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ROBERT W. BERLINER
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A Biographical Memoir by

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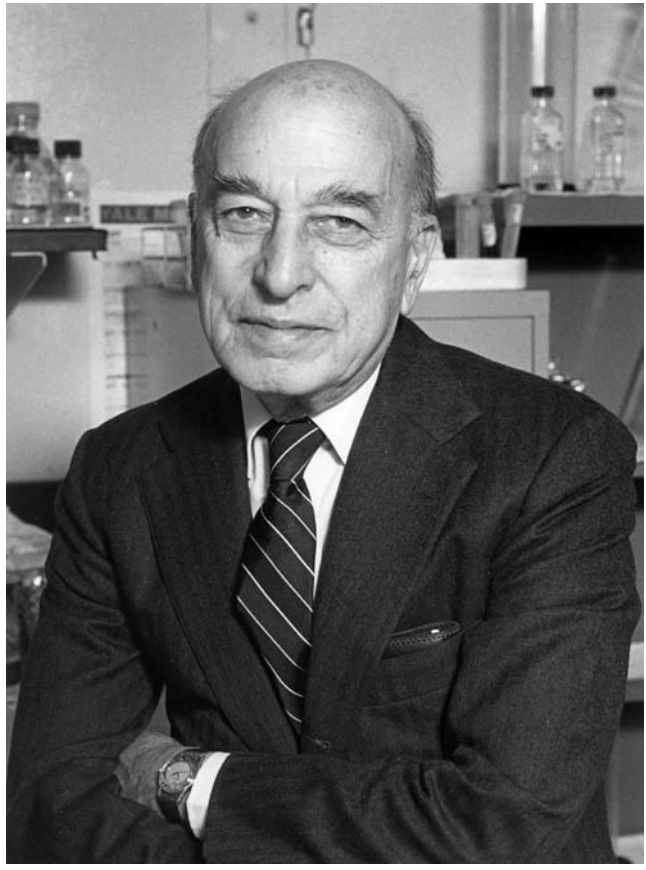
Biographical Memoir



Robert W Berliner

ROBERT W. BERLINER

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BY GERHARD H. GIEBISCH AND THOMAS J. KENNEDY

ROBERT WILLIAM BERLINER, Professor Emeritus of Cellular and Molecular Physiology, Professor Emeritus of Internal Medicine and Dean Emeritus of the School of Medicine, all at Yale University, died at the Yale New Haven Hospital on February 5, 2002, just a few weeks short of his 87th birthday. He contributed in a major way to our understanding of renal function, played a leadership role at the National Institutes of Health by creating one of the world's preeminent research centers devoted to the study of renal and electrolyte metabolism, and ended his remarkable career by serving as dean of the Yale University School of Medicine. His legacy also includes the training of numerous talented scientists and clinicians who assumed leadership positions at academic institutions throughout the world.

Bob Berliner was born in New York and grew up on Long Island, where he attended Woodmere Academy. As a teenager he developed a keen interest in birds, and he and his brother Benjamin published several papers in the 1930 and 1932 issues of *The Heron*, the official annual proceedings of the Woodmere Academy Bird Club. Through Lea, Bob's wife, I had the opportunity to browse through Bob's extensive and impressive handwritten notes in which he meticulously kept track of his ornithological pursuits. Bob was also a com-

mitted and successful camper. This activity led not only to his receiving the All Around Campers Senior Award in 1925 but also to his meeting his future wife, Lea Silver, who later learned to share Bob's enthusiasm for bird watching.

A successful student, Bob entered Yale College in 1932. He excelled in mathematics, graduated in 1936, and chose Columbia College of Physicians and Surgeons for his medical education. Asked why he did not consider Yale, he asserted that he preferred the more rigorous curriculum at Columbia, which included regular tests, over Yale, where students were not formally examined in their basic science courses. After receiving his M.D. in 1939, Bob stayed at Columbia and chose further training in internal medicine. Robert Loeb, a highly respected and distinguished internist, well known for his interest and pioneering exploration of deranged fluid and electrolyte balance, decisively stimulated Bob's lasting interest and curiosity about the kidney's role in abnormal water and electrolyte balance. One of Bob's earliest publications, with G. A. Perera, dealt with paroxysmal nocturnal dyspnea, in which they traced the movement of extracellular fluid from the extravascular spaces in the extremities to the intravascular thoracic circulation and the lungs during recumbency.

James A. Shannon was another individual who played a decisive role in Bob's career. Shannon had been a member of Homer Smith's Physiology Department at New York University, but had moved to the Department of Medicine to direct NYU's Research Series at the Goldwater Memorial Hospital. His intent was to extend his studies on the physiology of the kidney to humans, especially those with renal disease. Shannon's first recruits to his new venue were Bob, David Pearle, and John V. Taggart. Bob had hardly completed his initiation rites into the methodologies for renal functional

studies under Shannon's mentorship when the U.S. entry in World War II necessitated a radical redirection of the research agenda of the laboratory—from the function of the human kidney in health and disease to the chemotherapy of human malaria. A major research program, initiated shortly after the attack on Pearl Harbor and under the aegis of the Committee of Malarial Research (CMR) of the National Academy of Sciences, was charged to develop and explore new antimalarial agents. A. N. Richard, a distinguished renal physiologist, headed the CMR and recruited leaders for the malaria program whom he had known and with whom he had been associated during his career as a renal physiologist. These included E. K Marshall from Johns Hopkins, noted for his work on renal tubule secretion, who was called upon to play a major role in the design of the program. Marshall in turn persuaded Jim Shannon to join the project. They had known each other from time spent together at the Mt. Desert Island Biological Laboratory in Salisbury Cove, Maine.

The goal of the Goldwater group was to design protocols for effective treatment of malaria. The first step in this effort was the development of accurate techniques, principally fluorometric, for measuring drugs in blood, urine, and tissues. Clinical trials designed to develop optimal drug dosing for new antimalarial drugs followed. The investigations were remarkably successful. Bob Berliner's name appears on all the major papers from this period in the *Journal of Clinical Investigation*, along with David P. Earle and John V. Taggart, who became lifelong friends of Bob. The extended wartime interlude devoted to malaria research yielded not only a very productive research experience but also the close and cordial relation to Jim Shannon, who as Bob noted on the occasion of a memorial service for Shannon at the National Institutes of Health, was to show him "how to do good sci-

ence." The mutual respect and affection they had for each other played an important role in their future collegial interactions at the NIH.

With the end of World War II the malaria program was phased out and Bob continued at Goldwater on Columbia's Research Services from 1947 to 1950. He continued a study that turned out to become his first major independent contribution to renal physiology. Aided by the recent development of the flame photometer, Bob and Tom Kennedy carried out a series of ingenious renal clearance experiments that defined the main features of potassium excretion. These studies demonstrated that, in contrast with the behavior of most other ions that are reabsorbed after glomerular filtration along the renal tubule, potassium was both reabsorbed and secreted into the tubule fluid. They provided evidence that regulated potassium secretion was responsible for maintaining external potassium balance. Moreover, they demonstrated that potassium ions are secreted into the urine by exchange with the luminal counter ion sodium, a process responding to a variety of stimuli, including not only to changes in potassium intake but also to acid-base stimuli, steroid hormones, and diuretics. Bob Berliner's Harvey Lecture, delivered in 1960, provides a concise and tightly argued exposition of how potassium is handled by the kidney and how its transport is regulated at the cell level.

It should be noted that these studies of potassium were based exclusively on clearance experiments, providing only two types of information: the amount of potassium filtered at the glomerulus and the amount excreted in the urine. The magnitude, site along the nephron and the nature of the cell mechanisms of reabsorption, secretion, and exchange were deduced solely from analyses of blood and urine. It took ingenious thinking and analyzing and exceptionally clever

experimental design to derive the right answer. The sequence of critical observations began with an accidental finding of a study aimed at the effects of diuretics on sodium excretion. The striking dissociation of potassium excretion from its rate of glomerular filtration was noted. Moreover, showing that excretion could exceed the amount filtered when exogenous loads of potassium were administered provided the basis that the renal tubule epithelium could secrete potassium. Based on further clearance experiments, it was deduced that potassium reabsorption in the renal tubule precedes secretion that was correctly localized to more distal segments of the tubule; thus under most conditions filtered potassium made only a minor contribution to the amount excreted. These results also led to the conclusion that distal tubule secretion, and not changes in ion proximal reabsorption, was the main mechanism by which the kidney responded to those factors known to modulate potassium excretion. These observations and their correct interpretation marked a critical change in thinking about transport along renal tubules, since they were the first clear demonstration that a solute could be transported across the tubule epithelium in both directions and that final excretion rates in the urine resulted from simultaneous (proximal) reabsorption and modulated (distal) tubule secretion. It is remarkable how many features of these early concepts were later proven to be correct when micropuncture techniques and the development of methods for measuring potassium concentration in minute tubule fluid samples became available. From these early studies Bob Berliner emerged as a dominant figure in the field of renal physiology, a position that he maintained for many decades.

In 1950 Bob Berliner accepted the offer of his former mentor, James A. Shannon—who had been recently appointed director of Intramural Research of the newly created Na-

tional Heart Institute of the National Institutes of Health—to move to Bethesda as the chief of the NIH's Laboratory of Kidney and Electrolyte Metabolism. Shannon's offer tripled the resources at Bob's disposal at Goldwater, and was followed later by further substantial budget increases. At his new position Bob had the good fortune, the means, the insight, and the ability to attract, retain, and stimulate a large number of excellent young investigators. His initial group included Tom Kennedy, who followed Bob from Columbia, and Jack Orloff, who was recruited to work on the Columbia Research Services at Goldwater but later agreed to go with Bob to Bethesda. An important initial appointment was that of Robert Bowman, who led the very important Section of Technical Development in the Heart Institute.

Bob's laboratory soon emerged as one of the leading centers of renal physiology, devoting its efforts to studying discrete tubule functions by the newly emerging micropuncture techniques, hormonal effects, responses to extracellular volume expansion and volume contraction, and the mechanism of urine concentration and dilution.

There is hardly a laboratory of renal physiology or nephrology in the United States as well as abroad that does not count a former associate of Bob's and his Laboratory of Kidney and Electrolyte Metabolism as one of its members. He made his influence felt permanently by making the best possible choices first for his own lab but later for the entire National Heart (Lung and Blood) Institute (NHLBI) intramural program in recruiting laboratory chiefs, by astutely training and directing his colleagues, and by insisting on the highest standards of excellence. Three individuals who later received the Nobel Prize—Marshall Nierenberg, Julius Axelrod, and Chris Anfinsen—had close links to Bob. By either persuading them to come to the NIH or by seeing to

it that they remained in leadership positions at the NIH, he was instrumental in shaping their careers.

NIH amply recognized Bob's administrative talents. As mentioned, in 1950 he was appointed chief of the Laboratory of Kidney and Electrolyte Metabolism, a position he held until 1962. In 1954 he succeeded James Shannon as director of Intramural Research for the NHLBI. From 1968 to 1969 he was NIH director of Laboratories and Clinics and from 1969 to 1973, when this position was renamed, the NIH deputy director for science.

During Bob's leadership at the Laboratory of Kidney and Electrolyte Metabolism, his group, which initially included Tom Kennedy and Jack Orloff and was later enriched by a large number of especially gifted colleagues, carried out studies that significantly expanded our knowledge of renal electrolyte and fluid transport. The following discussion will provide only a brief overview of their most important contributions.

Bob's continued interest in potassium metabolism led to clarification of the role of sodium delivery in potassium secretion and the complex interactions between potassium and hydrogen ion excretion by the kidney, including an analysis of coordinated potassium shifts between cellular and extracellular compartments. His interest in acid-base-related changes in renal function also led to experiments defining the effects of carbonic anhydrase inhibitors, the nature of transtubular CO_2 gradients, and the mechanisms underlying ammonium excretion. His laboratory also helped define key factors modulating urinary concentration and dilution, emphasizing the interaction between glomerular filtration rate, vasopressin, and urea. Bob was aided in this effort by John Stevenson, an expert in transport modeling; they proposed a novel model for urinary concentration involving

the complex interactions between sodium, urea, and fluid movement in the renal tubules and the vascular elements of the renal medulla.

Although virtually all of the above mentioned studies involved the "traditional" approach of renal clearance methodology, Bob could not resist the siren call of micropuncture and microperfusion of single mammalian tubules. He realized the ultimate limitation of defining tubular transport solely by comparing filtered with excreted moieties of solutes. As a consequence, his laboratory pioneered two novel approaches. First, he initiated, with J. R. Clapp and J. F. Watson, the development of methods for puncture and collection of fluid from single tubules in the dog, an approach that was successfully applied by several investigators in the laboratory for investigating problems of fluid transport; osmolality changes; and sodium, potassium, and bicarbonate reabsorption in superficial tubules of the renal cortex. The exploration of the effects of several manipulations—such as extracellular volume changes and administration of diuretics, of vasopressin, and of cardiac denervation—became thus amenable to direct investigation at the tubule level. An interesting series of experiments dealt with the relationship between proximal tubule sodium reabsorption and peritubular protein concentration, contributing to the lively discussion of possible mechanisms of glomerulo-tubular balance, the phenomenon of proportionality between filtered sodium load and sodium reabsorption along the proximal tubule.

Bob's group also developed methods for exposing the rat renal medulla in vivo. Initiated by Sakai and Jamison, these studies made possible the puncture and collection of fluid from individual components of the renal medulla, including collecting ducts, long limbs of Henle's loop and juxtaglomerular vessels. Moreover, methods for the continuous mi-

croperfusion of water and electrolytes permitted the study of fluid and electrolyte movement in the loop of Henle. Taken together, these in vivo measurements of tubule function at the single nephron level yielded fundamental insights into the cell mechanisms underlying tubular transport.

Initiated by M. Burg, M. Abramow, and J. Grantham and effectively supported by Jack Orloff, the development of the method of perfusion of single isolated tubules in vitro was a further important development in the Laboratory of Kidney and Electrolyte Metabolism. This approach advanced the ability to alter independently the composition of tubule fluid and basolateral bath fluid, and to dissect and perfuse subcortical and medullary nephron segments that could not be approached from the kidney surface for puncture. The development of these demanding perfusion techniques made possible and was of fundamental importance for a very large number of experiments, because direct information about transport processes that could not be explored by conventional micropuncture techniques could now be obtained.

Another line of research initiated in the laboratory by J. Handler was the development of novel methods for growing renal tubule cells in culture. This method, later widely used by many investigators, provided a potent approach to gain insights into the metabolism of tubule cells. It proved especially important by defining the cell mechanisms of hormone actions. This combination of superb investigators, outstanding leadership, and generous support made Bob Berliner's Laboratory of Renal and Electrolyte Metabolism one of the premier centers of renal research. This was largely due to Bob's commitment to science in general and to renal physiology in particular. His presence was felt by his continuous involvement in research, including almost daily and intensive discussions of results with his colleagues, and his careful

reading of all manuscripts originating from the research teams under his direction. He had become the intellectual leader of one of the world's most productive laboratories in the field of electrolyte metabolism. By the mid- to late 1950s Bob had emerged as one of the dominant figures in the field and remained so long after he discontinued active participation in research. After Bob stepped down as its director in l962, the laboratory continued to flourish under the excellent leadership of Jack Orloff, with whom Bob maintained a close and warm friendship for many years. More recently the laboratory has remained a center of excellence under the effective guidance of Moe Burg and Mark Knepper.

In 1973 Bob Berliner decided to leave the NIH and accept the position of dean at the Yale School of Medicine. This decision must have been difficult, given the high esteem in which he was held by so many of his colleagues and the many friends he made at the NIH. It is probably fair to assume that Bob's decision to move to Yale was motivated by the change of the political climate in Washington, owing to the politicalization of the research enterprise at the NIH. At Yale, Bob applied the same strict standards of excellence that he had used at NIH. Despite heavy administrative duties he never lost interest in science. As a member of the Department of Cellular and Molecular Physiology (and holding a joint appointment in internal medicine), he followed new research developments, was available for advice, and maintained a remarkable intellectual presence. As in his previous administrative posts he won the confidence of people and provided inspired leadership of the medical school. He was an understanding and sympathetic dean.

Extracting money from the dean's office could be somewhat difficult. However, skillful chairmen learned that after several pleading interventions things usually could be made to

work out and the reduction of the initially requested amount of money could be made tolerable if one started out a bit on the high side. Bob served two full terms as dean, and when he retired in 1984 the medical school was stronger because of the quality of his appointments, improvement of facilities, and his insistence on high academic standards.

Bob remained active after his retirement. From 1984 to1991 he directed the Pew Scholars Program in the Biomedical Sciences, which annually provides long-term support for 20 scholars who propose to undertake riskier projects. Bob's role was to select the advisory committee, participate in the selection process, and manage the post-award administrative issues. He also remained active in his new home, the Department of Cellular and Molecular Physiology. He read and patiently corrected and improved manuscripts, and permitted no split infinitives. He attended departmental seminars and even had the patience to sit through the department's often lengthy faculty meetings although sometimes he took the liberty of leaving early. He was always available for advice, and in his quiet and effective manner contributed to the department's affairs.

What made Bob Berliner such an exceptional and revered colleague? Certainly his commitment to science and to renal physiology was deep, intense, and abiding, and he invested exceptional energy in reading and talking about and debating issues within his domain of interest. He had a keen analytical mind with a firm grasp of the essential problem at hand, and his capability for inductive and deductive reasoning was exceptional. Bob was reticent and retiring, never assertive or aggressive, and he was not given to displays of erudition at public meetings. He viewed self-promotion with great disdain. His ego was not invested in the outcome of a scientific problem, and he was exceptionally generous and willingly

accepted experimental outcomes by others that contradicted his prior positions. One of us (G.G.) had occasion to test his generosity. Having done some experiments as a junior investigator on the mechanism of potassium secretion in distal tubules that included an analysis of driving forces across the apical and basolateral membranes of principal tubule cells, we proposed a cell model that differed from that suggested by Bob. It was with some concern that Bob was approached, but he had not the slightest problem in accepting the new information, testimony to his scientific integrity and modesty. For him resolution of a problem would always depend only on the force of the experimental data that validated a scientific conclusion.

It is not surprising that Bob was the recipient of many professional honors. Bob Berliner was elected to and active in all of the major scientific societies in his field. He served as president of the American Physiological Society, the American Society for Clinical Investigation and the American Society of Nephrology, and as vice president of the American Association for the Advancement of Science. His achievements were recognized by his election in 1968 to the National Academy of Sciences, where he served on the Academy's Committee on Science and Public Policy, on the Council, on the Council of the Assembly of Life Sciences, on its Space Science Board, and in its Division of Medical Sciences (chairman). He was also a member of the Institute of Medicine, the Association of American Physicians, the Society for Experimental Biology and Medicine, the Society of General Physiologists, the Royal Society of Medicine, the Harvey Society, and the American Academy of Arts and Sciences. Leading journals in his areas of interest—*The American Journal of Physiology, Circulation, Journal of Clinical Investigation,* and *Circulation Research*—selected him for their editorial boards. He was chosen to coedit the

first edition of the renal section of the American Physiological Society's *Handbook of Physiology*. A few of the numerous honors and awards tendered him included the Distinguished Service Award of the Department of Health, Education and Welfare (now Health and Human Services); D.Sc. (Hon.) degrees from the Medical College of Wisconsin and Yale University; the Homer W. Smith Award in Renal Physiology; the Alumni Award for Distinguished Achievement by the College of Physicians and Surgeons of Columbia University; the Bicentennial Medal for Achievements in Internal Medicine by the College of Physicians and Surgeons of Columbia University; and the George M. Kober Medal of the Association of American Physicians (Orloff, 1984).

Bob's passions, aside from science, were his family and birds. Bob was happily married for 60 years to Lea, a woman who is warm, nurturing, outgoing, gregarious, and full of *joie de vivre*. A splendid hostess, she was the perfect complement that made them a wonderful integral couple. They doted on their children, warmly welcoming their spouses into their rich family life, and had unbounded admiration and affection for the grandchildren, who brought so much joy to their later years. The tributes to him expressed on the occasion of his memorial service by two of his children and by a son-in-law were touching testimonials to the values that he and Lea transmitted by word and example—integrity, high principle, generosity, modesty, consideration for the less fortunate, hard work, and perseverance—and to the tutelage they gave on the hobbies that had enriched their own lives: nature, sports, music, politics, puzzles, and many more. No man could hope to be more loved and admired by his extended family of children, their spouses, and their grandchildren. They include Robert W. Berliner Jr., Esq. (and spouse, Kathleen Ameche, and children, Sara

May, Amy Rose, and Seth R.); Alice Hadler (and spouse, James L. Hadler, and children, Peter B., Max W., and Eliza M.); Henry J. Berliner (and spouse, Mickey Kavanagh, and daughter, Juleah Mary P.); and Nancy Berliner, M.D. (and spouse, Alan J. Plattus, and children, Rachel B. and Samuel B. Plattus)—a loving family knit together in strong bonds of mutual respect, admiration, and affection.

Bob's other passion was birds. Weekend bird walks were ritual, whenever possible, and new friends and colleagues found Berliner's enthusiasm contagious even though many quickly developed immunity. Sanctuaries and flyways up and down the East Coast attained three-star status, and camping trips to the West expanded his list of sightings. (Given his remarkable memory, Bob never kept a list; he needed neither reminders nor demonstrable trophies, only the inner joy of better knowing nature's bounty.) Abroad for international meetings he was usually able to contact a kindred spirit in the host country and arrange to take a look at the local fauna. In retirement, trips to view, to him, exotic species became a major way of life. Lea reports that over the years they "birded" on every continent of the world.

Among his (slightly) less consuming enthusiasms were major league baseball and its statistics, solving the Sunday *New York Times Magazine* and the *Manchester Guardian* crosswords, *Saturday Review of Literature* Double Acrostics, countercurrent multiplication, etc.—and playing classical music. He was a good enough flutist to earn a seat in Mark Ellsworth's NIH Symphony Orchestra and derived great satisfaction from rehearsing and playing the classical repertoire.

The world lost a great scientist, an effective educator, and a warm human being when Robert W. Berliner died on February 5, 2002. Bob Berliner left a marvelous and permanent legacy of seminal scientific discoveries; of scientific descendants who were shaped under his tutelage, leaders

who substantively advanced the field of renal physiology; and of institutions advanced under his wise and farsighted guidance. He had a good, long, and rewarding life, but his passing leaves a huge hole in the lives of his surviving family, his many colleagues and collaborators, and his legion of friends, even though they retain a rich trove of fond memories.

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