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Tributes

Peter Mitchell, 1920–1992

Peter Mitchell was awarded the Nobel Prize for Chemistry in 1978 "for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory." When Mitchell first elaborated this hypothesis in 1961, it was revolutionary, entirely without experimental support, and opposed with near unanimity by the biochemical community. Its eventual success stands as a monument to a scientist of penetrating intellect and breathtaking imagination.

Mitchell entered Jesus College, Cambridge, in 1939, where he obtained a B.A. with honors and a Ph.D. in biochemistry with J. F. Danielli. He moved to the University of Edinburgh in 1955 and in 1963, he moved to a great house near Bodmin, Cornwall, that had become a near ruin. Mitchell, who was wonderfully talented in architectural design, worked for two years alongside the craftsmen and, with his own funds to restore Glynn House, which contained his family apartments and the research laboratories. Mitchell and his brother then endowed the Glynn Foundation with £240,000 of their own inheritance.

It was at Cambridge that Mitchell began his lifelong quest to understand the mechanism of energy coupling. Oxidative and photosynthetic phosphorylation were known to take place in mitochondria and chloroplasts, and these organelles were known to contain membrane-bound ATPase complexes and cascades of enzymes and coenzymes for carrying electrons from substrates to oxygen or water. The great unsolved problem confronting bioenergetics was how the energy released during electron transport drove the ATPase in the direction of ATP synthesis. The prevailing theory, based on the solid foundation of substrate-level phosphorylation, was that the respiratory chain passed the energy on to a high energy chemical intermediate which, in turn, passed the energy on to ATP through the ATPase. An intensive search was on to identify this intermediate, but this search had so far proved unfruitful.

At the time, no major role was attributed to the complexity of the structures responsible for oxidative phosphorylation nor to their close association with the lipid membranes. Enzymes were generally viewed

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as scalar catalysts containing active sites that brought about a chemical reaction. During the late 1950s, Mitchell and Jennifer Moyle developed the concept of vectorial metabolism in which the chemical reaction assumes direction by virtue of structure within the enzyme that can channel chemical reactants and products along specific pathways. Mitchell recognized that the consequences of vectorial metabolism would be greatly amplified in enzymes that were plugged with a specific orientation through thin biological membranes.

These ideas were elaborated in an elegant paper published in *Nature* in 1961. According to the chemiosomotic hypothesis, the enzyme complexes of oxidative phosphorylation are plugged through the inner mitochondrial membrane in such a way that they transport protons in one direction. Protons being ejected by the respiratory chain would flow back through the ATPase, causing synthesis of ATP. Thus, it is the protonic potential difference between the aqueous phases on either side of the membrane that serves as the high-energy intermediate, and the elusive chemical intermediate could not be found because it did not exist. Mitchell had invented new types of protonic batteries that can be called upon to perform work, and biological energy conservation became a problem in membrane transport.

Mitchell gave us an extraordinarily complete and accurate picture not only of how mitochondria and chloroplasts transform energy, but also how they survive within the cell under the stress of constant and rapid movements of ions and water across their membranes. At this physiological level, he succeeded magnificently in achieving his lifelong goal of unifying metabolism and transport. He worked to the end of his life to perfect the deeper concept of vectorial metabolism upon which the chemiosmotic theory was based, and this work continues to energize biochemical research.

In Mitchell's work, the idea comes before the experiment, and the hypothesis, constructed to be refutable, is a prerequisite for experimental design. His achievements stand as a constant inspiration, not only because his dazzling intuition eventually proved to be correct, but also because of the philosophical purity of his method. For many of us, no one stands so firmly as a model in upholding the ideals of the scientific method.

Peter Mitchell the man was an unusually attractive merger of erudition with *joie de vivre* and gentle good humor. He projected this positive energy with such uncommon grace that he enriched the lives of all who knew and loved him. I remember hours of spirited scientific discussions, and most of all I remember laughter and the shared pleasures of good food and wine and good conversation. At the end, Peter was neither fearful nor resentful of death and expressed gratitude for having led a full and happy life. His many friends are also grateful for their joyful memories of him. Peter died quietly at Glynn on 10 April after a brief illness.

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