

Sachs J R & Welt L G. The concentration dependence of active potassium transport in the human red blood cell. *J. Clin. Invest.* 46:65-76, 1967.
[Dept. Medicine, Univ. North Carolina Sch. Medicine, Chapel Hill, NC]

The sodium/potassium pump is believed to exchange three sodium ions from the inside of the cell for two potassium ions from the outside. This paper demonstrated that predictions based on this model about the way in which the pump rate should vary with the outside K concentration could be verified with human red blood cells. [The SC[®] indicates that this paper has been cited in over 170 publications since 1967.]

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May 24, 1984

"The experiments described in this paper were performed while I was a postdoctoral fellow in the laboratory of the late Louis Welt at the University of North Carolina (UNC). While I was a medical student, I became interested in the mechanisms by which Na and K concentrations are regulated in animal cells, so that when, at the end of my clinical training, I learned that Welt was spending a sabbatical year in Dan Tosteson's laboratory at Duke University working on the Na-K ATPase of red-cell membranes, I applied for a postdoctoral fellowship with him. During my first few months, Welt was still working in Tosteson's laboratory, and I went along to learn techniques. One of the scientists I met there was Tom McManus, who knows everything worth knowing about red cells. He taught some of what he knows to me.

"My first project at UNC was a clinical one that interested Welt and that also resulted in a highly cited publication.¹ While this was underway, I became aware of the experiments of Post and Jolly,² which showed that the Na pump exchanges Na and K in a 3:2 ratio, and of their important proposal that the pump is stoichiometric with a fixed coupling ratio so that three Na and two K ions are transported per cycle. It seemed to me that if it is necessary for two K ions to be transported per cycle, then the relation between the pump rate and the external K concentration should be sigmoid rather than hy-

perbolic. I performed some experiments, and to both Welt's and my surprise, the sigmoid relation was unmistakable. We then thought of an experiment that made use of the K congeners Rb, Cs, and Li, which are transported by the pump in place of K. We predicted that if the K influx was measured at a low K concentration (at which most of the pumps had a single K ion bound) and at varying congener concentrations, then stimulation of the influx should be seen at low congener concentration (when a congener-K pair is transported) and inhibition at high K concentration (when both K ions are replaced by the congener). This turned out to be the case.

"The major obstacle to the experiments turned out to be the transport of the isotope, ⁴²K, which has a 12.4-hour half-life and which we needed at high specific activity. The isotope was shipped from Boston and, for some reason, usually missed its stop at the Raleigh-Durham airport and went on to Atlanta. Since it took the rest of the day to recover it, the experiments usually began at midnight. On the other hand, my location at Chapel Hill put me in the way of a great deal of valuable advice and encouragement, not only from McManus and Tosteson, but also from Joe Hoffman, who was a frequent visitor to the area, probably because of the high quality of the golf courses.

"I believe there are several reasons for the popularity of the paper. Sigmoid curves relating pump activity to the concentration of its substrates have turned out to be common for this enzyme, and this was one of the first studies in which the side of the membrane at which the effect was exerted could be unambiguously determined. The experiments demonstrated that the kind of analysis of pump activity that could be performed using red cells was somewhat more sophisticated than was thought at the time. This paper was the first full paper I wrote, and so the methods section was written in enough detail that the experiments could easily be repeated.

"I recall that I enjoyed everything to do with performing these experiments and writing the paper. If the paper has turned out to be useful, I am glad. For recent work in this field, see reference 3."

1. Welt L G, Sachs J R & McManus T J. An ion transport defect in erythrocytes from uremic patients. *Trans. Assn. Am. Physician.* 77:169-81, 1964. (Cited 140 times.)
2. Post R L & Jolly P C. The linkage of sodium, potassium and ammonium active transport across the human erythrocyte membrane. *Biochim. Biophys. Acta* 25:118-28, 1957. (Cited 250 times since 1957.)
3. Hoffman J F & Forbush B III, eds. *Current topics in membranes and transport. Volume 19. Structure, mechanism, and function of the Na/K pump.* New York: Academic Press, 1983. 1043 p.