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MINIREVIEW

Milestones in Early Poliomyelitis Research (1840 to 1949)

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I shall restrict my remarks to some papers on poliomyelitis, published in the period from 1840 to 1949, which I personally consider highly significant. The work on foot-and-mouth-disease by Friedrich Loeffler and Paul Frosch (17), first reported in 1897, has recently been reviewed several times, and the development of molecular picornavirology is also well known to the younger generation of virologists. After publication of the fundamental works of Jacob Heine (1840) (10), Adolf Strümpell (1885) (28), John Rissler (1888) (21), and Oskar Medin (1891) (18), it was in particular Ivar Wickman who in 1907 and 1911 (29) presented the most-detailed clinical and epidemiological observations on poliomyelitis after the devastating Scandinavian epidemic in 1905, with 1,031 cases. Wickman recognized the seasonal occurrence of the disease in Sweden in the late summer and early fall, with a dramatic peak of about 370 cases in August, and emphasized the large percentage of abortive and nonparalytic cases and their relevance for the spread of the infection by direct contact from person to person. Before Wickman, the thesis of poliomyelitis infection by direct contact had been highly controversial. He tracked by meticulous investigations the spread of infections in small parishes, e.g., in Traestena with about 500 inhabitants, mostly living in isolated, widely dispersed homes. Forty-nine persons became ill, 26 of them with significant paralysis. As a common source for radial spread of the infections Wickman identified Traestena's school with diseased and, most importantly, with apparently healthy children. Sometimes family visits caused the spread of the infection. Wickman also reported that 21.4% of the victims were older than 14 years, an age distribution uncommon before epidemic poliomyelitis had emerged around 1880.

Wickman's important research has only rarely been appreciated, perhaps due to the more or less simultaneous discovery of the etiologic agent by Karl Landsteiner and Erwin Popper in November-December 1908 (14). The history of the etiology of poliomyelitis is a history of errors. I mention only the "coccus era," when several investigators were prejudiced by a supposed parallelism between poliomyelitis and meningitis epidemica.

However, all in all, bacteriological findings were negative; likewise, attempts to transmit the disease to the usual laboratory animals, such as rabbits, guinea pigs, or mice, failed. Landsteiner and Popper (14) injected intraperitoneally into two Old World monkeys (*Cynocephalus hamadryas* and *Macacus rhesus*) a suspension of spinal cord from a 9-year-old boy who had succumbed to severe poliomyelitis after four days of illness. The two monkeys, in good condition, had been available from previous experiments with syphilis. The inoculated material, which was bacteriologically sterile, yielded negative results when injected into rabbits, guinea pigs, and mice. The two monkeys, however, exhibited lesions in the spinal cord, medulla, pons, and brain stem that were indistinguishable from those observed in cases of human poliomyelitis. One of the monkeys, the rhesus monkey, developed complete flaccid paralysis of both legs. Landsteiner and Popper were unable to passage the agent, but this was achieved soon afterward and independently in 1909 by Römer (22), Flexner and Lewis (8), Leiner and von Wiesner (15), and Landsteiner and Levaditi (13).

A note on the speed of publication in the comparatively slow, nonelectronic early 20th century may be of interest. Landsteiner's patient died on 18 November 1908, and Landsteiner reported on the successful transmission of the agent to monkeys and the histopathologic changes in the session of the k.k. Gesellschaft der Aerzte in Wien held in Vienna, Austria, on December 18, 1908. The proceedings of the session were published in the Wiener klinische Wochenschrift in issue 52, in 1908.

As early as 1910, Flexner and Lewis (9) had cautiously suggested that poliovirus gained access to the central nervous system via the nasal mucosa, a hypothesis supported by experiments with monkeys performed by Flexner's group and by Leiner and von Wiesner: swabs containing poliovirus were introduced into the nose and rubbed vigorously over the upper nasal mucous membrane, with ensuing clinical poliomyelitis. Flexner's views on the strict neurotropism of poliovirus and on its entry into the body by the nasal route (see above) dominated poliovirology so that other experimental evidence was more or less neglected for about 25 years until the 1930s. In particular, the exciting results of a young Swedish team consisting of Carl Kling, Wilhelm Wernstedt, and Alfred Pettersson published in 1912 (11, 12) were disregarded: the authors had demonstrated poliovirus in fatal and nonfatal cases of poliomyelitis, not only as expected from the oropharynx and trachea but also from the small intestine. Certainly, one possible interpretation of the presence of virus in the intestines was that it had been swallowed. But the clue of poliovirus present in the intestines and its pathogenic significance was not seriously pursued. Revival of poliovirus infection as an intestinal disease came mainly from the work of Trask and Paul at Yale University (20) and the definite report by Albert Sabin and Robert Ward in 1941 (26) on the natural history of human poliomyelitis. By meticulous technique (the authors performed necropsies of fatal polio cases themselves), they proved that the virus is distributed predominantly in two systems: (i) certain regions of the nervous system and (ii) the alimentary tract.

The presence of virus in the walls of the alimentary tract appeared to be primary localization and portal of entry. Virus was absent in the nasal mucosa, olfactory bulbs, and anterior perforated substance, which suggested that neither the upper

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respiratory tract nor the olfactory pathway is of significance in cases of natural human poliomyelitis.

Another highpoint of poliovirus research was the finding in 1931 by the Australians Frank M. Burnet and Jean Macnamara (4) that there existed antigenic differences between strains of poliovirus. So far, a complete similarity of the different strains had been assumed. The Australian authors compared the famous Rockefeller MV strain with a local strain isolated in Melbourne and found striking differences in cross-immunity experiments and neutralization tests in monkeys. The report was treated with scepticism, since it came from unknown investigators on a remote continent. But in light of the ill-fated vaccine trials of 1935, the significance of this finding was particularly realized by Hammon, Francis, and Rivers (2). Finally, the question was settled by the Committee on Typing of the National Foundation for Infantile Paralysis early in the 1950s (5).

A further highlight of poliovirus research was the adaption of the Lansing strain of poliovirus to mice by the persistent efforts of Charles Armstrong in 1939 (1). This meant that at least one strain of poliovirus was available for research purposes in an animal far less expensive than the monkey.

Some years earlier Maurice Brodie et al. (3) had already tried with ingenious techniques to reproduce poliovirus in mice for Brodie's vaccine trials, but with the vaccine failures this work was neglected. All the more must Armstrong's persistence be admired. In this context it should be mentioned that Max Theiler (quoted by Paul [20])—in analogy to his work on yellow fever—performed more than 150 mouse passages of the Lansing strain and observed a dramatic attenuation—a term used first by John Kolmer of Philadelphia in connection with poliomyelitis vaccines—of the virus after intracerebral inoculation of monkeys with results of from 100 to 0% paralysis. In passing, I should like to mention that among all contemporary virologists, it was Max Theiler and likewise John Enders who were highly regarded by Albert Sabin.

There were attempts as early as 1913 by Constantin Levaditi (16) to replicate poliovirus in tissue culture. But as Sabin and Olitsky (25) stated in their famous paper of 1936, "there is no unequivocal evidence that the virus of poliomyelitis has as yet been successfully cultivated outside the body."

Sabin and Olitsky used various carefully dissected tissues of 3- to 4-month-old human embryos, e.g., brain and cord, lungs, kidney, liver, and spleen. The virus was the already mentioned MV (mixed virus) strain of the Rockefeller Institute, a virus mixture prepared by H. L. Amoss in 1914 and kept for decades through numerous intracerebral passages in monkeys (23). The authors found that the virus multiplied readily only in the presence of nervous tissue, as evidenced by experiments with monkeys, including neutralization tests. The experiment appeared interesting at the time but of no practical value.

Despite this depressing failure and in view of the mounting evidence of the extraneural multiplication of poliovirus (see above), John Enders and his young collaborators Thomas Weller and Frederick Robbins made further attempts to cultivate poliovirus in vitro, in particular after Weller's successful cultivation of mumps virus in vitro. Enders and coworkers (7) demonstrated the dramatic replication of Lansing virus (testable in mice) in human embryonic cultures composed chiefly of skin, muscle, and connective tissue from the arms and legs, in cultures of human embryonic intestine, and in those of nervous tissue. It was Robbins who first recognized differences in cell morphology between inoculated and uninoculated cultures (24a). Enders coined the term cytopathic effects (CPE).

The implications of this famous paper, published in Science on 28 January 1949, were enormous and well recognized by the authors but surprisingly not by all colleagues in poliomyelitis research, at least initially. Enders et al. readily demonstrated the multiplication of all three poliovirus types in various primate tissues, in particular in nonnervous tissues, and showed that large amounts of virus could be propagated in vitro, that cultures most sensitive to the isolation of virus could be obtained in abundant amounts, and that precise quantitation of infectious virus could easily be achieved. Furthermore, besides Gilbert Dalldorf's and Grace Sickles' (6) isolation in newborn mice of coxsackieviruses, another major group of enteroviruses pathogenic for humans, the soon to be recognized potential of cell culture techniques led to the discovery of echoviruses, likewise important agents of human disease.

At the close of this century, younger virologists and clinicians find it difficult to appreciate the threat of poliomyelitis before 1954 (i.e., the prevaccine era), a disease annually crippling more than half a million people of all ages around the globe (in the United States alone about 21,000 paralytic cases were reported each year [19]) and often leading to death after a tortuous agony (14, 22). Enders' et al. work paved the way for the two kinds of effective poliovirus vaccine, the inactivated poliovirus vaccine of Jonas E. Salk (27) and the live oral polio vaccine of Albert B. Sabin (24). There has been a dramatic, worldwide decrease in the number of cases of poliomyelitis (virtual eradication of wild polioviruses has been reported in some European, Asian, Western Pacific countries, and the Western Hemisphere). Given enough political stability in the remainder of the world, the ambitious goal of the World Health Organization to eradicate poliomyelitis appears feasible.

Last but not least, the achievement of Enders, Weller, and Robbins was the starting point not only of modern poliovirology, but it launched the revolution rightly called molecular virology.

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