



Figure 1 Proton pumping in cytochrome *c* oxidase, based on the results of Wikström and colleagues⁸. The catalytic reaction, which occurs at the Fe_{a3}-Cu_B binuclear centre, is initiated by presenting di-oxygen to the fully reduced enzyme (R). During the oxidative phase, the O₂ molecule is cleaved by accepting two protons from the matrix side of the membrane and four electrons from the metal centres of the enzyme. At the end of this phase the enzyme is fully oxidized. About half of the proton translocation occurs during this phase. Some of the chemical energy released by the oxygen chemistry is conserved in a metastable conformation of the oxidized enzyme (the O~ state). If the subsequent reductive phase immediately follows the oxidative phase, the energy stored in the oxidized enzyme is released by completing the proton translocation. At the same time, two more protons are taken up from the matrix side of the membrane for formation of the two water molecules.

centres, this energy could be released through the charge translocation. The obvious candidates for such bonds are those formed by the coordination of exogenous ligands in the catalytic site (hydroxides, for example) with the iron and the copper in the O~ state^{2,11}. Or, they could be those formed by the intrinsic amino-acid residues that link the redox centres to the polypeptide. Indeed, on reduction of a closely related bacterial oxidase, one of the histidine bonds that coordinates to the copper atom in the catalytic site has already been seen to rupture¹². This suggests that bond breakage or formation could be involved in the energy release.

But it is also possible that the conserved energy in the O~ intermediate is distributed over many polypeptide bonds in the protein. Relaxation of the intermediate's conformation can be coupled to proton translocation on reduction of the metal centres. If this is the case, we need to identify the critical element that triggers release of the energy, allowing the charge translocation to occur.

One interesting possibility comes from consideration of haemoglobin. Here, binding of a ligand to the distal side of the haem moiety is coupled to protein conformational changes through the proximal histidine-iron bond that links the haem to the polypeptide. This cooperative interaction is detected in the resonance Raman spectrum of the transient species generated by photodissociation of carbon-monoxide-bound haemoglobin¹³. Changes similar to those

seen in transient spectra of haemoglobin have already been detected in the spectra of photodissociated carbon-monoxide-bound cytochrome *c* oxidase^{14,15}. It is conceivable that, on reduction of the enzyme, release of hydroxide from the haem moiety could trigger movement of the iron-histidine bond, thereby inducing the global conformational changes that are required for translocating the protons. If this process does turn out to trigger proton translocation, it is remarkable that nature could use nearly identical communication mechanisms in such vastly different proteins. □

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1. Babcock, G. T. & Wikström, M. *Nature* **356**, 301–309 (1992).
2. Han, S., Ching, Y.-c. & Rousseau, D. L. *Nature* **348**, 89–90 (1990).
3. Ferguson-Miller, S. & Babcock, G. T. *Chem. Rev.* **96**, 2889–2907 (1996).
4. Tsukihara, T. *et al.* *Science* **269**, 1069–1074 (1995).
5. Iwata, S., Ostermeier, C., Ludwig, B. & Michel, H. *Nature* **376**, 660–669 (1995).
6. Gennis, R. B. *Biochim. Biophys. Acta* **1365**, 241–248 (1998).
7. Gennis, R. B. *Proc. Natl Acad. Sci. USA* **95**, 12747–12749 (1998).
8. Verhovskiy, M. I., Jasaitis, A., Verhovskaya, M. L., Morgan, J. E. & Wikström, M. *Nature* **400**, 480–483 (1999).
9. Wikström, M. *Nature* **338**, 776–778 (1989).
10. Michel, H. *Proc. Natl Acad. Sci. USA* **95**, 12819–12824 (1998).
11. Mitchell, R., Mitchell, P. & Rich, P. R. *Biochim. Biophys. Acta* **1101**, 188–191 (1992).
12. Osborne, J. P. *et al.* *Biochemistry* **38**, 4526–4532 (1999).
13. Friedman, J. M. *Science* **228**, 1273–1280 (1985).
14. Sassaroli, M., Ching, Y.-c., Argade, P. V. & Rousseau, D. L. *Biochemistry* **27**, 2496–2502 (1988).
15. Findsen, E. W., Centeno, J., Babcock, G. T. & Ondrias, M. R. *J. Am. Chem. Soc.* **109**, 5367–5372 (1987).

Daedalus

No difference at all

Sexual equality is a hot topic nowadays. Men and women are held to be identical in all respects; or if not, they should be. Bertold Brecht remarked, of the implacable social engineering of the old East German regime: “Such a government should dissolve the people, and appoint another.” This idealistic aim, says Daedalus, is now feasible, at least in the sexual sphere.

The ‘default setting’ of a fetus is female. If a male Y chromosome is present, however, it stimulates the production of fetal testosterone, which sets development along the male path. In particular, this hormone powerfully influences the growing brain. Thus, pregnant women with toxemia used to be given doses of testosterone, to counter the condition. The girls born to such women often behaved in male ways, being aggressive, unromantic, and with little interest in babies. Conversely, pregnant women treated with supplementary oestrogens often give birth to boys whose later behaviour is typically feminine. They are often shy, or lack a proper obsession with sport or technology. Much depends on the timing and the dose of the modifying hormone.

So, says Daedalus, the way seems open to true sexual equality. Provided that the sex of the growing fetus can be determined early enough, the mother could be put on a well-judged programme of hormone treatment designed to cancel the mental sexual bias of the fetus without affecting its genital development. Feminist mothers will rush to demand the treatment. The next generation will no longer show the deplorable mental differences that oppose a just and equal society. Everyone, male or female, will be moderately aggressive, moderately sexual, moderately interested in both babies and technology, and capable of competing interchangeably in all walks of life.

The moral climate of society will improve dramatically. The demand for sex from men will at last be equalled by that from women, so prostitution will vanish. The rival art-forms of pornography and romantic fiction will merge into an intriguing new unisex romantic pornography. The long, traumatic sexual odyssey of so many adolescents will also be eliminated, for both sexes will share the same outlook and aspirations. Marriage and the family will benefit enormously from this new harmony. And the old line, “My wife (or husband) doesn’t understand me”, will be totally discredited.

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