

Robert Timmons McCluskey (1923–2006)

ROBERT B. COLVIN

ROBERT TIMMONS MCCLUSKEY (figures 14.1 and 14.2) was born on January 16, 1923, in New Haven, Connecticut. His father, Charles Ayling McCluskey, and his mother, Lora M. Timmons, met in France during World War I. Charles was a civil engineer laying telephone cable in the battlefields. Lora, a registered nurse, was assigned to the Army ambulance service. They married in New York in 1919 and settled in the Morris Cove area of New Haven, surrounded by various members of the McCluskey clan.

Robert, as he was known in the family (“Mac” or “Bob” to colleagues and friends), grew up climbing the rock formations in Fort Hale Park and exploring the Peabody Museum on Saturdays with his older brother, Donald. Favorite bedtime stories were readings of *Don Quixote* by their father. Piano lessons gave way to guitar lessons. His cats were named Tristan and Isolde, a nod to a fondness for opera. The family boats had mixed reviews: for Donald, sailing became a life-long hobby; for Robert, being in a boat had the added risk of drowning.

The two brothers spent their secondary and college years in New Haven. They attended Hillhouse High School, and after his four years there, Robert received an attendance award for not missing a day of school, a character trait that remained with him. The boys then followed their father’s path to Yale University. Robert was among 20 young men at Hillhouse who were awarded full tuition by the state. Robert majored in premed

and German literature, receiving his A.B. degree in 1944 under an accelerated program to prepare undergraduates for World War II. Summer classes, reduced vacations, and enrollment in the Navy’s ROTC were the orders of the day.

Dr. McCluskey obtained his M.D. degree from New York University (NYU) in 1947, where he was a member of the Alpha Omega Alpha medical honor society. From 1947 to 1950 he trained as a pathology intern and resident at King’s County Hospital in Brooklyn, which was affiliated with the Long Island College of Medicine (now Downstate Medical Center). He wanted to learn basic pathology, since the department at NYU was focused on immunology. Jean Oliver, the chair of the department at King’s County, was well known for his experimental studies of renal diseases, using techniques of micropuncture and microdissection. As a mentor, he may have stimulated Dr. McCluskey’s early interests in the kidney. Leopold Koss was one year ahead of him in the pathology program and taught him how to do his first autopsy. They remained close friends throughout their lives. Dr. McCluskey finished his pathology residency at Bellevue Hospital, an affiliate of NYU. In 1953 he was drafted into military service, and he served as a pathologist in Germany as a captain in the Army Medical Corps until 1955.

In 1955, Dr. McCluskey returned as an Assistant Professor of Pathology at the NYU School of Medicine under the direction of the new



Figure 14.1 Robert T. McCluskey, on sabbatical in England, 1960

chairman, Dr. Lewis Thomas, who was creating a premier pathology department, and young investigators were eager to follow his lead. It was here that Dr. McCluskey met the future Nobel laureate Baruj Benacerraf, who became a mentor, collaborator, and lifelong friend. Together they wrote a splendid series of 19 papers on immunopathologic mechanisms, mostly on T cell mediated hypersensitivity reactions, published between 1959 and 1983. Dr. McCluskey published seven papers (1958–1966) with Dr. Thomas, including one on a curious form of polyarteritis mediated by *Mycoplasma gallisepticum* in turkeys. It was typical Thomas—a bit of whimsy to explore serious questions. Perhaps this was the seed of Mac's later focus on vasculitis. At NYU he rose quickly through the academic ranks to be appointed full professor and Director of Laboratories at the University Hospital of NYU. Several years later many of his coworkers were to regroup and continue their research in Boston as colleagues and collaborators.

Dr. McCluskey met his future wife, Jean Ann White, at the Woods Hole Marine Biological Laboratories (MBL) in the summer of 1957, where they were taking graduate courses, she in embryology and he in physiology. Romance bloomed after he lent her his microscope. They were married after a short courtship on December 28, 1957, and were lifelong companions. Jean worked with Mac as a research assistant in his NYU laboratory and was a coauthor on a well-cited 1963 paper on delayed hypersensitivity. After they moved to Boston, she served as an Editorial Assistant of *Clinical Immunology and Immunopathology*, a journal Dr. McCluskey started as Coeditor in 1972. It continues under the name *Clinical Immunology* as the official publication of the Clinical Immunology Society.

They bought a summer house in Woods Hole when they moved to Boston, which became one of the family centers. Dr. McCluskey rarely missed the weekly Friday scientific lectures at the MBL or the annual immunology course organized by



Figure 14.2 Robert T. McCluskey

Charles Janeway. While their children, Anne Timmons and James Hubbard, were growing up, Jean worked with the Children's School of Science in Woods Hole; later she served on the Falmouth Historical Commission for 10 years and on municipal building committees. She currently serves on the High School Building Committee and remains a Town Meeting member.

In 1968, Dr. McCluskey was recruited to be Chairman of Pathology at the State University of New York at Buffalo, where he met Giuseppe Andres, who became a close friend and collaborator. Together they wrote 16 papers over a span of 26 years. Dr. McCluskey was the first to report what is commonly termed the WHO Classification of Lupus Nephritis in 1975 as an addendum to a review on lupus nephritis in the *Kidney Pathology Decennial*. The classification, whose source was quoted as a forthcoming "WHO memorandum" by Andres and his collaborators, was based on a 1974 meeting in Buffalo of Andres with Conrad Pirani and Victor Pollack. Apparently it was not actually sanctioned by the World Health Organization, and the "forthcoming" memorandum was probably never published, but it still became the standard for lupus glomerulonephritis for the next 40 years. That classification is the basis of the current system promulgated by the Renal Pathology Society and the International Society of Nephrology in 2004.

In 1971 Dr. Benacerraf recruited Dr. McCluskey to Boston to become the S. Burt Wolbach Professor at Harvard Medical School (HMS) and Chairman of Pathology at Children's Hospital. Here he again crystallized a strong immunopathology group, including Atul Bhan, Eveline Schneeberger, and Bernard Collins, all of whom stayed with him throughout the rest of his career at MGH. Bernie Collins was a brilliant and devoted laboratory technician who became an expert in immunofluorescence and a coauthor of 24 of Dr. McCluskey's papers.

While serving on the Search Committee for Dr. Benjamin Castleman's successor, Dr. McCluskey

found himself a candidate for the position and in 1974 he became Chief of Pathology at MGH and Mallinckrodt Professor of Pathology at HMS. In 1982 the Benjamin Castleman Professorship of Pathology was activated and Dr. McCluskey became the first incumbent. During his 17 years as leader of the MGH Department of Pathology (chapter 13), he expanded the staff and scope of the department, strengthening research, especially in immunopathology, and more than tripling the research space, at the same time maintaining and indeed enhancing the diagnostic service. He was a consummate politician and administrator, quiet, determined, and patient for the opportune moment. As a result, he succeeded in consolidating the myriad fiefdoms of the clinical laboratories at the MGH into a single division of Laboratory Medicine. He did not tolerate any whispers of dishonesty. He also did not take on battles until the circumstances made winning more than likely. By the end of his term as chief, owing largely to his superb administrative skills, the department was strong in all three branches of pathology—atomic, clinical, and investigative.

Dr. McCluskey's major scientific contributions were related to the immunopathogenesis of renal diseases, and though mostly basic, his insights invariably had applications to human disease. Over the course of 56 years as an investigator, he published 206 papers. His earliest investigative work, with Sigmund Wilens, was on permeability properties of the vascular endothelium in atherosclerosis. This led him to ask how vessels were injured by immune complexes. In the early 1950s immune complex disease had emerged, through the work of Frank Dixon and Frederick Germuth, as a new mechanism of glomerulonephritis and vasculitis, but little was known of the factors involved. In a series of elegant experiments in mice with Dr. Benacerraf, Dr. McCluskey showed that preformed immune complexes themselves could initiate glomerular and vascular inflammation, through release of vasoactive amines. Later studies with Giuseppe

Andres and John Klassen showed that immune complexes can deposit in the tubular basement membranes and cause autoimmune tubulointerstitial nephritis.

The clotting system in glomerulonephritis was another of Dr. McCluskey's early interests. With Pierre Vassalli, he showed that fibrin deposition was a universal feature of glomerular crescents, a hallmark of the most severe forms of glomerulonephritis in patients. Inhibition of the clotting system in animal models of glomerulonephritis had a beneficial effect, and this finding led to extensive clinical trials of anticoagulation for glomerulonephritis with crescents.

Another early and continuing interest was the function of T cells in allergic diseases. His seminal study with his wife, Jean, and Benacerraf showed that only a minority of the T cells in a delayed-hypersensitivity reaction were antigen specific, contrary to the dogma of the time (1963). This is his fourth most commonly cited paper and still is regularly referenced. The study led to the concept of lymphokines and their ability to recruit T cells independent of specificity. His later studies showed that T cells could mediate tubulointerstitial nephritis to autologous or exogenous antigen, and with Dr. Bhan he showed that T cells contribute to glomerular inflammation, another concept that was groundbreaking at the time.

One of Dr. McCluskey's lifelong goals was to find the autoantigen of membranous glomerulonephritis (MGN). He worked extensively on a form of MGN produced by immunizing rats with an extract of autologous kidney. He identified the autoantigen and showed that it was expressed by the glomerular podocytes and tubules. With Dr. John Smith at MGH he cloned the antigen, gp330, now termed megalin. Unfortunately, megalin turned out not to be the autoantigen of human MGN, but he pursued its function vigorously into his seventies, discovering that it was a member of the LDL receptor family that bound to thyroglobulin and played a role in thyroid disease. His persistent quest for

the function of megalin, even though it was not what he originally expected, shows his curiosity and joy in discovery.

In the clinical realm, Dr. McCluskey was well known for his pioneering application of immunofluorescence to renal biopsies. He wrote a classic paper on the subject with Dr. Albert Coons at HMS, who invented the immunofluorescence technique. As mentioned above, he was a key instigator of the WHO classification of lupus glomerulonephritis, which although modified by others many times over 30 years, has largely returned to his original formulation. With Ed Franklin of NYU he described the new syndrome of mixed cryoglobulinemia and glomerulonephritis, now known to be due largely to hepatitis C virus. This 1966 paper is still regularly referenced and is his second most frequently cited work. He also wrote the classic study of the natural course of post-streptococcal glomerulonephritis with David Baldwin and the first definitive description of drug induced allergic interstitial nephritis mediated by T cells (1968), still in the top 10 of his citations.

With Dr. John Niles of the MGH Renal Unit and Pathology, Dr. McCluskey investigated the pathogenesis of Wegener's granulomatosis, a severe inflammatory glomerulonephritis and vasculitis that curiously has no detectable immune deposits. His interest was prompted by a report that this disease was associated with antineutrophil cytoplasmic autoantibodies (ANCA). He led a group with Dr. Amin Arnaout that cloned an autoantigen that is one of the targets of ANCA, protease-3. This discovery led to a widely used diagnostic test for this family of diseases, as well as a new strategy to monitor disease activity. He was also a key member of the Chapel Hill group that developed the currently used classification system for vasculitis, whose report in 1994 is his most-often cited paper. As an example of his iconoclastic bent, he showed that the usual cause of Goodpasture's syndrome was not anti-GBM antibodies but ANCA. He also felt strongly that

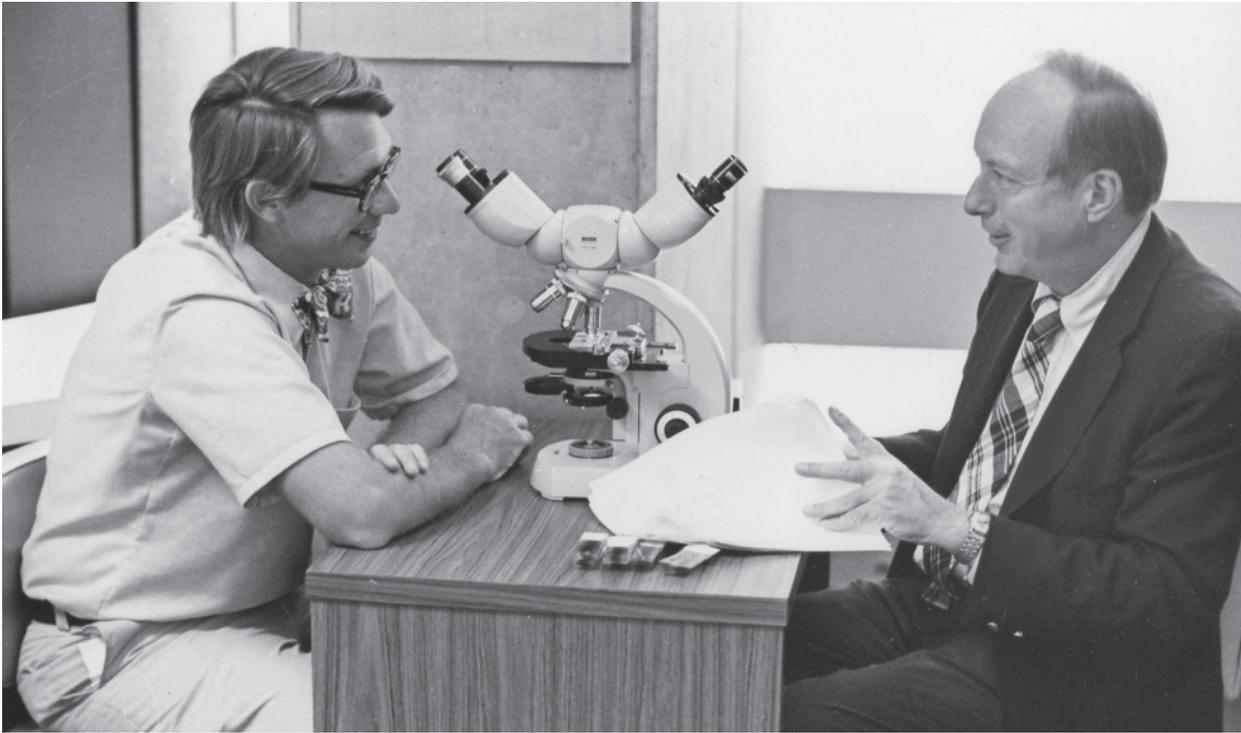


Figure 14.3 Robert T. McCluskey (right), conferring with Robert B. Colvin, late 1970s

a positive ANCA test obviated the need for a renal biopsy, the very basis of his career.

Dr. McCluskey mentored many people in the department, particularly Atul Bhan, later head of Immunopathology, and Robert Colvin (figures 14.3 and 14.4), later Chief of Pathology. With Dr. Bhan he wrote three classic papers that defined the distribution of T and B cells in lymphoid tissues (1980–1981), the first tissue application of the new monoclonal antibodies developed by Drs. Stuart Schlossman and Patrick Kung that detected T and B lymphocyte subsets. With Dr. Colvin he published studies of anti-tubular basement membrane disease, acute transplant glomerulopathy, and other forms of renal disease. They met on a regular basis to review interesting renal biopsies, departmental issues, and opportunities for new research. This writer found Dr. McCluskey incisive in his critiques, sometimes painfully so, sharp in his humor, often delightfully so, and absolutely honest in all his opinions.

The role of a mentor included, for Dr.

McCluskey, a disciplined interest in writing clear, understandable English. This often meant one-on-one sessions reviewing and rewriting research papers with colleagues or young investigators. He also ensured that his children respected the written word. Dictionaries of every kind filled his library; new words were committed to a raft of index cards and reviewed often. A brief lecture on the origin of the word often followed.

Dr. McCluskey expected the Pathology faculty to operate by the highest ethical standards. Nothing tested him more than the incident with John Long, a junior staff member at MGH who was accused of scientific fraud by a Pathology research fellow at the time, Stephen Quay. Dr. McCluskey quickly investigated the charges, sought input from others, including this author, who reviewed the data, and reported the findings to the MGH administration and the Dean of HMS. Even though some were urging more deliberation, within a week Dr. Long had been fired, a decision that was demonstrated to have been correct.

Dr. McCluskey worked tirelessly to establish the nascent field of immunopathology. He wrote extensively about the techniques and interpretation in clinical practice, created and directed a two-day biennial course on the subject at the United States and Canadian Academy of Pathology (USCAP) meeting for 14 years, founded and was Editor-in-Chief of the journal *Clinical Immunology and Immunopathology*, and, as a member of the original Immunopathology test committee for the American Board of Pathology, helped the new subspecialty get official recognition. He authored many definitive and critical reviews in his field, such as the chapter on immunologically mediated renal diseases in three editions of *Pathology of the Kidney* by his good friend Dr. Robert Heptinstall, Chairman of Pathology at Johns Hopkins. He instigated and coauthored the well-received textbook *Diagnostic Immunopathology* with Drs. Bhan and Colvin, which was based on their successful special course on immunopathology given for many years at USCAP's

annual meeting. Dr. McCluskey's clinical acumen was also reflected in 39 clinicopathological renal case discussions in the MGH Case Records in the *New England Journal of Medicine*.

Dr. McCluskey was a leader in academic pathology and nephrology, serving as President of USCAP, Councilor of the American Society of Nephrology, and member of the Scientific Advisory Board of the National Kidney Foundation. Among his honors are a Lifetime Achievement Award and Founders Award (2006) from the Renal Pathology Society, which had developed from his informal Kidney Club. He was the recipient of the Solomon A. Berson Medical Alumni Achievement Award at NYU (1985). Leo Koss selected Dr. McCluskey to give the first Jean Oliver Lecture at the New York Pathology Society. He was also a patient and much-appreciated teacher of the Pathology residents and fellows, who chose him at age 81 for the annual MGH Residents Teaching Award. The MGH Pathology Service sponsors the Robert T.



Figure 14.4 Robert T. McCluskey (left) and Robert B. Colvin at the unveiling of Dr. McCluskey's portrait, early 1990s

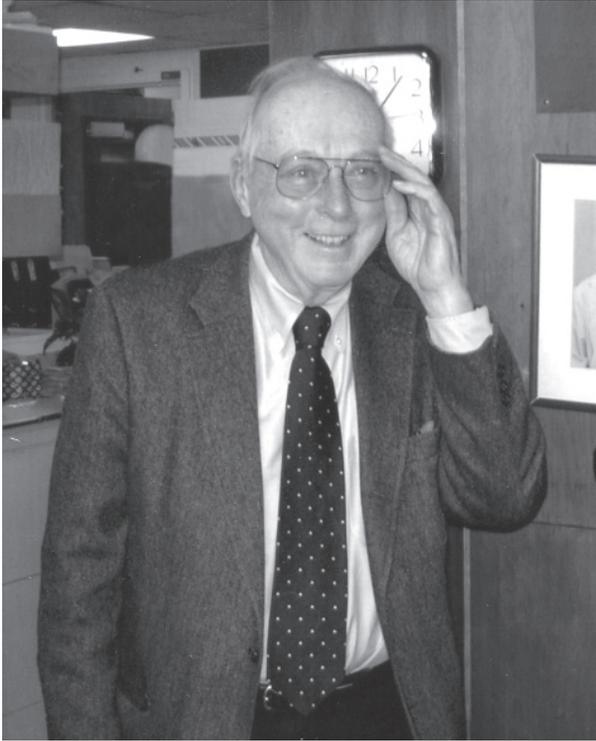


Figure 14.5 Robert T. McCluskey, in jovial mood at a surprise eightieth birthday celebration, 2003

McCluskey Fellowship, which is given annually to an outstanding resident interested in research in immunopathology.

A totally unexpected tribute came shortly before his death in 2006. His older brother, Donald, surprised him by establishing an endowment in Dr. McCluskey's name at the Yale School of Medicine, which funds a young scientist at an early stage of his or her career for four years. The first recipient is pursuing her research at the molecular level in embryonic stem cells, a field he was beginning to explore in earnest.

Dr. McCluskey was a remarkable human being. He was an avid reader of Shakespeare and was always ready with a pithy Elizabethan quote. For more than a decade he and neighborhood friends joined in summertime readings of Shakespeare's plays on his back porch, favoring the tragedies, but including comedies for a change of pace. His impeccable German was heard from

time to time upon suitable urging. He and Donald improved family gatherings with enthusiastic German drinking songs, Donald on accordion. Eveline Schneeberger recalls that in 1976 she flew with Dr. McCluskey and Bob Trelstad to New Jersey to meet with Julius A. Rippel of the Fannie E. Rippel Foundation to raise money for the MGH freeze fracture unit. After lunch, McCluskey and Rippel regaled their companions with a rousing rendition, in German, of *Die Lorelei*: raising money was never so pleasant and easy! His piercing intellect, self-effacing manner, curiosity, and dry wit were his characteristic traits, as well as an uncanny ability to deflate the pompous with a choice remark.

He shared with his friends not only Shakespeare but also Sir Winston Churchill stories and quotes. A shy man by nature, Mac did not hesitate to reveal his intellectual interests and curiosity. One year it was unsolicited lectures on the Dead Sea Scrolls. Astronomy was a favorite read. Explanations of black holes were usually lost on family audiences, but he persevered. For one Fourth of July, it was a reading of the Declaration of Independence to a respectful audience of children. Reprints and marked-up medical journals to match a current malady found their way onto family desks. His Christmas presents were often subscriptions to medical newsletters.

To those who did not work closely with him, Dr. McCluskey seemed a rather serious, formal person; he was almost never seen at work without a suit and tie, and one could rarely meet with him without an appointment. It was a great pleasure to all who admired him, including this writer, to observe that in his later years (figure 14.5), when, no longer burdened by the responsibilities of being chief, he interacted with staff and residents in a most friendly way, which resulted in his becoming much beloved by his students and colleagues.

Robert McCluskey developed high-grade prostatic cancer in his late seventies, receiving

radiotherapy and going through repeated episodes of chemotherapy, which necessarily caused fatigue and pain, but he worked on nevertheless, with astonishingly good spirits. During this time he enjoyed conversations with and letters from friends and colleagues around the world who contacted him to thank him for his friendship and guidance. He continued to sign out renal biopsies and participate in teaching until three months before his death on June 29, 2006. He specifically asked that no memorial service be held, but a “Memorial Minute” was prepared by his colleagues Baruj Benacerraf, Nancy L. Harris, E. Tessa Hedley-Whyte, Robert Heptinstall, Eveline Schneeberger, and Robert Colvin, upon which this chapter is based in part.

The life of Dr. Robert T. McCluskey exemplified the joy of science. He loved nothing more than a good idea and an experiment to test it. He had the highest standard of truth, always thorough, thoughtful, and skeptical. As Heptinstall noted in an award nomination letter for Dr. McCluskey, “I should like to record that when Dr. McCluskey assumed emeritus status at Harvard at the age of 70, rather than succumbing to the torpor of retirement on Cape Cod, he learned recombinant DNA technology and applied for—and obtained—an ROI to unravel the secrets of gp330. This, I feel, shows his true character.”

Dr. McCluskey’s remarkable legacy, in the magnitude of his medical contributions and his personal qualities, places him in the top echelon of all who have served the department, hospital, and medical school to which he devoted the last 35 years of his life.

Note: This chapter is based in part on B. Benacerraf, N. L. Harris, E. T. Hedley-Whyte, R. H. Heptinstall, E. E. Schneeberger, and R. B. Colvin, “Robert Timmons McCluskey: Faculty of Medicine—Memorial Minute,” *Harvard Gazette*, September 17, 2009; significant additions came from Jean McCluskey and Leopold Koss.

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