winds in clear air, is achieved largely by the use of improved signal processing techniques and by varying the frequency of the broadcasted signal. Thus, researchers have looked at snow storms, a hurricane, turbulence in clear air near the ground, and clear air winds at altitudes up to 15 kilometers. At much lower frequencies than those used to probe the atmosphere, oceanographers have even been able to measure the motion of waves and ocean currents up to 70 kilometers from the shore.

Doppler radar is rapidly becoming a popular research tool. Some data handling problems, including the rapid processing of three-dimensional data, have not yet been tackled. But larger Doppler networks (seven or more radars) are planned for the immediate future, and some researchers envision an operational network spanning the country to provide warnings of violent weather.

—RICHARD A. KERR

The 1978 Nobel Prize in Chemistry

Award of the Nobel Prize in Chemistry to Peter Mitchell honors the achievements of a strikingly original mind. A quarter of a century ago, Mitchell recognized that biochemical reactions associated with membranes may have a direction in space, and he set out, virtually alone, to explore the implications of this insight. The result was nothing less than a scientific revolution, in Thomas Kuhn's sense. During the past decade the paradigms of bioenergetics have been transformed under the impact of Mitchell's chemiosmotic theory; in time it may transmute our perception of how living cells function.

How do organisms generate energy and harness it to the performance of such useful work as movement, transport, and biosynthesis? By 1955, Fritz Lipmann's concept that adenosine triphosphate (ATP) serves as the universal energy currency had been assimilated. The function of the great metabolic highways—fermentation, respiration, and photosynthesis—was seen to be the production of ATP, which, in turn, supports various work functions by virtue of its energy-rich phosphoryl bonds. In outline, at least, bioenergetics seemed comprehensible, and what remained to be done was to work out the molecular details.

That proved to be a major undertaking, for the enzymes of oxidative and photosynthetic phosphorylation are firmly associated with the lipoprotein membranes of mitochondria and chloroplasts, respectively, and could not be satisfactorily studied in solution. Some of the most illustrious biochemists of a generation—P. D. Boyer, B. Chance, L. Ernster, D. E. Green, H. A. Lardy, A. L. Lehninger, E. Racker, E. C. Slater, and many others—devoted their efforts to the task of delineating the basic features of oxidative phosphorylation. In the upshot it was recognized that respiration is mediated by a cascade of enzymes and coenzymes that transport electrons from various reduced substrates to oxygen. The synthesis of ATP itself is catalyzed by a distinct enzyme complex, referred to as an ATPase (adenosinetriphosphatase) because its activity is usually assayed in the hydrolytic direction. In chloroplasts, likewise, electrons ejected when light is absorbed by chlorophyll travel along a series of carriers to the ultimate acceptor, water; ATP synthesis is mediated by an ATPase complex whose molecular structure closely resembles that of mitochondrial membranes. The issue of "energy coupling" was now sharply focused: how does the free energy released during electron transport drive the ATPase "uphill," in the direction of ATP synthesis? The search for molecular mechanisms was guided by the postulate that the respiratory chain and ATPase are linked by high energy intermediates, analogous to those discovered in reactions catalyzed by soluble enzymes. For a decade, one putative intermediate after another was proposed, examined, and rejected, with mounting frustration. Something had gone wrong, but what?

Peter Mitchell was not, to begin with, a properly licensed mitochondriologist. His intellectual roots lay in the study of metabolite transport across the cytoplasmic membrane of bacteria, a subject he had taken up while a student in Ernest Gale's laboratory in Cambridge. Transport, also, was bedeviled by a major conceptual difficulty: How can the scalar reactions of metabolism generate vectorial transport of substances into or out of cells? In 1958, Mitchell, together with former fellow student Jennifer Moyle, pointed out that enzymic reactions are intrinsically vectorial. Their direction in space is masked in solution but may become manifest when enzymes are incorporated into membranes. An enzyme complex may be so embedded within a membrane that the reaction pathway traverses the barrier, catalyzing at once a chemical reaction and the translocation of a chemical group: vectorial metabolism.

Pondering the implications of this principle led Mitchell, between 1961 and 1966, to formulate what he called the chemiosmotic hypothesis, a radical solution to the problem of energy coupling in oxidative and photosynthetic phosphorylation. Briefly, he proposed that the respiratory chain is an alternating sequence of carriers for hydrogen and electrons, so arrayed within the inner mitochondrial membrane as to transport protons across it. Since the mitochondrial membrane is essentially impermeable to the passive flow of protons, respiration generates an electrochemical potential gradient for H^+ with the matrix electrically negative and alkaline relative to the outside. Protons at the outer surface will seek to move back into the matrix, down the potential gradient; this proton current, analogous to the electron current produced by a battery, can be drawn upon to do work. The ATPase is a second, independent proton-translocating system that also spans the membrane; movement of protons through a channel within the ATPase complex, down the electrochemical gradient generated by respiration, drives the synthesis of ATP. The chemiosmotic hypothesis denied the existence of chemical links between the respiratory chain and the ATPase; they need not even be physically contiguous. What is required is that both complexes be localized in a single, topologically closed vesicle tight enough to sustain the proton gradient that effects their coupling.

It must be said that the chemiosmotic hypothesis found little welcome among biochemists. Mitchell had invoked strange principles with an almost mystical flavor; besides, there seemed at first to be good grounds for doubting the validity of some of his proposals. It was probably the open-minded skepticism of Efraim Racker that persuaded Mitchell that he must buttress his argument with solid data. But hard evidence was not easily come by, for it required the invention of methods with which to ask nature quite novel questions. Jointly, Mitchell

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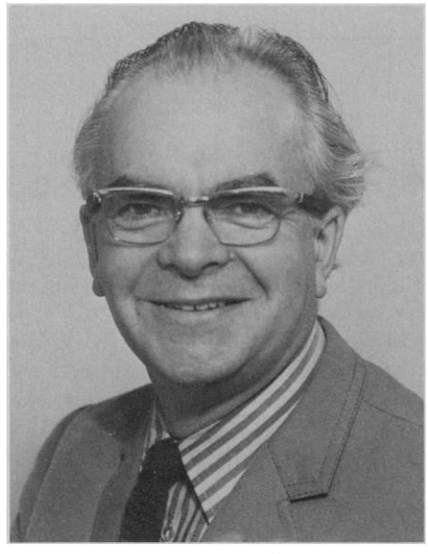
and Moyle began to weave a net of quantitative methods and observations designed to subject the predictions of the chemiosmotic hypothesis to rigorous test.

In rapid succession, they discovered that uncouplers of oxidative phosphorylation conduct protons across biological membranes; demonstrated that addition of a pulse of oxygen to anaerobic mitochondria elicts the transient appearance of protons at the cytoplasmic surface; extended the evidence for proton translocation to the ATPase complex of mitochondrial, chloroplast, and bacterial membranes; produced evidence that these proton movements are electrogenic; devised a procedure based on the distribution of K^+ (potassium ion) in the presence of valinomycin to measure the electrical potential across the mitochondrial membrane; and began to analyze the functional architecture of the ATPase complex. Concurrent studies, with Peter Hinkle, showed that the redox potential of respiratory carriers is a function of the transmembrane electrical potential; others, with Peter Scholes, documented respiratory proton transport in bacteria. It was a period of extraordinary productivity, both theoretical and experimental, intensified by the stormy debate, within the small community of bioenergeticists, over the legitimacy of chemiosmotic principles and practice. By 1970, the weight of evidence had begun to shift in Mitchell's favor, and a few disciples had come forward in Britain, the United States, and the Soviet Union. Today it is almost universally accepted that the coupling between the respiratory chain (or the photosynthetic apparatus) and the ATPase complex is, indeed, effected by the proton current. The molecular mechanisms by which respiratory chain and ATPase actually translocate protons and thereby interconvert chemical, electrical, and osmotic forms of energy, remain uncertain; this is at present the focus of research in several laboratories, and of continued debate. But the principle of chemiosmotic energy coupling is firmly established.

From the beginning, Mitchell was aware of the implications of his theory for membrane transport; that, after all, had been his point of departure. A proton current generated by the respiratory chain could be coupled to active transport by means of bifunctional carriers endowed with one binding site for the substrate and another for a proton. In 1962, Mitchell proposed that the familiar *lac* "permease" of *Escherichia coli* in fact mediates symport of lactose with one proton; a few years later, Ian West and Mitchell provided direct evidence for concurrent movement of H^+ and lactose. Students of transport proved relatively receptive to Mitchell's ideas and nomenclature, probably because Robert K. Crane had, as early as 1961, clearly formulated the concept of sodium cotransport for epithelial tissues. Nevertheless, a decade of vigorous debate elapsed before the central role of the proton circulation in microbial transport processes was generally admitted.



Peter Mitchell

So much for work completed; the wider implications are just becoming apparent. We owe to Mitchell a clear conception of the manner in which an ion current links the metabolic machinery to the performance of chemical, osmotic, and even (in bacteria) mechanical work. Membranes, so conspicuous in the architecture of life, define not only structural compartments but elementary units of function, ultimately based upon the directionality of chemical reactions in space. From this perspective, one can better appreciate the role of vectorial metabolism in sensory perception, in coupling stimuli to various responses, and in guiding growth and development. Ultimately, we may come to regard the chemiosmotic theory as a first long step toward understanding how life, like a flame, gives visible form to the flow of matter and energy through space.

Peter Mitchell's unconventional laboratory is almost as celebrated as his scientific contributions. After receiving his Ph.D., Mitchell taught for a number of years at Cambridge and Edinburgh, until ill health forced him to seek a kindlier climate. In southern Cornwall he found an 18th-century manor that had fallen into ruin and rebuilt it to his own design; today the restored classic facade screens a spacious building, part the home of the Mitchell family and part modern laboratory. From the foundation of the Glynn Research Laboratories to the present, its codirectors have been Mitchell and Jennifer Moyle, herself a meticulous and ingenious experimentalist who provided much of the factual foundation upon which Mitchell's theoretical genius could build. The laboratory is supported by a trust fund, supplemented by government grants and by the proceeds from a herd of dairy cows. It is a minute unit by modern standards (no students, a mere handful of postdoctoral investigators and long-term visitors over the years), yet it is deeply enmeshed in the scientific and intellectual crosscurrents of our time through extensive correspondence and a steady stream of visitors. Somehow, Mitchell still finds time for involvement in local affairs, matters of conservation, and the restoration of medieval farm houses. And I would like to believe that his prodigious creativity owes something to the peaceful meadows and wooded hills that surround his laboratory.

More than most contemporary scientists, Mitchell is conscious of the historical and intellectual continuity of science. He has been at pains to acknowledge that his own chemiosmotic theory incorporates strands that were the work of others: of the late Elmer Lund, who recognized 50 years ago that bioelectric potentials are generated by chemical reactions localized in cell surfaces; of H. Lundegårdh and Sir Rutherford Robertson, who first strove to give biochemical expression to this notion; and of the many investigators who generated the methods and the knowledge that Mitchell adapted, enlarged, and unified. He told me once that science is not a game like golf, played in solitude, but a game like tennis in which one sends the ball into the opposing court and expects its return. Just so was his own theory clarified and honed by the need to answer objections and to measure one hypothesis against another. Mitchell's achievement is not diminished by recognizing that his Nobel Prize honors both a singular man and the efforts of a generation of biochemists and biophysicists. Thanks to the one and to the many, we now understand in principle how cells generate useful energy and perform work.

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