CC/NUMBER 42
OCTOBER 20, 1986

This Week's Citation Classic®

Mitchell P. Coupling of phosphorylation to electron and hydrogen transfer by a chemi-osmotic type of mechanism. *Nature* **191**:144-8, 1961.
[Chemical Biology Unit, Zoology Department, University of Edinburgh, Scotland]

This paper outlined a hypothetical mechanism by which coupling in oxidative and photosynthetic phosphorylation might be achieved by the circulation of protons between a protonmotive redox or photoredox system and a reversible protonmotive ATPase, both plugged through the same topologically closed "coupling membrane." [The *SCI*® indicates that this paper has been cited in over 1,110 publications.]

Peter Mitchell
Glynn Research Institute
Bodmin, Cornwall PL30 4AU
England

June 10, 1986

The so-called "chemiosmotic hypothesis," outlined in this paper, was a special case of a more general concept of chemiosmotic action by enzyme-catalysed chemical-group translocation, which I had introduced several years earlier. The aim of the more general concept, which I began to formulate around 1950 while at Cambridge University, was to show how the supposedly spatially undirected chemical force of metabolism may be spatially directed through an osmotic barrier and could become the seat of "active transport" simply by appropriate vectorial organisation of the metabolic processes of chemical-group and electron transfer in ligand-conducting enzymes (now called osmoenzymes) plugged through a lipid membrane.

The general vectorial chemical concept of chemiosmotic action[1] (dubbed "chemiosmosis"[2]) provided the basis for explaining the phenomenon of coupling in oxidative and photosynthetic phosphorylation, by the circulation of protons between protonmotive redox-chain or photoredox-chain enzyme molecules and reversible protonmotive ATPase molecules, both plugged through the same topologically closed "coupling membrane." This application of chemiosmotic action incidentally paved the way for the integration of ideas and knowledge of solute and nutrient transport with those of protonmotive metabolism, because it was necessary to postulate specific proton-solute symporters and proton/solute antiporters to explain pH stabilisation and substrate uptake across coupling membranes. I owe much to David Keilin for encouraging me to persevere with these ideas.

The "chemiosmotic hypothesis" was explicitly based on four main postulates, which could be defined precisely enough to be relatively easy to test experimentally, as first discussed at length in a review published in 1966.[3]

The 1961 paper aroused little interest until after the publication of my 1966 review; but thereafter it stimulated much new experimental work and gradually led to acceptance of the hypothesis that coupling occurs by a chemiosmotic type of mechanism. As a result, I was the sole recipient of the Nobel Prize for chemistry in 1978. I should remark, however, that the vectorial metabolic basis for the protonmotive mechanisms of the redox and ATPase enzymes, which seemed to me to be the main theoretical and evolutionary justification for proposing the "chemiosmotic hypothesis," has not proved to be as attractive or acceptable to my biochemical colleagues as I had expected. Strangely enough, it may have helped to persuade some biochemists to take my hypothesis seriously to begin with, though they rejected this fundamental aspect of the hypothesis later. There is now much ongoing research designed to elucidate the protonmotive chemiosmotic mechanisms in general, and in particular to decide whether extrinsic proton pumping components are required alongside the chemical-group and electron conducting components.[4,5]

I suppose that my 1961 paper has been cited frequently because it marked a new departure in bioenergetics that has had widespread repercussions in biophysics, biochemistry, and physiology.[6]

1. **Mitchell P.** The correlation of chemical and osmotic forces in biochemistry. *J. Biochemistry* **97**:1-18, 1985.
2. ————. Chemiosmosis: a term of abuse. *Trends Biochem. Sci.* 9:205, 1984.
3. ————. Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. *Biol. Rev. Cambridge Phil. Soc.* 41:445-502, 1966. (See also: Mitchell P. Citation Classic. *Current Contents* (16):14, 17 April 1978.)
4. ————. Molecular mechanics of protonmotive F_0F_1 ATPases. *FEBS Lett.* **182**:1-7, 1985.
5. **Mitchell P, Mitchell R, Moody A J, West I C, Baum H & Wrigglesworth J M.** Chemiosmotic coupling in cytochrome oxidase. *FEBS Lett.* **188**:1-7, 1985.
6. **Skulachev V P & Hinkle P C,** eds. *Chemiosmotic proton circuits in biological membranes: in honor of Peter Mitchell.* Reading, MA: Addison-Wesley, 1981. 633 p.

1A-16