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Presentation of the 1999 A.N. Richards Award to Isidore S. Edelman

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I am privileged, and personally delighted, to present one of this year's Alfred Newton Richards Awards to Isidore S. Edelman. The occasion is particularly opportune for two reasons. First, in many of his studies, Dr. Edelman utilized the short circuit technique conceived and developed by his co-recipient, Hans Ussing. Second, for more than two decades, Dr. Edelman engaged in a gentle intellectual rivalry with Alexander Leaf, the recipient of the Richards Award two years ago, about the mechanism of action of aldosterone, a cardinal research interest of both Leaf and Edelman.

Dr. Edelman, or, as he is almost universally known, Izzy, is the Robert Wood Johnson, Jr. Professor *Emeritus* of Biochemistry and Molecular Biophysics at the Columbia University College of Physicians and Surgeons. He is also Director of the Genome Center at the same institution.

At the outset, I will note three characteristics of Dr. Edelman that I have observed in the 30-odd years that I have been privileged to know him.

His intellect is towering, and his research career has been, by any set of criteria, exceptional. His dissection of sodium homeostasis and its modulation by hormones represents a canon of work that not only spans more than half a century, but has few parallels in renal physiology in this century.

Second, Izzy is a genuinely warm human being and a renaissance citizen. By the latter term, I wish to connote the ecumenical scope of his knowledge. He is as well versed in music, literature and the arts as he is in biology.

Finally, Izzy violates the second law of thermodynamics. The great physicist-philosopher Eddington described entropy as "time's arrow," a poetic phrase indicating the inevitable disarray that attends the passage of time. In Izzy's case, we have an instance of negative entropy. His intellectual powers have amplified over the years. Felicitously, he is as vigorous today as he was three decades ago.

Now what academic heritage molded this remarkable man?

Dr. Edelman was born, raised and attended college in Brooklyn. He received his M.D. degree at Indiana University (1944), returned to Brooklyn for his internship, and then served in the U.S. Army Medical Corps in the immediate post-war period (1945–1947).

He began his research training at Montefiore Hospital in the Bronx under the intellectually seductive spell of the great Louis Leiter, who kindled in Izzy his life-long interest in sodium homeostasis. His stay in the Bronx also annealed two dissimilar New York accents, Bronxese and Brooklynese, into a patois which is both distinctive and pleasant.

Edelman then went to the Peter Bent Brigham Hospital (1949–1952), where he was bewitched by two extraordinary intellectual sorcerers, Arthur Solomon in Biophysics and Francis Daniels Moore, the Chair of Surgery. From Dr. Solomon, Edelman learned the techniques of isotope dilution. From Dr. Moore, Edelman learned about the metabolic changes in body fluid composition that occurred in surgical patients. One particularly exciting observation during this period was Izzy's recognition of water intoxication in patients who underwent mitral valve commissurotomy. This was one of the earliest accounts of hyponatremia following commissurotomy and was a key vector in the search for left atrial volume receptors that provided non-osmotic stimuli to vasopressin production.

In 1959, Liebman and Edelman published a brilliant paper on the anatomy of body fluids which summarized many of the lessons that Edelman had learned from Solomon and Moore (Fig. 1). As a medical student, it was a kind of Rosetta Stone for me. It is still a classic used for teaching salt and water balance to students and residents.

Edelman's first faculty appointment was as a member of the Department of Medicine at the University of California, San Francisco, where he served as Chief of the Medical Service from 1956 to 1958. Figure 2 shows Izzy together with his faculty and residents, as Chief of Service at San Francisco General. Take particular note of his appearance. You will see later that, even in physical terms, Edelman has been blessed by negative entropy.

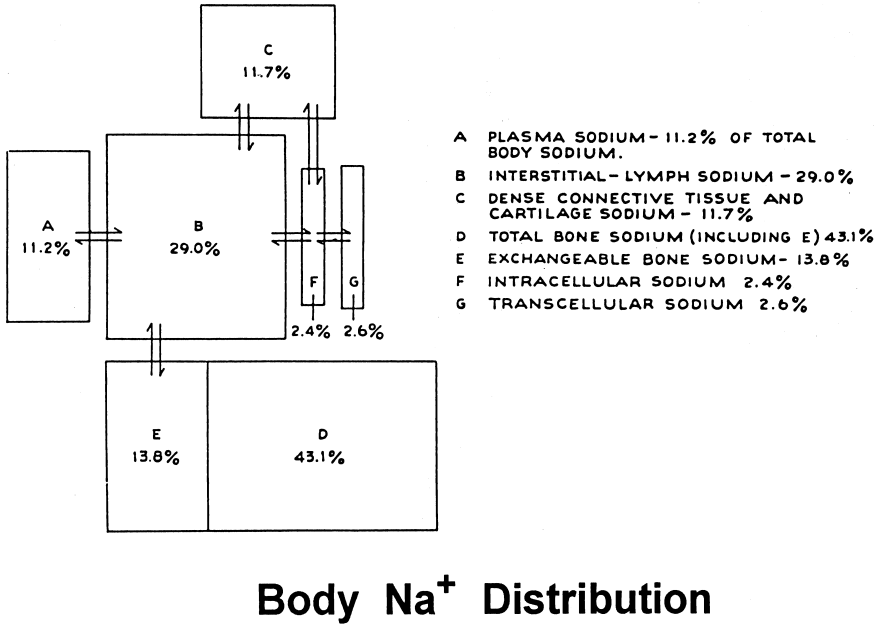


Fig. 1. Body fluid composition: The influence of A.K. Solomon and Francis D. Moore, 1949–1952. From Edelman and Leibman, *Am J Med* 27:257, 1959, with permission.

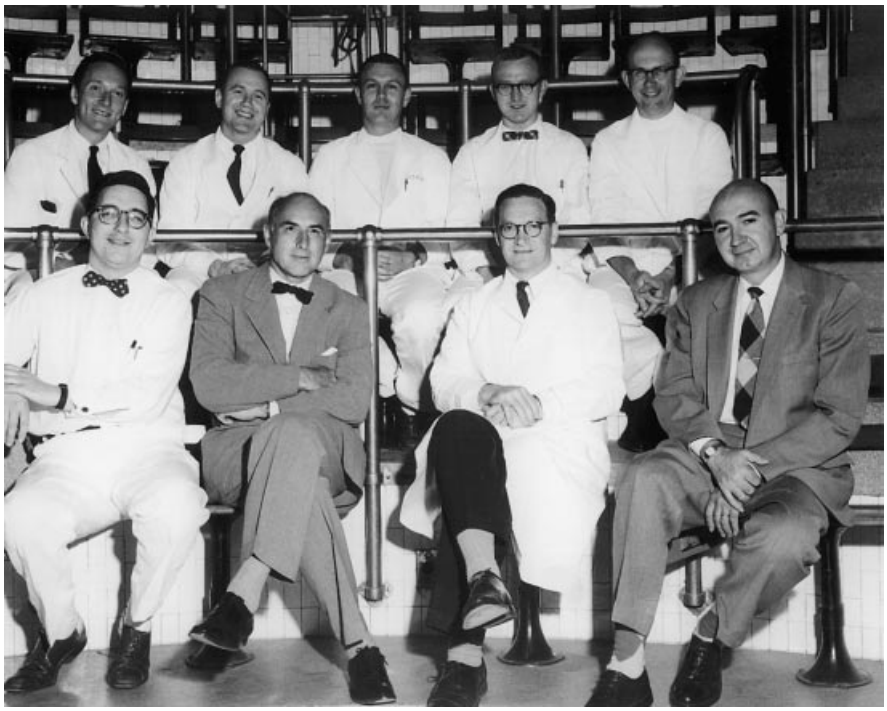


Fig. 2. Faculty and residents at San Francisco General pose with Izzy Edelman in 1956.

By 1960, Izzy had chosen to focus his efforts on research. Therefore he moved to the main UCSF campus where he was appointed Professor of Medicine and Physiology, and later Professor of Biophysics (1969–1978). The Figure 3 photograph was taken at a 1984 reunion of Edelman with many of his post-doctoral collaborators at UCSF between 1960 and 1978. You will note again that his physical appearance has changed minimally.

Finally, after 26 years in San Francisco, Edelman was attracted back to New York in 1978 as Chair of Biochemistry and Molecular Biophysics. In 1991, when he became *Emeritus* in that position, he was appointed Director of the Columbia Genome Center, a position he currently occupies.

I turn now to his cardinal research contributions. Because of time constraints, I will limit my comments to

Fig. 3. Dr. Edelman and some of his past collaborators at the University of California, San Francisco, in 1984.

those discoveries that have particular interest to the renal community, that is, the antinatriuretic action of aldosterone, and the role of thyroid hormone in regulating calorigenesis by modulating sodium transport.

I'll consider first the mechanisms of action of aldosterone. Simpson and Tait had elucidated the structure of aldosterone in about 1953, and while aldosterone was known to be sodium-retaining, virtually nothing was known about its mechanism of action.

Between 1964 and 1966, Edelman and his colleagues made two seminal observations that formed the cornerstones for an exceptional intellectual construct. First, Porter, Bogoroth and Edelman showed that the sodium acquisitiveness produced by aldosterone depended on messenger RNA-directed new protein synthesis (*PNAS* 52:1326, 1964). Second, Fanestil and Edelman provided the first demonstration of the nuclear localization of receptor-ligand complexes for any steroid (*PNAS* 56:872, 1966).

These two observations have been seminal to all of our information concerning the modes of action of aldosterone. How these two actions result in sodium retention occupied the better part of the next 20 years of work in Edelman's laboratory.

This model shown in Figure 4 illustrates the hypothesis formulated by Darrell Fanestil, George Porter and Edelman in 1967 for the possible effects of aldosterone. The most important point to note is that they anticipated that aldosterone might have pleiotrophic effects.

Specifically, they postulated three potential actions for

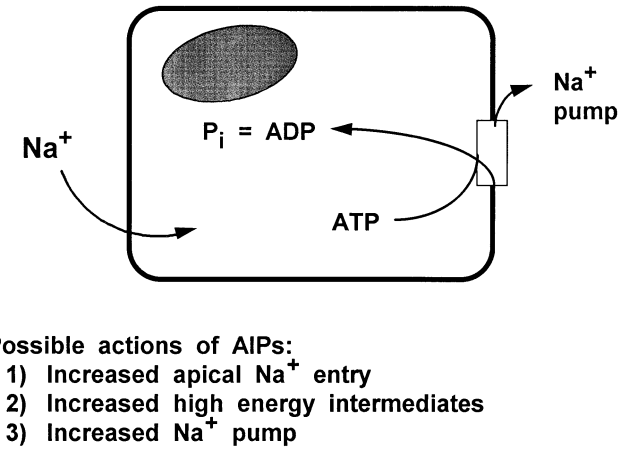
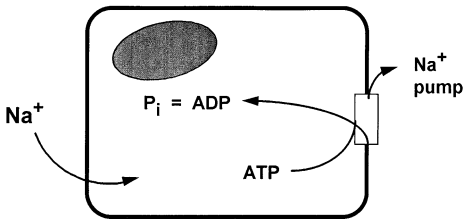


Fig. 4. A pleiotrophic paradigm for aldosterone effects. From Fanestil, Porter, and Edelman, *BBA* 135:74, 1967, with permission.

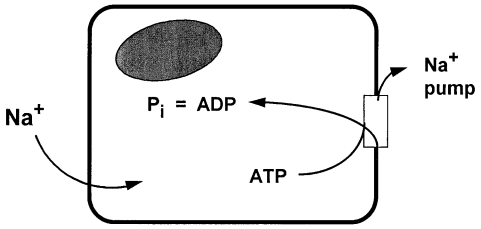
aldosterone-induced proteins, denoted in Figure 4 as AIPs. AIPs might increase apical sodium entry, they might increase the level of high energy intermediates within the cell, and AIPs might increase sodium pump activity. Fanestil, Porter and Edelman specified explicitly that all three of these effects might occur coordinately.

In their 1967 paper, Edelman's group showed that there was a synergism between the presence of metabolic substrate and sodium acquisitiveness. They therefore postulated that AIPs caused the biosynthesis of high-energy intermediates that activated the sodium pump.



Possible actions of AIPs:
1) Increased apical Na^+ entry by Na^+- independent ATP synthesis
2) Increased high energy intermediates
3) Increased Na^+ pump

Fig. 5. Pleiotropism of aldosterone effects: Na^+ entry and metabolism. From Garty, Edelman, and Lindemann, *JMB* 74:15, 1983, with permission.



Possible actions of AIPs:
1) Increased apical Na^+ entry
2) Mitochondrial ATP synthesis
3) Increased pump activity without increased pump abundance

Fig. 6. Pleiotropism of aldosterone effects: Na^+ pump modulation. From Park and Edelman, *Am J Physiol (Renal)* 245:F517, 1984, with permission.

Subsequently, Garty, Edelman and Lindemann showed directly that aldosterone increased apical sodium permeability, but only when toad bladders were replete with substrate (Fig. 5). These studies therefore linked possibility 1 and possibility 2 as coordinate components of the aldosterone cascade. Additional studies by Garty and Edelman, confirmed by Lindemann and by a number of other workers, then showed that most of the apical sodium channels activated by aldosterone resided in membranes, and that a key feature of aldosterone's action was to activate, or recruit, quiescent intramembranous sodium channels.

Finally, Park and Edelman showed that there were linked effects of aldosterone on increasing apical sodium permeability and basolateral sodium pump sensitivity to ouabain, with both effects being dependent on the metabolic state of the urinary bladder (Fig. 6). Put differently, Park and Edelman provided convincing evidence for the simultaneous action of the three possibilities that Fanestil, Porter and Edelman had first inferred nearly 20 years ago.

Figure 7 is a model for aldosterone action published in Seldin and Giebisch's treatise in 1992 by Bernard Rossier, one of Edelman's fellows at UCSF and the person who cloned ENaC, the amiloride-sensitive epithelial sodium channel affected by aldosterone. The exquisite symmetry of this interaction will not have been lost on you. In this scheme, Rossier shows that aldosterone binds to cytosolic receptors. We know today that these aldosterone receptors are found principally in the distal convoluted tubule and the cortical collecting tubule, and that they are of at least two types, Type I and Type II. While the Type I "mineralocorticoid" receptors have an equal affinity for aldosterone and glucocorticoids, functional specificity for aldosterone is conferred by renal 11β-hydroxysteroid dehydrogenase, which converts glucocorticoids to inactive metabolites.

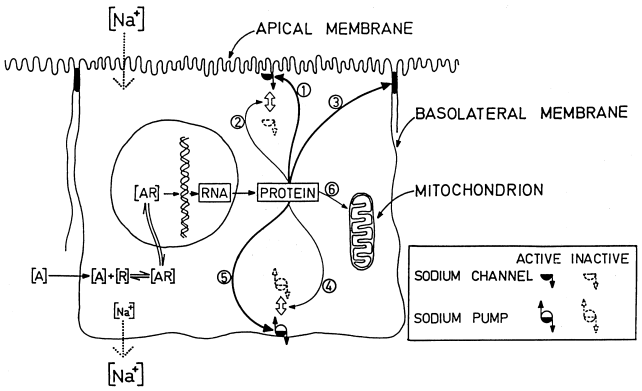


Fig. 7. Aldosterone: A pleiotrophic hormone. From Rossier in *The Kidney* (Seldin D. and Giebisch G, editors), 1992, pp. 1373–1409, with permission.

The ligand-receptor complexes then enter nuclei and initiate, by way of new protein synthesis, multiple actions. These include: increased apical sodium channel activity, either by intramembranous channel activation or by channel translocation to apical membranes; modulation of junctional complexes; activation of basolateral sodium pumps as well as addition of pumps to basolateral membranes; and finally, generation of high energy intermediates through mitochondrial ATP synthesis. This diagram (Fig. 7), which Rossier has described as "still accepted today," represents an elegant elaboration of the remarkably prophetic 1967 hypothesis by Edelman's laboratory about the pleiotrophic effects of aldosterone on its target tissues.

Another of Edelman's major research contributions, thyroidal thermogenesis, is also linked closely to sodium transport and (Na + K)-ATPase activity. In 1970 and 1971, Ismael-Beigi and Edelman discovered that the calorigenic response to thyroxin occurred by activating (Na + K)-ATPase, which, in turn, increased the rate of sodium transport (*PNAS* 67:1071, 1970 and *J Gen Physiol* 57:710, 1971). Thus, one might describe thyroxin as

a metabolic pacemaker. He and his colleagues then showed that T_3 increased the V_{max} but not the K_m of the (Na + K)-ATPase and increased the amount of tritiated ouabain binding to (Na + K)-ATPase (*J Clin Invest* 57:368, 1976 and *J Biol Chem* 251:7826, 1976). Thus, they concluded that the effect of T_3 was to increase the number of (Na + K)-ATPase molecules in basolateral membranes.

Edelman's research contributions can be summarized in five major areas: studies with Louis Leiter on renal hemodynamics and natriuresis; studies on body water composition under the tutelage of Arthur Solomon and Francis Daniels Moore; extraordinary work on the effects of aldosterone both on sodium absorption and on aldosterone-receptor interactions; and work on thyroid hormone as a metabolic pacemaker.

Lastly, as director of the Columbia Genome Project, Edelman has collaborated with investigators from a number of institutions in showing that the Wilson's Disease Gene, termed pWD, encodes a copper transporting ATPase. It is therefore likely that, in the future, Izzy may well move from sodium transport to copper transport.

Not surprisingly, Izzy's work has been recognized internationally. He has been elected to the National Academy of Sciences (1973) and to the American Academy of Arts and Sciences (1980). He has received the Homer W. Smith Award from the American Society of Nephrology (1980). He has been elected to the Institute of Medicine of the National Academy of Sciences (1983) and is a recipient of the Distinguished Service Award from Columbia University (1995). And today, we honor him, and ourselves, as one of our two A.N. Richards' Awardees (1999).

Dr. Edelman, on behalf of the International Society of Nephrology, it is my honor to award you the Alfred Newton Richards Award for distinguished scientific achievement.