30 April 1999

Science

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Pages 701–864 $8

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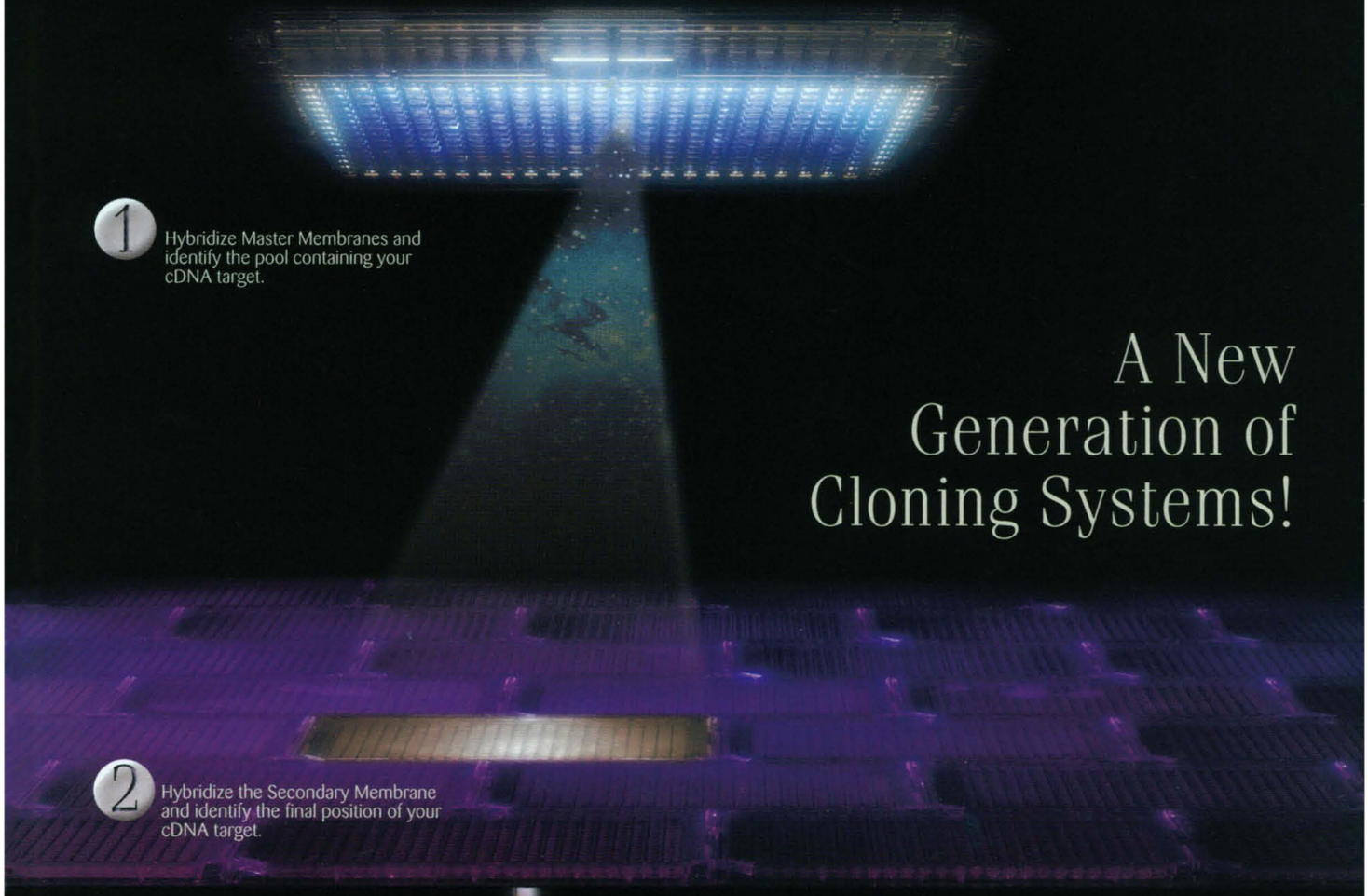

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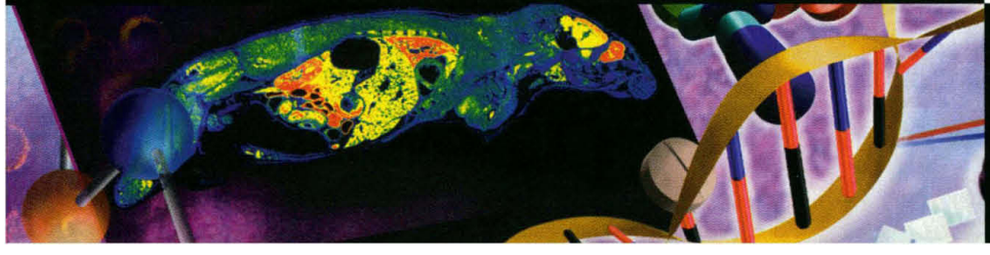

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COVER The cryptochromes are photoreceptors through which cells respond to blue light. A Review by Cashmore *et al.* (p. 760) in the special section on Signal Transduction (beginning on p. 755) summarizes recent evidence that cryptochromes function not only in regulation of plant growth, but also in entrainment of the endogenous biological clocks of a broad range of organisms—from plants and insects to mammals. [Collage: concept by A. Cashmore, created by Ann Elliot Cutting]

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Death and deformity by natural causes

DEPARTMENTS

NEWS

NEWS OF THE WEEK

NEWS FOCUS

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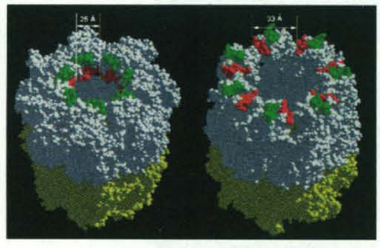
REPORTS



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Practice makes perfect

SIGNAL TRANSDUCTION

REVIEWS

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

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SCIENCE'S COMPASS

745

With an artistic spirit?

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785

A tale of two twists

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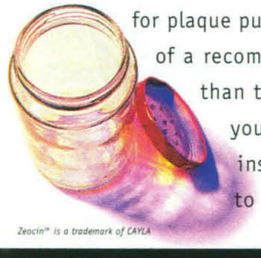

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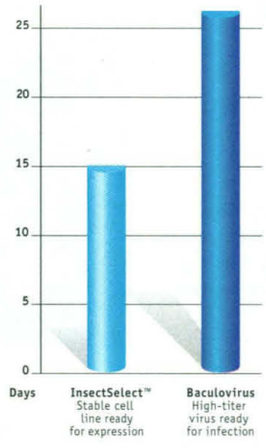

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TUNNELING TO A SOLUTION

Many problems in physics, chemistry, and biology require finding the minimum energy configuration of the system. One classical method is simulated annealing—the system is heated into an excited state and then cools and reconfigures into a local energy minimum. For extremely large or complex systems, the cooling time may be prohibitively long. Brooke *et al.* (p. 779) demonstrate a method of quantum cooling at temperatures where thermal annealing cannot proceed. Instead, the system reconfigures by quantum tunneling and the minimum is achieved at a faster rate than with thermal annealing. Quantum annealing may provide an algorithm for implementation in quantum computers for large optimization problems.

KEEPING THEIR HEADS DOWN

Sauropods, some of the largest herbivorous dinosaurs, are noted for their long necks and tails. Stevens and Parrish (p. 798) present computer models of the range of motion of the articulated necks of two sauropods, *Diplodocus* and *Apatosaurus*, to determine their feeding habits. Although sauropods have been depicted with their necks bent into a position nearly perpendicular to the ground and feeding in the treetops, their long necks actually had a limited range of motion and could not be bent into a vertical position. These large herbivores were constrained to gather food from about eye level to slightly below ground level if they stayed on all four legs. The real food chain advantage these long-necked dinosaurs may have had was the ability to gather food from the bottom of shallow lakes or ponds.

TUNING CHIRALITY

Helical architectures such as DNA and helical motives in proteins may assemble further to form helical superstructures. Engelkamp *et al.* (p. 785) used similar principles to design molecules that self-assembled into fibers consisting of helical superstructures. The chirality of these fibers can be tuned by the addition of potassium ions, which change the stacking of the molecules in the fibers, resulting in loss of helicity in the fibers. The materials may find use in optoelectronic applications or as sensors.

FROG DEFORMITIES DECIPHERED

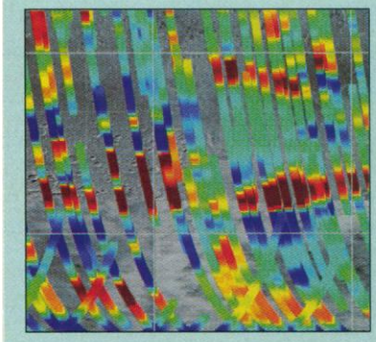
The decline in amphibian populations and rise in incidence of amphibian deformities is not in question. However, none of the suggested causes—ultraviolet radiation, biocides, hormone mimics, or infectious agents—has been decisively linked to the changes. Johnson *et al.* (p. 802) and Sessions *et al.* (p. 800) now provide strong support for the involvement of a trematode parasite (see the news story by Kaiser). Morphological studies of field populations of frogs indicate mechanical perturbation of limb development consistent with trematode cyst infestation, and experimental exposure of tadpoles to trematode larva caused abnormalities that closely match those found in field sites.

CAPTIVE CELLULAR COPPER

The antioxidant enzyme superoxide dismutase (SOD) requires copper (Cu) as a cofactor, and generation of the Cu-bound form of SOD in yeast cells requires the Cu chaperone for superoxide dismutase (yCCS). Rae *et al.* (p. 805; see the Perspective by Lippard) report results that help establish how the chaperone protein functions and why it is required in vivo. In an in vitro system, yCCS alone directly provided Cu to SOD1 and activated the enzyme. However, the yCCS protein was only required at very low concentrations of Cu. In vivo, if intracellular concentrations of free Cu were allowed to increase (either by exposure of cells to high Cu concentrations or by removal of proteins that sequester Cu), yCCS would no longer be needed for activation of SOD. Taken together, the results indicate that the intracellular concentration of free Cu is normally very low—no more than 10^{-18} molar, or much less than one free Cu atom per cell.

ENTRY EFFECTS

Although the finding that human immunodeficiency virus–type 1 (HIV-1) uses co-receptors such as CCR5 or CXCR4 for entry into cells has raised considerable excitement in the field, it has been unclear whether entry by one means or the other has different effects on disease progression. Harouse *et al.* (p. 816) compared infection of rhesus macaques with two chimeric viruses, one expressing the envelope gene from an HIV that would use CCR5 and the other from a CXCR4-dependent virus. When CCR5 was used, there was a rapid loss of $CD4^+$ T cells in the intestine but a gradual depletion in the peripheral circulation. When the CXCR4-dependent virus was used, there was a dramatic decrease of peripheral $CD4^+$ cells and no decrease was seen in the intestine. These results indicate that co-receptor utilization is an important determinant of pathogenesis and provides a new model for vaccine testing.



MARTIAN MAGNETISM AND PLATE TECTONICS

Unlike Earth, Mars appears to have no global magnetic field generated by an interior dynamo. Previous measurements by the magnetic field experiment and electron reflectometer (MAG/ER) on board the Mars Global Surveyor (MGS) showed that no global field is currently generated but magnetic anomalies were detected in the crust. MGS has since reduced its orbit, and MAG/ER measurements made at lower altitudes indicate not only relatively strong magnetic features but a linear pattern correlated to the surface geology in some regions (see the news story by Kerr). Acuña *et al.* (p. 790) and Connerney *et al.* (p. 794) show that the older, more heavily cratered terrain in the southern hemisphere has linear bands of magnetic features, where the direction of the radial component of the magnetic field alternates between the positive end pointing in toward the center and pointing out toward the surface. These alternating linear stripes are reminiscent of the magnetic stripes on Earth's sea floor that delineate tectonic plate spreading. The authors suggest that plate tectonics may have operated on Mars early in its history and that the "bar code" pattern is a relic trace of this previous activity. Thus, Mars may once have had a dynamo generated by fluid motions in a metallic core that allowed plates to move on the surface and the magnetic signature related to the dynamo to be retained in the cooling lavas on the surface.

CONTINUED ON PAGE 711

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 709

BECOMING ATTRACTIVE

How do the right cells find each other to orchestrate a specific immune response? Tang and Cyster (p. 819) report that immature dendritic cells (DCs) that migrate from the skin acquire properties that allow them to attract specific T cells to their proximity. The immature DCs pick up antigen in the skin and then migrate to the draining lymph nodes. These fresh immigrants secrete the chemokine MDC (macrophage-derived chemokine), which allows T cells that have recently been activated by antigen to find the DCs. The concentration of antigen-specific T cells in the proximity of the DC is thus increased, which increases the probability of appropriate activation and an effective immune response.

STRETCHING PROTEINS ON THE RACK

Proteins are synthesized as linear polypeptides that fold into mostly globular structures in which the hydrophobic amino acids generally are sequestered in the interior. The chaperonin complex GroEL-GroES collects misfolded proteins by binding to exposed hydrophobic parts and then enabling the proteins to unfold and make an additional attempt. Shtilerman *et al.* (p. 822) use the kinetics of proton exchange to show that large rearrangements of the substrate protein occur in the initial binding event and that the unfolded protein is then released from the chaperonin complex to try folding again on its own. The initial rearrangement may be akin to stretching the polypeptide into a more linearized state.

FINE-TUNING CANCER THERAPY

In order to grow, solid tumors must receive an adequate supply of blood, and tumor cells often produce factors that stimulate angiogenesis (the formation of new blood vessels). A variety of molecules that inhibit angiogenesis are being developed as cancer therapies. Bergers *et al.* (p. 808) tested four different angiogenesis inhibitors in a transgenic mouse model that mimics the multistage progression of tumors in their natural tissue microenvironment. These inhibitors, which included angiostatin and endostatin, showed different efficacy profiles as a function of the stage of tumorigenesis. Thus, optimization of antiangiogenic therapy will require consideration of the tumor stage being targeted.

SAVING LIVER CELLS

Understanding the mechanisms of viral clearance is important to designing therapies and understanding viral pathogenesis. Although it had been thought that hepatitis B DNA disappeared from acutely infected individuals as a result of the destruction of virus-infected liver cells, Guidotti *et al.* (p. 825) used a chimpanzee model of infection to show that more than 90% of the virus was cleared without significant destruction of hepatocytes and occurred before maximal infiltration of T cells into the liver.

TECHNICAL COMMENT SUMMARIES

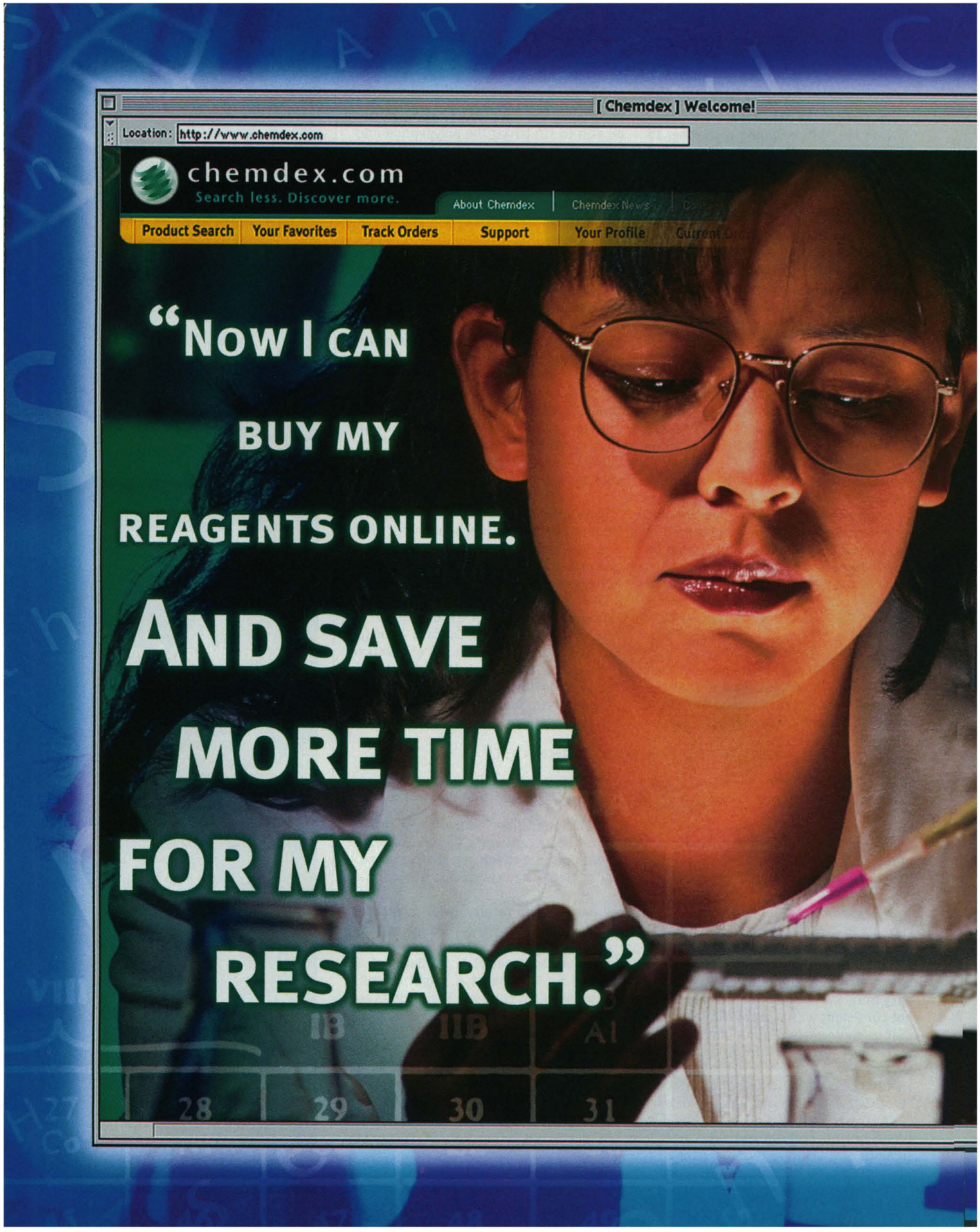
Whether "Slip-Mode Conductance" Occurs

The full text of these comments can be **seen at** www.sciencemag.org/cgi/content/full/284/5415/**711a**

L. F. Santana *et al.* (Reports, 13 Feb. 1998, p. 1027) found that "activation of the β-adrenergic receptor or protein kinase A [PKA] in rat heart cells transformed [the sodium] Na^+ channel into one that is promiscuous with respect to ion selectivity, permitting calcium ions (Ca^{2+}) to permeate as readily as Na^+." They called this transformation "slip-mode conductance."

H. B. Nuss and E. Marbán made whole-cell patch clamp recordings of membrane currents in Chinese hamster ovary (CHO) cells that expressed the α and β1 subunits of the Na^+ channel. They conclude that the reports of "slip-mode conductance" represent a technical artifact, possibly arising from suboptimal voltage control. C. W. Balke *et al.* studied whether the induced Ca^{2+} current observed by Santana *et al.* might actually arise from a tetrodotoxin-blockable Ca^{2+} current through Ca^{2+} channels. Their results are not consistent with a change in selectivity classical Na^+ channels induced by conditions that promote channel phosphorylation.

In response, J. S. Cruz *et al.* present new data from experiments on the co-expression of the α and β1 or β2 subunits, or both, of the human heart Na^+ channel in HEK293 cells. With the use of a method similar to that of Nuss and Marbán, they show "that Ca^{2+} can permeate Na^+ channels in an heterologous expression system" following "PKA phosphorylation" of the channel, which "provides strong evidence in support of [their] original findings and hypothesis." Cruz *et al.* also show that the Na^+ channel β subunits play an important role in heart cell function.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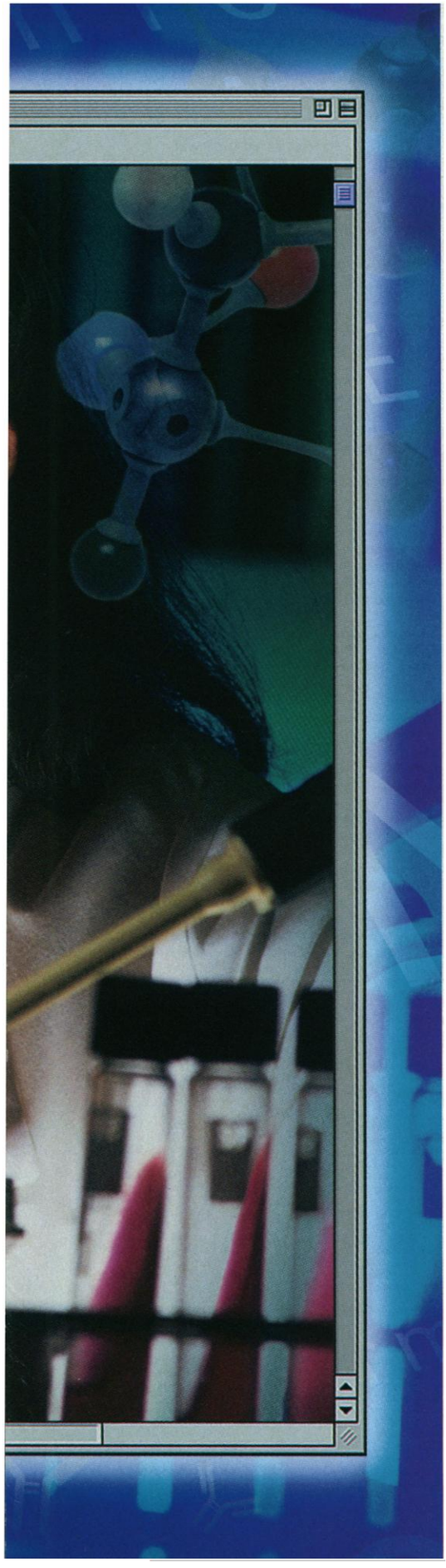

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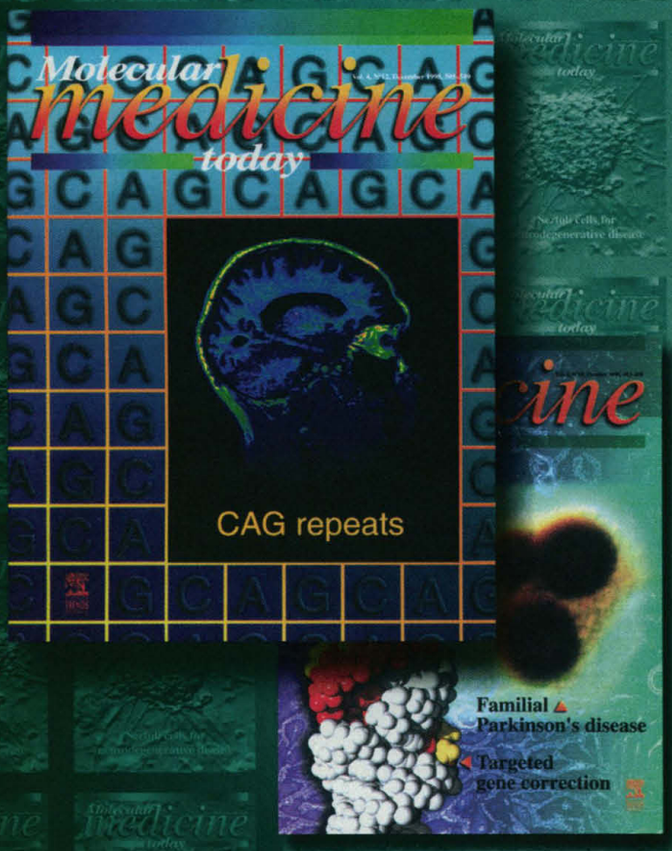
Molecular medicine today



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- Towards gene therapy of diabetes mellitus, *F. Levine*
- Virulence factors of helicobactor pylori: implications for vaccine development, *C. Josenbans*
- Expanded capacity adenoviral vectors, *M. Morsey & C.T. Caskey*
- Applications of telomerase research in the fight against cancer, *S. Sukumar* et al
- The etiology of scleraderma: new perspectives, *C. Arlett* et al
- Xeroderma pigmentosum and the role of UV-induced DNA damage in skin cancer, *H. van Steeg & K. Kraemer*
- Fluid shear stress as a modulator of endothelial phenotype, *J. Topper & M. Gimbrone*
- Sertoli cell transplants to treat neurodegenerative disease, *P. Sanberg* et al
- Heat shock protein-peptide complexes for immunotherapy of human cancer, *P. Srivastava & D. Przeplorka*

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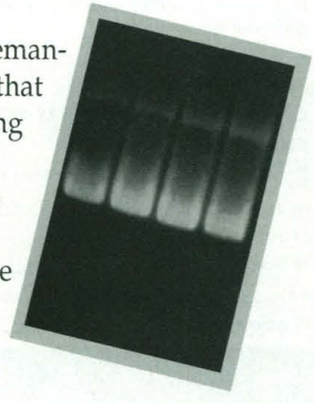

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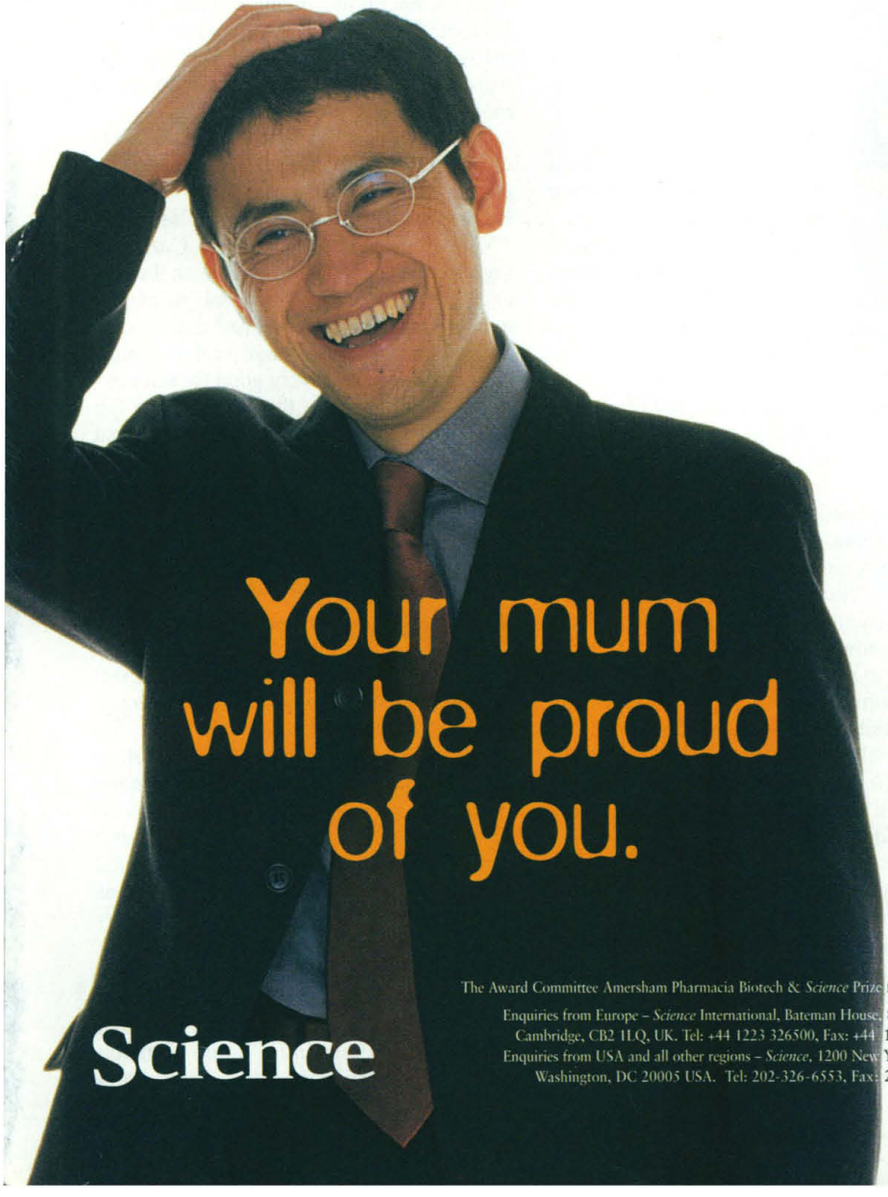

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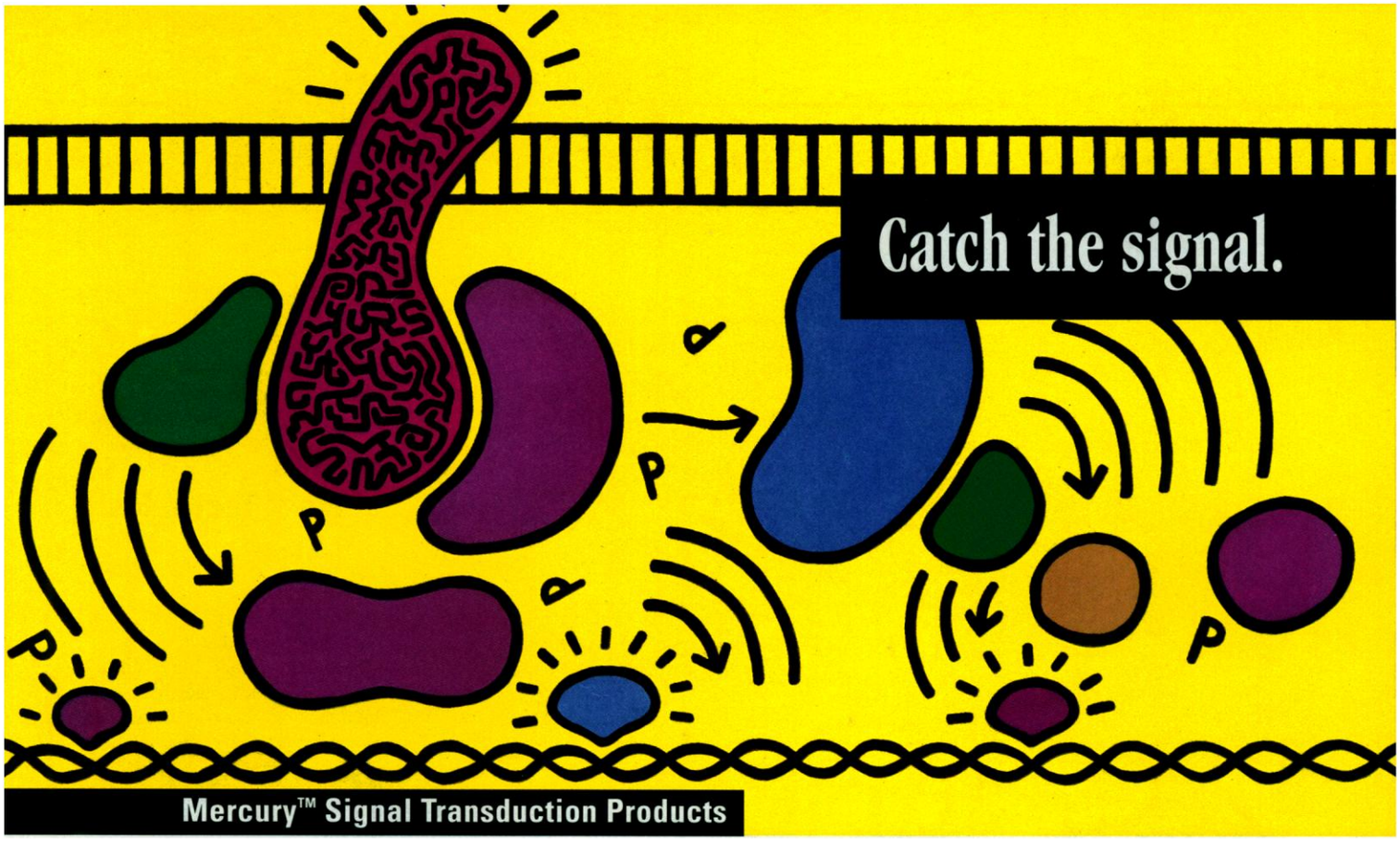

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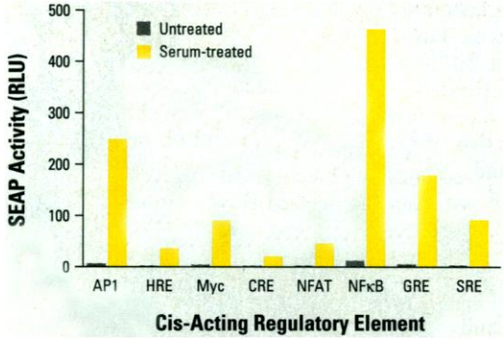

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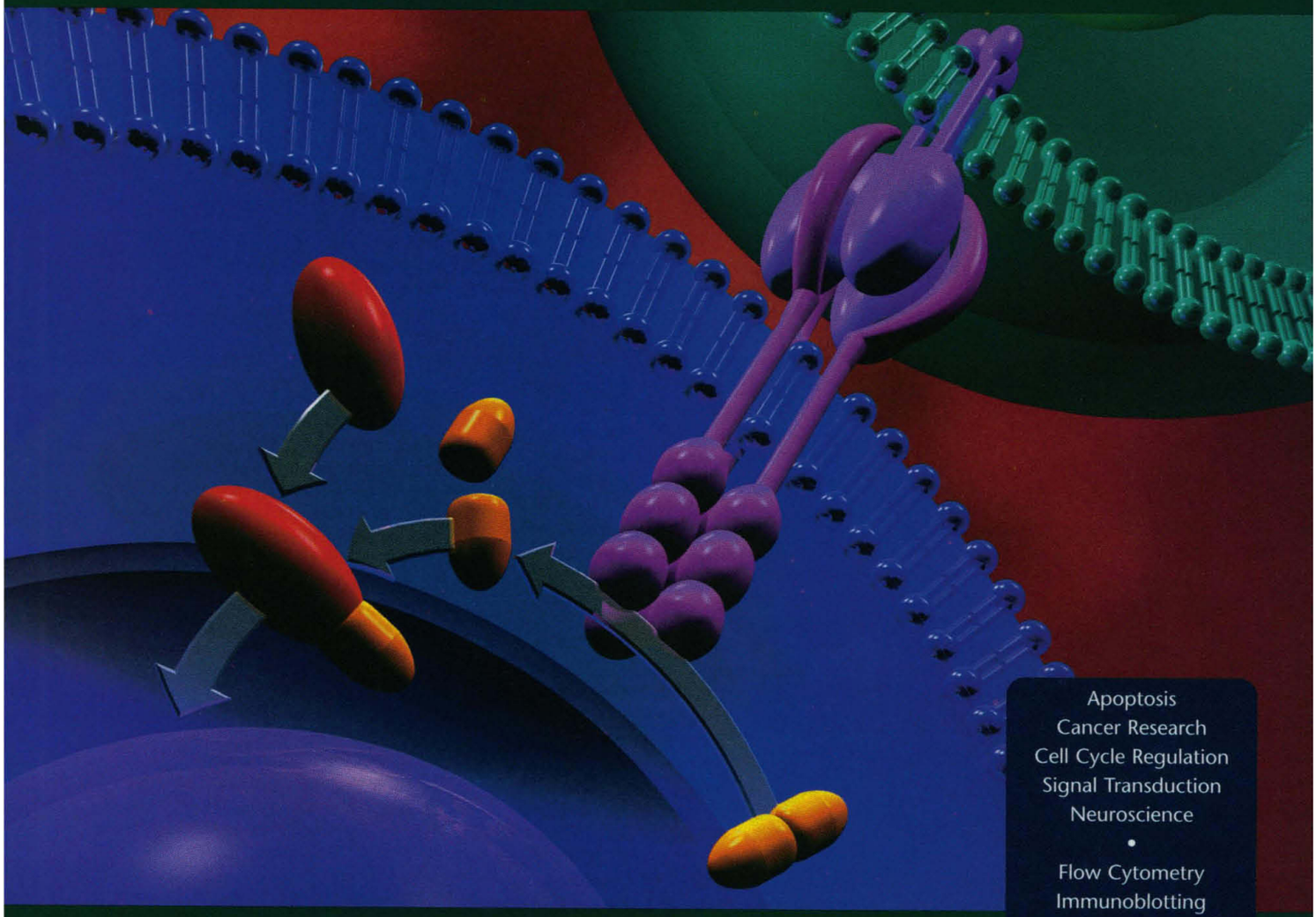

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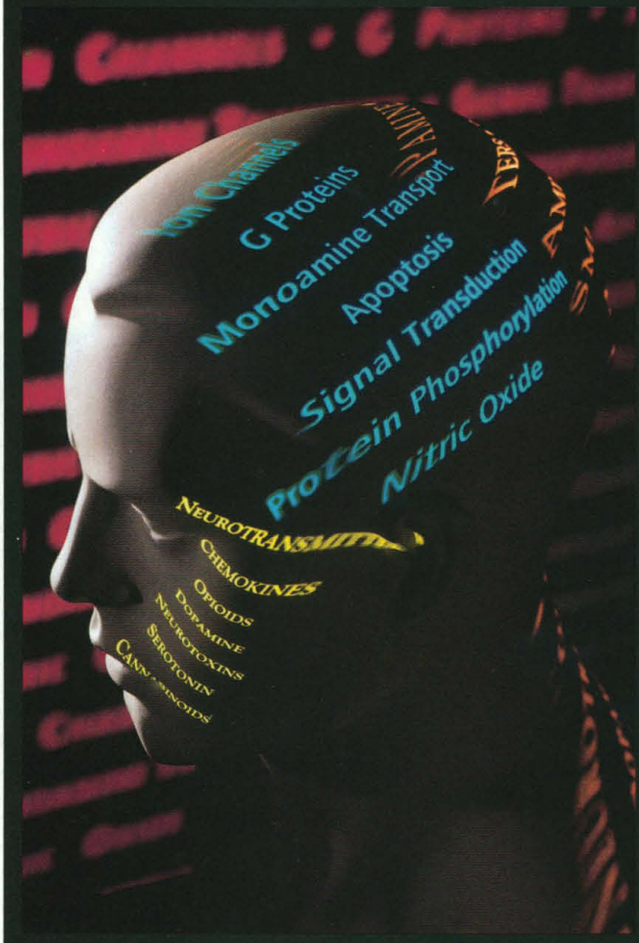

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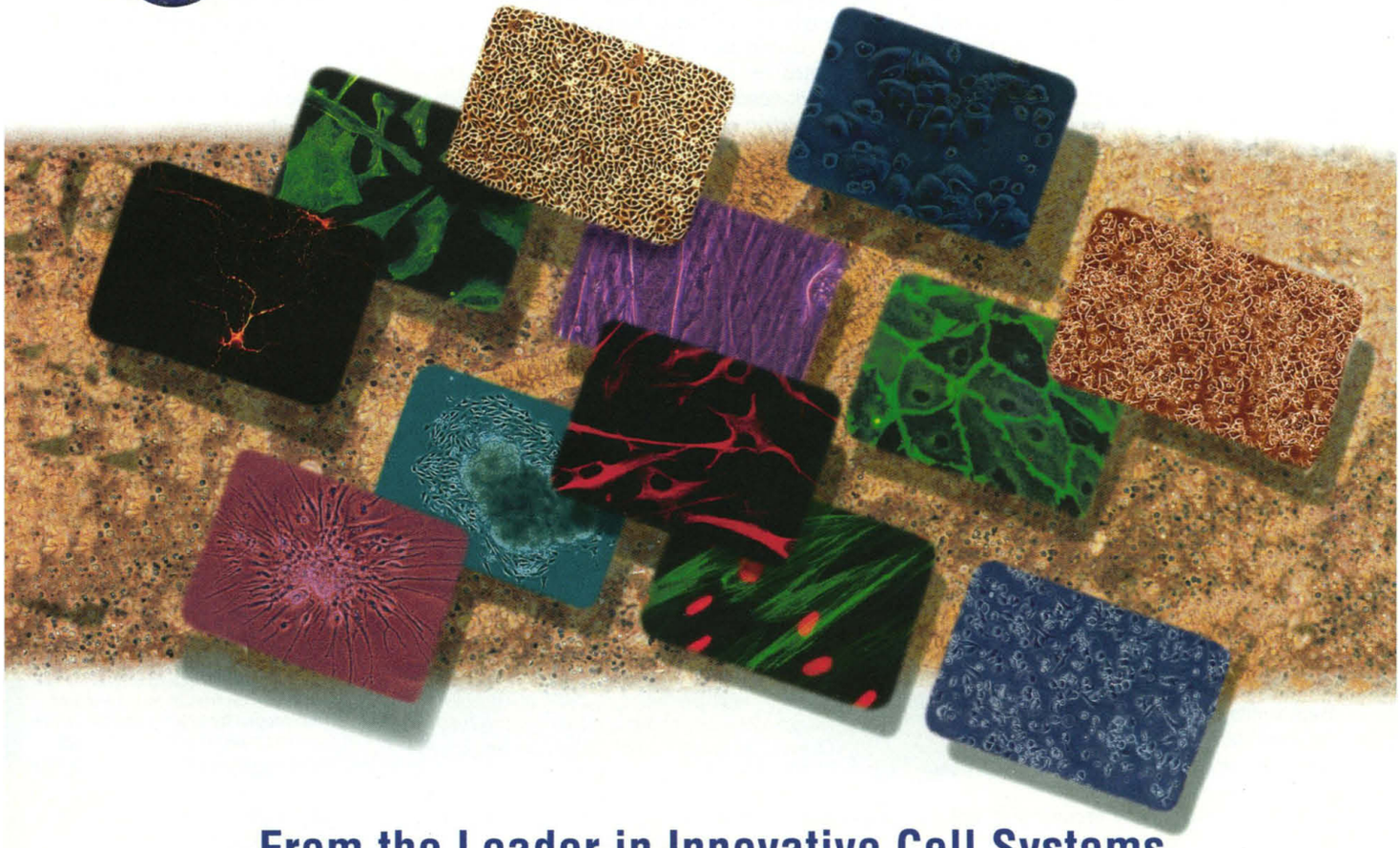

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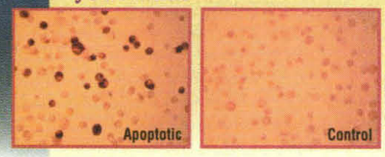

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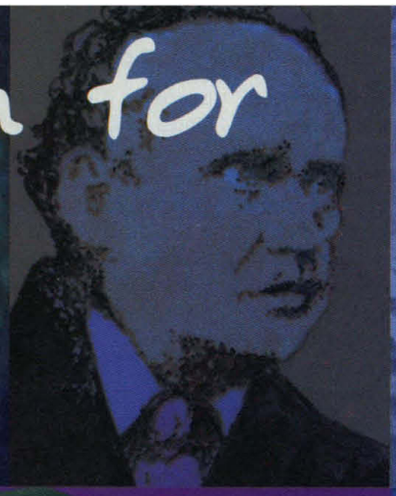

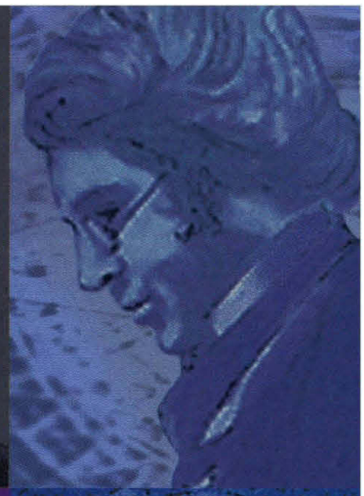

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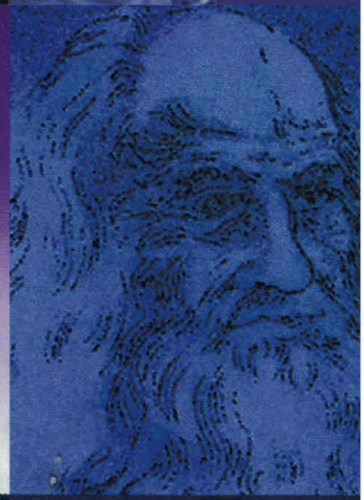

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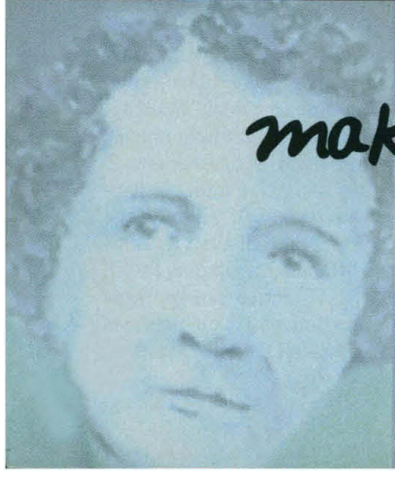

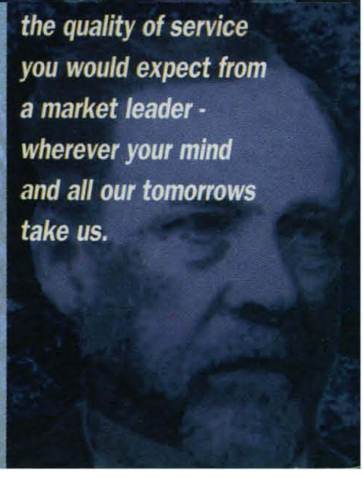

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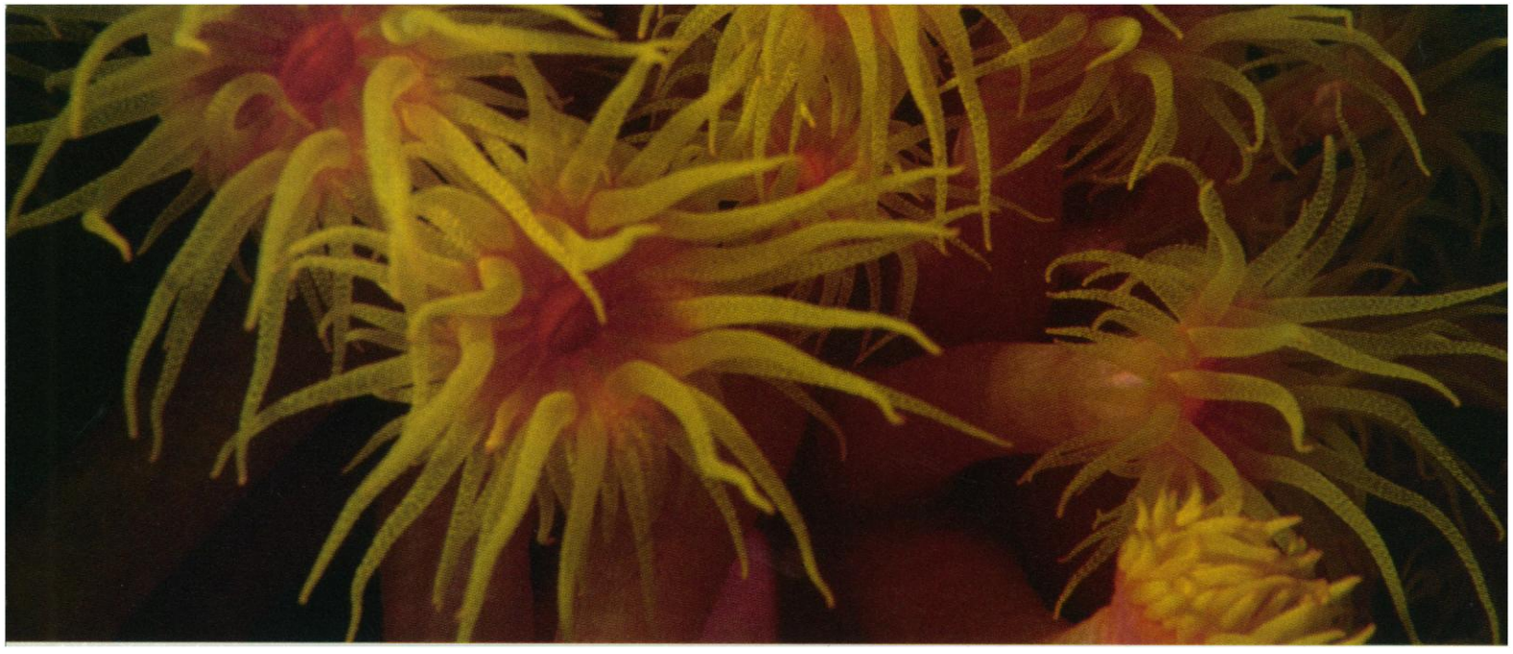

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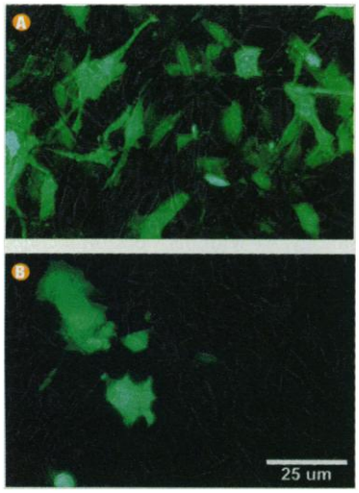

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