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Ussing H H & Zerahn K. Active transport of sodium as the source of electric current in the short-circuited isolated frog skin. *Acta Physiol. Scand.* **23**:110-27, 1951. [Laboratory of Zoophysiology, University of Copenhagen, Denmark]

By aid of an adjustable electromotive force in series with the isolated frog skin, the skin potential can be totally short-circuited. It is thus possible to determine simultaneously the current which can be drawn from the skin and —using radioactive sodium —the influx and outflux of sodium. With Ringer solution on both sides, the short-circuit current is exactly equal to influx minus outflux, i.e., the net active transport of sodium. [The *SCI*® indicates that this paper has been cited over 1,250 times since 1961.]

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"The origin of bioelectric potentials and bioelectric currents had been a matter of dispute since the discovery of the phenomena in the middle of the 19th century.[1] For individual cells, like those of muscle and nerve fibers, the potential had been related to the uneven distribution of potassium between cells and surroundings. When isotopes became available it was realized that both sodium and potassium exchanged readily across most cell membranes, and the idea of a 'sodium pump,' maintaining low sodium and high potassium concentration in cells, was advocated by several groups, including our own. Others maintained that the uneven ion distribution was due to colloid chemical properties of cytoplasm rather than to active sodium transport. Therefore, we turned to the study of certain epithelia where net transport of sodium chloride was known to take place.

"In 1949, I was able to demonstrate that chloride uptake through the frog skin could be a consequence of the electric potential difference between inside and outside, whereas sodium transport took place against both concentration and potential gradients, thus being due to active transport.[2] It then became desirable to demonstrate, not only that the sodium transport was active (which I considered proven beyond doubt), but also that active sodium transport was the sole source of the electric asymmetry of the frog skin.

"Partial short-circuit could be achieved by connecting inside and outside solutions with a copper wire, using reversible electrodes. I did a quick and dirty extrapolation which indicated that the influx of sodium as measured with 24-Na would be of the same order of magnitude as the estimated true short-circuit current, but the resistance of solutions and electrodes made it impossible to test the hypothesis. At the International Physiology Congress in Copenhagen, 1950, I was to give one of the main lectures on active sodium transport, and I badly needed some striking experiment to prove my point. Shortly before the deadline for summaries, it suddenly dawned on me that a battery and a variable resistance in series with the skin could be used to create the desired situation. I asked our mechanic to build a chamber from a piece of celluloid tubing. Zerahn wired up the circuit, while I did the glass blowing, and within less than a week we knew that the hypothesis was correct.

"Our paper had an immediate impact because it provided a firm basis for the concept of active sodium transport. Later the short-circuit method became a standard procedure in the study of ion transport phenomena in epithelia, and this is probably why the paper is still being cited frequently. More recent work is reported in 'Transport pathways in biological membranes.' "[3]

1. **DuBois-Raymond E.** *Untersuchungen über Tierische Elektrizität I-II.* Berlin: G. Reimer, 1848. 1154 p.
2. **Ussing H H.** The use of tracers in the study of active ion transport across animal membranes. *Cold Spring Harbor Symp.* **13**:193-200, 1948.
3. **Ussing H H, Erlij D & Lassen U.** Transport pathways in biological membranes. *Annu. Rev. Physiol.* **36**:17-49, 1974.