Howard L. Bachrach

1920–2008

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
George F. Vande Woude

NATIONAL ACADEMY OF SCIENCES

HOWARD LLOYD **BACHRACH**

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Howard L. Bachrach

By George F. Vande Woude

Howard L. Bachrach, a biochemist and virologist, made seminal contributions to the study of the molecular biology and immunobiology of viruses affecting both humans and livestock. He leaves a scientific legacy of identifying new approaches in virology and developing mechanisms for mass-producing viruses and their subunits for research purposes. His discoveries have had a lasting impact in the prevention of dreaded animal and human diseases. His purification and visualization of poliovirus contributed to the development of the polio vaccine by Jonas Salk, and his pioneering application of genetic engineering techniques led to the production of the first recombinant DNA vaccine.

Soon after earning a bachelor's in chemistry from the University of Minnesota in 1942, Bachrach got into wartime work for the Joseph Seagram company on the development of synthetic rubber, followed by a stint at the U.S. Office of Scientific Research and Development Laboratory doing research on high explosives. He then returned to Minnesota, earning a Ph.D. in 1949, with a dissertation on the hog cholera virus. He received a USDA-sponsored appointment to work on foot-and-mouth disease in Denmark, did essential background work on the poliomyelitis virus at UC, Berkeley starting in 1950, and was appointed in 1954 to the USDA's new Plum Island (New York) Animal Disease Center, where he remained for the rest of his career.

Howard Lloyd Bachrach was born in Faribault, Minnesota, on May 21, 1920, and grew up in that small farming community. He was the second of three sons born to Harry and Elizabeth (Panovitz) Bachrach. His father, also born in Faribault, owned a men's clothing store established in 1877 by Howard's grandfather, Solomon. The business remained in the family for over 100 years, one of Minnesota's oldest family-run firms. Howard was salutatorian of his high school class and, though standing only 5'6" and 120 pounds, he captained the golf team to the southern Minnesota high school champi-

onship in 1938. It was an early instance of Howard's being successful at whatever he undertook; anyone who knew him would expect nothing less.

Howard and Shirley (circa 1944).

Howard earned a bachelor's degree in chemistry, cum laude, from the University of Minnesota in 1942, and soon after married Shirley Faye Lichterman, whom he met at the university. Having majored in music and arts, Shirley added cultural interests to their life together and was a supportive and encouraging partner as Howard pursued his scientific career. In 1943, as part of the war effort, he worked briefly at Joseph Seagram and Company on the development of synthetic rubber, starting with the fermentation of grain by Aerobacter aerogenes. He then worked for three years on high explosives research at the U.S. Office of Scientific Research and Development Laboratory in Bruceton, Pennsylvania. A course in the chemistry of explosives during his undergraduate studies, taught by organic chemist Lee Erwin Smith, who had conducted explosives research in World War I, had helped prepare Howard for this work. His boss at Bruceton was George B. Kistiakowsky, who later became science advisor to President Eisenhower. In recognition of Howard's contributions to the high explosives research project, he received the Naval Ordnance Development Award.

After the war Howard returned to the University of Minnesota in quest of a Ph.D. He studied thermodynamics for a year under the noted physical chemist Frank H. MacDougall, a disciple of Max Planck. In his pre-dissertation research work (funded by the Army Quartermaster Corps), Howard worked on the role of water in bread staling—primarily, the study of the cross-linking of starch molecules to produce a rigid structure. For his dissertation, entitled "Physico- and Immuno-chemical Studies of the Hog Cholera Virus" (HCV), Howard first estimated the size of the virus. Using an air-driven ultracentrifuge to pellet the virus, he demonstrated that vaccine made from the supernatant liquid that contained soluble HCV subunits (later shown to be capsid proteins) were as immunogenic in swine as vaccine made from the pelleted virus itself after its inactivation.

Howard earned his doctorate in 1949 with a major in biochemistry and a minor in organic chemistry. Soon afterward his career in animal virology took a big step forward when he received a special appointment from the U.S. Department of Agriculture (USDA) to work at the Danish Institute for Foot-and-Mouth Disease Research, a high-containment animal virus research facility in Lindholm, Denmark. There Howard determined the sedimentation constant of the most highly contagious animal virus, the foot-and-mouth disease virus (FMDV). This determination was the breakthrough that began serious study of the virus's molecular properties and molecular biology (1).

Headlines heralding the poliovirus breakthrough discovery (circa 1954).

On returning to the United States in 1950, Howard joined the newly established Virus Laboratory at the University of California-Berkeley, headed by Wendell Stanley, who had received the 1946 Nobel Prize in chemistry for demonstrating that crystalline tobacco mosaic virus was a nucleoprotein. Stanley put Howard and Carlton Schwerdt to work under a grant from the National Foundation for Infantile Paralysis. Their research focused on the isolation and purification of poliovirus, the agent of poliomyelitis—which had reached pandemic proportions, particularly among children, in the first half of the 20th century. They used tissue culture infectivity assays, butanol extraction, tryptic digestion, and differential centrifugation to successfully purify and quantify poliovirus particles that possessed high specific infectivity in the central nervous system tissue of cotton rats (2). This purification and visualization of poliovirus particles in 1954 was crucially important in the fight to control the nationwide scourge of paralytic poliomyelitis, allowing scientists to develop more precise tests of the effectiveness of prospective polio vaccines.

Plum Island Animal Disease Center (circa 1985).

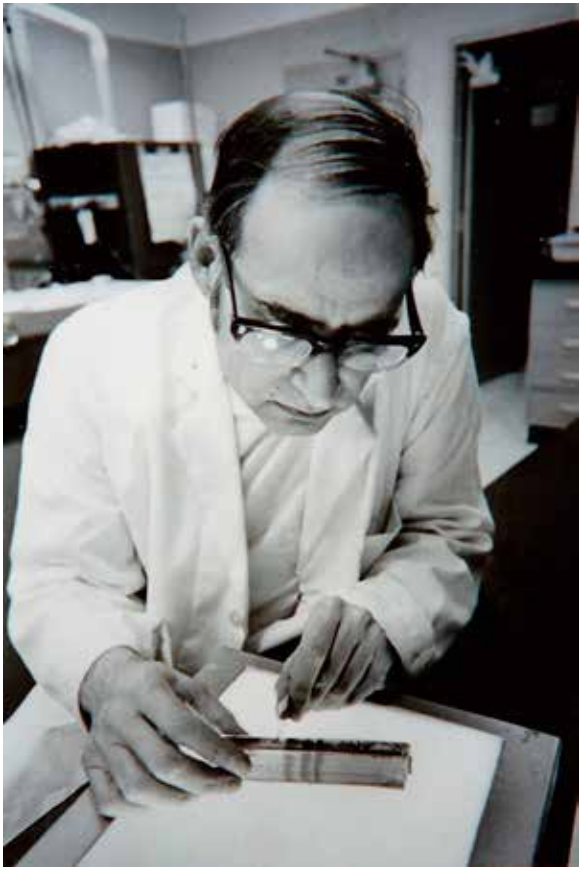
Foot-and-Mouth disease

Howard's experiences with virus purification and characterization set the stage for the next—and the major—part of his career, which was dedicated to studying FMDV. Outbreaks in Mexico (1946-1954) and Canada (1952) caused serious concern about the possible spread of the disease to the United States. Responding to this concern, and with the advice of the USDA and leaders of the livestock industry, Congress authorized the creation of a center for research on FMD and other exotic livestock diseases. In 1954 the Plum Island Animal Disease Center (PIADC) was established at the very remote and rural east end of Long Island, New York. The choice of Plum Island, a mile and a half offshore, was crucial for reducing the possibility of contact between the contagious animal viruses being studied and the wild animals and livestock outside the center.

Given his successful research on the viruses of hog cholera, FMD, and polio, Howard was sought after by USDA officials, including the director of the Bureau of Animal Husbandry, Bennett T. Simms. Howard's poliovirus experience was a particularly valuable asset, because poliovirus and FMDV are members of the same family, now called *Picornaviridae*. Howard was a perfect fit for organizing and heading the Biochemical and Physical Section of the PIADC, and he was singly responsible for initiating a basic molecular virology research effort focused on FMDV. He also participated in the design of special laboratory suites that would prevent accidental release of exotic viruses such as those responsible for diseases like African swine fever, Rift Valley fever, and rinderpest.

Further, Howard played a key role in the development of the core support facilities that became a valuable part of the research experience at PIADC. For example, he established a research core to produce FMDV. The virus production facility centered on Howard's design of large-scale tissue culture using a roller-bottle system. The facility produced FMDV in milligram quantities (3,4). The availability of the highly purified virus in quantity was crucial for carrying out experiments on viral purification and characterization, viral stability, the immunogenic potency of viral vaccines in animals, and an ultrasensitive infectivity assay (5-9). It provided the opportunity to study in detail

virus assembly and how viruses interrupt host-cell metabolism. Once the center was running and Howard's accomplishments became clear, Jacob Traum, at that time PIADC's chief scientist and professor emeritus of veterinary medicine from Berkeley, remarked, "Everything Howard touches turns to 'scientific gold.'"



Howard at work in the lab at PIADC (circa 1970).

The success of the virus production core reflects another of Howard's capabilities. Not only was he a first-rate scientist, but he was also a skilled engineer who vastly improved the productivity of the laboratory by developing equipment that is still widely used in modern laboratories. He was comfortable with the scientific equipment and procedures of the time, such as spectrophotometers, preparative and analytical ultracentrifuges, electron microscopes, gas and liquid chromatographs, amino acid analyzers and protein sequencers. When procedures or equipment were not available, Howard could and would devise them. Beyond the large-scale tissue culture system, for example, he developed timing devices for automating equipment for nighttime runs and large-scale preparative electrophoresis carried out in externally/internally cooled, hollow, cylindrical, 8M urea-polyacrylamide gels, which yielded protein bands that were visible without staining.

When work began at Plum Island in 1955, Howard had large goals in mind for his research program. He had focused his career on an important world problem in foot-and-mouth disease, and it was one that involved both basic science and applications. The challenge brought out Howard's unwavering perseverance to succeed, regardless of a problem's apparent intractability. Despite the Center's remote location and low profile,

Howard was able to recruit investigators with exceptional credentials. His research group generally consisted of five or six permanent scientists, technicians, postdoctoral fellows, and, often, visiting foreign scientists, plus a clerk-assistant. Working in high-containment laboratories and animal rooms under strict safety guidelines, on a remote island that was accessible each day only by boat, demanded regimented attention to procedure and to the clock—conditions that were an added burden for all. Yet the scientists were well motivated by the importance of the research, and their experiments were highly successful.

Starting up a research program staffed with highly qualified scientists in a new facility located in a potato farming and fishing environment 100 miles from New York City was a major challenge in itself. Howard's success was truly a spectacular achievement and a testament to his organizational and recruiting abilities. I was one of the first postdoctoral fellows selected to join PIADC in 1964. I did not meet Howard or any of the other staff members until the day I arrived. Understandably, I had all kinds of apprehensions about what this position would turn out to be, but my desire to learn about virology and about the many systems and technologies at PIADC outweighed my anxiety. One of the keys to becoming confident in my new position was the formal and informal discussion amongst the staff. These discussions were facilitated each day as all of the scientists were available courtesy of the boat trips to and from the island. These were times when Howard was very interactive, talking about relevant issues, such as how viruses caused disease and progress that could be made by trying to prevent or cure viral infections. Howard was a serious, well-established virologist, and it was through my association with him that I was exposed to fundamental principles and concepts of the field of virology.

I was fortunate to begin my postgraduate career in Howard's laboratory, because as a mentor he was outstanding. He was one of the two men—the other being my graduate school advisor, Frank Davis—who helped shape my career in the fields of virology and molecular biology, respectively. Howard and I remained in contact as colleagues for over four decades. When he invited me to write his biographical memoir, I was deeply honored. He provided me with a document that contained his personal reflections on his life and career. These notes have blended well with the details of my own experiences with Howard as a mentor and lifelong friend.

Working on Plum Island was special time in my career, and it was a wonderful environment in which to study FMDV. We were at the beginning of the revolution in molecular virology. Howard took care of all of his team members—Ralph Arlinghaus, Dick Ascione, me, and others—and we had a great experience. Howard was not a micro-

manager; he made sure you had appropriate funding and facilities to accomplish your studies, and he let you go. He strongly emphasized the benefits of collaborations with scientists in other research labs on the island. He also maintained close associations with veterinarians who could help determine the immuno-protective efficacy of the products of our research. Finally—and importantly—Howard imparted to his Ph.D. associates the need to master the art of writing a scientific article, which he had learned early in his graduate research was a necessary skill for a scientist.

The labs were designated as "high containment," and everyone was banned from visiting any farm for a five-day period after being in a laboratory.

Our daily routine in the laboratories certainly deserves discussion. To enter, researchers and staff would leave their personal belongings in the outer lockers, shed their clothing, go through a turnstile and, on the other side, dress into lab clothing and footwear. The labs were designated as "high containment," and everyone was banned from visiting any farm for a five-day period after being in a laboratory. Years later, it was shown that virus could be found in the nasal membranes of a person exposed to an infected animal for even a short period of time, so having the ban in effect was a wise and valid restriction. The strict lab entry protocols did occasionally create problems. More than once, a visitor, after disrobing, failed to don lab clothes in the changing area, not recognizing that the next door did not lead to a room for putting on the lab gear but opened directly into the laboratory. There was ample surprise (and embarrassment) for both the visitor and staff if a visitor walked into the lab wearing only underwear!

In 1961 Howard was deservedly appointed to succeed Jacob Traum as chief scientist, though he continued his active research role as the head of Biochemical and Physical Investigations. In 1964 his paper (produced with two colleagues) entitled "Chemical and physical properties of virtually pure foot-and-mouth disease virus" (10) was selected as an ISI Citation Classic. In 1965 he and his associates were awarded a citation by President Lyndon Johnson for producing 100–300 milligrams of purified FMDV weekly, which made possible innumerable valuable studies. Also in the mid-1960s Howard's team made the discovery that the encapsidated (enclosed in a protein shell) FMDV virions were disrupted upon heating, revealing the mechanism of thermal degradation of FMDV (11). These studies were based on absorbance-temperature profiles occurring at various ionic strengths, cation type, pH, and under the influence of formaldehyde and gamma irradiation (12-15).

After my fellowship in Howard's lab, I served as staff research virologist at Plum Island until 1972. When I had decided to move on, I began the task of applying for positions at various research institutions. I remember being discouraged when one of my applications did not receive a response. Howard told me, "Don't worry about it, that's not an enviable place to be and it wouldn't be good for your career." When I later received an offer from the National Cancer Institute (NCI), Howard was very proud. He did not want me to leave, but he did want me to continue to build my career. Much later, first at the NCI's basic research program in Frederick, Maryland, and subsequently at the Van Andel Research Institute in Grand Rapids, Michigan, I used research cores as a key element in building world-class research centers, thanks to what I learned from Howard at Plum Island.

In 1976 Howard and his associates reported that FMDV RNA has a 3' poly-A tract and that a precursor protein is cleaved to capsid proteins during cell-free synthesis programmed by the virus's RNA (16,17). This was the first report of these findings in a picornavirus. Later Howard's lab extracted infectious RNA from transmissible gastroenteritis virus (later classified as a coronavirus) and showed it to be infectious for FMD. His lab also succeeded in demonstrating that caliciviruses contain a single major protein. Following David Baltimore's description of classification of viruses by their replication scheme (Baltimore, *Bact. Rev.* 35:235-241, 1971), Howard attempted to organize into a single scheme the comparative molecular strategies of replication of all classes of animal viruses. It was a novel classification approach, developed well before its time and accomplished without the modern tools of computer technology.

Howard's long-standing research goal was fulfilled when he discovered that, of the four different coat proteins isolated from FMDV, the 24-kilodalton-(kDa)-coat protein could induce a protective immune response in both swine and cattle (18,19). Furthermore, he showed that a 13-kDa peptide fragment from cyanogen-bromide digestion of that 24-kDa protein was similarly effective in producing an immune response. Conventional methods for producing the protein in the large amounts needed for vaccine production, however, were not practical. Howard and his team thus turned to a new route, a recombinant DNA strategy that would be able to produce the amounts of protein needed for a safe, inexpensive vaccine (20,21).

The first step would be to identify codons of the protein's gene on the viral genome, which they accomplished by sequencing amino acids of the protein so that the nucleotide sequences could be predicted. Then, working with scientists at the private biotechnology

company Genentech, they reverse-transcribed the FMDV genomic RNA into DNA. The resulting DNA fragment was identified by sequencing and was cloned into a plasmid for insertion into *E. coli* bacteria. After replicating the bacterial transformants, they isolated a 47-kDa fusion protein representing the majority of the host cell's protein. Most importantly, the protein produced immunity in both cattle and swine. The development of this vaccine for foot-and-mouth disease was the first recombinant-DNA vaccine for any disease of animals or humans and represents a major milestone in both viral and veterinary research.

This report of the recombinant FMDV vaccine published in 1981 began the era of recombinant protein vaccines. George Poppensiek, a PIADC alumnus and former dean of the New York College of Veterinary Medicine, congratulated Howard and his collaborators at Genentech for their achievement. Of this milestone, Howard said, "The result has been fulfilling, and I am grateful to be around to see it, considering where I could have been if it weren't for the miracle of modern surgery." What Howard was referring to was that, owing to his history of familial coronary artery disease since 1958 (at age 38), he had undergone coronary artery bypass surgery in 1978 and again in 1979. Howard had nevertheless managed, without revealing his condition to his co-workers for two decades, to maintain a vital and competitive research program. By 1981, however, perseverance, medication, and surgery were not enough, and Howard was forced to retire from active research. While he never adjusted fully to the life of retirement, the change no doubt extended his life.

Howard's career with the federal government spanned 10 administrations, from Franklin Roosevelt to George H. W. Bush. In spite of many USDA administrative decisions that challenged Howard's progress and diminished the extent of his support, he maintained a timely research program that enabled this country to accomplish contemporary research in exotic animal viruses. Not surprisingly, he appeared still to be at work in the lab in the 1980s, judging from his VP3 molecular cloning venture. He remained engaged in the research community and served as a consultant to PIADC. He also consulted with the Walter Reed Army Institute of Research, the USDA's East Lansing Poultry Laboratory, the USDA's Cooperative State Research Service, the NCI (on HIV and AIDS), the National Research Council, Texas A&M University's Institute of Biosciences and Technology, and the Congressional Office of Technology Assessment. Altogether Howard published 14 articles and chapters after his retirement.

President Reagan presenting Howard with the National Medal of Science (1985).

Howard's scientific career brought him many awards. He received a USDA Certificate of Merit in 1960 and a U.S. Presidential Citation from President Lyndon Johnson (as mentioned earlier) in 1965. In 1982 he was elected to the National Academy of Sciences, a prestigious award that Howard cherished. He also received the USDA Distinguished Service Award and the AAAS Newcomb Cleveland Prize, an award given annually by *Science* magazine for a paper that "includes original research data, theory, or synthesis; is a fundamental contribution to basic knowledge or a technical achievement of far-reaching consequence; and is a first-time publication of the author's own work." He received three more awards in 1983: a prestigious Alexander von Humboldt Award, the National Award for Agricultural Excellence, and the National Medal of Science, which President Ronald Reagan presented to him at a White House Ceremony. The accompanying citation read:

> *For his pioneering research in molecular virology, including identification of the FMD immunizing protein, and his collaborative role in the use of gene splicing to produce the first effective protein vaccine for use in animals.*

In 1987, Howard was elected to the USDA's Agricultural Research Service's Science Hall of Fame.

Howard credited much of his success in research to rigorous training in organic chemistry, physical chemistry, and biochemistry and to learning early how serious research is done. These valuable experiences occurred at Bruceton (1942-1945) with the physical chemists George Kistiakowsky, Duncan Peck MacDougall, Martin Paul, Franklin Long, and Frank Westheimer; at Minnesota (1946-1949) with his advisor, chemist David R. Briggs; in Denmark (1949-1950) with the FMD experts; and at Berkeley (1950-1953), the world's leading virus research laboratory at that time, including Robley Williams, Gunther Stent, Howard Schachman, William Harrington, Arthur Pardee, C. A. Knight,

National Medal of Science Reception at the White House, 1985. Front row, left to right: Corrine Bachrach (Howard's sister-in-law), Eve Bachrach (daughter), Shirley Bachrach (wife), Howard Bachrach.
Back row, left to right: Harold and Edithe Lichterman (Howard's brother-in-law and sister-in-law), Joe Bachrach (Howard's brother), Ellen Edwards (cousin), and Harrison Bachrach (son).

and Heinz Fraenkel-Conrat, most of whom were National Academy members.

Throughout the course of his career, Howard had a lasting impact on his former postdocs and associates, passing on lessons he had learned from his many mentors. In addition to me, others whom Howard helped to mature as productive researchers were Ralph Arlinghaus, Richard Ascione, Sydney Breese, Jr., Rodes Trautman, Marvin Grubman, Barry Baxt, and Nando Chatterjee. Ralph Arlinghaus had been recruited because of his success in the Dick Schweet lab, where he discovered the mechanism of peptide bond formation; Ralph brought modern methods of biochemical studies to Howard's group. Ralph reflected on Howard's influence as a mentor and leader:

> *An important feature of Howard's career was his teaching. Howard was a constant source of support and direction to many of us in his chemical virology group. The laboratories were well equipped and, just as important, they were set up and manned in a way that allowed scientists like myself to function efficiently. This was an amazing accomplishment considering his extensive administrative duties. While I was at PIADC, Howard worked in the lab, was active in providing direction and consultation to many of us.*

Howard, Shirley, their daughter, Eve, and their son, Harrison, lived in the small community of Southold on the north fork of eastern Long Island. Shirley served as a Cub Scout den mother and a Brownie troop leader, gave piano lessons to local children, and was active in the American Association of University Women and the League of Women Voters. As president of the latter, she helped block the Long Island Lighting

Company from siting a second nuclear power plant nearby. Howard was a typical father—except for the part where he taught his children about atoms, the phases of matter, and the three laws of thermodynamics. He was of the opinion that their young minds were ready for more advanced information than the public schools offered, and he wanted to prepare them for the future revolution, the one occurring right now, in information technology in biology and genomics.

Bachrach family photo: Howard, Shirley, Harrison, Laura, and Alexander (circa 2005).

Eve and Harrison both recall their Dad's lifelong passion for golf, and they were supportive of his playing, sometimes caddying for him when they were young. Howard would take them to the local driving range to watch him hit buckets of balls and afterward often take them to the nearby local miniature golf course and treat them to a few rounds. Notably, Howard set the course record there with 16 holes-in-one. Howard played golf at country clubs on eastern Long Island throughout the years he lived there, and in 1956 he won the Class A championship at Gardiner's Bay Country Club on Shelter Island. He displayed his trophy from that championship all his life alongside the many science medals and awards he amassed.

Howard had a third coronary bypass in 1990 and, unfortunately, the surgery was not very successful. However, Howard's residual angina was greatly ameliorated by a high lysine/ascorbate regimen believed to inhibit lipoprotein(a) and regenerate collagen, which was suggested to him by Linus Pauling at the 1991 National Academy of Sciences annual meeting. The outcome of this regimen was published by Pauling, in collaboration with Howard, as a case report.

When Howard and Shirley retired to Florida in the 1990s, they chose a home in Lake Worth sited on 2 top-flight golf courses. Howard played golf there into his 80s, and on a good day he could shoot pretty close to his age. Eve recalls that when she visited her parents in Florida in the 1990s and 2000s, her Dad would again take her to the country club to watch him hit balls and practice his putting.

Howard died June 26, 2008, in Atlantis, Florida. He is remembered for his contributions to the study of the molecular biology and immunobiology of viruses affecting both humans and livestock. Howard leaves a scientific legacy of identifying new approaches in virology and developing mechanisms for mass-producing viruses and their subunits. His work on the purification of the poliovirus made possible the development of the vaccine against the disease by Jonas Salk and, with Genentech, of the first recombinant cDNA vaccine.

He was survived by Shirley, to whom he was married for 65 years; Eve (retired from the practice of law in Washington, DC); Harrison (an oncologist in Mesa, Arizona); Harrison's wife, Laura; and a grandson, Alexander.

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