Robert J. Huebner

1914–1998

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Kay Huebner

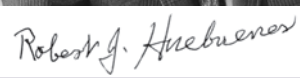
NATIONAL ACADEMY OF SCIENCES

ROBERT JOSEPH **HUEBNER**

February 23, 1914–August 26, 1998

Elected to the NAS, 1960

Photograph courtesy of the Office of NIH History



By Kay Huebner

Robert Huebner, M.D., spent his entire career in the U.S. Public Health Service, devoting most of his time to searching out the causes of infectious diseases. He participated in the isolation and characterization of more than 400 viruses and other infectious agents during his 40 years of epidemiological research, contributing to the control and understanding of Q fever, epidemic pleurodynia (Bornholm disease), herpangina, and AIDS. He was the first virologist to identify the causative agent of rickettsial pox. He conducted the first study of the prevalence of the coxsackie virus in a community and classified previously unknown types of the virus. He identified the source of childhood pharyngoconjunctivial fever, an adenovirus type 3, for which he developed a vaccine. A notable contribution was his exploration of cancer-inducing viruses in animals that led to his designation of certain tumor virus genes as "oncogenes", that had the potential to cause cancer, contributing greatly to the knowledge foundation for solid-tumor virus research.

Huebner began premed studies at Xavier College, completing his baccalaureate at the University of Cincinnati. He earned his M.D. degree at St. Louis University in 1942. Joining the Public Health Service, he worked at a Marine Hospital, then was a medical officer on a Coast Guard ship, then became a researcher at the National Institutes of Health, where he served in the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute.

Robert Joseph Huebner, the first of the five sons and four daughters of Joseph and Philomena Huebner (nee Brickner), was born on February 23, 1914, in Cheviot, Ohio. (I will hereafter refer to him as Bob, the way he preferred to be addressed by a multitude of colleagues and friends.) His parents were both first-generation citizens whose own parents had emigrated from Germany in the late 1800s. The families were not well off

Bob at 9 years in front, with sisters Marian and Bea behind him and brother Joe on their left.

but worked very hard at small businesses, in clothing manufacturing, and in homemaking; Joseph Huebner owned a movie theater in Cheviot that was ultimately unsuccessful.

Though the family income did not allow college attendance for most of his brothers and sisters, Bob began premedical studies at Xavier College in 1937, finished his undergraduate studies at the University of Cincinnati, and in 1938 entered the St. Louis University School of Medicine. Though it was against the rules, he had to work several outside jobs to meet expenses during medical school and almost lost his place there for these infractions. He graduated in June 1942, ranked in the top five of his class of 100 (1).

Bob then joined the U.S. Public Health Service (PHS) during World War II and was assigned to the Marine Hospital in Seattle, and then to the Coast Guard ship U.S.S. Hemlock in Alaska as a medical officer. In July 1944 he transferred to a position as a researcher at the National Institutes of Health (NIH) (1). From 1944 to 1949 he was a PHS commissioned officer in the National Microbiological Institute's Laboratory of Infectious Diseases and continued at the lab as chief of the Section of Virus and Rickettsial Diseases. In 1956 he became chief of the Laboratory of Viral Diseases (LVD) of the newly renamed National Institute of Allergy and Infectious Diseases (NIAID).

Bob married in 1939 and, like his dad before him, fathered nine children, of whom I was number two. Our family lived for part of this time on the NIH campus in Bethesda,

Maryland, a much smaller and quieter place than it is now. Campus families lived in duplex houses on Cedar Lane, and we kids would roller skate around the housing circle and celebrate Christmas together at Top Cottage. In 1951 the family moved to a farm near Frederick, Maryland, from which Bob commuted daily to NIH. He was a city boy who threw himself wholeheartedly into farming, reading books on contour farming to learn how to avoid erosion and becoming an expert on the breeding of Black Angus cattle. Berdie, who was a country girl born and bred, was the perfect helper in this endeavor. We children necessarily became fledgling experts and very hard workers as well.

September 1942. Bob Huebner and his brothers were called home on emergency leave from the Armed Forces when their father had a serious heart attack. Their father survived to see his sons home safely after World War II. Joseph F. Huebner (left); Richard H. Huebner (center); Robert J. Huebner (right). (Photo courtesy Catherine Huebner.)

Throughout Bob's research vocation and farming avocation, his energy and dynamism were among his most outstanding assets. In 1968 he was appointed chief of the Laboratory of RNA Tumor Viruses at the National Cancer Institute (NCI), a move that made us a little sad, as we were very fond of visiting the lab at NIAID. But he had been seduced by his burgeoning research in RNA tumor viruses of chickens and rodents and had become very interested in possible links of such viruses with human cancers. He held this position until 1977, when he became an expert for the Laboratory of Cellular and Molecular Biology at NCI, where he stayed until his retirement in 1982.

Early research at the LVD

One day, shortly after the end of World War II, Bob was the only PHS officer on duty at the National Microbiological Institute when a call came in from New York City authorities requesting investigation of a disease outbreak that was causing violent, body-racking fevers and skin lesions among residents of crowded apartments in a section of Queens. The illness had already caused the death of an 11-year old boy.

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When Bob hastened to New York in response to the call, a local exterminator, Charles Pomerantz, led him to an apartment where the wallpaper appeared to be moving before their eyes, set in motion by billions of mites. That led to Bob's discovery of the first known cases of rickettsial pox, a variety of the diseases caused by rickettsia, microorganisms larger than viruses and smaller than bacteria that in this case were spread by those billions of mites. The infected mites were thought to have arrived in the United States in the luggage of Russian immigrants.

When the findings were confirmed, Bob called his new friend, the exterminator. ''Well, Charlie, we've made it! Bravo!" ''I was stricken dumb," Mr. Pomerantz told the *New Yorker* shortly afterward. ''That we included me" (2). This story became a TV film a little later, and the Huebner family all watched it together and finally understood the whole story, about which they had heard bits and pieces for months, especially regarding Mr. Pomerantz.

Following this piece of epidemiological detective work, Bob was dispatched to California on a new case, the mystery of Q fever, which can strike cows, sheep, goats, and even dogs and cats but had apparently spread to people. He found the cause in vats of unpasteurized milk. Again the organisms were members of the rickettsia family. As in New York, finding the cause led to the end of the outbreak. But dairy farmers did not like taking the blame, and they pressured state health authorities, who politely but firmly invited Bob to leave California.

Too bad for us! Several of us children had accompanied our parents on this first adventure in California and enjoyed it very much. I remember that it was the only time we attended a school where the girls wore colorful dresses instead of uniforms and the days were filled with sunshine. I also remember that a bakery truck and a vegetable truck visited our neighborhood, and my lifelong love of artichokes and bear claw pastry was born there. Father said we were renting our house from a "fan dancer," something I only understood many years later when eight of us nine siblings had to undergo splenectomies to "cure" our hereditary spherocytosis, an autosomal dominant familial anemia inherited from our mother. Father said I would not be able to be a fan dancer with my splenectomy scar, so the light dawned. Monetary awards that father received for his disease

discoveries made possible the purchase of a dishwasher, very useful for a family of six children (as we were at that time), and a down payment on our soon-to-be beloved farm near Frederick, Maryland.

In 1953 Bob and PHS colleagues Wallace Rowe and Janet Hartley, with dreams of learning the causes and developing eventual cures for the common cold, inoculated human tonsil cell cultures with secretions from people with colds and then injected what remained of the cultures into human tumor cells, where they first detected a virus later called adenovirus. Forty-seven strains of adenovirus were eventually discovered and linked to human diseases, including colds and other acute respiratory illnesses (4-6). In these cultures Bob and his colleagues also discovered the human cytomegalovirus, now known to be a hazard for organ transplant recipients, infants whose mothers became infected during pregnancy, and AIDS patients (7). "There were great moments in virology," said Robert M. Chanock, Bob's successor at the Laboratory of Infectious Diseases, who noted that the body of Bob's work "put him up there with Sabin," developer of the oral polio vaccine (1). Unfortunately, Bob and his colleagues' dreams of curing the common cold were dimmed by the growing realization that there were just too many causes.

Bob and Rowe concluded that the viruses, with expression of their T antigens associated with adenovirus oncogenic activity, could trigger dangerous cell overgrowth—that they could interact with a non-viral gene to produce tumors (6). In later work, after research on RNA tumor viruses associated with cancers in chickens and rodents, Bob and fellow researcher George Todaro proposed their oncogene hypothesis in the *Proceedings of the National Academy of Sciences* (8, 9).

Stuart Aaronson, later a colleague at NCI and now at Mt Sinai Hospital in New York, wrote that during Bob's long career at NIH as a laboratory chief at NIAID and later at NCI, he

> *...trained many scientists and physician-scientists who went on to academic leadership roles throughout the country. His galvanizing leadership and formidable persuasive skills are credited with helping to create a national virus cancer program (VCP) in the late 1960s, which increased research funding by millions and established a research base for many major discoveries in biology that followed (3).*

Aaronson stated that it was tragic that Bob's illness prevented his wisdom and experience from being mobilized in the fight against the viral epidemics and cancers later identified partly as a result of his vision. Bob was the scientific mentor for others in addition to Aaronson, who, in the obituary he wrote for Bob, noted that

> *at the NIH, ... he made it possible for me and others to establish scientific careers in an atmosphere where creativity and drive were constantly encouraged. He had an intuitive sense for the essence of a problem and how to pursue it. He was blunt and outspoken, yet full of warmth and charm, always ready to discuss his latest experiments and ideas as well as to provide advice. His network of collaborators spanned the world, and he stayed in communication with his colleagues through a constant stream of memos and correspondence....He provided an outstanding role model of integrity and leadership (3).*

Bob also was a very sociable scientific leader and invited many interesting guests to our farm home for dinner and/or weekend visits. He was one of the first U.S. scientists to begin visiting Communist countries in Eastern Europe. He would invite scientists from Russia, Czechoslovakia, and other countries, to visit the U.S. These visits seemed very exotic to us at home. During the long years of the Cold War these were some of the few glimpses we had into those countries, and we kids on the farm were always trying to figure out which of the guests were the secret police "minders" of the scientific types. It was particularly exciting for me when, as a college student with a strong interest in becoming a researcher, I could sit around the table after dinner, absolutely rapt while listening to visitors talk virology. An especially memorable discussion, involving the Swiss scientist Roger Weil, about SV40 DNA and how you could isolate it by centrifugation in a CsCl gradient based upon the superhelical structure of its double-stranded circular genome, was very difficult to tear myself from when it was time to sleep.

Viruses and cancer at NCI

In 1958 Bob, based on his extensive experience in virus research, began his investigations of so-called C-type retroviruses (also known as RNA tumor viruses) and their roles in viral oncology (1). With Hartley and Rowe he studied the incidence of infection among various strains of laboratory mice, and then in feral animals in rural and urban settings—country mice and city mice, so to speak. He and his colleagues demonstrated widespread serologic evidence of infection but rare occurrences of cancer in mice in their natural setting. They also confirmed the oncogenic nature of adenovirus infection in hamsters

and discovered the presence of non-producing virus in the tissues of infected animals with tumors, the T or tumor antigens, which are the "footprints" of viral presence. These observations led to important new studies, including the discovery of group-specific antigens in avian and mouse retrovirus infections. Bob also participated in the studies of the so-called "helper viruses," C-Type viral leukemia strains providing the envelope genes that enabled otherwise non-producing sarcoma virus strains to produce infectious virus. With extensive studies of antisera and searches for evidence of viral antigens in tissue specimens, Bob and his colleagues were able to eliminate adenoviruses as causes of human cancers, in spite of the ability of adenoviral T antigen genes to transform cells into fast-growing cultures with properties similar to proliferating tumor cells (6).

Bob Huebner mid-career.

Bob then began to concentrate his efforts on the study of retroviruses, which could clearly cause cancer in rodents, as potential candidates for human cancer causation. Murray Gardner, a long-time colleague in the VCP, declared,

> *Based on three of Huebner's cardinal observations [on RNA viruses], 1) the presence of viral group specific antigen in rodent embryo tissues, 2) the relative immunologic tolerance of animals to their endogenous RNA tumor viruses and 3) the epidemiology of naturally occurring cancer, Bob correctly predicted the genetic transmission of RNA tumor genes ...He repeatedly emphasized that the potential for cancer is in all of us, and whether the disease occurs depends on the interaction of oncogenes with other environmental and host genetic factors...Looking back fourteen years later it's clear that Bob's vision was 'right on,' and that*

> *oncogenes and their activation by retroviruses and other stimuli may well prove to be a common denominator in carcinogenesis (1).*

Bob's extensive laboratory observations of the RNA viruses led to his concept of the oncogene (a term he originated), a transforming factor in the development of cancer. His questioning of the nature of the oncogene led him later to support the studies of the laboratory of Michael Bishop and Peter Vogt and colleagues in the seminal publication describing the likely cellular origin for the original viral sarcoma gene, when they demonstrated that the precursor of the oncogene, the proto-oncogene, was a component of normal tissue (the genome) that by a variety of stimuli underwent genetic mutation to the malignant transforming gene (10).

Bob spent the last few years of his career primarily studying the immunology of retroviral infection in mice. He was the driving force or mainspring of the VCP. His talent in recruiting and coordinating the activities of many investigators active in the program earned for him the title of "My General Patton" from Carl G. Baker, former NCI director. According to Ed Scolnick

> *The genius was Huebner. He had the vision, the vision of what to do, he was not mean-spirited, he could see the role for basic research as well as targeted research, and he contracted with quality scientists. Not always traditional approaches, but quality people. That could not be said for some of the other people in charge of the program. But I think Huebner was a great man, a really great man.*

Scolnick summed up the strength of Bob's research career, stating, "Huebner clearly was a giant in the field, stimulating many ideas in oncogenesis" (1). Vincent DeVita, who reorganized the VCP administratively in the early 1980s by eliminating contracts, shedding some investigators, and drastically slashing funding, nevertheless said, "The Virus Cancer Program, which history will record as a very, very important program…I think is one of the greatest contributions the Cancer Institute has made to science—seven Nobel Prizes have come out of it…"

Carl Baker stated

> *The progress made in the understanding of cancer causation, especially with regard to genetics, was outstanding between 1953 and 1973. Even more impressive has been the progress after that period. Viral oncology studies contributed greatly to this progress…The finding of oncogenes,*

Elliot Richardson, secretary of Health, Education and Welfare as it was then designated, presenting the Rockefeller Public Service Award to Bob Huebner December 2, 1970. (Office of NIH History files, from the private papers of Dr. R. J. Huebner.)

viral and cellular, was an exceptionally important development in cancer research."

Robert Gallo, co-discoverer of the AIDS virus, credits the discoveries, reagents, and techniques developed in the VCP's retrovirus research with providing the tools and handles for studying the human retroviruses:

Many of the advances in retrovirology provided a whole new generation of investigators in AIDS research the confidence to work with the techniques developed by their predecessors in the Virus Cancer Program. These successes in the [VCP], and the... discoveries in non-tumor virology, as well as his admirable personal qualities, stand as a lasting legacy for Bob Huebner (1).

Bob was a member of the American Epidemiological Society, the International Union Against Cancer, the American Association for the Advancement of Sciences, the Federation of American Societies for Experimental Biology, and the American Academy of Microbiology, among other scientific organizations. He received numerous awards for his viral research, among them the Pasteur Medal of the Pasteur Institute in 1965, the Distinguished Service Medal of the Public Health Service in 1966, the Kimble Methodology Research Award in 1970, and the Rockefeller Public Service Award the same year. President Richard Nixon presented Bob with the National Medal of Science at a White House reception on February 16, 1970, recognizing his "contributions to the modern understanding of the biology of viruses and their role in the induction of diverse diseases." In 1960 Bob was inducted into, and subsequently participated actively in, the National Academy of Sciences. He also received the Rockefeller Public Service Award.

Sometime after his retirement Bob began to be afflicted by Alzheimer's disease and, from 1991 on, lived at the Veterans Administration Medical Center in Coatesville, Pennsylvania. This genius of medical research in pursuit of viruses and other agents of disease

who became a major force in the battle against cancer died on August 26, 1998, at age 84. The cause of death was pneumonia, medical authorities said.

Bob and our family had lived for years at our Frederick farm, where he and his first wife, Berdie, raised their children, and where one son, Edward Nelson "Eddie" was tragically killed by a hunter at 38 years of age, leaving behind two young sons, Justin and Robert, and their mother, Carol. Bob's oldest son, R. James "Jim," lost his battle with gastric cancer not long after his father's death. Both deceased sons had sons and daughters who had children of their own who still visit the Maryland farm for family celebrations. Bob left behind his beloved second wife, Harriet, of Rockville; seven children—Elizabeth Pfeiffer of Great Falls, Virginia; me; Geraldine Wyman of Santa Cruz, California; Virginia Huebner, Sue Creamer, Mary Louise Barnard, and Daniel Huebner, all of Frederick; 11 grandchildren—and his sister Catherine Huebner of Cheviot, Ohio, who contributed much of the background for this biography. Harriet, his wife and long-time executive assistant, described Bob as

> *a man of endless depth and generosity of spirit. He had a large and in many ways, disparate, staff, all of whom were treated as peers. He... trusted them all to be conscientious and creative, from research associates to animal caretakers. As a consequence he had likely the most productive staff at the NIH.*

She also wrote to Peter Raven of the Academy in 1998, "Robert is now a victim of Alzheimer's disease which has robbed him of everything but his ineffable sweetness."

ACKNOWLEDGMENTS

Note: A biography, *Robert J. Huebner, M.D.: A Virologist's Odyssey*, by Edward A. Beeman, was completed in 2005 for the Office of NIH History at the National Institutes of Health and is available on the internet at http://history.nih.gov/research/downloads/HuebnerBiography.pdf; sections of this biography were excerpted in Wikipedia at: https://en.wikipedia.org/wiki/Robert_Huebner. Obituaries for Huebner appeared in the *New York Times* and in the American Association for Cancer Research's journal *Cancer Research*, written by Holcomb B. Noble and Stuart Aaronson. I have paraphrased and quoted freely from these references in preparing this biography.

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