THE FACULTY OF MEDICINE
Harvard University

Alexander Leaf

Alex Leaf died at the age of 92 on 24 December 2012. He was a long-time faculty member of the Massachusetts General Hospital (MGH) and Harvard Medical School, where he served as chief of the Department of Medicine at MGH (1966–1981), and as the Jackson Professor of Clinical Medicine and later the Ridley Watts Professor of Preventive Medicine at Harvard Medical School.

Alex Leaf first came to MGH in 1944 as an intern, left to finish his residency at the Mayo Clinic, and returned to MGH in 1949 as a fellow in medicine, working with famed endocrinologist Fuller Albright, MD. A superb investigator, Dr. Leaf was tapped by Howard Means, MD, then chief of medicine, to help create MGH's first renal laboratory. He went on to serve as chief of the Renal Unit from 1951 until 1983.

Alexander Leaf was one of the founders of the scientific basis of nephrology. That most of his contributions are now textbook knowledge is perhaps the reason why most nephrologists today would not know what he achieved. His early work, similar to that of the other founders of our discipline, examined the mechanism by which the kidney controls salt excretion. He defined a critical role for adrenal steroids, before the identification of aldosterone. His studies on water metabolism also led to many insights into the mechanism of action of vasopressin. In fact, he demonstrated (with Bartter) that when humans were given continuous doses of vasopressin and drank large volumes of water, they diluted their body fluids and developed volume expansion leading to salt excretion, showing the primacy of the role of sodium balance in the control of extracellular fluid volume. When a patient with a lung tumor was found to resemble these research subjects (some of whom were the authors of the paper!), it was clear that the syndrome of inappropriate antidiuretic hormone secretion was described. In fact, some Europeans began calling this syndrome the Leaf–Bartter syndrome.

In tribute to their dedicated efforts to science and medicine, deceased members of the Harvard Faculty of Medicine (those at the rank of full or emeritus professor) receive a review of their life and contributions with a complete reflection, ***a Memorial Minute****.*

Leaf's interests in defining cellular mechanisms of ion transport were stimulated by a sabbatical stay at Oxford in the laboratory of Hans Krebs. He decided to study the regulation of the ionic composition of cells by testing what was then considered the critical paradigm in this process, active water transport. Several investigators in the late 1940s showed that cells swelled when they were poisoned. Such studies were interpreted to mean that cells were hyperosmotic to the extracellular fluid. By that time, it was shown that isotopic water could readily exchange across cell membranes, and hence it was concluded that the continuous influx of water must be balanced by its active transport out of the cell. In a series of compelling studies, Leaf proved this idea false. First he showed that ingestion of large volumes of water readily equilibrated with the total-body water, diluting the extracellular space. He then found that cell swelling in poisoned tissues was due to the entry of not just water, but also solutes (NaCl). When one divided the number of osmoles of solutes accumulated by the amount of water taken up, there was isotonic expansion of the intracellular space consistent with the now recognized passive movement of water down an osmotic gradient. Returning to Boston, Leaf used the first instrument developed to measure the freezing point depression of these tissues. This osmometer showed that the intracellular osmolality of a variety of mammalian tissues was the same as that of blood, except for the kidney medulla. The latter finding laid the groundwork for the understanding of the mechanism of urinary concentration. But these studies also established Alexander Leaf, already a distinguished renal physiologist, as a major figure in the nascent field of cell physiology.

During his stay in Krebs's laboratory, Leaf got to hear and meet Hans Ussing, who had just begun to examine active sodium transport across frog skin. On his return to Boston, Leaf established the toad urinary bladder as a model membrane for studying the cellular mechanisms of salt and water transport. In parallel with Ussing's group, he established that transepithelial sodium transport occurs across two rate-limiting steps; entry into the cell from the lumen was passive and down an electrochemical gradient, while exit was active, requiring an input of energy into the Na,K-ATPase. These landmark studies showed that hormones such as vasopressin and aldosterone had direct effects on renal transporting cells and that it was possible to localize their effects on one or another membrane. Vasopressin increased the water permeability of the luminal membrane, a finding confirmed by more recent molecular studies. Aldosterone increased sodium transport in the toad bladder, and Leaf and colleagues demonstrated that the basic mechanism of action of aldosterone was to increase the permeability of the apical membrane to sodium, a view that was quite controversial but has remained the dominant idea in the field to this day.

After his tenure as Chief, Medical Services at MGH, Alex was asked to organize and chair a new Department of Preventive Medicine at Harvard Medical School. This allowed him new-found freedom to pursue research interests focused on preventive cardiology. By 1990, there were already suggestions that the highly polyunsaturated n-3 fatty acids of fish oil might have protective effects against the development of coronary heart disease, particularly in preventing ischemic-induced fatal ventricular arrhythmias. Leaf sought to learn the mechanism of this effect and found that n-3 fatty acids need only to partition into the lipophilic environment of the phospholipids cell membrane in order to exert their

antiarrhythmic action. This effect in turn was found to be due to a modulating action of the free fatty acids on the voltage-dependent sodium and the L-type calcium currents in all-excitable tissue. This seminal work revealed that a basic control of cardiac and neural function occurred through common dietary fatty acids that had been largely overlooked. Over subsequent years, the effects of n-3 fatty acids on human physiology and pathology have been shown to be complex, but Leaf's work remains a paradigm of clinical investigation.

In closing, Alex will be remembered as a person of integrity and academic commitment. He took over what was arguably the best department of medicine in America and made it better. He recruited outstanding staff and trainees, several of whom went on to become Nobel laureates. He fostered exceptional research programs supporting a wide range of efforts in both basic and clinical science. He never lost sight of his role to community and humanity. His later years were devoted to making us aware of the devastating consequences of the public-health threats of nuclear war, climate change, and ignoring cardiovascular health.

Hearing of his passing, two of Alex's former residents and Nobel laureates, Mike Brown and Joe Goldstein, noted, "Alex was a great physician-scientist in the true sense of the hyphenated word, which in recent years has taken on a different meaning. His passing signals not only the end of a great man, but also of a golden age of investigational medicine."

I agree.

Respectfully submitted,

Dennis Ausiello