Hilary Koprowski and the first orally administrated polio vaccine (OPV)

Hilary Koprowski i pierwsza doustna szczepionka przeciw polio

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Summary

Polish-born physician Hilary Koprowski became one of the most insightful scientists working in the field of virology and immunology in second half of the 20th century. Among his long-term research projects were those which focused on oral vaccines. His rabies vaccine is still used today and Koprowski should also be recognized as one of the pioneers in the field of monoclonal antibodies used in the diagnosis and therapy of melanoma [7]. This paper discusses the history of Koprowski's method, derived from the concept of the Nobel Prize winning virologist Max Theiler, which provided attenuated poliovirus by repeated intracerebral passage of poliovirus in cotton rats, which finally resulted in the development of the very first oral polio vaccine – OPV [11, 27, 33]. Although overshadowed by Jonas Salk's inactivated poliovirus vaccine (IPV) and Albert Sabin's OPV vaccine, Koprowski's OPV should not be neglected nor forgotten.

Keywords: Hilary Koprowski, oral polio vaccine, virology, history of medicine

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It is possible that polio was already known in ancient Egypt, however it is only a supposition, with no firm evidence coming from paleopathological field [6]. Until the 19th century we did not have convincing data about polio, although it was certainly circulating through the ages. The first clear medical description comes from 1813 and belongs to Italian surgeon Giovanii Battista Monteggia [4]. When in 1840 German physician Jakob Heine analyzed a group of clinical sings and symptoms classifying them as a separate pathological entity, polio was still a relatively rare disease [9]. But it was in the second half of the century when poliomyelitis entered the epidemic scale, triggering further and more intensive research. It was not until 1890, during another polio pandemic attack in Europe and the United States, when the

Swedish pediatrician, Karl Oskar Medin, made a detailed description of the disease, suggesting the possible ways it spread [29]. In 1905 Otto Ivar Wickman was able to bring convincing clinical and statistical data showing that polio could be transmitted between human subjects. He also coined a name for it – *Heine-Medin disease* [5, 34].

In 1909 Carl Landsteiner and Erwin Popper, summarizing the results of their experimental and histopathological research, suggested the viral nature of the Heine-Medin disease [25]. Even when their assumption was soon to be proven, there was still the unsolved problem of the exact mechanism and routes of the viral transmission and the very nature of the virus was until the 1930s under discussion. That challenge became more complicated when in 1931 Frank M. Burnet and Jean Macnamara revealed that more than one type of poliovirus exist [5]. When in 1935 Maurice Brodie failed to produce a safe and effective polio vaccine, it became obvious that Burnet and Macnamara were right [1]. The subject of investigation – namely, polio causing pathogen – was shrouded in mystery [12]. The next element of the puzzle was added in 1941. During their experiments, Howe and David Bodian managed to infect chimpanzees with a poliovirus administrated to the animals orally. Therefore, it was then assumed that the disease could be transmitted by the oral route.

Finally, in 1949 John Franklin Enders, Thomas Huckle Weller and Frederick Chapman Robbins were able to multiply all three poliovirus types. They were able to cultivatie the poliovirus in human non-nervous tissue cultures. Their method could be used in various primate tissues and now large amounts of virus could be propagated in vitro [5]. This was the start of the race for an effective polio vaccine. One of its competitors was the Polish-born virologist, Hilary Koprowski.

Hilary Koprowski (1916-2013) was born in Warsaw to an assimilated Jewish family. He received a medical degree from Warsaw University in 1939 (became doctor honoris causa of Medical University of Warsaw 61 years later) and fled the country that year due to Germany's invasion of Poland. Via Italy, Spain, Portugal he escaped to Brazil, where he worked in Rio de Janeiro for the Rockefeller Foundation in search for the yellow fever vaccine. From Brazil he emigrated to the USA. (Fig. 1)

In 1944 Koprowski joined the Section of Viral and Rickettsial Research at Lederle Laboratories of the American Cyanamid Company at Pearl River, New York [30]. Already interested in a research project concerning poliomyelitis, he began work with Tom Norton and Walsh McDermott, which lead to the successful isolation a poliovirus from the blood of a human patient [19]. A year later, the polio vaccine research program was activated [24].

During the late 1940s, Hilary Koprowski and his team at Lederle Laboratories began to work on the method that could attenuate type 2 polio virus through monkeys and cotton rats (Sigmodon hispidus). The resulting attenuation was achieved after cotton rat and monkey to monkey transfer, and in January 1948 Koprowski self-administrated the live-virus oral vaccine material [8]. The results were very promising and no side effects were detected. This started the further experimental trials.

As Koprowski recalls: "On February 27, 1950, when a six-year-old boy who had no antibodies against type 2 virus was given by Dr. Jervis, Mr. Norton and myself – an emulsion which tasted like cod-liver oil and was in reality a suspension of cotton-rat cord and brain tissue which had been infected with approximately three million mouse lethal doses of the TN strain (named after Thomas W. Norton)" [15].

The child was under careful clinical observation and intensive laboratory tests were conducted. In the final conclusion, it became obvious that intestinal infection with the virus was present; however, no sings or symptoms of illness were detected. Blood analysis showed that after 15 days from OPV administration, specific antibodies were clearly visible. Nevertheless, Koprowski's research team was careful and patient. The next trial was conducted not earlier then 44 days later. Another child, who was not immune to the type 2 virus, received OPV and again the antibodies developed. The lack of alarming symptoms of the disease could be confirmed [15, 16].

This encouraged Koprowski to continue his research on a larger scale. Next, 18 children received orally the emulsion, so there were 20 subjects in total. This time, the attenuated poliovirus emulsion was mixed with chocolate milk and again "in not a single instance were there any sings of illness noted" [16]. Koprowski was heavily criticized for performing tests directly on children, without firm and multiple data from animal experiments.

Although Koprowski's team continued research, they were now trying to prove that all experimental procedures were fully transparent and conducted only when "permission of each child's parents had been legally obtained" [18]. The selected group of sixty-one children, with no antibodies against type 2 poliomyelitis virus detected, were fed the TN strain of the virus. Some days after feeding, the virus was isolated from the stool of 29 children. No viremia nor any clinical signs of illness were observed, and specific antibody presence was evident in most of the patients.

The years 1953–1954 were marked by intensive experimental investigations. It was becoming obvious that type 1 (so-called Brunhilde strain) was responsible for most of the cases of paralytic polio throughout the world. This is why the research was now advancing on two, interrelated roads of strains examination. Koprowski, again with Jervis and Norton, published a paper summarizing their next experiments with the TN strain of rodent-adapted poliomyelitis virus. They fed nine chimpanzees and observed that all the animals developed homotypic antibodies. Two of them became intestinal carriers of the virus and none showed clinical signs of the disease [17].

In the same year, the results of comparative studies, which included chimpanzees, cynomolgus and human subjects, were presented. As the researchers acknowledged, "It will be noticed that out of 54 human beings […] 31 became intestinal carriers and all 54 developed homologous antibodies" [18]. In the meantime, Koprowski's team was experimenting with two laboratory virus strains (Sickles and Mahoney) "passaged together until adapted to the Swiss mouse" and then on next selected mouse group. This eventually gave the new, SM strain a subline with no virulency when rhesus and cynomolgus monkeys were target for it [22, 24]. Then they decided to push the tests further. Two human subjects with no antibodies against type 1 poliomyelitis virus present were given a mouse adapted type 1 strain, while another individual with no antibodies against types 1 and 2 detected, received mixture of mouse adapted type 1 and type 2 strains. None of them evolved clinical signs of illness or viremia. All three excreted virus in the stools [20].

A year later, Koprowski was trying to argue that his OPV can produce antibodies for both types of poliovirus in humans [14]. In 1956 Koprowski's team summarized the results of the clinical tests, in which a group of 225 human individuals was subject of investigation. Some of them received SM (type 1) poliomyelitis virus, which was given to them in capsules, others were given TN (type 2) virus in milk suspension. The antibodies were, as it was observed

already previously, clearly emerging in all cases. None of the patients developed the typical sings of illness after ingesting the living poliomyelitis virus [23], which again confirmed the efficiency of Koprowski's OPV [22]. No side effects were detected [28].

It can be estimated that the first attempt to develop a live-virus polio vaccine was completed [3]. The effectiveness of Koprowski's vaccine was first tested on a larger scale in Kongo, Africa [26, 31] and in Poland [32], in both cases with positive results.

In United States, however, there was strong reserve towards Koprowski's vaccine model, which in consequence led to the introduction of Jonas Salk's vaccine, accepted in the USA in 1955, and Albert Sabin's – another Polish-born researcher of Jewish descent – vaccine in 1961.

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