



Maurice R. Hilleman

1919–2005

BIOGRAPHICAL

Memoirs

*A Biographical Memoir by
Paul A. Offit*

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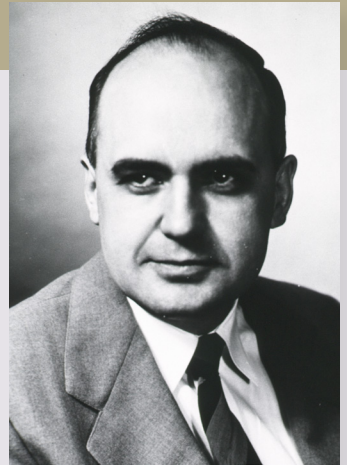
MAURICE RALPH HILLEMAN

August 30, 1919–April 11, 2005

Elected to the NAS, 1985

Virtually unknown to the general public, Maurice Hilleman was a creative and dedicated microbiologist who developed more than 40 vaccines against serious human and animal diseases, many of which are still in use. His work is generally believed to have saved the lives of hundreds of millions of people around the world. Among his most notable achievements were the development of a vaccine against Hepatitis B; the creation of the combined measles-mumps-rubella (MMR) live-virus vaccine; and the discovery of shift and drift mutations in influenza viruses, leading to the realization that a new flu vaccine would have to be formulated and hurriedly manufactured every year to prevent a deadly worldwide pandemic.

Hilleman finished at the top of his 1941 graduating class at Montana State University and then earned a Ph.D. from the University of Chicago in 1944. His first professional position was at E.R. Squibb & Sons (now Bristol-Myers Squibb). Beginning in 1947 he became head of the Army Medical Center's Department of Respiratory Diseases. In 1957 he was named chief of Merck and Company's virus and cell biology unit, remaining with Merck until his mandatory retirement at age 65 in 1984. Post-retirement, he directed the Merck Institute for Vaccinology till the last year of his life.



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By Paul A. Offit

Maurice Hilleman was born on Saturday morning, August 30, 1919, in Custer County, Montana, in the midst of the worst pandemic in U.S. history. He was the eighth child of Anna and Gustave Hilleman. After Maurice's birth, and to the surprise of the homeopath who delivered him, a second child, Maureen, was also born, but still and lifeless. The doctor tried desperately, though unsuccessfully, to revive her.

Hours after the birth, while still holding her infant son, Anna suffered a seizure. Her body stiffened, her eyes rolled up in her head, and her arms and legs twitched rhythmically and unstopably. This episode was the first of many. The doctor declared that Anna was suffering from eclampsia, a disease unique to pregnant women, caused by swelling

of the brain. Anna knew that she was dying, so she called her husband, Gustave; his brother, Robert; and Robert's wife Edith, to her bedside. She asked Gustave that their older boys remain on the family farm with him; that three of the younger children be sent to live with her relatives in Missouri; and that the infant, Maurice, be raised by Robert and Edith, who lived just down the road. Two days after Maurice's birth, Anna, like her baby daughter, died. Maurice was the only one who survived the birth. "I always felt that I cheated death," he would later say.

Although he lived with his aunt and uncle in a house separate from those of his brother and sister—all of whom were later reunited with Gustave—Maurice worked on the family farm. "We sold anything that people would buy," he recalled:

Potatoes, tomatoes, cabbage, lettuce, radishes, corn, squash, cottage cheese, dressed chickens, hatching eggs, eating eggs, and pumpkins. We made brooms from the straw of sorghum sugar—brooms that lasted forever. When I was old enough to tell the difference between a weed and a plant, I was sent out into the sun, working from sunup to sunset. My jobs were to pick berries, bring in the horses, feed and water the chickens, collect eggs, keep the chicken coop real clean, shovel [droppings] from the roost, and pick beans.

As a teenager attending Custer County High School in Miles City, Maurice landed a job as assistant manager at the J.C. Penney store, helping "cowpokes pick out chenille bathrobes for their girlfriends." In Depression-era Montana, this was a highly sought-after job, and ensured Maurice's future. But one of his brothers suggested that he forget about J.C. Penney and go to college. After graduating from high school in 1937, Maurice won a full scholarship to Montana State University in Bozeman. In 1941, he graduated first in his class, having majored in chemistry and microbiology.

He applied to ten graduate schools, hoping to get a doctorate in microbiology. "I came from Montana State University, this small agricultural school," said Maurice. "These people would see a letter from some cowboy in Montana [and] I assumed that it would be in the wastebasket pretty quick." On the top of the list was the University of Chicago. "To a westerner, the United States ended in Chicago," he recalled. "Chicago was the mecca." He was nevertheless accepted to all ten schools, each offering a full scholarship.

While at the University of Chicago, Maurice struggled to find a research project, eventually settling on chlamydia, a disease caused by a sexually transmitted microbe that at

the time scientists thought was a virus. Within a year, he found that chlamydia's infectious agent wasn't a virus but a small bacterium that, unlike other bacteria, grew only inside of cells. Maurice's finding eventually led to a treatment for the disease. He was only 25 years old when he made this discovery.

In 1944, after graduating from the University of Chicago with a Ph.D. in microbiology, Maurice went to work for E. R. Squibb in New Brunswick, New Jersey. At the time, when the United States was planning a campaign of Pacific island conquests aimed at advancing toward the Japanese homeland, the military became concerned about Japanese encephalitis virus (JEV), a common infection in the region. Transmitted by mosquitoes, JEV causes seizures, paralysis, coma, and death in one of every three of its victims, with another third left with permanent brain damage. While at Chicago, Maurice found that a vaccine for JEV could be made by growing the virus in mouse brains and inactivating it with formaldehyde. Under Maurice's supervision, 30 women working eight-hour shifts and processing two mice per minute, harvested about 30,000 mouse brains a day. Because the JEV vaccine was given as a series of three doses, it took about three months to make enough vaccine to immunize 600,000 American troops. Military epidemiologists never performed studies during the latter stages of the Second World War to determine whether Maurice's JEV vaccine worked, but it is likely that the vaccine prevented the disease in thousands of soldiers.

Between 1948 and 1957, Maurice studied influenza virus at the Army Medical School (renamed in 1953 the Walter Reed Army Institute of Research). While there, he defined a series of progressive minor yearly antigenic changes, now called "antigenic drift." He also found that these minor changes were occasionally interspersed with major antigenic changes, now called "antigenic shift," which accounts for the roughly three influenza pandemics that occur every century.

In 1957, in his final year at Walter Reed, Maurice read an article in *The New York Times* about an influenza epidemic in Hong Kong that had affected about 10 percent of the population. "My God," said Maurice. "This is the pandemic. It's here." Maurice correctly predicted that the epidemic in Hong Kong presaged a major worldwide pandemic. Knowing that influenza virus vaccine was made in hen's eggs, Maurice urged farmers not to kill their roosters, even though it was late in the hatching season. He then coerced six vaccine makers into making 40 million doses of vaccine, bypassing the Food and Drug Administration's Division of Biologics Standards, the principal U.S. vaccine regulatory agency. "I knew how the system worked," he said. "So, I bypassed the Division of

Biologics Standards, called the manufacturers myself, and moved the process quickly. The most significant thing I told them was to please advise their chicken producers not to kill the roosters or we won't have enough fertile eggs." Maurice knew that the production of millions of doses of influenza vaccine would require hundreds of thousands of eggs a day and that farmers typically killed their roosters late in the hatching season.

Maurice became the first person in history to accurately predict an influenza pandemic and to make a vaccine in advance of its entry into the United States. When it was over, the pandemic had killed seventy thousand Americans and four million people worldwide. But his quick actions saved thousands of American lives. For his efforts, Maurice was awarded the Army's Distinguished Service Medal. "On that particular day," he recalled, "I was told to appear at the White House at 10 a.m. and bring my wife—and to wear a necktie for God's sake."

Maurice later left Walter Reed to work for the pharmaceutical giant, Merck, where he remained for the rest of his life. While at Merck, he made a number of life-saving vaccines.

On March 23, 1963, at 1:00 a.m. Jeryl Lynn, Maurice's five-year-old daughter, walked into her father's room and stood at the edge of his bed. "Daddy," she whispered, "my neck hurts." Maurice woke up and gently touched the side of his daughter's face. There, at the angle of her jaw, he felt a lump. Jeryl winced in pain. She had swollen parotid glands, a sure sign of mumps. Maurice then did something that only a scientist would do. He walked down the hall and told the housekeeper that he would be going back to the lab but would be back soon. (Maurice's wife, Thelma, had passed away years earlier.) Maurice picked up swabs and broth from the lab, drove back home, gently woke up his daughter, swabbed the inside of her mouth, placed the swab in broth, and drove back to the lab. Between 1963 and 1967, Maurice attenuated his daughter's strain of mumps virus by serially passing it chick embryo cells. The final vaccine, termed the "Jeryl Lynn" strain, has dramatically reduced the incidence of mumps and consequent deafness in the United States and the world.

In the mid-1960s, Maurice took a measles virus vaccine created by Dr. John Enders and colleagues at Boston Children's Hospital and further attenuated it by passing it 40 times in chick embryo cells. Although Enders' vaccine worked, it had a high incidence of side effects of fever and rash. The side-effects rate was so high that the vaccine was given in one arm while attenuating immune serum globulin was given in the other. Maurice's vaccine, which was introduced in 1968, was named the "Moraten strain," for More

Attenuated Enders. Since 1968, Maurice's strain of measles vaccine is the only one that has been used in the United States. By 2000, a virus that routinely caused about two million cases, 50,000 hospitalizations, and 500 deaths a year was eliminated. Worldwide, the number of people killed by measles every year has decreased from eight million to less than two hundred thousand.

Also, in the mid-1960s, Maurice advanced the work of a Scottish virologist named Alick Isaacs and a Swiss biologist named Jean Lindenmann, who had first isolated interferon, and found a way to mass produce it. This enabled Maurice to revolutionize the field of interferon research. Because he was the first to purify it, Maurice was the first to detail interferon's physical, chemical, and biological properties. He found that interferon inhibited the growth of many human and animal viruses and that it not only prevented viral infections but prevented cancers caused by viruses. Maurice reasoned, correctly, that interferon would be useful in treating chronic infections and cancers. Many have argued that his work on interferon was worthy of the Nobel Prize.

In the late 1960s, Maurice took a strain of rubella (German measles) virus that had been modified by Harry Meyer at NIH and further attenuated it by serial passage in duck embryos, calling it HPV77-duck. The vaccine was on the market in the United States between 1969 and 1979. During that time, Merck distributed one hundred million doses in the United States, and the rubella epidemic, which was expected to occur between 1970 and 1973, never happened. Because of Maurice's efforts thousands of children were spared the devastating effects of congenital rubella syndrome, which included permanent and severe defects of the eye, ear, and heart. In 1979, Maurice's vaccine was succeeded by one developed by Dr. Stanley Plotkin at the Wistar Institute. By 2005, rubella was eliminated from the United States.

In the early 1970s, Maurice made the first cancer vaccine—for chickens. At the time, about 20 percent of all chickens in the United States were affected by Marek's disease. Caused by a herpesvirus, Marek's attacked the legs, causing paralysis; chickens died because they couldn't get food or water or because they were trampled by other birds. Farmers called it "range paralysis," referring to infected chickens as being "down in the leg." No treatment was available. Farmers simply culled chickens from the flock and destroyed them.

Having grown up on a farm, Maurice had seen Marek's disease and remembered it. When Ben Burmeister, a veterinary researcher in Michigan, found that a herpesvirus similar to Marek's virus also caused disease in turkeys and quail, Maurice saw his

opening. He took Burmeister's turkey herpes virus, grew it in the laboratory, injected it into one-day-old chicks, and found that they were protected against challenge with Marek's virus. Maurice's vaccine, the first to prevent cancer in any species, revolutionized the poultry business. Excess production caused the price of chickens to drop from \$2 per broiler to forty cents and eggs from fifty cents per dozen to five cents.

In the late 1970s Maurice made the first cancer vaccine for people. Following up on the work of Saul Krugman, Maurice took blood from gay men in New York City who had been infected with hepatitis B virus and separated whole virus particles from discreet particles containing only hepatitis B surface antigen. He then subjected the preparation to a series of chemical treatments that included pepsin, urea, and formaldehyde—a treatment that Maurice proved would kill any residual virus that might have been present in human blood. His hepatitis B vaccine, which was first licensed in 1981, was on the market until 1986, when it was replaced by a recombinant DNA vaccine.

Later, when it was shown that gay men in New York City in the late 1970s were at high risk of being infected with not only hepatitis B virus but another virus that was later identified as the cause of AIDS—human immunodeficiency virus (HIV)—Maurice proved that HIV couldn't survive any of the chemical treatments, let alone all three. Ironically, Maurice's blood-derived hepatitis B vaccine, made from the most dangerous starting material ever used, was at the time probably the safest, purest vaccine ever made.

For his efforts, Maurice received the Lasker Award in 1983; was elected to the National Academy of Sciences in 1985; and received the National Medal of Science in 1988, presented by President Ronald Reagan.

Americans today live thirty years longer than they did a hundred years ago. Some of this increase was caused by advances such as antibiotics, purified drinking water, improved sanitation, safer workplaces, better nutrition, safer foods, the use of seat belts, and a decline in smoking. But no single medical advance has had a greater impact than vaccines. More so than any award or medal he received, Maurice's greatest monument is the fact that his vaccines are estimated to save about eight million lives a year.

Following a six-month struggle with disseminated cancer, Maurice Hilleman died on April 11, 2005 and was laid to rest near his home in Chestnut Hill, Pennsylvania. His obituary appeared on the front page of the New York Times—fame at last.

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