# This Week's Citation Classic®

**Diamond J M & Wright E M.** Biological membranes: the physical basis of ion and nonelectrolyte selectivity. *Annu. Rev. Physiol.* 31:581-646, 1969.
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Physically similar ions or nonelectrolytes often have very different biological effects. A familiar example is the difference in the membrane permeabilities of sodium and potassium. Our review summarized the empirical patterns and sought the underlying physical explanations. [The *SCI*® indicates that this paper has been cited in over 495 publications.]

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We began to collaborate when we were both postdoctoral fellows at Harvard in 1965. At our first discussion we discovered that each of us had independently and accidentally discovered the same quick and simple method for determining relative nonelectrolyte permeabilities of biological membranes. The method used streaming potentials to measure reflection coefficients. With this method we spent one year measuring a mass of numbers (the reflection coefficients of 206 nonelectrolytes in rabbit gallbladder mucosa) and another year relearning enough organic chemistry to interpret those numbers. At that stage we met George Eisenman, who had been measuring and interpreting selective ion permeabilities of artificial membranes, and we went on to make those measurements on a large scale (again for the gallbladder epithelium), since they too were quick and simple. Thus, we were guided partly by the availability of methods whose potential uses we realized.

After those experimental studies the work for our review article (completed in 1968) proved satisfying. Both ion and nonelectrolyte permeabilities, especially the former, were "hot" subjects at the time. Dozens of published empirical studies were available that, taken together, defined shared patterns and theoretical ideas that were simple in principle but that generated richly complex predictions through changes in a few variables. Our review did three things: it showed the patterns behind the diverse empirical studies; it tried to set forth clearly the physical principles underlying ion selectivity, which we had struggled to understand from the theoretical papers of others; and it presented a new theory of nonelectrolyte selectivity that we derived in the late stages of writing the review. This theory rested on incremental free energies of transferring nonelectrolyte substituent groups between vacuum, water, and model lipid solvents.

Our review probably was frequently cited because it presented difficult material clearly, provided order out of masses of detail, made many specific predictions, and interpreted important biological phenomena in terms of physics and chemistry. In subsequent years ion selectivity has continued to command attention,[1,2] but the unsolved problems of nonelectrolyte selectivity that we noted in 1969 remain largely ignored, although this is discussed in a recent book chapter by W.D. Stein.[3] In particular, the differences in membrane structure responsible for the differences in nonelectrolyte permeability patterns described early in this century still await explanation.

1. **Eisenman G & Horn R.** Ionic selectivity revisited: the role of kinetic and equilibrium processes in ion permeation through channels. *J. Membrane Biol.* 76:197-225, 1983.
2. **Eisenman G & Dani J A.** An introduction to molecular architecture and permeability of ion channels. *Annu. Rev. Biophys. Biophys. Chem.* 16:205-26, 1987.
3. **Stein W D.** Simple diffusion across the membrane by layers. *Transport and diffusion across cell membranes.* Orlando, FL: Academic Press, 1986. p. 69-112.