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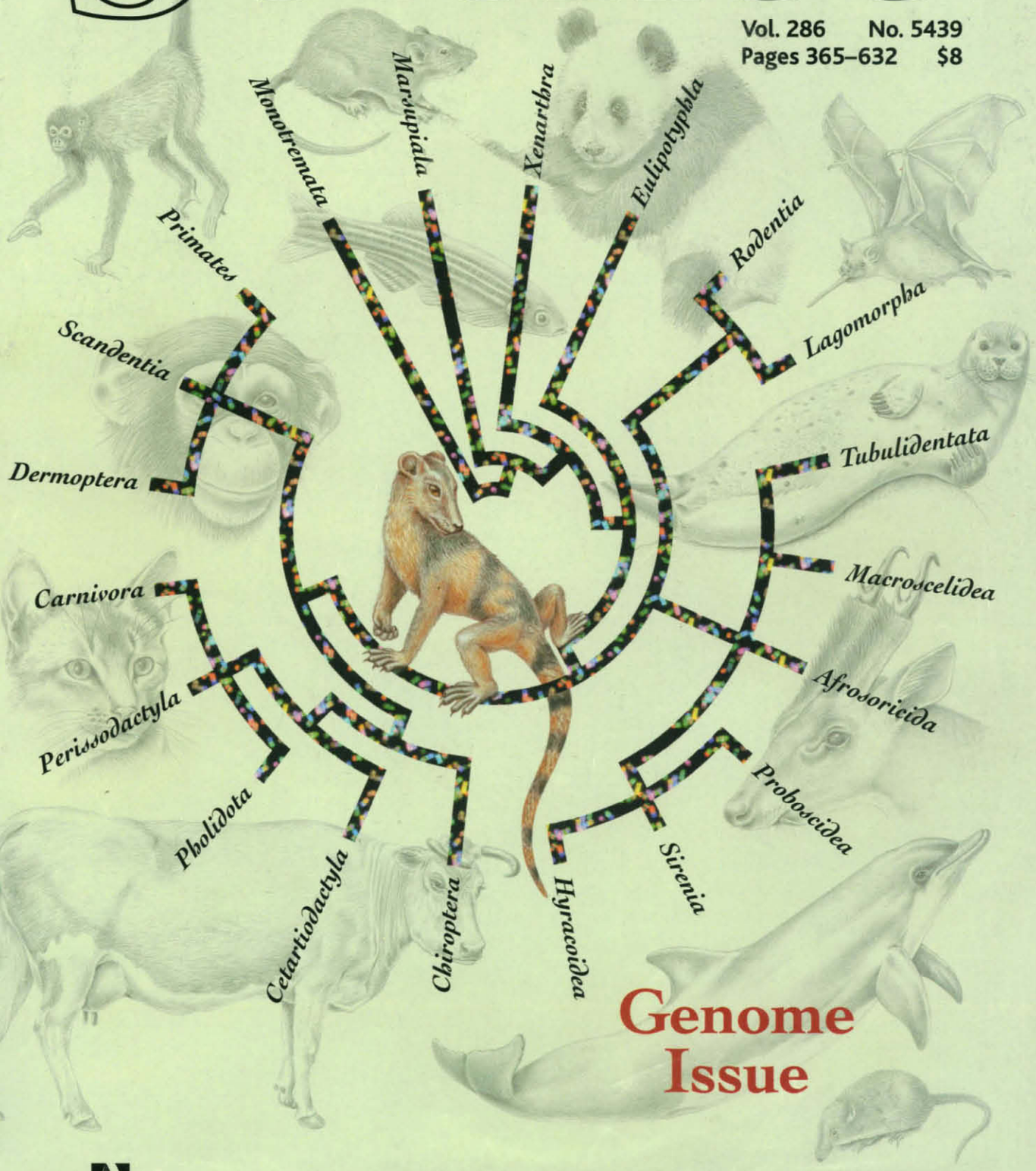

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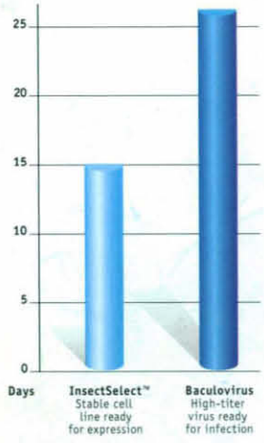

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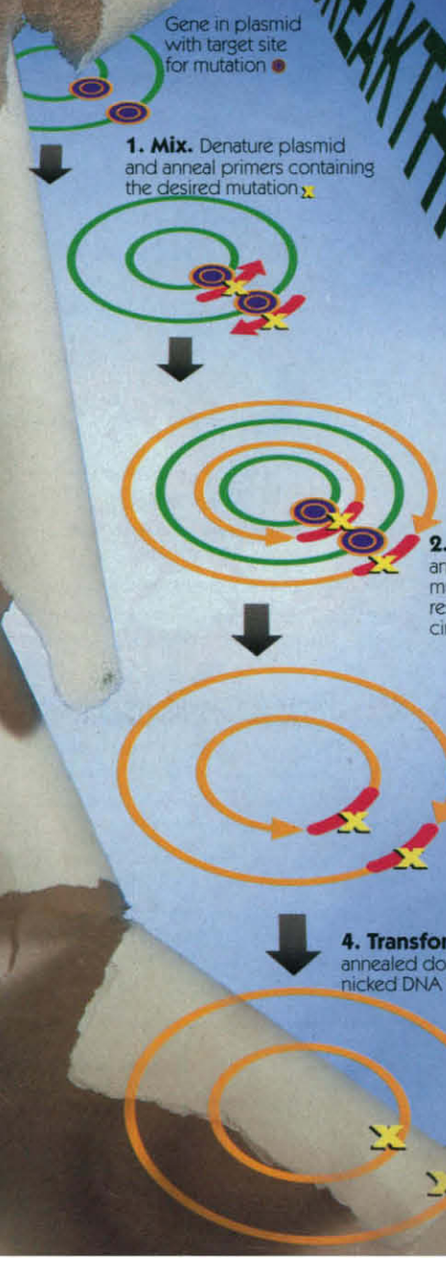

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COVER Genomic information illuminates our history, from the primordial mammal (center) to human migrations, and our future. In a chart and in a review on p. 458, comparative genomics is used to highlight the similarities and differences between extant mammalian species. Features in the Genome special section (beginning on p. 443) and related items include improvements in technology and efforts to extract meaning and benefit from the DNA sequence. [Illustrations and design: Katharine Sutliff]

[PRIMORDIAL MAMMAL ADAPTED FROM PRIMARY RECONSTRUCTION BY M. A. KLINGER (ILLUSTRATION) AND Z. LUO (CONCEPT), CARNEGIE MUSEUM OF NATURAL HISTORY]

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392

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NEWS

NEWS OF THE WEEK

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RESEARCH

RESEARCH ARTICLES

REPORTS

GENOME

NEWS

VIEWPOINTS

REVIEWS

See related Editorial on p. 409 and Report on p. 531.

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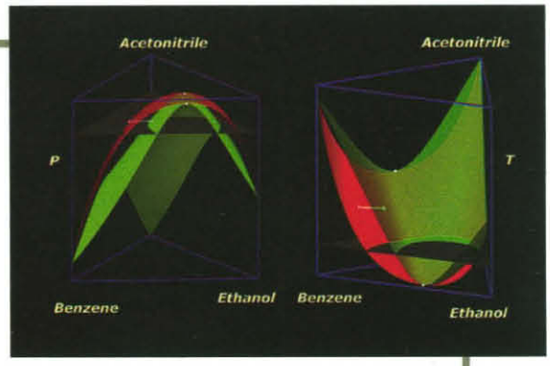

430

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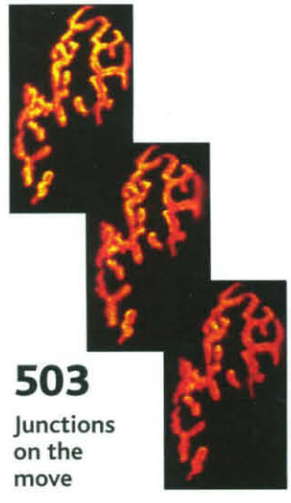

503

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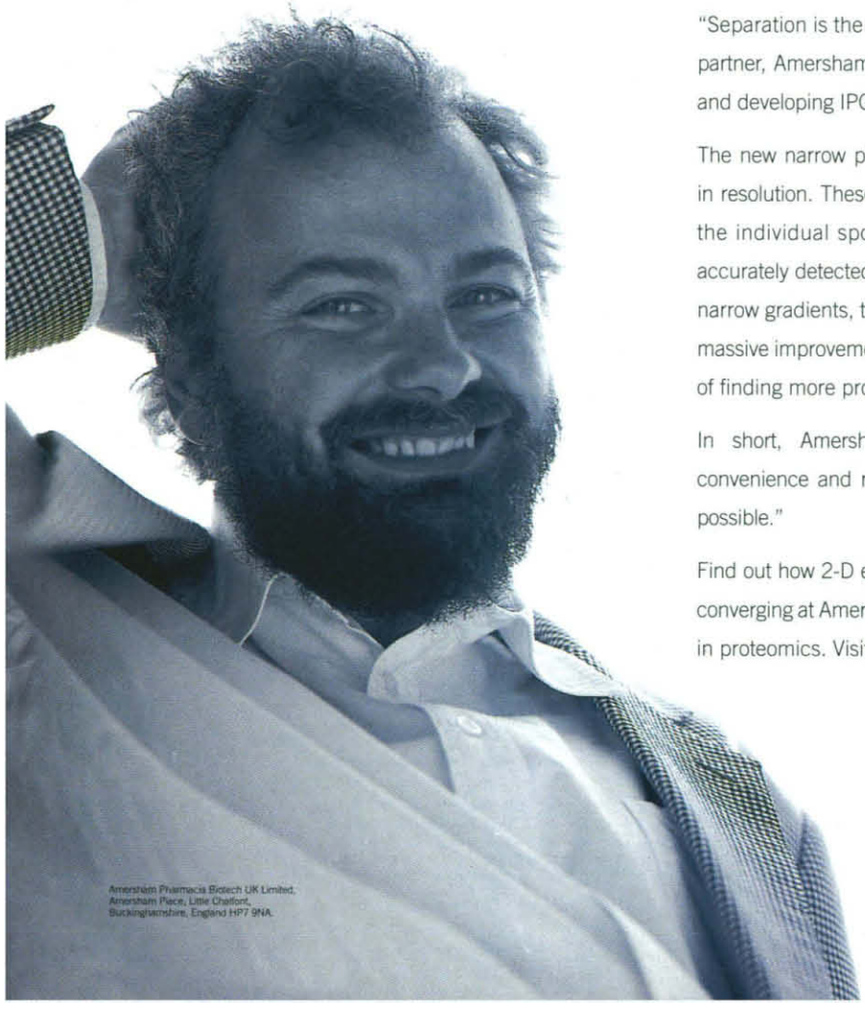

Dr. Hanno Langen, head of the proteomics group at Hoffmann-LaRoche genetics department.

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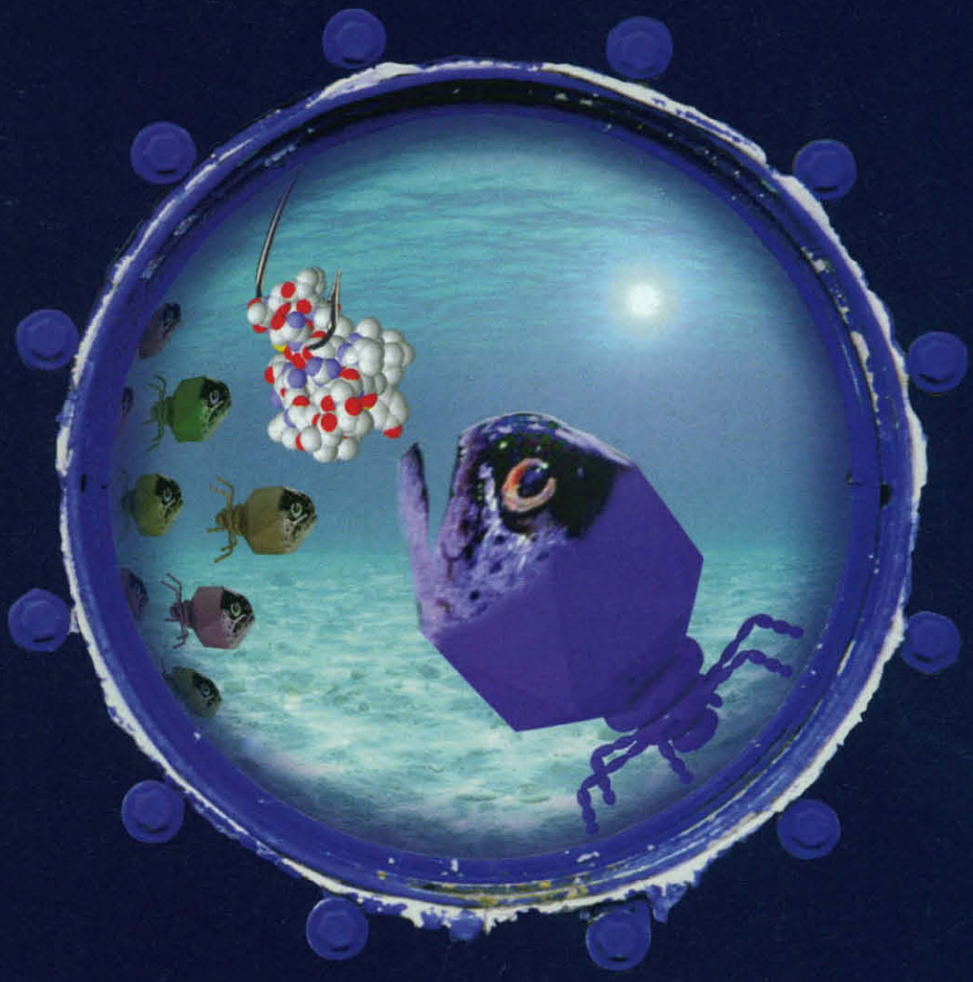

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WHAT'S AT FAULT UNDER NEW ZEALAND?

The South Island of New Zealand is being pulled apart by the large strike-slip Alpine fault that separates the northwestward moving Australian plate from the southeastward moving Pacific plate. Does the faulting of the upper crust continue into the underlying mantle lithosphere, or do these lower regions shear in a ductile manner? Molnar *et al.* (p. 516) measured seismic anisotropy and delays of seismic *P* waves (compression waves) on the South Island, which measure strain and lateral inhomogeneity, respectively, in the upper mantle. Their results indicate that the mantle beneath the island is continuous and is being sheared by the crustal deformation. Thus, the crustal fault does not cut down through the mantle.

EXPANDING NETWORKS

Networks consist of a number of vertices that are connected to each other by edges in some manner. Barabási and Albert (p. 509) analyzed the structure of some very large networks, including a sample of pages on the World Wide Web (>300,000 vertices), the network of actor collaborations (>200,000 vertices), and the power grid system in western United States (>5000 vertices). They found that the topology of the networks, that is, the probability P that a vertex is connected to k other vertices, can all be described by power laws $P(k) = k^{-\gamma}$, where γ may range from 2.1 to 4. Conventional network analyses predict an exponential relation of the topology rather than a power law, which suggests that vertices with a large number of connections should be absent in very large networks. The model provided here allows the network to grow by adding vertices and prefers to connect new vertices to ones that are already well connected. This model reflects aspects of real-world behavior—for example, people tend to link their new Web page to ones that are already popular.

BARRIER CONTROL IN MAGNETIC TUNNEL JUNCTIONS

A tunnel junction consists of two electrodes closely separated by an insulating barrier. If the two electrodes are ferromagnetic, the spin of tunneling electrons can be polarized and the tunneling rate should depend mainly on the direction of the magnetic moment in each of the ferromagnetic layers, not the choice of the insulator. De Teresa *et al.* (p. 507) show that this simple picture is not correct. They find varying results for different insulator materials (even reversals in the spin of the electrons that preferentially tunnel) and show that, counter-intuitively, it is the electronic density of states at the metal-oxide interface that determines how the tunnel junction operates. These results provide a new route for optimizing magnetic tunnel junctions.

PLATING OUT GOLD

A giant submarine gold deposit exists off the coast of Lihir Island, Papua New Guinea. McInnes *et al.* (p. 512) dredged mantle xenoliths from this region to determine the provenance of the gold enrichment. They measured the osmium and oxygen isotopic concentrations and determined that most of the trace elements, including the gold, were derived from the mantle. The trace elements are concentrated near Lihir Island because the subduction of the Pacific plate under the Australian plate has stalled in this area, which allows a flux of fluids and melt from the mantle to remove trace elements and concentrate these elements in the oceanic crust.

BACK AND FORTH OVER TIME

The North Atlantic Oscillation (NAO) is a large-scale seesaw in sea-level atmospheric pressure that is thought to be a major influence on ocean convection and air-sea forcing in that region. It is of great interest to paleoclimatologists to find proxies for the NAO so that climate may better be linked to past patterns of atmospheric circulation. Keigwin and Pickart (p. 520) may have found such a proxy in two sediment cores from south of Newfoundland. These cores provide a record of sea surface temperature changes caused by variability in the position of a minor bifurcation of the Gulf Stream that moves north and south in concert with reversals of the NAO. This type of information should help to clarify the patterns of ocean-atmosphere circulation during periods of warm, interglacial climate.

WRITING BETWEEN THE LINES

The lithographic methods used to print magazines in color or to fabricate integrated circuits return several times to the original substrate and print additional features in registry with those already on the surface. Hong *et al.* (p. 523; see the news story by Service) show that a recently demonstrated scanning probe method for writing nanoscale lines or dots on a surface, "dip pen" nanolithography, can now write on a surface several times in different "colors." Registration marks on the surface allow a line of organic molecules to be placed between existing lines of a different chemical composition without disturbing the original pattern. New lines can be placed within 5 nanometers of existing lines.

HOLDING OFF BACTERIAL INVASIONS

One of the first lines of defense against microbial invaders are the defensins. These small peptides, which are produced by both invertebrates and vertebrates and provide an initial barrier that is bactericidal or bacteristatic (see the Perspective by Ganz), are the subject of a research article and a report. Tang *et al.* (p. 498) identified an unusual defensin in primates, rhesus theta defensin-1, that is a cyclic peptide. Genetic analysis revealed that the cyclic peptide originates from two separate loci. Two propeptides are produced that ultimately are trimmed and stitched together to form the active cyclic defensin. This unusual form for an animal peptide suggests that enzymes may exist that catalyze the cyclization reaction and, if so, these may not be their only substrates. Yang *et al.* (p. 525) report that human β-defensins can attract immature dendritic cells and T cells through the use of the CCR6 chemokine receptor, whose only other known ligand is LARC (also called MIP-3α). Thus, these peptides not only provide initial antimicrobial protection, but they attract the cells of adaptive immunity to provide a more efficient immune response.

DEATH OF A SYNAPSE

Neurotransmitter receptors form dense clusters at neuromuscular junctions—that is, until signal transmission across that synapse ceases. As Akaaboune *et al.* show

CONTINUED ON PAGE 375

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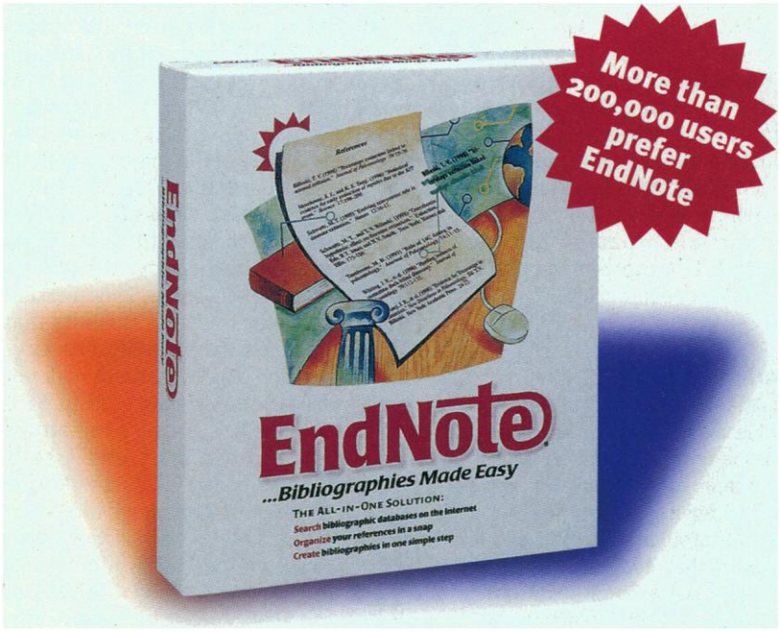

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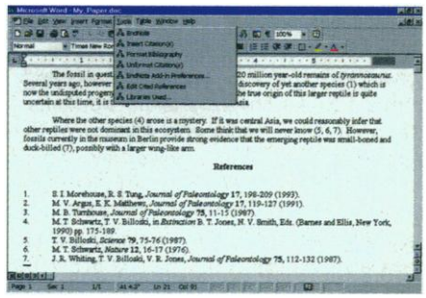

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(p. 507; see the Perspective by Salpeter), an apparent lack of signal on the postsynaptic side results in the acetylcholine receptors first migrating away from the junction and then being degraded. The resulting changes can be apparent in a matter of hours. Thus, neuronal activity regulates the density of receptors at the synapse.

OUT OF ASIA, TOO

What was the geographical origin of the anthropoid primates, and from which primitive primate group were they derived? These questions have been the subject of much debate among primate paleontologists for decades. Jaeger *et al.* (p. 528) describe newly found fossils from a primate that lived in Myanmar during the middle Eocene (about 20 million years ago). This finding strengthens the case for Asian as well as African anthropoid clades and suggests an affinity with the tarsiids rather than other primitive primate groups. Their results also suggest that the anthropoid clade diverged from other primates very early, possibly before the Eocene.

TAIL WAGGING THE CHANNEL

Improper function of the chloride channel known as the cystic fibrosis transmembrane regulator (CFTR) is associated with debilitating diseases in humans. Conductance of the channel is regulated in a complex manner. One mechanism of regulation requires phosphorylation of the channel in the so-called regulatory or R domain, which relieves an inhibitory effect of this domain on channel function. Naren *et al.* (p. 544; see the news story by Hagmann) now provide evidence that another region, the amino-terminal tail of the channel, also has critical regulatory effects. The amino-terminal tail appears to promote phosphorylation-induced conductance of the channel through interaction with the R domain. The results present a new potential target for drug development aimed at modification of CFTR channel activity.

IDENTIFYING TUMORS THROUGH GENE EXPRESSION

The ability to classify tumors into different categories has critical ramifications for making decisions about therapies. Golub *et al.* (p. 531) provide a proof-of-principle study to show that gene expression patterns can be used to classify cancer classes. A class-prediction procedure was able to use bone marrow from patients and distinguish acute myeloid leukemia or acute lymphoblastic leukemia. The procedure could have been used to identify these classes even if they had not been known previously to exist.

COMPETITION AND COMMUNITY

The stability of an ecological community is thought to depend on the number of species it contains and the strengths of the interactions between them. Using a combination of theoretical approaches, Ives *et al.* (p. 542) show how the effects of competitive interactions and species number on community resilience depend on parameters such as the intrinsic rate of population growth and cross-correlations between exogenous factors that affect different species. They find that the number of species and interspecific competition have little influence on variance in community-level attributes such as total biomass; rather, total community biomass depends only on how the constituent species respond to environmental fluctuations.

PLASTIC BRAINS

Emerging evidence suggests that neurons in certain areas of the adult primate brain, such as the hippocampus and olfactory bulb, are capable of dividing. In a histochemical study, Gould *et al.* (p. 548) have found new neurons in the prefrontal cortex and inferior and posterior temporal cortex (regions connected with neural plasticity related to learning and memory) in Old World monkeys. They suggest that these new neurons originate in the subventricular zone and migrate through the white matter to the neocortex, where they differentiate into mature neurons and extend their axons to become integrated into the local circuitry.

RESEALING DNA

Topoisomerase I (topo I) is a critical enzyme in DNA replication that works by breaking the DNA backbone, allowing the DNA to untwist, and then resealing the break. During this process, a covalent intermediate is formed between topo I and its DNA substrate. If this bond is not eventually broken, the cell will die. Pouliot *et al.* (p. 552) have cloned the gene for an enzyme that hydrolyzes this bond in yeast and they show that it is conserved in higher eukaryotes. This enzyme, tyrosine-DNA phosphodiesterase, may have implications for improving the efficacy of certain cancer chemotherapeutic drugs, such as camptothecin, which act by stabilizing the covalent topo I–DNA complex.

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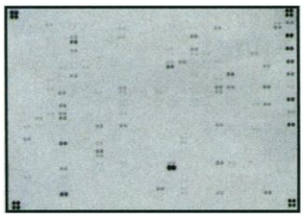

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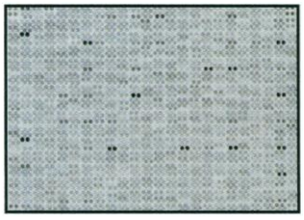

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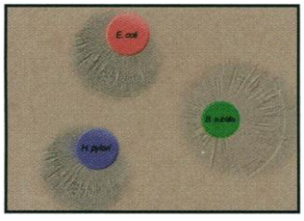

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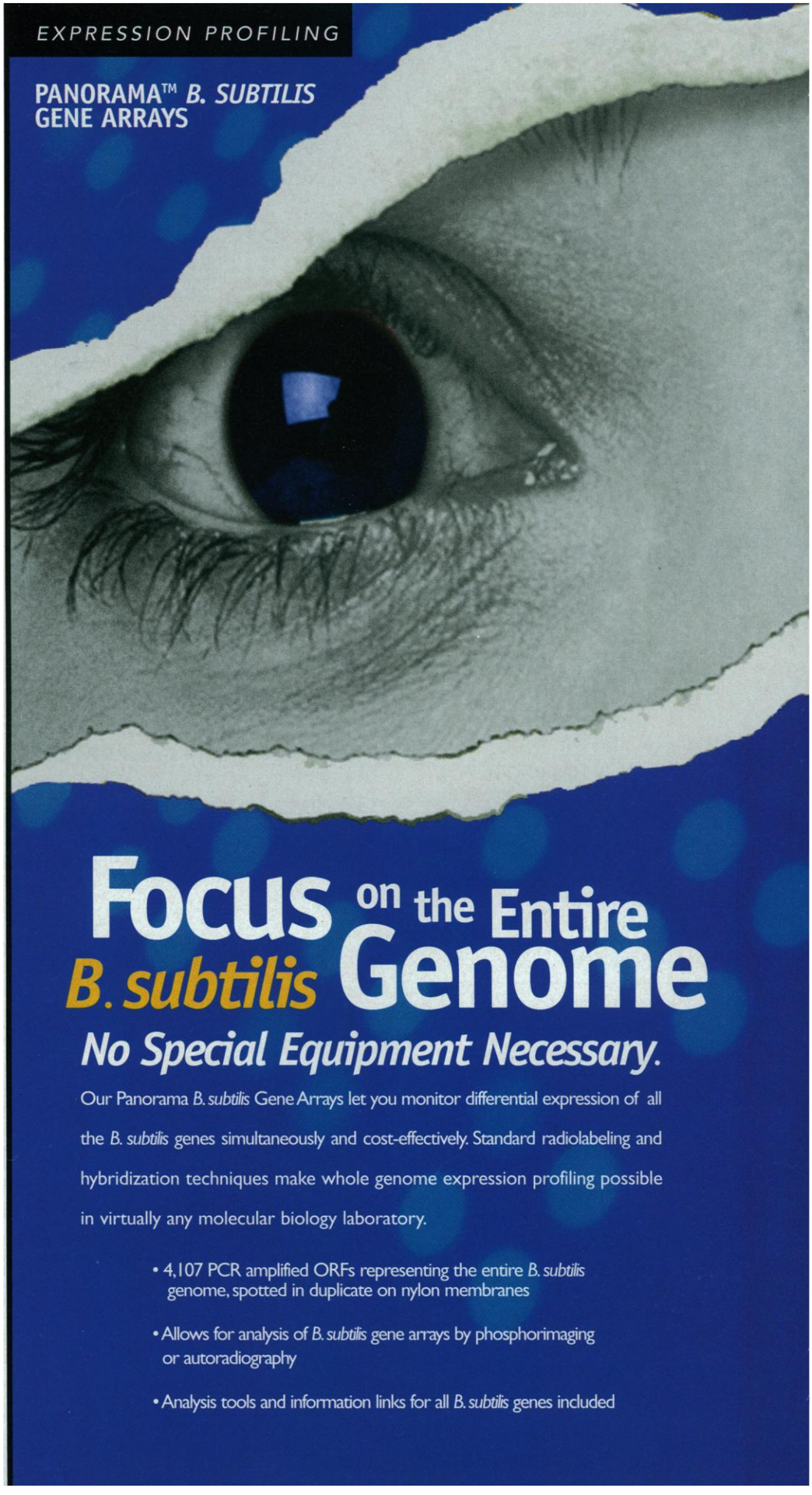

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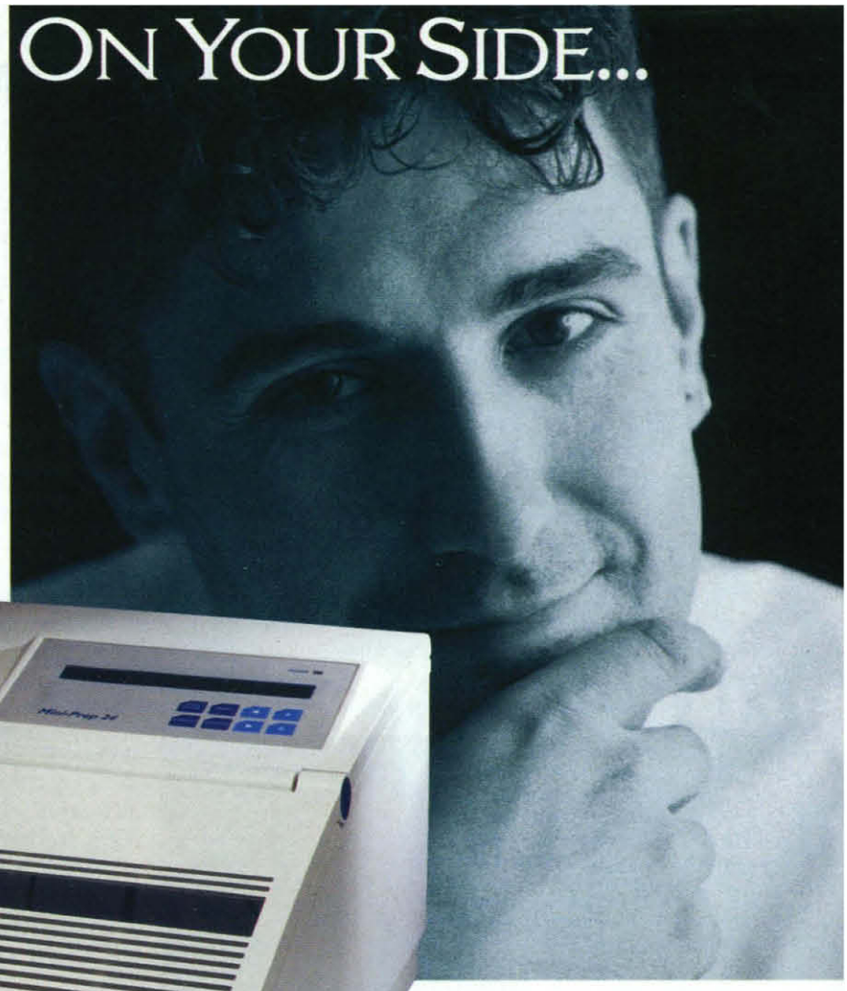

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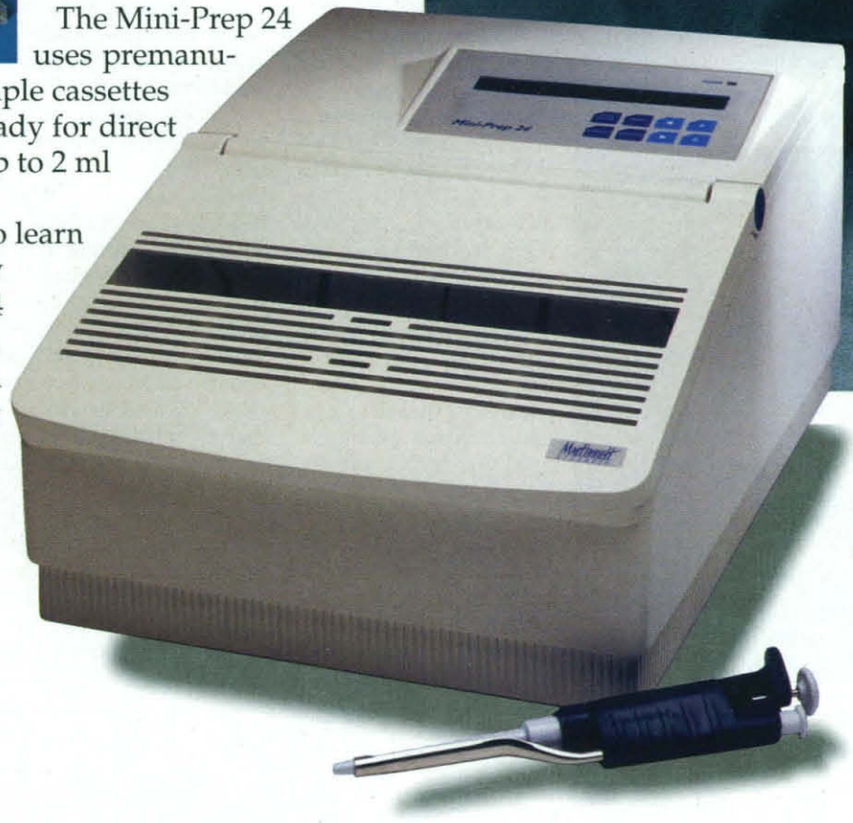

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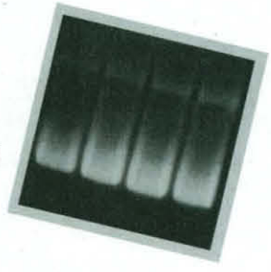

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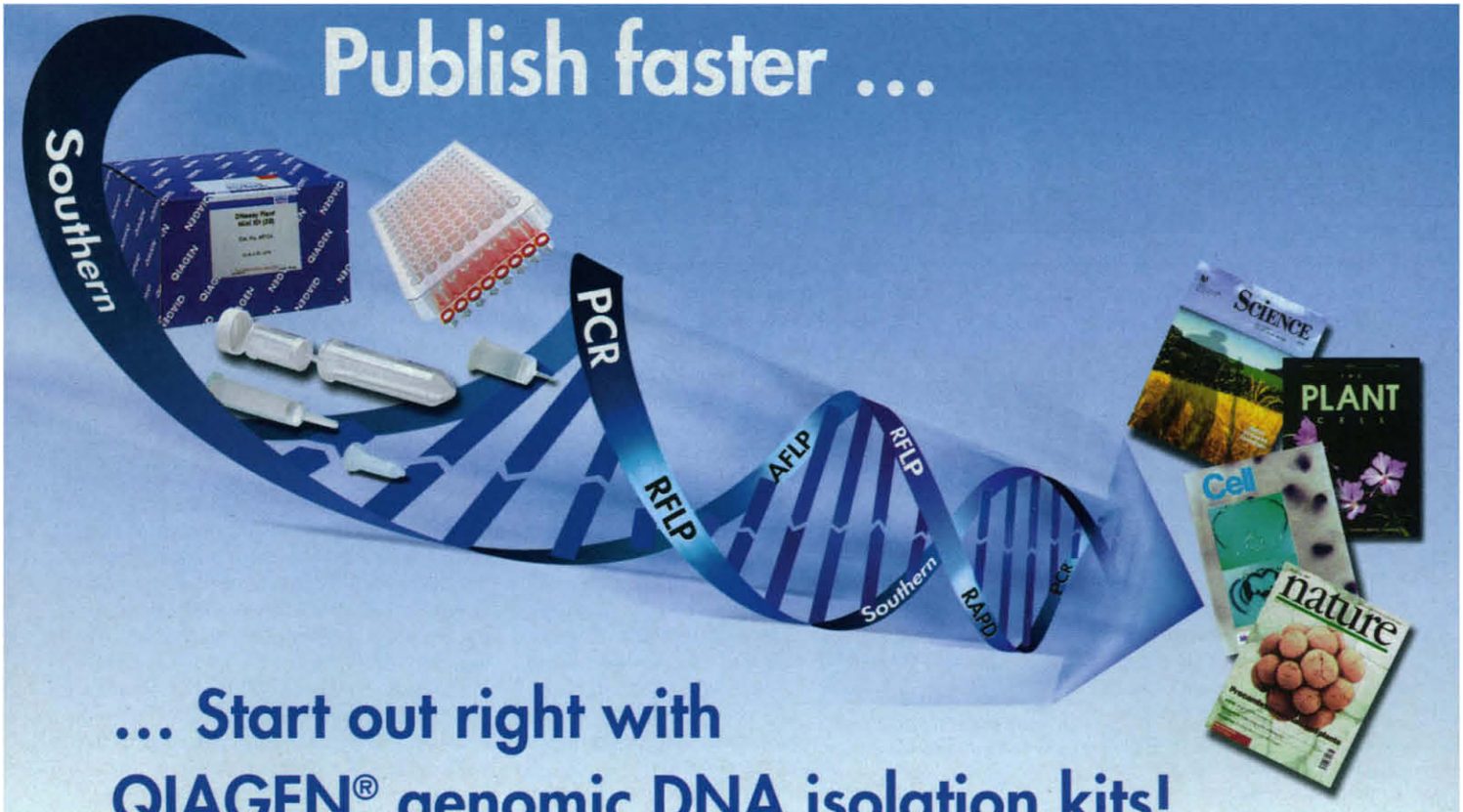

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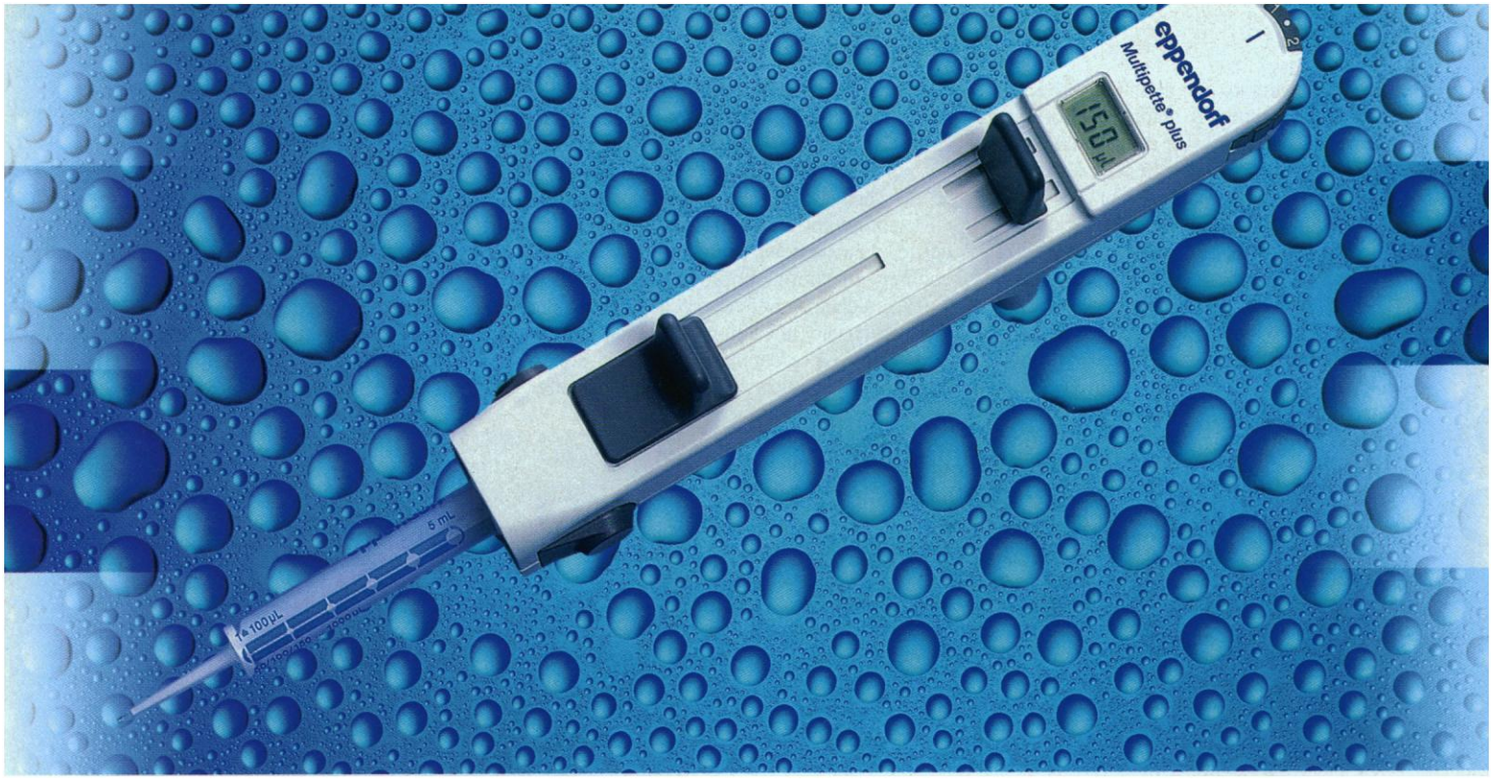

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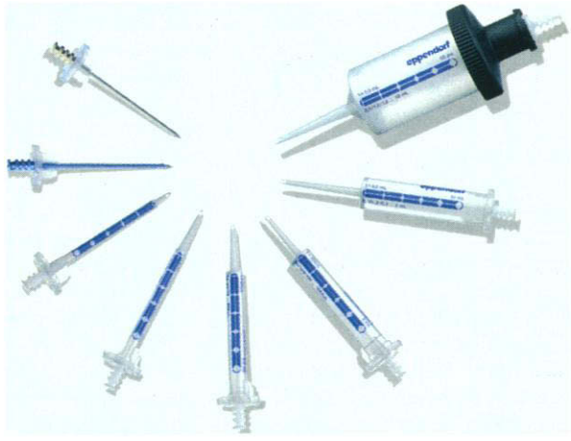

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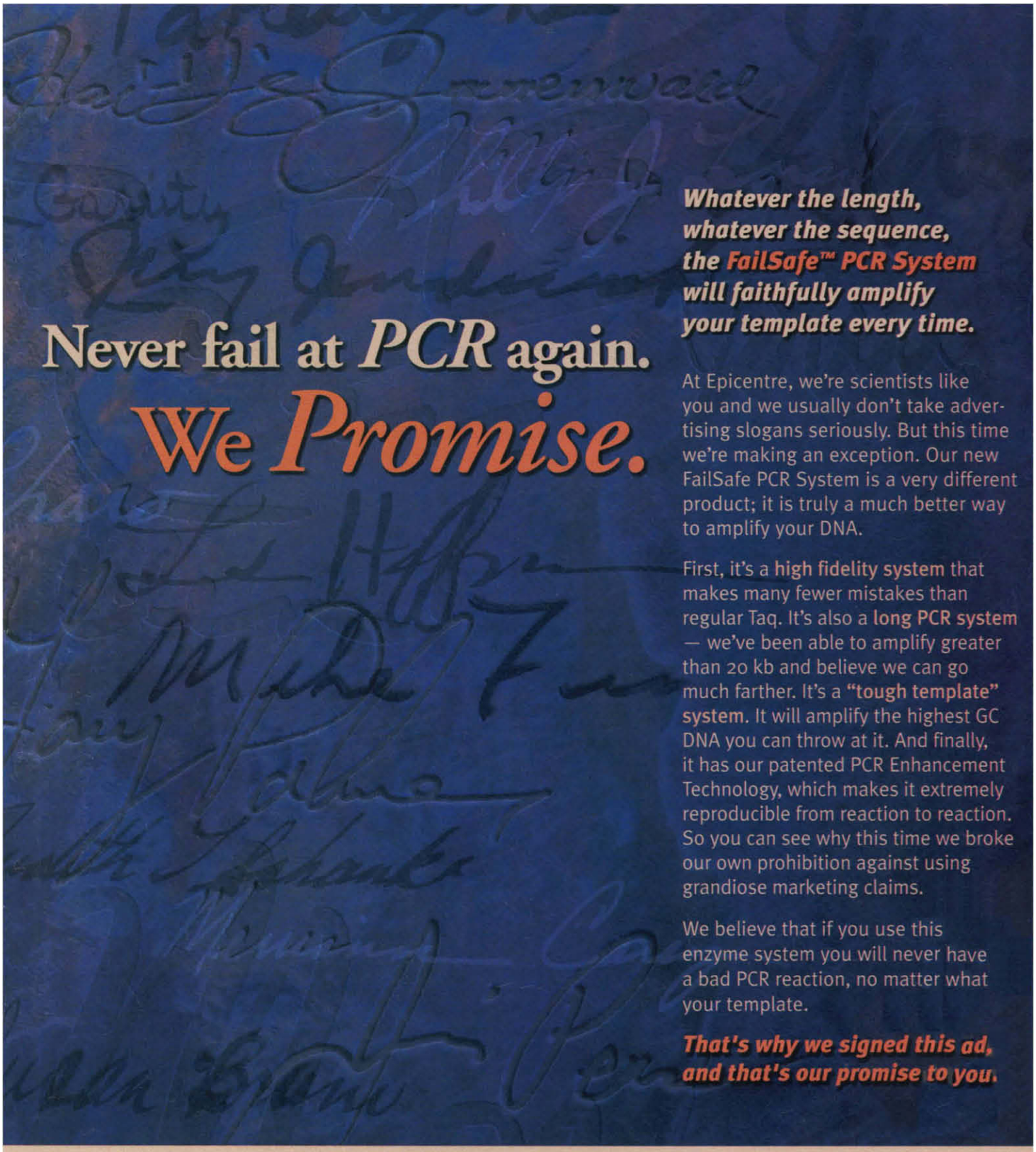

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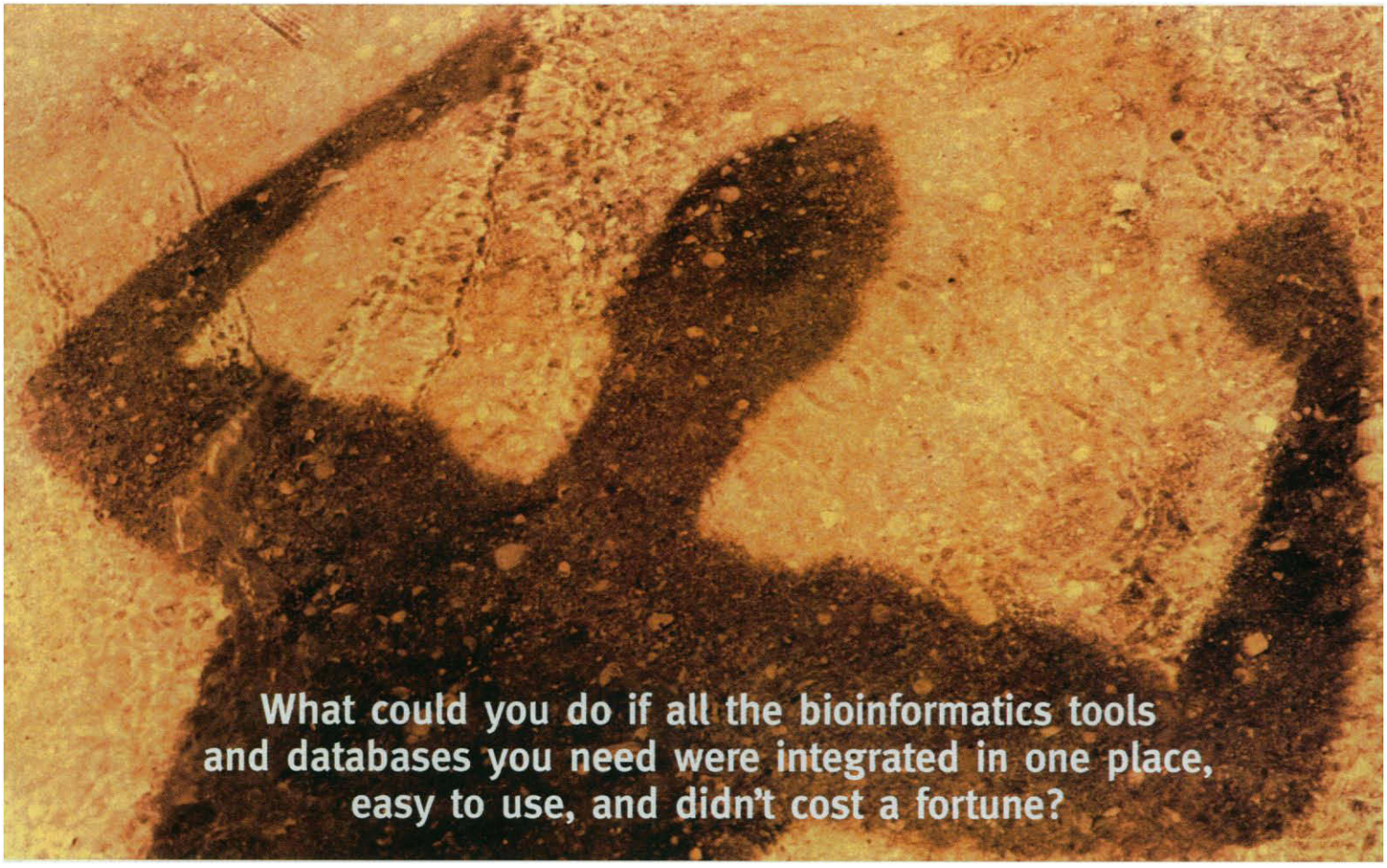

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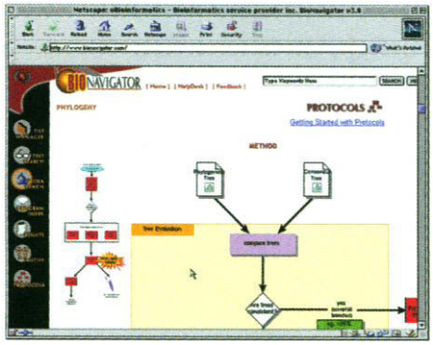

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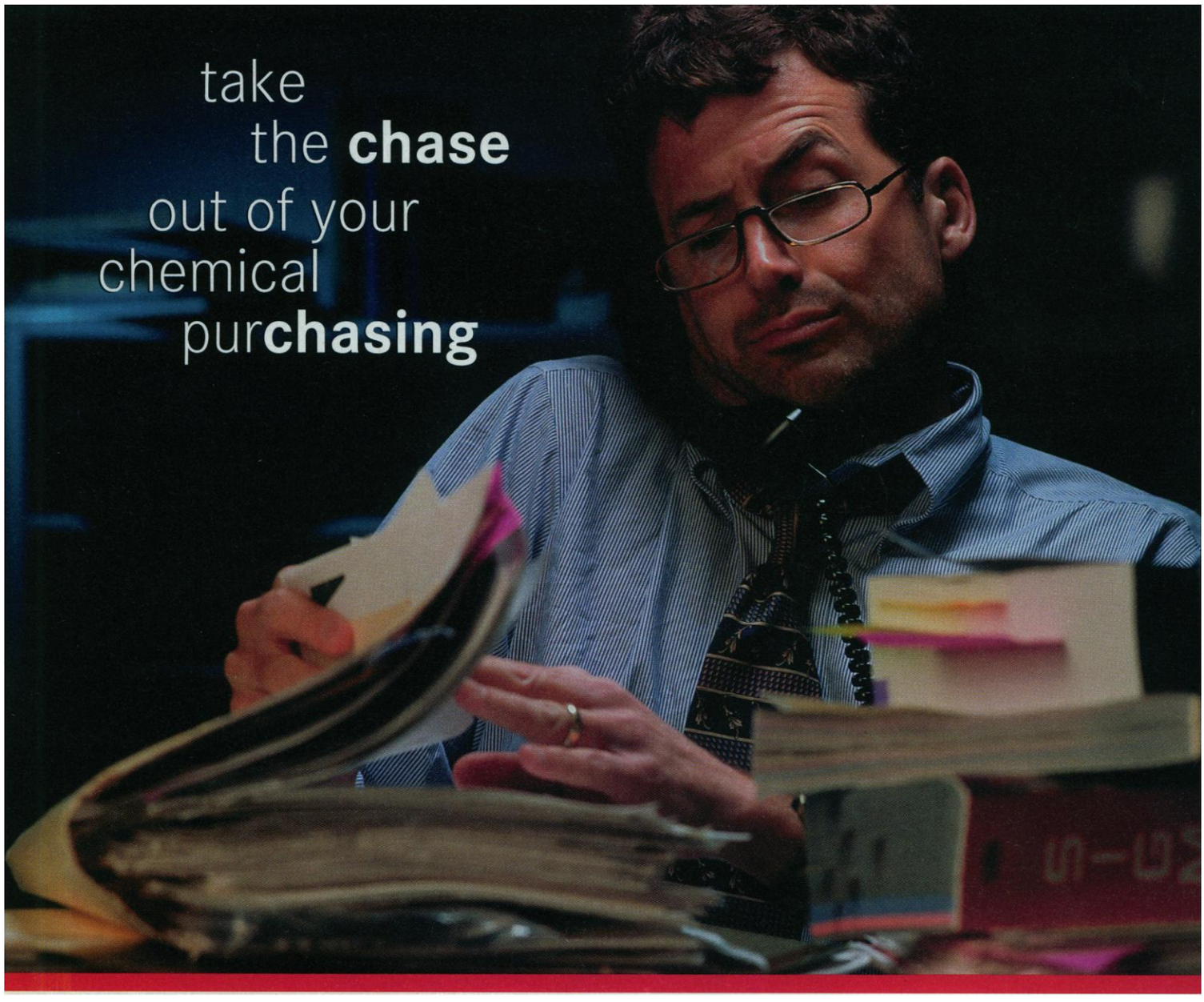

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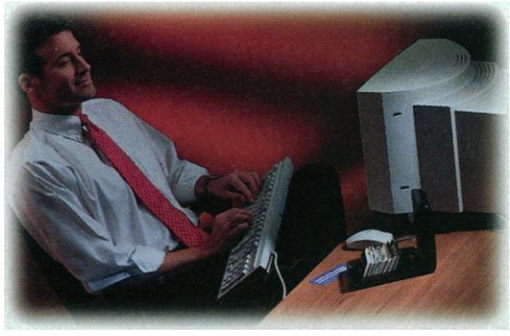

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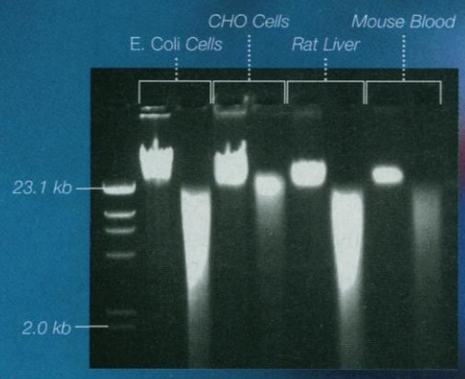

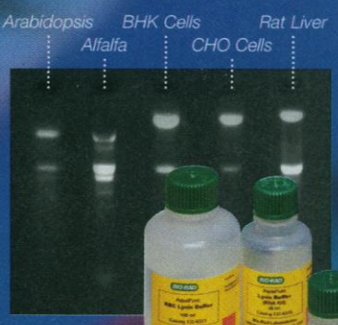

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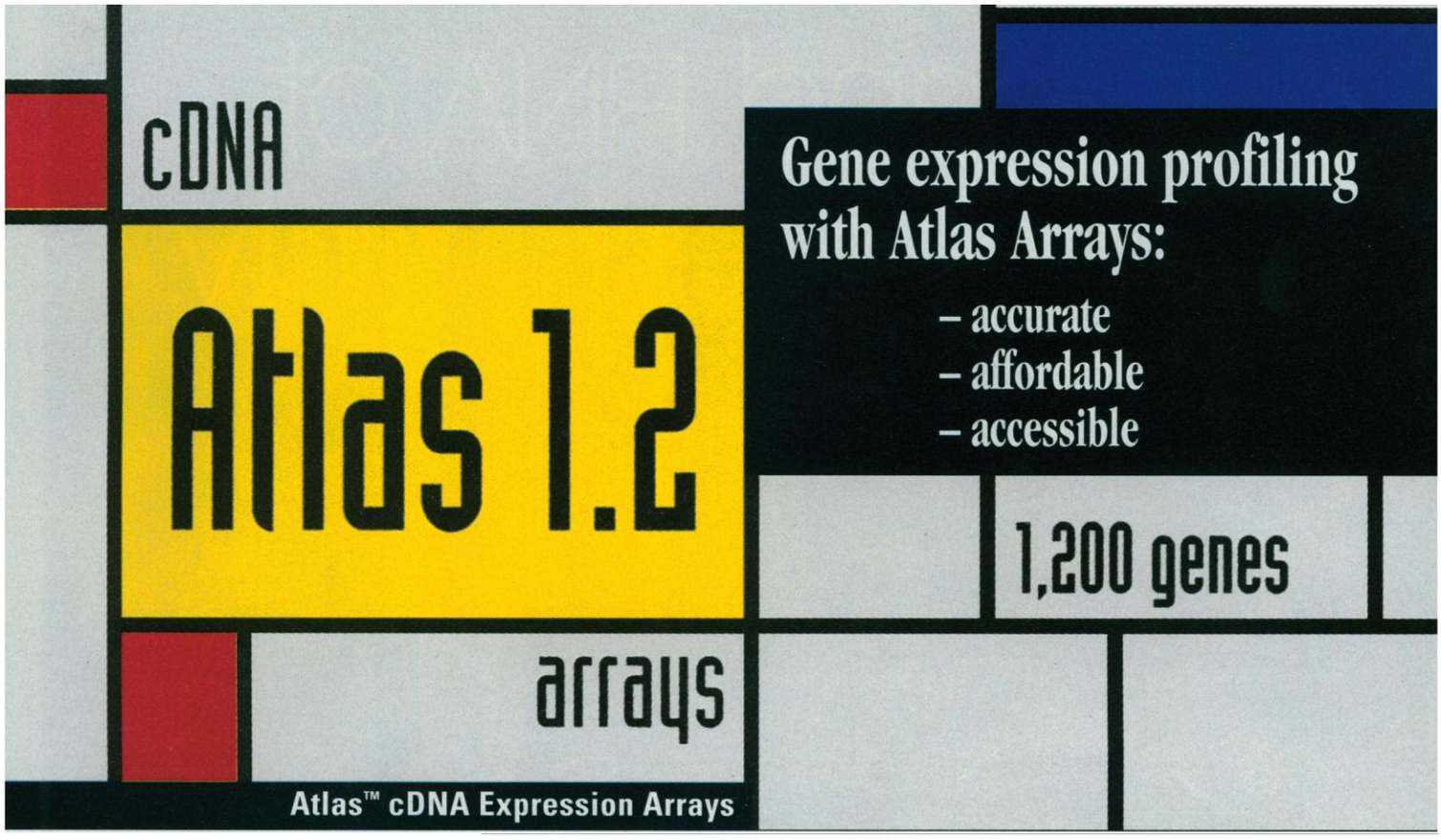
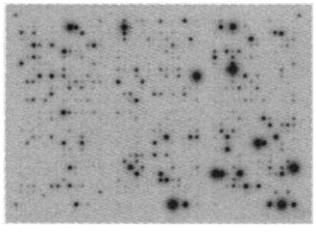
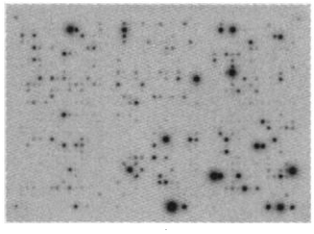


Illustration inspired by the art of Piet Mondrian (1872–1944).

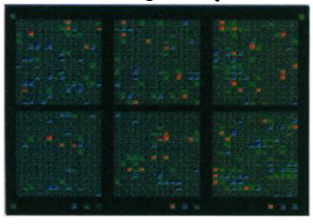
MCF-7 breast cancer cell line



MCF-7 transformed with erb B2



AtlasImage Analysis



AtlasImage 1.0 was used to compare hybridization patterns obtained with the Atlas Human Cancer 1.2 Array. Red indicates up regulation greater than 2-fold and blue indicates down regulation greater than 2-fold.

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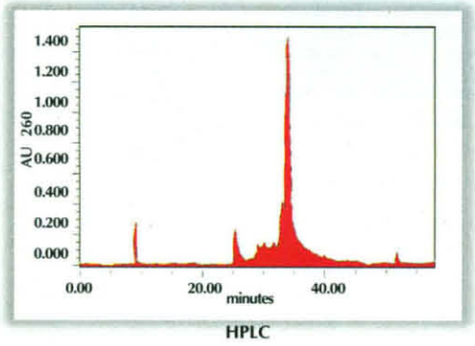

Figure 1

HPLC

Figure 2

PAGE

Show Me! *After manufacture, FRET probes are initially purified by HPLC, followed by denaturing PAGE. The HPLC chromatogram of a FRET probe is shown in Figure 1. Figure 2 shows an analytical PAGE electrophorogram of the crude FRET probe (lane 1), following HPLC purification (lane 2), and final product after denaturing PAGE purification (lane 3). [Denaturing gel analysis of the HPLC purified FRET probe confirms that not all of the synthesis failure sequences are removed (lane 2)]. The additional purification by PAGE removes those remaining failure sequences that can lead to increased background noise in the PE-ABI 7700 Detection System.*

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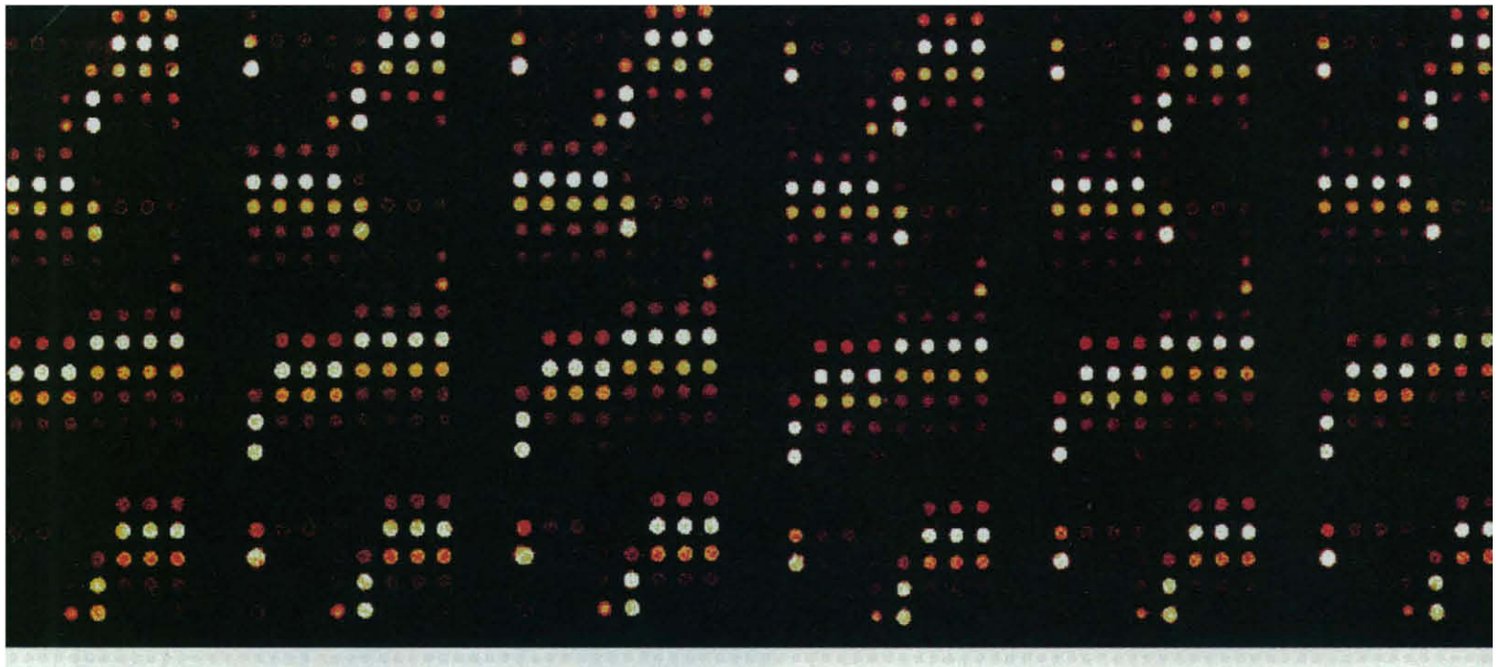

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Array and rice images courtesy of Andrzej Kilian, Damian Jaccoud and Richard Jefferson, CAMBIA.

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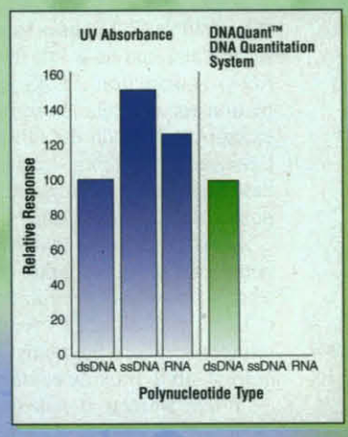

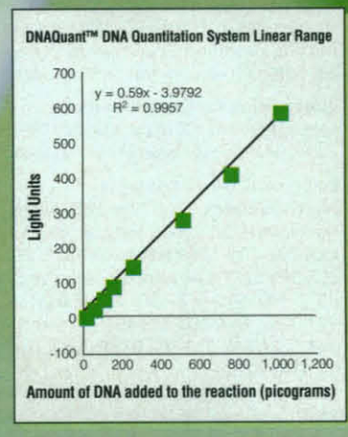

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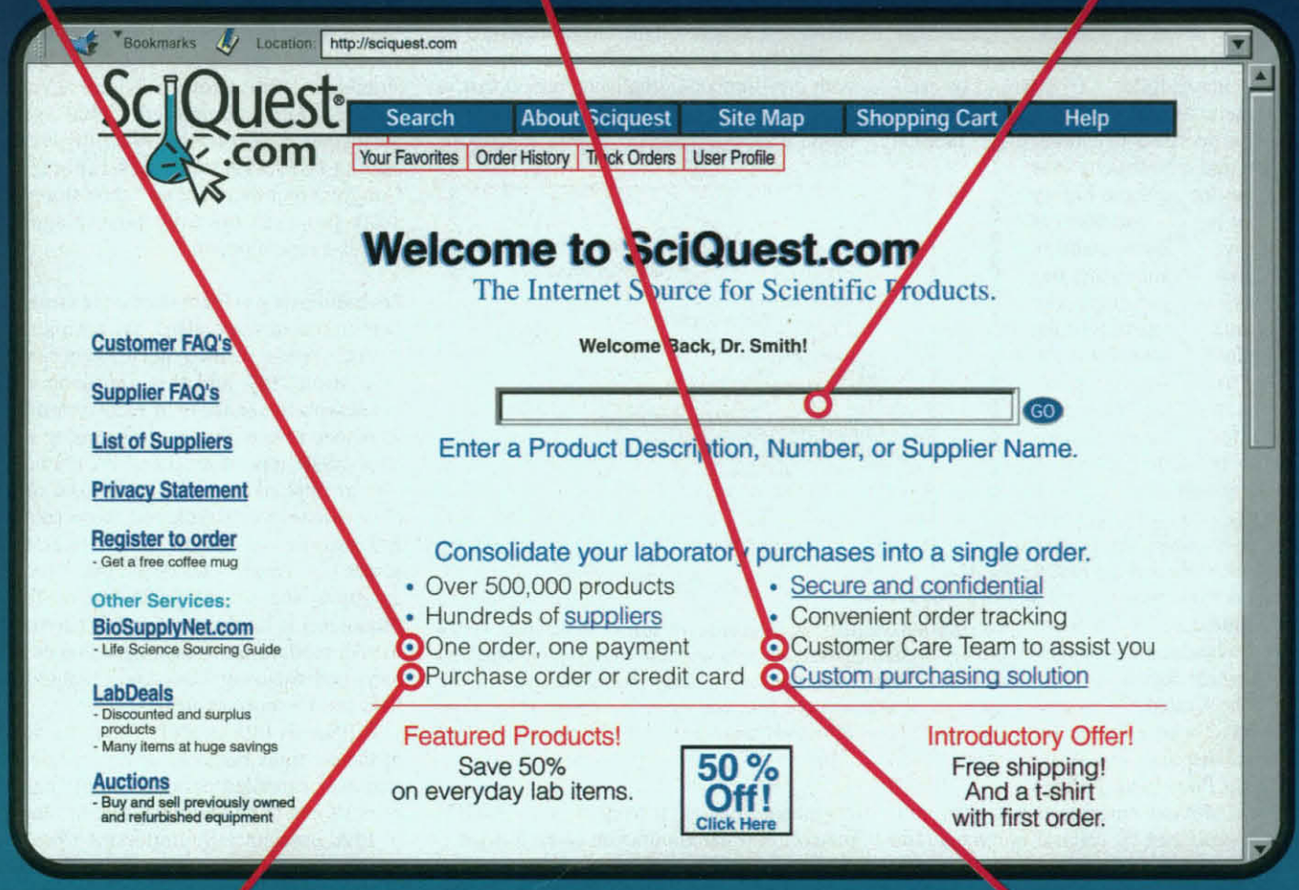

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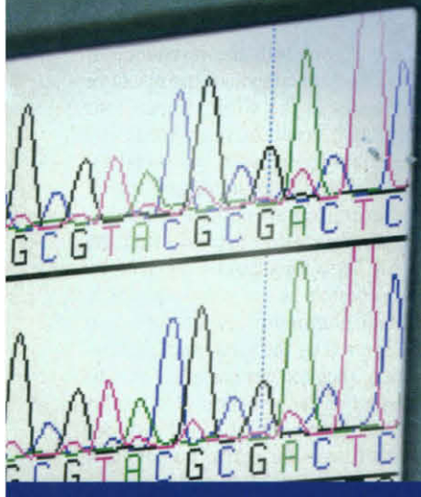

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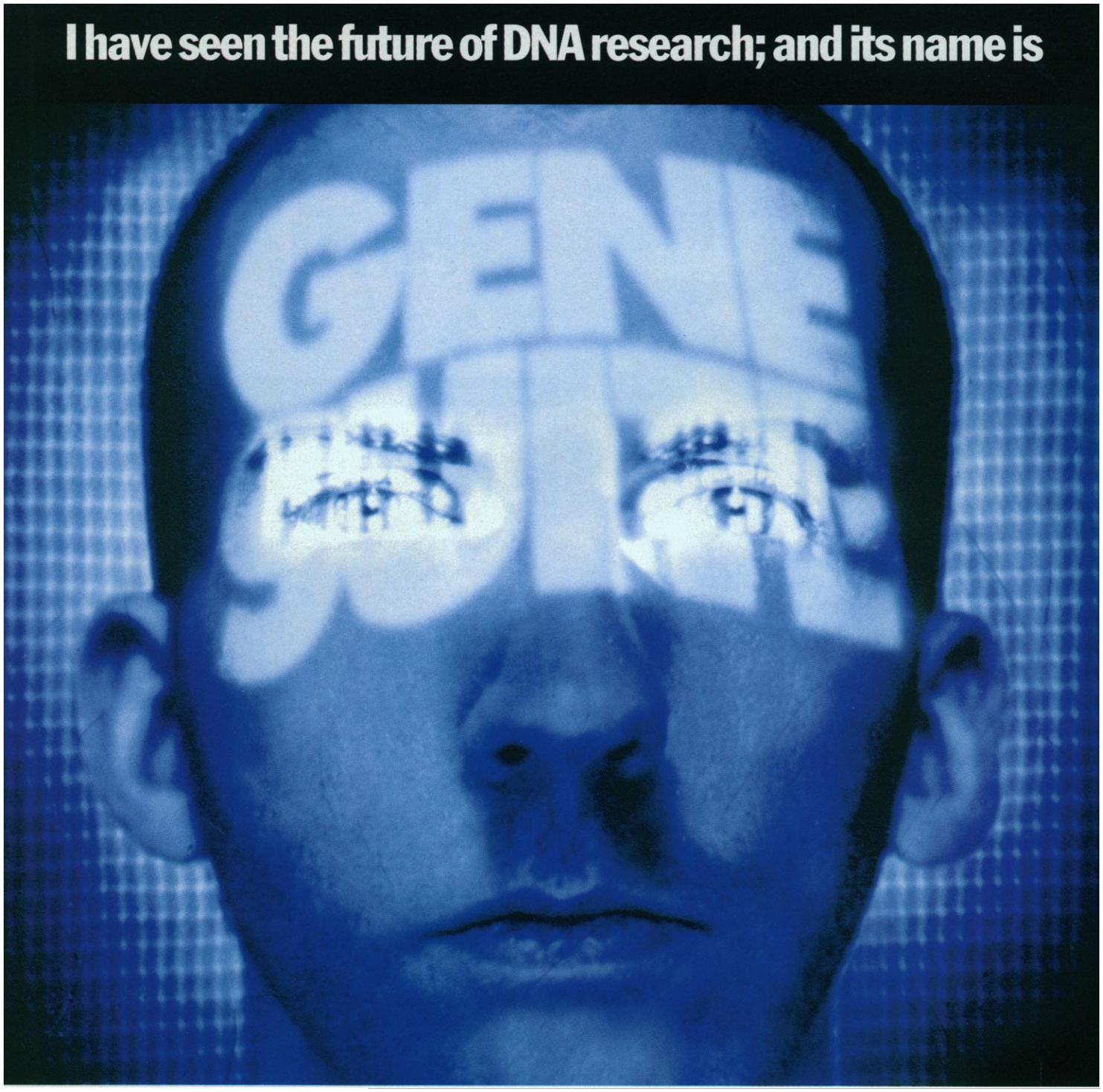

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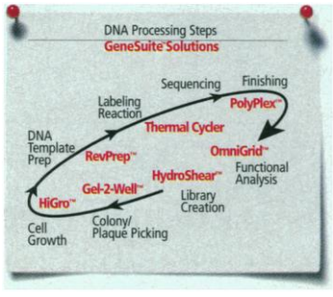

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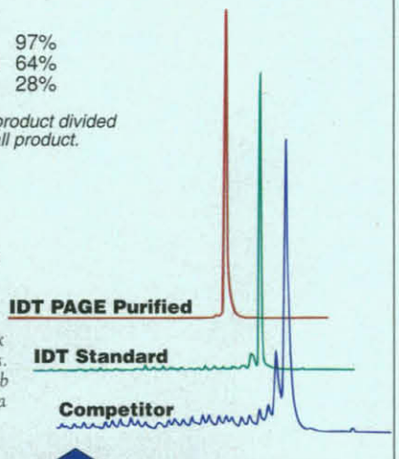

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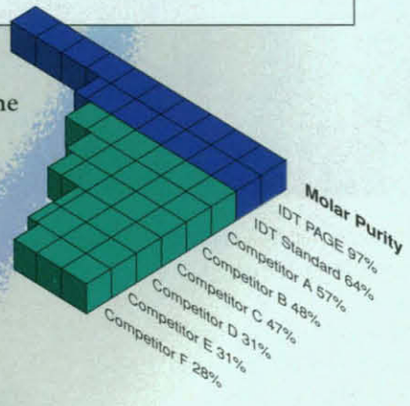

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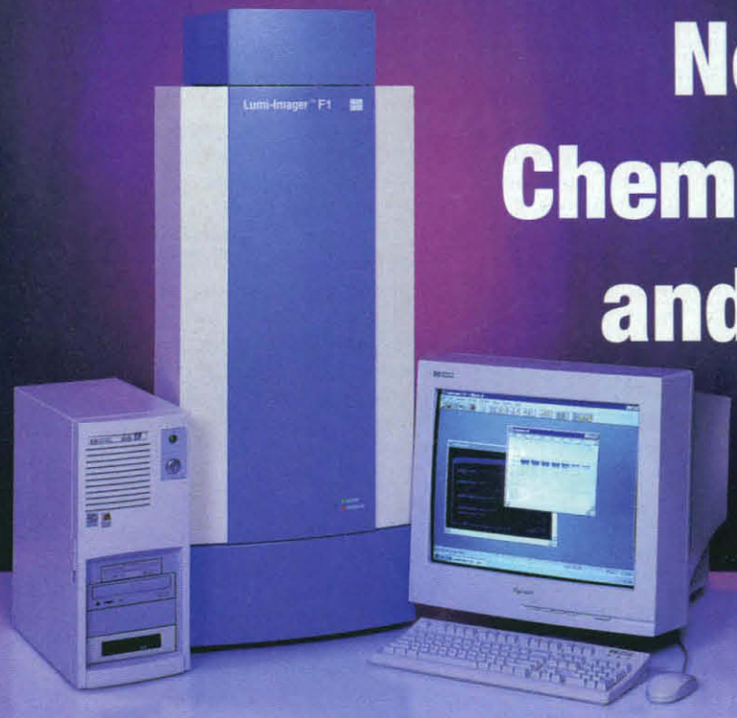
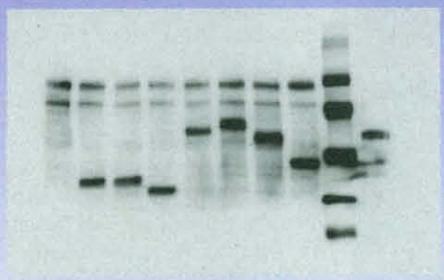
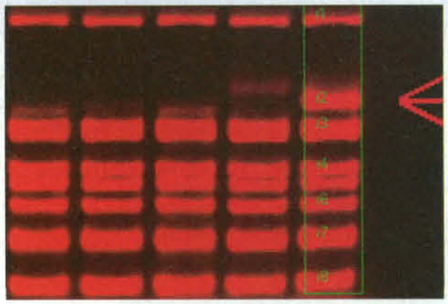


Western blot



Protein Truncation Test of human APC gene

DNA gel



Fluorescein-labeled PCR product (arrow) separated from Molecular Weight Marker II on Texas Red-stained gel.

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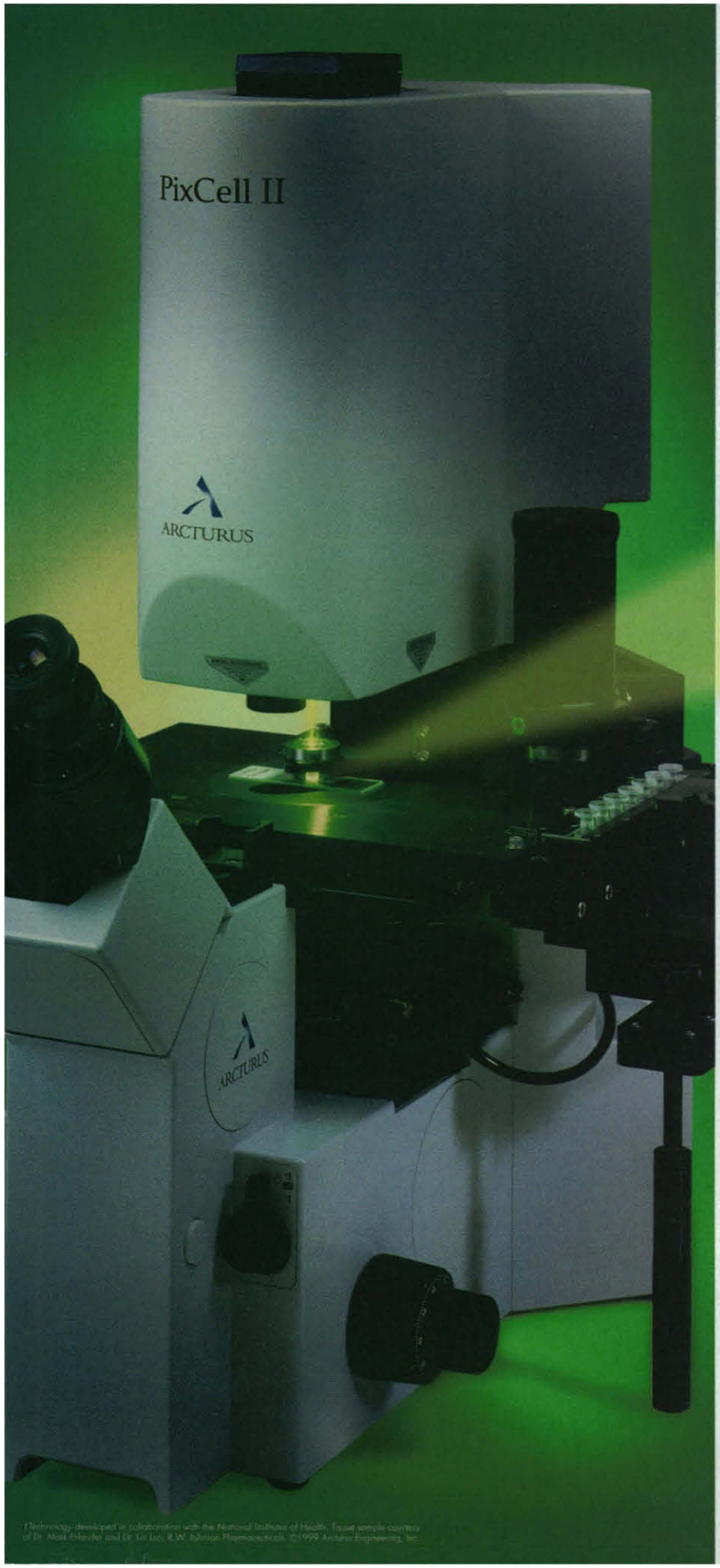

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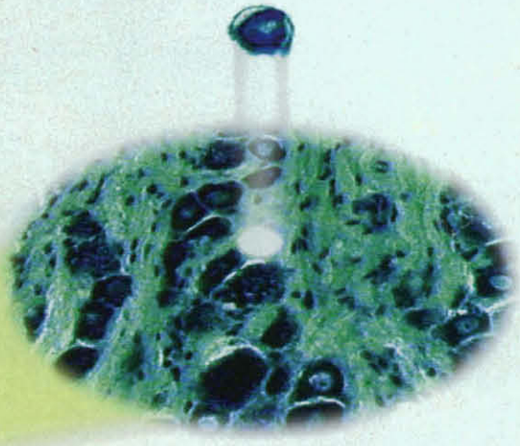

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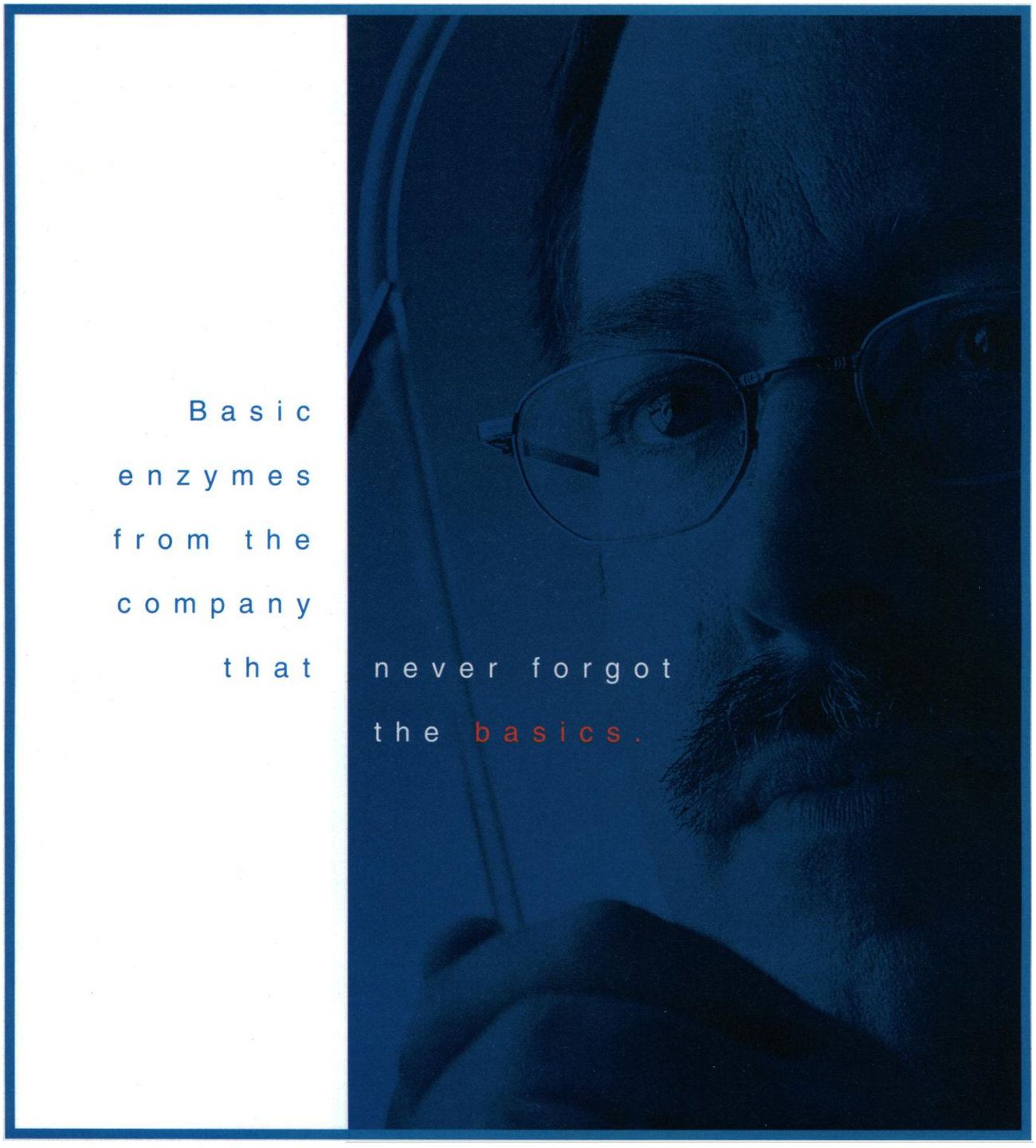

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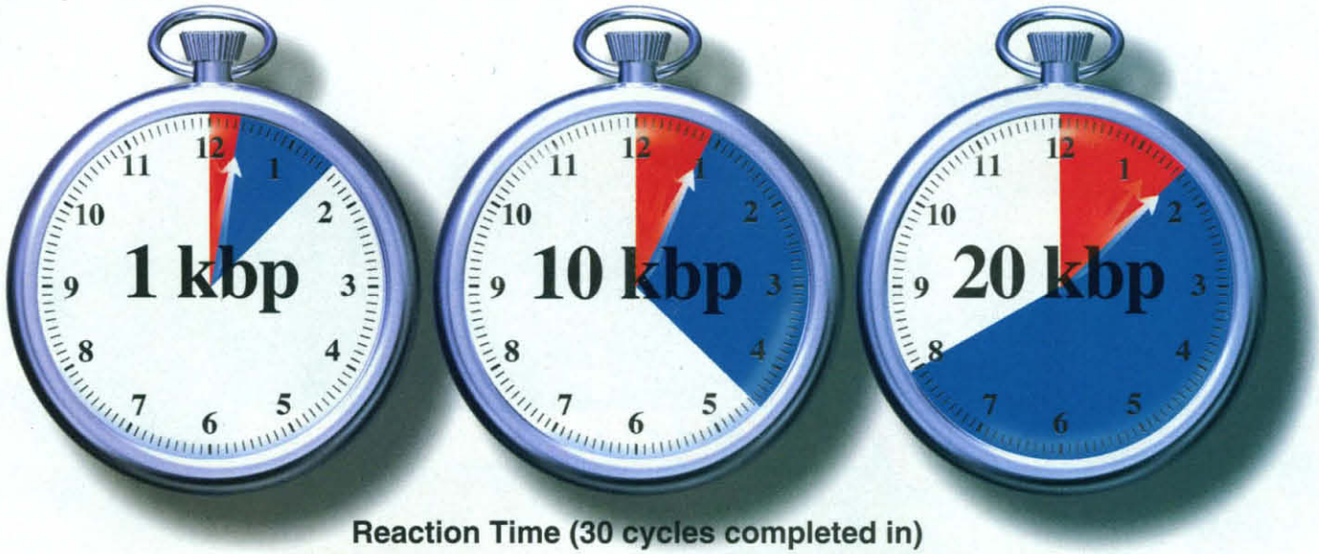

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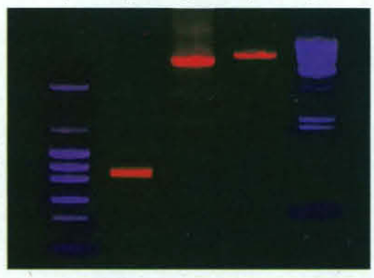

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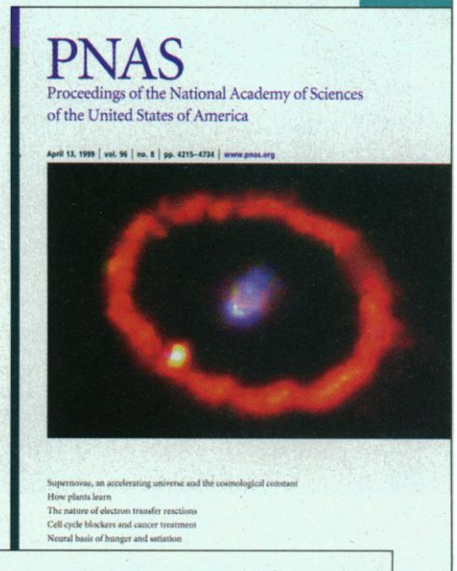

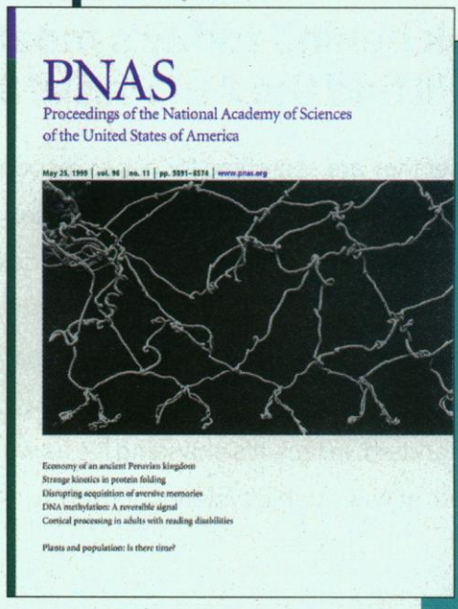

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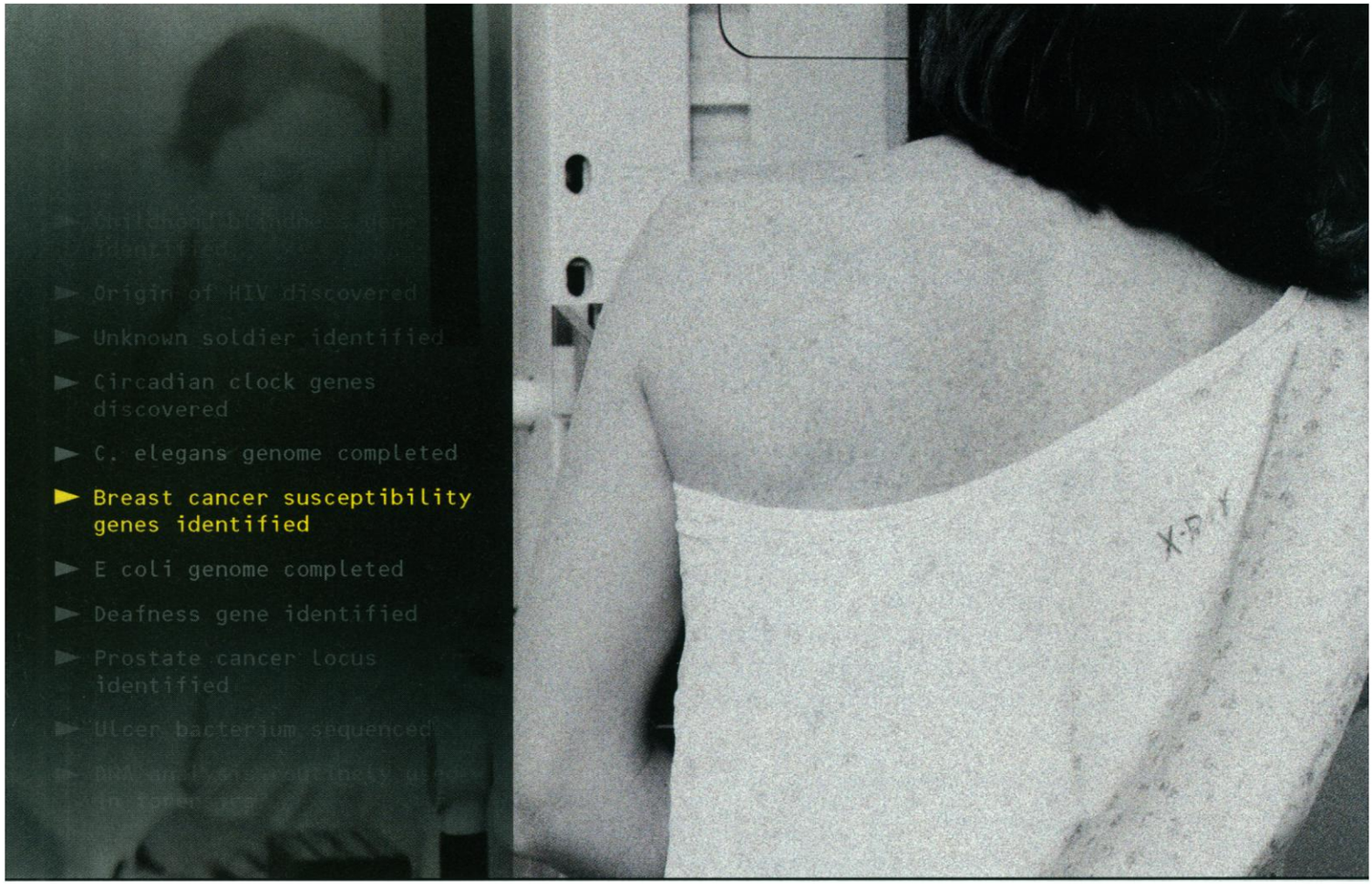

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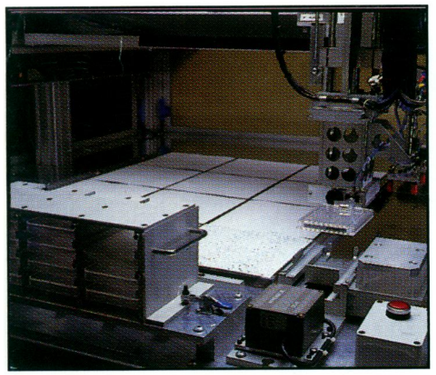

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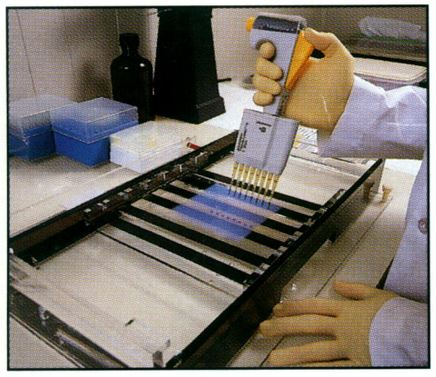
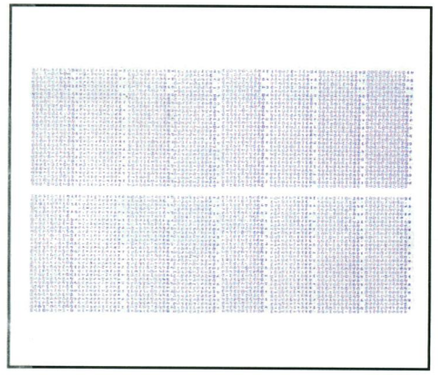


cDNA Based EST Collections

First proposed by Jim Sikela (Wilcox, A.S. *et al., Nucleic Acids Res* 1991 Apr 25;19(8):1837-43) and first carried out on a large scale by Craig Venter (Adams, M.D. *et al., Nat Genet* 1993 Jul;4(3):256-67) the sequencing of cDNAs has helped revolutionize genomics. The I.M.A.G.E. Consortium (LLNL), with a generous donation from Merck & Co. and later by Sandoz Pharma Ltd., Howard Hughes Medical Institute and NIH, has created an invaluable collection of end-sequenced cDNA clones from the human, mouse, rat and other genomes. Together the clones and their associated sequence data have proven useful in all areas of genomics including comparative genomics. Research Genetics is one of five distributors of this valuable resource.

Research Genetics offers a number of cDNA libraries from different genomes as well as different tissues. Currently these include human, mouse, rat and *Drosophila*. Many of these libraries are available on high-density colony membranes. A number of new libraries, including plant and tissue-specific libraries, are under construction.

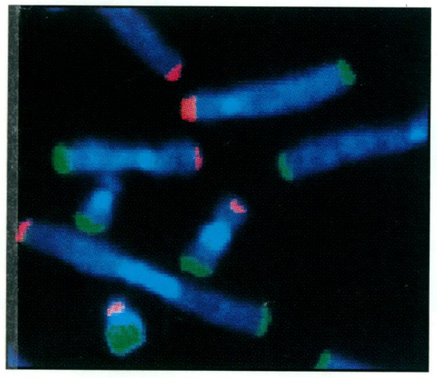


GeneFilters® Microarrays

Research Genetics offers a variety of DNA microarrays covering over 25,000 human genes, 10,000 rat genes and every ORF in the yeast genome. Cross species hybridization experiments have shown that these microarrays can be useful in comparing gene expression in human and mouse genomes (Becker, K., *Resources* Vol. 4, No. 1). As more genes, species and genomes are added to this collection, comparison of similar genes in different organisms will be possible.

Pathways™ Software

Pathways™ software was designed specifically for use with GeneFilters microarrays. The software imports and stores .gel or .tif files from phosphor imaging systems, and locates, calculates, and stores the spot intensities from those files. The software is capable of analyzing images from single membranes or graphically comparing two different images, as well as "bookmarking" genes of interest for easy future reference. An internal database provides instant, on-screen identification of each spot as it is selected.



Chromosome Band Specific Libraries and Cytogenetically Mapped BAC Clones

Research Genetics offers two resources that are proving useful not only in their respective genomes, but also in comparative genomics. The first is a collection of 300 human chromosome band specific libraries produced from chromosome microdissection in collaboration with Jeff Trent's laboratory. The second is a growing collection of BACs that have been mapped cytogenetically and in some cases sequenced and mapped by radiation hybrids or other methods. Resources such as these have been very useful in mapping syntenic regions between different species.

Science

X Genome Maps Ten

Comparative Genomics

MAMMALIAN RADIATIONS

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Resources for Comparative Genomics

Radiation Hybrid Mapping Panels

Where available, radiation hybrid mapping has proven to be the method of choice for mapping genomes. This technique was used to produce the first ever transcript map of the human genome, recently updated to contain over 30,000 transcripts (Deloukas, P., *et al., Science* 1998 Oct 23;282(5389):744-6). Research Genetics offers a number of radiation hybrid mapping panels for different genomes including human, mouse, rat, canine, baboon, zebrafish and porcine.

MapPairs® Microsatellite Markers

The discovery of polymorphic genetic markers based on simple sequence repeats led to the first high-density genetic map of a mammalian genome (Dietrich, W., *et al., Genetics* 1992 Jun;131(2):423-47). These markers, referred to by various names including microsatellites, short tandem repeats (STR) and simple sequence repeats (SSR), are sold by Research Genetics under the trade name MapPairs. The markers have been used to construct whole genome genetic maps for many species of plants and animals. Subsequent maps and markers have proven useful in positional cloning projects, especially when combined with radiation hybrid maps. MapPairs markers are available for over twenty species including over 10,000 for human, over 6,000 for mouse, and over 4,000 for rat.

Large Insert Genomic Libraries

The construction of vectors capable of holding very large inserts was a crucial step in the human genome project. Both Maynard Olson and Hiroaki Shizuya were leaders in this effort (Burke, D.T., *et al., Science* 1987 236:806-812, and Shizuya, H., *et al., Proc. Natl. Acad. Sci., USA* 1992 89:8794-8797). Research Genetics archives and distributes clones from one of the world's largest collections of YAC, BAC and PAC libraries. A number of ways of screening these libraries are available including high-density colony membranes, DNA pools and custom screening by our research staff. BAC end sequencing projects currently under way will make these collections even more useful for positional cloning and comparative genomics.

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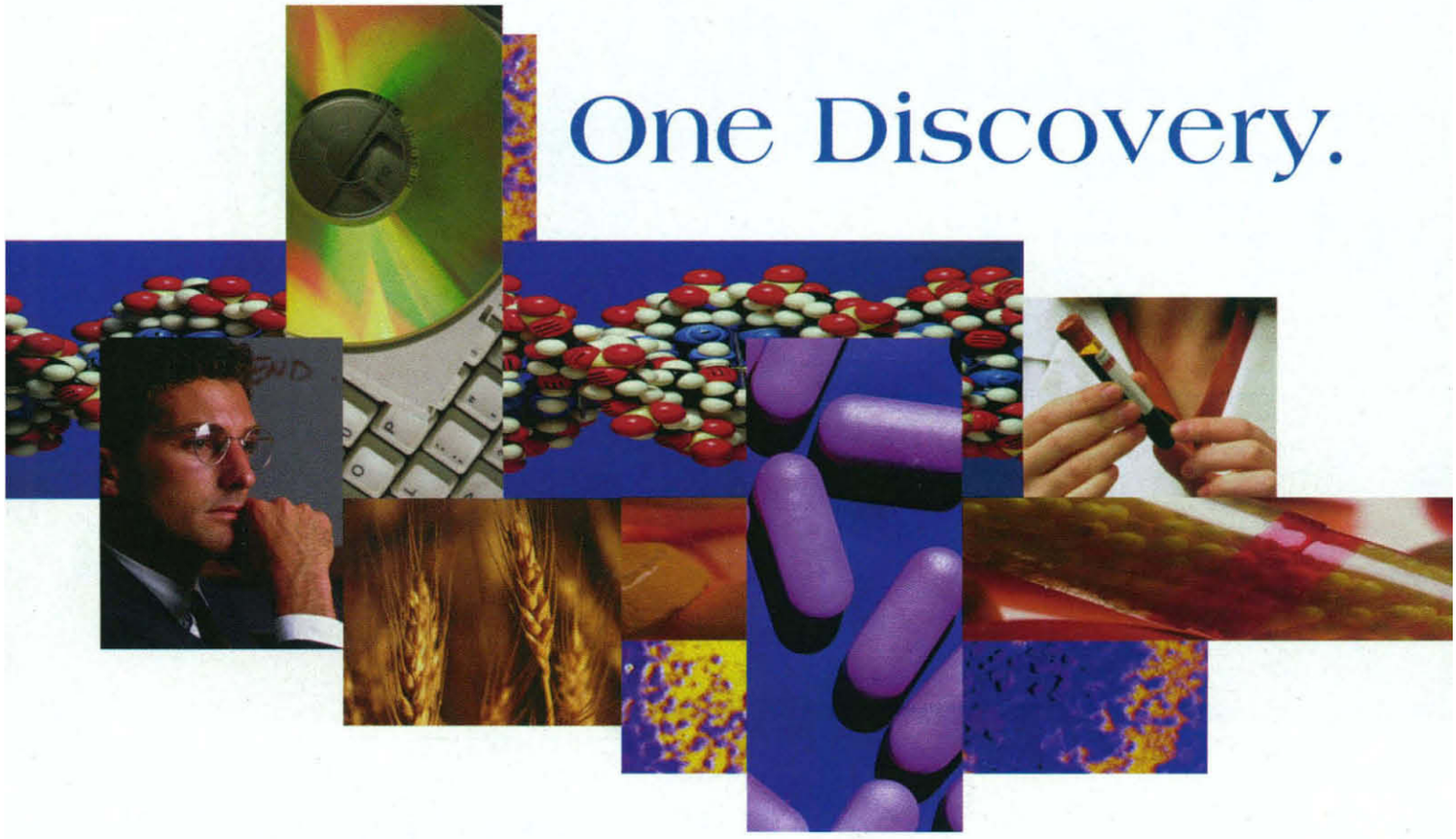

InforMax Leads The Industry In Bioinformatics.

A pattern is emerging from the chaos: InforMax is standardizing bioinformatics. Our products are driving research at 60 pharmaceuticals, 250 biotechs and 500 universities worldwide. Securely integrating private research with global databases. Running complex customized search algorithms. Processing DNA and protein sequence analyses at once-impossible speeds. As of now, more than 10,000 researchers rely on our software's exclusive ResearchLogic™ system to accelerate inquiries into the mysteries of genetics... and run the race for rapid drug discovery.

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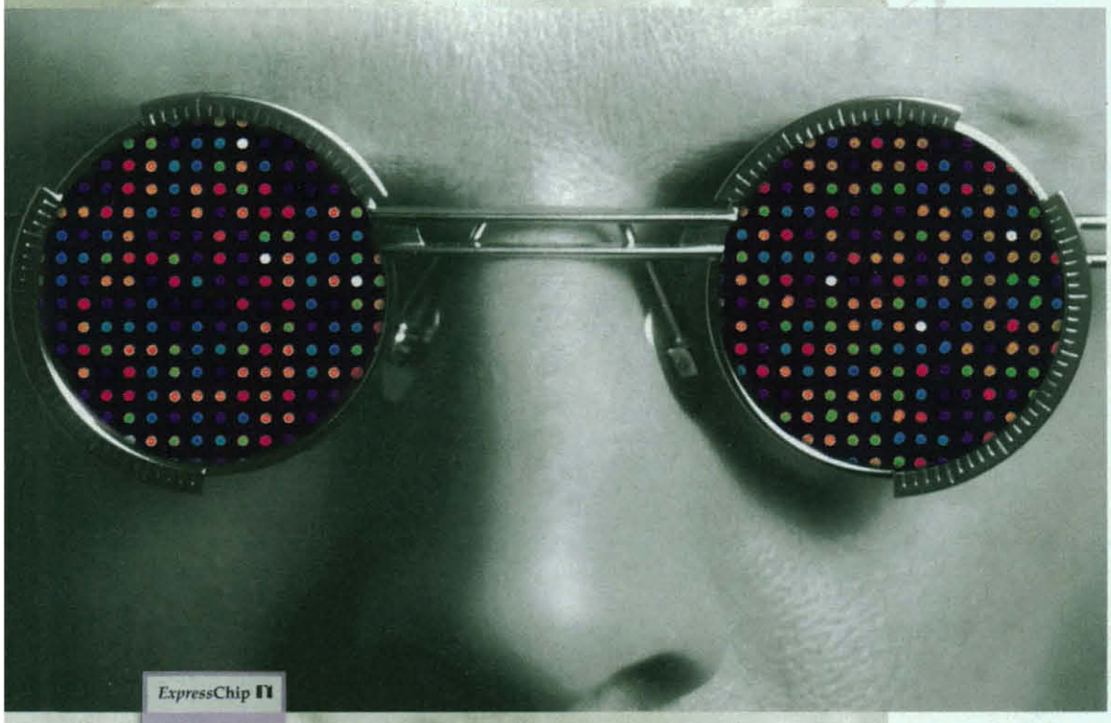

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