



Robert Timmons McCluskey



Robert T. McCluskey, a pioneer in the field of immunopathology, died June 29, 2006 at the age of 83. He was the Benjamin Castleman Professor of Pathology, emeritus at Harvard Medical School (HMS) and former Pathologist-in-Chief at Massachusetts General Hospital (MGH).

Dr. McCluskey (“Mac”) was born January 16, 1923 in New Haven, Connecticut, where he was raised with his older brother Donald. He received his A.B. degree from Yale in 1944 and his M.D. degree from New York University (NYU) in 1947. His training in pathology at King’s County and Bellevue Hospitals was followed by military service in Germany. He returned as a faculty member in Pathology at the NYU School of Medicine under the direction of Lewis Thomas, who had created one of the premier pathology departments. It was here that Mac met future Nobel Laureate Baruj Benacerraf, who became a lifelong friend. Other notables at NYU at the time were Stuart Schlossman, Gloria Gallo, and Chandler Stetson. Mac’s career blossomed and in 1962 he was appointed Professor of Pathology and Director of the Laboratories at NYU. In 1968 he 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.

In 1971 Benacerraf attracted Mac to Boston with his wife Jean and children James and Anne, to become the S. Burt Wolbach Professor 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.

While serving on the Search Committee for Dr. Benjamin Castleman’s successor, Mac found himself a candidate for the position and in 1974 he became Chief of Pathology at MGH and Mallinckrodt Professor of Pathology. In 1982 the Benjamin Castleman Professorship of Pathology was activated and Mac

became the first incumbent. During his 17 years as leader of the MGH Department of Pathology, he expanded the staff and scope of the department, strengthening research, especially in immunopathology, and more than tripling the research space. Mac was a consummate politician and administrator, quiet, determined and with patience to await the opportune moment. As a result, he succeeded in consolidating the myriad clinical laboratory fiefdoms 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, due largely to his superb administrative skills, the department was strong in all three branches of pathology -- anatomic, clinical and investigative -- a solid base for the next Chief, Robert Colvin, to build upon.

Mac's major scientific contributions were related to the immunopathogenesis of renal diseases, and while mostly basic, his insights invariably had applications to human disease. Over the course of 56 years as an investigator, he published 206 papers.

Mac's earliest investigative work was on permeability properties of the vascular endothelium in atherosclerosis with Sigmund Wilens. This led him to ask how vessels were injured by immune complexes. In the early 1950's immune complex disease had emerged as a new mechanism of glomerulonephritis and vasculitis through the work of Frank Dixon and Frederick Germuth, but little was known of the factors involved. In a series of elegant experiments in mice with Benacerraf, Mac showed that preformed immune complexes themselves could initiate glomerular and vascular inflammation, through release of vasoactive amines. Later studies with 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 Mac's early interests. With Pierre Vassalli, he showed 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 of Mac's 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 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 Bhan, showed that T cells contribute to glomerular inflammation, another concept that was heretical at the time.

One of Mac'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 John Smith he cloned the antigen, now termed megalin. Unfortunately megalin turned out not to be the autoantigen of human MGN, but Mac pursued its function vigorously into his 70's, 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, Mac was well known for his pioneering application of immunofluorescence to renal biopsies. He wrote a classic paper on the subject with Albert Coons at HMS, who invented the immunofluorescence technique. Mac 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. Mac 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.

With John Niles, Mac investigated the pathogenesis of Wegener's granulomatosis, a severe inflammatory glomerulonephritis and vasculitis that curiously has no detectable immune deposits. Mac's interest was prompted by a report that this disease was associated with antineutrophil cytoplasmic autoantibodies (ANCA). He led a group with 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. Mac was a key member of the Chapel Hill group that developed the currently used classification system for vasculitis. 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 a positive ANCA test obviated the need for a renal biopsy, the very basis of his career.

Mac worked hard 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 helped the new subspecialty get official recognition as a member of the original Immunopathology test committee for the American Board of Pathology. He authored many definitive and critical reviews of his field, such as the chapter on immunologically mediated renal diseases in 3 editions of *Pathology of the Kidney* by his good friend Robert Heptinstall. Mac's clinical acumen was also reflected in 39 clinicopathological renal case discussions in the Case Records of the MGH in the *New England Journal of Medicine*.

Mac was a leader in academic pathology and nephrology, serving as President of the USCAP and the International Academy of Pathology, Councilor of the American Society of Nephrology, and member of the Scientific Advisory Board of the National Kidney Foundation. Among his awards are a Lifetime Achievement Award and Founders Award from the Renal Pathology Society, a society that had developed from his informal Kidney Club. He was the recipient of the Solomon A. Berson Medical Alumni Achievement Award (1985). He was a patient and much appreciated teacher of the pathology residents and fellows, who choose him at age 81 for the annual MGH Residents Teaching Award.

Two awards are named in his honor. At the MGH, the Department of Pathology sponsors the Robert T. McCluskey Fellowship, which is given annually to an outstanding resident interested in research in immunopathology. At the Yale School of Medicine, his brother Donald McCluskey established in 2006 the Robert T. McCluskey Endowment that funds an early stage investigator for four years to pursue an idea of his or her choice, without restrictions.

Mac was a remarkable human being. He was an avid reader of Shakespeare and was always ready with

a pithy Elizabethan quote. For a decade he sponsored regular dramatic readings of Shakespeare with his friends on his porch, favoring the tragedies. His impeccable German was heard from time to time in a stirring rendition of Die Lorelei. 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.

Mac's life 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 Mac, "I should like to record that when Mac 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 R01 to unravel the secrets of gp330. This, I feel, shows his true character."

Mac bore the last months of his illness with enormous dignity and courage, working at the MGH until three months before he succumbed to prostate cancer. He kept his good humor until the end, enjoying conversations and letters from colleagues all over the world who had contacted him to say how much his friendship and guidance meant to their careers. His keen insights and delightful company will be missed the countless friends and colleagues and family.

Respectfully submitted by

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