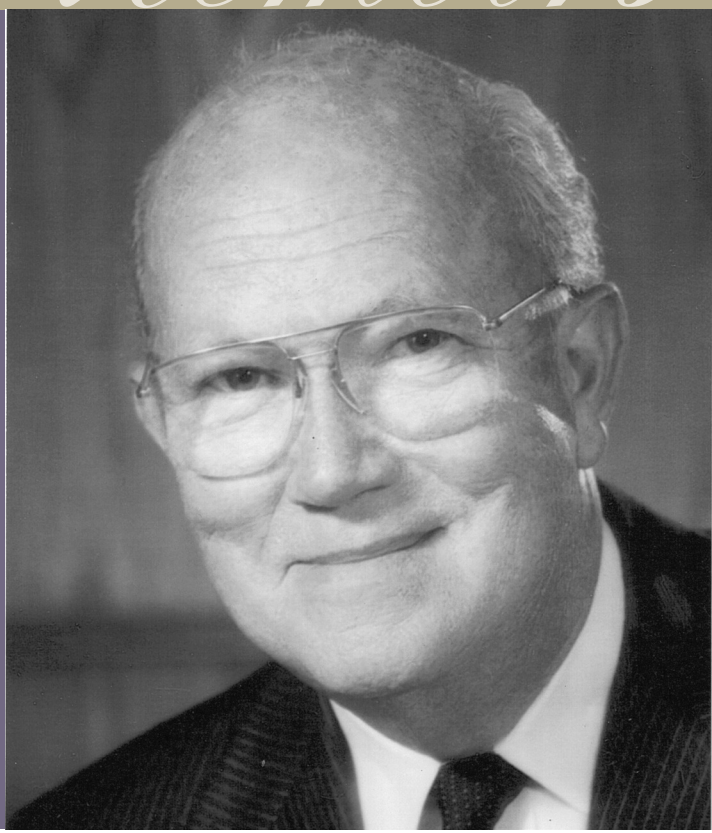
Karl H. Beyer Jr.

1914–1996

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Garabed Eknoyan

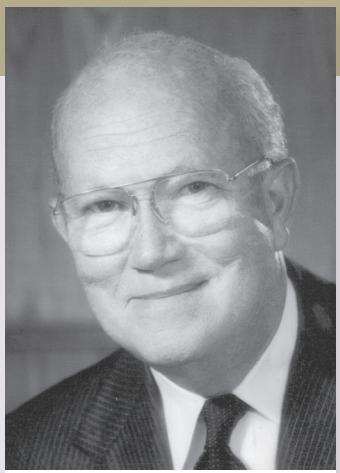


NATIONAL ACADEMY OF SCIENCES

KARL HENRY BEYER JR.

June 19, 1914–December 2, 1996

Elected to the NAS, 1979



Karl H. Beyer was a renowned pharmacologist who led pioneering research in the development of new drugs for treating such debilitating conditions as gout, hypertension, and heart failure. Most notably, his development of the drug chlorothiazide to prevent edema and to lower blood pressure launched the field of diuretic therapy and improved and saved the lives of millions of people. He also was a pioneer in bringing recognition to scientists working in industry, rather than academia. His second career as a teacher inspired numerous students to continue his efforts to improve human health and quality of life.

By Garabed Eknoyan

Karl Henry Beyer, Jr. was born on June 19, 1914, forty days before the declaration of the First World War. His paternal grandfather, Conrad Beyer, had emigrated from Germany to Paducah, Kentucky in 1858. His father, Karl H. Beyer, was a veterinarian who had moved from Paducah to Henderson, Kentucky, and become a farmer. His mother, Lennie (née Beadles) Meyer was a homemaker who gave as much of her time as she could spare to the Methodist Church. Beyer grew up in Henderson, a rural tobacco town of about 12,000 inhabitants on the banks of the Ohio River in western Kentucky. The oldest of three children, he recalled of his childhood: "We, my two sisters and I, grew up in the church actually between church and music, being taught to love flowers, the land and animals, and the social life of the town, it was a pleasant environment in which to live." His early pleasure in nature gave way to science when at the age of 12 his father gave him a toy Chemcraft chemical set. Fascinated with his new plaything, he built a makeshift laboratory bench in his room, where he devoted his leisure time to amateur chemical experiments, animal dissection, and reading biology books.[1] Notable amongst his readings was a 1931 Christmas gift, *Creative Chemistry,* a technical chemistry text by journalist and chemist Edwin Slosson on the vital role of chemistry in national

progress during the First World War.[2] In the process, he developed a keen interest in the sciences, which with his juvenile predilection for chemical experiments proved to foreshadow his lifelong interest in chemistry. Add to that the encouragement of a good science teacher in high school, and you had the making of a future experimental investigator. Another childhood hobby imparted by his mother was the love of playing the piano, which became a lifelong avocation as he continued to play the piano for relaxation, usually after dinner. As a student, and for the rest of his career, Beyer proved to be of sharp intelligence and calm humor with exceptional drive, energy, and determination. He grew up into the tall, fine-looking classic southern gentleman that he had been raised to be in rural Kentucky. Throughout his career as an experimental biologist, he always acknowledged his teachers and credited his co-workers. On August 9, 1940, while still a university student, he married Annette (née Weiss) Beyer with whom he had two daughters: Annette Beyer-Mears, who went on to become an academic ophthalmologist, and Katherine Beyer Cranson, who became a schoolteacher.

Graduate Education

Beyer attended college at Western Kentucky State College (now University) in Bowling Green. After graduating in three years with a double major in chemistry and biology, he remained there for another year (1935-1936) as an instructor in chemistry. He then attended the University of Wisconsin-Madison on a scholarship in medical physiology secured for him by his college chemistry teacher, John T. Skinner, with whom he had authored one of his first scientific publications. It was a report on the detoxification and excretion of Benzedrine, the first brand of amphetamines marketed as a central nervous system stimulant in the 1930s.[3] That proved to be a predictor of the career he would pursue.

At Madison, his professor and dean of the medical school, Walter J. Meek, recommended that he obtain a degree in medicine along with a Ph.D. in physiology. As he recalls, "there was nothing dramatic about it" and that is what he did. As a result, he was trained in the study of function but retained his interest in chemistry by working in the university's chemistry department on the mechanism of action, structural determinants of function, and metabolism of sympathetic amines.[1] This early interest in sympathetic amines would guide most of his early research as a student and post-graduate trainee. It was at Madison that he synthesized and studied metaraminol, a potent alpha-adrenergic vasoconstrictor amine that he took with him to the private sector, where it was ultimately marketed as Aramine by Merck, Sharp & Dohme (MSD) in 1987. Also, the potential role of naturally occurring sympathomimetic amines in causing elevated blood pressure

aroused his interest in the treatment of hypertension, an area in which he would ultimately make his major contribution in the 1950s as an established investigator in renal pharmacology.[4]

By the time he finished his Ph.D. in physiology in 1940 and M.D. in 1943, Beyer had acquired a solid base in the basic sciences and published eighteen research papers that would have qualified him for a tenured position at an academic institution. But as the self-motivated determined individual that he was, he had already set his mind on a career dedicated to the advancement of therapeutics. As he said of himself: "I wanted to be able to synthesize compounds which seemed interesting, and then have the capacity for evaluating such agents potential therapy in patients,"[1] a noble goal that would drive his life's work for the next thirty years. As the archetype of the multitalented experimental scientists being trained at the time, he proved to be a pioneer of new methods for the development and study of drugs, an active contributor to the golden age of practical therapeutics that was just emerging, and a visionary participant in the new intellectual world of scientific medicine then in the making.

His Times

The period between the two world wars during which Beyer came of age and flourished was the worst of times (worldwide conflict) but also the best of times (scientific progress). It was a transformative period in scientific investigation in general and in medical research in particular. It was a time when medical therapy was moving from the descriptive *materia medica* of old and transitioning into an investigative science that encompassed the study of the mode of action of drugs on living tissue and their therapeutic application in clinical practice. It was a time that organic chemistry was moving from the analysis of therapeutic agents to the design of new drugs based on their interaction with body function. It was a time that clinical trials were just coming into fashion and soon would become an integral component of the marketing of new drugs.

Hand in hand with the development of scientific investigative chemistry came improvements in the industrial manufacture of chemical compounds. What begun as the study of plant alkaloids in university research laboratories in the first half of the nineteenth century evolved into the first chemical firms producing industrial dyes in the second half of the century, initially in Germany but soon thereafter worldwide. With progress in chemistry, commercial chemical companies with their roots mostly in the dye trade began their own quest for new compounds with biological activity by fostering fundamental research and development. In the process, they began to build in-house research

laboratories and employ professional scientists to develop new commercial therapeutic agents. It was a time when a career in the chemical industry was becoming an accepted norm.[5,6,7]

There was also developing pharmacological interest in the kidney because of the renal excretion of drugs and the expanding interest in the effect of drugs on renal blood flow, glomerular filtration, and tubular transport.[8,9] Two prominent founders of renal physiology who would influence Beyer's future work were James A. Shannon and Homer W. Smith, who had been temporary employees of pharmaceutical companies, Shannon at E. R. Squibb and Sons and Smith at Eli Lilly and Co. Others developed and maintained a productive consulting relationship with the pharmaceutical industry as they progressed in their academic careers. One such individual who would also influence Beyer's career was another founding father of renal physiology, Alfred N. Richards. A University of Pennsylvania pharmacologist, Richards is credited with the introduction of the 1924 landmark method of renal micropuncture for the study of kidney function and served as a long-term consultant and then member of the Board of Directors of Merck & Co. in Rahway, New Jersey. Other notable pharmacologists who had already contributed to the study of the kidney were John Jacob Abel of the University of Michigan, who developed the first "artificial kidney" in 1914, and his successor at Michigan, Arthur R. Cushny, who published *The Secretion of the Urine* in 1917, a major critical review of the evidence for glomerular filtration and tubular reabsorption in the production of urine that shaped subsequent studies of kidney function. It was to the membership of this elite group of renal pharmacologists that Beyer's chosen career would lead.[1,5,6,7]

Becoming a Renal Pharmacologist

At the time that Beyer first ventured into renal pharmacology in 1943, the understanding of kidney function was still rather rudimentary but beginning to progress at a rapid rate from that of a mere excretory gland into a vital organ essential for maintaining the homeostasis of water, electrolytes, and the acid-base balance of the body.[8,9] The availability of an accurate measurement of the glomerular filtration rate developed by Homer Smith and Alfred Richards had set the stage for the study of the secretion and reabsorption of filtered constituents as they traversed the renal tubule.[8,9,10] For the next two decades of his career, Beyer would contribute, conceptualize, pioneer, and provide leadership in research in each of these developing areas in renal physiology, and specifically in their application to renal pharmacology.

It was in this intellectual setting that on May 1, 1943, Beyer, at the age of 29, accepted a position as Assistant Director of Pharmacological Research at Sharp & Dohme, an apothecary shop in Baltimore founded in 1845 that had expanded into the production of drugs and in the fashion of industrial pharmaceutical firms started its own research laboratories in Glenolden, Pennsylvania. One thing that attracted Beyer to Sharp & Dohme was the strength of its chemistry department under the directorship of James M. Sprague, an earlier graduate of the University of Wisconsin who had joined the firm in 1937. From the outset, their departments worked in close cooperation at Sharp & Dohme and continued to do so after its merger with Merck and Co. in May of 1953.[1,11] Of note, despite their close association at work, the two scientists never co-authored an article together.

That was just about the time when the concept of drug design was coming into bloom in the wake of the discovery of the sulfa drugs. Prontosil, the first widely used sulfonamide, had been marketed in 1935 and would become the subject of the 1939 Nobel Prize in Physiology or Medicine granted to German bacteriologist Gerhard Domagk, then a professor at the University of Münster. Domagk had discovered the antibacterial effect of prontosil in 1932 while working in the laboratories of the Bayer Corporation, part of the industry combine of I. G. Farben, a large German chemical conglomerate that manufactured azo dyes, fertilizers, photographic material, and drugs. Research had shown that azo dyes containing a sulfonamide group had an affinity for bacteria, arresting their nutrition and hence their multiplication. It was as a mauve dye, an aromatic hydrocarbon derived from coal tar, that prontosil was discovered in 1925 in Germany and then identified as a pro-drug metabolized to its active bacteriostatic form, sulfanilamide, in France. At the time that Beyer joined Sharp & Dohme, the company had already acquired a position of leadership in sulfonamide research under the leadership of James Sprague and developed some of the most widely used of these new miraculous compounds with antibacterial activity.[11,12,13] In sum, what had begun in the first decade of the twentieth century as the "magic bullet" of Paul Ehrlich's "chemotherapy" had launched in the third decade of the century the era of the bacteriostatic sulfa "miracle drugs," which in turn paved the way for the "golden era" of true bactriocidals, led by penicillin and streptomycin, in the 1940s. As he embarked on his new career, Beyer became involved in the study of these new wondrous compounds, albeit indirectly and rather peripherally. But it was those tangential studies of chemotherapeutic agents that would shape his career and pave the way to his major medical contribution to therapy in the 1950s, the thiazide diuretics.

At Sharp & Dohme, the first project assigned to Beyer was to figure out a solution to a major complication of the sulfa drugs, acute renal failure resulting from their crystalline precipitation in the renal tubules. He set himself to build a renal research team at Sharp & Dohme with the calm optimism, meticulous planning, and determination that characterized everything he undertook. Setting up a renal program that would address the sulfa problem eventually determined the course of his subsequent career as an investigator in renal physiology and a leader in renal pharmacology. In preparation for his new task, Beyer spent a month during June and July of 1943 in the laboratory of James A. Shannon at Goldwater Memorial Hospital in New York to learn renal clearance techniques.[1] While there, he met and recruited John E. Baer, a pharmacologist with a degree in organic chemistry who would soon become a valued colleague and play a significant role in Beyer's subsequent contributions to renal pharmacology.

At the time Beyer began his work in the closing years of World War II, penicillin was coming into clinical prominence, but its supply was scant and its clinical utility significantly hampered by its short duration of action because of its rapid renal elimination, principally by renal tubular secretion. One of the most pressing medical questions of the war effort, coordinated by the Committee on Medical Research of the National Research Council, headed by Alfred Richards, was how to prolong the retention of penicillin in the body.[12,13,14] Beyer, now versed in renal physiology, was familiar with the concepts of renal tubular secretion and its competitive inhibition. Exploring this possibility was suggested from reports of the tubular inhibitory effects of para-aminohippuric acid (PAH) by Homer Smith, who was using PAH in measuring renal blood flow. In 1944, Beyer discussed the possibility of using PAH to inhibit penicillin secretion with Alfred Richards, who encouraged him to do so. He was then able to obtain 100,000 Oxford units of precious penicillin from Chester S. Keefer, the "penicillin czar" in charge of its national allocation. In clearance studies on trained dogs, PAH did suppress the clearance of penicillin, but the animals required large doses of PAH (100 gm) administered intravenously.[12] By then, improvements in extraction methodology, use of more productive strains of *Penicillium*, and expansion of dedicated manufacturing facilities had increased the production of penicillin, so resorting to inhibition of its renal excretion became unnecessary.[1,14] But it was these studies that paved the way for Beyer's study of drugs that inhibit renal tubular transport.

Discovery, Development, and Delivery of the Thiazides

From this work on the competitive inhibition of penicillin secretion came the discovery of drugs that inhibit the renal transport of inorganic acids, notably caronamide in

1947 and then its improved form probenecid in 1951. Probenecid inhibited penicillin secretion but also increased the excretion of uric acid. Hence, the marketing of probenecid as Benemid, a uricosuric agent for the treatment of gout in 1957.[1,12,13] Importantly, it was from knowledge accrued on kidney function from research on the sulfas and penicillin that would come work on the renal modulation of electrolyte balance—an endeavor that would lead to the major contribution of Beyer to therapeutics, the thiazide diuretics. By then, Sharp & Dohme had merged with Merck and Co., and the move to Merck's larger and better-equipped West Point Research Laboratories in Pennsylvania favored the progression of work on diuretics.[11]

The principal diuretics then available were the organomercurials that had been introduced in the 1920s, but these were of limited clinical utility because of their renal tubular toxicity and restricted in their use to the emergency treatment of edema rather than in preventing fluid overload. Historically, diuretics were considered substances that increase urine flow and thereby water excretion. The importance of salt intake in the generation of edema was recognized at the turn of the twentieth century from measurements of urinary chloride, but it was only after the availability of the flame photometer for measuring sodium and potassium in the mid-1940s that abnormalities of sodium metabolism in general and in edema in particular began to be identified and examined in earnest.[8,15] By the same token, there was increasing laboratory and clinical evidence that dietary salt intake aggravated hypertension, whereas a very low salt intake was effective in treating hypertension. Notable in this regard was the strict, literally punitive diet of rice and fruit juice developed by Walter Kempner in the late 1930s for the treatment of hypertension. To his credit, Beyer argued that what was needed for the control and management of edema and hypertension was an effective diuretic that increased salt and water excretion by the kidneys safely when administered orally. To this end, and in the footsteps of Homer Smith (who had introduced the term *natriuretic* in 1957), Beyer introduced the term *saluretic* to make it clear that what needed to be accomplished was inhibition of the renal salt (sodium and its accompanying anion chloride) reabsorption, with its consequent osmotically obligated water loss. *Saluretic* also provided a refinement to *diuretic*, which implied a net increase of urine volume per unit time regardless of its composition, by emphasizing the increased excretion of sodium chloride as the urinary constituents of the diuresis, hence the term *saluretic diuretics* that came into vogue. Still, the use of the term *water diuresis* continued to prevail and as late as 2005 the discovery of thiazide diuretics was hailed as that of "releasing the flood waters."[15,16]

Analogues of sulfanilamide were known to inhibit carbonic anhydrase in the kidney with increased renal excretion of sodium bicarbonate and the consequent onset of metabolic acidosis, a detrimental complication that limited their clinical utility as diuretics. That sulfanilamide relieved severe congestive heart failure in patients by increasing sodium and water excretion was reported in 1949. It was these clinical leads into the natriuretic effect of sulfonamides that reinforced the chemical quest that would lead to the first orally effective saluretic agent, chlorothiazide.

The organic chemistry department headed by James M. Sprague had been actively involved in the study of sulfonamide chemistry, from which the researchers had derived their substantial contributions to the sulfa drugs produced at Sharp & Dohme in the 1940s. It was their familiarity with the structure-activity relationship of sulfonamides that would lead Sprague and his colleague Frederick C. Novello to the synthesis of chlorothiazide in 1952. Essentially, the substitution of a carboxyl group for that of the amino group in sulfanilamide produced a carbonic anhydrase inhibitor that did increase sodium chloride excretion but was rather too weak to be clinically useful. The subsequent introduction of a sulfamoyl group led to the synthesis of a new compound with a benzothiadiazine heterocyclic nucleus that would become chlorothiazide.[16,17]

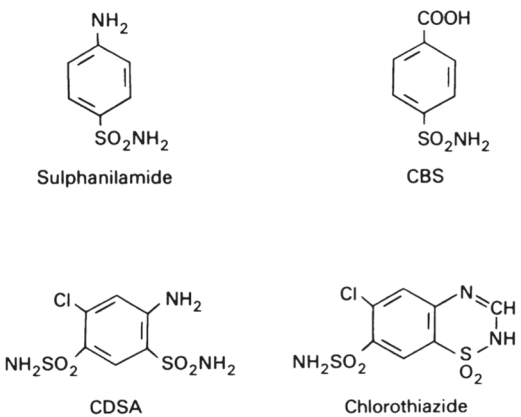


Figure 1. Structure of sulfonamides basic to the discovery of chlorothiazide.

To the major delight of Beyer and his renal team, the injection of chlorothiazide increased the excretion of sodium chloride, rather than sodium bicarbonate, in the urine of the trained dogs they had been using in their clearance studies. The favorable outcomes of the clinical trials that followed in rapid succession documented the dramatic effectiveness of chlorothiazide in preventing edema and reducing the blood pressure in hypertension. These were transformative results that launched the whole field of diuretic therapy, which would save the lives of millions.[16-19] Chlorothiazide was marketed as Diuril, the first oral diuretic in 1957, and followed by hydrochlorothiazide as Hydrodiuril in 1958. As prototypes of an expanding series of heterocyclic sulfonamides with saluretic properties, they launched the synthesis of a

series of related chemical structures with diuretic properties. Importantly they remain a component of the management of edema and hypertension to this day. Few therapeutic agents for the treatment of any disease can claim such staying power. Rather appropriately, it came to be rumored in the hallways of the company, that the history of diuretics and antihypertensives should be divided into two parts: first the era of BC or "before chlorothiazide," and second the era of AD or "after Diuril."

Recognition

Beyer's highly effective leadership in the multidisciplinary effort of developing and coordinating the launch of Diuril made him world-famous. And he was correspondingly honored for his contributions to the knowledge of pharmacology, the understanding of renal physiology, and his leadership in the discovery of the thiazides. For his contributions to therapeutics, he was elected President of the American Society of Pharmacology and Experimental Therapeutics in 1964, overcoming a long-standing stigma attached by the society to workers in industry. For his contributions to the discovery of thiazide diuretics, he shared with John Baer, James Sprague, and Frederick Novello the Lasker Foundation's Special Public Health Award in 1975. In recognition of his contributions to the physiological and therapeutic sciences, he was elected the National Academy of Sciences in 1979. He was also recognized by his alma mater with the Distinguished Service Award of the Wisconsin Alumni Association in 1968, and an Honorary Doctor of Sciences Degree by the university in 1972. Of the many other awards he received, most notable are the Canada Gairdner International Award in 1964, the CIBA Award for Hypertension Research of the American Heart Association in 1979, and the McKeen Cattell Distinguished Investigator Award of the American College of Clinical Pharmacology in 1986.

The well-earned promotions at MSD that followed moved Beyer away from his close association with the renal team he had set up to that of shepherding the research and development of new compounds being isolated and synthetized in the MSD Research Laboratories.

Unfortunately, in 1972 he was diagnosed with a brain meningioma necessitating surgical removal, which left him weakened, with improving residual motor impairments. That led to his decision to retire the following year from his position as Director of the Merck Institute for Therapeutic Research and Senior Vice President for Research at MSD.

A Second Career

After 30 years at MSD, on July 31, 1973 at the age of 59 Beyer left industry to embark on his second career as a teacher, because as he put it, "ultimately I wanted to go back to teaching." The permanent teaching position he accepted was that of Visiting Professor in the Department of Pharmacology at the Milton S. Hershey Medical Center of the Pennsylvania State University. There he embarked on research in hypertension and uremia and on teaching graduate students for the next decade before retiring in 1983 from his second career as a teacher. Initially, he would fly from Wings Field, in Blue Bell, Pennsylvania, near his hometown for a 27-minute flight to Hershey on a two-engine, six-seat airplane that he owned. But as time went by, he drove to Hershey and gradually reduced his visits there to a few per month. In 1978, he authored a book, *Discovery, Development and Delivery of New Drugs,* on his philosophy of teaching pharmacology as a clinical subject rather than as the field molecular biology into which it was evolving.[12]

At the suggestion of James Shannon, Beyer also accepted another position upon retiring. From 1974–75, he served as the Scholar-in-Residence at the John E. Fogarty International Center for the Advanced Study of Medical Sciences on the grounds of the National Institutes of Health in Maryland.[1] Other notable academic teaching positions he held were Clinical Professor in the Department of Pharmacology of the University of Miami School of Medicine from 1978–80 and Visiting Professor at the Center for Biomedical and Biophysical Sciences and Medicine of the Harvard Medical School from 1984–90. Invited lectures throughout the world kept him busy for most of his free time between teaching assignments.

Conclusion

Although he trained as a physician, Beyer never practiced medicine. His training, however, set his graduation goal of "what to do in medicine that would be worthwhile," and his training in physiology research and love of chemistry set his path on "how to do it." The thirty years of diligent, dedicated work on this goal culminated in the discovery, development, and delivery of the thiazide diuretics that have improved the quality and saved the lives of more patients than a practicing physician could ever aspire to accomplish.[18,19] In a career dedicated to the design and discovery of new therapies he obtained 18 drug patents. Four of the drugs he developed are still in use: chlorothiazide, hydrochlorothiazide, probenecid and metaraminol. The two things Beyer was proudest of in his retirement were his flying and handcrafted furniture. Other hobbies that kept him occupied were piano music and gardening. He died at the age of 82 from complications of heart failure on December 2, 1996.

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