Peter Mitchell and His Chemiosmotic Theories

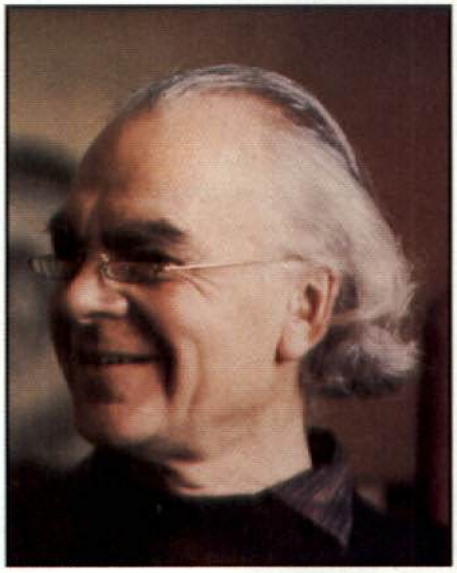
Ridiculed at first, Mitchell's ideas about proton motive force proved to be visionary

Milton H. Saier, Jr.

During his life, Peter Mitchell put forth such radical ideas concerning cellular energetics that some scientists considered him a crackpot. Today, however, he is recognized as one of the most original and insightful biologists of all time. His chemiosmotic theories provide the basis for understanding a variety of energy interconversion mechanisms in living organisms.

In 1978, Mitchell received the Nobel Prize in Chemistry for his ideas and work on biological energy generation, processes he termed "vectorial metabolism." Prior to that time, intense conflict, lasting nearly two decades and termed by many the "Chemiosmotic Wars," had divided scientists concerned with the mechanistic bases of photosynthesis, oxidative metabolism, molecular transport, and cellular motility into bitterly feuding camps. During this period, the eccentric Mitchell worked in a secluded research institute of his own creation in Cornwall, England, with only a few devoted followers to establish the validity of his chemiosmotic hypotheses. Only in the late 1970s did he achieve wide recognition for his insightful concepts and relentless work. He died of cancer on 10 April 1992 at the age of 71.

Mitchell was an intellectual dynamo who nearly single-handedly revolutionized our ideas about how photosynthesis and the metabolism of foodstuffs are coupled to the synthesis of the chemical energy currency of the cell, adenosine triphosphate (ATP). As such, he is an important part of science history and therefore worthy of study for his own sake.



Peter Mitchell

But there are other reasons for examining the development and accomplishments of this one man.

Mitchell was a heretical but prophetic scientist; it took the scientific community nearly 20 years from the time he formulated his ideas to acknowledge his theoretical contributions. What intellectual, psychological, and social factors provided him with visionary insight into previously unexamined natural processes? What were his primary theoretical contributions to science, and to what extent did his predictions prove to be correct? Perhaps by examining the life, philosophy and accomplishments of Mitchell, we can gain an understanding of the attitudes and conditions which promote (or thwart) the personal development of productive creativity and individuality.

Milton H. Saier, Jr., Professor of Biology at the University of California, San Diego, studies membrane transport processes. He has recently completed a biography of the late Peter Mitchell.

Mitchell's Early Development Provides Few Clues to Later Genius

Peter Dennis Mitchell was born on 29 September 1920. His father, Christopher Gibbs Mitchell, was a talented engineer who, by the end of his life, had designed road systems for about one-fifth of England, an accomplishment for which he was awarded an O.B.E. (Order of the British Empire), which he used to call his "Old Boiled Egg." Peter's mother, Kate, on the other hand, was an imaginative musician and artist with little knowledge of science or mechanical devices. Partly because of their differences, the parents constantly bickered, and the young Peter wondered why they didn't just stop their fussing and be more sensible. After they separated, Peter and his older brother Bill were brought up by Kate, who passed on to them her appreciation of art and music, her atheistic beliefs, and her conviction that rules and regulations were to be regarded with suspicion. It was each person's responsibility to question dogma and to act in accordance with the dictates of reason.

As boys, Bill and Peter had few outside friends, and, when not together, they became solitary individuals who preferred their activities to the company of others. They frequently undertook tasks together, building machines or concocting explosives, with Bill reading about the project and dictating a course of action while Peter performed the work. When accidents occurred, their mother merely affirmed the responsibility of the experimenter for any fault without expressing disapproval. Her admiration for Peter provided him with incentive to develop his exploratory ambitions and analytical pursuits. Surprisingly, his childhood interests in electrical and mechanical devices later proved applicable to biology.

Peter's primary schooling was highly structured and disciplined. He was responsive to praise and reward but sensitive to criticism and punishment. In response to punishment for poor performance, he tended to forget facts under pressure. Only when related details were integrated into a meaningful working framework or hypothesis could he master them. Intelligence and aptitude tests taken at the age of 12 seemed to show that he was of only slightly above average intelligence, although his problem solving and mechanical abilities were decidedly superior. He performed so poorly on the Cambridge University entrance exams that his entry into Cambridge was initially denied and depended on a special intervening letter from his headmaster.

Early Solitary Habits Continue at Cambridge

In October, 1939, at the age of 19, Peter arrived in Cambridge to begin what would prove to be a 16-year stay, first as an undergraduate, then as a graduate student, and finally as a laboratory instructor. He retained his solitary habits, taking long morning walks and spending his spare time reading, playing the violin, studying philosophy, and talking with a few close friends. In his undergraduate years he was particularly influenced by two devoted lecturers: Ernest Baldwin, who had written some early textbooks in biochemistry, and Edgar Adrian, who taught nerve physiology and the movement of charged particles or ions across membranes. During his graduate studies, three instructors, each working in a different area of biochemistry, served as his primary teachers. These were James Danielli, who worked on membranes; David Keilin, who characterized the mitochondrial respiratory chain; and Malcolm Dixon, an enzymologist. Danielli, together with his friend and fellow student Hugh Davson, formulated a revolutionary model of cell membranes and then proposed how molecules pass through them. Keilin studied electron flow in mitochondria, suggesting that electrons pass sequentially from substrates to a variety of proteins before they reduce molecular oxygen to water. Dixon exposed Mitchell to the vast and rapidly advancing field of enzymology, forcing him to put his views of vectorial metabolism within a firm molecular framework. Although Mitchell often had difficulty in mastering new subjects, he worked devotedly and claimed that "being a good student is like being a good baby: if you're not getting enough, you're probably not sucking hard enough."

At the end of his second undergraduate year at Cambridge, Mitchell barely passed his first exam in Natural Sciences, which included Mathematics, Physics, Chemistry, Physiology, and Biochemistry. At the end of his fourth year he took his second exam in Biochemistry and did somewhat better. The fact that Einstein had received comparable low marks proved reassur-

ing to Peter. The additional fact that many less worthy students of the sciences had also received low marks did not seem to concern him at all. Mitchell was curious about the world and the nature of humanity, not about its view of him.

During his Cambridge years, Mitchell often paced about the laboratory in sandals and unconventionally colorful Bohemian attire with a lion-like look, blond hair flying. He started numerous projects, typically disappearing into a dimly lit room where he would carry out an experiment, only some of which he would finish. Frequently it was his assistant, Jennifer Moyle, who brought the experimental work to a reasonable state of fruition. Because his original Ph.D. thesis was rejected by his examining committee, he was forced to devote nearly three additional years to the study of penicillin, a topic he found of marginal interest, in order to receive his Ph.D.

His views were considered heretical for many years, but they provided key insights into how cells produce and use energy

Ideas from Greek Philosophy Shape Notions about Membranes

During his student years, Mitchell became intrigued with early Greek philosophy. The Greek experimental view of truth seemed to provide a foundation for modern scientific thought. Heraklitus had said, "You cannot step twice into the same stream because although the river is the same by name, the water has flowed on." Plato more concisely stated: "All things are passing, and nothing abides." And Aristotle reiterated: "All things are in motion; nothing steadfastly is." According to Mitchell, this central principle of the Greek philosophers also encompasses chemistry and physiology. Chemistry relates to the states of molecules and their transformations (statids, or scalar quantities) but is insufficient as a sole description of life (see table). Living things are among the *flowing* things (fluctids, or vectorial quantities).

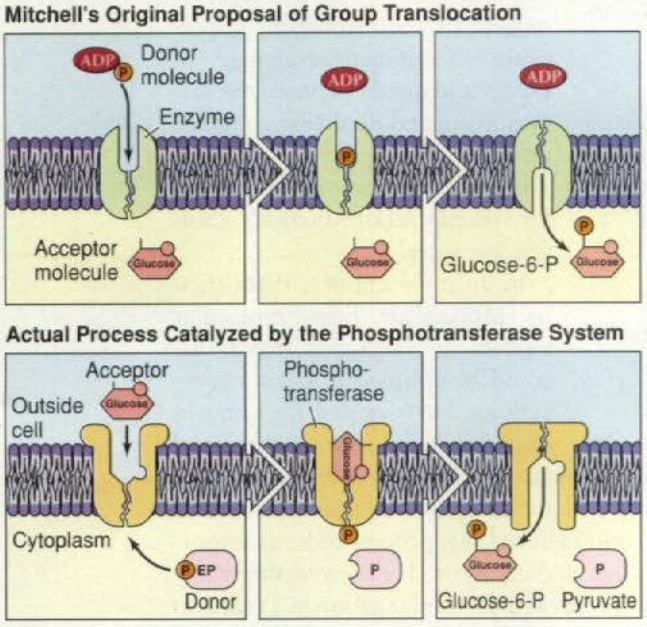
Mitchell came to believe that the definition of life must encompass both scalar processes (chemical interconversions or metabolism) and vectorial processes (nutrient acquisition, product release, and all other transmembrane transport phenomena). Further, these processes must occur in spatially defined compartments (the organism, cell, or organelle) maintained in an open system (the environment, the extracellular millieu, or the cytoplasm, respectively). Continual exchange of energy and matter between the various living and nonliving compartments is a prerequisite for life. These concepts provided the basis for virtually all of Mitchell's scientific advances.

In an early inquiry, Peter tried to rationalize how molecular movement (vectorial reactions) could be coupled to chemical reactions. He invented the concept of *group translocation*, the direct coupling of transmembrane solute transport to the chemical modification of the translocated solute, and believed this process to be as important as enzyme catalysis. He viewed the transported species as a molecular group in a reaction catalyzed by an enzyme that transfers a chemical group of one molecule (the donor) to another molecule (the acceptor) (Fig. 1, top). If the donor is bound to the membrane-spanning enzyme on one side while the acceptor is bound on the other side, then the group transferred will be translocated across the membrane once the products dissociate from the enzyme. He was

Statids and Fluctids

Term	Definition	Biological Equivalent	Examples
Statids	Scalar quantities (occurring within one compartment)	Structures; metabolism	1) Enzyme-catalyzed chemical interconversions 2) Enzyme-catalyzed substrate oxidations 3) Macromolecular assembly processes
Fluctids	Vectorial quantities (occurring between compartments)	Transport; group translocation	1) Movement of molecules into and out of cells and organelles 2) Electron flow between carrier proteins coupled to proton movements 3) Cell movement driven by ion transport

FIGURE 1



Comparison of the original proposal of group translocation, suggested by Mitchell in 1958 (top), with the actual process of group translocation as catalyzed by the bacterial phosphotransferase system (bottom). In Mitchell's original proposal, a donor such as ATP (ADP-Ⓟ) transfers a phosphoryl group to an acceptor molecule such as glucose. The group transferred is also the group transported. In the reaction catalyzed by the phosphotransferase system, phosphoenolpyruvate (PEⓅ; the donor) transfers its phosphoryl group to glucose (the acceptor). In this case, the acceptor molecule (glucose), rather than the group transferred (Ⓟ), is transported. Contrary to Mitchell's notion of group translocation, sugar phosphorylation via the phosphotransferase system (the energy coupling step) is believed to be superimposed on the transport process rather than integral to it.

imagining the activity of an enzyme in an asymmetric membrane structure rather than in a homogeneous aqueous solution. In essence, Mitchell suggested that the movement of molecules across membranes could be explained in terms of conventional biochemistry.

This concept later proved applicable to a bacterial enzyme system called the phosphotransferase system. The phosphotransferase system both transports and phosphorylates sugars (Fig. 1, bottom). Transport of a sugar such as glucose is mediated by a protein embedded in the membrane which binds the sugar (the acceptor molecule) on the external surface of the cell and releases a phosphate ester of the same sugar (the product of the reaction) inside the cell. In this process, a cytoplasmic domain of the transport protein becomes transiently phosphorylated at the expense of the phosphoryl donor, phosphoenolpyruvate. The phosphorylated protein serves as the energy source for both sugar accumulation and its phosphorylation.

This phosphotransferase system bears the essential features of Mitchell's group translocation process, that is, the coupling of vectorial and chemical processes. However, in contrast to the group translocation system originally described by Mitchell, the sugar acceptor rather than the phosphoryl group is transported. Further, in contrast to Mitchell's early notion, the phosphorylation reaction which provides the energy for accumulating sugar inside the cell is now believed to be superimposed on the transport process rather than integral to it.

Move to Edinburgh Leads to Fruitful Period

In 1955, Mitchell accepted a permanent position at the University of Edinburgh in Scotland. Although he loved the intellectual environment of Cambridge, his teaching position there was tenuous and his talents poorly appreciated. Jennifer Moyle accompanied him to Edinburgh, where she earned her Ph.D. while continuing their collaborative efforts. The work in Edinburgh led shortly to Mitchell's first chemiosmotic hypothesis.

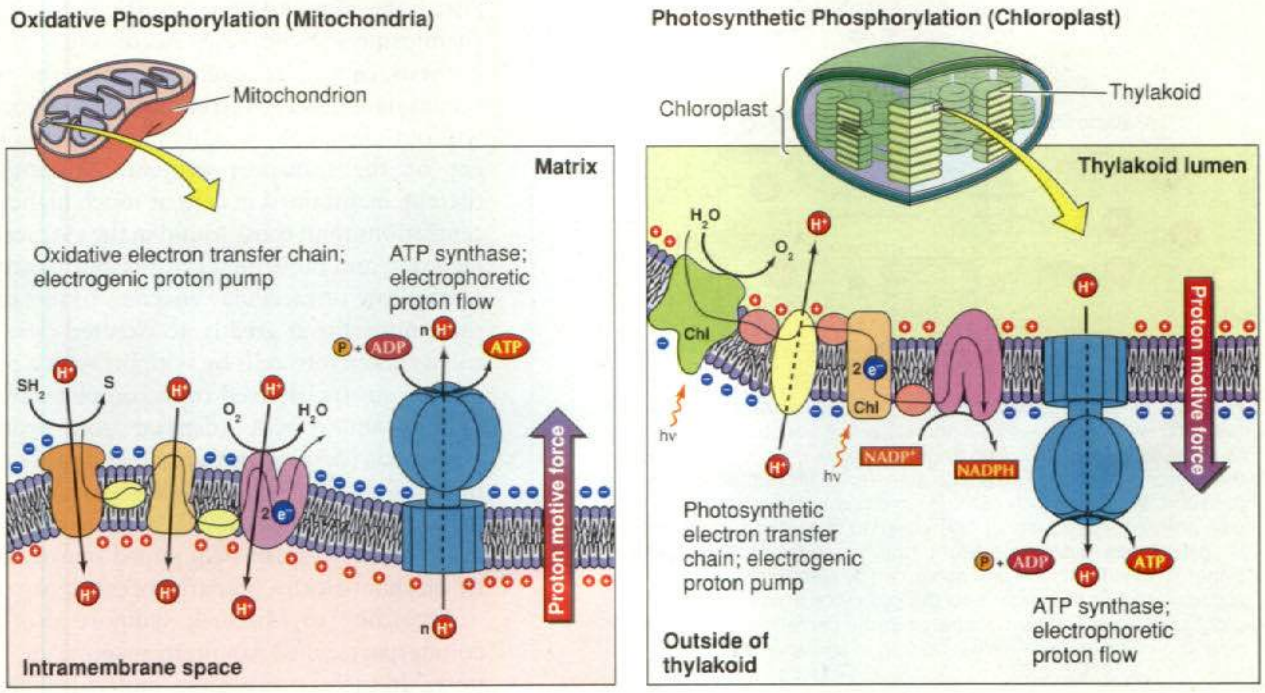
Substrates, organic molecules such as pyruvate and fatty acids, are oxidized in organelles of eukaryotic cells called mitochondria. In this process, extracted electrons are passed along an electron transfer chain to react with molecular oxygen. During this process, called oxidative phosphorylation, the chemical energy currency of the cell, ATP, is produced. The prevailing view of the day was that substrate oxidation—the removal of electrons from a substrate molecule (the electron donor) and the subsequent transfer of these electrons to another molecule (the electron acceptor)—was directly coupled to the synthesis of ATP from ADP and inorganic phosphate. Such a direct coupling mechanism, now termed "substrate-level phosphorylation," is catalyzed by cytoplasmic enzymes both in the anaerobic breakdown of sugars via glycolysis and in the aerobic metabolism of organic acids via the Krebs cycle. Substrate-level phosphorylation requires neither membranes nor compartments. Although the enzymes that catalyze

oxidative phosphorylation are embedded in membranes, many scientists considered this fact inconsequential, because several reports indicated that membranes could be disrupted without loss of ATP synthesis during oxidative phosphorylation. Meanwhile, however, Mitchell argued that proton (H^+) movements across biological membranes are directly coupled to electron flow and ATP synthesis, and that only indirectly are oxidation reactions coupled to ATP synthesis. Moreover, these proton transport-coupled processes are absolutely dependent on membrane integrity, which maintains two compartments and enables transmembrane ion gradients to form.

Mitchell Develops Three Distinct but Related Hypotheses

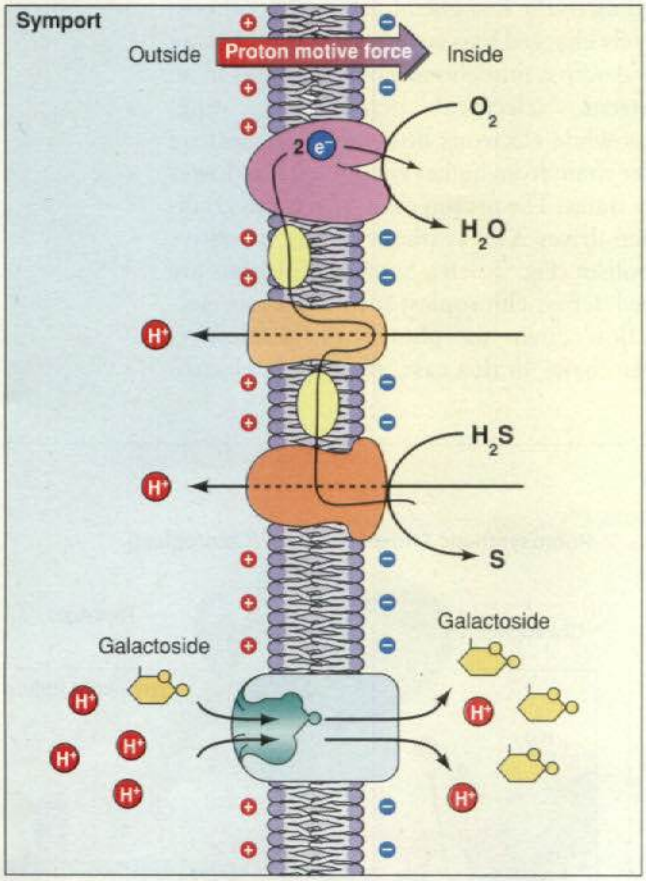
According to the first chemiosmotic hypothesis, positively charged ions such as protons (H^+) are pumped across mitochondrial membranes in an electrogenic (electrical potential-generating) process while electrons flow down an electron transfer chain from higher energy states to lower energy states. The proton electrochemical gradient then drives ATP synthesis during oxidative metabolism (Fig. 2, left). Similarly, protons are pumped across chloroplast membranes as electrons flow down the photosynthetic electron transfer chain. In this case, the proton electro-

FIGURE 2



Schematic depiction of oxidative (right) and photosynthetic (left) phosphorylation. In both processes, electrons flow from a high energy state to a low energy state in a process which is coupled to the electrogenic pumping of protons (H^+) to generate an electrical potential (negative inside mitochondria and bacteria, but positive inside chloroplasts) as well as a pH gradient. The electrical potential plus the pH gradient together comprise the proton electrochemical gradient that Mitchell referred to as the proton motive force (pmf). In oxidative metabolism (left), electrons are extracted from a reduced substrate, SH_2, to yield the oxidized substrate, S, and after passage through the electron transfer chain, they are used to reduce molecular oxygen (O_2) to water (H_2O). In photosynthesis (right), electrons are extracted from water (H_2O) to yield oxygen (O_2) in a process that requires the absorption of light ($h\nu$) to activate the extracted electron in a chlorophyll (Chl) molecule. After passage through the electron transfer chain, the electrons are utilized to reduce the enzyme cofactor NADP to NADPH. The ATP synthetic step is the same in both processes. Protons (H^+) flow electrophoretically down their electrochemical gradients, in an energy-yielding process, through the transmembrane portion of the ATP synthase to allow synthesis of ATP from ADP and inorganic phosphate (P_i) in the portion of the enzyme complex that protrudes from the membrane (bottom, left and right). The coupling of proton flux to ATP synthesis is now believed to be indirect, due to conformational changes in the enzyme complex, contrary to Mitchell's proposal of direct coupling.

FIGURE 3



Example of solute:cation symport, also called secondary active transport (bottom) driven by a primary active transport process (top) as proposed by Mitchell. The diagram depicts the coupling between the proton-translocating electron transfer chain (the primary active transport system) which extrudes protons as electrons pass from one protein constituent of the chain to the others (top) and an H^+:galactoside symport system (the secondary active transport system), which uses the pmf generated by electron flow to drive the accumulation of the sugar into the cell cytoplasm (bottom). These processes were first demonstrated in the bacterium *E. coli* but are now known to occur in similar fashion in all living cells.

chemical gradient thus generated drives ATP synthesis during photosynthesis (Fig. 2, right). Because mitochondria and chloroplasts seem to have derived from bacteria during evolution, it is not surprising that oxidative metabolism and photosynthesis in microorganisms are about the same as in organelles of eukaryotic cells. Mitchell referred to the proton electrochemical gradient generated across the membrane as the proton motive force (pmf) by analogy with the electron motive force (emf) of a battery. However, his critics mockingly claimed that pmf stood for "Peter Mitchell force," which they considered imaginary.

Undaunted, Mitchell explained that a membrane-bound enzyme couples the synthesis of ATP to the electrophoretic (electrical potential dissipating) flow of protons across the membrane and down the previously generated electrochemical gradient. pmf energy thus drives ATP synthesis. Although these ideas were not conceptually difficult, it took nearly 20 years of experimental work in many laboratories before they were accepted as scientific dogma.

In explaining how a solute accumulates against a concentration gradient, Mitchell proposed that the electrophoretic H^+ flow is coupled via a transport protein to the transmembrane accumulation of a cellular nutrient (Fig. 3). This cotransport process notion, or "symport," became known as Mitchell's second chemiosmotic hypothesis. According to this hypothesis, cells utilize energy stored in the pmf to accumulate nutrients from the external medium without chemically modifying either the nutrient or the transport protein. Nutrients are thereby maintained in cells at much higher concentrations than those found in the extracellular medium, and these high cytoplasmic concentrations allow intracellular enzymes to metabolize these nutrients at greatly accelerated rates. Nutrients taken into cells by symport with a proton include sugars (derived from complex carbohydrates), amino acids (derived from proteins), fatty acids (derived from fats), and other essential biological substances such as vitamins and metabolic intermediates. Waste materials and toxic substances can be pumped out of the cell by mechanistically similar processes.

According to Mitchell, symport also has a counterpart called countertransport, or "antiport." In such a process, one molecular species is exchanged for another—for example, Na^+ for H^+, or Cl^- for HCO_3^- (Fig. 4). Mitchell's initial experimental evidence for symport and antiport processes has subsequently been extensively documented in studies conducted in many laboratories.

In the simplest possible case, termed "uniport," only one ionic or molecular species passes through the membrane at a time, without being coupled to the movement of another molecular species. In uniport situations, neutral molecules do not accumulate against concentra-

tion gradients, but their transport across membranes down concentration gradients is facilitated. Mitchell called the proteins that catalyze all of these transport processes "porters" and correctly suggested that they might function by similar mechanisms. Although these ideas were based primarily on studies with bacteria, these processes also occur in the cells and organelles of animals, plants and fungi.

As a boy, Mitchell learned that mechanical devices used for different purposes employ common principles. Some of these principles later proved applicable to biology. For example, Mitchell likened the bacterial flagellum to elements within the steam engine. Just as steam driven through an orifice can turn the wheels of a locomotive, the flow of H^+ through an orifice in the flagellar "proton engine" might rotate components of the flagellum, and thus propel a bacterium (see Fig. 5). This notion, Mitchell's third chemiosmotic hypothesis, was proven correct only many years later.

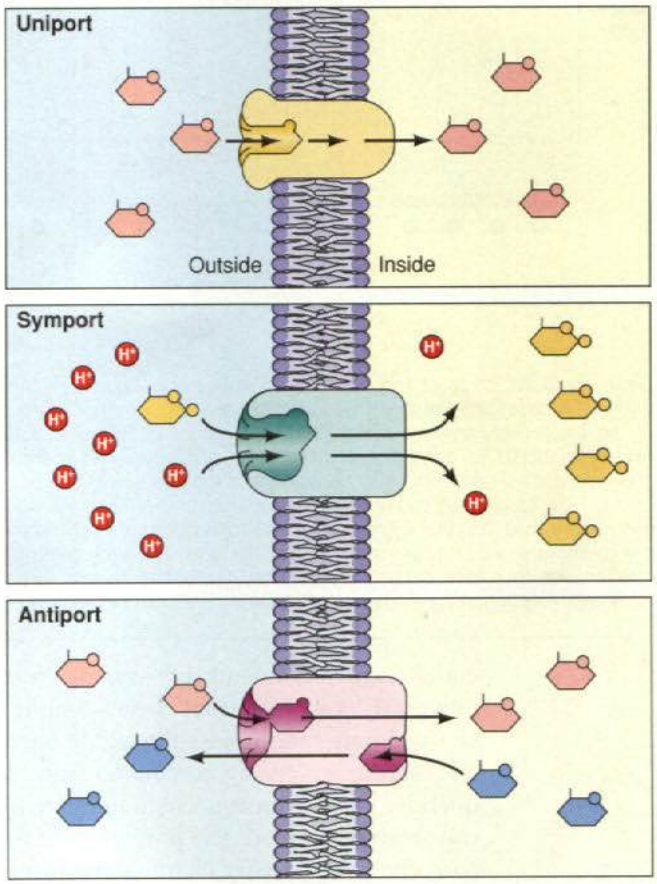
Three Hypotheses Share a Unifying but Controversial Theme

There is a simple unifying theme to all three chemiosmotic hypotheses. In each case, a molecular process is coupled to the transport of protons across a biological membrane. According to Mitchell's first hypothesis, electron flow and ATP synthesis are separately coupled to H^+ transport. According to the second hypothesis, solute accumulation or expulsion is driven by H^+ transport. According to the third hypothesis, cell movement (flagellar rotation) is energized by H^+ transport. In each case, the pmf serves as the energy source that drives these processes.

Mitchell first presented these ideas to the scientific community in 1960. Sir Hans Krebs, then Professor at Oxford, whose work had led to an understanding of the "Krebs Cycle" for organic acid oxidation, called these ideas a retrograde step and compared them to the "vital forces and moments" discussed by Justus Liebig in *Animal Chemistry*, published in 1842. Krebs believed that the "bag of enzymes" concept was an adequate description of the living cell, and that there was no need to propose mysterious forces such as transmembrane electric fields and potentials. Moreover, he did not approve of Mitchell's experimental approaches, which emphasized great leaps but omitted proofs that Mitchell deemed obvious or uninteresting. Krebs insisted that every relevant control experiment be conducted.

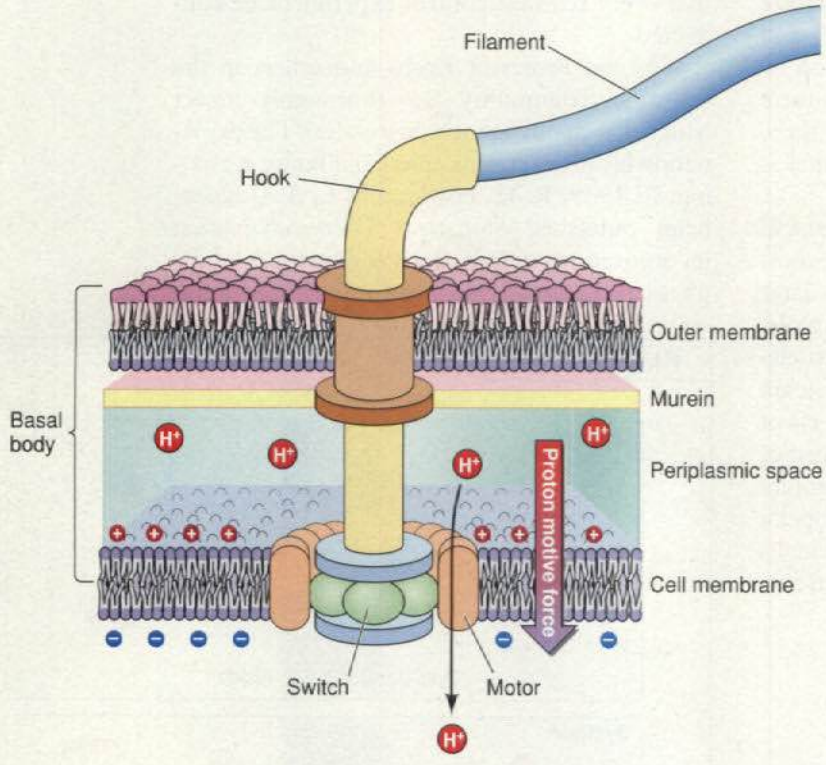
Why did Professor Krebs and others in the scientific community so thoroughly reject Mitchell's chemiosmotic postulates? The explanation lay in part on accepted, but faulty reasoning. In 1939, R. H. Fowler and E. A. Guggenheim published *Statistical Thermodynamics*, incorporating computations and methods of the physical chemist, J. Willard Gibbs. In this influ-

FIGURE 4



Three types of porters: uniporters (top), symporters (middle), and antiporters (bottom). Uniporters catalyze the transport of a single species independently of any other; symporters catalyze the co-transport of two dissimilar species (usually a solute and a positively charged ion, H^+) in the same direction, and antiporters catalyze the exchange transport of two similar solutes in opposite directions. A single transport protein may catalyze just one of these processes, two of these processes, or even all three of these processes, depending on conditions. Uniporters, symporters, and antiporters have been found to be structurally similar and evolutionarily related, and they function by similar mechanisms.

FIGURE 5



Generalized structure of the gram-negative bacterial flagellum. Structural components within the basal body of the flagellum allow the inner portion of this structure, the rods of the basal body and the attached hook/filament complex, to rotate. The outer rings remain statically in contact with the inner and outer cell membranes and cell wall (murein), anchoring the flagellar complex to the bacterial cell envelope. Rotation is driven by the flow of protons through the motor from the periplasmic space, outside the cell membrane, into the cytoplasm in response to the electric field and proton gradient across the membrane which together comprise the pmf. A switch determines the direction of rotation, which in turn determines whether the bacteria swim forward (due to counterclockwise rotation of the flagellum) or tumble (due to clockwise rotation of the flagellum).

ential text, electroneutrality was put forth as a universal law, and that belief implied that charged ions cannot pass through a barrier unless accompanied by a counter ion. Consequently, ion movements could not give rise to a transmembrane electrical potential. At the *macroscopic* level, massive charge separation generates the buildup of an excessive electric potential that can result in electric discharge, and the system can blow up.

However, these arguments are invalid at the microscopic level, where slight charge separations, with excess positive charges on one side of a biological membrane and a net negative charge on the other side, can generate an electrical potential of several hundred millivolts. It is lucky for living organisms that the principles of electroneutrality proved to be invalid at the microscopic level. Indeed, transmembrane electrical potentials account for all bioelectric phenomena, including those involving nerve conduction and muscle contraction.

Physical Problems Force Departure from Edinburgh

In 1963, Mitchell developed severe peptic ulcers and was forced to retire from his stressful academic position at the University of Edinburgh. He moved to a dilapidated mansion called Glynn House situated on 80 acres of farmland on the edge of the Bodmin Moor in remote Cornwall. For the first two years, he halted all scientific studies to become a farmer and devote himself to restoration of the mansion.

Only after he had recovered his health did he, Jennifer Moyle, and a few other researchers tackle the tremendous task of gaining direct experimental evidence for his hypotheses. Financed from his own pocket with help from his brother Bill, Mitchell equipped a laboratory in the central part of his mansion and published articles and books on his own printing press. At Glynn House, proton pumping out of mitochondria during substrate oxidation was demonstrated, and dissipation of the resultant pmf was shown to prevent ATP synthesis. Proton pumping into chloroplasts during light-driven photosynthesis was also demonstrated, along with the dependence of ATP synthesis on the pmf. He also obtained evidence that comparable processes occur in bacteria. Moreover, he proved that in *E. coli*, uptake of the sugar lactose via the lactose permease protein is accompanied by proton uptake. Dissipating the pmf prevents accumulation of lactose. Meanwhile, researchers in other laboratories showed that dissipation of the pmf across the membranes of bacterial cells abolishes motility. Gradually, as many laboratories confirmed and extended these findings, the chemiosmotic principles set forth by

Mitchell and the central role of the pmf in cellular energy interconversion became accepted.

Mitchell believed that pure scientists need to be free to do research and make discoveries in the same way that artists should be free. This stature, he argued, must entail freedom from bureaucracy and immunity from social responsibility. Any discovery with potential for good also has potential for evil, and the more important a discovery, the greater its potential in either direction. The responsibility for the use of a creation or discovery lies with society and not with the artist or the scientist. The principal responsibility of the basic scientist, as the artist, is creation itself, and the socially irresponsible scientist is one who does not add to our knowledge about the natural world.

While Mitchell spent most of his life studying molecular interactions, in his last years he came to realize that the world most needs a basic understanding of human interactions. He suffered as a result of social intolerance for his novel concepts. Like Mitchell, each of us has the responsibility to respect the individuality of others and to seek the intellectual and emotional wealth within us. Mitchell passionately believed that tolerance and the gentle art of open-minded inquiry can facilitate communication across barriers of dogmatism for the creation of a better, more conscious world.

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