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C W Gottschalk

CARL W. GOTTSCHALK

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BY MAURICE B. BURG

CARL W. GOTTSCHALK made critical discoveries in renal physiology and pathophysiology with innovative techniques of micropuncture. One of his earliest findings was definitive proof of how urine is concentrated by countercurrent multiplication. That discovery catapulted him to the front ranks of renal physiologists early in his career. In the following years he made many more important observations about the mechanism of urea excretion by the kidneys, the role of renal nerves in salt and water excretion, urinary acidification, and pathophysiologic mechanisms of acute and chronic renal disease. Because of the brilliance and quality of his research he was widely recognized as a leader in renal research.

EARLY LIFE

Carl William Gottschalk was born on April 28, 1922, in Salem, Virginia, to Lula Helbig and Carl Gottschalk. His father had been born in Germany and emigrated to South Africa, where as a machinist he fabricated and repaired cigarette-making machines. Then, at age twenty-two he came to the United States. He lived most of his life in Salem, Virginia, where he owned a movie theater, automobile repair shop, and other downtown property. Carl William Gottschalk's older brother is a mathematician and was formerly head of that department in Wesleyan College in Middletown, Connecticut.

As a boy, Carl was studious, focused, and quiet. His early and ardent penchance for collecting stayed with him his whole life. His earliest collections were of stamps, coins, and most notably butterflies. At age fifteen he discovered a new butterfly in the hills of Virginia. The butterfly named for him, *Stryman cecrops gottschalki*, became the subject of his first scientific paper (1942). This precocious paper combined two of the great passions in his life, namely, science and collecting.

Carl graduated from Roanoke College in 1942 and the University of Virginia Medical School in 1945. His time in medical school was abbreviated because of the urgency of World War II. He took his medical internship at the Massachusetts General Hospital.

In Boston during his internship he met Helen Scott, a nursing student from Pennsylvania. They married in 1947 and had three children: Carl Scott Gottschalk, now an architect; Karen Gottschalk Strehlow, a pathologist; and Walter Parks Gottschalk, director of the Water Purification Plant of Chapel Hill, North Carolina.

Following his internship, Carl was drafted into the army as a medical officer and was stationed at the Army Medical Research Laboratory in Fort Knox, Kentucky, where he investigated physiological effects of cold exposure in humans. During his travels at that time he assembled a unique collection of Canadian arctic butterflies that now graces the Peabody Museum of Natural History at Yale.

REVIVING MICROPUNCTURE

Carl's interest in kidney micropuncture began during a postdoctoral fellowship with Eugene Landis at Harvard

Medical School between 1948 and 1952. He began by performing some kidney studies with Daniel Tosteson (1951), then a Harvard medical student. At the time they were surprised to observe increases in urine excretion when the kidney was partially infarcted by ligation of branches of the renal artery. Since, from the literature, the best explanation seemed to be changes in renal interstitial pressure, Carl, who was already interested in cardiology and hemodynamics, began a systematic study of renal interstitial pressure using small hypodermic needles and large glass pipettes. However, it became obvious to him that insertion of what he later (1990) called a “crow bar” into the renal parenchyma damaged many tubular and vascular structures and that a proper study would require micropuncture of individual tubules and micro vessels. It was not until a few years later, however, when he had finished his medical residency at Harvard and had started as a fellow in cardiology at the University of North Carolina in Chapel Hill in 1952 that he was able to assemble the necessary equipment to begin micropuncture.

Renal micropuncture had been developed at the University of Pennsylvania jointly by A. Newton Richards, who for many years was chairman of pharmacology, and Joseph T. Wearn, a young physician who had joined Dr. Richards’s laboratory in 1921. Richards’s group produced a series of famous reports, notable for their reliability, detail, and cautious interpretations, which established beyond doubt and in great detail the nature of renal glomerular filtration and of selective tubular reabsorption. The studies were confined to amphibian kidneys until 1941. Then, two persons in Dr. Richards’s group, Arthur M. Walker and Phyllis A. Bott, working in collaboration with Jean Oliver (who was later a close associate of Carl’s) and his able assistant, Muriel C. MacDowell, extended this work to mammalian species. In

1941 they published two landmark micropuncture studies in rodents. That same year when World War II intervened, the Richards laboratory was permanently disbanded as Richards and most of his coworkers entered national service. No other laboratories filled the gap, so that when Carl Gottschalk wanted to use the technique, there was no one to teach him.

Carl learned why the micropuncture technique had lapsed from Richards himself. He discovered that "Dr. Richards did not encourage the revival of the micropuncture technique after World War II and advised me, and I suspect others, against entering the field" (1969). Lest Richards be misunderstood, Carl added, "I am certain he had no selfish or proprietary motivations for doing this; rather he was concerned that a field to which he devoted so much of his life would be sullied by less competent workers." Richards and his colleagues took almost unbelievable care to assure the correctness of their results. Dr. Richards's reluctance arose from the fear that others less meticulous would publish misleading results. This fear was clearly misdirected in Carl Gottschalk's case, considering the greatness of Carl's eventual accomplishments with the technique.

Richards's advice aside, Carl set up a micropuncture laboratory at the University of North Carolina in Chapel Hill. He had moved to Chapel Hill as a cardiology fellow and instructor in 1952. When asked later why he chose that position, Carl said that it was the only job offer he had. He liked clinical medicine, but he recognized early in his career that it was science that tugged hardest at his heart and soul and that he could not combine the two if he wanted to succeed in either. So within a few years, he dedicated himself to bench research and began the challenging task of setting up the micropuncture laboratory with little space and less money. Carl's laboratory initially was very modest.

It had the dimensions of a chicken coop and a $2,000 grant from the Edgecomb County North Carolina Heart Association. In collaboration with Margaret Mylle, who became his long-term associate, he began working in earnest and soon published studies of the hydrostatic pressure in the tubules and small vessels of the rat kidney (1956). From 1957 to 1992 the American Heart Association supported Carl as an established investigator and then as a career investigator, which made it possible for him to discontinue clinical activity and devote his life to bench research.

A DECISIVE MICROPUNCTURE EXPERIMENT

Carl addressed what was the most important problem in renal physiology at the time. He later summarized the background in a commentary accompanying re-publication of his original landmark article (1959) as a "Milestone in Nephrology" in the *Journal of the American Society of Nephrology*. He recalled that in the 1950s renal physiologists understood reasonably well how the urine is diluted. In the absence of antidiuretic hormone some renal epithelial cells are impermeable to water, so that active reabsorption of NaCl lowers the concentration in the remaining fluid. The mechanisms responsible for high concentration of the urine remained perplexedly undefined, and investigators had little recourse but to invoke the active transport of water out of the nascent urine. However, nowhere in the animal kingdom was there a proven example of active transport of water, so this explanation was both unsatisfying and unproven.

An alternative hypothesis, the countercurrent theory, had been proposed by the Swiss physical chemist Werner Kuhn, but it was not generally accepted by renal physiologists of the day. Kuhn's hypothesis invoked passive diffusion of water out of the collecting ducts into the fluid surrounding them in the renal medulla and involved salt transport by the loop of Henle to concentrate the surrounding fluid. A striking feature of Kuhn's model was that transport between the countercurrents of fluid moving up and down in adjacent limbs of the hairpin-like loop of Henle in the renal medulla concentrates the fluids both in the loop and the surrounding tissue; these fluids become progressively more concentrated as the tip of the renal medulla is approached. In support of his theory Kuhn actually constructed and tested countercurrent model systems and demonstrated several arrangements by which concentrated solutions could be produced in compartments separated by semi-permeable membranes. The theory attracted little immediate notice because it was published in German in 1942 at the very height of World War II.

Simultaneous evidence for the theory came in a collaboration between Kuhn and Heinrich Wirz, who was in the Physiology Department of the University of Basel, where Kuhn chaired the Department of Physical Chemistry. Over a five-year period they demonstrated several of the predicted consequences of the countercurrent theory. They found by cryoscopic measurements of kidney slices that there is an osmotic gradient in the renal medullary tissue with the highest concentrations at or near the tip of the renal papilla. By micropuncture they found a corresponding gradient in the blood vessels (vasa recta) of the renal medulla. Also, by micropuncture they found that during hydropenia the concentration of solutes in distal tubular fluid at the surface of the cortex increases from that of a dilute solution at the start of the distal tubule to a concentration similar to systemic plasma (but never higher) near the end of the distal tubule during antidiuresis.

Despite Wirz's extensive experiments there was no experimental proof for one critically important prediction of the theory, namely, that fluid in the bend of the loops of Henle should be hyperosmotic not only in antidiuresis but also in water diuresis. Notwithstanding his efforts, Wirz had been unable to micropuncture the loops of Henle because he could not distinguish them from vasa recta on the surface of the renal papillae of living animals.

There was very serious skepticism about the countercurrent theory. When Homer Smith, then the acknowledged "dean" of renal physiology, visited Chapel Hill in 1953, Carl had the opportunity to discuss the countercurrent concept with him. Carl recalled (1997) that Smith said "the smart boys don't believe in it." Nevertheless Carl found the countercurrent hypothesis attractive and credible, perhaps because he had no formal training in renal physiology and was not burdened by establishment biases. Smith did not change his opinion until much later after he had the opportunity to review the data in Carl's paper, and even then he confessed that he didn't like it.

Other highly respected authorities also remained skeptical of the countercurrent theory, which seemed unbelievably complicated. There was an ongoing search for other mechanisms. For example, Robert Berliner, then at the National Institutes of Health, speculated that the fluid in the bend of the loop of Henle might be hyposmotic, and he was developing indirect evidence to support his theory. Hypertonicity of the loop of Henle fluid clearly was the smoking gun. Finding it was the evidence needed to prove the countercurrent hypothesis.

By this time Carl and Margaret Mylle had substantial experience in micropuncture of renal tubules exposed on the cortex of the rat kidney, as well as expertise in confirmation of the localization of the puncture sites with microdissection techniques. Further, J. A. Ramsay and R. H. J. Brown had described a method for measuring the osmolality of nanoliter volumes of fluid. Based on the published description, Gottschalk and Mylle constructed a similar instrument. They were soon able to confirm the 1941 work of Walker, Bott, Oliver, and MacDowell that fluid in proximal tubules at the surface of the renal cortex maintains the same osmolality as plasma and also the later work of H. Wirz that fluid in early distal tubules has a low osmolality, regardless of the urinary concentration. However, the hardest challenge remained: the sampling of fluid in the loop of Henle.

It was so difficult at the time to distinguish loops of Henle from vasa recta in vivo that Carl took special pains to describe his method for doing so in his preliminary report in *Science* (1958). As evidence that the collected fluid was from renal tubules and not blood vessels, Gottschalk and Mylle showed that it did not contain appreciable protein. As well, they injected dye followed by microdissection, showing that the punctured loop was contiguous with more proximal and distal parts of the nephron.

The classic report (1959) is remarkable for its thoroughness and the extraordinary care with which the experiments were conducted. They used four species of mammals with different kidney anatomy under three different conditions, namely, hydropenia, water diuresis, and osmotic diuresis. The results were unequivocal. The data from nine hamsters, one kangaroo rat, and one *Psammomys obesus* showed virtual equality of osmolality in collecting ducts and at the bend of the thin loops of Henle during antidiuresis. This was a technical triumph, providing final decisive evidence for the countercurrent hypothesis. Carl later wrote (1997), “Nothing I had ever done before or have done subsequently was as thrilling as obtaining these data.”

LATER STUDIES

Over the next thirty years, Carl made many more advances in renal physiology, which he published in more than 100 papers. His influence extended to numerous scientists whom he trained and collaborated with. Prominent among these is Bill Lassiter, who initially joined Carl to add his expertise with the use of radioisotopes to the research. Bill remained a long-time collaborator and friend. One of their first collaborative efforts yielded, as was so often the case in that laboratory, a surprising and exciting discovery (1961). They found a large net addition of urea to the fluid in the loop of Henle, indicative of urea recycling in the renal medulla. That and additional urea recycling pathways discovered subsequently facilitate concentration of urea in the renal medulla and urine during antidiuresis.

Another important discovery was the direct role of renal innervation in the renal tubular handling of sodium chloride. It had been known for many years that denervation of a kidney increases the rate of salt and water excretion by that kidney. The burning question was whether the denervation acts by decreasing renal tubular transport or increasing glomerular filtration. A change in glomerular filtration too small to be measured directly by renal clearance methods could easily do this. The micropuncture experiments in Carl's laboratory settled the issue conclusively by showing directly that the renal nerves affect the rate of salt reabsorption by the tubules. With Elsa Bello-Reuss and others, Carl found by direct measurements that denervation decreases sodium reabsorption by the proximal tubule (1975) and that renal nerve stimulation increases the rate (1976). With Romulo Colindres the observations were later extended to conscious, unanesthetized animals (1986). As with the experiments on the concentrating mechanism, Carl designed careful and insightful experiments that proved to be decisive.

There were also pioneering studies in urinary acidification (1960), calcium excretion (1963), potassium depletion (1965), glomerular dynamics (1980) and much more, including some very important observations on the pathophysiology of acute (1968, 1975) and chronic (1974, 1975) renal failure. Carl and his colleagues found that in diseased kidneys the rate of filtration in individual nephrons and the hydrostatic pressure in individual tubules varied over a large range. In each nephron, however, the rate of reabsorption by proximal tubules is in balance with the rate of filtration so that the fraction reabsorbed proximally varies no more in diseased kidneys than in normal ones. For an individual in balance at any salt intake, as filtration rate falls, the same amount of salt can be excreted only if the fraction of the filtered salt that is excreted is increased. That means that each distal tubule must reabsorb a smaller part of what is delivered to it. Carl named this process the adaptive nephron.

Associated with these later studies, were numerous trainees and collaborators whose lives Carl touched. When Carl first set up his laboratory, micropuncture was limited to it and a very few other newly established laboratories. Carl trained or invited to his laboratory many young scientists who wanted to be on the cutting edge of renal physiology. Many of them went on to prominent positions. They include Karl Ullrich, who studied tubule fluid composition (1963) and electrochemical potentials (1963); Michael Kashgarian, who investigated transtubular electrochemical potentials (1963); Thomas Biber, who studied acute tubular necrosis (1968); Francois Morel, who developed tracer microinjection measurement of tubule permeability (1965); Andrew Baines and Paul Leyssac, who studied proximal tubule function (1968); Klaus Thurau, who studied glomerulotubular feedback; Marjorie Allison, who studied chronic renal failure (1975); and Bill Finn, who studied acute renal failure. William Arendshorst, who shared in studies of glomerular ultrafiltration dynamics (1980) and acute renal failure (1975), succeeded Carl as head of the micropuncture laboratory.

SERVICE AND AWARDS

In addition to his research, Carl Gottschalk established an impressive record of service. One of his major contributions was serving as president of the American Society of Nephrology (1975-76).

Another stellar instance of his service was as chair of what came to be called the Gottschalk Committee. The actual name was the Special Committee on Kidney Disease, initiated by the Bureau of the Budget in 1966. At that time Belding Scribner's development of methods for continuing access to blood vessels had made it possible for chronic hemodialysis to keep alive and in reasonable condition patients with end stage renal disease. The demand for such treatment greatly exceeded the availability of equipment and trained people to supply it. The Gottschalk Committee was charged with determining the prevalence of chronic renal disease in the country, the percentage of such patients that could be treated with dialysis, and whether dialysis had in fact moved from an experimental to a therapeutic procedure. The committee contained individuals of widely varying backgrounds, specialties, and opinions. Robert Berliner, who sat in as an observer, attests to the remarkable job that Carl did to bring that ill-assorted group to a consensus. The conclusions and recommendations were far-reaching. The committee reported that there were a large number of patients with chronic renal disease who could be treated successfully with dialysis and they recommended that no one should be denied these forms of treatment for financial reasons. The recommendations served as effective ammunition in the hands of those who later successfully lobbied for the passage of the end stage renal disease amendment to

Public Law 92-603. That legislation has saved the lives of literally tens of thousands of patients. Carl also served on numerous other university and national advisory committees.

He was on the editorial boards of *Physiological Reviews*, *Circulation Research*, *American Journal of Physiology*, *Journal of Applied Physiology*, and *Kidney International*. He edited the third edition of *Diseases of the Kidney* with Lawrence Early and the fourth through sixth editions with Robert Schrier.

He delivered numerous distinguished lectures, including a Bowditch Lecture, and a Harvey Lecture. He received numerous awards including the Homer Smith Award in Renal Physiology, the David Hume Award of the National Kidney Foundation, the A. N. Richards Award of the International Society of Nephrology, and the first Berliner Award for Excellence in Renal Physiology. He received honorary degrees from Roanoke College and Universite de Mons-Hainaut. He was elected to the National Academy of Sciences in 1975.

Carl was professor of medicine and physiology at the University of North Carolina from 1961 to 1992 and distinguished research professor of medicine and physiology from 1992 until his death. He served on almost all important committees of the university and remained a major figure in university life.

COLLECTOR AND HISTORIAN

Carl was a close friend of Jean Oliver, a distinguished renal anatomist and pathologist. Oliver, who had no children, considered Carl a protégé, virtually a son. When Oliver became depressed after his wife's death, Carl and his wife Helen gave Oliver much support. Oliver collected rare books, Chinese and Japanese paintings, and other works of art, many of which he bequeathed to Carl. He also gave Carl all of his original lab notebooks and photomicrographs of his kidney dissections. Carl's widow Susan Fellner has donated this material to the Wilson Library of the University of North Carolina.

Carl had always been a collector. The association with Oliver resulted in Carl's extending his interest in collecting to rare scientific books and Asian art. Carl and Helen and two other couples spent a month in a vicarage in London every year for about eight years. It was there that he fine-tuned his collecting, becoming known to every rare book dealer in the city. They sent him catalogues regularly and called if they had a special volume he was seeking. So, over the years, and especially after the death of Helen, when he was terribly lonely, Carl systematically amassed an extraordinary collection of rare books in the fields of nephrology and in physiology, anatomy, and pathology, usually but not invariably related to the kidney. His house had to be enlarged to hold the collection, and then enlarged again. It was fortunate that by the time the garage succumbed under the tide of books there were almost no works bearing on the field of renal physiology and renal disease that Carl did not already possess. He was especially keen to possess first editions and in the end had them for all important works over several centuries, with only very few frustrating exceptions still remaining. He shared his passion for collecting with Leon Fine and J. Stewart Cameron. Cameron recalls that, as Carl's collection became more and more complete, the hunt for rare volumes in the excellent condition that he always demanded became ever more difficult and therefore ever more exciting. One of Carl's greatest joys was to have Leon, Stewart, and other scholars and book lovers visit the library in his home. He would beam with delight as he showed his treasures, touched the linen pages, and viewed the engravings. Each book was catalogued with its provenance, date of purchase, price, and recent catalog price.

The collection has been donated to the Rare Books Library of the University of North Carolina library system. A section of the rare books reading room of the Wilson Library has become a closed alcove to house his collection. Carl's kidney-shaped desk, lamp, chair, and Chinese scholars table, as well as the oriental rug from the great room of his house, furnish the Gottschalk collection space.

Not only did Carl collect medical books but many other books as well. He donated his nearly complete collection of first editions of Robert Louis Stevenson to the Rare Books Library of the University of North Carolina in 1997. Fine editions of most of the classics of English literature sat on the shelves around his home. He liked to touch beautiful books and took pleasure in browsing through them whenever the fancy struck. No lending library for Carl: he wanted them available around him.

He went about collecting Chinese and Japanese porcelains in the same scholarly manner he pursued his books. After reading extensively, he combed the antique shops in London for beautiful, old objects. Particularly after Helen died, he spent much of his retirement time seeking beautiful works of art, both contemporary and old, for his home. The family joked that Carl felt that the purpose of walls was as spots for pictures or old maps and of floors to be covered with Oriental carpets.

Carl's penchant for medical history, particularly that related to the kidney, was no less than or different from his approach to science. It led him to edit with Robert Berliner and Gerhard Giebisch a book on the history of renal physiology and a historical archives series in *Kidney International.* He formed and chaired for 15 years the Commission for the History of Nephrology of the International Society of Nephrology.

THE LAST YEARS

The death of Carl's beloved wife Helen in 1988 from amyloidosis was a low point in his life. Carl's prolonged sorrow after Helen's death came to a happy ending when he met and married Susan Fellner, a nephrologist. Considering their respective occupations, it is fitting that they met during a Homer Smith Symposium at that bastion of renal physiology, the Mount Dessert Island Biological Laboratory. Just four months before his death Carl and Susan attended a meeting in Sydney, Australia. At that time he was a happy newlywed, full of energy and enthusiasm. Unfortunately their marital bliss had lasted less than two years when Carl died suddenly and unexpectedly from a cardiac arrhythmia.

In summary, no one who knew Carl failed to use the word modest to describe him. He was just that: unassuming, unpretentious, confident in his abilities but never blowing his own horn. He was gentle. He never had a harsh word. His criticism was always in the most constructive of guises. He was gentle with his family, his beloved dog Zoe, his colleagues, with all who knew him. He was a Southern gentleman without treacle or artifice. He was even somewhat motherly. That is, he was nurturing, protective, and caring of friends, family, and colleagues alike. His sense of fairness was so well known that he was asked to chair important university, national, and international committees. His integrity and fairness insured against bias in the proceedings. He was widely trusted because he held firmly to what he knew was right and proper.

Carl's scientific contributions were monumental. He designed and conducted micropuncture experiments that were decisive for establishing principles behind urinary concentration, neural control of salt excretion, function of remnant nephrons in failing kidneys, and much more. Behind these scientific achievements was a warm and generous person. Carl's modest manner concealed a piercing intelligence. His quiet, unaffected manner, his superior knowledge about many things and his inclination to convince with understated logic and without bombast made him a congenial and much admired colleague. He is sorely missed by the many associates, students, and friends whose lives he touched.

DURING THE PREPARATION of this memoir, I made use of family information provided by Susan Fellner; of memorial remarks by Robert Berliner and J. Stewart Cameron; a memorial written by William Blythe (In Memoriam, Carl William Gottschalk (1922-1977), *Kidney Int.* (53[1998]:1-2); and "Carl W. Gottschalk's contributions to elucidating the urinary concentrating mechanism" by Heinz Valtin (*J. Am. Soc. Nephrol.* 10[1999]:620).

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