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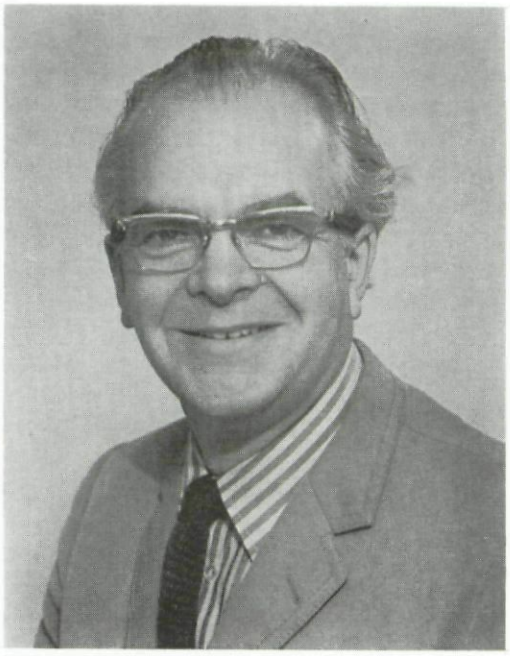
Obituary
In memoriam: Peter Mitchell, 1920–1992

Peter Mitchell's recent death gives us an appropriate opportunity to reflect on a great man and a great scientist. Readers of this obituary will already know the main features of the life and scientific contributions of Peter Mitchell. They will have read the obituaries by Garland in *Nature* (30th April, 1992), and by Hinkle and Garlid in *Trends Biochem Sci* (August, 1992). They will in any case know the biography in outline; the 1961 paper in *Nature*, the grey books, the 1978 Nobel prize for chemistry, etc. I should like therefore to take this opportunity to note some of the more microbiological and some of the lesser known aspects of Peter's life and scientific work.



Peter Mitchell, 1920–1992. (Photo reprinted with the permission of the Biochemical Society, London, UK.)

Pre-Glynn

After graduating in biochemistry at Cambridge in 1942, Mitchell's first scientific project was on thiol antidotes to arsenical poisons, the so-called British Anti-Lewisite or BAL, working at Cambridge under J. F. Danielli. His lasting benefits from this period seem to have been a warm appreciation of Danielli and Danielli's interest in membranes and surfaces. Danielli also introduced Mitchell to Keilin, who made a deep impression on the young man, though perhaps more emotional than intellectual. Mitchell's PhD thesis, however, dated 1950, was entitled 'Nucleic acid synthesis and the bactericidal action of penicillin', and it was then, immediately after the war, that Mitchell became, by accident (as he said), a microbiologist, working for part of the time in conjunction with the MRC Unit for Chemical Microbiology of which E. F. Gale had just become Director. He also started his long and very fruitful collaboration with Jennifer Moyle, which lasted 35 years until her retirement in 1983.

There are a number of papers from this period which are not much referred to these days — papers concerning various types of phosphate compounds, glycerophosphate–protein complexes, and the Gram stain. Mitchell and Moyle referred to one phopshate fraction as XSP (excess phosphate), and later positic acid (as this fraction was characteristic of Gram-positive organisms). This was eventually recognized as being the same as the soluble teichoic acid described some years later by Baddiley. Though Mitchell acquired many of the techniques of 'chemical microbiology', this was not to prove the arena of his finest contributions. He approached biology not as a chemist would, but always with the eye of an engineer; his models involved channels, articulations, balistics and pressures — mental equipment he brought from an engineering family background and a boyhood spent in his own (well-equipped) engineering workshop.

During the next five years (1950–1955) Mitchell held the post of University Demonstrator, a position he recognized to be privileged in that he had little teaching, and tended to get involved in everyone else's problems. With the freedom allowed him in this post, Mitchell started developing his ideas on membrane structure, osmotic forces, and transport processes, ideas that we now recognize to be the foundation stones of his *magnum opus*.

During these five years Jennifer Moyle was working with Malcom Dixon on pig-heart 'isocitric enzyme' (isocitrate dehydrogenase (NADP) decarboxylating, EC 1.1.42). Mitchell became very interested in one particular aspect of that work, namely the tight binding of the oxalosuccinate intermediate to the enzyme (off rate 0.012 min^{-1} according to Moyle). From that observation Mitchell (and Moyle)

developed the concept of a microspace inside the centre of the bifunctional enzyme in which oxalosuccinate, the product of one enzyme activity (the dehydrogenase) and the substrate of the second (the decarboxylase), could accumulate and exert a thermodynamic pressure — his concept of microchemiosmosis. I was always puzzled by this; first because no-one else talked of the enzyme in this way (or even referred to Moyle's work!), but even more because this idea is at variance with the experimental fact that oxalosuccinate, though it cannot leave the enzyme, can freely bind and react. I now realize that Peter Mitchell was not using the idea to explain the enzyme but the enzyme to explain the idea, an idea which 'nature' could have used though she perhaps chose not to in this case. This predominance given to the idea was a striking characteristic of Mitchell's thinking.

Another topic tackled by Mitchell in this period was the uptake across the bacterial membrane of phosphate and arsenate; in this field his engineering approach found more scope and his ideas seem to have been more incisively original, timely and sound. It is hard for us now to realize that at that time a large part of the microbiological community did not accept the necessary existence of a cell membrane, i.e. of an osmotic barrier at the cell surface. Mitchell's work on phosphate uptake was the first detailed study of the kinetics of transport in bacteria. His somewhat startling conclusion, however, that in resting organisms phosphate–phosphate exchange is more than a hundred times faster than either net influx or net efflux, was not taken up by others for some 30 years. Nor was it fully explained by Mitchell. He suggested that the most probable explanation was that a membrane protein became alternately phosphorylated and dephosphorylated, so that what traversed the membrane was not phosphate but phosphoryl groups. Though this model is not now believed to be correct, these experiments were undoubtedly important in the development of Mitchell's chemiosmotic thinking. There seemed here to be tight, almost perfect, coupling between two transmembrane fluxes, in this case the influx and the efflux of phosphate; but the Ussing/Widdas concept of antiport, thus dramatically exemplified, was easily extended at a later date.

During the late 1950s the idea of covalent chemical changes being concurrent with transport took a terrible grip on Mitchell's mind. He generalized and developed what he called the concept of group translocation. While acknowledging the elegance of Monod's proposal of separate permease and β-galactosidase proteins, Mitchell repeatedly pointed out that a membrane-bound β-galactosidase would suffice, and would allow the free energy of lactose hydrolysis to drive the accumulation of galactosyl and glucosyl units. Monod of course proved to be right; 'nature' had overlooked Mitchell's neat and simple scheme. Peter turned to glucose and discussed in several papers how glucose could enter a cell and become phosphorylated in a single co-ordinated process if the kinase enzyme were asymmetrically placed in the membrane. The translocated group would not be glucose, but glucosyl. Crane proved this to be wrong for rabbit ileum by showing that deoxy-analogues of glucose incapable of being phosphorylated could be taken up by intestinal preparations. Mitchell and Moyle also believed that succinate probably entered bacteria as succinyl groups (esterified e.g. to CoA) and suggested that amino acids might similarly be taken into cells by their activating enzymes. In all these examples 'nature' could be said to have let Mitchell down. But the idea of group translocation was a great idea. In the mid-1960s, Kundig, Ghosh and Roseman eventually described the bacterial phosphtransferase system in which sugars are indeed phosphorylated as they are translocated. Here is a nice example of the answer turning up before the question.

Experimentally, what had to be done was to establish reliably which enzymes were truly embedded in the membrane, and this Mitchell and Moyle set out to do. The picture that emerged may have been a bit devastating for the concept of group translocation, but it was obviously crucial to the development of the richer idea of the chemiosmotic proton cycle; for the enzymes strikingly present in bacterial plasma membranes were the dehydrogenases (and ATPase). What luck that Mitchell was working on bacteria!

The concept of the periplasm has become a commonplace, but it may not be widely known that both the word and the concept are Mitchell coinages; the result of looking at plasmolysed cells through a microscope. It is also worth remarking that the crucial experiments by which Mitchell and Moyle first showed that dinitrophenol catalyses the transfer of H^+ across membranes were performed on bacteria.

Cambridge will have many memories of Peter Mitchell. I have heard stories of a steam-filled lab, of a novel method for determining protein molecular weights, of black (protest) lab-coats. In Edinburgh, likewise, the attentive listener may hear of a slightly older Mitchell; a lively contributor to every discussion on every topic, an energetic man with a large head, a mischievous grin, and very tight trousers. It was at Edinburgh in the fifties, renovating the old manse at Carrington for his new family, that Peter acquired the taste for large-scale house-building, an enthusiasm that became perhaps the prime amongst his numerous interests. In 1963 Mitchell resigned his Readership at Edinburgh and invited Jennifer Moyle to join him in building and running a private laboratory amongst the rubble and litter of a derelict mansion in Cornwall.

Glynn

Cambridge and Edinburgh can only be seen as a

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preparation for Glynn. There, at last, the man and the scientist had scope. From that remote and isolated laboratory in its tranquil rural setting 'The Wizard of Bodmin' dazzled the scientific community for two decades with his virtuosity. It seemed he could predict and explain everything, for Mitchell's key unlocked door after door of the 'many-mansioned house'. He had conceived this time an idea that 'nature' had indeed exploited, to the full. Out of the laboratory Mitchell dazzled no less than in it. He built houses, and yachts, he farmed 150 acres, managed an estate of a dozen houses, sailed, minted silver pieces and copper-bottomed saucepans, and bottled and marketed spring water; and this seemed in no way to distract him from his science but to stimulate him rather, nor even to deprive him of the time to relax with his family or holiday on a Greek Island.

The reader will have seen formal photos of Mitchell in his middle and later years. Here are two completely different glimpses that hung unobtrusively for many years at Glynn House; one of an unbuttoned Mitchell driving a tiny tractor towing his youngest son in a trailer, and another showing a white-coated Mitchell parading a prize bull at the Royal Cornwall Show. Where the Glynn drive joins the main road there swung a modest painted sign; Britton Chance once teased Mitchell, while the sign announced the farmer to be Peter Mitchell, the picture above the name was not of himself but of a pedigree Jersey cow; but how could Brit know the way things are done down there in Cornwall. Peter got much closer.

Peter Mitchell was very competitive and relished controversy, but he was also very appreciative of the human and cultural things that enhance the quality of life, appreciative of people, of the humane; even if he occasionally found these feelings had to be subordinated.

We thankfully remember a man who had great intellectual gifts of memory and tenacity, great creative gifts of imagination, originality and energy, and great human gifts of zest, humour, and charm. Adieu, and thank you Peter.

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