The First Measles Vaccine

Like in the more familiar story of polio vaccine, the development of the first successful live attenuated vaccine against measles began in the laboratory of John Enders. One of the greatest virologists of the 20th century, Enders pioneered the technique of viral tissue culture, which makes it possible to grow viruses in vitro in cells nourished in laboratory media. In 1949, he and his pediatric infectious disease fellows Thomas Weller and Frederick Robbins showed that poliovirus could be cultivated in tissue of nonneuronal origins, a discovery that set the stage for the first successful vaccines against the disease and led to a Nobel Prize in 1954. Enders himself was a remarkable character. He never tried to patent his work or share results with the media before peer review. He was consistently generous in sharing his knowledge with potential competitors, and despite his personal wealth he was equally known for his frugality; fellows learned to wash their own glassware, and every year the "chief" returned unspent grant money to the National Institutes of Health. Above all, Enders took seriously the role of mentor, rounding each day beside the benches of his select group of fellows with his bow tie, vest, and jacket asking, “Well, what’s new?” A positive response was often rewarded by an hour-long conversation.

In 1954, while the national field trials of Jonas Salk’s polio vaccine captivated media attention, Enders and pediatrician Thomas Peebles successfully cultivated measles virus in human kidney cell culture for the first time. Ever-ingenious in finding sources for his tissue cultures, Enders obtained kidneys from a neurosurgeon colleague who treated hydrocephalus by performing a unilateral nephrectomy and connecting a shunt to carry cerebrospinal fluid to the ureter. Peebles traveled the Boston, Massachusetts, area with a throat swab in search of measles outbreaks in private boarding schools. His first, and most famous, success involved an 11-year-old boy named David Edmonston, whose name became attached to the strain that would become the source for the first measles vaccine.

Enders decided to play a much more “hands-on” role with measles vaccine than he had with polio. He was unhappy with how the polio vaccine saga had unfolded after he had left its development to others. Less than a month after the Salk vaccine’s approval and licensure in April 1955, it became apparent that some of the vaccine lots were contaminated with wild polio. The ensuing disaster, in which some 260 children developed paralytic polio from the vaccine, was widely blamed at the time on Cutter pharmaceuticals. Enders, however, believed Salk’s own inactivation process had been at fault. He wanted to stay personally involved to be sure that the measles vaccine’s development would proceed more smoothly.

An immediate problem was to find a new human tissue culture system; Enders’ neurosurgery colleague was no longer removing kidneys to place shunts. Two new members now joined the Enders team: the Yugoslav virologist Milovanovic (who would later be put in charge of polio vaccine production in Yugoslavia) and a pediatric infectious disease fellow, Samuel L. Katz. Enders set his eyes on the placentas being discarded across the street by the Boston Lying-in Hospital: “There are those nice amnions that lie in the placenta,” he observed to his colleagues; “Let’s do something with them.” Milovanovic and Katz set forth and returned with fresh placentas, from which they could peel off the amniotic membranes and trypsinize their cells to make beautiful cell cultures. Because humans were the sole natural host of measles, Enders reasoned that...
the virus could be attenuated by being adapted to a nonhuman species. Earlier investigators had grown influenza, mumps, and yellow fever viruses in embryonated chick eggs; indeed, in the 1930s Max Theiler and Hugh Smith used this system to develop the attenuated yellow fever vaccine still used today. After some early false starts, Milovanovic and Katz succeeded in establishing measles vaccine in this system. The next step was to repeat this success in tissue cultures obtained by trypsinizing chick embryos. Although at first it was not clear whether anything was growing at all, characteristic cytopathic changes appeared in the fifth passage.

After 3 years of work (involving 24 passages through human kidney tissue culture, 28 through human amniotic cell culture, 6 in fertilized hens’ eggs, and 13 in chick embryo cell cultures), the investigators finally felt ready to test the modified Edmonston strain in monkeys. The injected monkeys developed a strong antibody response but no fever, viremia, or rash, which is consistent with successful attenuation. After more safety trials in monkeys, it was time to test the vaccine in humans. As the only physician on the team, Katz played an increasingly central role at that point. Following the time-honored tradition of autoexperimentation, the lead investigators first tested the strain on each other. Their antibody titers rose, and no adverse effects followed. Next, Enders and Katz approached the Walter E. Fernald State School near Waltham, Massachusetts. This was an institution typical of many others of the time that provided long-term custodial and medical care for severely handicapped children with conditions such as microcephaly, trisomy 21, and cerebral palsy. “They lived in dormitories,” Katz recollected, “and they had really severe outbreaks of measles every few years—not just with morbidity, but with mortality.”

Conducting a clinical trial among institutionalized children raised significant ethical questions. Indeed, just 10 years earlier, the Fernald School had permitted nontherapeutic nutritional studies without informing families that their children were being given radioisotopes. Given that research ethics in the 1950s remained largely unregulated, some historians have argued that the Nuremberg code’s powerful articulation of informed consent in 1946 had little impact on American research until the 1960s. In this light, it is notable that Katz explained the trial in person to every parent, and the ensuing article clearly stated that no child was given the vaccine without written parental consent. Every morning and afternoon Katz and technician Ann Holloway went to the school, examined the children, took throat swabs, and drew blood specimens. Returning to the laboratory, they attempted to detect measles virus from their samples but never did. A number of the children developed fevers and an evanescent rash but “seemed perfectly fine—in fact, it was a little bit like roseola,” Katz recounted. The children had nonetheless developed antibodies, and when the next measles outbreak struck the Fernald School, all of them were totally protected.

Enders and Katz then recruited a number of colleagues from around the country to test the vaccine in children in other settings, both institutionalized and home-dwelling. The resulting articles appeared together in the New England Journal of Medicine on July 28, 1960. Written by figures who were on their way to becoming pediatric leaders in their own right, such as Saul Krugman, C. Henry Kempe, and Robert Haggerty, they joined those of Enders, Milovanovic, and Katz to provide an impressive justification of the first live measles vaccine.

The subsequent story can only be traced briefly here. The Edmonston strain became the basis for the first measles vaccine licensed in the United States in 1963 and for the still-more attenuated products developed in the next several years by Anton Schwarz at Pitman Moore-Dow and Maurice Hille-
man at Merck.\textsuperscript{14} By the end of the decade, the annual number of measles cases in the United States had decreased from several million to several thousand.\textsuperscript{15}

Although the domestic eradication of measles proved to be more difficult than optimists in the late 1960s predicted, the remarkable safety record of measles vaccine (incorporated into Merck’s MMR combination against measles, mumps, and rubella in 1971) is worth noting. In contrast to whole-cell pertussis and live polio vaccines, which were at the center of highly visible vaccine-safety controversies in the 1970s and 80s, measles vaccine enjoyed wide public acceptance. It figured prominently in the rise of school mandates as a strategy for promoting vaccination.\textsuperscript{16} Families who declined it did so not so much for reasons of safety than questioning the clinical severity of measles (as was the case, ironically, with David Edmonston’s decision not to vaccinate his own son).\textsuperscript{17}

This long period of relatively little safety controversy ended abruptly with the rise of the MMR/autism controversy in 1997. Perhaps because Britain did not begin to routinely vaccinate infants with the MMR vaccine until the late 1980s, the vaccine began to be used on a widespread basis in that country at the same time that the number of autism cases were rising. The MMR vaccine/autism hypothesis has been discredited on many fronts.\textsuperscript{18,19}

For parents, one of the most intuitively persuasive objections may simply be the fact that the United States had used the MMR vaccine widely since the early 1970s and yet experienced no corresponding rise in autism cases.

From a global perspective, measles vaccine has been one of the greatest public health breakthroughs of the 20th century. It is fitting to think of its origins 50 years ago in the no-frills laboratory of a Connecticut Yankee scientist John F. Enders.

\textbf{REFERENCES}


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