Steven C. Hebert: a personal dedication


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I remember vividly the phone call I received at 7:30 in the morning on April 15, 2008, from a friend of Steve Hebert, who told me, “Steve is dead.” When I rushed to Steve’s house, about 10 minutes from ours, I was told by Pat, Steve’s wife, that Steve had mentioned mild stomach discomfort the night before but had gone to bed without complaint. She found him dead next to her the next morning. Steve had died in his sleep, apparently from cardiovascular disease. As we waited for the arrival of the funeral service and I recovered from the initial shock, the severity of the personal loss became clear to me.

Steve was the paradigm of the gifted self-made man. He was born in Rockford, Illinois. His family moved to Inagua, a small Bahamian island, where his father, an electrical contractor, was in charge of developing salt recovery facilities. He was effectively home-schooled for several years before the family returned to Fort Lauderdale, Florida. Although his parents had not attended college, they had, as Steve told it, a deep interest in higher education and thus encouraged Steve’s educational efforts. He entered Florida State University at age 15, majored in math and physics, but discovered an early interest in medicine and finished college in three years before entering the University of Florida Medical School. Two of his teachers stimulated his early interest in fluid metabolism and research: the nephrologist Robert Cade, who later developed Gatorade, and Tom Maren, a pharmacologist who studied carbonic anhydrase, a critical enzyme for acid–base transport.

Another interest became the focus of Steve’s attention when he met a lovely nurse, Patricia Robertson, and they married in 1970. The couple then moved to Pat’s trailer to Birmingham, where Steve joined the residency program in internal medicine at the University of Alabama–Birmingham (UAB). During medical rounds he attracted the attention of Thomas Andreoli, the newly appointed chief of nephrology at the UAB Hospital. I believe that this event played a major role in the subsequent fateful transition in Steve’s life from an undefined interest in medicine to the pursuit of research. After his residency, Steve stayed at UAB as a research fellow with Tom Andreoli, whom he credited with kindling a lasting fascination with renal electrolyte metabolism. Their personal friendship lasted until Steve’s untimely death. However, Steve never lost interest in patient care or in kidney disease. After his fellowship ended in 1975, he was drafted and spent two years in the Navy, stationed at Eastern Virginia Medical School in Norfolk, where he was assigned to a clinical nephrology unit, which stimulated his interest in understanding the mechanisms underlying abnormalities in fluid and electrolyte metabolism. After his military service, Steve returned to Alabama, where he was appointed assistant professor in Tom Andreoli’s nephrology section.

Steve studied the mechanism of salt and water transport in the cortical collecting tubule and the thick ascending limb of Henle’s loop. He used the technically demanding method of isolated perfused tubules, which he learned from Jim Schafer, with whom he also started a lasting friendship. He first identified the individual ion transporters of the apical and basolateral membranes, thereby providing a cell model that accounted for normal transport characteristics. During this period he maintained a cordial relationship with his main competitor, Rainer Greger in Freiburg. When Tom Andreoli moved to Houston in 1979 to become the chair of medicine, Steve accompanied him there. During his five-year stay he worked with Peter Friedman to identify the mechanism of the effect of antidiuretic hormone and diuretics on transport in the thick ascending limb. They also traveled to the Mount Desert Island Biological Laboratory in Salisbury Cove in Maine, where they studied water and urea movement in the kidneys of cartilaginous fish.

In 1984 Steve accepted a faculty position at Harvard in Barry Brenner’s renal section. There, Steve made an audacious decision to clone the main distal salt transporters of the nephron, which changed his career. Steve recalled from his Mount Desert Island days that the sodium-chloride cotransporter is expressed in high concentrations in the flounder bladder, and he succeeded in cloning it from that epithelium. A few years later, Steve and his colleagues also succeeded in cloning and defining the molecular structure of the furosemide-sensitive mammalian sodium-potassium-chloride cotransporter. These triumphant studies established Steve as a world leader in renal physiology. Steve’s discovery and cloning,
in 1993, of a potassium channel (ROMK) that shared many properties with a small-conductance potassium channel in the apical membrane of principal collecting duct cells also drew us closer professionally. The clinical relevance of this discovery was demonstrated when it became apparent that a subfamily of patients with Bartter's disease lacked ROMK. At that time, our group had analyzed single potassium channels in isolated mammalian collecting ducts, which had many similarities to Steve's cloned potassium channel, and thus started a most fruitful collaboration. He and I discussed the possibility, and I remember how delighted I felt when Steve told me that he would work with us. There followed quite a few years, from the mid-1990s to almost the present, of what might be described as our 'scientific togetherness,' when our professional association developed into a true friendship. Our collaboration spanned not only Steve's years at Harvard, but also his time at Vanderbilt, where he had moved to become head of the nephrology section in 1997, and finally his years at Yale, where he was appointed chairman of the Department of Cellular and Molecular Physiology in 2000. Steve was a true collaborator in the deepest sense of the term. He was noncompetitive, always willing to share data, and it was exciting to discuss data with him and to plan new experiments. Writing joint papers with him was rewarding, and Steve even managed to turn grant writing into a positive and gratifying experience!

Steve made another discovery with far-reaching clinical implications when he cloned an extracellular calcium-sensing receptor with Ed Brown, an endocrinologist and colleague at Brigham and Women's Hospital. The identification of this G protein-coupled receptor, which acts as a calcium monitor in the parathyroid gland, provided a bold and innovative idea in physiology, since the receptor recognized and bound an ion but also was sensitive to very small changes in the extracellular calcium concentration in the millimolar range. The receptor was also expressed in the kidney and intestine, where it plays an important role in regulating salt and water transport. Moreover, this discovery also led to collaboration with the pharmaceutical industry and the successful development of calcium-receptor agonists that can be used in the treatment of hyperparathyroidism. Steve's interest in marine biology alerted him to the possibility that calcium sensors may be involved in regulating fish metabolism and growth, especially during the transition from fresh to salt water, and this led him (with Ed Brown and William Harris) to found a biotechnology company, MariCal.

A more recent development in Steve's research was his fascination with the possible role of the calcium-sensitive receptor in gastrointestinal transport, especially the possibility of treating secretory diarrhea with agents activating the calcium receptor. With John Geibel, a Yale colleague, he showed in animals that enhanced fluid secretion by the gut due to a number of bacterial toxins, including that of cholera, can be blocked by activation of intestinal calcium receptors, suggesting a new avenue of treatment for infantile diarrhea, a major health problem worldwide. Steve was hoping that his research could have an impact on human disease, and it is especially sad that he could not further pursue these studies so close to his heart.

As time passed, my professional collaboration with Steve developed into a true friendship, and when Steve and Pat came to New Haven and settled close by, my wife Ilse and I saw them quite often. We also traveled together, enjoyed trips to New York to the Metropolitan Opera, and participated together in symposia, attending meetings from the Rockies to Sicily! Steve was an ardent photographer and, in his spare time, loved to work in the garden of their lovely home in Woodbridge—he was just as skillful with the chain saw as with micropipettes! Pat became a good and faithful friend of ours. With a PhD in epidemiology, she had a scientific career of her own and participated, at Brigham, Vanderbilt, and Yale, for many years in a wide range of epidemiological studies. I will always be grateful for the help and sympathy both Pat and Steve extended to my wife during her fatal illness early this year.

Steve was not only a superbly gifted investigator but a true creative force in science. He advanced multiple areas in short order, and was never afraid to venture into new areas and solve major research challenges. A man of vision and enormous drive, he was dear to me and will be sorely missed by all of us.