Harold S. Ginsberg

1917–2003

BIOGRAPHICAL *Memoirs*

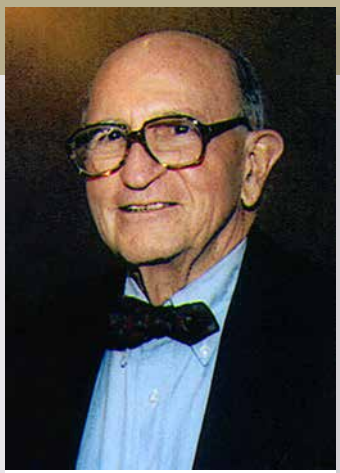
A Biographical Memoir by
Arnold J. Levine

NATIONAL ACADEMY OF SCIENCES

HAROLD SAMUEL **GINSBERG**

May 27, 1917–February 2, 2003

Elected to the NAS, 1982



By Arnold J. Levine

Harry Ginsberg was one of the founders of modern virology. He began his career with research in epidemiology, describing the pathogenesis of viral infections, the course of infections, and their outcomes. This was followed by the isolation of novel viruses. Harry was associated with the identification of several adenovirus serotypes that caused acute respiratory diseases, atypical pneumonia, and respiratory illnesses common to children. His lifelong study of the adenoviruses made this group of viruses one of the most intensively explored and better understood classes of viruses.

Having identified the adenoviruses and their pathogenic consequences, Harry changed his research direction, helping to create the field of the molecular biology of animal viruses. His research uncovered each of the phases of viral replication, and he was among the first to apply chemotherapy to interrupt virus replication and prevent pathogenesis. In addition, he studied how a virus could inhibit the synthesis of cellular RNA and proteins and how viruses redirected cellular metabolism for the propagation of these agents.

He then changed his research direction for a third time, employing molecular genetics to uncover the functions of adenovirus genes and their regulation. As it became clear that some adenovirus serotypes could cause cancers in animals, Harry's research group prepared the antiserum from tumor-bearing animals to unravel the viral tumor antigens. The genetic studies he carried out were used to demonstrate that these tumor antigens were the very proteins that were encoded by the viral oncogenes that initiated and propagated these cancers. These studies led to the realization, by several different laboratories, that these viral oncogene products interacted with and inactivated two major human tumor suppressor proteins, leading to a novel mechanism for the origins of these cancers. The Ginsberg laboratory set the background for these advances in our

A young Harold Ginsberg.
(Photo courtesy of the Ginsberg family.)

understanding of human cancer biology at the cellular and molecular level. After his formal retirement from the university, Harry returned to his origins and roots, exploring a novel animal model system to understand the molecular basis of adenovirus pathogenesis during viral pneumonias of cotton rats.

Harry Ginsberg contributed to the field of animal virology in two additional ways: in service to the field of virology and as an educator for post-doctoral fellows, graduate students, and medical students. Harry was one of the authors of the most commonly employed textbooks in microbiology for undergraduate, graduate, and medical students. He also authored a more specialized text in virology. Harry trained numerous postdoctoral fellows and graduate students who went on to populate positions in academia and in the pharmaceutical industry, as well as at biotechnology companies.

Harry's career in science spanned several critical phases in the development of the field of virology. When he started his studies in epidemiology, pathogen virus isolation and identification dominated his research efforts. As different virus groups were classified, the field moved into the molecular biology and genetics of animal viruses, defining gene functions, and understanding the molecular basis of viral replication. Selected areas in the field of virology came under an intensive focus to determine how some viruses can cause cancers, the role of oncogenes, and in some cases, the tumor suppressor genes that have led to our present day understanding of the origins of human cancers. Remarkably, Harry Ginsberg helped to formulate this path and actively participated in each stage, thereby helping advance our knowledge. His career comprised fifty years of progressive research, and his leadership in science, education, and the establishment of the field of animal virology was groundbreaking.

Early background

Harold Samuel Ginsberg was born on May 27, 1917, in Daytona Beach, Florida. His father, Jacob Ginsberg, was born in 1878 in Poland. Jacob and his wife, Anna Ginsberg (born around 1888), settled in Daytona Beach in 1908, and are considered its first Jewish family. They created a business making and selling Panama hats, Ginsberg's Panama Hat Store, on Beach Street. The retail stores from 200 North Beach Street to 200 South Beach Street would be dominated by Jewish retailers for the next 80 years. The Ginsbergs had three sons, Benjamin (killed in action in Germany in 1944 during World War II), Joseph (an attorney in Daytona), and Harry, and a daughter, Zelda. In 1924, Harry's father helped form the Daytona Hebrew Association, which changed its name shortly thereafter to Temple Israel. Jacob Ginsberg became the President of Temple Israel in 1927 and served as its President again in 1939 and in 1944. Harry's mother, Anna (also known as Annie), was President of the Temple Israel Sisterhood in 1929 and in 1950. She was also remembered for fundraising efforts to assist Mary McLeod Bethune, an American educator and civil rights leader best known for starting a school for African-American students in Daytona Beach that eventually became Bethune-Cookman University, and for being an advisor to President Franklin D. Roosevelt.

As a young man growing up on the beach, and throughout his life, Harry Ginsberg was an avid swimmer and tennis player. From an early age, he wanted to be a scientist, but there was a lot more support for a son becoming a medical doctor. After graduating from Seabreeze High School, Harry attended college at Duke University, where he earned three letters: in tennis, swimming, and football. He gave up football when practices conflicted with his laboratory courses in biology and chemistry. When forced to choose between football and science, science won out. Harry financed his way through college playing the saxophone in a dance band. Music and art remained among his lifelong passions. After graduating from Duke University in 1937, Harry attended Tulane University School of Medicine. In 1941, he was a resident at the Mallory Institute of Pathology in Boston, Massachusetts. From 1942 to 1943, Harry was at Boston City Hospital in the Harvard University 4th Medical Service.

The Army 1943–1946

He next served in the US Army from 1943 to 1946, attaining the rank of Lieutenant Colonel. It was during this time, while posted in England, that Harry made the observation that patients in his hospital who were receiving blood transfusions were at high risk of contracting hepatitis (1947). This was one of the early contributions to the field

that associated an infectious agent in blood with hepatitis (hepatitis B and C viruses were later found), and it created a path for the isolation of these viruses. For this work, Harry received the Legion of Merit Award from the US Army.

Ginsberg during his army service.
(Photo courtesy of the Ginsberg family.)

Virology: replication and disease implications

From 1946 to 1951, Harry was a resident Physician Associate at The Rockefeller University Hospital in New York City, where he worked closely with Frank Horsfall. It was during this period that Harry was introduced to virology. He studied the rubella, mumps, and pneumonia viruses of mice (PVM). Harry focused his research on PVM and the pneumonia it caused in mice. He described the virus replication cycle and showed that the degree of viral replication was related to the severity of the pneumonia. At this time, The Rockefeller University Hospital was a hotbed of excellent research. Ginsberg and Horsfall introduced the concept of chemotherapy to interrupt a viral infection and block virus multiplication (1950). They followed this up with studies interrupting PVM replication, using polysaccharides. Based upon these research accomplishments, in 1951 Harry was offered a position as Associate Professor of Preventive Medicine in The School of Medicine at Western Reserve University (now Case Western Reserve), where he worked closely with J. H. Dingle. In 1953 they published a paper describing an agent (RI-67) associated with Acute Respiratory Disease (1953).

Adenoviruses and adenovirus-initiated cancers

This was the beginning of a series of papers identifying the newly isolated adenoviruses and their association with acute respiratory disease, pharyngitis, and infections of the adenoids and tonsils (1955, 1956). Because the human adenoviruses could be isolated from the adenoids and tonsils (both lymphoid organs) of healthy volunteers, Ginsberg realized that these viruses could also be found in a latent or carrier state and healthy individuals could also transmit these agents. He was able to mimic the latent state in

cell culture and explore its properties. The human adenoviruses were to become Ginsberg's lifelong scientific passion. He was to explore them from their isolation and the description of the pathology they caused, through their molecular characterization, and on to a deep understanding of how viral genes functioned and even how some of these adenoviruses caused cancers.

By 1960, Ginsberg had accepted the position of Chairman and Professor of Microbiology at the University of Pennsylvania Medical School, a post that he held for thirteen years. During this time, Harry built and led a strong Microbiology Department and created an exceptional training environment. Having begun his career in the budding field of virology as an epidemiologist—isolating viruses and associating them with disease processes—Harry now helped to create a new research direction in the molecular biology of animal viruses. Working closely with his technical assistant of many years, Mary Dixon, who ran a very organized laboratory, Harry began the molecular characterization of the adenoviruses (1961). During these years, the Ginsberg research group explored the different synthetic stages of these viruses. They characterized the changes in host cell metabolism and the inhibition of the cells' biosynthetic machinery (1967). They explored viral chemotherapy to block virus replication and studied early and late virus protein synthesis. When some of the adenoviruses were shown to cause cancers in animals, Ginsberg's group was among the first to identify the adenovirus viral-encoded tumor antigens (1968). These viral-encoded tumor antigens played a key role in helping to discover the functions of human tumor suppressor genes, such as p53 and the retinoblastoma protein. Harry's research laid the groundwork that uncovered how the adenoviruses caused tumors in animals. In yet another interesting research transition, the Ginsberg group began to focus its efforts on the isolation of adenovirus mutants, so as to better characterize the genes of these viruses and their functions (1972).

From 1973 to 1985, Harry held the posts of Chairman and Higgins Professor of Microbiology at the College of Physicians and Surgeons of Columbia University in New York City. There, he continued his focus on adenovirus molecular genetics and biology, as well as the study of adenovirus-initiated cancers (1975). Under Harry Ginsberg's leadership, Columbia had a vibrant and exciting microbiology department that made several important contributions to modern molecular biology. One of the faculty members of that department contributed the viral genes (the herpes simplex thymidine kinase gene) necessary to demonstrate DNA-mediated transfer into cells and selection of those cells in culture (S. Silverstein). These new techniques opened up a whole new area of molecular biology. "His contributions to the field were numerous" and "His discoveries involving

the genetics of adenoviruses paved the way for the development of gene therapy. He was certainly a giant in his field" said Dr. S. Silverstein, a former colleague of Dr. Ginsberg's at Columbia University. Harry became an emeritus Professor at Columbia University in 1988.

Awards, recognition, and service

From 1971 to 1972, Harry was appointed the chairman of the Board of Governors of the American Academy of Microbiology. During 1972 to 1975, he was a member of the National Board of Medical Examiners and chaired the Microbiology Committee of that board from 1975 until 1984. Ginsberg was one of the founding members of the American Society of Virology and was its president from 1983 to 1984. He was the chairman of the Virology study section at the NIH (1970–1972) and he chaired the NIH Microbiology and Immunology Advisory Council (1977–1981). Harry was the editor-in-chief of the *Journal of Virology* (1979 to 1984). He was a member of the Harvey Society presenting one of the lectures at Rockefeller University and was its president from 1984 to 1985. He was elected to the Institute of Medicine (now the National Academy of Medicine) in 1979 and to the National Academy of Sciences in 1982. In the Academy, he was chairman of the section of Medical Microbiology and Immunology from 1985 to 1989 and was the chairman of his class from 1989 to 1993.

Education and students

In addition to his outstanding set of research accomplishments and service to the field of virology, Harry was a leader in training the next generation of virologists. He was one of the authors of "THE" microbiology textbook for undergraduate, graduate, and medical students (1980). He and Dulbecco then authored a text in virology that was widely used in graduate student courses throughout the United States.

Harry was also a remarkable mentor to his students and postdoctoral fellows. He was, for many of them, a father figure who always gave sage advice. Although he was demanding in his science, he was warm and friendly in his encouragement of everyone who worked with him. Harry's first graduate student at the University of Pennsylvania had taken his microbiology course while in dental school and then transferred into graduate school to work with him in the new area of animal virology. While working in the laboratory, Harry came in to inform the student that the student's mother had just called to object to his leaving dental school. While this was of some obvious embarrassment to the student, Harry had explained to her why doing research was a high calling and the most important path a young man could take. Remarkably, the mother was happy, Harry was

Harold and Marion Ginsberg, at their 50th wedding anniversary.
(Photo courtesy of the Ginsberg family.)

happy, and the young man (who was me) never forgot it. Harry's students and postdoctoral fellows went on to populate the major universities in the United States and several foreign countries. All of these progeny stayed in the area of virology and cancer research, discovering new oncogenes and tumor suppressor genes during their careers. One of Harry's students (Lee Babiss) went on to become the head of research at a major pharmaceutical company. Harry's intellectual progeny and his grandchildren in science all carry with them his enthusiasm, commitment, and dedication to science as his legacy. Harry Ginsberg was a father figure to his students, as well as "one of the founding fathers of modern virology and microbiology" (quoted from S. Silverstein, a colleague of Harry Ginsberg's at Columbia University).

NIH

After retirement, Harry would not leave the laboratory. He accepted a position in Robert Chanock's laboratory at the NIH and worked at the bench in Bethesda, MD. During this time, Harry went back to his roots and explored the molecular basis of adenovirus pathogenesis (1989). In 1992, he became a Fogarty International Scholar, and in perfect symmetry with his early research in isolating adenoviruses from patients with pneumonia, his last publication (numbering 200 in all) introduced the cotton rat as an excellent model system to explore pneumonia caused by adenoviruses (1993).

Reminiscences

Harry Ginsberg was married to Marion Reibstein Ginsberg for fifty-three years. They had four bright and talented children, Benjamin, Peter, Ann, and Jane, and eight grandchildren. During summers in Woods Hole, Harry taught his children to swim and play tennis. "Every day, rain or shine, hot or cold, calm or rough waters, Harry would take his four kids to swim in the bay at Woods Hole. In later years, even though walking on the beach became difficult because of his arthritis, he would still make it down to water's edge, toss down his cane, and head into the bay for a long swim" Marion Ginsberg

recalls. At Woods Hole every summer Harry would pair up with Seymour Cohen for doubles tennis, several of those years winning the doubles tennis tournament. When on sabbatical in Switzerland in 1966 and 1967, he taught his children to ski. As Marion Ginsberg noted, "Riding the ski lift with Harry usually meant hearing about his latest experiment, explained to a ten year old with great enthusiasm."

Harold S. Ginsberg died on February 2, 2003 of pneumonia in Woods Hole, MA.

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