NATIONAL ACADEMY OF SCIENCES

# HENRY G. KUNKEL
1916–1983

---

*A Biographical Memoir by*

JACOB B. NATVIG AND J. DONALD CAPRA

*Any opinions expressed in this memoir are those of the author and do not necessarily reflect the views of the National Academy of Sciences.*

*Biographical Memoirs*,

Photograph courtesy The Rockefeller University Archives.

# HENRY G. KUNKEL

*September 9, 1916–December 15, 1983*

BY JACOB B. NATVIG AND J. DONALD CAPRA

HENRY G. KUNKEL WAS a true pioneer in immunology. During his lifetime, he led in an area of medicine and basic science that dates back to the turn of the twentieth century. His work placed him in the company of Emil von Behring, Ehrlich, Landsteiner, and other giants in the field. From the middle 1940s he was one of the world leaders in applying the fundamental scientific principles of immunology to clinical medicine, framing a field now termed clinical immunology. Early in his career he proposed that myeloma proteins could serve as models for normal immunoglobulins and antibodies. His intuition proved correct, and his work and the work of others that followed changed the course of immunology. He (and many of his trainees) used myeloma proteins to decipher the chain structure of immunoglobulins and antibodies. This chain structure allowed the definition of immunoglobulin classes, subclasses and genetic markers, which led to the first mapping of immunoglobulin genes to their respective chromosomes. His discoveries also reverberated through cellular immunology through his identification of major histocompatiblity complex (MHC) class II molecules as separate entities, and the genetic linkage of MHC classes I and II molecules with factors in the complement system. Thus, his work had enor-

mous influence on the entire course of basic immunology. At the same time it established pathogenetic mechanisms that brought new diagnostic tools to the clinic.

Despite his intense interest in basic science, his first love was clinical medicine, which he looked upon as an avocation. Here he made major contributions to the diagnosis, and to understanding the pathogenesis of many diseases, and employed new therapeutic strategies for the treatment of many of these same diseases. His work substantially impacted our understanding and subsequent treatment of chronic liver disease, systemic lupus erythematosus, rheumatoid arthritis, primary immunodeficiency disorders, and lymphoproliferative diseases. In addition to his basic science and clinical contributions, he was one of the most sought after teachers and mentors for young scientists interested in the new field of immunology. His trainees included one Nobel Laureate, four members of the National Academy of Sciences and many distinguished scientists, including department chairs, institute presidents, deans, and others who are conducting both basic and clinical research throughout the world. His trainees are prevalent in the United States and Europe, and particularly in Scandinavia, where he had spent a happy and productive year as a visiting investigator with Nobel Laureate Dr. Arne Tiselius in Uppsala, Sweden.

Henry Kunkel's parents clearly helped focus his passion. He was born in Brooklyn on September 9, 1916, the son of the distinguished botanist Louis O. Kunkel and his wife, Johanna Kunkel. His father was a professor of plant pathology at the Rockefeller Institute (later university), who would later be elected to the National Academy of Sciences. His mother was an ardent horticulturist. His parents' passion for botany and biology kindled his interest at a very early age. He once told how he and his friends as children

often had competitions to collect the widest variety of flowers as they played in the fields. In his later life, hybridizing irises became a major hobby. He grew up in Yonkers, New York, and in Princeton, New Jersey. He became an accomplished tennis player, and while at Princeton was elected captain of the varsity tennis team. His competitive ability served him well as he continued to hone his scientific skills. This spirit of competition was balanced by his passion for scientific understanding. It was a rite of passage for all his students to "take him on" on the tennis courts. Few won.

He graduated from Princeton University in 1938 and attended Johns Hopkins University Medical School, earning his M.D. in 1942. After spending two more years in training, as a house officer at Bellevue Hospital in New York City, he joined the U.S. Navy. He served in the European theatre as a physician and participated in the Allied invasion of Italy, during which several marines with hepatitis came under his care. This was a major turning point in his life. In 1945 he came to the Rockefeller Institute and Hospital in New York City (which later became the Rockefeller University) and because of his experience with hepatitis, was assigned to the navy's infectious hepatitis program. He maintained a lifelong interest in liver disease and, indeed, his first exposure to immunology was through his interest in hepatitis. He was appointed an assistant member at Rockefeller in 1947, associate member in 1949, and a full member in 1952. He became an adjunct professor of medicine at Cornell University Medical School in 1973. He was named the Abby Rockefeller Mauzè Professor in 1976. Except for the year 1950-1951 at the Biochemical Institute in Uppsala, Sweden, he remained at the Rockefeller University throughout his career.

Although he performed some research as a medical student, it was while he was a house officer that he became

interested in clinical investigation. At Bellevue he was greatly influenced by Dr. William Tillett, then chief of the medical service. Tillet instilled in him the value of formal clinical investigation, and fired his enthusiasm for this work. Upon arriving at the Rockefeller Institute for Medical Research, he joined the laboratory of Charles L. Hoagland. The Hoagland Laboratory studied infectious hepatitis and, as noted above, was affiliated with the Naval Research Unit at Rockefeller. Kunkel rapidly developed an interest in both the clinical and biochemical events associated with various liver diseases. One year after he arrived at the Rockefeller Institute, Hoagland died unexpectedly at a very young age, and shortly afterward, Kunkel was appointed to head the laboratory. In the absence of a formal mentor his intellect and intuition were tested and forged at this critical juncture.

During this early period, he displayed his brilliance in clinical investigation. His studies on liver disease led to the description of two important clinical syndromes. One dealt with young females with liver disease and hypergammaglobulinemia. These patients often displayed active arthritis and positive LE cells. The second syndrome described in collaboration with Edward H. Ahrens Jr. was primary biliary cirrhosis. His analysis of these syndromes testified to his gift in identifying and linking important issues in clinical research by studying only a few patients in great depth.

In studying liver disease Henry Kunkel observed disturbances in the patients' serum proteins and named his service at the Rockefeller University Hospital the Protein Metabolism Unit. His method for measuring serum proteins, such as gamma globulins, by turbidimetric flocculation, using zinc sulphate, was widely used clinically in the 1950s and 1960s. He noted that a markedly elevated gamma globulin

level in some patients with cirrhosis was associated with increased numbers of plasma cells in the bone marrow. This finding, in conjunction with the observation that marked increases in gamma globulin were also seen in patients with multiple myeloma, led him to postulate that myeloma proteins made by malignant plasma cells were reflective of normal gamma globulin. He used simple immunochemical techniques, primarily the generation of antisera and antigenic analysis by Ouchterlony immunodiffusion, to demonstrate antigenic similarities between myeloma proteins and normal immunoglobulins. The discovery was for many years rather controversial so that even the Nobel Laureate Rodney Porter and many others considered the myeloma proteins as paraproteins. Kunkel's seminal discovery of myeloma proteins as models for normal immunoglobulins markedly facilitated unraveling the genetics and structure of antibody molecules. It also marked the beginning of his lifelong study of immunoglobulins and B cells (immunoglobulin-producing lymphocytes), using B cell tumors as a model system.

His scientific career was greatly impacted by his year of study in the laboratory of Arne Tiselius in Uppsala. Here he solidified his concept that integrating basic sciences was crucial to forming a deeper understanding of clinical problems. In the Tiselius laboratory he learned physical chemistry and became an expert in free-boundary electrophoresis. His ingenuity in the laboratory was again displayed when he used pevikon, a commercial starch, as an inert solid support to separate large volumes of serum into focused electrophoretic bands. For many years pevikon block electrophoresis was used in his and later many other laboratories to isolate large amounts of homogeneous myeloma proteins for structural and antigenic analyses. In the 1950s Kunkel also made another seminal observation using pevikon block electrophoresis by identifying in normals a previously un-

known hemoglobin (Hb) that he termed Hb A2. He also found Hb A2 very much increased in thalassemia minor. The finding of two hemoglobins in normals also influenced his thinking about immunoglobulin classes and subclasses. Henry Kunkel had a true knack when it came to recognizing the importance of identifying the right tools for specific scientific applications. His laboratory had the third Beckman Model E analytic ultracentrifuge comercially available and one of the earliest commercial preparative ultracentrifuges. Both analytic and preparative ultracentrifugation techniques served him well, and were used extensively in the Kunkel laboratory between 1950 and 1970.

During that period, his laboratory contributed significantly to our understanding of gamma globulin structure and genetics. An essential discovery was the finding that myeloma proteins and normal antibody molecules possessed individual antigenic specificities that were later termed idiotypic specificities. The interpretation of these individual specificities was at first perplexing. Ultimately, they were shown to be markers for the variable regions of antibodies, providing a major conceptual insight into the new field of antibody diversity. Later, cross-idiotypic specificity related to the antigen-binding site was described, and has since been used to define groups of antibodies with similar antigenic reactivity.

Using his keen perspective, he identified relationships among many myeloma proteins and normal immunoglobulins from thousands of Ouchterlony plates. He identified 19S IgM as a class of immunoglobulin distinct from 7S IgG. Four subclasses of human IgG were discovered. A second IgA subclass with no disulfide bond linking its heavy and light chain was described. His laboratory described the heavy and light chain structure of immunoglobulin as well as the two classes of light chains (kappa and lambda). The genet-

ics of human immunoglobulins were largely worked out with homogeneous myeloma proteins and the heavy chain linkage groups were delineated. In addition, immunoglobulin deficiencies with absence of subclasses of IgG were described. His laboratory was instrumental in the initiation of the chemical characterization of the complement system. Clq was described as the first chemically defined component of the classical pathway. The scope and impact of the totality of these discoveries cannot be overstated.

It was during this period that we both came to his laboratory as fellows. It is safe to say that the training period in the Kunkel laboratory was the transforming event of our lives. Under his tutelage, we learned the skills that have kept both of us grounded as investigators. We both took from his laboratory the philosophy of studying the patient, then studying the disease, and then applying the principle back to normal physiology. The relationships established in his laboratory have not only been rewarding throughout the years, they have also influenced how we set up our laboratories and our interactions with our students. The impact of these training years in his laboratory was profound.

During this time, his laboratory also contributed significantly to clinical immunology, impacting two important autoimmune disorders: systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). His work in SLE was directly related to the liver disease syndromes associated with hypergammaglobulinemia and arthritis. He realized SLE as a distinct clinical and pathologic entity with no dominant liver manifestations. His laboratory demonstrated that SLE resulted from the mounting of an autoimmune response against nuclear constituents. Antibodies specific to DNA—ribonuclear proteins, including Sm, histones, mitochondria, and microsomes—were all described. Most importantly, the

concept of immune complex diseases was proposed and proven by demonstrating the presence of specific autoantibodies in kidney eluates and showing the circulation of these complexes during disease flares. Today SLE is considered the prototypic autoimmune disease. In the case of rheumatoid arthritis, rheumatoid factors were shown to be 19S IgM antibodies. This IgM existed in the serum as a complex with 7S IgG. Other immune complexes were also described. In particular, IgG-IgG complexes involving IgG rheumatoid factor were detected in high concentrations in synovial fluids of these patients, and he realized that these might play a significant role in complement activation and inflammation.

In the 1970s he turned his investigative effort to study the cellular basis of the immune response. He continued his early strategy of studying a few patients well. He selected antinuclear antibodies (ANA) as an important focus for his laboratory, in addition to continuing his efforts to understand B cell maturation. With simplicity and elegance his laboratory showed that IgM and IgD were the primary membrane immunoglobulins. These two antibodies were shown to have identical V regions on the cellular level as demonstrated by anti-idiotypic antibodies. In addition, the idiotypic determinants were used as tumor markers for B cells, thus demonstrating for the first time that differentiation was not arrested in most cases of B cell leukemias. His laboratory also described a marker on B cells that was later shown to be CD40, a major costimulatory molecule for B cell activation and differentiation.

In the area of immunodeficiency, defective genes were identified in families with specific deficiencies in Ig subclasses. The cellular basis for immunoglobulin deficiency was explored in conjunction with demonstrating T cell helper factors for normal B cell activation and differentiation. Dif-

ferentiation of T cells was demonstrated in some patients with B cell leukemias and in patients with common variable immunodeficiencies. And a class of T cells was identified that was capable of reversing some cases of immunodeficiency. The latter provided some of the first evidence for direct T-B interaction in B cell activation.

In his unique style, and with his scientific accomplishments, he established himself as a supreme model for what today we call a clinical scholar. He consistently uncovered basic immunological principles by studying patients. His peers sometimes felt that the issues he studied were mundane, only realizing later the full impact of his investigations. He was able to identify important issues that were suitable for fruitful scientific exploration, using the tools of his time. He often broke ground in a new field of investigation and then moved on to the next area, leaving other investigators to fill in the details. He had a unique talent for applying the tools and concepts learned in other fields to his own investigations. He expressed his excitement and enthusiasm for science clearly through a twinkling of his eyes when he encountered exciting ideas. His standard of scientific rigor was unsurpassed. He felt strongly that he could not publish any work that was not formed to the very best of his intellectual ability, putting great emphasis on reproducibility, accuracy, and critical interpretation of the data. Above all, he put a premium on originality. He advised his trainees upon leaving his laboratory to think big. Throughout his scientific career, he put that advice into his own practice.

Henry Kunkel had the foresight to identify and address the difficulties inherent in training clinical investigators. His thoughts on this topic first emerged formally in his 1962 presidential address for the American Society for Clinical Investigation, “The Training of Clinical Investigators,” a topic

that at the time was largely ignored. He made a deliberate decision early in his scientific career to focus his mentoring primarily on M.D. applicants. He understood that these M.D. applicants would require a considerable effort to train, and he consistently worked to turn them into outstanding clinical investigators. This is demonstrated by the large number of his trainees who assumed leadership positions in immunology, both in the United States and abroad. His philosophy of science had a profound influence on his trainees. Nearly all emerged from his tutelage with a strong Henry Kunkel imprint, which placed great emphasis on originality, accuracy, and the significance of one's investigative work. In his 1975 presidential address to the members of the American Association of Immunologists he gave a strong plea for enhanced ethics, which exemplified Kunkel's concerns for the integrity of the scientific enterprise (*Journal of Immunology*, vol. 115, no. 1, Jul. 1975).

Henry Kunkel was also a family man. His wife, Betty, was an accomplished figure skater and skating instructor. In addition, she was an important social partner in his professional career and was a gracious hostess for his many friends and students from all over the world. His children inherited a keen sense for matters of science. His younger son, Henry ("Hank"), acquired expertise in informatics and became a successful data management expert in banking and financial areas. In addition, he continued his father's interest in plant genetics. His eldest son, Louis, became an outstanding molecular biologist and geneticist. Louis's election to the National Academy of Sciences marked (to our knowledge) the first such three-generation NAS membership. His daughter, Ellen, was a promising neuroscientist. Despite her tragic early death, she made a substantial impact in the field.

Kunkel served on numerous editorial boards. Most importantly, he was an editor for the *Journal of Experimental Medicine* from 1960 until his death. He was also the cofounding editor for the major review series in immunology, *Advances of Immunology*. Through his editorship for these two important scientific journals, he had considerable influence in advancing the field of immunology during his lifetime and beyond. Through his contributions in science, training, and public service, he earned the right to be called an immunologist's immunologist.

Henry Kunkel received numerous awards and prizes, including the Lasker Award for Clinical Research. He was awarded honorary doctorate degrees from the University of Uppsala and from Harvard University during its 300th anniversary. He served on numerous committees and organizations, including on the council for the National Institute of Arthritis and Metabolic Diseases and as president of the American Society of Clinical Investigation and the American Association of Immunologists.

In closing, we believe Jonathan Uhr and Donald Seldin best captured the essence of the man with these two sentences (Journal of Immunology vol. 132, 2144-2145, 1984):

> His loyalty to and affection for his students and friends were unsurpassed. Nevertheless, his influence will continue to be felt as his former students carry on in their leadership roles and train a new generation of students with the same high standards that Henry represented.

WE ARE INDEBTED TO Drs. Alexander G. Bearn, Nicholas Chiorazzi, Shu Man Fu, Morten Harboe, Henry Metzger, and Robert Winchester for advice in writing this memoir. As helpful background material, we have used the special issue of the *Scandinavian Journal of Immunology* for Henry G. Kunkel's sixtieth birthday in 1976 (vol. 5, nos. 6-7, Sept. 1976); Henry G. Kunkel 1916-1983, An Appreciation of a

Man and His Scientific Contributions and a Bibliography of His Research Papers (*Journal of Experimental Medicine*, vol. 161, pp. 869-896, May 1985), and a biography of Henry G. Kunkel published by the Henry Kunkel Society in 2001.

## SELECTED BIBLIOGRAPHY

1949

With E. H. Ahrens Jr. The relationship between serum lipids and the electrophoretic pattern, with particular reference to patients with primary biliary cirrhosis. *J. Clin. Invest.* 28:1575-1579.

1955

With R. J. Slater and S. M. Ward. Immunological relationships among the myeloma proteins. *J. Exp. Med.* 101:85-108.

1957

With E. C. Franklin. Immunologic differences between the 19 S and 7 S components of normal human gamma-globulin. *J. Immunol.* 78:11-18.

With H. H. Fudenberg. Physical properties of the red cell agglutinins in acquired hemolytic anemia. *J. Exp. Med.* 106:689-702.

With R. Ceppelini, U. Muller-Eberhard, and J. Wolf. Observations on the minor basic hemoglobin component in the blood of normal individuals and patients with thalassemia. *J. Clin. Invest.* 36:1615-1625.

1959

With H. R. Deicher and H. R. Holman. The precipitin reaction between DNA and a serum factor in systemic lupus erythematosus. *J. Exp. Med.* 109:97-114.

1960

With G. M. Edelman, J. F. Heremans, and M. T. Heremans. Immunological studies of human gamma-globulin. Relation of the precipitin lines of whole gamma-globulin to those of the fragments produced by papain. *J. Exp. Med.* 112:203-223.

1961

With H. J. Muller-Eberhard. Isolation of a thermolabile serum protein which precipitates gamma-globulin aggregates and participates in immune hemolysis. *Proc. Soc. Exp. Biol. Med.* 106:291-295.

1962

With M. Harboe, C. K. Osterland, and M. Mannik. Genetic characters of human gamma-globulins in myeloma proteins. *J. Exp. Med.* 116:719-738.

With M. Harboe and C. K. Osterland. Localization of two genetic factors to different areas of gamma-globulin molecules. *Science* 136:979-980.

With M. Mannik. Classification of myeloma proteins, Bence Jones proteins, and macroglobulins into two groups on the basis of common antigenic characters. *J. Exp. Med.* 116:859-877.

1963

With M. Mannik and R. C. Williams. Individual antigenic specificity of isolated antibodies. *Science* 140:1218-1219.

1964

With J. C. Allen, H. M. Grey, L. Martensson, and R. Grubb. A relationship between the H chain groups of 7S γ-globulin and the Gm system. *Nature* 203:413-414.

With H. M. Grey. H chain subgroups of myeloma proteins and normal 7s γ-globulin. *J. Exp. Med.* 120:253-266.

1965

With H. M. Grey and M. Mannik. Individual antigenic specificity of myeloma proteins. Characteristics and localization to subunits. *J. Exp. Med.* 121:561-575.

1966

With E. M. Tan, P. H. Schur, and R. I. Carr. Deoxyribonucleic acid (DNA) and antibodies to DNA in the serum of patients with systemic lupus erythematosus. *J. Clin. Invest.* 45:1732-1740.

1967

With D. Koffler and P. H. Schur. Immunological studies concerning the nephritis of systemic lupus erythematosus. *J. Exp. Med.* 126:607-624.

1968

With R. C. Williams and J. D. Capra. Antigenic specificities related to the cold agglutinin of gamma M globulins. *Science* 161:379-381.

1969

With J. B. Natvig and F. G. Joslin. A "Lepore" type of hybrid gamma-globulin. *Proc. Natl. Acad. Sci. U. S. A.* 62:144-149.

1971

With J. B. Natvig and T. E. Michaelsen. Evidence for recent duplications among certain gamma globulin heavy chain genes. *J. Exp. Med.* 133:1004-1014.

1974

With R. J. Winchester, F. G. Joslin, and J. D. Capra. Similarities in the light chains of anti-gamma-globulins showing cross-idiotypic specificities. *J. Exp. Med.* 139:128-136.

With S. M. Fu, H. P. Brusman, F. H. Allen Jr., and M. Fotino. Evidence for linkage between HL-A histocompatiblity genes and those involved in the synthesis of the second component of complement. *J. Exp. Med.* 140:1108-1111.

1975

With S. M. Fu and R. J. Winchester. Similar idiotypic specificity for the membrane IgD and IgM of human B lymphocytes. *J. Immunol.* 114:250-252.

With R. J. Winchester, P. Wernet, B. Dupont, C. Jersild, and S. M. Fu. Recognition by pregnancy serums of non-HL-A alloantigens selectively expressed on B lymphocytes. *J. Exp. Med.* 141:924-929.

1978

With S. M. Fu, N. Chiorazzi, J. P. Halper, and S. R. Harris. Induction of in vitro differentiation and immunoglobulin synthesis of human leukemic B lymphocytes. *J. Exp. Med.* 148:1570-1578.

1985

With L. Mayer and D. N. Posnett. Human malignant T cells capable of inducing an immunoglobulin class switch. *J. Exp. Med.* 161:134-144.