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MINI-REVIEW

Redox-Linked Proton Translocation by Direct-Coupled Ligand Conduction

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Abstract

The term "direct-coupled" is considered in the context of redox-linked proton translocation mechanisms, and the origins of this concept, its philosphical implications, applications, and contributions to the development of bioenergetics, are discussed.

Key Words: Vectorial metabolism; Curie's principle.

Introduction

Though many workers have contributed to our understanding of specific mechanisms, the general concept of redox-linked proton-translocation by direct-coupled ligand conduction is the creation of one man; to date Peter Mitchell is the author of essentially all elaborations and discussions of this subject. For comprehensive, succinct, accurate, and authoritative accounts of this type of proton-translocation the reader is referred to one or other of Mitchell's own publications (see references). The present brief chapter offers a comment here and there and maybe an element of critical assessment.

Nomenclature

The following definitions seem trite, and almost superfluous, but these terms embody much of the history and philosophy of Mitchell's theory of

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chemiosmotic energy coupling and it is no doubt for that reason that some of the public discussions of proton-translocation mechanisms seem to have been unduly concerned with nomenclature, and to involve an element of stake-claiming. My objective here is not to trace the lineage of these concepts, but to increase clarity.

Nomenclature may have evolved. In Mitchell's recent papers (e.g., Mitchell, 1985) the term ligand is seen to refer to any particle (group, molecule, ion, electron) that may be ligated, or bound (ionically, covalently, noncovalently, or however an electron is bound in an orbital). And conduction is any process of directed movement in space. So the flow of ATP molecules into and out of an enzymic active site can be described as ligand conduction. Indeed, all chemical and biochemical reactions will be seen to be ligand-conduction processes. Ligand conduction is not a type of process but a way of looking at a process, focusing on the vectorial movements through space; a ligand-conduction diagram is a way of drawing that process, with arrows representing the conduction pathways. (See, for example, Fig. 4.) There does not (in current usage) have to be a symport process, a *con*-duction of one particle *ligated* to another.

Where this does occur, where the conduction pathways of two ligands overlap, and the thermodynamic free energy of one ligand flowing down its potential gradient can be transferred by the tight rules of the conducting pathway to the other particle carried up its potential gradient, the term *direct-coupled ligand conduction* is used (Mitchell, 1985).

If one ligand is the proton and the other ligand an electron, the pathway that allows the direct coupling of these two transmembrane fluxes entails the existence of a third ligand (X) that can ligate a proton and an electron. The tight rules of the conduction pathway arise if both X and $X–e^-–H^+$ (the triple complex) are able to cross the insulating and hydrophobic membrane, but the free proton, the free electron, and the duple complexes ($X–e^-$ and $X–H^+$) cannot. It is not necessary that the proton binding be obligatorily linked to electron binding, but if that coupling is tight, the duple complexes will not exist (at an appreciable concentration) and so, of course, cannot travel.

Where the specificity rules of the conduction pathway allow only the conduction of a particle that contains both the covalently bound proton and the electron, this direct-coupled ligand conduction can lead to *redox-linked proton conduction*; reduction of the ligand X on one side of the membrane will lead to the uptake of protons from that side; oxidation of the triple complex on the other side will deposit protons. The driving force for the translocation of the liganded proton comes from the reduction of X at one redox potential on one side of the membrane and the oxidation of the triple complex at a more positive redox potential on the other side. If this free energy is not to

be lost, it is necessary not only that the free proton be unable to cross the membrane, but also that the duple complexes either do not exist or cannot travel, and that the conduction pathways of the free electron be strictly determined. For example, it must be impossible, somehow, for electrons at $E_h = -50\,\text{mV}$ in cytochrome b_{566} or at $E_h = +50\,\text{mV}$ in cytochrome b_{562} to reach the Reiske centre at $E_h = +280\,\text{mV}$ other than *via* the prescribed pathway (*i*-site, QH_2, *o*-site).

The term "redox-linked proton translocation by ligand conduction" (omitting the "direct coupling" restriction) seems inapplicable to proton translocation by a pore, selective or unselective, where the proton is the only particle that moves. But it does not rule out much else. Generalized redox-linked proton-translocating mechanisms like those discussed by Krab and Wikström (1987) can be regarded as indirectly linked ligand-conduction mechanisms (Mitchell, 1981). At the appropriate pH, cytochrome b_{562} can be regarded as a ligand that binds a proton when reduced; but the electron is (presumably) not directly associated with the proton, but spends most of its time at a site somewhat remote. However, even in ubiquinone the electron clearly moves at least partially out of the hydrogen atom into the π-orbitals of the ring, changing the absorption spectrum. How direct is direct? The point about direct coupling can become rather philosophical. (See below).

Though technically outside the scope of this chapter, it is interesting to note the possible extension of direct-coupling mechanisms to redox-driven Na^+ translocation (Dimroth, 1987).

Mitchell has pointed out the equivalence of looping the path of the proton across the membrane, and looping the membrane across the path of the proton (Mitchell, 1979a). Can one similarly equate the movement of ligand across the membrane and the effective movement of the "membrane" past the ligand—the sort of motion envisaged by those who talk of gated pores (and see Mitchell, 1957)? A pedant could object that such motion does not seem properly described as ligand conduction. Similarly, it may be felt that $OH^-/-e^-$ antiport (or antifer; Mitchell, 1987) is conceptually different from the original notion of direct-coupled proton translocation discussed below.

So much for nomenclature.

History and Philosophy

Mitchell seems to have introduced the term "ligand conduction" in the late seventies, but the concept is much older. Since the fifties he has repeatedly drawn attention to the fact that all chemical reactions involve a vectorially directed flow of reactants relative to each other. Normally the individual

molecules in a chemical reaction are randomly oriented, so the macroscopic reaction has no observable vectorial consequences. If, however, in a bimolecular reaction one (macromolecular) reactant is oriented in a membrane the motions of the other reactant into, out of, or through the macromolecule become oriented as well. The chemiosmotic point of view, with its emphasis on this vectorial aspect of chemistry, has undoubtedly stimulated enormous advances in our understanding of bioenergetics.

Mitchell has acknowledged Lundegårdh, Conway, Davis, and Robertson as forerunners and contributors to the development of the concept of the proton-translocating redox chain. The mechanisms that those earlier workers discussed were certainly direct-coupled redox-linked ligand-conduction mechanisms, but it is worth pointing out that they were not *proton*-translocating; they were conceived to be electroneutral, and to lead to acidifications, alkalifications, or salt movements.

The strength of thermodynamics is that it can make statements whose truth does not depend upon the mechanism involved. Important truths can be established in advance of detailed structural information or even knowledge of the components of the system. The weakness of thermodynamics is exactly the same; thermodynamics does not discuss mechanisms. Although the chemiosmotic description of bioenergetics has incorporated a lot of thermodynamics, Mitchell's key point is an essentially mechanistic one, albeit one that he hopes will carry the *a priori* force of a thermodynamic truth. He has insisted repeatedly that, as transport work involves a vector, its driving force must also involve a vector. He has cited the principle of Pierre Curie, that "effects cannot be less symmetrical than their causes" (Mitchell, 1972). He has argued that the vectorial movement of mass against a force must involve, ultimately, the exchange of momentum; and if the driven particle must gain velocity (a vector quantity) in order to cross the membrane, then, by the law of conservation of momentum, some other mass must lose velocity, and thus momentum. The direct-coupling philosophy points to the co-transported ligand itself as the source, *immediately and ultimately*, of that momentum. The existence of cogs and levers has, of course, always made it clear that the momentum of the driving and driven particles need not have the same orientation in space, but Mitchell has always chosen to emphasize the possibility that they might be collinear in this way, as this would be the most direct type of direct coupling (Mitchell, 1981).

To my knowledge there has been essentially no discussion of these aspects of Mitchell's work (See, however, West, 1981). Nor will there be one here; I shall only invite the reader to consider a few questions. (1) Does transport work always involve a vectorial force? There is directed movement, but is there a directed force? The chemical activity gradient against which the work is done is more imaginary than the gravitational field or the electric

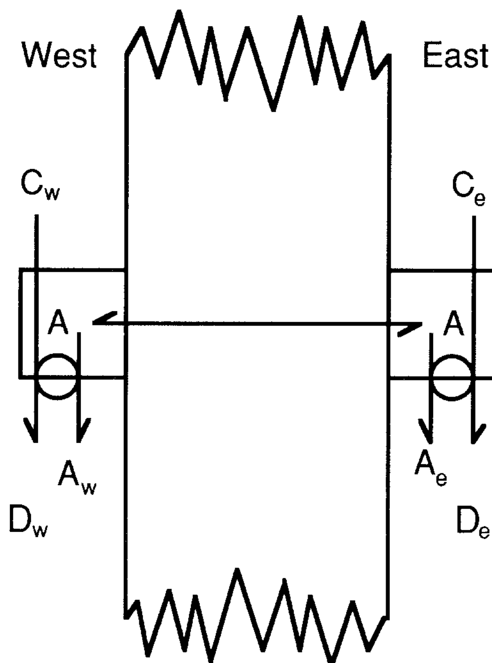

Fig. 1. A diagram to show how the transmembrane transport of A might be driven by the transformation of C to D without C or D crossing the membrane.

field force. Individual molecules will experience no net, mechanical, force; individual molecules will make the transition from east to west across a membrane as frequently and as rapidly as the reverse transition. No net work is therefore done during individual transport events. Net "downhill" transport depends on the statistical fact that there are more molecules in one phase than the other. Presumably, therefore, such a diffusion process could be driven in the "uphill" direction by a reaction for which there were more reactants than products without the transfer of directed momentum during individual transport events. (See Fig. 1). (2) Does the electron have any significant momentum collinear with that of the moving proton; and is that the momentum that provides the work for proton translocation? I think not. The electron's rest mass is very small. (3) Where there are levers, etc., and the momentum of the driving process has a vector at right angles to the membrane normal, do we not immediately have to abandon the concept of collinear ligand conduction and to concede that indirect coupling is very possible? Similarly, symport between proton and, for example, lactose is clearly indirect, in that lactose does not itself bind protons. (4) Perhaps the driven particles do not acquire momentum in a westerly direction, any more than the membrane moves in an easterly one. Indeed, it seems likely that there is no

net momentum change in the system as a whole, only a movement of particles relative to membrane. (5) In a system driven by statistical factors ("forces"), it seems obvious that the actual kinetic and mechanical forces that cause motion come from the thermal energy of the whole ensemble of molecules that constitute the medium, solvents as well as solutes (West, 1981).

Mitchell has clearly believed that Nature will be found to share his own preference for a collinear vector (Mitchell, 1976), but he has not greatly elaborated the thinking behind that belief, beyond the occasional reference to "simplicitly" and "evolution." Of the two the latter seems to me the sounder basis. (Few students find the Q-cycle simple, but most will be struck by the amazing conservatism that links Rhodobacter, yeast, spinach, and man.) The evolutionary argument must start by asking how an evolving cell could exploit processes that would occur without complex protein machinery. The first time that a quinol, located in the membrane but reduced by internal substrates, was oxidized by an electron acceptor, protons would have been deposited either into the medium or into the cytoplasm. Cells in which the former occurred would find themselves with a proton-motive force across their cell membranes. The respiratory chain could have evolved from there.[2]

The originally postulated H-conducting loop led to the prediction of a fixed H^+/e^- stoichiometry of 1, and this rigidity has often been cited as a merit; it made the hypothesis testable. However, we shall see below that the ingenious use of semiquinone forms can produce models predicting almost any stoichiometry. Further, we can identify another way in which a directly coupled mechanism can produce fractional stoichiometries. When fumarate is reduced to succinate by two electrons, two protons are taken up as well; as the p*K* of the carbanions is around 20, these protonations can be said to be strongly coupled. The p*K* of ubiquinol is around 11 (Rich and Bendall, 1980), so protons and electrons are still fairly strongly coupled here. The p*K* of flavin and ubiquinone semiquinone radicals (around 5) are such that, at physiological pH, deprotonation is not 100% linked to oxidation (Rich and Bendall, 1980); however, the extent of protonation (and thus tightness of coupling) can be dictated in part by the protein of the quinone-binding site. Where the duple complexes can both exist and travel, tightness of coupling depends on properties of the catalytic protein, and there can be fractional stoichiometries, often called "slip" (Eddy, 1980).

In his most recent papers Mitchell has perhaps moderated his claims regarding the superiority of direct coupling, for he expresses only the view that it is more "strategically wise" to explore the direct-coupled possibilities before postulating indirect mechanisms (Mitchell, 1985). This may turn out

[2]This paragraph seems to me to be of crucial importance from various points of view (history of ideas, theories on inductive reasoning, etc.), but it requires no special emphasis in the context of the present essay.

to be a matter of taste (. . . *non disputandum est.*), and cannot be true for certain systems (e.g., lactose–proton symport). However, in 1976 Mitchell was able to say that the only *understood* mechanism of proton translocation by the respiratory chain was the direct-coupled one (Mitchell, 1976); and that is still as true today.

Examples

Established Examples

The only well-established cases of redox-linked proton translocation by direct-coupled ligand-conduction mechanism are the Q-cycles of chloroplats, mitochondria, and certain bacteria, and the Q loops of other bacteria such as *Escherichia coli.* That is to say, all known cases of proton translocation by this type of direct-coupled mechanism involve quinones as the H^+ and e^- binding ligand X, i.e., plastoquinones, ubiquinones, or menaquinones. These quinones are good candidates for the role; there is strong coupling between protonation and reduction, and quinones are lipid soluble and have adequately high diffusion constants in and through the membrane in both protonated and unprotonated forms (thus in both reduced and oxidized forms). The roles of ubiquinone and menaquinone in bacteria such as *Escherichia coli* have not been fully investigated, but would seem to correspond to the H-carrying limb of a classical Mitchellian loop (Ingledew and Poole, 1984; Anraku and Gennis, 1987).

Proposed Examples

Mitchell proposed a number of ways in which the demonstrated proton translocation by the NADH : ubiquinone oxidoreductase segment of the respiratory chain could result from a directly coupled type of mechanism. In 1966 Mitchell suggested (Mitchell, 1966a) that NADH itself carry 2 H atoms outwards, the nonheme iron groups carry 2 electrons inwards, and $FMNH_2$ carry a further 2 H atoms out ($4\,H^+$ translocated per $2\,e^-$). It was, of course, known that NAD carriers 2 electrons but only one hydrogen on the pyridine ring. However, it was suggested (Mitchell, 1972) that the second hydrogen could travel as a proton on the phosphate group (not, therefore, the most direct of direct couplings). After it had become clear that the ubiquinol : cytochrome *c* oxidoreductase segment of the chain translocated four protons per $2\,e^-$, and his successful elaboration of the elegant Q-cycle, Mitchell redrew the NADH : ubiquinone oxidoreductase segment with half the stoichiometry ($2\,H^+$ translocated per $2\,e^-$), using only $FMNH_2$ as H carrier and nonheme iron groups as electron carriers (Mitchell, 1979b). However, no experiments have been devised to test any of these schemes.

In the meantime it has become widely accepted that the stoichiometry of the NADH : ubiquinone oxidoreductase segment must (almost certainly) be greater than $2H^+/2e^-$; values of $3H^+$ (DeJonge and Westerhoff, 1982), $4H^+$ (Hinkle, 1981), and $5H^+$ (Lemasters, 1984) have all been derived from thermodynamic poising experiments, though the direct measurements of Lawford and Garland (1972) and Ragan and Hinkle (1975) have not been adequately reinvestigated. Since 1980, a number of schemes have been proposed that incorporate concepts from the Q-cycle to explain higher H^+/e^+ stoichiometries (Hinkle, 1981; Ragan, 1987; Krishnamoorthy and Hinkle, 1988; Ragan, 1990). In 1986 Ragan proposed (Ragan, 1987) an ingenious but hypothetical scheme for the NADH : ubiquinone oxidoreductase segment whereby it could translocate 2, 3, 4, 5, or $6H^+/2e^-$ by direct-coupled mechanisms. He incorporated two concepts from the Q-cycle; breaking the $2e^-$ transfers into two $1e^-$ transfers, and allowing the electrons to pass twice across the membrane (Fig. 2). Krishnamoorthy's and Hinkle's scheme is simpler and resembles Mitchell's 1979 scheme except that the flavin is proposed to cycle between the $FMN^{\cdot -}$ radical and the fully reduced $FMNH_2$ form in $1e^-$ steps ($2H^+/e^-$).

These schemes deserve to be further elaborated. They do not yet explicitly incorporate all the considerable information we now have about redox midpoints, the redox titration curves of semiquinone radicals of ubiquinone and FMN, the site of action of rotenone, and the effect of ATP, ΔpH, $\Delta\psi$, and rotenone on radical and nonheme iron e.p.r. signals. More explicit formulations might display further testable features. However, it is worth remarking that all current attempts to explain proton translocation by NADH : ubiquinone oxidoreductase use direct-coupled ligand-conduction concepts.

Mitchell also suggested a direct-coupled mechanism for the energy-linked transhydrogenase (Mitchell, 1966a). The tritium labelling experiment of Lee *et al.* (1965) had already shown that the ring hydrogen of NADH is transferred to NADP without mixing with water, ruling out the translocation of *that* hydrogen (and ruling out, therefore, the direct-coupled rationale); but Mitchell again pointed to the possibility that the two hydrogen nuclei could travel as protons on phosphate groups of either nicotinamide or flavin nucleotides (Fig. 3). There is, of course, no *a priori* reason to suppose that these travel back and forth across the osmotic barrier, but they must travel into and out of enzymic active sites oriented in the membrane. However, like the similar schemes for the NADH : ubiquinone oxidoreductase segment, these ideas have not attracted experimental testing. (See J. B. Jackson, this volume, for further discussion of energy-linked transhydrogenase.)

It was argued that proton translocation by cytochrome oxidase could not be directly coupled, because none of the redox centres of the enzyme

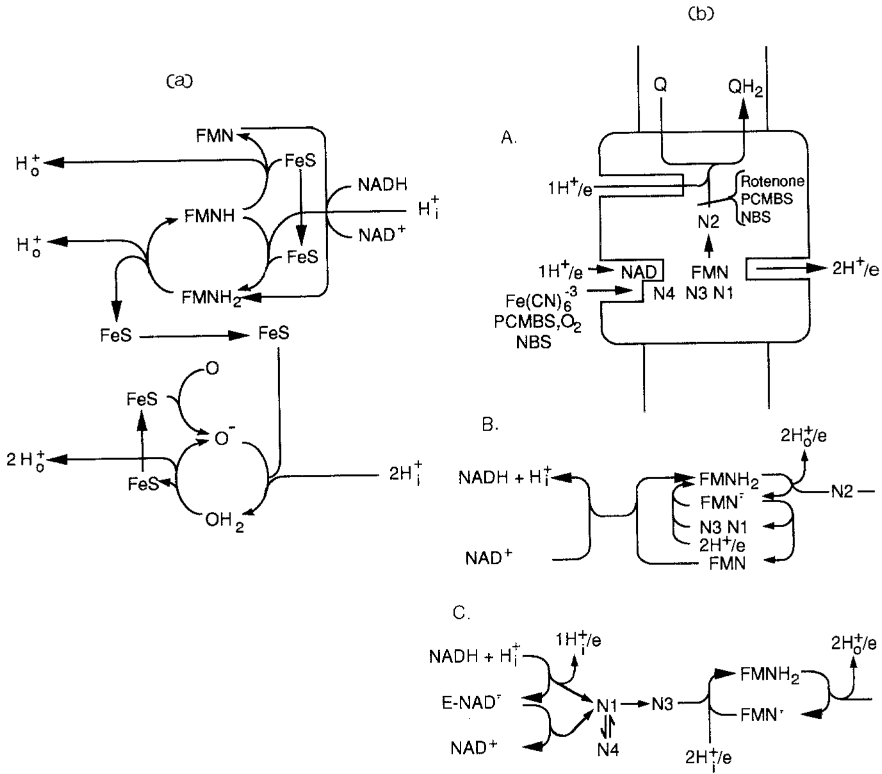

Fig. 2. Hypothetical schemes for direct-coupled proton translocation by complex I. (a) Scheme of Ragan (1987). (b) Schemes of Krishnamoorthy and Hinkle (1988). B is described as a flavin cycle, C as showing single-electron transfer from NADH. (Both are produced with permission.)

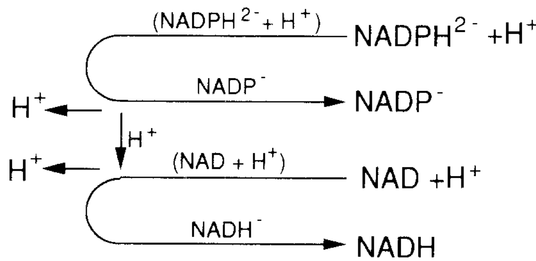

Fig. 3. Hypothetical scheme suggesting that $2H^+$ might be translocated by direct coupling to the phosphate groups of NAD and NADP nucleotides during hydride transfer by the energy-linked transhydrogenase. (Reproduced with permission from Mitchell, 1972.)

(Cu_A, Cu_B, Fe_a, Fe_{a3}) were H carriers; all were electron carriers. However, we pointed out (Mitchell *et al.*, 1985) that the $O_2/H_2O_2/H_2O$ system is itself a proton-coupled redox carrier system with many appropriate features. Redox midpoints and pK values are in the right range, protonation is strongly coupled to reduction, and all three forms are adequately mobile in the membrane. Analogies were drawn between QH_2 and O_2H_2 (i.e., H_2O_2), and a number of ways were described in which cytochrome oxidase could catalyze direct-coupled proton translocation using H_2O_2 as an H-carrying reductant, the essence of these being two sites of oxygen reduction (an *i*-site of proton input and an *o*-site of proton output) and reducing equivalents passing between these not as electrons but as H atoms of H_2O_2. Some predictions of this type of scheme have been demonstrated experimentally (Wrigglesworth *et al.*, 1987; Gorren *et al.*, 1988), such as a role for oxygen species in speeding electron transfer between Fe_a (putative *i*-site) and Fe_{a3} (putative *o*-site), and the ability of H_2O_2 to reduce Fe_{a3}. However, only one site of O_2 reduction can be detected, the bimetallic, cyanide-binding, Fe_{a3}–Cu_B centre.

Mitchell's more recent suggestions involve redox-linked reorientations of OH^- (or O^{2-}) and H_2O ligands around Cu_A (Mitchell, 1987) or Cu_B (Mitchell, 1988) (See Fig. 4). There are reasons for believing that proton coupling cannot be at Cu_A (Rich *et al.*, 1989). There is an elegance of simplicity about these latest proposals, and their fundamental postulates seem almost self-evident: that H_2O and OH^- can be ligands of Cu(I) and Cu(II), that electronation encourages protonation and oxidation encourages deprotonation, and that there is a change in ligand geometry on reduction of the copper. Wikström's data showing that $\Delta\tilde{\mu}_{H^+}$ reverses two of the four steps of dioxygen reduction (Wikström, 1989) might superficially incline one to favor the bivalent version [in which Cu_B accepts and donates 2 electrons at a time, and the reorientating ligand is the oxide ion (O^{2-}) rather than the hydroxide ion (OH^-)] as preferable to the $1e^-$ version. However, Wikström's data indicate $2H^+$ translocated per $1e^-$ transfered to oxygen and point to transfer of electrons between the A half of the molecule (Fe_a, Cu_A) and the B half of the molecule (Fe_{a3}, Cu_B) as the proton-translocating redox step. In these recent schemes of Peter Mitchell, the proton is carried by a ligand of the redox metal centre but the geometry of its movement is totally unrelated to that of the electron (so neither symport not antiport). And the oxygen ligand in these latter schemes is not a redox substrate, but is just one possible ligand of the redox centre. Philosophically, therefore, these mechanisms are equivalent in one respect to those proposed earlier by Chan's group (Gelles *et al.*, 1987) where cysteinyl and tyrosyl ligands of Cu_A were proposed similarly to reorientate round the copper atom. Such schemes may or may not be classed as direct-coupled, but illustrate the pointlessness of spending too much time on semantics. [To avoid sterile discussion as to whether his

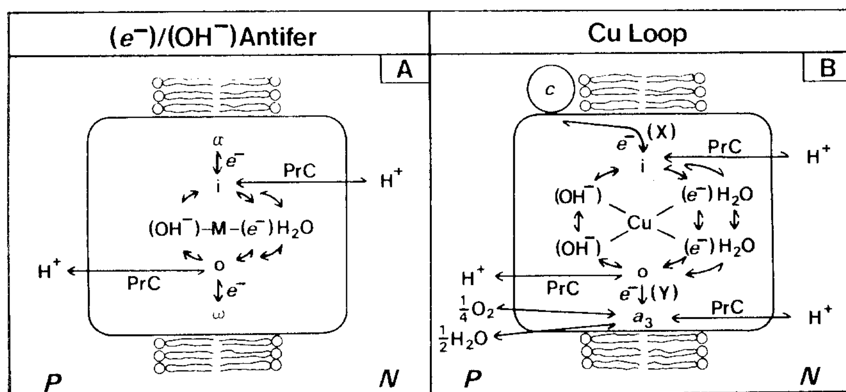

Fig. 4. So called "ligand-conduction diagrams" of hypothetical proton-translocating mechanisms based on hydroxide-motive "$(e^-)/(OH^-)$ antifer" and "Cu loop" systems. (From Mitchell, 1987, with permission).

latest scheme is or is not a "loop", Mitchell has called it a "zoop" (Mitchell, 1988.)]

Other workers have tentatively pointed to other less direct possible sites of proton uptake such as formyl and propionate groups on heme *a* (Krab and Wikström, 1987). Both types of mechanism depend on redox-linked reorientations. In the case of cytochrome oxidase, the more direct mechanisms do not seem to be more explicit than the less direct, and it seems premature at this stage to choose between them on philosophical or, indeed, on "strategic" grounds.

Summary

In summary, Mitchell's concept of direct coupling seems to me to have little or no philosophical basis, but it has found dramatically successful applications, and continues to stimulate the imagination into conceiving possible proton-translocating mechanisms.

References

Anraku, Y., and Gennis, R. B. (1987). *Trends. Biochem. Sci.* **12**, 262–266.
Eddy, A. A. (1980). *Biochem. Soc. Trans.* **8**, 271–278.
Gelles, J., Blair, D. F., and Chan, S. I. (1987). *Biochem. Biophys. Acta* **853**, 205–236.
DeJonge, P. C., and Westerhoff, H. V. (1982). *Biochem. J.* **204**, 515–523.
Dimroth, P. (1987). *Microbiol. Rev.* **51**, 320–340.
Gorren, A. C. F., Dekker, H., Vlegels, L., and Wever, R. (1988). *Biochem. Biophys. Acta* **932**, 277–286.

Hinkle, P. C. (1981) In Chemiosmotic Proton Circuits in Biological Membranes (Skulachev, V. P., and Hinkle, P. C., eds.), Addison-Wesley, Reading, Massachusetts, pp. 49–58.
Ingledew, W. J., and Poole, R. K. (1984). *Microbiol. Rev.* **48**, 222–271.
Krab, K., and Wikström, M. (1987). *Biochem. Biophys. Acta* **895**, 25–39.
Krishnamoorthy, G., and Hinkle, P. C. (1988). *J. Biol. Chem.* **263**, 17566–17575.
Lawford, H. G., and Garland, P. B. (1972). *Biochem. J.* **130**, 1029–1044.
Lee, C. P., Simard-Duquesne, N., Ernster, L., and Hoberman, H. D. (1965). *Biochim. Biophys. Acta* **105**, 397–409.
Lemasters, J. J. (1984). *J. Biol. Chem.* **259**, 13123–13130.
Mitchell, P. (1957). *Nature* **180**, 134–136.
Mitchell, P. (1966a). *Chemiosmotic Coupling in Oxidative and Photosynthetic Phosphorylation*, Glynn Research, Bodmin, England.
Mitchell, P. (1966b). *Biol. Rev.* **41**, 445–502.
Mitchell, P. (1972). *J. Bioenerg. Biomembr.* **2**, 5–24.
Mitchell, P. (1976). *J. Theoret. Biol.* **62**, 327–367.
Mitchell, P. (1979a). In *Membrane Bioenergetics* (Lee, C. P., Schatz, G., and Ernster, L., eds.), Addison-Wesley, Reading, Massachusetts, pp. 361–372.
Mitchell, P. (1979b). *Eur. J. Biochem.* **95**, 1–20.
Mitchell, P. (1981). In *Oxygen, Fuels, and Living Matter*, Part 1 (Semenza, G., ed.), Wiley, London, pp. 1–160.
Mitchell, P. (1985). *J. Biochem.* **97**, 1–18.
Mitchell, P. (1987). *FEBS Lett.* **222**, 235–245.
Mitchell, P. (1988). *Ann. N.Y. Acad. Sci.* **550**, 185–198.
Mitchell, P., Mitchell, R., Moody, A. J., West, I. C., Baum, H., and Wrigglesworth, J. M. (1985). *FEBS Lett.* **188**, 1–7.
Ragan, C. I. (1987). *Curr. Top. Bioenerg.* **15**, 1–36.
Ragan, C. I. (1990). *Biochem. Soc. Trans.* **18**, 515–516.
Ragan, C. I., and Hinkle, P. C. (1975). *J. Biol. Chem.* **250**, 8472–8476.
Rich, P. R., and Bendall, D. S. (1980). *Biochem. Biophys. Acta* **592**, 506–518.
Rich, P. R., West, I. C., and Mitchell, P. (1989). *FEBS Lett.* **233**, 25–30.
West, I. C. (1981). In *Chemiosmotic Proton Circuits in Biological Membranes* (Skulachev, V. P., and Hinkle, P. C., eds.), Addison-Wesley, Reading, Massachusetts, pp. 509–523.
Wikström, M. (1989). *Nature* (*London*) **338**, 776–778.
Wrigglesworth, J. M., Grahn, M. F., Elsden, J., and Baum, H. (1987). In *Cytochrome Systems: Molecular Biology and Bioenergetics* (Papa, S., Chance, B., and Ernster, L., eds.), Plenum, London, pp. 697–703.