Isidore S. Edelman

Isidore S. Edelman (affectionately known to friends and colleagues as Izzy) was a member of the post-war generation of scientists who established the scientific basis of renal physiology and ushered it into the era of cellular and molecular explanation. His identification of the inductive mechanism of action of aldosterone on sodium transport assures his place among the modern masters of the field. However, this relatively recent work was only one of his many contributions. His initial studies measuring the fluid spaces in both healthy and diseased states have become textbook fact, and hence, as is the case with such "textbook" knowledge, is assumed to have emerged *sui generis* while its authorship remains hidden.

Izzy was born and raised in Brooklyn. He first attended Brooklyn College and later transferred to the University of Indiana where he received his bachelor's degree in chemistry. After unsuccessful application to 17 medical schools, this Phi Beta Kappa graduate was accepted into the University of Indiana's medical school where he received his MD degree in 1944. He interned at the Greenpoint Hospital in Brooklyn and then served in the Psychiatry Service of the US Army in Panama. Always the investigator, Izzy tested the hypothesis that two psychiatrists confronted with the same patients would come to the same diagnosis; he found that they failed to do so. After discharge from the army, he became a resident and then a fellow at the Montefiore Hospital in the Bronx where he studied the effect of dietary salt intake on the hemodynamics of the kidney, publishing two related papers in the *JCI*. He then moved to Boston to continue his research career.

Immediately after World War II, the US government established the Atomic Energy Commission (AEC), a small part of whose mandate was to supply scientists with radioisotopes for medical and scientific research. Izzy was one of the first research fellows supported by the AEC. He worked at the Peter Bent Brigham Hospital at Harvard Medical School in the laboratory of surgical research established by Francis Moore and used deuterium and radioactive isotopes to examine the volume of distribution of water and electrolytes in healthy and diseased humans. These landmark studies, begun in 1949, established what we now know about the compartmental distribution of sodium, potassium, and water in bodily fluids in healthy men and women and in those with edematous states produced by heart failure or cirrhosis. Fourteen related papers from his research group were published in the *JCI* between 1950 and 1959, and together they form a pillar of the received ideas of this field; it is difficult to envisage a time when this information was either unknown or controversial.

Izzy had some friends who were members of the Communist Party and had attended parties with them; several of the other guests at these affairs were also probably members of the party. These innocuous social gatherings came to haunt him when the plague of McCarthyism spread over the country. He was called before the House Un-American Activities Committee and asked to "name names." Because he was a fellow of the AEC, the agency — presumably finding him a security risk — withdrew his fellowship. Several vituperative newspaper articles were written about him (and others) at Harvard, and as is well known, the university failed to support its faculty, a record that is often denied but whose extent has begun to be examined now that the 50-year embargo on its archives is being lifted. Luckily, the American Heart Association came to Izzy's rescue and continued to fund him as one of their first Established Investigators. Izzy remained grateful to the AHA for its stand and, in fact, before his death, said that he wanted all charitable contributions donated in his name to go to the AHA. Despite the fact that he was an optimist by nature and believed in the university as an island of civility in an imperfect world, this *contretemps* gave him a severe lesson in the cowardice of institutions and is likely to have been the cause for his jaundiced view of figures of authority in the university including, one should add, himself when he became such a figure. Izzy was always a generous supporter of the weak and defenseless, constantly aware of the way by which a majority, even when it does not attempt to destroy a minority, can dismiss its complaints as paranoia and conspiracy theories. Perhaps this experience had made him even more aware of these issues. For this, his presence in our university will be missed very much.

Izzy was recruited to the newly established University of California, San Francisco (UCSF), Medical Center as a starting assistant professor in 1954 where his laboratory was initially located in the San Francisco General Hospital, a facility with no research space. Here, through support from the AHA and a private donor, he was able to continue his groundbreaking work examining body fluid spaces in healthy subjects as well as in those suffering from a number of edematous states. It was also becoming clear from the work of others that vasopressin and especially the newly identified hormone aldosterone exerted

a dramatic influence on the distribution of sodium and water in many of these disease states. His work on the effects of these hormones on body fluid distribution led him to search for a more basic understanding of the processes involved in sodium transport across epithelia, further spurred by a sabbatical year spent in Linus Pauling's laboratory at the California Institute of Technology.

The leading investigators in salt and water balance had been energized by the studies of Hans Ussing on sodium transport across frog skin in which the double-membrane model of transport provided both theoretical and experimental tools with which to analyze the mechanism by which hormones might enhance sodium absorption. Sodium was shown to traverse epithelia in two steps: entry into the cell from the lumen occurs along an electrochemical gradient, while exit is mediated by Na,K ATPase. Izzy began to study the mechanism of action of aldosterone and vasopressin on sodium transport across the urinary bladder of the toad *Bufo marinus,* a convenient model for these responsive tissues developed by Alexander Leaf at Massachusetts General Hospital. In a remarkable series of studies, Izzy demonstrated that aldosterone increases the entry of sodium into epithelial cells. Further, using labeled aldosterone, he found that the hormone diffuses into the cytoplasm where it binds to a large macromolecule and the complex of aldosterone and its receptor is then translocated into the nucleus. Inhibitors of RNA and protein synthesis blocked aldosterone's effect on sodium transport, indicating that the mineralocorticoid receptor is likely to be a transcription factor. These studies were received with much-deserved accolades, and Izzy was elected to the National Academy of Sciences in 1973.

Izzy was interested in the effect of many hormones on sodium transport. He began a new series of studies on the mechanism of the well-known calorigenic or thermogenic effect of thyroid hormone. He found that the increased heat production was a result of stimulation of active sodium transport in most cells with a consequent increase in ATP hydrolysis. The surprising finding was that almost half of the cellular energy output was devoted to sodium pumping and that thyroid hormone could modulate this rate. The effect was produced by activation of the Na,K ATPase in muscle and other thyroid hormone–responsive tissues, a finding that launched Izzy's interest in the structure and regulation of the sodium pump, an interest that remained evident for the rest of his career. Later, he studied several other P-type ATPases, including copper- and zinc-transporting ATPases.

Izzy's interest in quantitative analysis was clear from his first paper on psychiatric diagnosis, but this interest flourished when he began his work on ion transport. A sabbatical year at the Weizmann Institute of Science in Israel brought him in contact with the charismatic theoretician Aharon Katchalsky. Students studying ion transport across membranes at that time were mesmerized by the application of nonequilibrium thermodynamics to these processes, and Katschalsky was *the* guru for a generation of investigators. But Izzy's interest in biophysics developed along different lines, more consonant with what he learned from Linus Pauling: that the secret to biophysics lay in understanding the structure of molecules, not the application of phenomenological equations to complex processes. Izzy was one of the first to see the importance of structural biology and began to recruit structural biologists to San Francisco.

Izzy moved to Columbia University College of Physicians and Surgeons to chair the Department of Biochemistry and Molecular Biophysics in 1978 at a particularly critical time. The fortunes of all New York institutions are tied to the health of the city's economy, and New York in 1978 was not in a happy state, having just barely escaped bankruptcy. Luckily for Columbia, this did not deter Izzy, and he began an active program of recruitment in structural and molecular biology. His abilities as a recruiter were astonishing. He managed to convince investigators to move to Washington Heights, an area of Manhattan that was blighted and for some time better known as the crack cocaine capital of the world rather than a neighborhood where science might flourish. He began his recruitment efforts with junior scientists, and his success in bringing in a few potential stars lured more established investigators to the Department. His influence was seen in other departments where he was also involved in the recruitment of junior and senior faculty members. How he managed to convince all to move to Washington Heights remains part of the legend that his tenure has become. Within a few years, the Department, under his leadership, became one of the premier departments in the country and probably the world, leading the way in a number of fields, including structural biology, molecular biology, and more recently, developmental biology.

After retirement from the Department of Biochemistry, Izzy was appointed as the head of a newly established Columbia Genome Center where his efforts were successful, though not on the same scale as his achievements in shaping the Department of Biochemistry. Perhaps the resources were not there, and the Center required immense resources, a situation that the chronically underfunded Columbia University faced in competition with other financially flush universities and biotechnology companies. He continued to be actively involved in research on ion-motive ATPases, successfully purifying a zinc-dependent P-type ATPase. When he retired, he maintained an office in the Center for Computational Biology and Bioinformatics, where he planned to identify motifs that mediate zinc binding in various transport proteins. Unfortunately, this work was left unfinished at his death.

Izzy was a gregarious and generous mentor and confidant. Conversations with him showed the breadth of his knowledge of biomedical research, perhaps a consequence of his diverse background in classical fields such as medicine and physiology and his leadership roles in building departments of modern biomedical research. This background and his personal attributes allowed him to have a wide network of friends who shared one or another aspect of his protean interests. It was a delight to talk to him about a subject and to see him immediately identify the one expert in the area, then pick up the phone and immediately get informed answers to what appeared to be an arcane problem. His influence on a generation of students and post-doctoral fellows is guaranteed to keep his memory alive; many of his students are senior members of a variety of medical schools all over the world. In this role, he was a nurturing mentor and a kind person who welcomed differences of opinion and guided the careers of his trainees long after they left his laboratory. Edelman's personal influence on his colleagues looms large, and his role in building centers of research excellence at both UCSF and Columbia University assures that his impact will be felt for a long time to come.

Qais Al-Awqati
Columbia University College of Physicians and Surgeons, New York, New York, USA.
qa1@columbia.edu