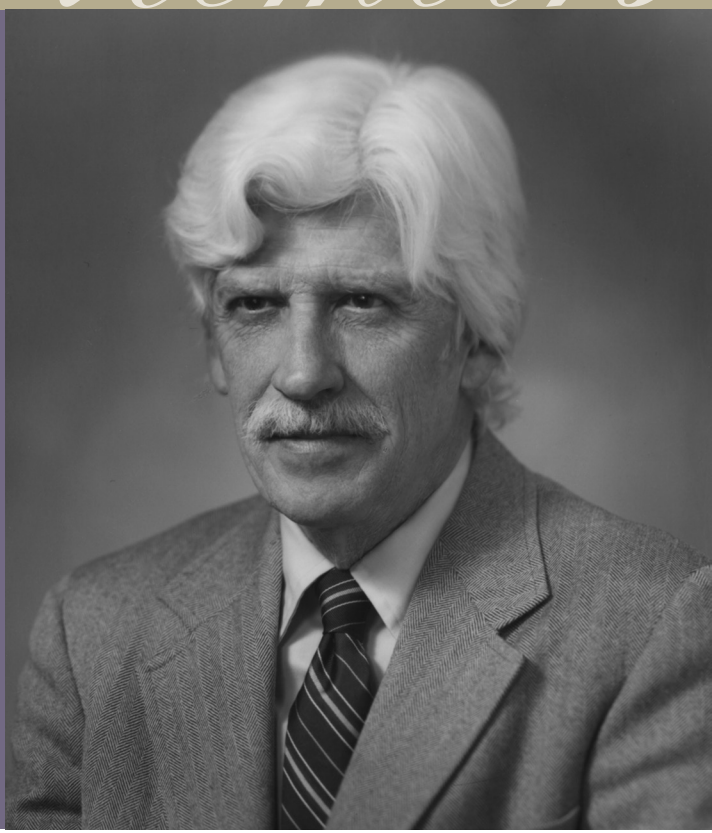
Joseph E. Rall

1920–2008

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Ira Pastan
and Michael Gottesman

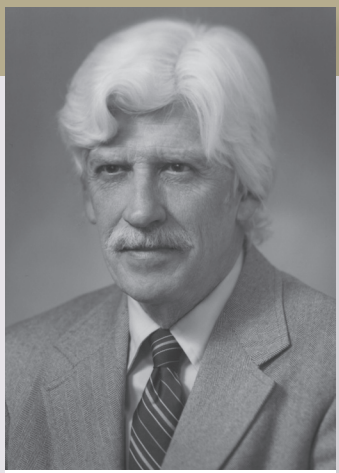


NATIONAL ACADEMY OF SCIENCES

JOSEPH EDWARD **RALL**

February 3, 1920–February 28, 2008

Elected to the NAS, 1980



Photography by The Joseph E. Rall Collection, Office of NIH History and Stetten Museum

By Ira Pastan and Michael Gottesman

Joseph "Ed" Rall was an internationally acclaimed thyroidologist and accomplished manager of science who created an academically oriented intramural research program at the National Institutes of Health (NIH). At a time of rapid expansion of government investment in research, he put his stamp on the tone and direction of intramural research, a legacy that endures to this day. As a dedicated mentor and charismatic leader, he recruited and helped train an entire generation of successful intramural scientists.

Ed's arrival at the NIH in 1955 soon led to his establishment of the Clinical Endocrinology Branch (CEB) in the newly launched National Institute of Arthritis and Metabolic Diseases (NIAMD, now known as NIDDK). He recruited scientists with diverse backgrounds but a shared interest in a single endocrine organ, the thyroid. This focus, and the talented scientists who joined Ed's group, led to several critical discoveries that established the preeminence of the NIAMD group.[1]

Ed characterized serum thyroxine-binding proteins and initiated treatment of thyroid cancer with potassium iodide. This work was done with his long-time friend and collaborator Jacob "Jack" Robbins. Their work led to the understanding of how toxicity from radioactive iodine from nuclear accidents, such as those at Three Mile Island, Chernobyl, and Fukushima, could be prevented using orally administered iodine, and he played a critical role in establishing this treatment as standard of care.

Ed was born in Naperville, Illinois, on February 3, 1920. Bold, if not at times seemingly indomitable but never pretentious, he was raised in an erudite environment, the son of a college president. His father, Dr. Edward Everett Rall, led North Central College from 1916 to 1946, through two world wars and the Great Depression.[2] His mother, Nell Platt Rall, was attuned to music and the arts. He had uncles on both sides of his family who were physicians. From an early age, Ed developed interests in science, sports,

The Rall family, circa 1926. (The Joseph E. Rall Collection, Office of NIH History and Stetten Museum.)

and the arts, all of which he would maintain throughout his life. He also met the love of his life on that college campus, albeit as a toddler. Prof. Edward E. Domm, who led the bible department at North Central, was a close friend to Ed's parents, and his daughter Caroline would become Ed's wife.

Ed had a happy childhood spent on the college campus. He took to playing piano and riding horses. Like many young boys, he had a chemistry set. But as he would humorously relay years later, his was a grand set indeed because the professor of chemistry at North Central would provide him with any chemical he wanted, as he was the son of the school's president.[3] Many adventures followed. Ed often was joined by his brother David, born in 1926. The brothers would remain close throughout their lives. (David would serve as director of the NIH National Institute of Environmental Health Sciences from 1971 to 1990 and become the founding director of its National Toxicology Program.) After Ed graduated with a degree in zoology from North Central College in 1940, he moved to Chicago to attend Northwestern University Medical School. While there, Ed was a teaching assistant in pharmacology and got his first taste of research in experimental medicine, publishing papers on the parasympathetic nervous system with Carl Dragstedt, the scientist who discovered the role of histamine in anaphylaxis.[4]

Ed interned at Wesley Memorial Hospital in Chicago that year and then moved to the Mayo Clinic in Rochester, Minnesota, for a fellowship, from 1945 to 1946. Caroline, whom Ed married in 1944, took a lab position there as well. The war was over, but the draft was still on. Ed joined the U.S. Army Medical Corps in 1946. He was promoted to captain in March 1947 and was stationed in Germany, eventually becoming Chief of Pathology at a hospital near Nuremberg and joined by Caroline. These were jovial times, as well. Eugene Brody, a prominent psychiatrist and Ed's friend for more than sixty years, spoke of meeting Ed for the first time during these years. Ed had organized a journal club

Ed and Caroline in a lab at the Mayo Clinic, 1949. (The Joseph E. Rall Collection, Office of NIH History and Stetten Museum.)

with medical officers and reservists that frequently involved good-humored satire and the lampooning of the regular army commanding officers.[5] Ed's tour of duty ended in 1948, and he returned to the Mayo Clinic to continue his training as a resident.

The Launch of an Illustrious Career in Science

At the Mayo Clinic, Ed studied endocrinology and thyroidology under Raymond Keating, Alexander Albert, and Marschelle Power, all early leaders in radioiodine kinetics research.[6] As Ed would relay, he was allowed to "play" there for several years because he didn't cost his mentors that much.[7] The Mayo Clinic was not a degree-granting organization then. So, through a special arrangement with the nearby University of Minnesota, Ed worked on a Ph.D. on the topic of metabolism of labeled thyroid hormone. The degree was granted in 1952, but Ed had moved to New York in 1950 to become an attending physician at Memorial Hospital and then an associate at the Sloan Kettering Institute under Rulon Rawson. Off to a fine start, Ed won the 1950 Van Meter Prize from what was then the American Goiter Association for his essay "Iodine Compounds in the Blood and Urine of Man."[8] At Sloan Kettering, Ed pioneered the use of radioactive iodine (I-131) in studies of thyroid function and applied that to the treatment of metastatic thyroid cancer in what could be described today as a Phase 1 clinical trial. This may well be the first example of what is currently called "theranostics," the use of a radioactive compound to both diagnose and treat a disease. More broadly, Ed became a key member of a stellar team of radiation physicists and clinicians treating patients.

Although certainly not the most accomplished clinician and scientist at Sloan Kettering, Ed nevertheless garnered a reputation as being competent, affable, and approachable. He seemed to hold court at lunch, the liveliest at a large round table with a cast of about a dozen regulars, such as Marty Sonnenberg, Bill Money, Oscar Bodansky, Leonard Hamilton, Mary Peterman, Jack Oppenheimer, Joe Alpers, and Jamshed Tata. Ed's deep laugh was particularly recognizable and remarkable.[9]

Jack Robbins, whom Ed met on a visit to New York in 1949, would become Ed's closest friend and collaborator. Jack was lured to the NIH in 1954, and Ed followed soon after. In 1955, DeWitt "Hans" Stetten of the NIH recruited Ed to organize and lead the CEB at the National Institute of Arthritis and Metabolic Diseases (now the National Institute of Arthritis and Musculoskeletal and Skin Diseases). Although government pay was slightly lower, the freedom to pursue science was immense. Within just a few years, Ed assembled one of the world's leading centers for basic and clinical thyroid research. Personal recruits included Christian Anfinsen, Martin Rodbell, and Baruch Blumberg—

Ed with Jack Robbins in Atlantic City, 1951. (The Joseph E. Rall Collection, Office of NIH History and Stetten Museum.)

all of whom won Nobel prizes in subsequent decades. Ed's eye for scientific talent was no fluke. His success was built on a breadth of knowledge of endocrinology, coupled with enthusiasm and personal involvement that enabled labs to flourish.

Ed's research program was becoming established during this time. The use of radioactive iodine to treat thyroid cancer and hyperthyroidism allowed Ed to examine its binding partners. He and Jack Robbins explored thyroid proteins labeled with radioactive iodine-containing thyroid hormone, including thyroglobulin, which contained the secreted thyroid hormone in blood, and the association of the hormone with other serum proteins.[10] Robbins and Rall published a seminal paper on thyroid binding proteins, "Proteins Associated with the Thyroid Hormones," in 1960 in *Physiological Reviews.* This work led to the then revolutionary, and now classic, hypothesis that it is the free thyroid hormone, not that bound to protein, that is responsible for its biological effects.[11]

Ed's work with radioactive materials at Sloan Kettering had brought him in contact with staff at Brookhaven National Laboratory in New York and, in particular, Robert Conard, who would become director of the Marshall Islands study of radiation-induced thyroid cancer caused by atomic bomb testing in the so-called Pacific Proving Grounds between 1946 and 1962. As a result of that relationship, Ed was enlisted to visit the Marshall Islands in 1957 and 1959 to study and treat the residents there caught in the nuclear fallout.[12] He would return several times in the 1970s for follow-up health checks. Ed's body of work on this topic led to his involvement with the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation. Also, in 1959, Ed was part of one of the first scientific delegations to the Soviet Union, participating in a rare exchange of ideas and good wishes during a period of open hostility between the U.S. and U.S.S.R.[13] Ed won the Arthur S. Flemming Award in 1959 in part for this international service.

An Astute Administrator

Under Ed's guidance, the CEB became a destination for bright endocrinologists from around the world, including Rosalind Pitt-Rivers, co-discoverer of triiodothyronine, and Nino Salvatore, a Fogarty Scholar who later helped reform the Italian educational system.

One of us (Ira Pastan) had the honor to be part of this illustrious group, recruited to the CEB in 1959. When Ed took the position of Director of Intramural Research for the entire NIAMD, he handed over the reins of the CEB to Jack Robbins. He nevertheless remained active in the CEB's direction, and with Jack would continue to recruit a dazzling array of talent, including Robert Lefkowitz and Harold Varmus. Others came from more than a dozen countries to create a sort of international consortium that lives to this day.[14] Ed also was an early promoter of excellent women scientists and supported Maxine Singer and Elizabeth Neufeld, among others.

Add one more Nobelist to the list that Ed supported: Marshall Nirenberg. Ed offered Marshall—a junior postdoc at NIAMD before his rapid rise to prominence in 1962—endless encouragement and advocated for resources to support his important work, even after Marshall moved to the National Heart Institute during the "Great Code Race."

During Ed's 20-year reign as Scientific Director of NIAMD, a position that granted him total control of that institute's intramural budget, he continued to significantly shape the work environment of the entire NIH. He was a strong proponent of high-quality, rigorous basic science, as well as physical proximity between bench scientists and clinicians, two hallmarks of the modern NIH intramural research program. Also, in the 1950s and 1960s, recent medical school graduates were all but certain to be drafted into military service. A somewhat little-known program existed in which a select few could perform their military duty in the U.S. Public Health Service at the NIH as clinical investigators. Appointments in the 1950s were largely based on an "old boy's" network of recommendations by professors at Harvard, Cornell, and Columbia. But Ed diversified the applicant pool with the formalization of the Clinical and Research Associates Program, whose participants became known informally as the "yellow berets."[15] NIH still had the Harvard and Columbia crowd but now also attracted the likes of Michael Brown and Joseph Goldstein, graduates of the University of Pennsylvania and the University of Texas, respectively.

Ed always found ways to cut through red tape whenever it reared its head. He could be combative, sparring frequently with NIH leadership, including NIH directors, but was always adroit in securing funding or equipment when needed. With just a phone call or two, he managed to solve your biggest problems. As an example, one of us (Michael Gottesman) was told by his draft board to report for military service despite having been accepted into the Commissioned Corps of the Public Health Service to work at NIAMD; in a single phone call, Ed resolved the issue and changed the trajectory of a future

researcher's career. Ed carried these traits from NIAMD to a trans-NIH position, Acting Deputy Director for Science, which he held from 1981 to 1982, and then a similar, newly created position, Deputy Director for Intramural Research (DDIR), in 1983.

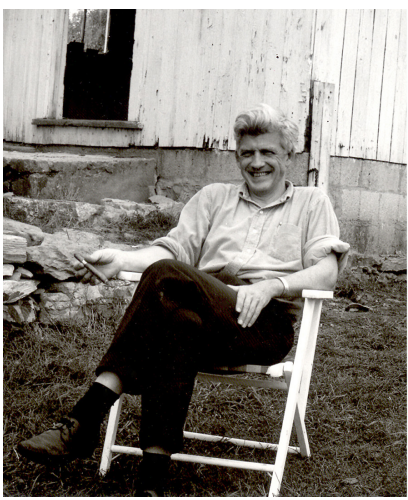
In this quintessential science management role, Ed advised the NIH director on general scientific matters and intramural research policies, and he coordinated the intramural research program activities in more than a dozen NIH institutes. As DDIR, Ed also represented the NIH Office of Intramural Research in matters both external and internal. Externally, he interfaced with the Department of Commerce regarding implementation of the Federal Technology Transfer Act (FTTA) of 1986; with the CIA on a number of sensitive issues, including disposition of former biological weapons agents; with the National Science Foundation and the State Department concerning participation in arctic research issues and delegations to the Soviet Union to explore scientific collaborations; and with the White House Office of Science and Technology Policy (OSTP) concerning federal laboratories and high-temperature superconductivity.[16] Internally, Ed established the Intramural Research Training Award (IRTA) Fellowship Program, developed consistent policies on granting of visa waivers and petitions for permanent residency, and developed the basic structure for the unique personnel systems that exist for intramural scientific staff today, such as the Senior Biomedical Research Service (SBRS) and flexible appointment mechanisms. A seminal achievement, with Ed's deputy Philip Chen, was the establishment of the Cooperative Research and Development Agreement (CRADA) at the NIH, which allowed NIH scientists to interact with private partners to speed the commercialization of technology, enabled by the FTTA.[17] Ed was NIH's boldest advocate for innovation, and through his savviness the NIH obtained highly expensive new equipment, such as PET and MRI machines.

And then there's the intangible. Unlike most federal facilities, the NIH Bethesda campus—particularly before the Oklahoma City bombing and the subsequent gating of the perimeter—maintains a college-like atmosphere, and Ed was one its indirect architects. His early love of the arts manifested in his support for plays, concerts, and other cultural events on the Bethesda campus, as well as green spaces for sports and leisure. Ed recommended the addition of a cultural lecture as part of the high-profile NIH Director's lectures, with the goal of enriching the NIH scientific community. After his death, in 2008, this annual lecture was renamed the J. Edward Rall Cultural Lecture—now the premier event of the year. The series has since welcomed lecturers as diverse as cosmologist and Nobelist John Mather, author Maya Angelou, journalists Sanjay Gupta and Diane Rehm, actress and director Barbra Streisand, and the Dalai Lama.

Upon Ed's death, Marshall Nirenberg noted that Ed followed in his father's footsteps. Ed, in essence, was the dean of the NIH. And one of us, DDIR Michael Gottesman, benefits daily from the innovative programs and academic atmosphere that Ed brought to the NIH.

The Polymath of the Party

Ed was a true Renaissance man, with a constant desire to expand his knowledge based on an impressive command of physics, chemistry, biology, mathematics, and clinical studies that informed his farsighted decisions. Yet beyond the science and administration, Ed was a warm and inviting man who hosted countless parties at his house. These were riotous fun, quite often involving role playing and frantic sports. (One of us, Ira Pastan, banged his head so hard during one soccer game that, ironically, the memory is engrained!) Ed's favorite sport was tennis, and he played with dozens of NIH scientists. He joked that all the important decisions about the NIH were done at the Linden Hills tennis court, where many members of the NIH staff played tennis in the morning before work. Other pastimes included sailing, skiing, and skating the C&O canal. He sailed with Chris Anfinsen up and down the Atlantic. He did it all with enthusiasm. His was a life of long-lasting friendships. Ed's family—wife Caroline, daughter Pia, and son Ed, who we called "Busty"—shared a large farm on the banks of the Potomac River with the families of Jack Robbins, Barry Blumberg, and Wilfred Rall, a distant cousin. The place was short on amenities, such as running water and heat, but long on good times. Jack described the farm as the opposite of a time-share, because the four families would go there not when it was empty but rather when everyone could make it. The families continued to meet even after the early death of Caroline in 1976, and the younger generations continue to meet today. Jack, it should be noted, accomplished in his own right and Ed's closest friend for nearly sixty years, died just three months after Ed.



Ed relaxing at his farm, 1960s. (The Joseph E. Rall Collection, Office of NIH History and Stetten Museum.)

Ed Rall died on February 28, 2008, a few weeks after his 88th birthday. He lived and breathed science, eloquently championed and defended the scientific process, and left an indelible mark on the NIH and the people associated with it.

ACKNOWLEDGEMENTS

The authors would like to thank the following people for their contribution to this biography: Phil Chen, Ed and Sue Rall, Priscilla Rall, Janet Smith, Christopher Wanjek, and Richard Wyatt.

NOTES

1. M. Gershengorn. 2012. History of the clinical endocrinology branch of the national institute of diabetes and digestive and kidney diseases: Impact on understanding and treatment of diseases of the thyroid gland. *Thyroid* 22:109-111.
2. Presidents of North Central College. Presidential Terms: 1861–2012. Retrieved July 31, 2020.
3. J. Edward Rall, oral history, June 30, 1998. Retrieved July 31, 2020.
4. J. Robbins. 2008. In memoriam: Dr. Joseph Edward ("Ed ") Rall, 1920–2008. *Thyroid* 18:667-668.
5. Eulogy for J. Edward Rall by Eugene Brody, March 4, 2008.
6. J. Robbins. 2008.
7. J. Edward Rall, oral history.
8. J. E. Rall. 1950. Iodine compounds in the blood and urine of man. *J. Clin. Endocrinol. Metab*. 10:996-1006.
9. Eulogy for J. Edward Rall by Jamshed Tata, March 4, 2008.
10. J. Robbins. In memoriam.
11. J. Robbins and J. E. Rall. 1960. Proteins associated with the thyroid hormones. *Physiol. Rev.* 40:415-489.
12. J. Wolff and P. R Larsen. 2008. Dr. Joseph Edward Rall. *Nat. Clin. Pract.* 4:359.
13. H. Grasso and M. Lyons. 2014. A life collected: Joseph Edward Rall (1920–2008). *The NIH Catalyst* 22(1):10-12.
14. J. DeMouy. 1995. NIDDK Rall, Robbins recall 40-year careers. *The NIH Record* 47(1):4-5.
15. S. Khot, B. S. Park, and W. T. Longstreth Jr. 2011. The Vietnam War and medical research: Untold legacy of the U.S. doctor draft and the NIH "yellow berets." *Acad. Med.* 86:501–508.
16. P. Chen, e-mail message to author, August 3, 2020.
17. Ibid.

SELECTED BIBLIOGRAPHY

1953 With C. G. Foster, J. Robbins, R. Lazerson, L. E. Farr, and R. W. Rawson. Dosimetric considerations in determining hematopoietic damage from radioactive iodine. *AJR Am. J. Roentgenol.* 70:274-282.

1960 With J. Robbins. Proteins associated with the thyroid hormones. *Physiol. Rev.* 40:415-489.

1966 With R. A. Conard. Elevation of the serum protein-bound iodine level in inhabitants of the Marshall Islands. *Am. J. Med.* 40:882-886.