Wandering in the Gardens of the Mind: Peter Mitchell and the Making of Glynn

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Peter Mitchell received the Nobel Prize in Chemistry, in 1978, for his "contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory." The authors describe the development of Mitchell's theory as he worked a) as a graduate and postdoctoral student at Cambridge University (1942–1955), b) on the faculty at the University of Edinburgh (1955–1964), and c) as the director of the Glynn Research Institute (1964–1987). Glynn is a mansion that Mitchell renovated and turned into a personal research institute, located near Bodmin in Cornwall, England. *Gardens of the Mind* is the title of a BBC interview in which Mitchell compared the human mind to a garden where facts and ideas are planted, which one keeps on rearranging. After his death in 1992, Helen Mitchell (his second wife) created a garden at Glynn with a plaque that is inscribed "Remembering Peter Mitchell in whose gardens of the mind we wander in joy and gratitude."

Mitchell proposed the chemiosmotic theory in 1961. This theory describes the link between oxidation and phosphorylation (ATP synthesis) as a proton and voltage gradient across biological membranes. Electron transport creates the gradient, and the gradient is used to drive ATP synthesis. The older, alternative hypothesis of oxidative phosphorylation, developed from ideas of Fritz Lipmann by W.C. Slater, was that respiration produced a non-phosphorylated, energy-rich intermediate (~X) that leads to ATP formation. At the time that Mitchell proposed his hypothesis there was not a shred of evidence in support of it, and this led to a conflict between Mitchell and the "establishment."

The authors obtained their information from interviews with Mitchell, letters written to and from Mitchell, and from the scientific literature. The authors interviewed Jennifer Moyle, an important collaborator with Mitchell for more than 30 years. The authors also interviewed approximately 60 people who worked in bioenergetics and in biochemistry; and these sources are cited in the *Notes* section at the end of the book. In addition to relating the development of the theory, there is considerable material about Peter Mitchell's personal life and the interaction of his science and philosophy.

Mitchell came from an upper middle-class family with money that enabled him to afford a Rolls Royce in the 1940s. He attended college in Cambridge at the time of World War II, where he was known for his flamboyant dress: a burgundy purple jacket, shirt open as far as the waist, and shoulder-length hair—Mitchell's eccentricities are found throughout the book.

Mitchell worked for his doctoral degree in the Department of Biochemistry at Cambridge, at the time one of the leading programs in the world. The department was headed by F.G.H. Hopkins, a 1929 Nobel Prize laureate in Physiology or Medicine, for his work on growth-promoting vitamins. Hopkins was universally courteous, and he even had " a capacity to suffer fools gladly." Mitchell became a research student with James Danielli, a noted membranologist. Mitchell combined the ideas of Hopkins on the dynamic aspects of biochemistry and those of Danielli on membranes, and this combination led to the chemiosmotic theory. Fred Sanger was in the Department at Cambridge with Mitchell, and we are told that Mitchell was surprised when Sanger won his first Nobel Prize because Mitchell did not think that Sanger was that smart.

Mitchell's research during the Cambridge years was good but not outstanding. His first dissertation was rejected by the examining committee. David Keilin remarked that "Peter is too original for his examiners." Mitchell's second dissertation was on the mechanism of action of penicillin on bacteria, which passed muster, and he received a Ph.D. in 1950. Some of his early experiments lacked important components, and this prompted Hans Krebs to mutter, "But he hasn't done the controls," while listening to a presentation of Mitchell's in the 1950s.

David Keilin, who was the director of the Molteno Institute, was a major influence on Mitchell at Cambridge. Keilin discovered and described cytochromes, and during his Nobel lecture, Mitchell acknowledged Keilin's great influence. The authors quote a story about a prank that Keilin performed at a formal party that delighted Mitchell, as he was not accustomed to seeing a professor behave in this fashion. In his last year at Cambridge, Mitchell and Jennifer Moyle performed experiments on phosphate uptake into bacteria, and this work led him later to the study of the mechanism of oxidative phosphorylation.

Mitchell was more creative and productive at Edinburgh than at Cambridge. It was during this period that he began to link metabolism with membrane transport. He sought a holistic approach to biology, and this involved theory that was well ahead of experimental evidence. One of the main points of this biography is that, for Mitchell, theory came first and experiments later. This is opposite to the strategy of most scientists for whom experimental results come first, and theories to explain the results come later.

When Mitchell began thinking about oxidative phosphorylation, he corresponded with W. C. Slater to learn the state of knowledge of the field. Mitchell also corresponded with R. J. P. Williams, who had the idea that intramembranous protons played a role in polyphosphate synthesis. However, Mitchell never mentioned this correspondence or Williams' papers on this subject when he published his first paper on the chemiosmotic theory. The relationship between these two was acrimonious from then on. The biography contains considerable information on the many polemics that characterized the "ox phos wars." "The oxidative phosphorylation field had the reputation that if you went to a Federation meeting, all the meetings were crowded because everybody . . . knew there would be a damned good fight there."

The authors describe the creation of the Glynn Research Institute and the renovation of the Glynn mansion into a home and laboratory. Because of bothersome problems associated with academia, Mitchell was skeptical about whether universities were appropriate places to carry out creative work. Jennifer Moyle moved to Glynn with Mitchell as a research collaborator, and the two of them were the directors of the Institute.

There is an extensive discussion of Glynn as a research institute, including its staffing, finances, and the refuge that it provided Mitchell. The number of workers, including Mitchell and Moyle, ranged from five to 10. Glynn was isolated, but Mitchell invited workers to spend a few days there to conduct experiments or for discussion. The Glynn Research Institute published a *Gray Book*, in 1966, in which Mitchell introduced the concept of the proton motive force and elaborated on his other ideas of oxidative phosphorylation. This small book marked the point from which a real interest in the chemiosmotic theory began. Copies were distributed to scientists working in bioenergetics, including Fritz Lipmann.

In 1971, I was a postdoctoral fellow with Lipmann, and I asked him what he thought about the Mitchell hypothesis (as it was called then). He told me that he thought that it was correct because it was general. At that time there were only a handful of scientists who accepted the notion. In 1975, as an assistant professor, I asked Hans Krebs what he thought about the Mitchell hypothesis. He said he thought it was wrong because it was too general! Then he added that the formulation of the hypothesis was important because it stimulated considerable good research.

The authors describe the difficulties in determining the number of protons that are translocated per electron pair, transported from NADH to oxygen. The values ranged from six to 12. The precise stoichiometry is still in question, 25 years later, although most scientists seem to accept a value of 10 determined by Peter Hinkle in 1992. Hinkle studied at Glynn in 1968 after receiving his Ph.D., and he described firsthand the close collaboration of Mitchell and Moyle. Hinkle served as an interpreter of the chemiosmotic theory in the United States at Cornell University, where Efraim Racker and Andre Jagendorf were working.

There is a complex story about the creation of the several reviews on oxidative phosphorylation that occur in the *Annual Reviews of Biochemistry*, in 1977. This is probably the only issue of *Annual Reviews* that contains several chapters devoted to a single topic. Racker sought to publish these reviews, and it required his considerable effort to gain the consent of the authors in putting these papers together. One motive for publishing them was to improve the image of bioenergetics and thereby enhance the prospects for funding. The reviewers included Paul Boyer, Briton Chance, Lars Ernster, Peter Mitchell, Efraim Racker, and W.C. Slater. Racker accepted the chemiosmotic theory in principle, while the others (except Mitchell) were uncommitted.

These reviews of the state of oxidative phosphorylation may have paved the way for the Nobel committee to seriously consider the chemiosmotic theory. Mitchell received the award in 1978, and his wife, Helen, and Jennifer Moyle attended the ceremonies with him. The award was not for the theory but for his contribution to an understanding of the process of energy transfer. The Nobel selection committee was aware that Mitchell's ideas on how the proton gradient is generated and how the ATP synthase operates were wrong. I heard a prominent biochemist state that Mitchell received the Nobel Prize for "bioimagination."

Mitchell considered leaving the bioenergetics field, but there was a controversy on whether cytochrome oxidase could pump protons. Mitchell thought it could not, and the story of his long conversion to accept the results requires a chapter. Mitchell seems to have never accepted the idea that changes in protein conformation might play a role in ATP synthesis. His notion was that almost anything could be explained by this idea, and it did not lead to precise experiments. Nevertheless, Paul Boyer received the Nobel Prize in Chemistry, in 1997, for his work on the elucidation of the enzymatic mechanism underlying the synthesis of ATP, reflecting protein conformational changes.

The book gives a complete story of Mitchell as a person and as a scientist. His various illnesses took their toll. He had gastric ulcers from time to time, during which he was forced to stay away from work. He became deaf, and he suffered from a botched surgical procedure in 1972 that was performed to alleviate this problem. As a result of the operation, he developed intermittent vertigo, or dizziness, and he had noises in his ears that made sleep difficult. He also suffered a nervous breakdown—called hysterical dissociation—in 1977.

His dalliances are chronicled, but he was able to put such matters out of his mind. Some 10 years after the divorce from his first wife, Eileen, he attended the wedding of their daughter, and he noticed a woman who looked familiar. He asked whether he knew her, and she replied, "Yes, I was your first wife!"

In this engaging and thoughtful book, the authors describe the personality and idiosyncrasies of Mitchell in an even-handed fashion. They have done a superb job in tracing the development and eventual acceptance of the chemiosmotic theory by the scientific community. This biography is informative and can be read profitably by undergraduate students, "mitochondriacs," and scientists of all persuasions. This book also is highly recommended for those with an interest in bioenergetics.

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Cellular and Molecular Immunology (5th Ed.)
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Whereas biochemistry depends heavily of the tools of immunology for its progress, our understanding of immunology depends increasingly on the techniques of cell biochemistry and molecular biology. This sentence could be made into an excellent examination question by adding "Illustrate" or "Discuss," but it would be a "big" question. We are fortunate now to have a number of excellent immunology textbooks that attempt to explain the details of this ever-expanding field, and that also of course have the most far-reaching medical significance. On the whole, students like immunology and see its relevance, but are more and more challenged by its complexity. Hence the need for good text books.