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A reappraisal of the contribution of Friedrich Loeffler to the development of the modern concept of virus

Jean Witz

Immunochemie des Peptides et des Virus, CNRS, Strasbourg, France

Most virology textbooks, with the exception of the Afterword of A. J. Levine's chapter in the third edition of Field's Virology (1996), emphasize the contribution of Martinus Beijerinck (1898) to the birth of the modern concept of virus and they refer to Friedrich Loeffler (1898) only because he was the first to have shown the filterability of the animal virus *Foot and mouth disease virus*.

Following Adolf Mayer [9] who first described the mosaic disease of tobacco and demonstrated that the sap of diseased tobacco plants was infectious, Dimitri Ivanowsky (1896) showed that such saps remained infectious after filtering through Chamberland filters. Beijerinck confirmed Ivanowsky's observations and further showed that the infectious agent could diffuse through several millimeters of an agar gel, from which he concluded that the agent could not be a bacteria. Beijerinck also showed that the infectivity of sap remained constant during serial infections of plants, providing evidence that the agent could not be a toxin, since it was able to replicate itself in living organisms. The relative contributions of Mayer, Ivanowsky and Beijerinck have been extensively discussed by Bos [2]. Beijerinck was the first to use the term *virus* for such an infectious agent. He was, however, convinced that the agent was a liquid (or a solute: mentioned p. 6, line 16, in his 1898 article). In the title of his article he therefore named it: *contagium vivum fluidum*, or contagious living liquid.

Beijerinck thought his interpretation was confirmed by the observation that the sap filtered through Chamberland candles was less infectious than unfiltered sap. He explained this reduction as resulting from adsorption of the agent to the surface of the filter, mainly at the beginning of the filtration. In a control experiment he found that the less diffusible (granulase) of two enzymes present in malt extracts was more strongly retained in Chamberland filters than the more diffusible enzyme (maltase), until saturation was reached. In a footnote of his 1898 paper (see Appendix I) he stated that he could not agree with Loeffler's conclusion that the agent of foot-and-mouth disease was a particle and not a liquid.

Friedrich Loeffler and Paul Frosch had been appointed in 1886 by the Government in Berlin to investigate the cause of foot-and-mouth disease and to find a way to protect cattle against the disease. The conclusions of the investigating Committee are described in two articles published a few months before the appearence of Beijerinck's paper (Reports 1, 2 and 3: Loeffler and Frosch, 1898; Report 4: Loeffler, 1898; this latter article was cited by

Beijerinck, see above). These reports deal essentially with veterinary aspects of the disease, and with the successful development of an immunisation procedure of cattle by injection of a mixture of diluted filtered lymph from pustules and blood from diseased animals. A detailed account of the early developments of animal virology in Germany has been given by Horzinek [4]. In the course of these investigations (Report 3) Loeffler and Frosch found that no bacteria responsible for the disease could be found in the lymph of pustules, and that the lymph remained infectious after dilution (at 1/40) and filtration through Kieselguhr filters, the equivalent of Chamberland candles. They also provided evidence that the agent was able to replicate in animals and, therefore, could not be a toxin, since the infectivity remained constant in the course of serial inoculations of 20 µl of pure lymph, diluted and filtered. In the fourth Report, Loeffler [7] reported the loss of the infectivity of the diluted lymph after repeated filtration through Kitasato filters, which possessed a finer grain than Chamberland filters. Loeffler concluded that the agent of foot-and-mouth disease was too large to pass through these very fine grain filters. He concluded that viruses are particles and not liquids (see Appendix II) and therefore came much closer to the modern concept of virus than anybody else at the time.

A definite confirmation of the idea that viruses were particles came later, with Felix D'Herelle's [3] description of bacteriophage plaques, Max Schlessinger's [10] measurements of the molecular weight of bacteriophages, and the visualisation of tobacco mosaic virus particles in the electron microscope [5].

Appendix I

Beijerinck (1898) Footnote 2, p. 7

Ich kann darum auch dem Schluß von Herrn Loeffler in Bezug auf die corpusculäre Natur des Virus von Mund- und Klauen-Seuche (Centralblatt für Bacteriologie, Erste Abteilung, Bd. 24, pag. 570, 1898) nicht beipflichten.

[I cannot agree, therefore, with the conclusion of Mr. Loeffler concerning the corpuscular nature of the Virus of Foot and Mouth Disease].

Appendix II

Loeffler (1898) p. 571, 1.10–13

Für die Annahme, daß es sich bei dem Virus um ein corpusculäres und nicht etwa um ein gelöstes Agent handelt, spricht die mehrfach gemachte Beobachtung, daß verdünnte Lymphe, welche wiederholt durch sehr dichte Kitasatofilter hindurch gesaugt waren, nicht mehr im Stande waren, empfindliche Tiere zu infizieren, selbst wenn die einem Quantum von 4/50 ccm reiner Lymphe entsprechende Menge des Filtrates zur Injektion gelangte.

[The evidence that the virus is a corpuscular and not a soluble agent is provided by the repeated observation that the diluted lymph, filtered several times through very tight Kitasato filters was no more able to infect susceptible animals, even if an amount of filtrate corresponding to 4/50 ml of pure lymph was used for injection.]

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Author's address: Dr. J. Witz, Immunochemie des Peptides et des Virus, UPR 9021 du CNRS, Institut de Biologie Moléculaire et Cellulaire, 15 rue Descartes, F-67084 Strasbourg, France.