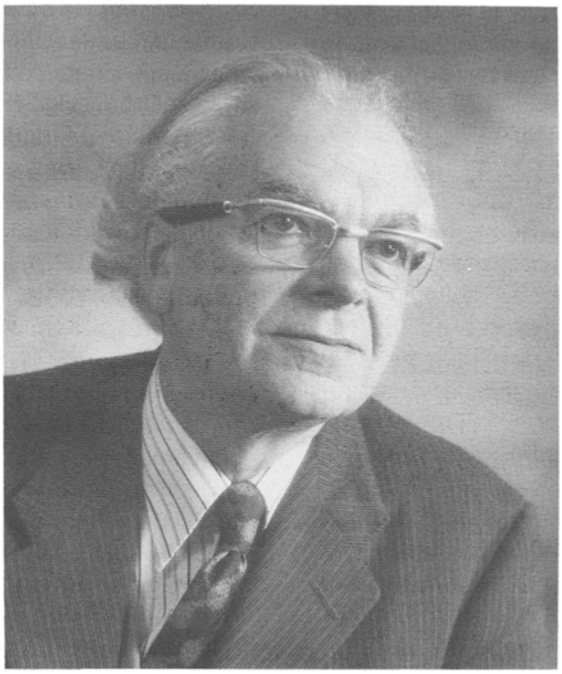
Photosynthesis Research **35**: 1–4, 1993.

Obituary



Peter Mitchell (1920–1992)

Peter Mitchell died last April. His passing marks an era in which the chemiosmotic hypothesis introduced a revolution which has echoed beyond bioenergetics to all biology, and shaped our understanding of the fundamental mechanisms of biological energy conservation, ion and metabolite transport, bacterial motility, organelle structure and biosynthesis, membrane structure and function, homeostasis, the evolution of the eukaryote cell, and indeed every aspect of life in which these processes play a role. The Nobel Prize for Chemistry in 1978, awarded to Peter Mitchell as the sole recipient, recognized his predominant contribution towards establishing the validity of the chemiosmotic hypothesis, and *ipso facto*, the long struggle to convince an initially hostile establishment.

The seeds of the chemiosmotic hypothesis, which lay in Peter's attempts to understand bacterial transport and homeostasis, were pollinated by the earlier ideas of H. Lundergärd, Robert Robertson, and Robert Davies and A.G. Ogston, on the coupling of electron transport and ATP synthesis to proton gradients. Mitchell's 1961 paper in *Nature* outlined the hypothesis in the form of several postulates which could be subjected to test. In retrospect, it was a great strength of this first paper that Peter did not go into too much detail; the ideas were new and strange, and were introduced to a field dominated by a few major laboratories with their own different ideas about how the coupling between electron transport and phosphorylation occurred. It is interesting to look back and remember how sparse the clues were on which the hypothesis was based. At the time, the chemical hypothesis, based on analogy with Ephraim Racker's mechanism of substrate level phosphorylation linked to triose phosphate oxidation, seemed secure. A few niggling difficulties were apparent. Why did so many different reagents act as uncouplers? Why were the enzymes of oxidative phosphorylation associated with the mitochondrial membrane? Why did coupling seem so dependent on the maintenance of structure? How did mitochondria maintain their osmotic balance? How did substrates get in and out? But these must have seemed second-order problems to the main protagonists. It was these niggles that Mitchell's hypothesis addressed.

I first met Peter in 1962 when he visited Brian Chappell in Cambridge to talk mitochondriology. I was in my second year of Ph.D. research, and becoming familiar with the field. Brian had, at the start of my apprenticeship, set me to work in the library with Peter's 1961 paper as a starting point. I must confess that I had little idea at the time of the importance of the paper; I didn't know enough, either of the background bioenergetics or the physical chemistry, to understand what the issues were. But by the time of Peter's visit, I had become involved in the work on mitochondrial ion transport initiated by Brian in collaboration with Guy Greville, and Brian had become interested in mechanisms. Peter arrived in an elegant if ancient Bentley convertible, and wrapped us in a corduroy enthusiasm. He was in trouble with his hypothesis, because three labs claimed to have disproved it by isolating the intermediates expected from the chemical hypothesis. Peter was undaunted, and engaged in a mischievous discussion of the data and its validity. The challenge of the upstart chemiosmotic hypothesis to the prevailing chemical view of mechanism was to become a running battle, in which Peter engaged the establishment single-handed for several years before the first of a growing band of brothers (and sisters) joined him in the fray. The early work from André Jagendorf's lab on H^+-uptake and pH-jump driven ATP synthesis by chloroplasts, the parallel work on ion and metabolite transport in mitochondria from Chappell's lab, the work on ionophores and uncouplers by Bert Pressman, and by Brian Chappell and myself, the development of 'artificial' membrane systems by Alec Bangham and by Paul Mueller, and Mitchell's own work with Jennifer Moyle on proton measurements following O_2 pulses, had demonstrated before 1965 the activities expected from the hypothesis, but it was to be ten years before the established leaders in the field were coaxed into a grudging acceptance of the hypothesis.

The bones of the chemiosmotic hypothesis were fleshed out by Mitchell in subsequent publications, most notably the two slim volumes published by Glynn Research Ltd. in 1966 and 1968, known affectionately in the laboratory as the Little Grey Books of Chairman M. Mitchell's views were discussed in detail in an important review, A Scrutiny of the Chemiosmotic Hypothesis by Guy Greville, published in 1969, which established the seriousness of the challenge. The field was evolving rapidly, and to those of us on the chemiosmotic side, the body of evidence favoring that point of view looked overwhelming. The hypothesis found early favor among the photosynthetic community, perhaps because of the elegance of the early demonstrations from Jagendorf's lab, the explanation of amine uncoupling, the utility of the electrochromic membrane voltmeters, perhaps also because of the more physico-chemical bent of the field. The eventual acceptance by the biochemical community came with the demonstration of reconstituted proton pumping activities for the isolated and purified enzymes of respiratory and photosynthetic chains in liposomes, mainly from Racker's group, and the demonstration of coupled phosphorylation in the chimeric bacteriorhodopsin-ATP-ase liposome system by Walter Stoeckenius and Racker. Another important element was the growing physico-chemical sophistication of the bioenergetics community, especially among the younger research workers.

Readers of *Photosynthesis Research* will need no guide to the present status of chemiosmosis. The ideas Peter Mitchell introduced, which seemed so rare at the time, are now the common currency of all our discussions. The field has gone on to explore the deeper ramifications, from molecular mechanism at one end, through the compartmentalization of the eukaryote cell and metabolic integration, to evolution at the other. Although the chemiosmotic hypothesis was Peter's most important contribution, he continued to introduce new ideas, include the Q-cycle hypothesis, which has dominated discussion of the mechanism of electron transfer and proton pumping in the quinol oxidizing complexes since 1975, and now seems well established as the basic mechanism. I found myself initially on the opposite side of the Q-cycle controversy. Of course, there seemed to me perfectly good reasons for thinking that the Q-cycle as then formulated was wrong, and Peter was always attentive in listening to them. In trying to account for our objections (based on observation of electron transfer kinetics in photosynthetic bacteria), he quite early pointed out that the role of the Rieske iron–sulfur center might be crucial ('Don't you think the electron might be getting hung up on the Rieske?'). Our own results subsequently showed this to be the case, and led us to a modified Q-cycle mechanism which was among the models discussed by Peter in his 1976 review (see Mitchell 1976).

Although Peter won most of his battles, he suffered a few defeats. The long controversy about the proton-pumping activity of cytochrome oxidase involved some fairly heated debates before it finally went to Mårten Wikström; and it looks as if the mechanism of ATP synthesis through the F_1–F_0 ATP-ase is more along the lines envisaged by Paul Boyer than through Peter's earlier proposals. In both these cases, with the benefit of hindsight it looks as if Peter underrated the role of the protein and the subtlety of evolution in designing molecular mechanism. It was part of Peter's charm that, no matter how strongly he held his views, his stance was based on sound principles and experimental results, was always well argued, fair, and devoid of malice. When convinced, he conceded graciously; if his own views prevailed, he was happy to recognize the contributions of his opponents, and his unfailing habit of giving credit where credit was due allowed for an easy reconciliation.

Peter's contributions have been formally recognized through the many honors, prizes and degrees conferred on him over the years. He was a Fellow of the Royal Society, a Foreign Associate of the National Academy of Sciences (USA) and of the Académie des Sciences Française, Honorary Fellow of the Royal Society of Edinburgh, Fellow of Jesus College, Cambridge (his *alma mater*), and an Honorary member of the Society of General Microbiology, and the Japanese Biochemical Society. He received honorary doctorates from the Technical University, Berlin, the Universities of Exeter, Chicago, Liverpool, Bristol, Edinburgh, Hull, East Anglia, Cambridge and York. Among other honors and prizes awarded were the CIBA Medal and Prize of the Biochemical Society in 1973, the Warren Triennial Prize (jointly) from the Trustees of the Massachusetts General Hospital in 1974, the Freedman Foundation award of the New York Academy of Sciences in 1974, the Feldberg Foundation Prize in 1976, the Rosenberg Award of Brandeis University in 1977, the Lipmann Lecturer, Gessellschaft für Biologische Chemie, 1977, the Medal of the Federation of European Biochemical Societies in 1978, Nobel Laureate in Chemistry in 1978, the Copley Medal of the Royal Society in 1981, and the Medal of Honor of the Athens Municipal Council in 1982.

The dry facts of Peter Mitchell's life do him scant justice, and although he was at ease with his fame, I am sure he would not wish to be remembered simply in terms of the many prizes and honorary degrees heaped on him. Peter listed among his leisure interests (and here I quote from the International Who's Who), family life, home building, the creation of wealth and amenity, the restoration of buildings of architectural and historical interest, music, thinking, understanding, inventing, making, sailing. I can picture him filling out the questionnaire which elicited this list. There would have been a wry amusement in the task of defining himself, and a certain self-deprecation, but Peter would have tackled the job with characteristic honesty, diligence and intelligence.

Glynn House and Glynn Research Ltd. (later the Glynn Research Foundation), were the happy outcome of a spell in hospital in the early 1960s. On the recommendation of his doctor, Peter was looking for a vacation home in the South where he could recuperate. The estate agent showed him the burnt-out shell of a country mansion, and Peter, more in jest than earnest, said he would give £x,000 for the lot. He was surprised when, a few weeks later, the man called him in Edinburgh and said It's yours. Using his private resources, Peter had the building remodelled, with the west wing as a residence, and the east wing and adjoining areas as research laboratories, library, seminar room, workshop, etc., to accommodate a small research group.

Over the years, Peter and Helen welcomed many friends and colleagues to the now beautifully restored Glynn House, and were unfailingly gracious and hospitable. Friendships were important to Peter. He enjoyed conversation, and treated topics both high and low with a mixture of deep seriousness and impish humor. Discussions were a test bed for his latest ideas, and he relished the pursuit of odd angles and new perspectives. He held the view that science progresses though open discussion, and abhorred the notion that ideas or information should be closeted away, hidden from 'the competition'.

Peter's approach to science was based on philosophical principles; he was interested not only in the science, but in the mechanism of scientific discovery. He was fascinated by the nature of creativity, the practice of science as a social system, the validation of scientific 'truth' – indeed, the whole process of science in action. He was much affected by Popper and his ideas about the scientific method, and Popper's influence can be seen in Peter's insistence that hypotheses should be framed in the context of experimental tests. He regarded experimental results as of prime importance, and was as much interested in the intriguing observation as in the author's interpretation. He believed strongly that science advances through the contributions of individuals, and that each individual is responsible for selection or discrimination with regard to any piece of information. He thought that much of the effectiveness of a successful scientist lay in the adequacy of this filtration process. This view was captured in a nice remark he once made to me, that 'The trouble with most scientists is not that they don't have good memories, but that they don't have good forgeteries.' Although in private he was not reluctant to criticize, he was generous and helpful in his more public interactions, and treated with respect the opinions of others, especially younger research workers coming into the field.

In the wider context of his social and political views, Hayek was an early influence, and Peter would emphasize the role of the individual, and freedom of economic and political expression. Much of his thinking in the last 15 years was directed towards human and social problems, especially towards identifying mechanisms for conflict resolution. In this context, he saw the bioenergetics community as a microcosm and a vehicle for experiment, and the Round Table Discussion meeting he organized at Glynn, was at least partly motivated by this interest. Although he had little time for socialism, he was a very human person, aware of his own foibles and vanities, and found through this a sympathy with the common human lot. His belief in the individual was tempered by a recognition that in a rational order, rights are earned and exercised in the context of the responsibilities each owes to society. He held to a set of standards, those of the gentleman, which many would see as archaic, and these and his talents raised him above the fray. His inspiration, humor, friendship, and the high standards of scholarship and behavior he brought to our field will be sorely missed.

I am grateful to Helen Mitchell for her kindness in supplying the picture of Peter Mitchell.

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June 29 1992
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