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The beginnings of animal virology in Germany

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

Cicero 'De Amicitia' 23, 87

At the turn of this century, when Martinus Willem Beijerinck had formulated his concept of the *contagium vivum fluidum* as a new category of infectious agents (see VDN in Arch. Virol. 140: 613–619 (1995) – L. Bos: "The embryonic beginning of virology: unbiased thinking and dogmatic stagnation"), similar filtration experiments were performed with an animal pathogen in Germany. They led to the discovery of the cause of foot and mouth disease (FMD) in cleft-footed animals and its identification as a virus. The following discussion of the early days of animal virology is largely based on a book by Klaus Munk published this year – "Virologie in Deutschland: die Entwicklung eines Fachgebietes" (Karger Basel, 1995). The author dedicated it to Prof. Dr. Werner Schäfer, the Nestor of German virology, who also graciously provided the illustrations accompanying the present article.

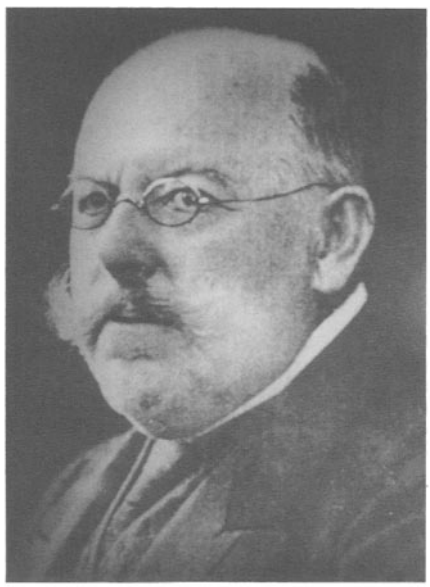

Fig. 1. Prof. Friedrich Löffler

Foot-and-mouth disease

Animal virology started in 1898 with the discovery of FMD virus. The finding resulted from a close collaboration between Friedrich Löffler (Fig. 1), 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; there Löffler had been Koch's assistant until his appointment to the Greifswald chair in 1888. Interpretation of the experimental results as infectious units of very small dimensions was along the lines of thought Robert Koch had initiated – medicine was in the bacteriology era where everything was focused on the search for causes of

contagious diseases. This has been a very successful approach, as exemplified by the discovery of the causes of anthrax and tuberculosis.

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; M.C.H.] 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):

> *"I thank you very sincerely for the kind words you have been good enough to address to Me. They give Me great pleasure. I also thank you for the honour you have all shown Me by your cordial welcome.*
>
> *I wish your labours at the Congress all the success you are expecting from them, for the good of all nations.*
>
> (Renewed and enthusiastic cheers).
>
> The *President* then called upon Dr. *Löffler*, professor at the university of Greifswald, for his paper:
>
> Prof. *Löffler: Your Royal Highness*! Gentlemen! Allow me first to thank the Committee of the Congress for having invited me to speak to you on my researches concerning vaccinations against foot and mouth disease; it may appear that by doing so I trespassed on ground which does not belong to me. However, I have been appointed by my Government to make those researches and I will tell you how it occurred.
>
> Foot and mouth disease is spreading more and more every year; and every year it costs the German Empire enormous sums. Necessary measures had been taken with the greatest care; suspected grounds had been closely sequestrated; this measure had been extended to whole communes and even to entire districts; disinfection had been carefully carried out and notwithstanding all this, the disease kept spreading. This state of affairs could not be allowed to go on, and it became evident that scientific study alone would enable people to find an efficacious means of fighting the disease. 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 etiology 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 great results obtained in struggling with some infectious diseases of man by the discovery of the virus, and the scientific study of the biological character of those diseases, indicated the road to be followed. Many learned men had already found micro-organisms which they considered as the virus of foot and mouth disease. It was necessary in the first place to establish which of those organisms causes the affection; but all our researches remained without results and absolutely negative.

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".

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 odor, acrid and salty taste, poison in general, snake and scorpion venom (see the quote above, from Cicero's 'De amicitia' [On friendship] where it may be translated as "... the venom of one's own bitterness").

The research institute on Riems Island

Friedrich Löffler was appointed to the new Chair of Hygiene in Greifswald in 1888; in his studies on FMD he continued to maintain close contacts with Paul Frosch and Robert Koch's Institute in Berlin. He was faced with a serious problem though: for his FMD experiments no quarantine measures could be taken, neither at the Institute nor in the stables, and disease outbreaks occurred in the surroundings time and again. The Department of Agriculture therefore urged the Department of Education (that was responsible for the universities) to ban further research on FMD in Greifswald, and in February 1907 Löffler was indeed forbidden to continue his work. In anticipation of such a measure Löffler had made proposals to improve the conditions, and he had written to his superiors in 1906 "that the situation of a future institute should be such that it would intrinsically prevent the dissemination of infectious material. An island would optimally suit such a purpose". Indeed, Riems Island in the Baltic Sea was the first choice. In 1907 it was visited by a committee that provided the following report: "Riems Island is about ten kilometers distant from Greifswald as the crow flies, ... the property of farmer Müller." The farmer was willing to lease the island or even to sell it. The report continues:

"The risk of disseminating foot and mouth disease would be reduced to a large extent by the very situation of the island. Farmer Müller seems well suited to remain active during the period that the experiments will be performed on Riems Island. Initially these will be limited to the production of protective serum following standard procedures". Two years passed after Löffler's proposals before the necessary buildings were erected and the work could begin.

Löffler sent the following message to the Prussian Secretary of Agriculture, Domains and Forestry, announcing the begin of the studies: "I obediently inform Your Excellency that after a fresh lymph sample had arrived from Vickowo on Monday, October 10, 1910 I forthwith commenced my work on Riems Island". This date marks the birth of the first institute dedicated to the investigation of animal viruses world-wide. On December 8 of the same year it was given the name "Research Institute Riems Island" which should undergo several changes in the course of its vagarious history.

The first building on the island was intended to house the assistants, to provide rooms for meetings and to accommodate guests. It still exists today, as the last architectural monument from Löffler's times (Fig. 2). Later on it was to become Otto Waldmann's home, from where he could keep good watch and ward of his assistants. Laboratories where first domiciled in the farmer's barn, later in the same building. An isolation stable for 20 cattle and 20 pigs was put up next.

Fig. 2. Original accommodation of the Research Institute on Riems Island

In 1913 Friedrich Löffler was appointed Director of the Robert Koch Institute in Berlin and thence visited the island only infrequently. After his death in 1915 the experimental work on the Riems had practically come to an end. It was revived, however, when Otto Waldmann (Fig. 3) was appointed Head of the Research Institute Riems Island in 1919. His assignment was "... to find new ways of efficiently combatting foot and mouth disease through investigation, to take up serum production and to make it so inexpensive that its broad use would become financially feasible".

Fig. 3. Prof. Otto Waldmann

Waldmann's experimental work led to a first success that proved crucial for the further study of FMD: in 1920 he succeeded to transmit the infection to guinea pigs by plantar inoculation. The possibility to grow the virus in a small laboratory animal reduced the need for costly cattle experi-

Fig. 4. Riems Island, with ropeway to the mainland for animal transport

ments. Through this finding the guinea pig assumed such a prominent role amongst laboratory animals that the scientists erected a monument in its honour. It can still be admired on the Riems.

Under Waldmann's aegis the Riems developed into a full-fledged FMD research station. In 1923 he had a laboratory building raised, as well as several quarantine stables. Additional structures for 800 cattle, a slaughter house, a canteen, as well as lodgings for the collaborators followed. An important novelty was the construction of a ropeway to the mainland for transporting animals (Fig. 4). In addition, a permanent harbour was dug out with a pier for the motor vessel "Geheimrat Löffler" that had been purchased in 1927. Another cable car for personnel was installed in 1940. In this year a new main building was inaugurated to accommodate the President's office, the library and the laboratoria. Vaccine production took place in its basement. In 1942, the construction activities were completed.

Early achievements in German FMD research

With its four departments (microbiology, headed by Erich Traub; pathology, by Heinz Röhrer; chemistry, by Gottfried Pyl; and vaccine production, by Hubert Möhlmann) research at the Riems "Reichsforschungsanstalt" (since 1943) focused on FMD pathogenesis, antigenic diversity and, of course, on vaccine development. Thus the cyclic nature of the infection and virus generalization was established, FMD virus was adapted to growth in mouse brain, its sensitivity to diverse disinfectants was studied, a third serotype 'C' was identified, and in 1943 complement fixation was introduced for the diagnosis and identification of serotypes. The most important achievement for veterinary medicine was

the development of a formaldehyde-inactivated, aluminium hydroxide-adjuvanted vaccine in 1938 that proved efficient and safe in the epidemics during the two following years. While research was extended to include other economically important animal diseases (Teschen disease, influenza, hog cholera, Newcastle disease) and later also viruses suspected to become important in biological warfare (rinderpest virus), the focus remained on FMD. After the traumatic end of World War II the laboratories were rebaptized "Institutes for FMD Control" in 1946, to become the showcase for animal disease control during the decennia of the German Democratic Republic, under the pompous name of "Friedrich-Löffler Institute Riems Island of the German Academy for Agricultural Sciences at Berlin". Today, the Riems laboratories form part of the Federal Research Centre for Virus Diseases of Animals, together with the Tübingen research unit.

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