

FOCUS: YALE SCHOOL OF MEDICINE BICENTENNIAL

Putting Together the Pieces of Polio: How Dorothy Horstmann Helped Solve the Puzzle

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Dr. Dorothy Horstmann, epidemiologist, virologist, clinician, and educator, was the first woman appointed as a professor at the Yale School of Medicine. Horstmann made significant contributions to the fields of public health and virology, her most notable being the demonstration that poliovirus reached the central nervous system via the bloodstream, upsetting conventional wisdom and paving the way for polio vaccines. In 1961, she was appointed a professor at Yale School of Medicine, and in 1969, she became the first woman at Yale to receive an endowed chair, which was named in honor of her mentor, Dr. John Rodman Paul. In this review, the major scientific contributions of Dr. Dorothy Horstmann will be highlighted from her more than 50-year tenure at Yale School of Medicine.

INTRODUCTION

Dorothy Millicent Horstmann was born in Spokane, Washington, on July 2, 1911 [1]. She spent much of her youth in San Francisco and earned her undergraduate degree from the University of California, Berkeley in 1936. Four years later, Horstmann graduated from the University of California, San Francisco with a medical degree. Concurrent with Horstmann's development as a scientist and clinician was the development of polio as one of the most

feared diseases in the United States. Although rare in the late 19th century, polio epidemics began to occur more frequently in the early 1900s. One of the worst epidemics took place in 1916, when a polio epidemic tore through the northeastern United States [2], claiming nearly 6,000 lives and leaving more than 27,000 people paralyzed. This epidemic first put polio in the national spotlight, and by the time Horstmann came to Yale, polio was quickly becoming the nation's most feared disease [3].

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†Abbreviations: WHO, World Health Organization; IDSA, Infectious Disease Society of America.

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Polio is caused by an RNA virus, which was first identified by the Viennese scientists Karl Landsteiner and Erwin Popper in 1908 [4]. Ninety percent of people infected by poliovirus never develop symptoms. The majority of those who develop symptoms have a mild illness, while approximately 10 percent develop the most severe form of the disease: acute flaccid paralysis [5]. Paralysis occurs when the virus invades the central nervous system and destroys motor neurons, which are required for muscle contraction [6]. This nervous tissue damage usually leads to a temporary paralysis. However, in the case of more severe damage, the patient permanently loses the function of those muscles. Permanent paralysis most often occurs in the muscles that control the legs or breathing. The latter led to death unless the patient was placed in an iron lung. The prospect of an iron lung, a pressurized metal chamber that served as a respirator for the patient, was one of the most dreaded consequences of polio infection.

HORSTMANN'S EARLY YEARS AT YALE

Yale hired Horstmann (Figure 1) in 1942 as a Commonwealth Fellow in Internal Medicine under the tutelage of Dr. John Rodman Paul. In 1931, together with Dr. James Trask and other Yale scientists, Paul started the Yale Poliomyelitis Study Unit to respond to the ever-increasing epidemics of polio [7]. Paul was a pioneer in the field of epidemiology and formed a new discipline called clinical epidemiology, which focused on “exploring the multiple factors contributing to the occurrence of disease in individuals and in population groups” [8]. Horstmann applied these techniques in her studies of poliovirus.

In the early 1940s, leaders in the field of polio research, such as Simon Flexner at the Rockefeller Institute in New York City, believed that poliovirus infected the brain by traveling through the nerves in the nasal passage [9]. The reason for Flexner's beliefs about polio pathogenesis and transmission was due to the experimental model used to



Figure 1. Dorothy Horstmann is pictured in her office at the Epidemiology and Public Health Laboratory Building. Though Horstmann's faculty appointment was in pediatrics and epidemiology, her office and laboratory were both located in the epidemiology department. Photo courtesy of Dr. I George Miller.

study polio. Flexner and his colleagues used virus isolated from brain tissue of monkeys that exhibit paralysis to infect other groups of monkeys via intracerebral inoculation. The passaging of the poliovirus only through brain inoculation led to the adaptation of a lab strain of the virus that only infected nervous tissue. Furthermore, when Flexner would later attempt to inoculate monkeys orally with the lab strain of the virus, no disease symptoms would develop. Flexner's findings falsely led scientists to believe for decades that poliovirus could only replicate in nervous tissue and could not cause central nervous system infection as a result of oral delivery of the virus [10]. Horstmann and her colleagues believed in a different picture of transmission and would soon defy the conventional wisdom that poliovirus exclusively infected the nervous system.

During 1943 and 1944, Horstmann and the Yale Study Unit were asked to investi-

gate five different outbreaks of polio in the United States. Those occurred in New Haven, Connecticut, Chicago, Illinois, and Bakersfield, California, in 1943, and in and around Hickory, North Carolina, and New York City in 1944. The findings were published in a series of four articles in 1946 [11-14]. Horstmann and her colleagues systematically determined whether virus could be recovered from pharyngeal swabs, oropharyngeal washings, feces, and blood from patients and their contacts during the outbreaks. These studies were unique in several ways. The approach of taking samples from multiple sites over multiple days from a single patient had never been done in such a comprehensive manner. This was important to determine how long the virus persisted in the pharyngeal and gastrointestinal tract and to determine the relative importance of each site during infection. The majority of fecal samples were positive for poliovirus over multiple weeks while viral recovery from the pharyngeal tract was transient and infrequent. These results, along with the findings of other scientists, pointed to the gastrointestinal tract, and not the nasal passage, as playing an important role in polio pathogenesis. One puzzle that remained was how the virus transited from the gastrointestinal tract to the brain if the virus was acquired by way of ingestion and not inhalation.

HORSTMANN'S SIGNIFICANT BREAKTHROUGH IN POLIO PATHOGENESIS

During the New Haven outbreak in 1943, Horstmann collected blood from all 111 suspected polio cases admitted to Yale-New Haven Hospital. Only one sample out of the 111 tested positive for poliovirus [11]. Although the significance of this finding seemed minimal since it was such a rare event, there were unique characteristics of this one case that caught Horstmann's attention. In the majority of the 110 other cases admitted to the hospital, blood was drawn after polio symptoms such as paralysis had developed. The one positive case, a 9-year-

old girl living in New Haven, presented to the hospital, and blood was drawn within six hours of developing mild disease. The girl never developed paralysis. This difference in timing between the cases led Horstmann to look closer at the period between infection with the virus and onset of symptoms. Her results would fundamentally change the conventional wisdom of polio transmission and pathogenesis.

To test whether the bloodstream played a role in polio pathogenesis, Horstmann performed a series of experiments in monkeys and chimpanzees. First, the animals were fed poliovirus orally to follow what Horstmann and others previously had shown to be the natural route of infection. Then blood samples from these animals were taken each day for 7 days after infection to determine if and when poliovirus could be found in the blood. The results were surprising. Poliovirus was detected in the blood within 4 to 6 days of the feedings before onset of paralysis in the majority of the animals tested [15]. These findings were later independently confirmed by David Bodian at John Hopkins University [16]. The results indicated why previous scientists, and Horstmann herself, had so often failed to detect virus in the bloodstream: They had waited too long. Previously, blood samples were taken after the onset of more severe disease symptoms, such as paralysis. By this time, polio-specific antibodies already would have been circulating in the bloodstream, effectively neutralizing the virus. Therefore, at the time of the blood draw, no virus would be detectable in the blood. Horstmann went on further to show that virus could be recovered from the blood of contacts of polio patients who later developed disease or remained asymptomatic [17]. These discoveries overturned the general consensus in the scientific community that poliovirus solely infects nervous tissue and paved the path to the current model of poliovirus transmission and pathogenesis.

Dr. John Enders, who won the Nobel Prize for his work on developing a tissue culture method to replicate poliovirus, credited Horstmann with shaking "the widely

held feeling that the virus grew solely in nerve cells” [18]. Enders further went on to say about Horstmann’s discovery that “everyone was relieved to find that poliomyelitis was not an exceptionally bizarre disease, but similar to others.” Further praise for Horstmann’s discovery was communicated in a private letter to Horstmann from Yale’s distinguished historian of medicine, John F. Fulton, MD, DPhil, who proclaimed: “This disclosure is as exciting as anything that has happened in the Yale Medical School since I first came here in 1930 and is a tremendous credit to your industry and scientific imagination. . . . It is also medical history” [19]. Horstmann’s discovery also had important implications for the development of a polio vaccine.

HORSTMANN'S DISCOVERY LEADS TO A POLIO VACCINE

Horstmann’s discovery provided the specific anatomic sites in which to stop poliovirus — the blood and gastrointestinal tract. Vaccines against viruses typically use an attenuated form or components of the pathogen to reproduce the quality of the immune response that is elicited upon natural infection. An oral polio vaccine that closely mimics the natural route of infection of the virus could be used to elicit antibodies in the blood and gastrointestinal tract that would later block poliovirus infection. Horstmann and Paul’s seroepidemiologic surveys further supported the use of an oral polio vaccine. In a study conducted in Casablanca, Morocco, from 1947 to 1953, polio cases were compared between European and native Moroccan populations [20]. The study illustrated some striking differences in polio epidemiology between the two groups. The European group had 20-fold higher rates of polio and the majority of cases were more than 2 years old. When the native Moroccan population was surveyed for polio antibodies in the blood, the majority of children had antibodies by 2 years of age, and these antibodies persisted in the population for decades. Exposure to poliovirus infection as infants seemed to elicit antibody production

that protected the Moroccan children from disease later in life. The results of these seroepidemiologic studies by Horstmann and others supported the development of a vaccine that elicited antibodies in the blood and gastrointestinal tract.

At the same time Horstmann and others published their results pointing toward an oral polio vaccine as the best option to protect against polio infection, testing began in the United States with an inactivated polio vaccine. That vaccine, developed by Jonas Salk, was a form of killed poliovirus delivered by subcutaneous injection [21]. The vaccine did generate protective polio-specific antibodies in the blood in children and adults but not in the gastrointestinal tract. Furthermore, the inactivated polio vaccine required the use of sterile needles, which are not readily available in resource poor settings, while an oral polio vaccine did not require needles. Therefore, Horstmann and her colleagues supported the further development of an oral polio vaccine. Though several groups were developing oral polio vaccines, the vaccine created by Albert Sabin soon reached the forefront. Sabin was a clinician and virologist who had been in the vanguard of polio research for decades. His vaccine induced the best antibody response while having the least neuropathogenic effects in monkeys and chimpanzees [22,23]. Since vaccination with the inactivated polio vaccine had already begun in the United States, scientists looked outside the country to test the oral polio vaccine in humans.

Massive trials of the oral polio vaccine were started in the Soviet Union in 1956. Although Soviet scientists reported favorable results with the oral polio vaccine, much of the world was skeptical of the Soviets’ findings and called for outside validation of their results. Without this validation, no recommendations would be given for use of the oral polio vaccine. The World Health Organization (WHO†) asked Horstmann, by now a well-respected scientist in the polio field, to validate the Soviets’ results. By the time Horstmann arrived in the Soviet Union in 1959, close to 15 million children had received the oral polio vaccine in Russia,

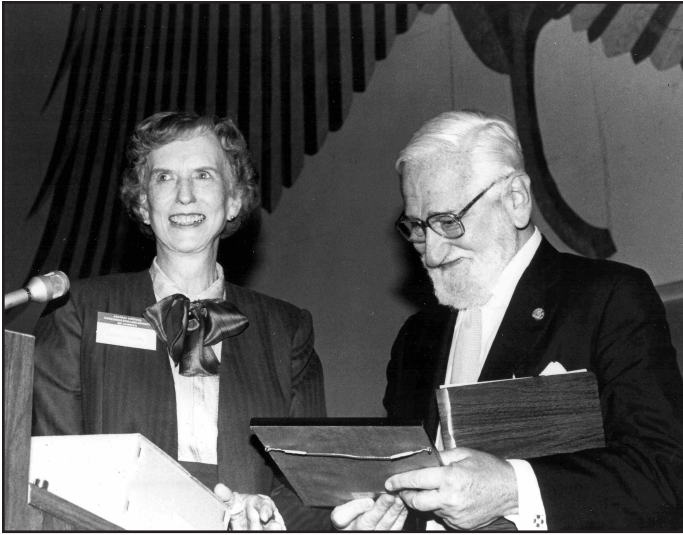


Figure 2. Dorothy Horstmann and Albert Sabin at the Infectious Disease Society of America (IDSA) annual conference in 1984. Horstmann was the first woman president of the society in 1975. Horstmann is pictured here giving an award to Dr. Albert Sabin after Sabin delivered the Maxwell Finland Lecture. Photo courtesy of Dr. I George Miller.

Czechoslovakia, and Poland. Horstmann spent 6 weeks evaluating the Soviet scientists' results. Her subsequent favorable report to the WHO about the vaccine trials in the Soviet Union led the way to worldwide acceptance of the oral polio vaccine and licensing of the vaccine in the United States in 1961 [24]. Not long after the licensing and widespread use of oral polio vaccine in the United States, the last person-to-person transmission of wild poliovirus in the United States was detected in 1979 [25].

HORSTMANN AS A CLINICIAN AND EDUCATOR

Horstmann's experience studying polio, which primarily attacks the young, naturally led her to change her focus from internal medicine to pediatrics mid-career. When Horstmann described her experiences working on polio epidemics, she said, "It had a dramatic immediacy. When you deal with an epidemic you realize it's an urgent thing. There was so much to be learned" [19]. Horstmann's later research in polio went on to further characterize the immune response elicited from the oral polio vaccine in vaccinated persons and contacts in the United States and worldwide [26-28]. Horstmann also became an expert in many other childhood and congenital viral diseases and published several research articles about the

clinical epidemiology of Rubella, Coxsackie, and Echo viruses. Horstmann's research on Rubella virus was instrumental in the licensing of the Rubella vaccine in children in the United States in 1969 [29].

Horstmann continued her work at Yale with a joint appointment in both Pediatrics and Epidemiology. Horstmann was the first woman to be appointed a tenured professor in 1961 in the Yale School of Medicine and was the first woman at Yale to receive an endowed chair. The endowed chair was in honor of her colleague and mentor, Dr. John Rodman Paul. In addition to Horstmann's substantial contributions to science, she also made important educational contributions. In Horstmann's *Festschrift*, published in 1982 in honor of her retirement, her colleague, Dr. Robert Berliner, noted her imprint on clinical education at Yale School of Medicine. Berliner pointed out that Horstmann "enlarged the scope of infectious disease to embrace its public health aspects. She has also been a staunch supporter of the integration of diagnostic microbiology and virology into the practice and teaching of infectious disease" [30]. In addition to Horstmann's accomplishments as a clinician, scientist, and teacher, she contributed significantly to her professional community. Horstmann served as a president of the Infectious Disease Society of America (Figure 2) and was elected to the National Academy of Sciences in 1975.

In Horstmann's honor, an annual lectureship has been established at Yale in Pediatric Infectious Diseases and Epidemiology. Several notable scientists have spoken as part of the Dorothy Horstmann Lecture since its inception in 1991. These scientists include Nobel Prize winners, vaccine pioneers, and leaders in the fields of immunology and infectious diseases. Ten years after the establishment of the lecture, Dorothy Horstmann passed away in New Haven, Connecticut. In the words of her colleague Berliner, there was no one "more highly regarded as a person and as a university citizen" among the faculty than Dorothy Horstmann [30]. Her contributions as a polio pioneer, scientist, clinician, and educator have left an indelible stamp on the Yale School of Medicine.

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