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Importance and impact of veterinary virology in Germany

M. C. Horzinek

Veterinary Faculty, Virology Unit, Utrecht University, Utrecht, The Netherlands

Summary. The causative agent of tobacco mosaic and of foot and mouth disease (FMD) were recognized in 1898 as "filterable" or "invisible" – and eventually termed "virus". Four years later the viral aetiology of yellow fever was established, and the new discipline took off. Thus animal virology started with a veterinary problem, and Germany's contribution during the following decades came mainly from the chairs of veterinary teaching and research establishments in Giessen, Munich and Hanover, the Riems Institute, and the Federal Research Institute for Animal Virus Diseases in Tübingen. From a superficial bibliometric analysis, a wide divergence in impact figures is noted, with excellent contributions in international virology journals and lesser papers in German veterinary journals. The publications in the observed time frame reveal a fascination by virion structure, physical characteristics and structure-function relationships with little work published in journals dedicated to immunology and pathogenesis.

Scientific priority

The first German connection with virology – though not in the animal field – predates Martinus Willem Beijerinck's historic definition (1898) of the *contagium vivum fluidum:* Adolf Mayer (1843–1942), a chemist from Heidelberg, was appointed at the Agricultural School in Wageningen, the Netherlands, in 1876. He first reported on a disease in tobacco plants in 1882, named it 'tobacco mosaic', and showed that it could be serially transmitted in the apparent absence of microorganisms [6]. The causative agent of tobacco mosaic was to become the first model virus that revealed many secrets of virion structure. Dmitri Ivanovsky (1864–1920) is quoted for his classical filtration experiments in which he demonstrated 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 undoubtedly 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 [5]. 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.

In analysing priority claims one should appreciate conceptual originality rather than comparing publication dates. The polemics surrounding such claims reflect the Olympic spirit in science – *citior, altior, fortior* – giving the illusion that fame can be quantitated. Beijerinck's achievements for virology are sometimes disputed in this trivial sense, and 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 Ivanovsky's earlier publication, and he gave him credit. Ivanovsky, however, 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" [4]. In 1903, when further criticising Beijerinck's conclusion about the *contagium vivum fluidum*, Ivanovsky claimed it to be a *contagium vivum fixum*. He wrote: "...the persistence of infectivity of the filtered sap can only be explained by the assumption that the microbe produces resting forms..." (spores). All these quotes demonstrate that Ivanovsky did not grasp the scope of his observations, that in his mind Koch's Postulates had fossilised into dogma [2].

When assessing achievements of the early workers, who we would call virologists today, one should avoid the trap of anachronism; it is a semantic trap. Thus, "virus" meant something quite different to Ivanovsky and Beijerinck, to Löffler and Frosch, to Reed and Carrol, than it means to us. "Fluid" at the turn of the century was synonymous with "non-corpuscular" insofar as particles with dimensions were concerned that could not be visualised by light microscopy – electron microscopy not having yet been invented. It took another forty years to demonstrate the particulate nature of virions.

The beginnings of animal virology in Germany

At the same time, filtration experiments were also performed with an animal pathogen in Germany, which lead to the identification in 1898 of the cause of foot and mouth disease (FMD) as a "filterable" or "invisible" virus. The finding resulted from a close collaboration between Friedrich Löffler, professor and director of the Institute of Hygiene in Greifswald, and Paul Frosch, then employed at Robert Koch's Institute of Infectious Diseases in Berlin; Löffler had been Koch's assistant there, until his appointment to the Greifswald chair in 1888. In 1890, Robert Koch already had deplored the fact that many infectious diseases were still aetiologically undefined; at the occasion of the 10th International Congress of Medicine in Berlin 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."

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 in 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 Friedrich Löffler's report (in its original translation) reads for Tuesday, August 8th:

> "The necessary funds were granted by the German Empire and the Prussian State, and I was charged with the execution of the work, which at first I carried on in the Institute for Infectious Diseases in Berlin, afterwards, in that of Hygiene at Greifswald, with the assistance of Professor Frosch, and later, from January 1898, of Dr Uhlenhuth.
>
> When I undertook the work, the aetiology of foot and mouth disease was little studied. It was known that the disease was transmitted to cattle, pigs, sheep and goats, and that its germs might be carried by diseased animals and also by persons who had been in contact with them. The mode of action of the germ and the ways of infection were unknown.
>
> 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 the organisms in the fluid that we used."

In view of the semantic trap mentioned above it should be noted that Löffler used the word 'virus' in the generic sense. Since antiquity the term has been applied to denote slime, animal semen, foul odour, acrid and salty taste, snake and scorpion venom, and poison in general; an early quote can be found in Cicero's *De amicitia* (On friendship, written about 45 B.C.) where a person's "...virus acerbitatis..." may be translated as "... the venom of bitterness" [3].

Thus animal virology originated at the same time as plant virology, and it took only four more years before the viral nature of yellow fever, an arthropod-borne infection, was determined. Animal virology arose from the need to control a disease of economic importance, as exemplified above, and Friedrich Loeffler was less concerned with the properties of the foot-and-mouth agent than with its elimination from the Prussian cattle population.

Importance and impact of veterinary virology

Before commenting on the importance and impact of "veterinary virology" in Germany, some definition is required. This is where ambiguity starts. Friedrich Loeffler had a medical education, as had Paul Frosch, though he held the chair for Hygiene at the Berlin Veterinary School during the last twenty years of his life. Is veterinary virology that branch of the discipline to which persons with a veterinary education have contributed? Then the fundamental studies at the Max-Planck Institute for Virus Research in Tübingen by Werner Schäfer – a vet by training – on murine retroviruses would fulfil the criterion. Or is veterinary virology aimed at companion and farm animals, as medical virology is aimed at human health? Then Erich Traub's studies at the Federal Research Institute for Animal Virus Diseases in Tübingen (FRIAVD) on murine lymphocytic choriomeningitis virus should be excluded...

This is a moot point, of course. To approach the topic in a formal way, I shall examine the chairs, directors and presidents of veterinary teaching and research establishments in Germany. However, as every historian will confirm, chronological distance is a prerequisite for a fair assessment of the past. Also, I call persons in this group my friends, and I would not want to sacrifice this relationship by giving too little credit to one, or – perhaps worse – too much to his adversary. I therefore decided to do a 30-years literature analysis starting in the 1960ies, when veterinary virology took off.

In doing this, I analysed the literary production of the past professors of virology at the veterinary faculties in Giessen, München and Hanover and the presidents of the FRIVAD in Tübingen, under the assumption that their leadership is reflected by co-authorships of articles. This should suffice to define the German aspect.

I should also specify the distinction I make between 'importance' and 'impact'. An important finding would be one that may be or has been useful for veterinary medicine. This is difficult to formally assess – perhaps a review of filed patents and their applications in products that have reached the market would be a method. A finding with a high bibliometric impact, on the other hand, has contributed to the science of virology in general, irrespective of its applicability – it suffices that it is interesting for virologists. This distinction is both arbitrary and fuzzy, but it does follow bibliometric terminology.

Veterinary virology units in Germany

The most venerable institution dedicated to the teaching of infectious and epidemic animal diseases can be found at Munich University. It had been part of General Veterinary Pathology since 1790, later baptised 'Institute for Microbiology and Infectious Diseases of Animals', and was headed by Anton Mayr from 1963 to 1990 (Fig. 1). Having been trained as a virologist at the Bavarian Vaccine Establishment and at the FRIAVD in Tübingen, which he led for 4 years, he maintained the general microbiology perspective during his entire career. Toni Mayr's continuous interest was in the poxviruses, in a broader sense in their role as inducers of non-specific immunologic defence. He coined the term 'Paramunität' – a peculiarly German invention – and developed parapox- and avipoxvirus preparations to stimulate the non-specific defence. Though poorly defined, products developed from these studies reached the marketplace and were much used as an anti-infectious panacea, again mainly in Germany and the Netherlands. Mayr's impact on the animal health scene in Germany has been remarkable and multifaceted. The students loved him, he was a sought after speaker at veterinary conventions, a relentless advocate of 'practical virology', a prolific writer of articles and handbooks, a politician – certainly the most general 'veterinary microbiologist' amongst the key figures here discussed.

The first dedicated chair of virology at a veterinary faculty was established in 1964 in Giessen, and Rudolf Rott (Fig. 2) become its head. During the six years preceding his appointment, he had worked with Werner Schäfer at the

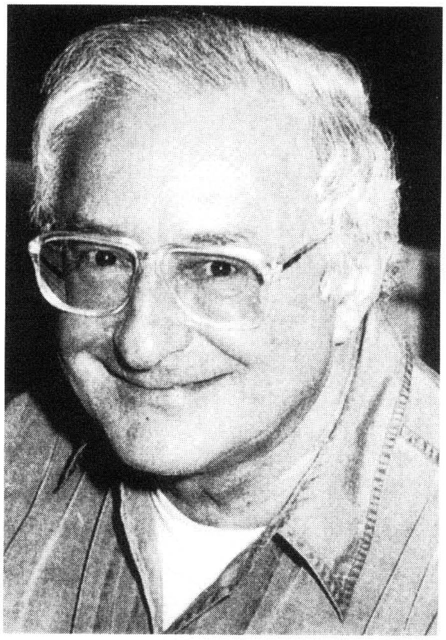

Fig. 1. Anton ('Toni') Mayr

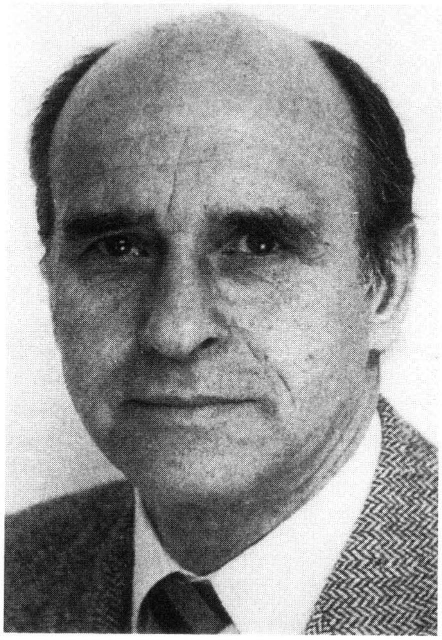

Fig. 2. Rudolf ('Rudi') Rott

Max-Planck-Institut für Virusforschung in Tübingen. The ortho- and paramyxoviruses should stay with him during his entire scientific life, until (and after) his recent retirement. In his laboratory, he established groups working on alpha-, flavi- and birnaviruses, and on Borna virus – a German favourite, which only Hanover succeeded to ignore. The groups directed by Rudi Rott have made seminal contributions to general virology, and he had a clear conception about what scientific quality means.

Rudi Rott was much admired, revered – and feared. When he entered a discussion, everybody held his breath. He was a relentless critic, very influential in the German science environment – especially in the German Research Council – but he also determined the face of German virology internationally.

In keeping my promise to avoid comments on acting Heads of Departments, I skip the Veterinary Faculty at Berlin, where virology assumed independent status as late as 1978. Its first professor, Hanns Ludwig, is one of Rudi Rott's disciples, as is Hermann Müller, who recently occupied the chair in Leipzig. By establishing a school of virologists, Rudi Rott followed Werner Schäfer's example; Schäfer's disciples eventually occupied seven chairs of medical and veterinary virology in German-speaking Europe (Giessen, Hanover, Wurzburg, Cologne, Heidelberg and Zurich).

The Veterinary School in Hanover appointed Manfred Mussgay (Fig. 3) as its first full professor of virology in 1964. Having worked on Venezuelan equine encephalitis and vesicular stomatitis virus as a visiting scientist in Gernot Bergold's lab in Caracas, he further exploited the alphavirus model, gradually focusing on

Fig. 3. Manfred Mussgay

Fig. 4. Bernd Liess

the characterisation of pestiviruses. In 1967, he left for Tübingen to become President of the FRIAVD; the administrative duties there made it difficult to continue hands-on research, but he went through the showers almost every day and supervised work mainly on foot-and-mouth disease virus and murine and bovine retroviruses. Manfred Mussgay was a meticulous experimental worker, a cheerful personality with a contagious laugh. His death in 1982 at the age of 55 years was a severe loss not only for his friends, of which I have been one, but also for virology.

After Manfred Mussgay had left Hanover, Bernd Liess (Fig. 4) became his successor. He, too, had a spell in a tropical country, having worked in Kenya with Walter Plowright on rinderpest virus. Upon his return to Germany, he focused on the pestiviruses causing swine fever and bovine viral diarrhoea/mucosal disease. This line of research determined the profile of the Hanover laboratory until today. However, his interest in morbilliviruses continued, and he co-authored articles on canine and phocine distemper viruses. Bernd Liess retired in 1996 and was followed by Volker Moenning, a second-generation disciple of Schäfer's and former FRIAVD president.

Bibliometric analysis

If the importance of virology in Germany for the veterinary profession is difficult to assess, as mentioned, its impact can be estimated. To get an impression of the gross number of publications dedicated to veterinary medicine and virology, respectively, I queried the time-unlimited PubMed Entrez database (http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?) of the U.S. National Library of Medicine/National Institutes of Health. MeSH (Medical Subject Headings) major topics and subheadings were used in the search, respectively. MeSH is a vocabulary of medical and scientific terms assigned to documents in PubMed by a team of experts. It is used for indexing articles, for cataloguing books and other holdings, and for searching MeSH-indexed databases, including MEDLINE.

From 1963 onward, about 137,000 "veterinary" articles were found as compared to about 208,000 papers containing "virus OR virology", both starting in 1963. The publication dynamics show a gradual increase in both categories in the late 1960's – most likely as a consequence of both the growth in funding of virus research and the increasing bibliometric activities of the Institute of Scientific Information (ISI). In the 1970–1983 period the ratio of virology/veterinary science papers remained fairly constant, with fewer indexed publications in the veterinary and medical sciences, with all their facets, than in virology alone. A conspicuous divergence occurred afterwards. In 1984, the retrovirus that causes AIDS was discovered, testing for antibodies was begun, HIV research took off, and many virologists jumped on the bandwagon that was propelled by a superabundance of funding.

The fraction of veterinary papers in the virology category was assessed by querying "((virus[MeSH Major Topic] OR virology [MeSH Major Topic]) AND veterinary [Subheading])", which resulted in 9707 hits – in other words: 4.7% of all indexed publications in virology contain the term "veterinary". When extending the query with "Germany" the number is reduced to 91. These figures are nothing but indicators, as may be expected from such a superficial analysis; thus "veterinary" may be absent from many papers on viruses affecting animals (resulting in a underestimate).

Subsequently, the names of the German virologists mentioned above were used to search PubMed; a steady stream of 22 ± 5 papers/year from 1968 to 1995 shows the productivity of the groups. The articles have appeared in the journals in Table 1, with additional bibliometric indicators. 'Total cites' is the number of times that each journal has been cited in a given year. The impact factor (IF) is a measure of the frequency with which the average article in a journal has been cited in a particular year (the number of current citations to articles published in a specific journal in a two year period divided by the total number of articles published in the same journal in the corresponding two year period). The immediacy index (II) is a measure of how quickly the average article in a specific journal is cited.

The following considerations are meant to provide "food for thought". Of the 640 publications examined, about 3/4 have appeared in 12 journals (in total, 91 journals have been used for publication). Only "virology" journals rank amongst the first 12, while the "veterinary" category journals are generally low ranking. A notable exception in Veterinary Microbiology, which (in the 1995 listing) ranks 7th in the "veterinary" subject listing, though only 38th in the "microbiology" category. The dichotomy between excellent virology journals and low-impact

Table 1. Listing of publications from the authors Liess, Mayr, Mussgay, Rott and Traub in the 1968–1995 period, with the numbers(#) of papers, total cites, journal impact factors (IF) and immediacy indices (II)

Total Publications with >1 pub./journal by Liess, Mayr, Mussgay, Rott, Traub, as listed in MEDLINE
(Ordered according to frequency)

	Journal	#	total cites	IF	II	Vir	Vet	Mic	Bio/MDS
1	Zentralbl Veterinarmed (J Vet Med B)	122	394	0.460	0.079	–	38	–	–
2	Arch Gesamte Virusforsch & Arch Virol	58	2768	1.384	0.323	12	–	–	–
3	Virology	54	23475	3.901	0.674	3	–	–	–
4	Deutsche Tierarztl Wochenschr	44	445	0.231	0.009	–	64	–	–
5	J Gen Virol	41	12589	3.410	0.444	5	–	–	–
6	Berl Munch Tierarztl Wochenschr	35	294	0.234	0.026	–	63	–	–
7	Zentralbl Bakteriol	27	1018	0.898	0.014	–	–	44	–
8	Tierarztl Prax	24	–	–	–	–	?	–	–
9	J Virol	20	45077	6.033	1.176	1	–	–	–
10	Med Microbiol Immunol (Berl)	20	587	2.145	0.136	–	–	19	–
11	Vet Microbiol	15	1516	1.076	0.202	–	7	38	–
12	Bull Off Int Epizoot	11	–	–	–	–	–	–	–
13	Fortschr Med	7	–	–	–	–	–	–	?
14	Intervirology	7	823	1.260	0.037	13	–	–	–
15	EMBO J	6	59817	13.505	2.281	–	–	–	5
16	Nature	6	257287	27.074	6.043	–	–	–	1

The right 4 columns show the ranking of the respective journals in in the indicated bibliometric categories (J Virol ranks 1st in the 'virology' category, Vet Microbiol ranks 7th in the 'veterinary' category etc.)

veterinary journals becomes even more pronounced, when "the German specialities" are compared with the rank listing in virology and the veterinary sciences (in the latter category only journals that would publish microbiological papers have been listed; Table 2). The language bias may have contributed to the skewed distribution that makes German journals rank behind for example Scandinavian, Czech and Belgian ones.

Veterinary virology publications from Germany in this time frame reveal the fascination by virion structure, physical characteristics and structure-function relationships – arguably Werner Schäfer's heritage. Amongst journals used only once by an author are very prestigious ones such as Cell (Rott), and many titles that are marginal to virology. Though "veterinary" would suggest interest in the animal's role in viral infections, there is little work published in journals dedicated to immunology and pathogenesis, e.g. no papers in Vet Immunol Immunopathol; Am J Vet Res, or Proc Soc Natl Acad Sci USA.

A comparison of immediacy indices reveals the dynamics in the various bibliometrical fields: if it took an article published in the Zentralblatt für Veterinärmedizin one year to be quoted, then an author publishing in the *Journal of Virology* would be cited within a month – an author writing in Cell 4 days. This is an arithmetic exercise, of course, but quite illustrative.

Table 2. Comparative subject category listing of journals where virologists might want to publish, with their rankings in the bibliometric categories 'virology', 'veterinary sciences', and 'molecular biology/immunology'

Comparative Subject Category Listing (SCI Journal Citation Reports 1995)							
Virology			Veterinary Sciences			Mol. Biology/Immunology	
Rank	Title	IF	Rank	Title	IF	Title	IF
1	J Virol	6.033	5	Vet Immunol Immpath	1.138	Cell	40.481
2	Adv Virus Res	5.120	7	Vet Microbiol	1.076	Nature	27.047
3	Virology	3.901	11	Vet Rec	1.014	Immunol Today	25.228
4	Semin Virol	3.625	15	Am J Vet Res	0.907	Science	21.911
5	J Gen Virol	3.410	16	Vet Pathol	0.879	J Expl Med	15.126
6	J Med Virol	2.232	19	Avian Dis	0.774	EMBO J	13.505
7	Virus Res	2.161	24	Res Vet Sci	0.717	PNAS	10.520
8	Antivir Res	1.849	25	J Comp Pathol	0.715	J Immunol	7.412
9	Rev Med Virol	1.780	28	Comp Immunol Microb	0.645	J Biol Chem	7.385
10	Virus Genes	1.472	30	Aust Vet J	0.627		
11	J Virol Methods	1.464	36	Adv Vet Sci Comp Med	0.516		
12	Arch Virol	1.384	38	J Vet Med B	0.460		
			The German Specialties...(<0.250)				
			62	Wiener Tierarztl Monat			
			63	BMTW			
			64	DTW			
			68	Schweiz Arch Tierheilk			
			70	Tierarztl Umschau			
			76	Monatsh Veterinarmed			
			87	Prakt Tierarzt			
			89	Kleintierpraxis			

Another priority issue

While Robert Koch and Louis Pasteur have become household names, so to speak, in microbiology, another figure in the virology, immunology, vaccinology triangle has been almost completely forgotten. I should like to draw the veterinary virologists' attention to a self-taught Dutchman, a miller and farmer, who is still remembered in his birthplace. A monument was recently erected in Winsum/Friesland to honour Geert Reinders (1737–1815), the 'inoculator' and saviour of the country from rinderpest. After the 1768 epidemic in the Netherlands 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", the protection transferred from an immune cow to its calf.

Geert Reinders published his observations in 1776 – Edward Jenner's vaccinia protection experiments appeared in press two decades later. At that time, however, Jenner was already a public figure, known as a skilful and popular surgeon, eventually becoming a member of the Royal Society due to his discovery of the nesting parasitism of the European cuckoo. Reinders' findings were published in Dutch and had a small readership. Historically, it would appear that veterinary vaccinology predated medical vaccinology – as veterinary virology preceded medical virology. The speed of progress, however, was quite different.

Scientific priority is of historiographic interest (where chauvinist motives may obfuscate the issue), but above all it is of importance to every scientist. However, being first chronologically is different from the priority perceived by the scientific incrowd, by academia, by the public. It takes social and political skills to convince the 'shakers and movers', the establishment, the referees of high-ranking journals, that one really has made a novel finding. Proverbially, only posterity will assess and acknowledge the inventor and the discoverer. The book on the rediscovery of viruses will eventually be written, probably by a retired professor, who saw his favourite finding go unnoticed, only to return in another countenance, published and publicised by a dynamic young colleague from a renowned research establishment.

There is no doubt that the cradle of virology was rocked about 100 years ago, in Russia, Prussia, and in the Netherlands; nor is there any doubt that a veterinary problem led to one of the greatest serendipitous discoveries in biology.

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Authors' address: Dr. M. C. Horzinek, Veterinary Faculty, Utrecht University, Virology Unit, Yalelaan 1, 3508 TD Utrecht, The Netherlands.