not coloured preparations, the various methods of cultures did not permit us to discover the virus in the fluid, where it ought to have been found, namely, in the contents of the aphthae.'

However, an entirely new and very interesting fact could be established. In order to see, whether the contents of the aphthous vesicles, when filtered and attenuated with water, would grant immunity, they were

passed through filters, which would with certainty hold back the most minute micro-organisms, for instance the bacilli of influenza. Still, the germ of aphthous fever did pass. In this way we were able to obtain a pure virus and to obviate any accidents that might arise from the presence of other organisms in the fluid that we used'.

The contagium vivum fluidum

Thus the discovery of a new kingdom of infectious agents was in the air around the fin de siècle, and the conceptual quantum leap was taken by Martinus Willem Beijerinck. He will always be remembered by virologists for his role in their discipline, but Beijerinck was a towering figure in general microbiology, as this Centennial attests. But what kind of a person was he?

In his youth, Beijerinck had been an awkward boy with a keen interest in botany. He began his studies in chemistry at the Delft Polytechnical School where he met Jacobus Hendricus van 't Hoff (1852–1911), the pioneer of stereochemistry who won the first Nobel Prize in chemistry (1901) for his work in chemical dynamics. The two boys supplemented their laboratory training with experiments performed on their own. After having received a doctorate in 1877 and a few years of teaching and research in botany, Beijerinck accepted the position of microbiologist at the Nederlandsche Gist en Spiritus Fabriek in Delft and was appointed Professor at his *alma mater* in 1895. With his two equally unmarried sisters he moved into quarters built for him (next to his laboratory) where he lived until his retirement in 1921. He died ten years later, disgruntled, isolated and surrounded by plants — having chosen in the last years of his life to go back to his first love, botany. (Lechevalier & Solotorovski 1965).

Beijerinck has been described as a difficult person to get along with, subject to attacks of depression. Although working on alcoholic fermentation he was strictly against its consumption; when being presented with a barrel of beer by his students at a celebration he reportedly had it dumped into a nearby creek. And a 'workaholic' he certainly was. He thought that a scientist should not marry, and he frowned upon any sign of friendship between students of opposite sex.

In 1898, Beijerinck, unaware of Ivanovsky's contribution to the cause of tobacco mosaic disease published six year earlier (Ivanovsky 1892) arrived at his definition of the *contagium vivum fluidum*, the living, liquid agent of infection. The qualification *fluidum* was meant to indicate a difference from bacteria to which Beijer-

inck alluded as the *contagium fixum* — which should be interpreted in the contemporary context. It was not appreciated at that time that proteins, although clearly soluble, might nevertheless have very high molecular weights. Substances were either corpuscular, microscopically visible, like bacteria and blood cells and hence in suspension, or dissolved (soluble) and by implication of low molecular weight. ‘It seems to me’ Beijerinck wrote ‘that the production of growth of a dissolved particle is not absolutely unthinkable, but it is very hard to accept, and the idea of a self-supporting molecule, which is a corollary of this view, seems to me obscure, if not positively unnatural’.

The genius of Beijerinck shows when he reconciled the two conceptions of the tobacco mosaic agent as, on the one hand, a molecule in solution, and, on the other, a pathogenic agent which multiplied: ‘There is another explanation to be considered, namely that the contagion, to reproduce itself, must be incorporated into the living cytoplasm of the cell, into whose multiplication, it is, as it were, passively drawn’ (cited from Waterson 1968).

In the heated glass house provided to him in Delft, Beijerinck performed a series of experiments that lead him to the following conclusions:

1. ‘The infection is not caused by microbes but by a living liquid virus’; this statement was based not only on the widely quoted porcelain filter experiments but also on observations of diffusion through thick layers of agar gel.
2. ‘Only growing plant organs where cellular division takes place are susceptible to infection. There only does the virus multiply’. Here he concludes that ‘outside of the plant no multiplication can be observed’ and adds that ‘the mode of multiplication of the virus reminds one, in many ways, of that of ... chromoplasts which also grow only within cellular protoplasm, even though they have an independent existence and function separately ...’.
3. ‘The virus can be dried without loosing its infectious property’.
4. ‘The virus can spend the winter in soil outside of the plant and in a dry state’.
5. ‘The virus is inactivated by boiling temperature’; here he excludes the possibility of dealing with sporulating anaerobic organisms.

Let us assess Beijerinck’s role in giving birth to virology. In my view it is more appropriate to analyze his conceptual originality rather than looking at the dates of his publications (Beijerinck 1889). The wish to idolize persons, to aggrandize a Nation by appoint-

ing its heros is universal, and the polemics surrounding priority claims reflect man’s craving for immortality. Publication dates, citation indices and impact factors are modern renderings of the olympic spirit in science — giving the illusion that fame can be quantitated. Beijerinck’s achievements for virology are sometimes disputed in this trivial spirit, and Dmitri Ivanovsky is quoted as his competitor, as having been the first. Beijerinck himself was more gracious than later historiographers in acknowledging that he did not know about Ivanovski’s earlier publication, and he gave him credit. This honesty is not universal for grand men in microbiology, as the recent biography of Pasteur shows (Geison 1995).

In a reaction to an article claiming Ivanovsky’s role ‘as the father of the new science of Virology’ (Lustig & Levine 1992), a careful analysis of this aspect has recently appeared (Bos 1995b). Ivanovsky is rightly quoted for his classical filtration experiments demonstrating passage of the causative agent of tobacco mosaic through the pores of a bacteria-proof Chamberland filter. His paper, read before the Academy of Sciences in St.Petersburg, Russia in 1892, is indeed a landmark in the history of virology. Of special significance for interpreting the author’s ideas, however, is his dissertation published in German while he was working in Warsaw (Ivanovsky 1903). In it he reiterated that he was dealing with a microbe which might have passed the pores of the bacteria-proof filter or might have produced a filterable toxin (Ivanovsky 1892). In reaction to Beijerinck’s report, he related that he had ‘succeeded in evoking the disease by inoculation of a bacterial culture, which strengthened my hope that the entire problem will be solved without such bold hypotheses’ (Ivanovsky 1899). Kluyver, Beijerinck’s successor in Delft, later wrote that ‘anybody reading Ivanovsky’s 1899 paper will have to acknowledge that this author, even seven years after he made his discovery, was not at all aware of its tremendously far-reaching importance, the main part of the paper being devoted to an attempt to prove contrary to all available evidence the bacterial nature of the contagious agent’ (Kluyver 1940). In 1903, when further criticizing Beijerinck’s conclusion about the *contagium vivum fluidum*, Ivanovsky claimed it to be a *contagium vivum fixum*. He wrote that ‘the persistence of infectivity of the filtered sap can only be explained by the assumption that the microbe produces resting forms, that is spores’ (‘Die Erhaltung der infizierenden Eigenschaften des filtrierten Saftes kann nur unter der Voraussetzung erklärt werden, dass der Mikrob ruhende Formen, d.h. Sporen

bildet'). Like particles of Indian ink, the contagium could pass through agar which made him conclude '*that the contagium of the mosaic disease is able to multiply in the artificial media*' ('Zusammenfassend gelange ich zu dem Schlusse, dass das Kontagium der Mosaikkrankheit sich in den künstlichen Nährböden zu entwickeln imstande ist'). This clearly demonstrates that Ivanovsky did not grasp the scope of his observations, or, as Bos put it, that in his mind theory (Koch's Postulates) had fossilized into dogma (Bos 1981).

The universal nature of the new agents defined in phytopathology and veterinary medicine became apparent when the US Army surgeon Walter Reed and James Carroll reported their findings on the cause of yellow fever (Reed & Carroll 1902). The authors nobly express their 'sincere thanks to Dr. William H. Welch of the John Hopkins University, who during the past summer, kindly called our attention to the important observations which have been carried out in late years by Löffler and Frosch, relative to the etiology and prevention of foot-and-mouth disease in cattle'. Again filtration through porcelain candles was used for ascertaining the novel nature of the infectious agents.

If the history of virology is to convey anything more than nostalgic sentiments it should teach lessons that are valuable now. When assessing achievements of the early workers which we would call virologists today, one should be careful not to fall in the trap of the anachronism. It is a semantic trap. Thus 'virus' meant something quite different to Ivanovsky and Beijerinck, to Löffler and Frosch, to Reed and Carroll than it means to us, and 'fluid' at the turn of the century was synonymous with 'non-corpuscular' only down to the dimensions that particles could be visualized. It took another forty years to demonstrate the particulate nature of virions.

About a century ago, the discovery of novel disease agents was 'in the air'. Rather, the tools were in the literature: methods and techniques developed in one domain were available to be utilized in another field, with tremendous results. What we perceive as modern science management, to cross the barriers between disciplines, to listen to scientists from other provinces has been a fertile attitude through the ages — it also stands at the origins of virology. At the time, formulating the virus concept was a bold act which — had it turned out wrong — would have brought ridicule to its author. It is the difference between folly and visionary insight that determines whether footprints are left in the cultural landscape, in the pursuit of immortality.

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