

Poliomyelitis

Background Paper

PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

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THE CONTROL OF POLIO provides an excellent example of the value of careful human clinical investigation. Unfortunately, animal experiments led to a number of false conclusions, causing the loss of many years' time in the struggle to control the disease.

Human Clinical Research Provides a Description of the Disease and Its Means of Transmission

In early recorded medical history, poliomyelitis was a sporadic disease, but beginning in 1835, small outbreaks were reported in the U.S. and U.K. In 1840, Jacob von Heine, a German orthopedic surgeon, provided the first detailed description of the disease, based on studies of patients, which correctly suggested that the spinal cord was the seat of involvement. In 1863, pathologists in France demonstrated nerve cell damage in the spinal cords of human patients.¹

The year 1887 marked the beginning of a series of worldwide epidemics. Studying human patients in Stockholm, epidemiologist Karl Oscar Medin described two phases of the disease, namely, the systemic phase of fever and generalized symptoms, and the neurologic phase, which signified the virus' invasion of the nervous system, leading to weakness or paralysis. During a large epidemic in Sweden in 1905, Medin's pupil, Ivar Wickman, studied polio patients and discovered that people with minor systemic cases often spread the disease before they were diagnosed and isolated.² These clinical observations were vital to later efforts aimed at disease prevention and control.

In 1908, Viennese immunologist Karl Landsteiner and his associate Ervin Popper noted that bacteria could not be found in infected human spinal cord tissue,^{1,2} correctly indicating that the cause was a virus.

How Animal Experiments Confused the Question of Transmission

Later, Landsteiner turned to animal experiments, studying the effects of the polio virus on various non-human species who were given the disease artificially. Unfortunately, these animal experiments directed attention away from the study of the human disease, and wasted researchers' time. John R.

Paul, historian and scientist at Yale's Poliomyelitis Unit, wrote, "Many who followed him became so entangled in the intricacies of research on the experimental infection that they were never able to shake themselves sufficiently loose to explore the human disease.... It was as if some of the main investigators, particularly in the United States, had become so transfixed with the importance of laboratory work on experimental poliomyelitis that they had, for the time being, arrived at the assumption that it was the only type of poliomyelitis research worth doing."¹

The animal experiments wasted valuable time. It wasn't until the 1950's that three distinct types of the polio virus were discovered. Paul suggests that progress may have been significantly faster if Landsteiner had focused on this problem instead.¹

Animal experiments also led investigators in wrong directions, sometimes with dangerous consequences. In 1909, Simon Flexner and Paul Lewis of the Rockefeller Institute in New York transmitted polio to monkeys by rubbing the nose and throat washings from infected people into the animals' nasal membranes.^{2,3} They became convinced that the infection passed directly into the brain from the nose, thus bypassing the systemic immune system—a misconception which became firmly entrenched for more than twenty years. In 1937, they tried to prevent polio by spraying children's noses with zinc sulphate and picric acid-alum. The trial was a failure, and some of the children lost their sense of smell permanently.^{2,4}

In contrast to these animal experiments, human pathology studies continued to lend support to the emerging hypothesis that early, non-neurologic cases spread orally and, by infecting the digestive tract, were responsible for the spread of the disease. In 1912, Swedish researchers found the polio virus in the contents and walls of human small intestines.² Unfortunately, animal experimenters incorrectly explained the virus' presence in the intestines as derived from swallowed nasal contents, and continued their work.

More Clues to Immunity

The first clues to the means of immunizing against polio came from studies of the natural immunity that occurs in patients recovering from mild polio virus infections. In

1910, researchers at the Public Health Service discovered antibodies to the poliovirus in humans who had recovered from the systemic (non-neurologic) illness. In 1912, a team of clinical investigators at the Rockefeller Institute found antibodies in healthy people in amounts similar to that in people convalescing from polio.² That same year, Swedish researcher W. Wernstedt developed the theory of naturally acquired immunity caused by mild, inapparent infection. This meant that exposure to the virus early in life could prevent disease later. His source of information was human epidemiological data.¹

Although these human studies paved the way for methods to prevent infection, animal experiments continued to misdirect research efforts, and it was to be another 25 years before investigators finally picked up the trail left by clinical researchers.

Animal Experiments and Failed Immunization

Still working with the false assumption that infection traveled from the nose directly into the central nervous system, Flexner and Lewis immunized monkeys against polio by the intraspinal injection of serum from recovered monkeys. In 1910, other investigators tried to treat people in the early stages of polio by injecting the serum of recovered patients into the patient's spinal canal. This technique was also tried intravenously in 1914, but without success.³ It was not until 1931 that controlled human studies proved the futility of serum injections for prevention or treatment.^{2,3}

Return to Clinical Study and Resultant Progress in the Understanding of Transmission and Immunity

In 1941, Albert B. Sabin, working in Cincinnati, demonstrated that the polio virus is not present in the nasal membranes of patients at autopsy, but is present in the digestive tract and the brain and spinal cord.² At almost the same time, persistently working with the animal "model," Howard Howe and David Bodian of Johns Hopkins infected chimps orally and studied the resultant occasional disease.² They ultimately demonstrated in animals what had already been found in humans, that the virus could be transmitted orally and could survive in the digestive tract.

In 1948 and 1949, Paul studied isolated Eskimo villages and determined that once immunity was gained through a minor or symptomless infection, it persisted for years. A few years later, in 1954, Bodian's group and Dorothy Horstmann of Yale, working independently, detected the virus in patients' blood before neurological signs were seen.²

These human data, together with previous human pathology studies demonstrating the presence of the virus in the intestines, not only confirmed the route of transmission, but also indicated that more serious cases could be prevented, pointing the way to vaccine development.

Virus Grown in Animal Cells Mutates and Misleads Researchers; Human Cell Culture Solves Problems

Before 1907, when living cell culture was developed,¹ laboratories used live monkeys to test for the presence of the polio virus. Experimenters working with the monkey "model" of the disease began cultivating the virus in monkey nerve tissue. This resulted in laboratory strains of virus which preferentially attacked the brain and spinal cord. Data obtained from these laboratory strains supported the misleading concept of a direct neurologic route of infection, and could not account for Medin's significant observations of pre-existing systemic (non-neurologic) disease.⁴

It was not until 1949 that John Enders, Frederick Robbins and Thomas Weller of Harvard University and Boston Children's Hospital cultivated the virus in human non-nervous tissues,⁵ and in the course of this work discovered distinctive changes in the cells, which helped replace the older animal tests used to determine virus presence. They won the Nobel prize in 1954.³

Animal experiments also inspired vaccines which turned out to be failures. In 1934, both John Kolmer of Philadelphia, and Maurice Brodie and William H. Park of the New York City Health Department developed vaccines from infected monkey spinal cords. In over 20,000 children vaccinated, twelve were paralyzed and six died. The vaccine was withdrawn.³ It is probable that since the virus was grown in monkey nerve cells, it mutated to attack nerve tissue much more aggressively than did the naturally-occurring virus. Today, cultivation of the polio virus in human cell culture can avoid the sometimes serious reactions produced by vaccines grown in the nerve tissues of animals.²

Vaccine Development: From Animal Experiments to Human Cell Cultures

Twenty years later, inspired by Enders' virus cultivation methods, Jonas Salk, Professor of Bacteriology at the University of Pittsburgh, began work with polio virus isolated from humans, seeking to make a vaccine. Although human tissue culture was available for production of the virus, Salk used monkey kidney tissue, believing that this was safer.⁶ The vaccine was unfortunately not as safe as he had hoped. The safety of this inactivated (killed) vaccine was tested first

“Work on prevention [of polio] was long delayed by an erroneous conception of the nature of the human disease based on misleading experimental models of the disease in monkeys.”

—ALBERT SABIN, M.D., DURING A 1984 HOUSE SUBCOMMITTEE

on monkeys, and its ability to affect immunity was tested on children who had recovered from paralytic forms of the disease.¹ Tissue culture methods for determining whether a virus was completely killed were still under development at that time.⁶

In 1954, the vaccine was given to 650,000 American children, and a placebo was given to 200,000. The later incidence of paralytic polio in the experimental group was just over one-quarter the incidence in the control group. However, soon after the experiment concluded, it was discovered that several batches of vaccine contained live virus. 204 vaccinated people and their family members contracted polio, causing eleven fatalities.³

Researchers now recommend cultivating the virus for Salk vaccine production in human connective tissue cells instead of monkey kidney cell preparations. Human cell-derived vaccines are just as effective, less expensive, and eliminate the serious danger of animal virus contamination.⁷ Safety testing is also possible without the use of animals. In 1982, the World Health Organization recommended dropping requirements for the animal inoculation safety test of the inactivated vaccine, and relying instead upon the more sensitive cell culture methods.⁸

W. Hennessen, a professor at the Bureau of Applied Immunology in Bern, Switzerland, notes, "It is common knowledge now that test systems became infinitely more sensitive when the animals used were replaced by other methods."⁸

In 1955, Sabin utilized Enders' methods of virus attenuation through multiple cell culture passage² to develop an oral live vaccine, using monkey kidney tissue.⁹ The vaccine was tested on monkeys, chimpanzees, and humans.³ By 1964, one hundred million doses had been given. Like the Salk vaccine, the virus can be produced for the live vaccine using human cells.¹⁰

Sabin vaccine manufacturers still test the vaccine by injecting it into the spinal cords of living monkeys. They use this test to check whether the live virus vaccine will cause polio, even though this test is time-consuming and expensive,¹¹ and difficult to correlate with effects in humans. The results vary excessively, according to the World Health Organization.⁸ Researchers at the National Institute for Biological Standards and Control in London write, "The degree of correlation between the neurovirulence of a poliovirus when inoculated into the central nervous system of a monkey and its safety in man is not

known at the present time."¹² Between 1973 and 1984, the Sabin vaccine caused 101 out of the 138 cases of paralytic poliomyelitis in the U.S.¹³

Researchers have developed a laboratory method of determining neurovirulence, which may provide a replacement for the monkey test. It is based on the detection of virus mutations commonly associated with increased neurovirulence.¹⁴

The history of research on polio shows the value of human clinical research, studies of human tissues, and human cell culture techniques. To the extent that animal experiments have been replaced by such methods, the research endeavor has been improved and accelerated.

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