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COMMENTS ON KERNAN'S MISREPRESENTATION OF THE ASSOCIATION-INDUCTION HYPOTHESIS IN HIS BOOK *CELL POTASSIUM*

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The ability of most animal and vegetable cells to accumulate potassium ions selectively while partly excluding sodium ions is a well-known fact. Kernan¹ duly recognizes in his book *Cell Potassium* that this phenomenon is attributed to cell membrane properties (the membrane or membrane-pump theory) or less popularly, to properties of protein and cell water in the bulk phase (the association-induction hypothesis).²

Kernan then discusses several experiments designed to test the alternative theories. This discussion gives the impression that the association-induction hypothesis has been disproven by different independent experiments and that further consideration of it is a waste of time. Review of the literature, however, leads to a different picture. Arguments set forth against the association-induction hypothesis have been rebutted, and new findings supporting the hypothesis were published before Kernan finished his book. A few examples follow:

(1) *Kernan wrote that the association-induction hypothesis fails to account for the electrical properties of the cell.*

But the basic electrical phenomenon of the living cell is the resting potential (RP). The literature reveals that Ling³ — who, incidentally, is the inventor of the microelectrode — has since 1959 compared experimental facts with theoretical equations for the RP according to both the membrane theory and the association-induction hypothesis. In 1978 Ling⁴ published an article entitled, "Two Opposing Views of the Cellular Electrical Potential: A Quarter of a Century of Experimental Testing." Experiments supporting the

association-induction hypothesis and not in harmony with the membrane theory were collected in this paper. One year later Ling⁵ presented an equation capable of explaining the entire profile of the RP at high as well as low external K^+ concentrations. With this equation Ling gave a molecular interpretation of those electrical properties phenomenologically accounted for in the membrane theory by the concept of an "electrogenic pump."

(2) *Kernan wrote that active transport of ions has been demonstrated in red cell ghosts.*

But Kernan did not mention the serious criticism of this claim published in 1975 under the title: "Red Blood Cell Ghosts: Hollow Membranes or Solid Bodies?"⁶ Those interested in the question of whether active transport has been really demonstrated in any membrane preparation may also read the article: "Do Isolated Membranes and Purified Vesicles Pump Sodium? A Critical Review and Reinterpretation."⁷

(3) *Concerning Ling's argument that the cell does not command enough energy to operate the postulated pumps, Kernan gives the impression that this position cannot be accepted because exchange diffusion was not considered.*

Kernan did not mention experimental facts ruling out the possibility that exchange diffusion may explain the proposed low energy consumption of a postulated pump.^{8,9} Kernan argues that the small difference in energy consumption of normal compared to ouabain-treated muscle supports the idea that the pump does not need much energy. With the information that exchange diffusion

may be ruled out, the small difference in energy consumption rather supports the association-induction hypothesis, according to which cellular proteins of ouabain-treated muscles switch cooperatively to another energy state now preferring Na^+ over K^+ at their anionic binding sites.^{10,11} Further consideration of energy requirement of the Na pumps has been published in ref. 12.

(4) *Kernan doubts the validity of the interpretation of published EMOC (effectively membraneless open-ended cell) data because he thinks that intracellular compartments and a significant extracellular compartment other than interstitial fluid have been neglected.*

But Kernan mentions neither the fact that the possible role of intracellular compartments was indeed investigated^{13,14} nor that experimental findings have shown that in muscle only the T tubules are open to the exterior.¹⁵⁻¹⁷ Ling established that an EMOC preparation whose hypothetical membrane pumps are made nonfunctional continues to accumulate K^+ and exclude Na^+ as in normal cells.¹³ By means of the EMOC technique, it was also shown that intact uninjured muscle cells have a K^+ mobility $\frac{1}{8}$ that of a dilute salt solution¹⁴

(5) *According to Kernan, the high K^+ activities measured in nerve, muscle, and oocytes speak against the association-induction hypothesis.*

Kernan mentioned neither the published comments of Ling in regard to the problem of activity measurements⁹ nor the finding of low K^+ activity coefficients in (apparently less excitable) intestinal mucosal cells¹⁸ (see also discussion in ref. 19).

(6) *According to Kernan, active transport of ions into plant cell vacuoles invalidates the association-induction hypothesis.*

Kernan apparently was unaware of Ling's discussion of active transport occurring in plant cells with vacuoles. In 1965 Ling proposed a cooperative adsorption-desorption pump derived from principles of the associa-

tion-induction hypothesis.²⁰ At no time did that hypothesis assert that active transport *per se* does not occur.

(7) *New experimental findings supporting the association-induction hypothesis were published before Kernan finished his book.*

These findings are amply described in articles with the following titles: "Potassium Adsorption Sites Visualized by Cesium and Thallium Under the Transmission Electron Microscope"²¹; " K^+ Localization in Muscle Cells by Autoradiography, and Identification of K^+ Adsorbing Sites in Living Muscle Cells with Uranium Binding Sites in Electron Micrographs of Fixed Cell Preparations"²²; "Visualization and X-Ray Microanalysis of Potassium Tracers in Freeze-Dried and Plastic Embedded Frog Muscle"²³; "Demonstration of Rb^+ , Cs^+ , and Na^+ Localization in Single Muscle Fibers by Autoradiography at 77°K"²⁴. The importance of these new findings for our molecular understanding of biological phenomena, such as oxidative phosphorylation, electrical potentials, and active transport, has been discussed recently in several publications.²⁵⁻²⁷ Moreover, recent studies in human lymphocytes confirm numerous major predictions of the association-induction hypothesis.²⁸⁻³¹

Since the publication of *Cell Potassium*, two additional pieces of supporting evidence for the association-induction hypothesis have been presented. The hypothesis maintains that ion distribution between the inside and the outside of a living cell can be attributed to (a) the capability of cellular proteins to selectively adsorb ions, and (b) the capability of extended cytoplasmic proteins to influence several layers of water molecules, thereby decreasing the water solubility of many cell solutes. Both phenomena have been shown recently to occur in *in vitro* preparations.^{19,32-34}

With the information given above, the interested reader may decide for himself how weak or strong the association-induction hypothesis really is. The reader also may ask

why Kernan's discussion of the hypothesis includes so few articles favoring it. In my opinion, this deficiency reflects a main weak point of our scientific peer review system: it strongly supports accepted concepts. "Open debate that smacks of heresy is squelched in the established journals."³⁵ New ideas proposed by a minority (and in the beginning usually a minority of one) have had little chance of being published in the more popular "established" journals. For the same reasons, perhaps, the established membrane theory is favored by Kernan at the expense of the association-induction hypothesis. The discussion of the association-induction hypothesis in *Cell Potassium* is typical of many prior reviews, and clearly demonstrates that by omitting or ignoring published experimental findings and theoretical considerations it is possible to give a poor picture of the minority view.

History shows that major steps in the advancement of science cannot occur without development of new ideas.³⁶ Editors of journals as well as sponsors of grant proposals should bear this in mind; they should support scientific controversies rather than suppress them by giving too much credit to established peers. "One cannot use the opinions of a party to a dispute to judge the validity of the opinion of its antagonist."³⁷

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