This Week's Citation Classic

Harold F M. Conservation and transformation of energy by bacterial membranes.
Bacteriol. Rev. **36**:172-230, 1972.
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This article set out to describe, simply and clearly, what Peter Mitchell's chemiosmotic theory proposes and how it applies to bacterial physiology. It was perhaps the first major literature review based on the premise that the theory is correct in principle. [The *SCI*® indicates that this paper has been cited over 560 times since 1972.]

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October 23, 1981

"Most scientists, even today, would rather praise Mitchell than read him. This was doubly true a decade ago, when few had made the effort to master his chemiosmotic theory,[1] and barely a handful were prepared to base their own research upon it. The biochemical establishment, with some honorable exceptions, had dismissed the theory as incomprehensible and probably wrong; microbiologists were largely unaware of the ideas that would shortly transform our conception of how bacteria generate useful energy and perform work.

"My own induction into the chemiosmoticists' thin ranks had taken place just a few years before. In 1968, my laboratory at the National Jewish Hospital in Denver was engaged in research on antibiotics that affect bacterial membrane function. My attention was drawn to a paper by W.A. Hamilton,[2] who claimed that the commercial antibacterial agent tetrachlorosalicylanilide (TCS) dissociates active transport from metabolism. This seemed to me unlikely, as substituted salicylanilides were known to be potent uncouplers of oxidative phosphorylation. Jim Baarda and I therefore examined the effect of TCS on *Streptococcus faecalis*, an organism that lives by glycolysis alone, and found, to my surprise, that TCS dissociated metabolite accumulation from glycolysis.[3] At that time, the only mechanistic hypothesis of uncoupling was due to Mitchell and Moyle,[4] who had shown uncouplers to function as proton-conducting ionophores. We confirmed that TCS conducts protons and suggested that it may short-circuit a cellular proton circulation.[3] During the next three years we found that glycolyzing cells generate both the pH gradient and the electrical potential predicted by the chemiosmotic theory. Well before that point I was convinced that Mitchell was right and that his ideas would revolutionize bacterial physiology.

"Unfortunately, few microbiologists seemed to see it that way. I felt that this was chiefly a problem in communication (Mitchell's writing tends to be abstract and quite forbidding) and determined to bridge the gulf of incomprehension with a literature review of my own. The gratifying success of this effort may be due to two features: the article set out to explain, as clearly and simply as possible, what the chemiosmotic theory says and how it applies to bacterial physiology, and it was the first major review by someone besides Mitchell that was squarely based on the premise that the chemiosmotic theory is correct in principle. I may have succeeded too well, encouraging students to acquire at second hand a superficial acquaintance with a profound idea; one must hope that a little knowledge is still better than none.

"During the past decade the chemiosmotic theory has been universally accepted as the basis for research and reflection on the energetics of both bacterial and eukaryotic cells. In my own later writings[5] I have tried to explore some of these wider ramifications. The heroic era of bioenergetics is now past, and the academic one is under way. But the molecular mechanisms of energy coupling remain to be clarified, and provide ample fuel for the controversies that keep bioenergetics a frontier of research."

1. **Mitchell P.** Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. *Biol. Rev. Cambridge Phil. Soc.* **41**:445-502, 1966. [Citation Classic. *Current Contents* (16):14, 17 April 1978.]
2. **Hamilton W A.** The mechanism of the bacteriostatic action of tetrachlorosalicylanilide: a membrane-active antibacterial compound. *J. Gen. Microbiol.* **50**:441-58, 1968.
3. **Harold F M & Baarda J R.** Inhibition of membrane transport in *Streptococcus faecalis* by uncouplers of oxidative phosphorylation and its relationship to proton conduction. *J. Bacteriology* **96**:2025-34, 1968.
4. **Mitchell P & Moyle J.** Acid-base titration across the membrane system of rat-liver mitochondria: catalysis by uncouplers. *Biochemical J.* **104**:588-600, 1967.
5. **Harold F M.** Ion currents and physiological functions in microorganisms. *Annu. Rev. Microbiol.* **31**:181-203, 1977.