Franklin H. Epstein—Researcher, Teacher, Clinician, and Humanist

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With the death of Franklin Harold Epstein on November 5, 2008, we lost another one of the fathers of nephrology. He made seminal contributions to research, clinical care, and teaching in nephrology and will be remembered fondly for his fierce devotion to humanity and compassion. Frank Epstein was the William Applebaum Professor of Medicine at Harvard Medical School, working every day in the Nephrology Division at the Beth Israel Deaconess Medical Center until just before his death at age 84. He had received numerous honors, most notably the John P. Peters Award of the American Society of Nephrology for outstanding contributions to the understanding of the mechanisms of disease in nephrology; the Bywaters Award of the International Society of Nephrology for contributions to the understanding of acute renal failure (ARF); the Edward N. Gibbs Award of the New York Academy of Medicine; and the David Hume Award of the National Kidney Foundation, its highest honor given to a distinguished scientist in the field of kidney and urologic disease. More than these accolades to Frank was his role as a model to those lucky enough to work with him: Incisive thinking, innovative ideas, questioning evidence, lifetime learning, and, most of all, respect for the individual.

Frank Epstein was born in Brooklyn, NY, in 1924 and graduated summa cum laude from Brooklyn College in 1944. He received his MD, cum laude, from the Yale University School of Medicine in 1947 and served as an intern and resident at the Yale New Haven Hospital. It was here that Frank fell under the spell of John P. Peters, a mentor who developed in Frank a lifelong passion for the field of fluid and electrolyte metabolism in health and disease. Frank had the utmost esteem for the critical thinking of Peters; he would be proud to know that we remember fondly for his fierce devotion to humanity and compassion. Frank Epstein was the William Applebaum Professor of Medicine at Harvard Medical School, working every day in the Nephrology Division at the Beth Israel Deaconess Medical Center until just before his death at age 84. He had received numerous honors, most notably the John P. Peters Award of the American Society of Nephrology for outstanding contributions to the understanding of the mechanisms of disease in nephrology; the Bywaters Award of the International Society of Nephrology for contributions to the understanding of acute renal failure (ARF); the Edward N. Gibbs Award of the New York Academy of Medicine; and the David Hume Award of the National Kidney Foundation, its highest honor given to a distinguished scientist in the field of kidney and urologic disease. More than these accolades to Frank was his role as a model to those lucky enough to work with him: Incisive thinking, innovative ideas, questioning evidence, lifetime learning, and, most of all, respect for the individual.

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Research Contributions

Frank had more than 370 publications, playing major roles in the genesis, performance, and writing of virtually all of them. We summarize his major research contributions in the following three broad fields of inquiry.

Physiology of Humans, Mammals, and Lower Vertebrates

Early in his career, the influence of Peters led Frank to classic studies in humans and animals of the renal responses to volume changes (1,2), potassium deficiency (3), and calcium disorders (4). He was an instrumental investigator in elucidating a central role for Na-K-ATPase in ion transport by the mammalian kidney and chloride-transporting epithelia (5-7). His interest in potassium metabolism was rekindled later in his career, as evidenced by a series of experiments he designed that elucidated the role of the sympathetic nervous system in extrarenal potassium distribution (8-10). In a similar vein, his early observations on the critical role played by medullary hyperosmolality to produce autoinfarction of the renal papilla with the attendant urinary concentrating defect seen in sickle cell disease (11) was complemented by the obverse observation that...
induction of hypoosmolality by hyponatremia could decrease the polymerization of sickle hemoglobin and mitigate the painful crises characteristic of this disease (12).

Frank was fascinated by the mechanisms by which fish maintain their sodium and chloride concentrations while swimming in either dilute fresh water or salt water in which the concentration of NaCl approximates 500 mEq/L (13,14). In a wide-ranging series of studies during a 44-yr period, many of which were carried out during his long collaboration with Patricio Silva at the MDIBL in Maine (15), Frank made insightful contributions to this question by studies of the rectal gland, a chloride-secreting organ that empties into the large intestine in elasmobranches (16) (Figure 2). Frank and his collaborators showed that chloride secretion is stimulated by vasoactive intestinal peptide (VIP) (17) and cardiac natriuretic peptide (CNP) (18). The active transport of chloride is powered by hydrolysis of ATP to ADP by the Na-K-ATPase on the basolateral side of the rectal gland (19). In further studies, Frank elucidated the role of the Na-K-2Cl transporter and the CFTR protein in this process (20). Chloride secretion was found to be stimulated by signals that led to increased intracellular cAMP, a process that accounted for the action of VIP (17). Volume expansion led to CNP release from cardiomyocytes. In turn, CNP led to release of VIP from nerves in the rectal gland and seemed to sensitize the gland to cAMP produced by VIP (18). In addition, CNP worked by activating protein kinase C and guanylate cyclase to achieve synergistic stimulation of active chloride transport by this parallel pathway (18,21). These studies formed the underpinnings for deciphering mechanisms that control active transport in many other epithelia. In his work at MDIBL, Frank trained, collaborated with, and helped nurture many generations of leaders in the field of epithelial cell biology.

Acute Renal Failure

Frank carried out a series of investigations using the isolated perfused rat kidney model to elucidate the mechanisms of acute ischemic renal injury. He focused his attention on the medullary thick ascending limb (mTAL) and argued that this region of the nephron was particularly vulnerable to hypoxic injury. He and his colleagues showed that during isolated perfusion of the rat kidney, hypoxic cell death occurred first in mTALs farthest from vascular bundles and near the inner medulla and that a higher O2 content in the perfusate improved the lesion (22), as did reducing transport work (23). He argued that the “anatomical location associated with a low O2 supply imposed by the medullary vascular system and its high rate of electrolyte transport” made the mTAL sensitive to O2 deprivation. Subsequently, he also found a susceptibility to hypoxic damage of the proximal tubules, greatest in the S3 segment,

Figure 1. Frank Epstein shown at a common workplace for him: In front of the Harvard Countway Medical Library in 1985.

Figure 2. Frank Epstein holding a dogfish shark at the Mount Desert Island Biologic Laboratory in Maine, 1983.
with protection conferred on tubules closest to the vasculature (24), in the more severe experimental ischemia-reflow models needed to cause ARF in intact rats (25). Using both the isolated perfused kidney and intact animal studies, he systematically investigated the effects of a number of infused metabolites to give rise to his perspective of ARF as largely a result of an imbalance between ischemic medullary hypoxic injury that was counteracted by protective modulators of transport, transport-related metabolism, and vasodilation, including prostaglandins, other eicosanoids, adenosine, nitric oxide, and CO (26).

Likewise, he showed that radiocontrast ARF caused selective mTAL injury in the rat (27) with endothelin release in both rats and humans (28,29), likely playing a role by renal vasoconstriction (30) counteracted by ANP and prostaglandin vasodilation.

In recent years, he attempted to extend these observations to noninvasive studies of renal ischemia in vivo. Using blood oxygenation level–dependent magnetic resonance imaging (BOLD MRI) to evaluate intrarenal oxygenation, he showed that radiocontrast administration or inhibition of the synthesis of prostaglandins or nitric oxide reduced medullary oxygenation in rats (31). In human BOLD MRI studies, he found that the low renal medullary oxygenation was greatly improved with water diuresis in young individuals but not in the elderly (32) or in middle-aged individuals with mild diabetes (33). In addition, inhibiting with ibuprofen the rise in urinary prostaglandin E2, which accompanied the diuresis only in young individuals, blocked the increase in medullary oxygenation as well (32). These human studies suggested that inability to improve medullary hypoxia in the elderly or individuals with diabetes or those on cyclooxygenase inhibitors may help to explain the increased susceptibility to acute kidney injury in these patients.

Pregnancy and Preeclampsia

Frank was fascinated by the physiologic changes during normal pregnancies and those complicated by preeclampsia. He believed that understanding the physiology of normal pregnancy would have implications far beyond pregnancy. In 1964, Frank published a landmark, single-authored article in the New England Journal of Medicine, in which he reexamined 48 women at approximately 15 yr after their toxemic pregnancies and found a higher prevalence of hypertension among them than in women with uncomplicated pregnancies (34). Importantly, he noted that the siblings of women with preeclampsia did not have an increased prevalence of hypertension, suggesting that preeclampsia may lead to hypertension over and above hereditary factors (34). This article was extremely controversial at that time and was dismissed by the thought leaders in the field, who believed that there were no long-term complications of preeclampsia. Several decades later, we now know that women with a history of preeclampsia have significant risk for hypertension, premature cardiovascular disease, and possibly chronic renal disease. And we believe that this risk may stem not only from metabolic abnormalities that predispose both to preeclampsia and to subsequent chronic disease, but also from the direct result of preeclampsia itself (35). During the 1980s, Frank worked closely with Barbara Clark and colleagues at the

Beth Israel Hospital, demonstrating the physiologic changes that occur in prostaglandin and endothelin metabolism during healthy pregnancies and in preeclampsia (36). During the last 10 yr of his life, Frank was instrumental in working with two of the authors of this article (S.A.K. and V.P.S.) in developing the hypothesis that disturbances in placental angiogenesis may be fundamental to the pathophysiology of preeclampsia and its related complications (37,38). Until the week before his diagnosis of brain cancer, Frank was a regular at the Friday morning labor and delivery conference at the Beth Israel Deaconess Medical Center. He built a strong relationship between obstetricians and nephrologists, paving the way for scientists and physicians from different departments to interact, collaborate, and discover. One of his collaborators in preeclampsia research, Dr. Ravi Thadhani at the Massachusetts General Hospital, commented, “Frank left his fingerprints in several areas of nephrology, and his contributions to preeclampsia, in particular, are a testament to their magnitude.”

Teacher

All of Frank’s numerous nephrology research and clinical trainees, including us, revered and emulated him. He set the standard by which we would measure our own careers. He brought out great effort in others, and his fellows have played major roles in our specialty throughout the world. His popularity as a teacher of medical residents and students at Yale and Harvard was legendary, stemming all the way back to receiving the Francis G. Blake Award for the teaching of clinical medicine voted by the Yale senior medical class in 1963. He taught the need to “look it up” as a practice throughout one’s career. He was very persuasive; one always seemed to lose an argument even when evidence favored that person’s side. He was the best interviewer of applicants for residency or fellowship: Students and residents whom he interviewed invariably wanted to come to the institution, often 100% of his interviewees accepting positions when selected. He continued to teach about fluid and electrolytes on weekly rounds in the intensive care units and as an attending at the bedside on the medical and renal services until the time of his death.

Clinician

Frank was, first and foremost, a physician. He cared for all patients and advocated for their welfare. In 1969, when hemodialysis was largely unsupported by insurance and the Yale New Haven Hospital administration was opposed to expanding this treatment on the basis of cost, Frank argued strongly for its need as a life-saving modality. Throughout his long career, he reminded us that “the physician is the patient’s doctor; his legal and moral obligation is to the patient, not the family, not even the community” (39). He emulated this in his clinic and hospital patient practice. At his funeral, one of the authors (R.S.B.) recounted his first encounter with Frank in 1967: “I had been taught at Columbia P&S to be precise, meticulous, and respectful—not to lean on a patient’s bed or encroach on their space. When I first went on rounds as a fellow with Dr. Epstein, upon seeing a very ill patient, he sat down on the bed, took the patient’s hand in his hands, and talked. Then
he got up and fluffed up the patient’s pillow before leaving the room. I knew right then that this was the kind of doctor that I wanted to be. We all would.”

Humanist

“Humanist: a person having a strong interest in or concern for human welfare, values, and dignity.”

Frank had a strong interest in the role of the physician as the patient’s advocate in the preservation of life (40). He formulated his concerns over years of seeing desperately ill patients in intensive care units, where, as the physician’s ability to prolong life improved, the driving forces of care often shifted to the concerns of relatives watching suffering patients, the needs of society to contain costs, or the patient’s “right to die” or have a “death with dignity” prompted “comfort measures only” when the patient’s condition was not clearly hopeless. His concern was backed, in part, by a study he did with co-workers at the Beth Israel Hospital in which 41 of 294 consecutive patients who were resuscitated after an in-hospital cardiac arrest lived to be discharged. At a 6-mo follow-up, 80% were alive, most had little recollection of the resuscitation, and the majority would want resuscitation again (41). Frank pointed out the importance of recognizing that physicians are interested parties, often suffering together with a failing patient, but we are not omniscient to predict outcomes, pain can usually be relieved, and only the patient can judge the quality of his or her life. He expressed this best in his view of our contract with our patient’s advocate in the preservation of life (40). He delivered without slides:

“We physicians belong to an ancient profession, standing apart from all others in its primary concern and respect for human life and its enmity to death. And in the long run, that attitude of the profession may be as important to society as any miracle that modern technical medicine can perform.

The fact is that for all our talk and our science, we do only a little. Life cannot be prolonged indefinitely, and death comes at last. But the little we can do has an importance that transcends the patient, for it carries a message to all our patients and to the last. But the little we can do has an importance that transcends life. And in the long run, that attitude of the profession may be as important to society as any miracle that modern technical medicine can perform.

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Disclosures

None.

References

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