The history of polio

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Poliomyelitis, also called the Heine-Medin disease or *poliomyelitis anterior acuta*, most commonly referred to simply as polio, has caused and still causes justified anxiety. We suppose it may have affected people even in prehistoric times, although there is no unequivocal evidence to support this assumption. The skeletal deformities revealed in the course of paleopathological research may have been caused by the paralysis which accompanies this disease; however, they may have had other underlying causes. Similarly, a lot of uncertainty is left by the descriptions preserved until our times, such as those concerning the physical disability of the Roman emperor Claudius. Today, it is difficult to definitively verify the information contained in the writings of Hippocrates or Galen. In other words, while we cannot exclude the permanent presence of polio in the human habitat, we do not have convincing evidence that polio-induced lesions were combined into the description we may now associate with the disease. The first more solid clue is the report by the Scottish writer **Walter Scott** who described the disease he had suffered from in his early childhood along with its sequelae. Today, the detailedness of the information provided by Scott allows us to assume that he was likely affected by a poliovirus infection. "A debility of the lower extremities" following a severe infection was described in 1789 by the English obstetrician **Michael Underwood**. Almost a quarter of a century later, in 1813, the Italian surgeon **Giovanni Battista Monteggia** provided a clinical description of the disease, and more than two decades later the London physician **Charles Badham** described in details an acute paralysis observed in four children.

However, **the landmark year in the history of polio research was 1840**, when the German physician **Jacob Heine** published a monograph in which he discussed in details 29 cases of patients he had studied and treated for over a dozen years. His extensive diagnostic skills, along with meticulous clinical records, allowed Heine to distinguish a group of patients that differed from those with cerebral palsy, mental retardation, rickets or encephalitis. Heine's patients were all affected by flaccid paralysis which involved one or two extremities, or manifested with hemiparesis. Heine associated this

condition with an early childhood infection accompanied by generalized symptoms typical for teething, which he associated at the time with an extensive inflammation of the anterior horns of the spinal cord.

When Heine published his monograph, polio was a rare disease, or at least had not reached an epidemic scale yet. And although the work of the German physician was extensively discussed, in particular among neurologists and pediatricians, it fell within the scope of interest of a small circle of specialists, similar to his second work dated 1860 that described 120 cases.

It was not until 1887, when the polio pandemic began and swept the northern hemisphere, that the disease stirred up an understandable interest among scientists. In 1890, when polio struck again in Europe and the United States, the Swedish pediatrician **Karl Oskar Medin** carried out a detailed analysis of the disease and demonstrated its infectious nature. He also considered its potential transmission routes.

However, another 15 years had to pass until Medin's student, **Otto Ivar Wickman**, having studied over 1000 pediatric patients, provided convincing clinical and statistical evidence supported by field study results in 1905, confirming that polio can in fact be transmitted between humans. He presented the final conclusions of these studies in his doctoral dissertation written in German. In 1907, to honor Heine's and Medin's contribution to the adequate recognition and characterization of the disease, **Wickman named polio the *Heine-Medin disease*.** The nature of the causative pathogen of the infection still remained an unresolved issue.

On 18 December 1908, at the meeting of the College of Physicians in Vienna, Karl Landsteiner and his assistant Erwin Popper presented high quality microscopic specimens of the material collected from the spinal cords of one human and two apes that showed the histopathological presentation of polio-induced acute inflammation which had already been known. The scientists harvested spinal cord extracts from a boy who died of this disease and then used them to inoculate two primates selected for this experiment, a macaque and a baboon, causing polio symptoms in these animals, which were subsequently confirmed by histopathological examination. Since the pathogen could not be isolated at the time, both scientists hypothesized – correctly, as we know today – that polio has a viral etiology and they referred to this pathogen as an "invisible germ".

A year later, several research teams were able to subculture the virus independent of one another. The points at issue remained the infection routes, which were ultimately

determined only in the early 1940s, when **Albert Sabin and Robert Ward** were conducting intensive autopsy examinations and demonstrated that the virus is primarily transmitted via two systems: the digestive and nervous systems.

As we know today, the poliovirus developed in the aquatic environment, especially in standalone reservoirs, where it could easily survive in soil, waste or feces. It exhibited a high resilience to external factors such as temperature or chemicals, and its incubation time could even exceed a month. In a word, it was an extremely tricky pathogen that could easily cause an epidemic.

To make things worse, polio was primarily a threat to children and young adults, causing fear that often descended into panic. No one could be certain of their own fate. A healthy, normally developing child would suddenly become weak and succumb to a rapidly evolving infection. If the virus paralyzed the chest muscles, the so-called iron lung that allowed to force respiratory action would be the only hope for the patients. Before the outbreak of the World War Two, the National Foundation for Infantile Paralysis was established in the US. The entrusted funds were spent on the development of laboratories and virology research programs which were aimed at the development of an effective vaccine.

The first attempts had already been made as early as in 1934. At that time **Maurice Brodie**, an Englishman, tested a vaccine containing the poliovirus inactivated with 10% formalin. The material for the vaccine was harvested from the spinal cord of an infected ape, and the first trials were performed in 20 experimental animals. While animal testing was successful, the results of clinical experiments in a group of 3000 children in California were so unfavorable that no further studies in humans were initiated. Trials of a vaccine developed by **John Kolmer** were performed simultaneously and yielded equally unfavorable results.

Meanwhile, at the beginning of the 1930s, a pair of Australian physicians, **Frank Macfarlane Burnet and Jean Macnamara**, published a report stating that the various poliovirus strains had different antigens. Initially, their results were met with much skepticism, but just a few years later there was more and more evidence indicating that Burnet and Macnamara were right. Poliovirus was not homogenous and three separate serotypes could be distinguished.

In 1948, **John Franklin Enders, Thomas Huckle Weller and Frederick Chapman Robbins** developed a technique for in vitro replication of all three poliovirus types in

various types of primate-derived tissues, including nervous tissue. They were also able to trigger the rapid proliferation of cultures which were particularly susceptible to the virus isolation methods. They also presented a simple method for accurate quantitative determination of viral infectivity. In a word, they created a strong foundation for vaccine development. Six years later, the three scientists together were awarded the Nobel Prize. In the second half of the 1940s, the polio epidemic worsened and soon became a real plague for the post-war world. It is therefore not surprising that research aimed at finding an effective method to eradicate the disease was intensified. A number of research teams initiated experimental work. Everyone was aware that the stakes were high.

Hilary Koprowski, a Polish virologist living in the US permanently since 1944 and an alumnus of the University of Warsaw, was one of those seeking an effective vaccine. Koprowski assumed that the starting point of his experimental model should be the identification of an animal species that is not affected by poliomyelitis in natural conditions, but at the same time is capable of reducing the pathogen's virulence as a carrier. The cotton rat turned out to be just the animal needed. The procedure was simple and involved harvesting brain sections from previously infected rats, which were then mixed with physiological saline. Subsequently, Koprowski injected the fluid into another group of rodents. Then brain sections were harvested again from them and the mixture was prepared. After over a dozen subcultures, a live but clearly weakened virus was obtained. Testing in apes showed that the mixture was not only effective, but also safe. None of the animals became ill. Moreover, no side effects were identified. The objective, which was to obtain immunity by mimicking the natural infection route of the virus, which could freely replicate in the intestines but was devoid of any ability to cause infantile paralysis, was therefore reached.

In 1949, Koprowski was the first to receive the vaccine against the poliovirus type 2. Neither he nor any of his associates who followed him and drank the horrid-tasting "cocktail" experienced any symptoms of the disease. On 27 February 1950, Koprowski's team carried out the first clinical trial of the attenuated oral polio vaccine (OPV). Further testing showed that, as expected, the child's body produced antibodies. As no alarming symptoms were observed, Koprowski decided to administer the vaccine to another 19 children. Yet again, no symptoms of the disease were observed, while all of the vaccinated children produced antibodies.

In spring of 1951, during a conference held by the National Foundation for Infantile Paralysis in Hershey, Pennsylvania, Koprowski publicly presented the results of performed tests, and a publication summarizing the efforts of the entire research team was published one year later.

Koprowski's presentation made an impression but did not trigger the immediate reaction of the US sanitary and epidemiological services that could have been expected. Although the first results were said to be very promising, Koprowski was criticized for the overly rash switch from animal studies to vaccine administration to humans. **Albert Sabin,** who at that time was already seeking his own OPV, openly accused Koprowski of a breach of medical ethics. And although the significance of the Polish virologist's work was acknowledged, his vaccine was not recommended and it was suggested that it should be further tested in animals. This hindered further clinical trials.

The first mass vaccinations by the "Koprowski's method" were not carried until 1958 in what was then Belgian Congo, where more than 250 000 children and infants were vaccinated over just six weeks. In autumn of 1959, thanks to the efforts of Professor Feliks Przesmycki, the director of the National Institute of Hygiene at the time, vaccinations against the poliovirus using Koprowski's vaccine were initiated in Poland. Croatia followed suit. Until 1960, 13 million people received the oral vaccine developed by Koprowski.

The first inactivated polio vaccine (IPV) was developed by the team led by **Jonas Salk**. At that time, a poliovirus cultured in ape kidney cells and then inactivated with formalin was used. In 1954, Salk's vaccine was tested in a placebo-controlled study in 1.6 million children in Canada, Finland and the United States. One year later, IPV was approved for the prevention of poliomyelitis and although it proved to be effective, over the years it was also shown that it was not completely safe. Further efforts were therefore undertaken to modify it.

Meanwhile, another research team led by Albert Sabin worked tirelessly to develop an effective vaccine. By analyzing the results of autopsy examinations of individuals who died of poliomyelitis, Sabin was able to demonstrate that poliovirus first replicated in and attacked the intestines, and only then entered the central nervous system. Sabin assumed that the vaccine should not only be cheap and easy to use, but at the same time it should also be effective against all three poliovirus types. In 1955, having performed tests in animals, Sabin decided to administer his oral vaccine to humans for the first time. The

results were encouraging. As Salk's solution had already been adopted in the United States as mandatory, Sabin, as previously Koprowski, was forced to conduct testing outside the US. It was not until the beginning of the 1960s that Sabin's oral vaccine was finally considered a more robust and safer method for the protection against polio. Koprowski's vaccine was not approved in the United States.

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