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*History of Chemistry*

# Half a century of the chemiosmotic hypothesis and the practice of science

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**ABSTRACT:** *The first published outline of the chemiosmotic hypothesis of biological energy transduction was published fifty years ago. It took many years for the ideas to be accepted despite their elegance. We outline the basis and history of the hypothesis and consider what can be learnt from it about the development of new ideas in science and what is required to persuade the community of a new idea given a pre-existing model.*

**Keywords:** *chemiosmotic hypothesis; creativity; energy transduction; history*

## Introduction

The elegance of biological energy transduction remains unappreciated by too many biochemists and textbook treatments tend to be superficial and errors are common. In essence, reducing potential ($\Delta E$) drives electron transfer through a series of membrane-spanning enzymes. The electron flow is coupled to the transfer of ions (usually $H^+$) across the membrane, thereby generating a transmembrane chemical potential ($\Delta\mu$). The $\Delta\mu$ is dissipated in driving the phosphorylation of ADP by ATP synthase, thereby contributing to the 'phosphorylation' potential ($\Delta G_p$) needed to drive many intracellular reactions. Of course, $\Delta\mu$ also drives other processes, including the operation of the bacterial flagellar motor, metabolite transporters and polypeptide translocation.

The foundations of this view of the biological interconversion of energy are

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embodied in the chemiosmotic hypothesis published by Dr Peter Mitchell in 1961 [1] and outlined briefly below. It took many years and the beautiful experimental results obtained by Dr Jennifer Moyle [2-4] to convince the rest of the scientific community. This culminated in the award of the Nobel Prize for Chemistry to Mitchell in 1978 [5]. In the past half century the chemiosmotic hypothesis has moved from radical heterodoxy to orthodoxy.

While much remains to be understood about the mechanisms of biological energy transduction, our purpose here is to discuss what the story behind the chemiosmotic hypothesis illustrates about the nature of science and the attitudes of scientists towards unorthodox ideas.

## THE CHEMIOSMOTIC HYPOTHESIS

The chemiosmotic hypothesis is based on four postulates, which we paraphrase from Mitchell [1]:

i. electron transfer chains translocate $H^+$;

ii. ATP synthase functions as a reversible $H^+$- translocating ATPase;

iii. the membrane has a low effective $H^+$ conductance; and

iv. the membrane should have the carriers needed to permit metabolites to permeate, and osmotic stability to be maintained, in the presence of a high membrane potential.

The first three postulates should be taken to include the translocation of $Na^+$ (in *Vibrio* spp. [6] for example) and postulate (ii) should also be taken to include the bacterial flagellar motor [7] and other Δμ-dissipating systems. The first two postulates provide a link between the redox reactions that generate Δμ (specifically, $\Delta\mu_{H+}$ or $\Delta\mu_{Na+}$) and processes that dissipate it. The third postulate is necessary in order that a significant $H^+$ or $Na^+$ concentration gradient can be maintained across the membrane, corresponding to an energized state. The fourth postulate reflects the need for various ions and metabolites to flow across energy transducing membranes. Parenthetically, we have observed a tendency to refer to this model as 'chemiosmosis', which Mitchell himself regarded as "a term of abuse" [8].

These postulates lead to a model of energy transduction in which the enzymes that catalyse redox reactions translocate $H^+$ or $Na^+$ across the membrane in which they are located generating a relatively positive (*p*) phase and a relatively negative (*n*) phase. The ATP synthase dissipates the potential energy in the charge gradient in the synthesis of ATP. Clearly electron transfer and the Δμ-dissipating systems are interdependent and together exert significant control on metabolism.

Before the widespread acceptance of the chemiosmotic hypothesis, many biochemists searched for the 'high-energy intermediate' coupling electron transfer to ATP synthesis. This intermediate was usually referred to as ~P ('squiggle' P) [9], because all sorts of 'high-energy phosphates' were identified. Mitchell's great contribution was to apply Guggenheim's [10, 11] thermodynamic formalism to the inner mitochondrial membrane, the chloroplast thylakoid membrane and bacterial plasma membrane. This led him to realise that the ~P sought by so many was actually $\Delta\mu$. Sadly, ~P can still be seen in references to the 'high energy bonds' of ATP [12, 13], which persist despite the well-known fact that the $\Delta_r H^{0\prime}$ of hydrolysis of ATP is smaller than that of other phosphates such as phosphoenolpyruvate [14, 15]. Two factors make ATP so useful: (i) the activation energy of hydrolysis is more than 100 kJ $\text{mol}^{-1}$ [16, 17] and so ATP is very stable, and (ii) the *in vivo* mass action ratio is many orders of magnitude smaller than the equilibrium constant. It is this disequilibrium that explains the usefulness of ATP hydrolysis rather than the strength of the phosphoanhydride bond.

## SOME HISTORICAL BACKGROUND

Much of Mitchell's work was carried out at the Glynn Research Institute located in a large house on the edge of Bodmin Moor in Cornwall. He had left the University of Edinburgh after being diagnosed with an ulcer and during a subsequent holiday he found the ruin that he restored and built into the Institute, with financial support from his brother. Once the building work was completed Mitchell invited Dr Jennifer Moyle to work in the Institute and, together, they carried out ground-breaking work. The fascinating histories of Dr Mitchell, the Glynn Research Institute and the chemiosmotic hypothesis have been reported previously [18-20].

The Institute was a remarkable place for many reasons, but one example might provide an illustration. In the 1990s the central hall of the Institute housed, among other things, a map of the world studded with pins representing all the labs working on biological energy transduction in 1967. A sea of white pins indicated those rejecting the chemiosmotic hypothesis; three red pins (marking the location of the Institute, and of Moscow and Baltimore where Professors Vladimir Skulachev and André Jagendorf, respectively, worked) represented those who accepted it.

The Glynn Research Institute developed into an important centre that attracted many eminent scientists from all over the world despite its relative remoteness. For example, the patrons of the parent Glynn Research Foundation included five Nobel Prize winners and the 25th anniversary of the Institute was commemorated by a conference in the Institute that was attended by bioenergeticists from all over the world. Following the death of Dr Mitchell in 1992, the Institute survived for only a short time [20], although a laboratory at University College London retains the name.

## THE NATURE OF SCIENCE

The history of the development of the chemiosmotic hypothesis illustrates several ideas about the nature of science. Specifically, it provides some insight into what is needed to (i) develop new ideas and (ii) persuade the community of a new idea given an accepted model.

Science is a good tool for pursuing logical sequences, but it requires imagination to make progress. For example, Jacques Hadamard [21] concluded that "... strictly speaking there is hardly any completely logical discovery. Some intervention of intuition issuing from the unconscious is necessary at least to initiate the logical work." In essence, a different perspective is necessary, which requires the freedom to think unconventionally and a broad background that enables the problem to be considered in a variety of ways.

Some physical isolation can be helpful in fostering the development of new ideas because daily interactions do not reinforce conventional patterns of thought. For example, Darwin spent five years without the daily company of other scientists on the Beagle during which he established habits that served him for the rest of his life [22]. On his return to England, Darwin chose to live rurally [22], which, combined with the effects of poor health, saved him from "... the distractions of society and amusement" [22]. The years 1665 and 1666, when plague forced Isaac Newton to live in relative isolation away from Cambridge, are often said to be the time when he did his most important work. Another example is Einstein, of whom Pais [23] remarked on his 'apartness' and Gardner [24] reported that he "... lived in solitude in the country and noticed how the monotony of quiet life stimulates the creative mind" (although we have been unable to identify the original source of this).

A broad technical background is especially helpful because new ideas are often identified at the intersection of research fields. Within a field there can be a tendency to employ well-established reasoning, perhaps even when it is clear that they do not work well. In the case of energy transduction, the application of physical chemistry was sufficiently novel in a field obsessed with the search for ~P. There is an historical precedent for this: the physicist Max Delbrück and his colleagues applied physical chemistry to nucleic acids and gene expression, thereby laying the foundations of molecular biology. According to Gunter Stent, Delbrück thought that the biochemists of that period had an "... agenda of explaining the simple through the complex" [25]. The long search for ~P might have prompted a similar assertion.

It is inevitable that the scientific community is resistant to new ideas because it requires substantial evidence to displace an accepted paradigm. However, this process is hindered by the use of demanding language and challenging concepts.

The language employed is important: what is ridiculous and incomprehensible to some might be a revelation to others. Mitchell suggested that the acceptance of the chemiosmotic hypothesis was delayed because it "…looked superficially more like physics than chemistry…", so it was not well received by biochemists [26], but he also suggested that communication was hindered "… because the basic concepts and attitudes of mind were so different …" [26]. Even those who were persuaded by the chemiosmotic hypothesis relatively early found Mitchell's presentation challenging. For example, André Jagendorf described Dr Michell as "... a ridiculous and incomprehensible speaker" [27] after their first encounter at a conference in Sweden. But for the intervention of a colleague [27], Jagendorf might not have been one of the early supporters of the chemiosmotic hypothesis.

Science shows tremendous resistance to change [28, 29] and it takes extraordinary perseverance to persuade the community. Almost 20 years separated the first description of the chemiosmotic hypothesis [1] from the award of the Nobel Prize to Mitchell [5]. During much of that time only a small number of laboratories were working on the hypothesis and there was considerable antipathy. Mitchell wrote that "... the existing large-scale system of communication in science often tends to encourage competitive antagonisms rather than open-minded appreciation …" [26]. There are many examples of ideas that subsequently prove to be highly influential being rejected arbitrarily by journals or treated with scepticism [30, 31], but there is no way of determining how many potentially useful ideas are lost just because they are unconventional. It might be argued that the diversity of funded research projects is limited by the the growing cost and proliferation of large-scale research, such as the multi-centre programmes supported by both the European Union and the Wellcome Trust, in a context of limited funding. One consequence of this is that it may be increasingly difficult to accumulate the evidence required to persuade the scientific community of unconventional ideas.

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