The red-light excitation induces spin on the ions [with CN surroundings, Fe(III) is low-spin (S = 1/2), whereas Co(II) becomes high-spin (S = 3/2)] and a new interacting Fe(III)-Co(II) pair. The important point is that the local electron transfer, at the molecular level (Fig. 2), switches on the interaction and allows the extension of the cooperative phenomenon throughout the network. It enhances the mean number of magnetic neighbors z. The ordering temperature T_C is therefore enhanced. The increase is weak (4 K) but significant. An even more exciting observation by Sato *et al.* is that the process can be partially reversed. Changing the color of the light is enough to go back to a state that looks like the initial one and to switch off some Fe(III)–C≡N–Co(II) interactions.

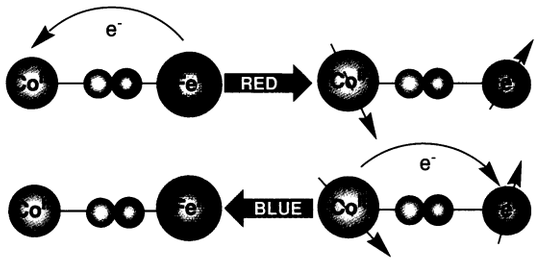


Fig. 2. Back and forth electron transfer induced by photons of different wavelengths through the molecular bridge, and the related magnetic changes.

The phenomenon observed by Sato *et al.* occurs in too low a temperature range (15 to 19 K) and is too slow (a few minutes) for practical applications. It demonstrates, nevertheless, that the tuning of long-range magnetic ordering is possible through a molecular excitation induced by photons. It is one of the necessary steps toward the design of molecule-based magneto-optical devices. Another step was announced recently by the same authors: They displaced electrochemically the T_C of the Mallah's compound (*4*) from 240 to 270 K, which is near room temperature (*7*).

The Prussian blues are far from perfect models. They are not truly molecular, but molecular-based (*8*), at the border between molecular and solid-state chemistry. They present many vacancies and defects and are often mixtures. It is amazing that such shortcomings of the oldest molecule-based inorganic system, which lies between molecular and solid-state chemistries, are the origin of the present discovery. The work of Sato *et al.* shows that we have still many things to learn from old systems, once we look at them anew.

References and Notes

1. O. Kahn, *Molecular Magnetism* (VCH, New York, 1993); D. Gatteschi, *Adv. Mater.* **6**, 635 (1994); J. S. Miller and A. J. Epstein, *Chem. Eng. News* **73**, 30 (2 October 1995); *Angew. Chem. Int. Ed. Engl.* **33**, 385 (1994).
2. O. Sato, T. Iyoda, A. Fujishima, K. Hashimoto, *Science* **272**, 704 (1996).
3. D. Babel, *Comments Inorg. Chem.* **5**, 285 (1986).
4. V. Gadet, T. Mallah, I. Castro, P. Veillet, M. Verdaguer, *J. Am. Chem. Soc.* **114**, 9213 (1992); T. Mallah, S. Thiébaut, M. Verdaguer, P. Veillet, *Science* **262**, 1554 (1993); W. R. Entley and G. S. Girolami, *ibid.* **268**, 397 (1995).
5. S. Ferlay *et al.*, *Nature* **378**, 701 (1995).
6. D. M. Adams, A. Dei, A. L. Rheingold, D. N. Hendrickson, *J. Am. Chem. Soc.* **115**, 822 (1993).
7. O. Sato, T. Iyoda, A. Fujishima, K. Hashimoto, *Science* **271**, 49 (1996).
8. O. Kahn, *Nature* **378**, 667 (1995).
9. The author acknowledges the hospitality of the Department of Inorganic Chemistry of the University of Barcelona, support from Iberdrola Company, and helpful comments from S. Alvarez, T. Mallah, R. Ouahès, and J. Ribas.

Diabetes Complications: Why Is Glucose Potentially Toxic?

Daniel Porte Jr. and Michael W. Schwartz

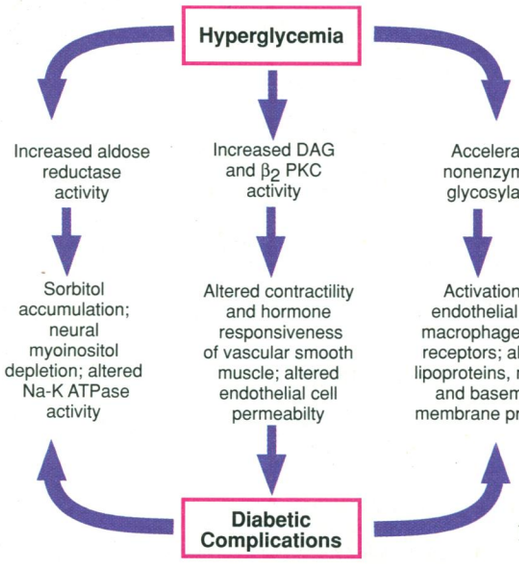
The discovery that insulin can save the life of a patient with diabetic ketoacidosis (acidic blood) or severe hyperglycemia (high blood sugar) was a landmark in the history of medicine. Despite insulin treatment, however, most diabetic patients eventually experience one or more of the long-term complications of the disease. These complications arise from chronic hyperglycemia, which causes damage to small- and large-caliber blood vessels and peripheral nerves, greatly increasing the risk of heart attack, stroke, blindness, amputation, and kidney failure. Exactly how hyperglycemia causes these complications has been debated for years, but the recent National Institutes of Health–sponsored diabetes control and complications trial (DCCT) clearly implicates glucose as a potentially toxic molecule (*1*). With today's technology, the blood glucose concentrations of diabetics cannot be completely normalized, a situation that has spurred the search for a way to prevent the toxic effects of glucose in the hyperglycemic patient. To accomplish this goal, the mechanisms of glucose-induced tissue damage must be understood and interrupted. In this issue of *Science*, an academic-industry collaboration reports progress in this direction. Ishii and co-workers (*2*) provide new support for the hypothesis that activation of the β_2 isoform of protein kinase C (PKC) in vascular tissue is a key step in the cascade of events through which glucose triggers diabetic complications (*2*).

PKC is a member of a ubiquitous family of enzymes that phosphorylate serine and threonine residues of intracellular proteins involved in signal transduction (*3*). In vascular smooth muscle, PKC activity influences contractility, mediates cell signaling initiated by hormones such as vasopressin and angiotensin II, and alters expression of specific genes (*4*). In endothelial cells, PKC influences permeability, presumably through effects on carrier-mediated transendothelial transport (*5*). Several isoforms of PKC are present in the microvasculature of the brain (*6*), where carrier-mediated transport of nutrients (glucose) and hormones (insulin) meet the brain's energy requirements and convey important physiologic signals (*7*).

The PKC enzyme system increases in activity in vascular smooth muscle and endothelial cells after in vitro exposure to hyperglycemia and in animal models of diabetes (*4*), but the presence of 12 isoforms of PKC has complicated the dissection of the activation. With the use of new molecular tools and specific antibodies, however, the β_2 isoform has been identified as potentially important in the vascular response to hyperglycemia. To test this hypothesis, Ishii *et al.* used a new, specific inhibitor of PKC β isoforms and showed that this inhibitor could normalize the elevated PKC activity in retina and kidney of diabetic rats. This effect is paralleled by normalization of the rate at which the kidney filters blood and of retinal blood flow, both of which are altered in diabetic animals and people. These results provide strong evidence that the β isoform is the key to the glucose-induced activation of PKC in vascular tissues and that this activation has pathophysiologic consequences.

Does this mean that some of the long-term complications of diabetes can be prevented by pharmacologic inhibition of PKC? The new findings are encouraging, but their clinical application is not quite yet

The authors are in the Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Department of Veterans Affairs Puget Sound Health Care System and University of Washington, Seattle, WA 98108, USA. E-mail: dporte@u.washington.edu



How too much glucose may lead to the long-term complications of diabetes. AGE, advanced glycosylation endproducts; DAG, diacylglycerol; PKC, protein kinase C.

appropriate. The connection between the endpoints measured by Ishii *et al.*—hyperfusion of the kidney and albuminuria—and the permanently impaired renal function of diabetics remains a reasonable but unproven hypothesis. The link between increased retinal blood flow and the eventual retinal hypoxia and capillary closure in diabetics is also tenuous. Nevertheless, the potential development of a specific enzyme inhibitor with minimal short-term toxicity in vivo opens up many possibilities for future, longer term study.

But the pathway from discovery to application in patients can be long and tortuous. Before the new inhibitor can be used therapeutically, some hurdles must be overcome. First is the issue of toxicity. There are many isoforms of PKC, and it must be determined that the new drug does not produce toxic side effects by its action on other forms of PKC. In addition, the β_2 isoform is heavily expressed in the central nervous system (CNS) (*3*). Because the inhibitor reduces retinal PKC activity to a value below normal, it is possible that the normal CNS function of PKC β might be impaired by the inhibitor and that such effects might be difficult to discern or require a longer time frame to be recognized. Second, the drug may not inhibit all of the complications of diabetes. PKC and its endogenous activator, diacylglycerol (DAG), are decreased, not increased, in peripheral nerve from diabetic animal models or after hyperglycemic exposure of normal tissues in vitro (*8*). The specific isoform affected is not yet known, but PKC activity may not be equally critical in all diabetic complications. Complete treatment of diabetic complications may therefore require additional drugs. Finally, other metabolic pathways that have been implicated in the toxic effects of hyperglycemia need to be considered, such as activation of the aldose-reductase pathway (*8*) or enhanced protein glycosylation (*9*) (see the figure). Both of these pathways contribute to potentially harmful effects of hyperglycemia that can be reversed by inhibitors of these pathways. Aldose reductase inhibitors have been under clinical testing for 20 years (*10*), but they remain to be proven effective enough to merit Food and Drug Administration approval (*11*). A potent inhibitor of protein glycation is also under clinical trial after a similar report of its efficacy in a diabetic animal model, published in *Science* 10 years ago (*12*), but its promise similarly awaits fulfillment.

Glucose is a molecule essential for life (particularly for function of the nervous system), but its concentration must be carefully controlled because of the powerful adverse effects of both too much and too little glucose. The manifestations of this toxicity are legion, and maintaining the concentration of glucose within a narrow window is extraordinarily difficult for many individuals (diabetes affects approximately 5% of adults). Alternate approaches, such as those based on the new information reported by Ishii *et al.*, are to be applauded, but the obstacles to the complete understanding of glucose toxicity and its prevention are formidable.

References:

1. DCCT Research Group, *New Engl. J. Med.* **329**, 683 (1993).
2. H. Ishii, *et al.*, *Science* **272**, 728 (1996).
3. Y. Nishizuka, *Nature* **334**, 661 (1988).
4. B. Williams, *J. Hypertens.* **13**, 477 (1995).
5. H. L. Hachiya, S. Takayama, M. F. White, G. L. King, *J. Biol. Chem.* **262**, 6417 (1987).
6. O. Hanson-Painton *et al.*, *Mol. Chem. Neuropathol.* **20**, 245 (1993).
7. M. Schwartz, D. Figlewicz, D. Baskin, S. Woods, D. J. Porte, *Endocr. Rev.* **13**, 387 (1992).
8. M. J. Stevens, E. L. Feldman, D. A. Greene, *Diabetic Med.* **12**, 566 (1995).
9. M. Brownlee, in *Diabetes Mellitus, Theory and Practice*, H. Rifkin and D. Porte, Eds. (Elsevier, New York, 1990), pp. 279–291.
10. R. G. Judzewitsch *et al.*, *N. Engl. J. Med.* **308**, 119 (1983).
11. M. A. Pfeifer and M. P. Schumer, *Diabetes* **44**, 1355 (1995).
12. M. Brownlee, H. Vlassara, A. Kooney, P. Ulrich, A. Cerami, *Science* **232**, 1629 (1986).

Speciation in Action

Jerry Coyne

In trying to understand the two great engines of biological diversity—adaptation and speciation—evolutionary biologists occupy an uncomfortable niche. Blessed with the immense challenge of reconstructing and understanding the evolution of organisms, we are cursed by the historical aspect of this enterprise, which regularly denies us the crucial experiments and observations to test our theories. All too often our questions are addressed rather than answered, and plausibility arguments must do in place of facts. Reconstructing the past is of course a perfectly valid way of doing science—if it were not, cosmologists and geologists would be out of business. Nevertheless, evolutionists often suffer from "molecular biology envy," the fear that we are not as scientifically rigorous as our colleagues down the hall with their big grants and decisive experiments.

To allay this insecurity, we search for evolution in real time and treasure our examples of adaptation in action, such as the case of melanism in the pepper moth that graces every general biology text. It is much rarer, however, to see speciation in action, because that process requires not just evolution at a single locus (as in the moth) but more extensive genetic divergence that makes populations reproductively incompatible. In a report in this issue of *Science*, Rieseberg and co-workers (*1*) have reproduced in the greenhouse the genetic changes leading to the formation of a naturally occurring species of sunflower and have shown that these changes are repeatable across independent experiments. This unique study bridges the gap between the experimental and historical aspects of our field.

The species in question is *Helianthus anomalus*, an outcrossing diploid restricted to swales and sand dunes in Arizona and Utah. (This species has long provided the Hopi Indians with food and pigment for facial decoration.) Molecular evidence (*2*) indicates that *H. anomalus* arose by recombinational speciation, a process in which two distinct species hybridize, and the mixed genome of the hybrid becomes a third species that is reproductively isolated from its ancestors.

The putative ancestors of *H. anomalus* are *H. annuus* and *H. petiolaris* (see figure), which occur widely in the western United

The author is in the Department of Ecology and Evolution, 1101 East 57th Street, University of Chicago, IL 60637, USA. E-mail: jcoyne@pondside.uchicago.edu