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Schultz S G & Curran P F. Coupled transport of sodium and organic solutes. *Physiol. Rev.* 50:637-718, 1970.
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This paper was the first comprehensive review of sodium-coupled organic solute transport across animal membranes and the "sodium-gradient hypothesis." [The *SCI*® indicates that this paper has been cited in over 1,055 publications.]

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The "sodium-gradient" hypothesis was first suggested by Robert Crane and his collaborators at a symposium on membrane transport and metabolism held in Prague in 1960; it was published in more complete form in 1962.[1] This pioneering insight was based on the findings that the active accumulation of some sugars by small intestine epithelial cells was dependent upon the presence of sodium in the bathing medium and that this accumulation could be inhibited by digitalis glycosides. During that period I was a postdoctoral fellow in the Biophysical Laboratories of the Harvard Medical School investigating potassium transport by *Escherichia coli*.

In the fall of 1962 I was summoned to service in the US Air Force and stationed in the Department of Bionucleonics of the School of Aerospace Medicine in San Antonio, Texas, where I was provided the most lavish laboratory facilities I have ever enjoyed. When I petitioned my commanding officer for permission to continue my studies on bacterial transport, my request was flatly denied! I was instructed, in unequivocal terms, to find a project more closely related to humans and the biological effects of radiation. After some reflection, I decided to study ion transport by mammalian small intestine employing the elegant "short-circuit technique" pioneered by Hans Ussing and previously only applied to amphibian epithelia. I teamed up with Ralph Zalusky, a hematologist who, before being beckoned to service, was involved in studies on pernicious anemia in William Castle's Thorndike Laboratory.

Early in the course of our studies we found that the addition of glucose to a previously sugar-free solution bathing the mucosal (apical) surface of rabbit ileum resulted in an immediate increase in the rate of transcellular sodium absorption. While the implications of this finding *vis-a-vis* the Crane hypothesis were immediately obvious, we could not rule out the possibility that the stimulatory effect of glucose was secondary to its role as a metabolic substrate resulting in the synthesis of ATP necessary for energizing the sodium pump at the basolateral membranes. We immediately placed "rush-orders" for a number of glucose analogues, some of which were accumulated by enterocytes but not metabolized, and others that were not accumulated by these cells.

The period between placing these orders and the receipt of these compounds seemed interminable, but the wait was worthwhile. When these analogues finally arrived, we quickly demonstrated that an increase in transcellular sodium transport could be elicited by sugar analogues that were accumulated by enterocytes but not metabolized; this increase could not be elicited by nontransported analogues. These findings were the first to clearly establish cotransport of sodium and sugars and prompted the double-membrane model for sodium-coupled sugar absorption published in 1964.[2] A year later this model was extended to include amino acids.[3]

I rejoined the Biophysical Laboratories at Harvard in 1964 and initiated an exciting collaboration with Peter Curran that continued until his untimely death in 1975. Together we developed the "influx technique" and provided unequivocal evidence for sodium-coupled sugar and amino acid transport across the apical membrane of small intestinal cells, thereby "nailing down" the basic tenet of the Crane-Schultz-Zalusky model.

By 1967, the year Curran and I were invited by the editorial board of *Physiological Reviews* to write this review, it was already clear that these processes are widespread throughout the animal kingdom. Indeed, in that year Peter Mitchell introduced the term "symport" to describe them in a classic paper that went on to distinguish between primary and secondary active transport;[4] proton-coupled symport processes characteristic of terrestrial bacteria, fungi, and algae had not as yet surfaced.

Since the publication of our review, the general subject of membrane transport coupled to ion gradients has become one of enormous proportion, and today there is no doubt that these processes represent the most prevalent forms of energy transduction by biological membranes.[5,6] Our review has probably been cited so often because it was the first comprehensive treatment of the conception and birth of this subject at a time when it was still in its infancy.

1. **Crane R K.** Hypothesis for mechanism of intestinal active transport of sugars. *Fed. Proc.* 21:891-5, 1962. (Cited 445 times.)
2. **Schultz S G & Zalusky R.** Ion transport in isolated rabbit ileum. II. The interaction between active sodium and active sugar transport. *J. Gen. Physiol.* 47:1043-59, 1964. (Cited 330 times.)
3. ----------. Interactions between active sodium transport and active amino acid transport in isolated rabbit ileum. *Nature* 204:292-4, 1965. (Cited 100 times.)
4. **Mitchell P.** Translocations through natural membranes. *Advan. Enzymol. Relat. Areas Mol.* 29:33-87, 1967. (Cited 155 times.)
5. **Semenza G & Kinne R,** eds. Membrane transport driven by ion gradients. (Whole issue.) *Ann. N.Y. Acad. Sci.* 456, 1985. 462 p.
6. **Schultz S G.** Ion-coupled transport of organic solutes across biological membranes. (Andreoli T E, Hoffman J F, Fanestil D D & Schultz S G, eds.) *Physiology of membrane disorders.* New York: Plenum, 1986. p. 283-94.

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