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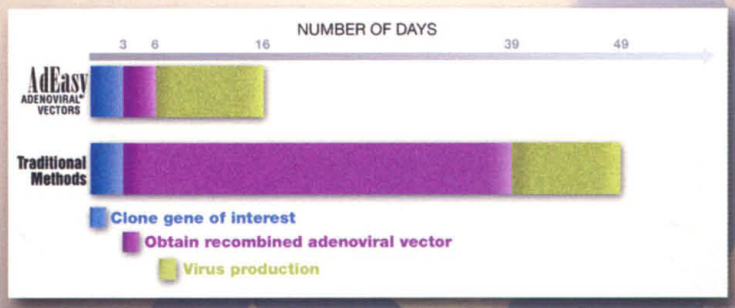

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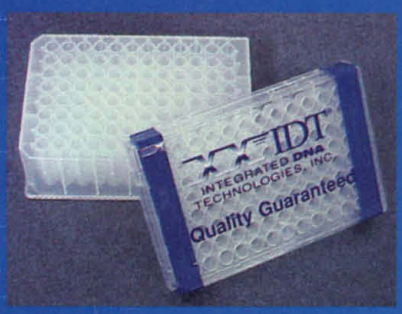

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Science

Volume 297 26 July 2002 Number 5581

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Cell therapies for damaged neurons

NEWS

NEWS OF THE WEEK

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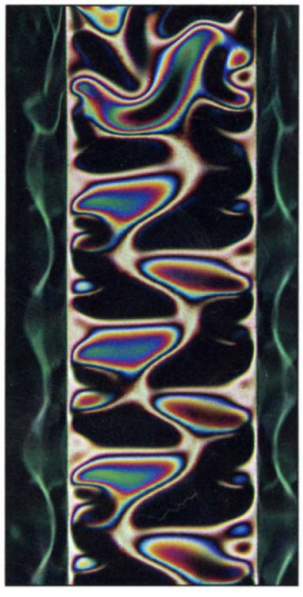

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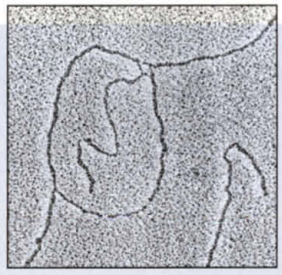
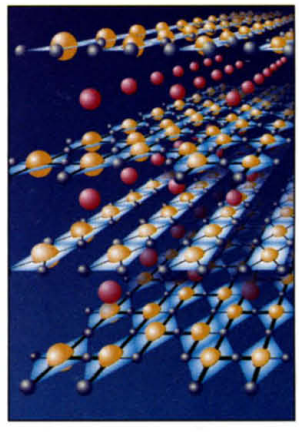
See also the Perspective on p. 534 and Reports on pp. 599, 602, and 606.



COVER 599

Electron micrograph showing a stalled DNA replication fork in a checkpoint-defective yeast mutant. Aberrant DNA replication is one mechanism postulated to contribute to genome instability. The molecular basis of genome instability and its role in cancer development are the subject of a special feature in this issue. [Image: J. M. Sogo *et al.*]



584

Charge moving along the cuprate ladders

New on *Science* Express The genome of *Fugu rubripes*

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CONTENT HIGHLIGHTS AS OF 26 JULY 2002

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SCIENCE EXPRESS www.sciencexpress.org

Whole-Genome Shotgun Assembly and Analysis of the Genome of *Fugu rubripes* S. Aparicio *et al.*

An analysis of the second publicly available vertebrate genome sequence, that of the pufferfish *Fugu rubripes*.

Imaging Quasiparticle Interference in $Bi_2Sr_2CaCu_2O_{8+\delta}$
▼ J. E. Hoffman *et al.*
499 Scanning tunneling microscopy of a high-T_c superconductor reveals quasiparticle interference patterns.

Current Rectification by Pauli Exclusion in a Weakly Coupled Double Quantum Dot System K. Ono, D. G. Austing, Y. Tokura, S. Tarucha

In a coupled two-dot system, Pauli repulsion prevents electron flow in one direction but allows flow in the other.

TECHNICAL COMMENTS

Antiangiogenic Therapy and *p53*

Yu *et al.* (Reports, 22 Feb. 2002, p. 1526) offered evidence that tumors in which the *p53* tumor suppressor gene has been inactivated (which happens in about half of human cancers) are less responsive to antiangiogenic therapy than tumors with normal *p53* function, a finding that raised a potential obstacle to cancer therapies involving angiogenesis inhibitors. Giaccia and Hammond, in a comment, question whether the HCT116 cell lines used in the Yu *et al.* study were appropriately chosen and hold that "more data are needed before [the study's] relevance to antiangiogenic therapy can be considered." Browder *et al.*, in a separate comment, maintain that the study's results "have been widely misinterpreted to imply that antiangiogenesis therapy will eventually fail," even though growth of both $p53^{+/+}$ and $p53^{-/-}$ cells in the study were "clearly inhibited" by antiangiogenic therapy. Kerbel *et al.*, in their response, discuss both the specific technical issues raised by Hammond and Giaccia and the broad implications of the Yu *et al.* study for antiangiogenic therapy.

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/297/5581/471a

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SINGAPORE: Teaching—A Meaningful and Challenging Career S. Zechariah

From nutritionist to teacher of teenagers.

GERMANY: Award for Laziness? E. von Ruschkowski

Should a professor who neglects her teaching and mentoring be rewarded with a research grant?

CANADA: Shortage? What Shortage? L. McKarney

Biotech leaders and health researchers say there is no shortage of good science talent in Canada.

US: LGBT Scientists Chart Their Own Course Y.-M. Chan and B. Lindstaedt

Gay, lesbian, bisexual, and transgendered scientists—a largely invisible minority in the community—face unique career challenges.

EUROPE: Where Ph.D.'s Are Well Paid A. Holmes

A British-born physicist wonders why more haven't caught on to the benefits of the well-rewarded Swiss Ph.D.

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Review: Innate Immunity, Local Inflammation, and Degenerative Disease P. L. McGeer and E. G. McGeer

An ancient immune system gone awry can cause MAC self-attack, chronic inflammation, and tissue damage.

Noteworthy This Week: The Nerve of Youth R. J. Davenport

Roving protein might invigorate developing neurons.

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signal transduction knowledge environment

Perspective: Binary and Graded Responses in Gene Networks M. Louis and A. Becskei

How transcriptional regulators can act as on-off switches or produce graded responses.

Perspective: Dubble or Nothing? Is HAUSP Deubiquitylating Enzyme the Final Arbiter of p53 Levels? S. A. Wood
▼ 543 How deubiquitylation of proteins, such as p53 and β-catenin, may fine-tune cellular responses.

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THIS WEEK IN Science

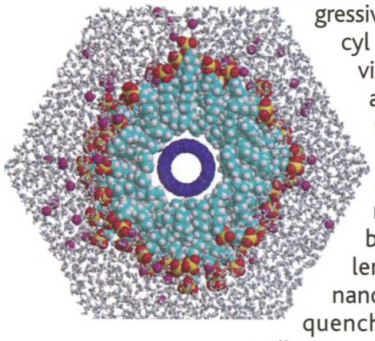
edited by Phil Szuromi

Protons Passing Through Water

In solution, a certain fraction of water molecules are dissociated into H_3O^+ and OH^-, and these species show much greater mobility than would be expected, based on comparisons to other ions. Spectroscopic studies of a mixture of HDO and D_2O by Bakker and Nienhuys (p. 587) suggest an explanation—that the O-H stretch vibrations in liquid water are highly anharmonic. The addition of hydrogen-bonding interactions stretches the potential energy surface and decreases the level spacing. In the second vibrational excited state, which is at an energy that is only 20% of the dissociation energy of the O-H bond, the proton is already highly delocalized.

Glowing Individuals

Single-walled carbon nanotubes with different diameters and chiralities are different molecules with their own individual properties, but studying these differences requires methods for separating and stabilizing the nanotubes from bundles and ropes in which they form. O'Connell *et al.* (p. 593) used aggressive sonication and sodium dodecyl sulfate (SDS) to stabilize individual tubes, which they are then able to purify using centrifugation. The semiconducting nanotubes, upon being freed from quenching interactions with metallic nanotubes, display band-gap fluorescence at wavelengths between 800 and 1600 nanometers. This emission can be quenched when the nanotube side walls are protonated under acid conditions.



Milky Way Interlopers

The globular clusters of old stars that populate the halo of the Milky Way Galaxy are thought to represent the oldest objects left over from the initial collapse of the proto-Galaxy. Oddly, the clusters form two groups with slightly different ages and other properties. Yoon and Lee (p. 578; see the Perspective by Clement) have found a planar alignment of the metal-poor group of clusters in the outer halo. They suggest that these clusters are interlopers from a satellite galaxy that formed just before the Milky Way but that did not retreat fast enough to retain these few stray clusters.

Monsoon Wetting

Variations in monsoon activity are an important but poorly understood aspect of global weather patterns. Anderson *et al.* (p. 596; see the Perspective by Black) analyzed the relative abundance of *Globigerina bulloides*, a surface-dwelling species of foraminifera that is a particularly good proxy for upwelling conditions like those produced by strong monsoonal winds, in order to reconstruct the intensity of the Southwest Asian monsoon during the past millennium. This record from the Northwest Arabian Sea chronicles an increase in monsoon strength during the past four centuries, from a minimum around 1600 A.D. to the highest values of the entire interval at present. Their results suggest that the Southwest Asian monsoon intensities will continue to increase in strength if Northern Hemisphere temperatures continue to rise.

And in Brevia ...

A carefully controlled replication by Wright and Czeisler (p. 571; see the news story by Barinaga) of results previously reported in *Science* show that light exposure to the back of the knees does not in fact phase-shift the human circadian clock.

Keeping the Forks on the Road

Any failure in the many steps of DNA replication can result in the loss of chromosome integrity through the introduction of double-stranded (ds) DNA breaks (see the Viewpoint by Carr). Two reports focus on replication fork progression. To determine how replication forks are monitored, Sogo *et al.* (p. 599; see the cover) directly visualized the structure of replication forks in wild-type and checkpoint defective yeast cells using electron microscopy. In wild-type cells, stalled replication forks expose short regions of single-stranded (ss) DNA. In checkpoint defective cells, replication intermediates with long ssDNA regions and reversed forks are found, suggesting that dsDNA breaks arise through inappropriate processing of the backed-up forks. The ATR/ATM family of chromosome-bound signal transduction proteins, which includes Mec1 in yeast, senses damaged or aberrant DNA and then triggers cell cycle arrest and repair. Cha and Kleckner (p. 602) show that in the absence of Mec1, DNA breaks occur in specific regions of chromatin, christened replication slow zones. Thus, Mec1 plays a role in replication fork progression during normal S-phase of the cell cycle.

Moving Up the Ladder Together

Complex interactions occur in the two-dimensional planes of layered copper oxide superconductors. One route to unraveling this complexity is to look for common behavior in simpler oxide materials. Blumberg *et al.* (p. 584) adopt this route to probe the spectroscopic, transport, and dielectric properties of the $Sr_{14}Cu_{24}O_{41}$ ladder compounds, materials that contain two-legged fragments of the CuO plane. The insulating phase forms a charge-ordered state that is depinned at low electric field and that may represent a new ground state of the cuprate superconductors.

Pain in the Gut

Helicobacter pylori, which infects around 50% of people around the world, can cause peptic ulcers and has been linked to gastric cancer. Mahdavi *et al.* (p. 573) have now isolated a receptor termed the sialic acid binding adhesin on *H. pylori* that binds to inflammation-induced sialyl-Lewis x (sLex) antigens on the gastric mucosa. Biopsies from infected and uninfected individuals show that the level of sLex is increased in infection. The interac-

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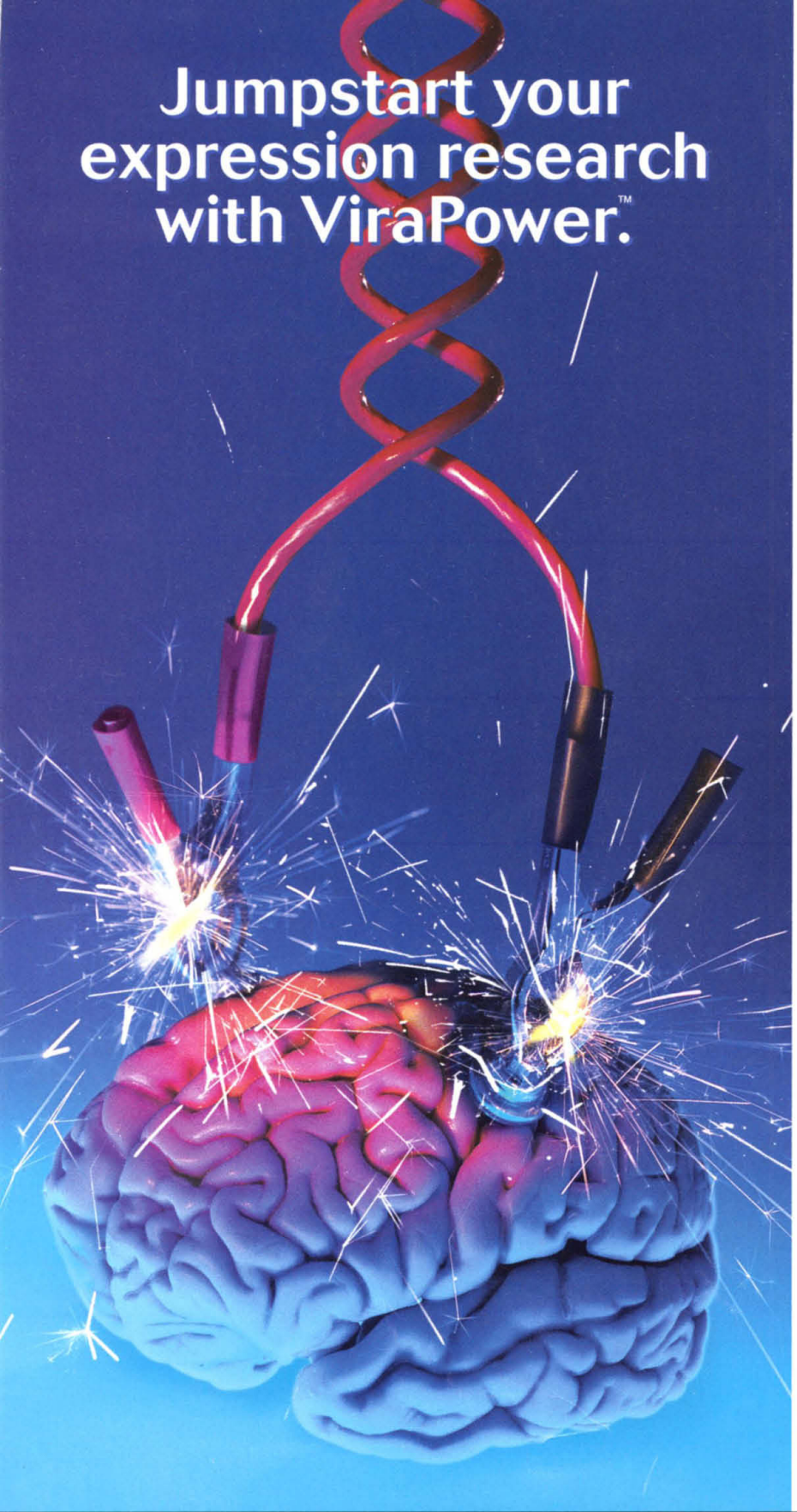

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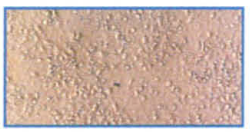

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tion between the sLex and the adhesin may thus contribute to the virulence and to the chronicity of *H. pylori* infections.

Damage-Response Team

A group of rare inherited disorders that are characterized by cellular sensitivity to DNA-damaging agents and chromosome instability have helped researchers piece together the molecular pathways by which cells respond to DNA damage. Howlett *et al.* (p. 606; see Perspective by Witt and Ashworth) have now found that a small subset of patients with the chromosome instability syndrome Fanconi anemia (FA) have biallelic mutations in the breast cancer susceptibility gene *BRCA2*. The BRCA2 protein, which is believed to function as part of the homologous recombination machinery, may function in the same DNA-repair pathway as the six previously characterized FA proteins. Further dissection of this pathway may reveal new targets for therapeutic intervention.

Revisiting a Controversial Diet Drug

Fenfluramine (d-FEN) was once widely prescribed in the United States as a weight loss medication, but it was withdrawn from the market in 1997 after reports of valvular heart disease and hypertension in a subset of patients taking the drug. As an appetite suppressant, d-FEN increases the availability of the neurotransmitter serotonin, but the central pathways that mediate the drug's anorectic effects have not been identified. Studying rodent models, Heisler *et al.* (p. 609) now report that d-FEN activates melanocortin signaling pathways in the arcuate nucleus of the hypothalamus, a system already well known to play a pivotal role in maintenance of energy balance in both rodents and humans. This new mechanistic information could aid in the development of less risky drugs for weight loss.

Getting It Straight

The assembly of actin filaments is required for processes such as cell division, the establishment and maintenance of cell polarity, and cell motility. The formation of branched actin filaments is now well understood, but how cells produce unbranched actin cables has been somewhat mysterious. Pruyne *et al.* (p. 612; see the Perspective by Chang and Peter) show how the formin homology domain on a yeast protein promotes the formation of unbranched actin filaments in vitro.

CREDIT: PRUYNE *ET AL.*

Sorting Out Receptors

What are the mechanisms by which different G protein–coupled receptors (GPCRs) are recycled to the cell surface or targeted to the lysosomes for degradation? Whistler *et al.* (p. 615; see the Perspective by Gray and Roth) describe the role that one protein, GASP (GPCR-associated sorting protein), plays in the fate of two structurally related opioid GPCRs. The carboxyl-terminal cytoplasmic domain of the delta opioid receptor, but not that of the mu opioid receptor, binds to GASP, and this interaction promotes transport to the lysosome. Several other endocytic receptors also interact with GASP, which appears to be a key player in regulating sorting to lysosomes versus recycling after endocytosis.

Homing in on Autoimmune Genes

Only few specific gene loci have been defined for autoimmune diseases. In mice, *Bphs* is an autosomal dominant locus influencing susceptibility to organ-specific autoimmunity. The susceptible phenotype controlled by *Bphs* also displays increased hypersensitivity to vasoactive amines (VAAS) induced by pertussis toxin. Ma *et al.* (p. 620) now show that the histamine H1 receptor (H1R) gene, *Hrh1*, encodes *Bphs* and that a three–amino acid difference could account for activity of the susceptibility locus. Deletion of *Hrh1* conferred resistance in a susceptible strain of mice to induced VAAS, as well as two forms of experimentally induced autoimmunity. Resistance correlated with reversal of T helper phenotype, which suggests that the *Bphs* locus confers susceptibility via dysregulation of T cell responses.

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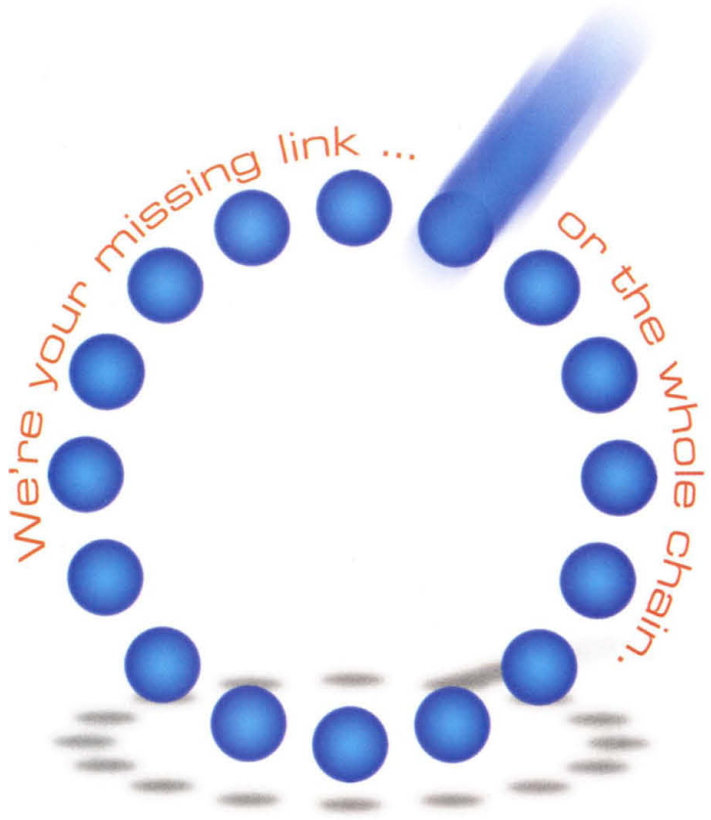

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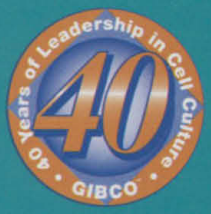

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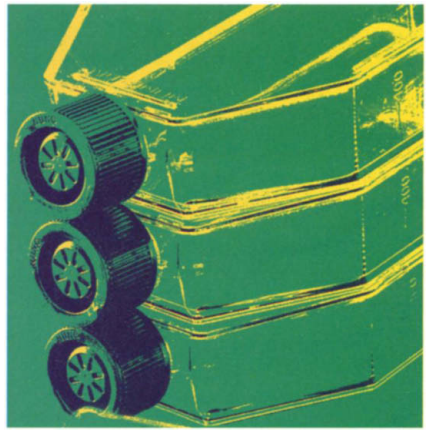

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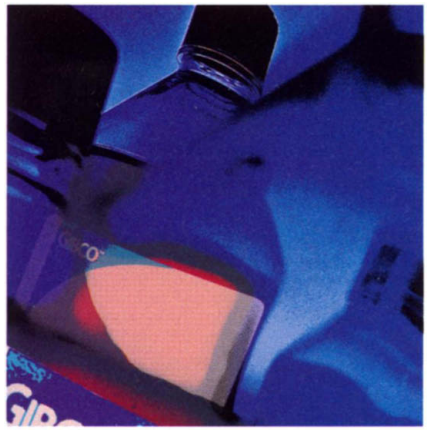

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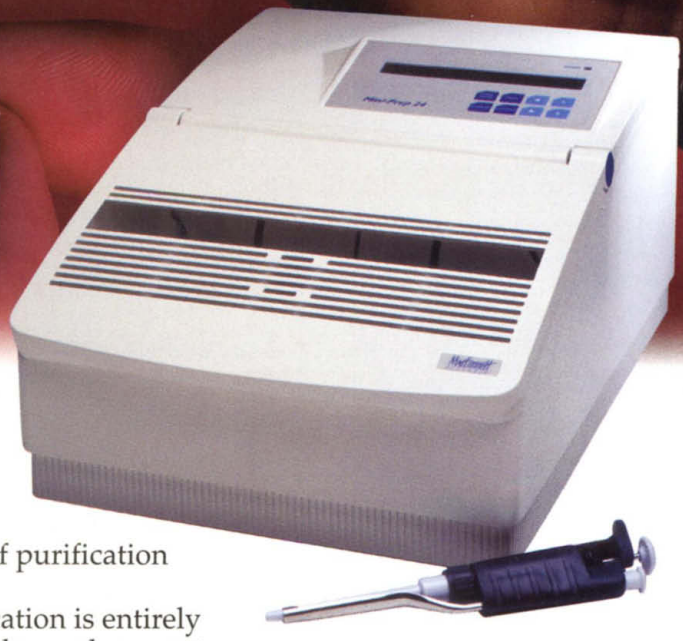

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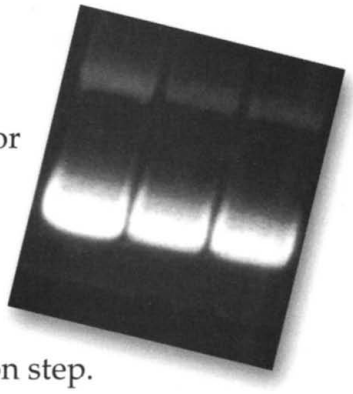

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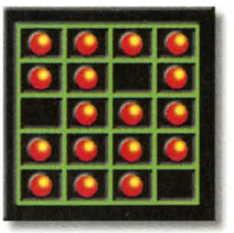

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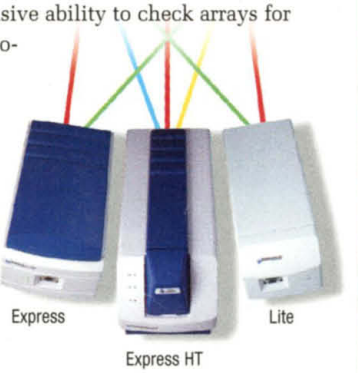

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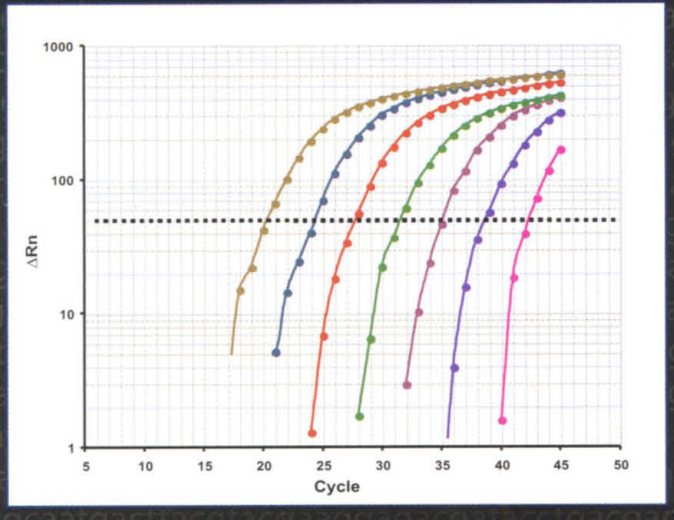

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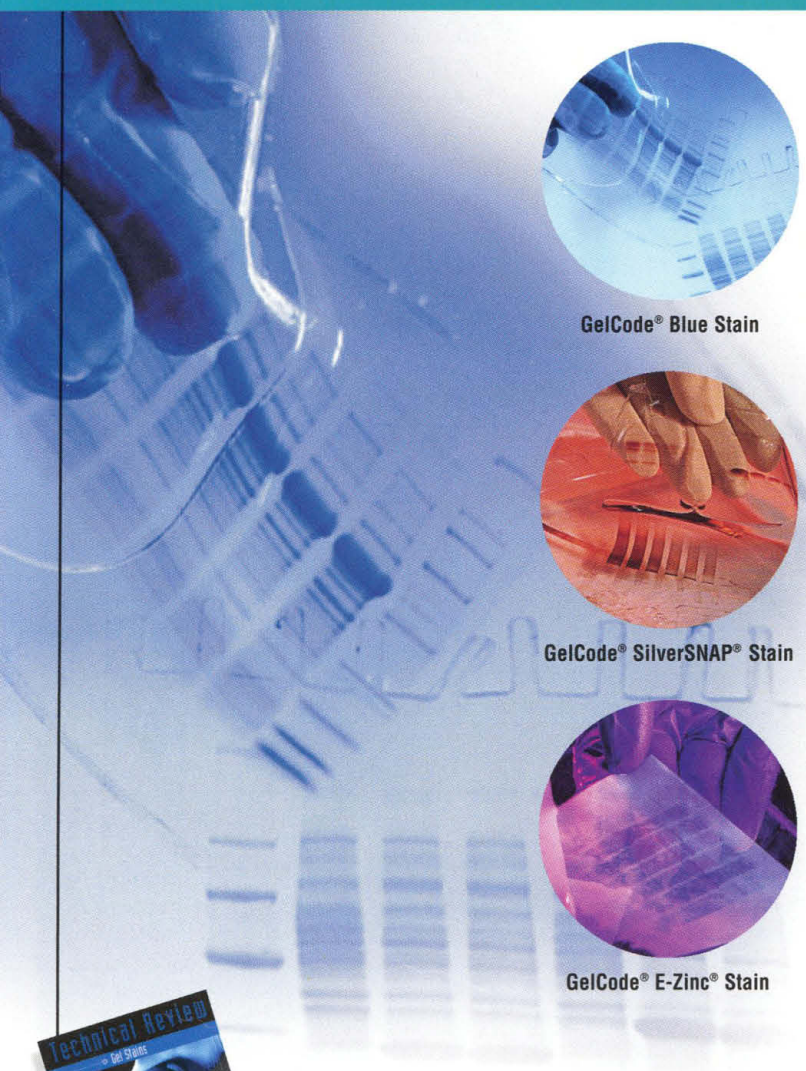

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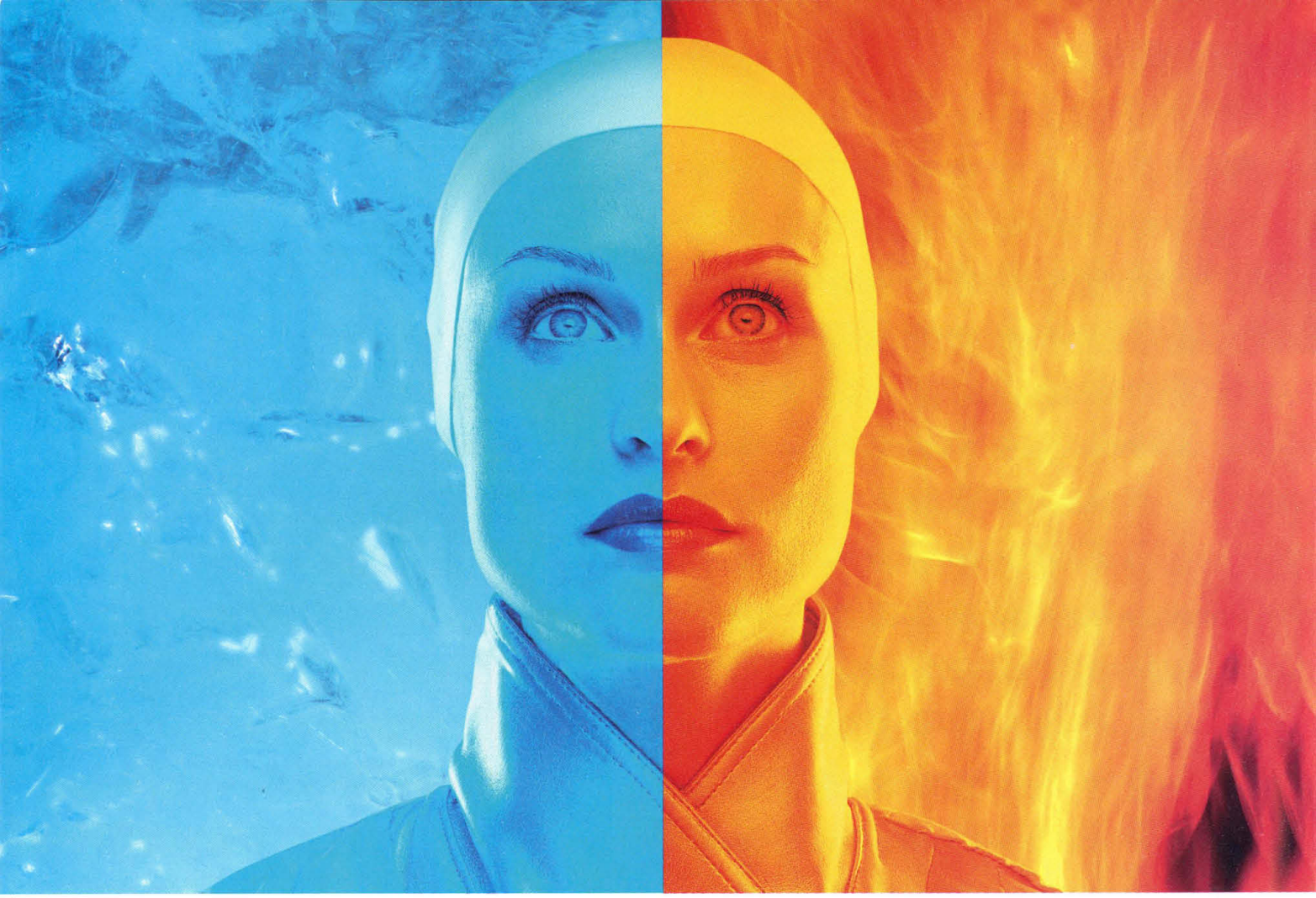

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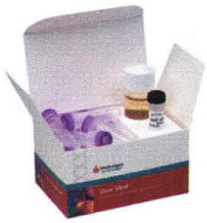

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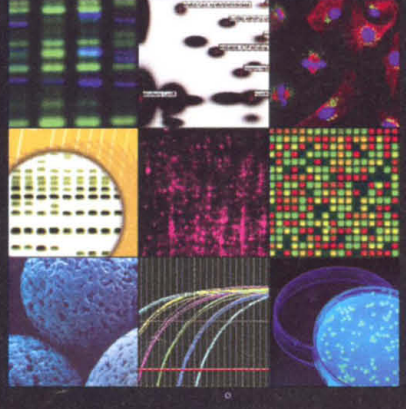

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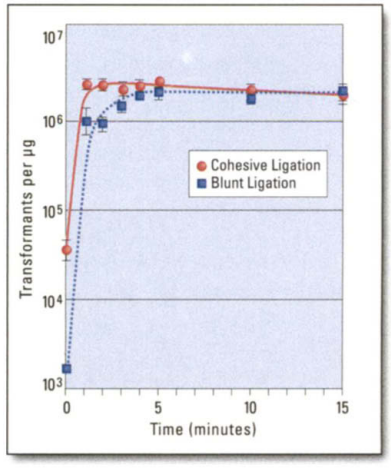

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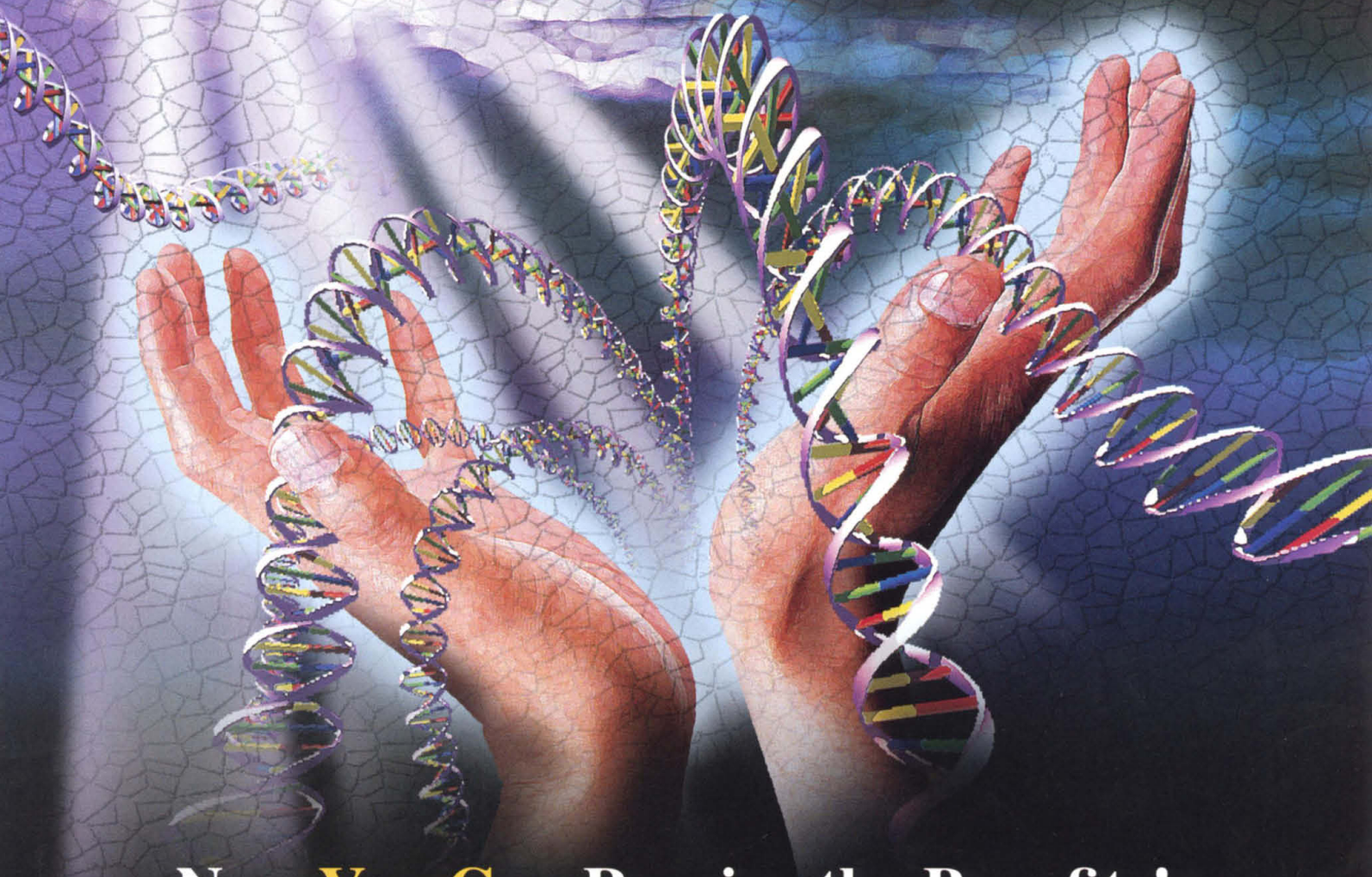

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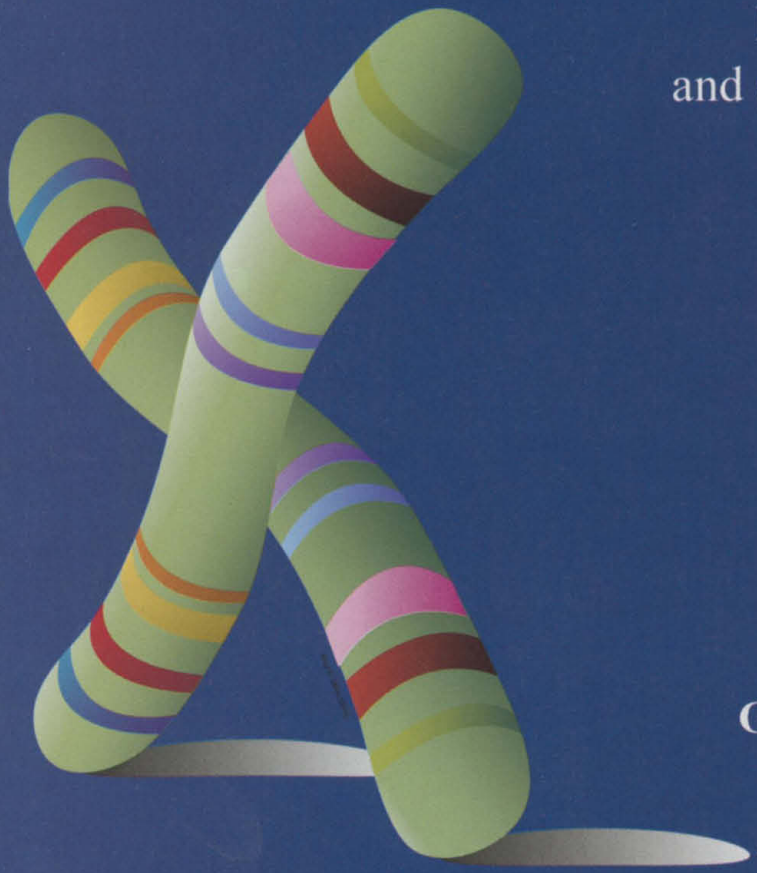

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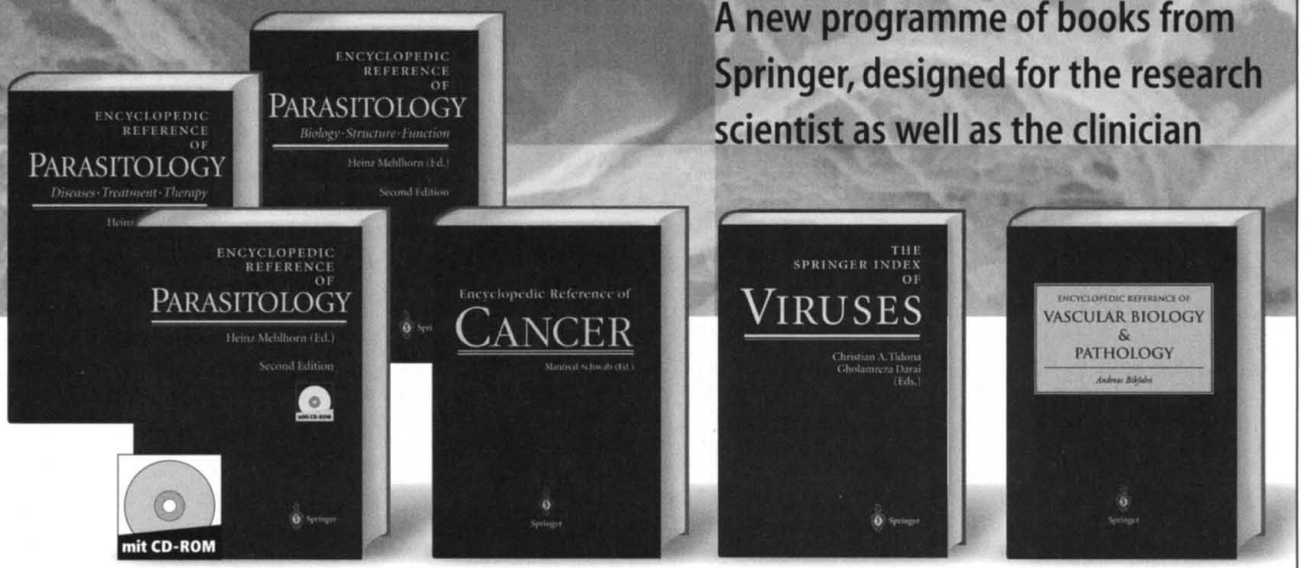

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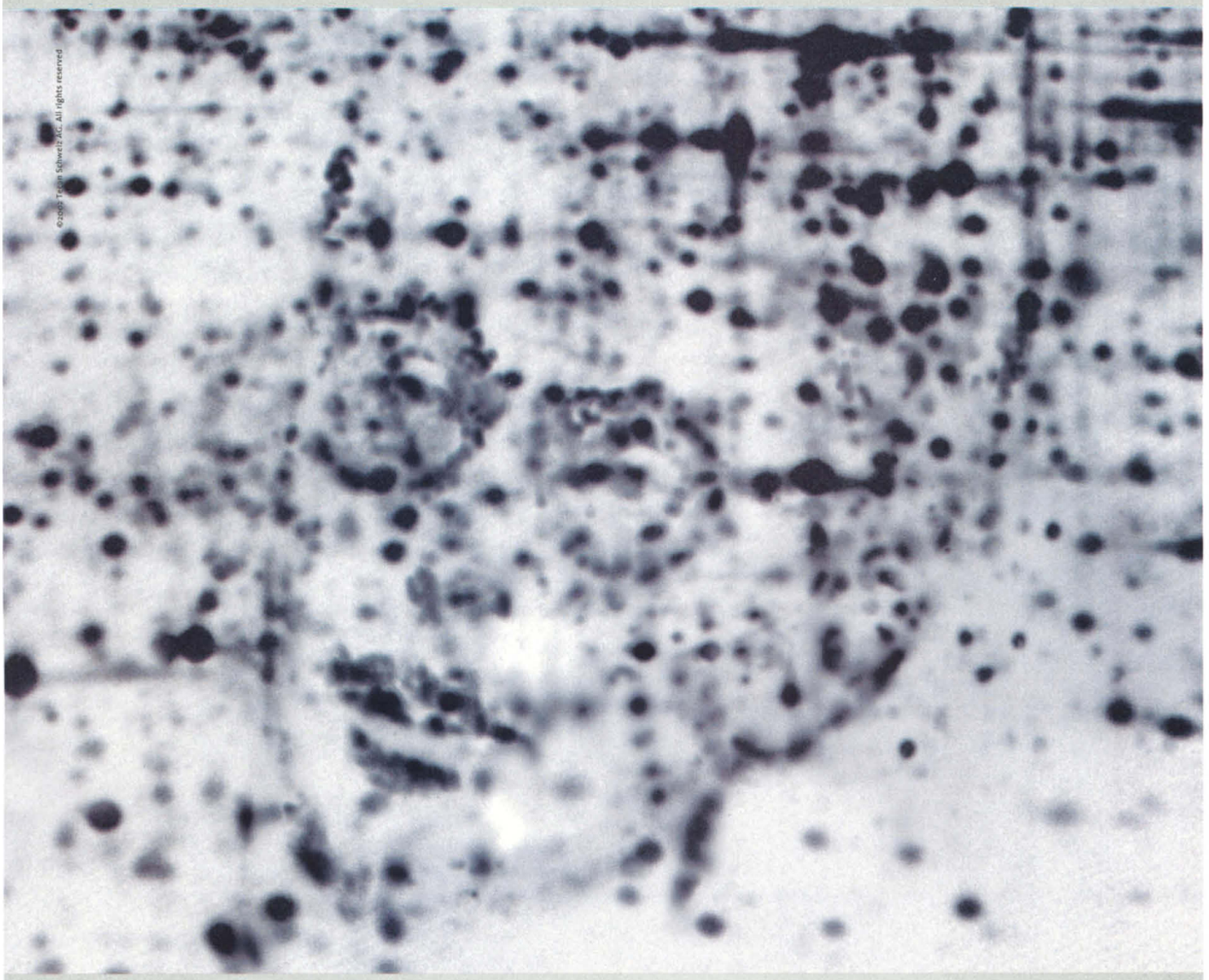

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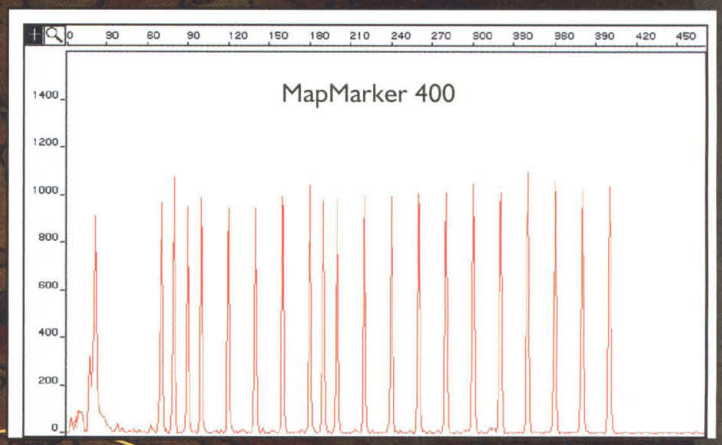

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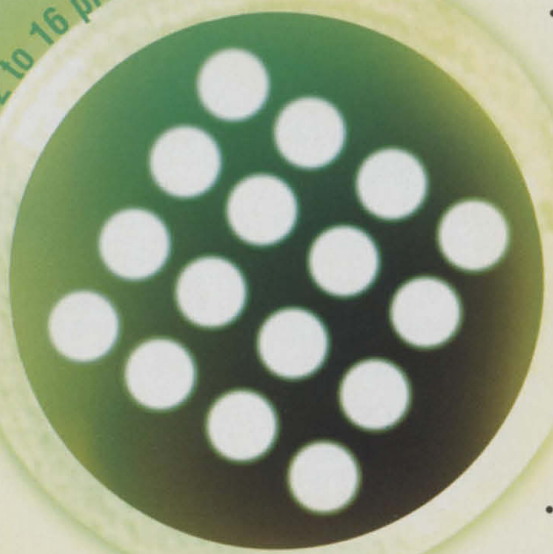

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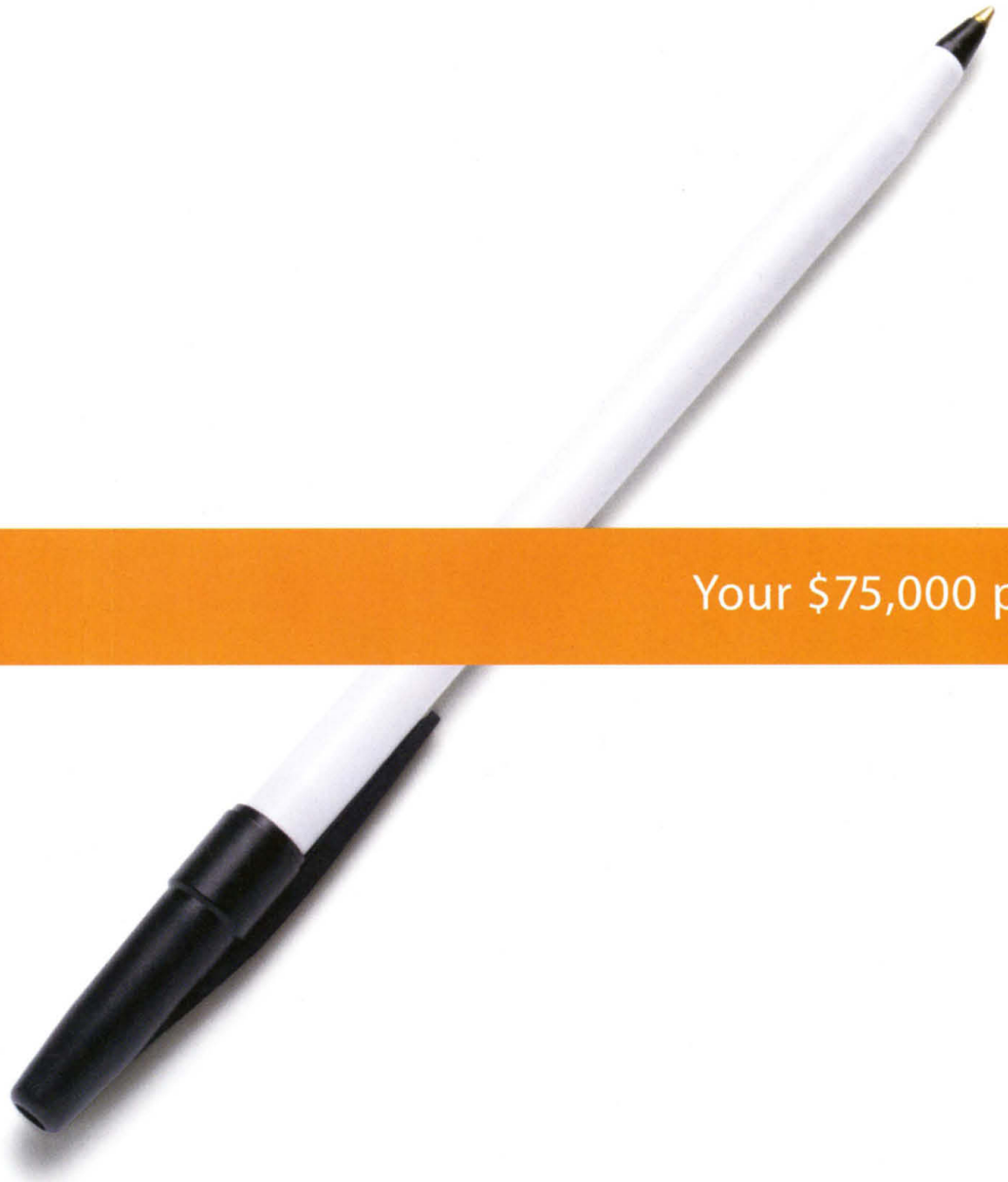

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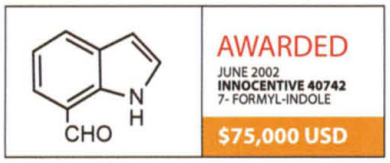

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