20 July 2001

Science

Vol. 293 No. 5529
Pages 381–560 $9

American Association for the Advancement of Science

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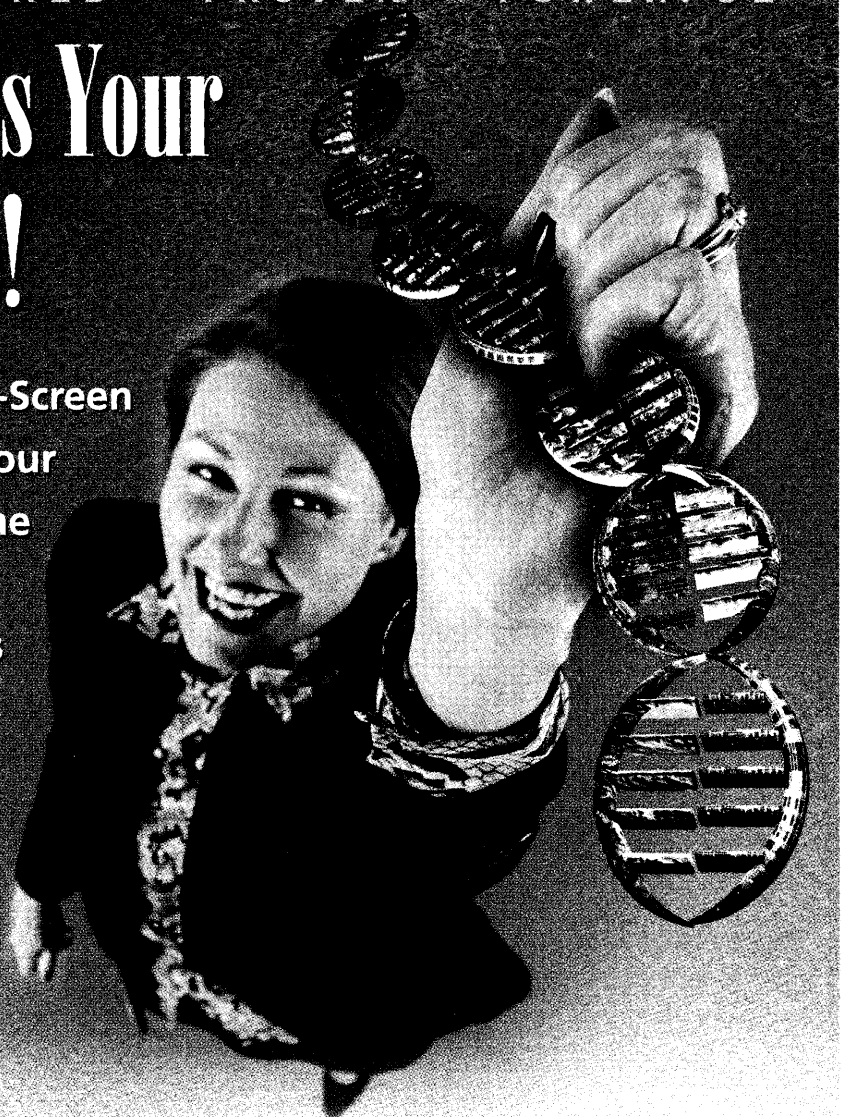

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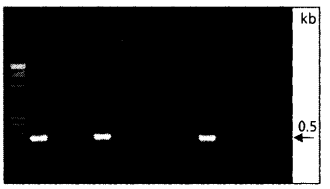
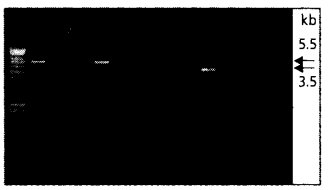


Master-Plate PCR screen using a pair of gene - specific primers to identify the positive pools *(12 pools with 40,000 clones each)*



Parallel screen using the 5′ vector-derived primer and a gene-specific reverse primer to determine extent of 5′- end sequence.

Alternate screen using the 3′ vector-derived primer and a gene-specific forward primer to determine extent of 3′ sequence

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Placenta	LLPC-1001
Skeletal Muscle	LMU-1001
Small Intestine	LSI-1001
Spleen	LLSP-1001
Testis	LTS-1001
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Brain (Adult)	MAB-1001
Embryo (12.5-Day)	MEB-1001
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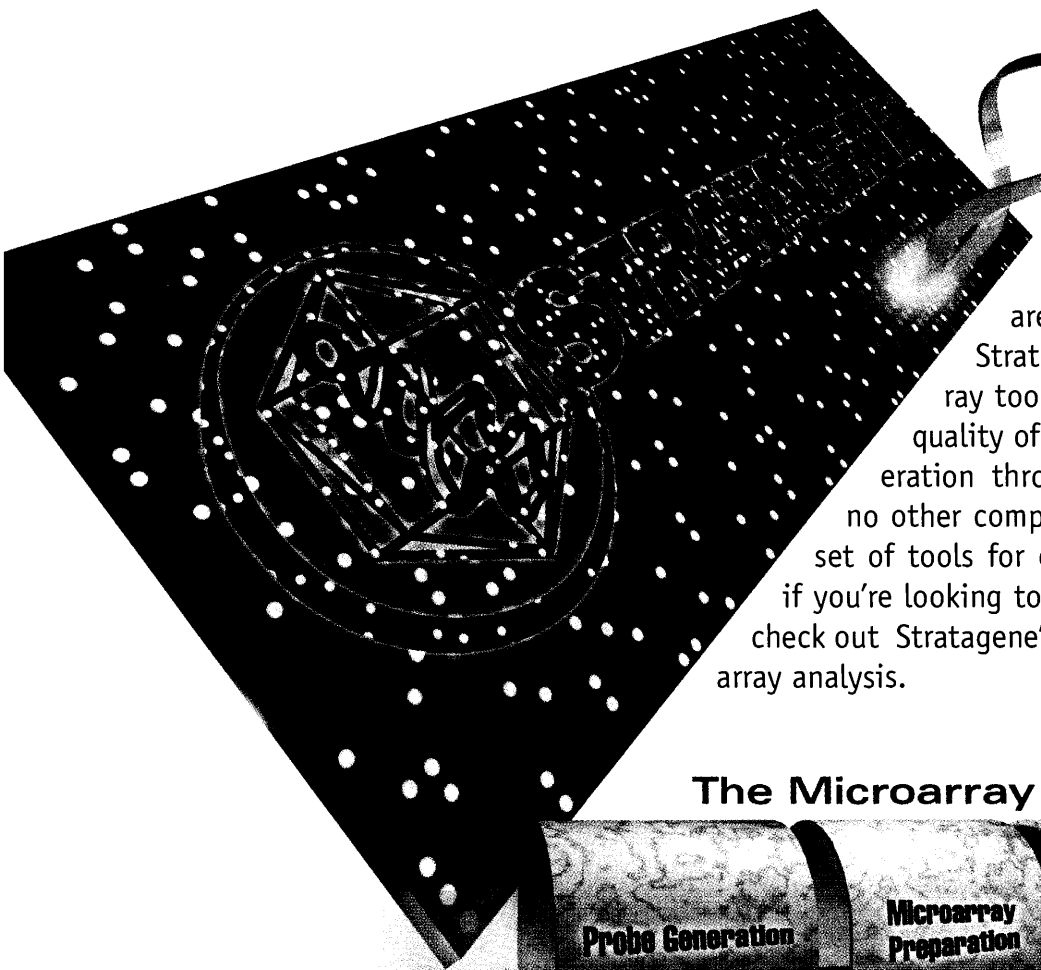

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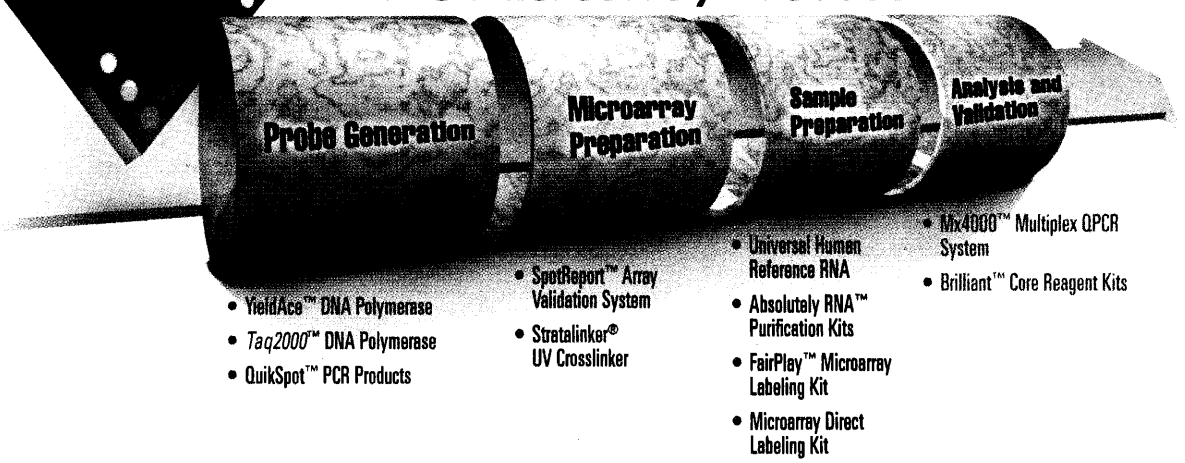

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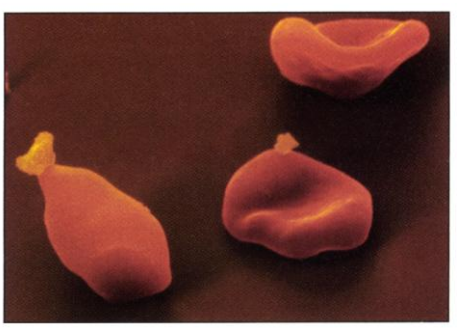

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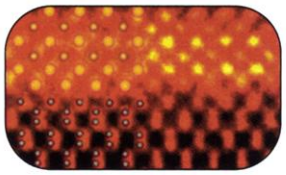

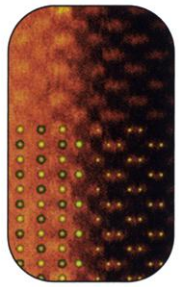

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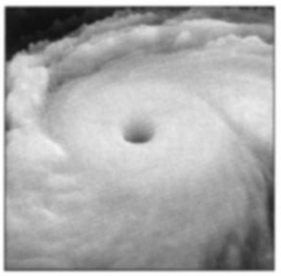
Crystalline perovskite oxides on silicon

RESEARCH

RESEARCH ARTICLE

REPORTS



COVER 474

Hurricane Mitch on 28 October 1998. Mitch, responsible for more than 9000 deaths in Central America, was one of 23 major hurricanes to develop in the Atlantic basin since 1995. This recent increase in activity is due to changes in tropical North Atlantic sea surface temperatures and atmospheric vertical shear, creating conditions more conducive to hurricane formation. These conditions are expected to continue for another decade or more. [Satellite-derived image: NOAA; H. F. Pierce and A. F. Hasler, NASA]

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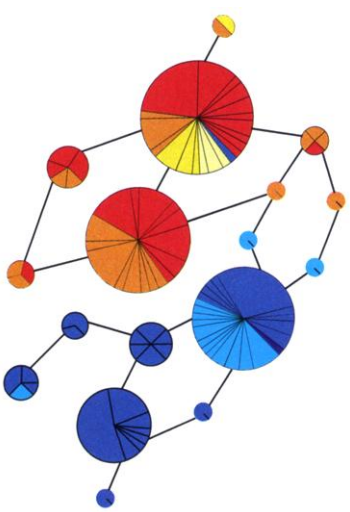
Human origins of malaria resistance



New on *Science* Express Weighing the black hole in M33

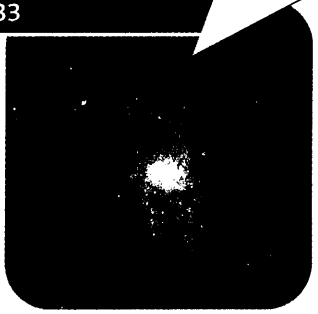


Image: Malin/IAC/RGO

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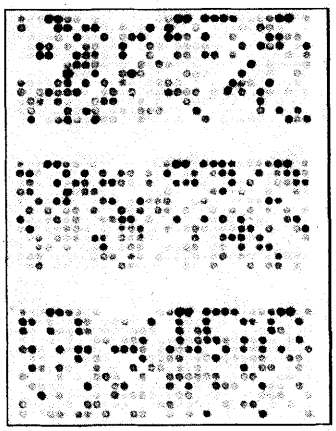

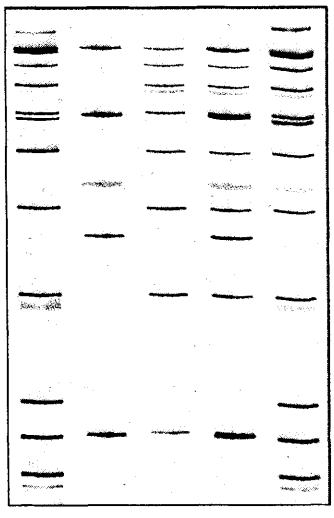

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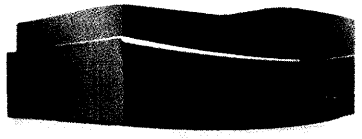

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Responding to Market Failures in Tuberculosis Control R. Gupta *et al.*

A World Health Organization–led effort has resulted in a substantial reduction in the cost of second-line drugs for treating multidrug-resistant TB in low- and middle-income countries.

No Supermassive Black Hole in M33? D. Merritt, L. Ferrarese, C. Joseph

Spiral galaxies with large bulges have supermassive black holes at their centers, but M33, which has a minuscule bulge, does not; hence, black holes may not all form in the same way.

Regulation of Transcriptional Activation Domain Function by Ubiquitin S. E. Salghetti, A. A. Caudy, J. G. Chenoweth, W. P. Tansey

Activation of transcription by the VP16 activation domain (AD) in yeast requires ubiquitination of the AD—a finding that demonstrates a new role for ubiquitin, separate from protein degradation.

science's stke www.stke.org

Perspective: RNA Localization Meets Wingless Signaling L. J. Manseau

Effective signaling is controlled by transcript location.

science's next wave www.nextwave.org

UK: Your Ph.D. Boss . . . Adversary or Super-Advisor? Part Two P. H. Dee

Our "Yours Transferably" columnist continues his look at the all-important student-supervisor relationship with advice on how to take the initiative and become an expert "boss-handler."

UK: Bioarchaeology Brings the Past to Life H. Cottle

Supported in part by a 10-year funding program from the Wellcome Trust, a new breed of archaeologist is more likely to be found in a shiny lab than in a dirty great hole in the ground.

US: Postdoc Network Digs In for Details R. Weibl

Join the rejuvenated Postdoc Network community—where postdoc organizations and offices come together to enhance the postdoctoral experience.

Canada: Financial Planning for Scientists, Part 10: More on Bonds C. Boulakia

Next Wave's financial guru digs deeper into the world of bonds, focusing on ratings systems and some of the key risks of investing in bonds.

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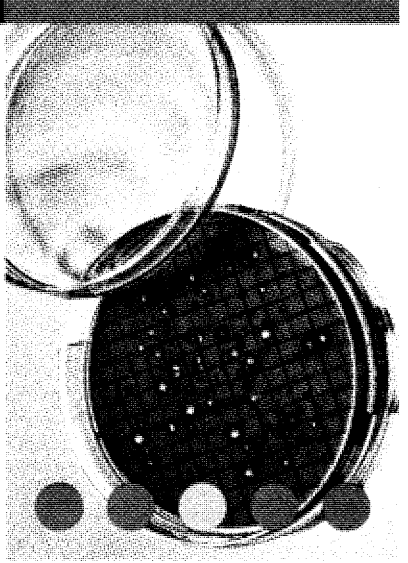
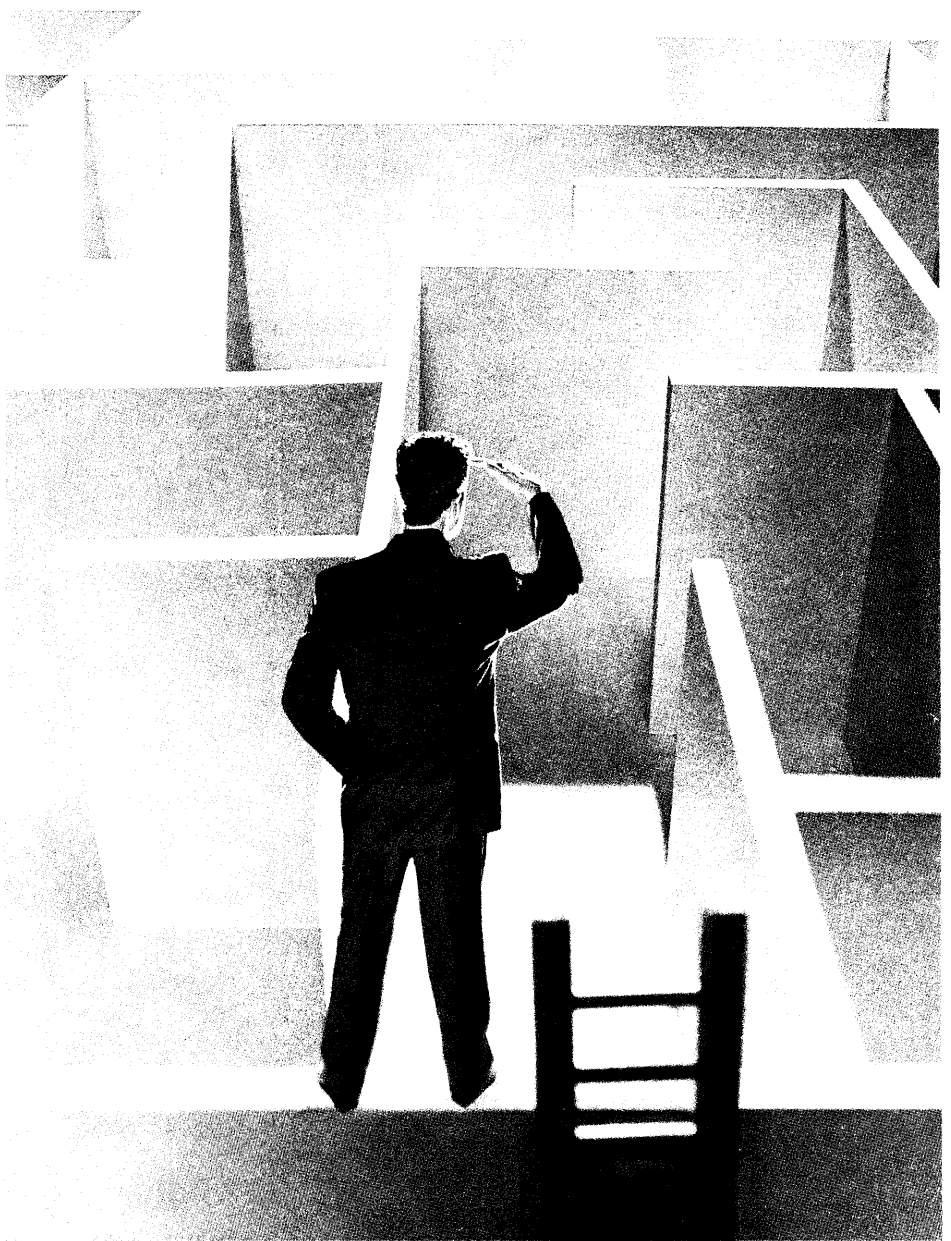


Quantitative gene analysis is now in sight.



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THIS WEEK IN Science

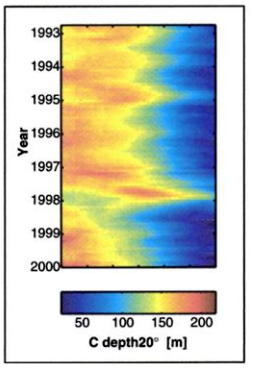
edited by Phil Szuromi

Crystalline Oxides on Silicon

As the size of transistors decreases, the need increases for a replacement for amorphous silicon oxide as the insulator in these devices. One alternative is to grow crystalline oxides on silicon, which should avoid the steric hindrance and bond-coordination problems inherent in amorphous oxides. McKee *et al.* (p. 468) demonstrate commensurate growth of cubic alkaline earth and perovskite oxides on silicon that results in high-quality interface regions with extremely low defect densities. The ability to manipulate the dielectric displacement and the inversion charge at the interface may lead to additional device functionality.

471 Carbon Swings in the Pacific

The cycles of El Niño and La Niña can have large impacts on the global carbon cycle, particularly in new production—that is, the marine productivity which is supported by nutrients imported into a given region, as opposed to that which occurs by local nutrient recycling. Turk *et al.* (p. 471) combine satellite measurements of sea surface height, ship and buoy measurements of isotherm depth, and local estimates of new production to infer equatorial Pacific basin–wide estimates of new production for the years 1992 to 1999. This period included an extremely strong El Niño and a moderately strong La Niña. Carbon export varied by a factor of 3 between these episodes.



CREDIT: TURK *ET AL.*

Measuring a Polymer's Reach

Most measures of polymer chains in solution provide insight into their average conformation, but fluctuations can produce excursions that change the overall shape and end-to-end length of the chain over time. Jeppesen *et al.* (p. 465; see the Perspective by Russell) attached polyethylene glycol, labeled at its free end with biotin, to one surface in surface force apparatus and labeled the opposing surface with its receptor, strepavidin. By determining the capture probability of the free biotin end as a function of distance between the surfaces, they show that rare highly extended conformations of the polymer play a key role in the binding process.

Staying in Shape

Many proteins form relatively compact molten-globule intermediates under mildly denaturing conditions, but high concentrations of denaturant proteins would be expected to produce an ensemble of conformations that approach statistical randomness. Shortle and Ackerman (p. 487) used nuclear magnetic spectroscopy to measure residual dipolar couplings in denatured forms of staphylococcal nuclease. Long-range order, in which chain segments retain their same relative orientations, persisted even in 8 molar urea.

Leggy Old Crustacean

In the hamlet of Comley, Shropshire, England, Siveter *et al.* (p. 479; see the Perspective by Fortey) have found a well-preserved crustacean in a temporary trench dug into Lower Cambrian limestone formations. Two specimens of the soft anatomy of these phosphatocopid arthropods are protected within partial to nearly complete carapaces and provide exquisite detail about the body and limbs in three dimensions. These early Cambrian specimens should help paleontologists decipher whether Crustacea evolved in the Precambrian or radiated more rapidly during the Cambrian explosion.

Warmer, Stormier Weather in Store

Average global temperatures will increase during the next century, largely because of anthropogenic modifications of the atmosphere, but by how much? Wigley and Raper (p. 451) have made probabilistic projections of future warming trends. They conclude that the most likely future is one in which warming will be closer to the middle of current estimates, rather than at the high or low extremes of the range. One consequence of global warming could be an increase in storminess. Goldenberg *et al.* (p. 474; see the cover and the Perspective by Bengtsson) report an increase in hurricane activity in the North Atlantic since 1995. They examined the meteorological record of tropical cyclones since 1944, and by comparing it to concurrent measurements of sea surface temperature and atmospheric vertical shear (two key factors in hurricane formation), present mechanistic support for the observed recent increase in the frequency of hurricanes there.

Malaria's Recent Origins

Despite the risk of hemopathology, mutations within the human gene encoding glucose-6-phosphate dehydrogenase are seen in more than 400 million African and Mediterranean people. The mutations have long been suspected to have become so common because the resulting hemolysis of mature red blood cells inhibits the establishment of the malaria parasite *Plasmodium falciparum*. Tishkoff *et al.* (p. 455 ✂; see the Perspective by Luzzatto and Notaro) have identified three highly variable markers at this locus that provide direct evidence of this relation and that date the origin of malaria to about 6500 years in Africa and to about 3300 years ago in the Mediterranean. Why is *P. falciparum* so variable in the protein sequences affected by host responses and drugs and yet shows almost no variation in housekeeping genes? Volkman *et al.* (p. 482; see the news story by Pennisi) sequenced 25 introns from housekeeping regions of eight parasite isolates, but only found eight single nucleotide polymorphisms, most of which were in regions of microsatellite polymorphism. These data hint not only to a recent, possibly single progenitor of *P. falciparum*, but also to a high mutation rate within the microsatellite repeats.

SNP'ing Through Population Heterogeneity

Analysis of genetic variation could revolutionize studies of disease susceptibility and allow treatment of disease to be tailored to the

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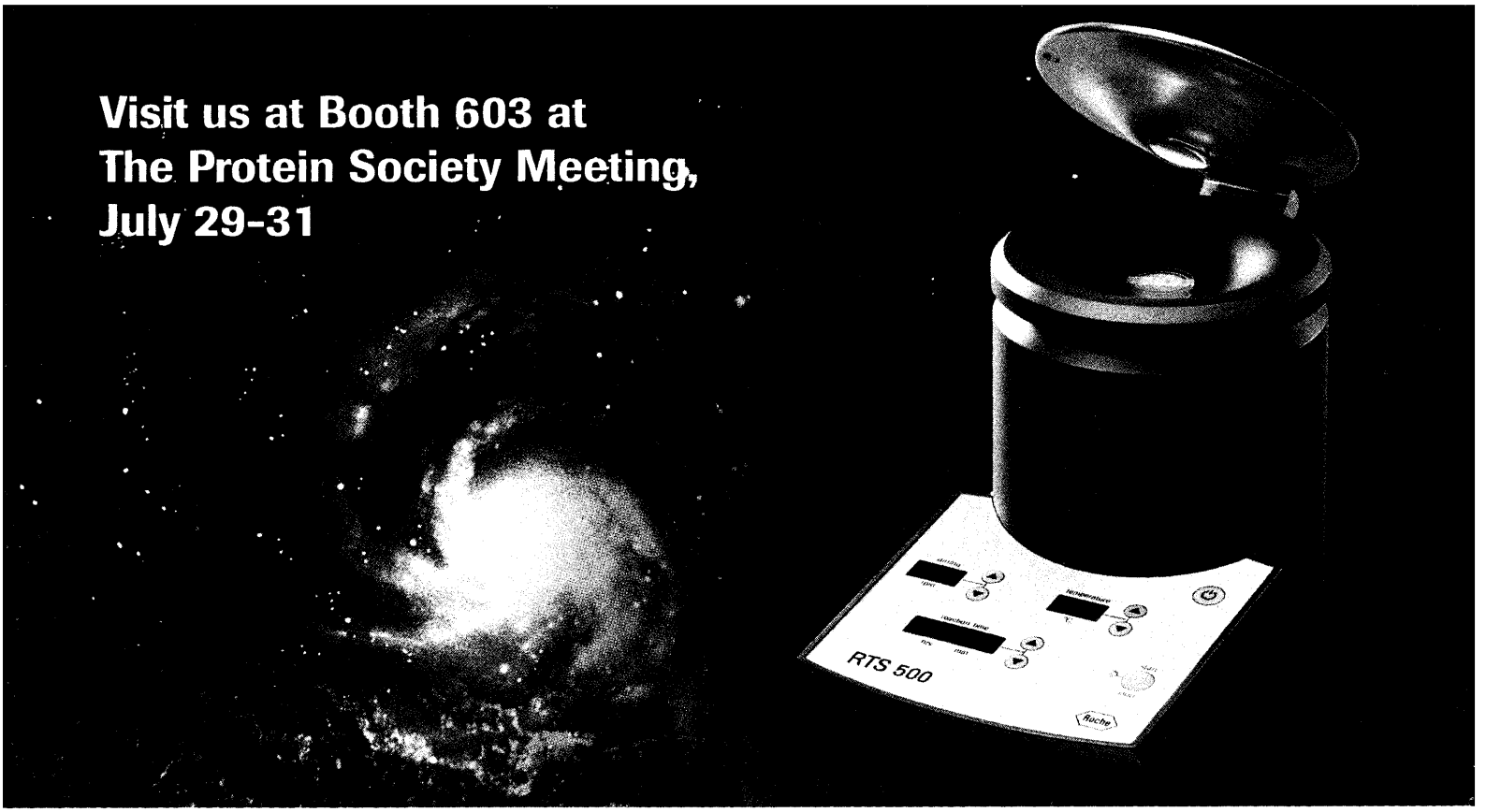
CONTINUED ON PAGE 391



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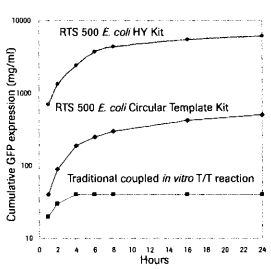

GFP expression (mg/ml, log scale) using the RTS 500 *E. coli* HY Kit and RTS 500 *E. coli* Circular Template Kit, versus a traditional coupled *in vitro* transcription/translation reaction.

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Schematic of a RTS 500 Reaction Device containing approximately 5 mg/ml of GFP following a 24-hour reaction.

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*The Rapid Translation System currently consists of a small benchtop RTS 500 Instrument (3.75 kg), the RTS 500 *E. coli* Circular Template Kit, the RTS 500 *E. coli* HY Kit, and the RTS 100 *E. coli* Circular Template Kit.
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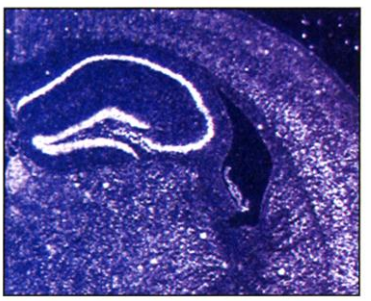
individual. Stephens *et al.* (p. 489) have identified single nucleotide polymorphisms (SNPs) from 313 genes in 82 individuals of different ancestral backgrounds. The SNPs were characterized according to frequency, distribution among populations and functional genomic regions, potential functional consequences, inferred mutation pattern, linkage, and organization within each chromosome in each individual (haplotype). The strength of the genetic association of pairs of SNPs (linkage disequilibrium), which is important in the identification of disease-related genes, could not be readily predicted from examining individual genes or genomic regions. Generally, haplotypes were more informative as genetic markers than the SNPs contained within a gene.

Redox Around the Clock



Circadian rhythms are controlled by an evolutionarily conserved transcriptional feedback system whose activity fluctuates as a function of the 24-hour light-dark cycle. Extrinsic factors, such as changes in food intake, can advance or delay the circadian clock, but the mechanism by which this "entrainment" occurs remains unclear. A key regulator of circadian rhythms, Clock, is expressed in the suprachiasmatic nucleus (the brain region regarded as the master pacemaker) and regulates the expression of genes encoding other clock components. Reick *et al.* (p. 506) and Rutter *et al.* (p. 510; see Perspective by Schibler *et al.*) show that the NPAS2 transcription factor performs a function similar to Clock in the mammalian forebrain and that the DNA binding activity of both these transcription factors in vitro is regulated by the redox state of NAD (nicotinamide adenine dinucleotide) cofactors. Because changes in food intake are associated with changes in cellular redox state, the authors propose that redox control of Clock and NPAS2 activity may explain how food and other extrinsic factors entrain the molecular clock.

CREDIT: REICK *ET AL.*

The Benefits of Huntingtin

The huntingtin protein is mutated in Huntington's disease, a fatal neurodegenerative disorder that strikes in middle age. It has been presumed that mutant huntingtin becomes toxic to neurons by forming aggregates with itself and with other intracellular proteins. Zuccato *et al.* (p. 493; see the Perspective by Trottier and Mandel) show that the loss of huntingtin's normal function results in death of striatal neurons in the brain. Wild-type huntingtin boosts the production of brain-derived neurotrophic factor, which striatal neurons require for survival.

Profile of a Killer

The international increase in antibiotic-resistant outbreaks of *Streptococcus pneumoniae* will only add to millions of deaths caused by this pathogen from pneumonia, meningitis, and other illnesses. Tettelin *et al.* (p. 498; see the news story by Ferber) have sequenced this pathogen's genome and found several clues into its pathogenesis and possible vulnerable points. The high percentage of sugar transporters (higher than any other sequenced prokaryote) suggests that it may occupy a distinct microenvironment within the respiratory tract. A motif potentially related to cell adhesion, large numbers of insertion sequences, and a possible targeting signal for surface-associated proteins were also observed.

Glutamate Receptor Clusters in Spontaneous Transmitter Release

Clues into the functional significance of spontaneous miniature synaptic potentials (minis), which result from the "random" fusion of synaptic vesicles at nerve terminals, have been revealed by Saitoe *et al.* (p. 514; see the Perspective by Verstreken and Bellen), who examined minis in mutant *Drosophila* with known defects in presynaptic function. Minis, as well as regulated neurotransmitter release, only occurred in the neuromuscular junctions of flies that possessed normal clusters of glutamate receptors in postsynaptic cells. The developmental clustering of glutamate receptors may be linked to spontaneous vesicle release as a prequel to functional synapse formation.

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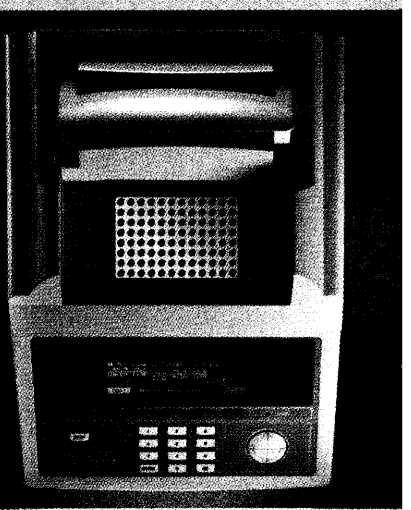

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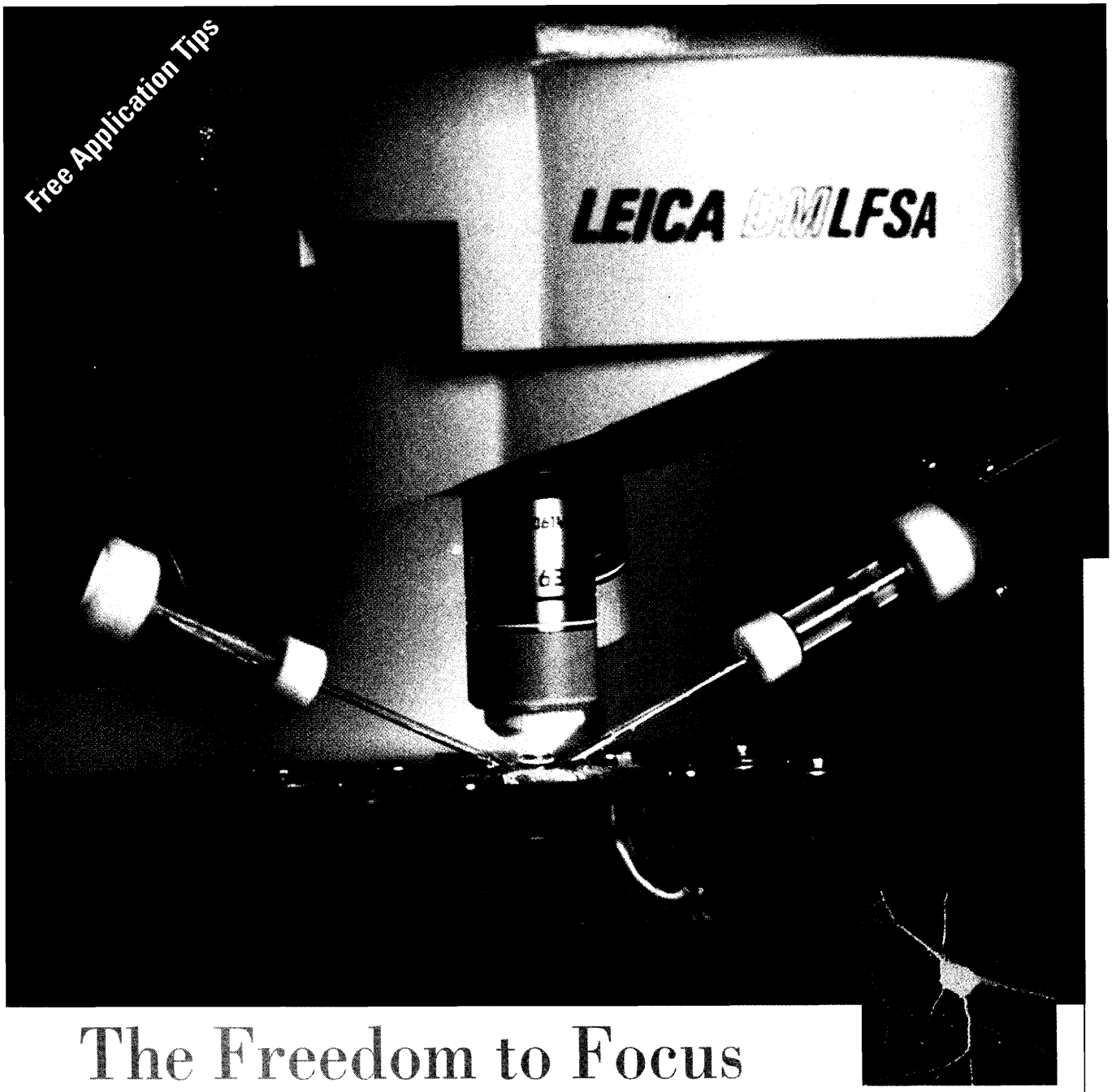

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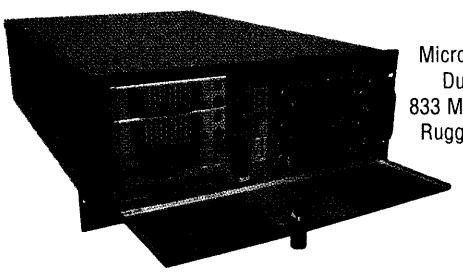

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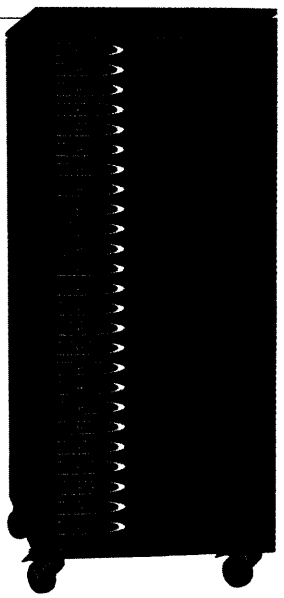

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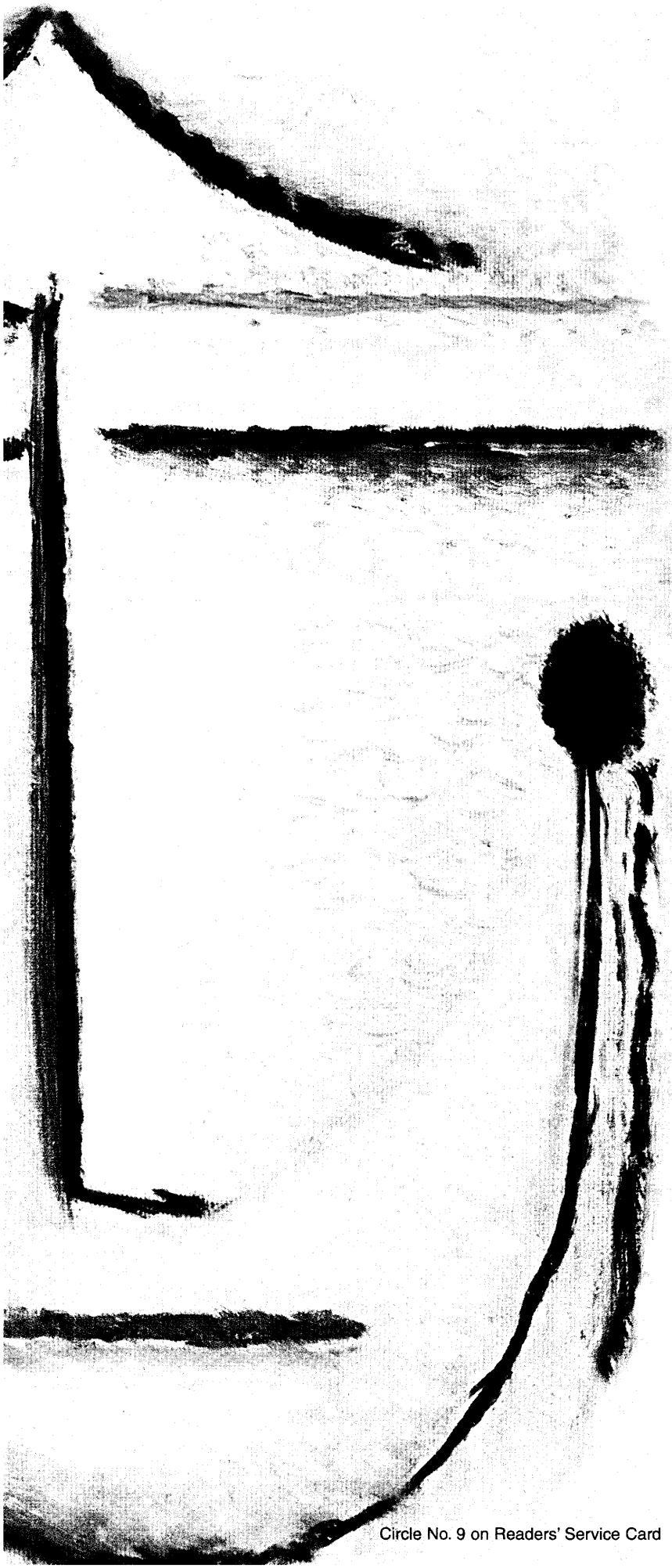

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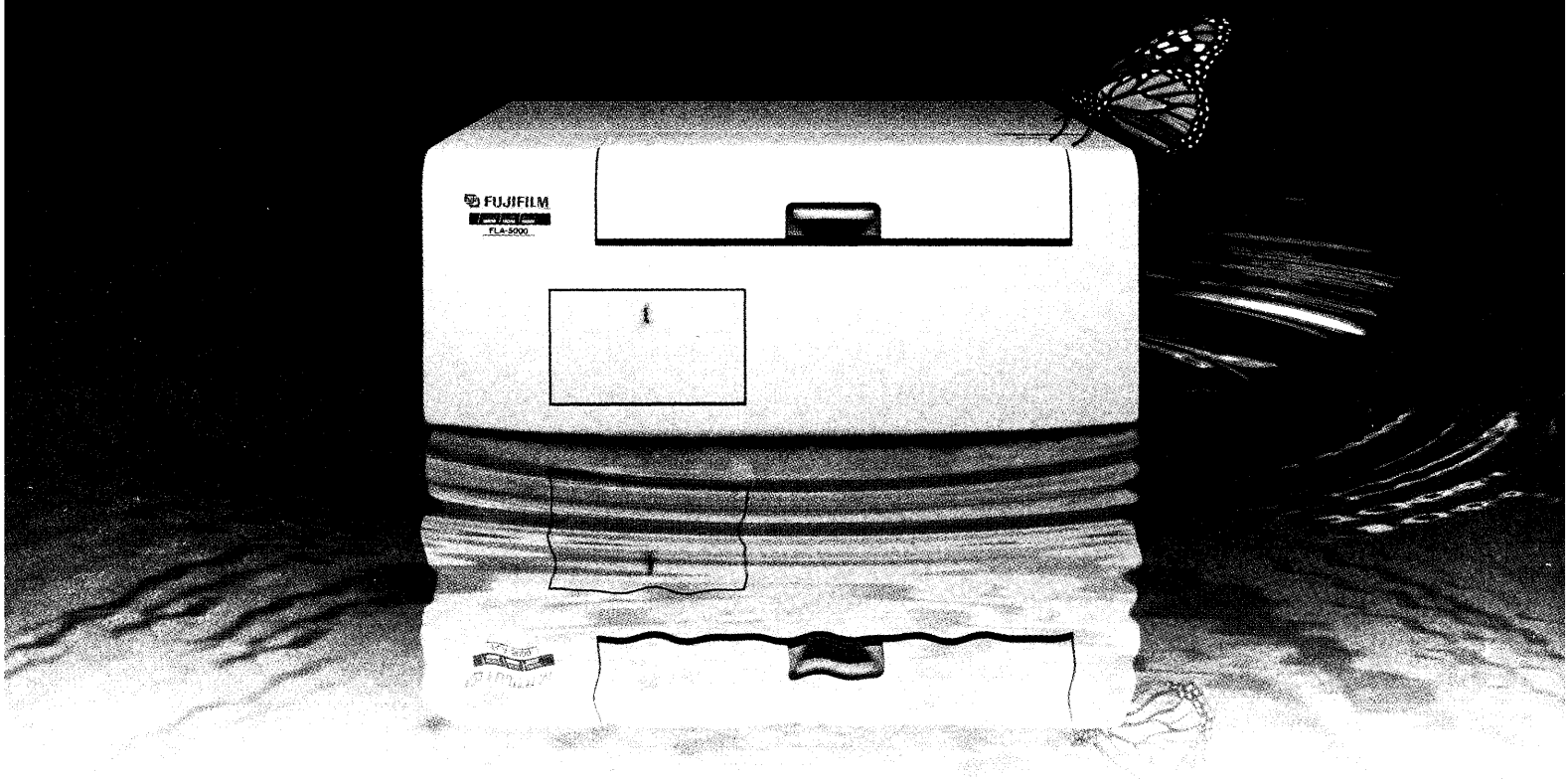

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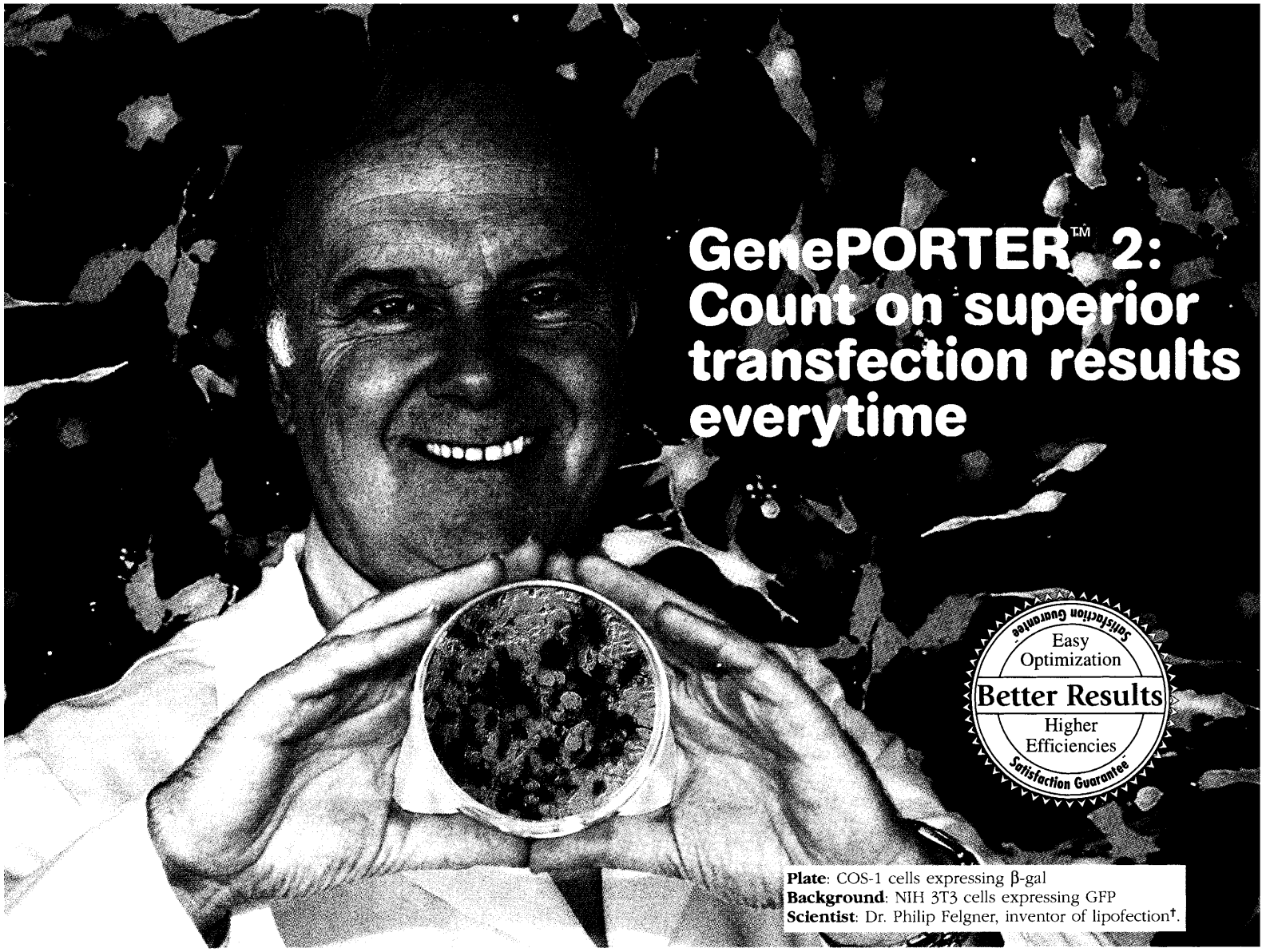

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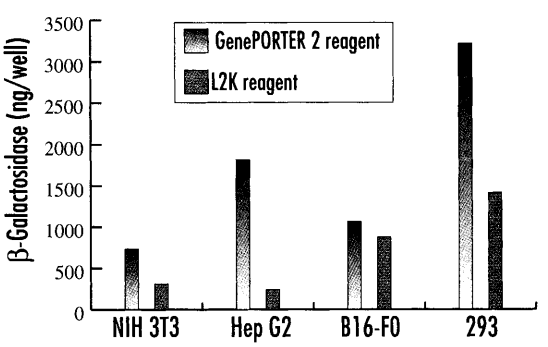

Figure 1. Comparison of GenePORTER 2 reagent with LIPOFECTAMINE 2000 reagent.

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† Felgner *et al.* (1987) Proc. Natl. Acad. Sci., USA, 84: 7413-7417

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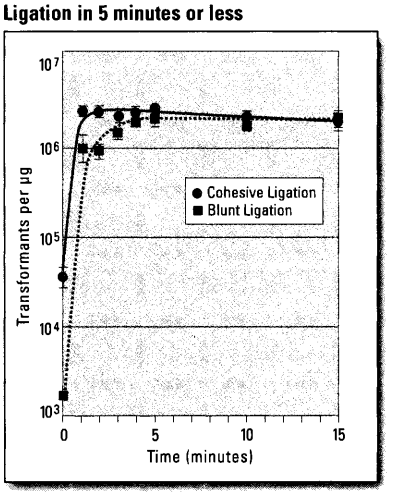

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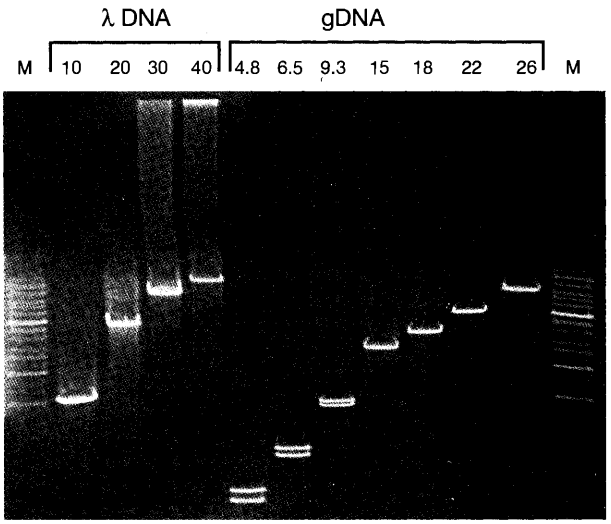

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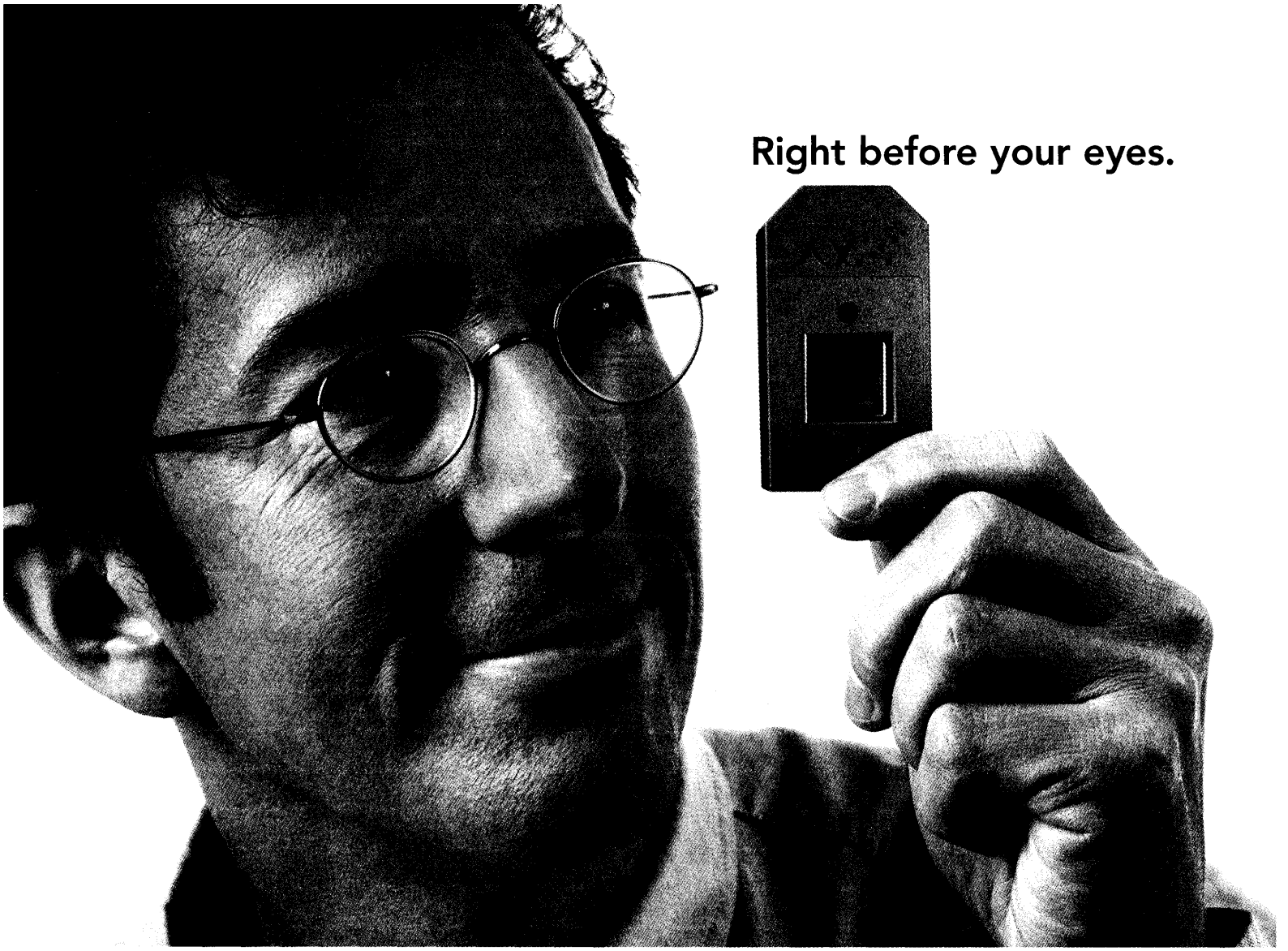

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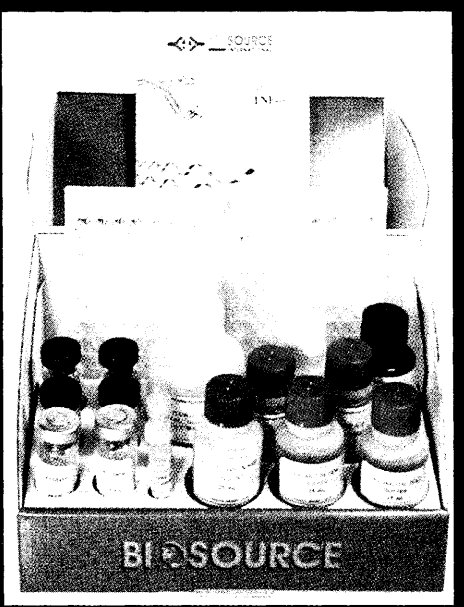

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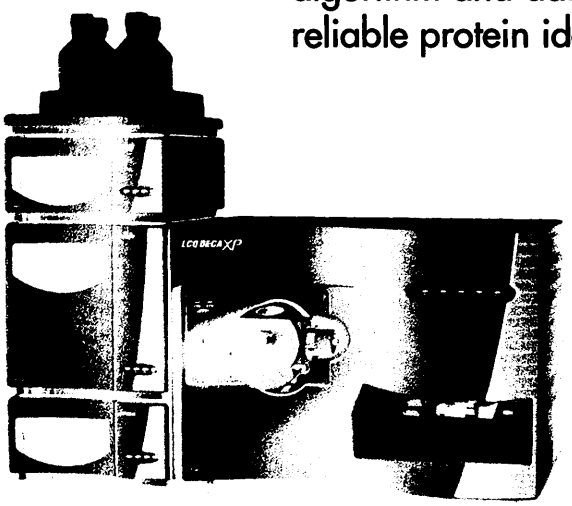

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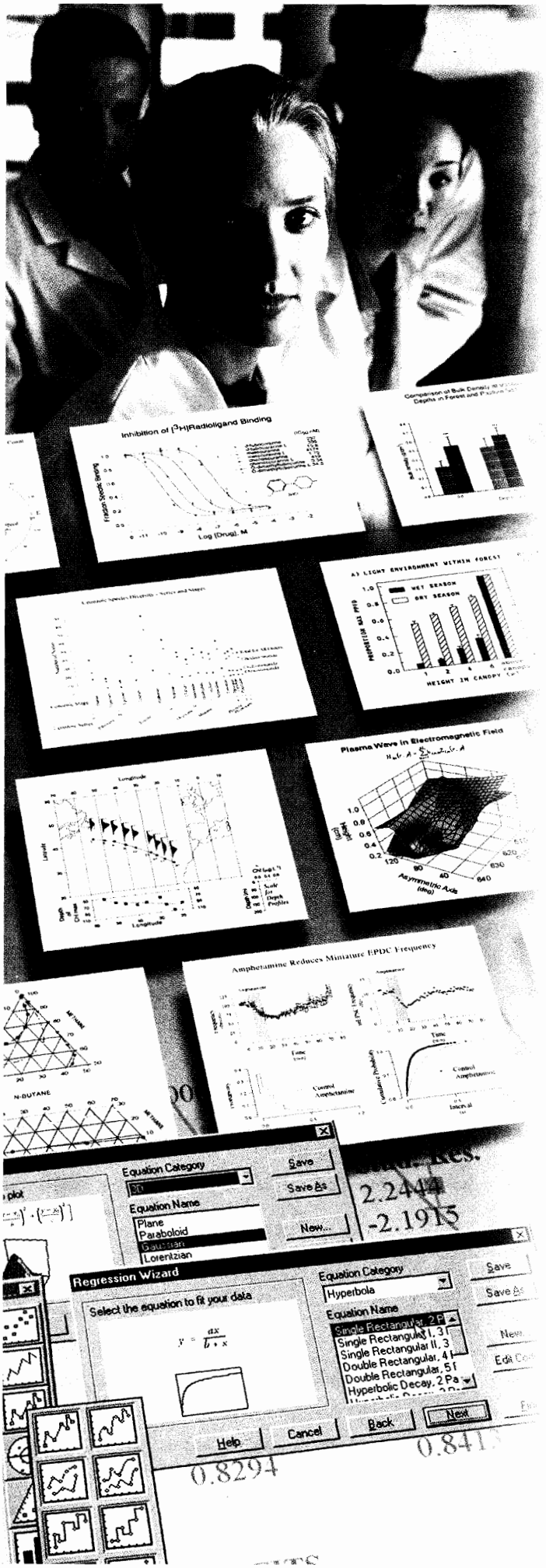

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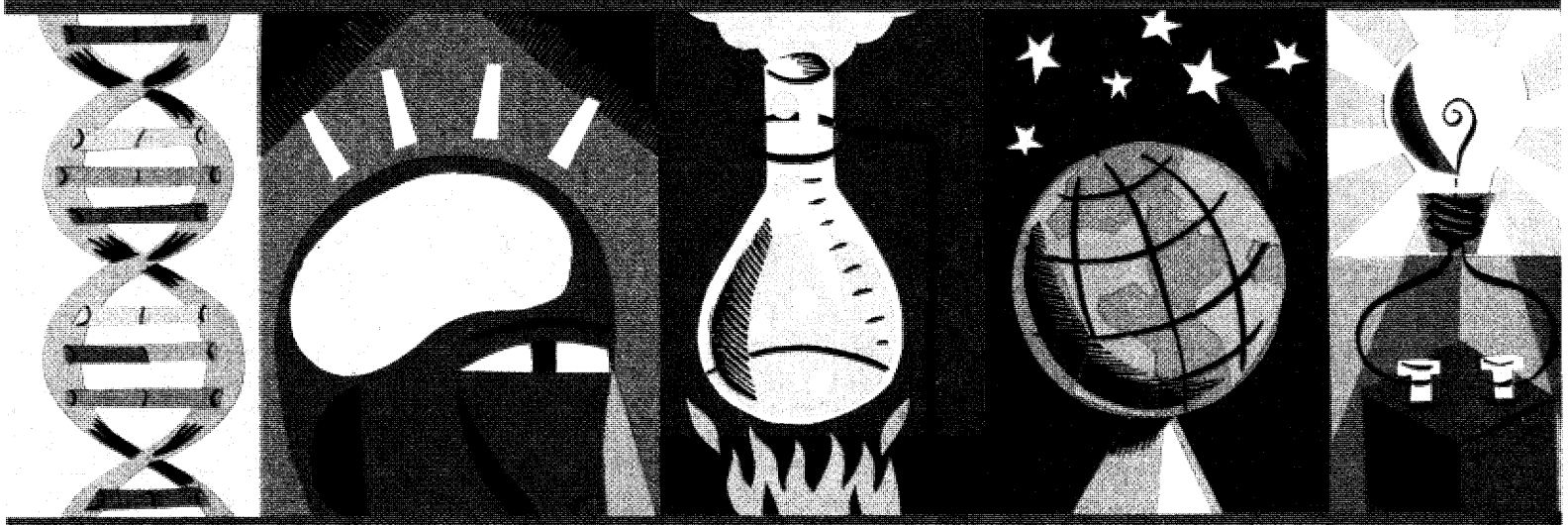

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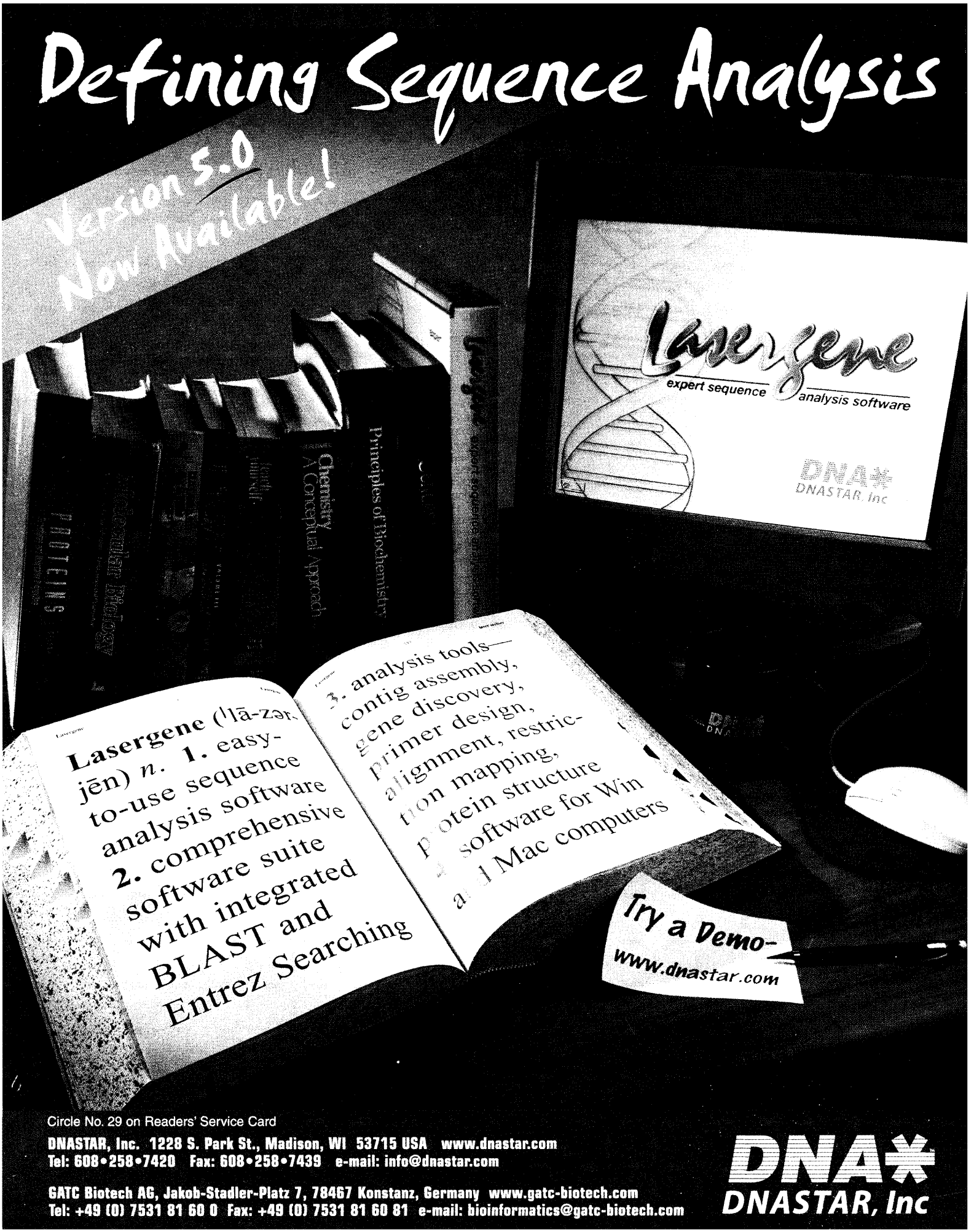

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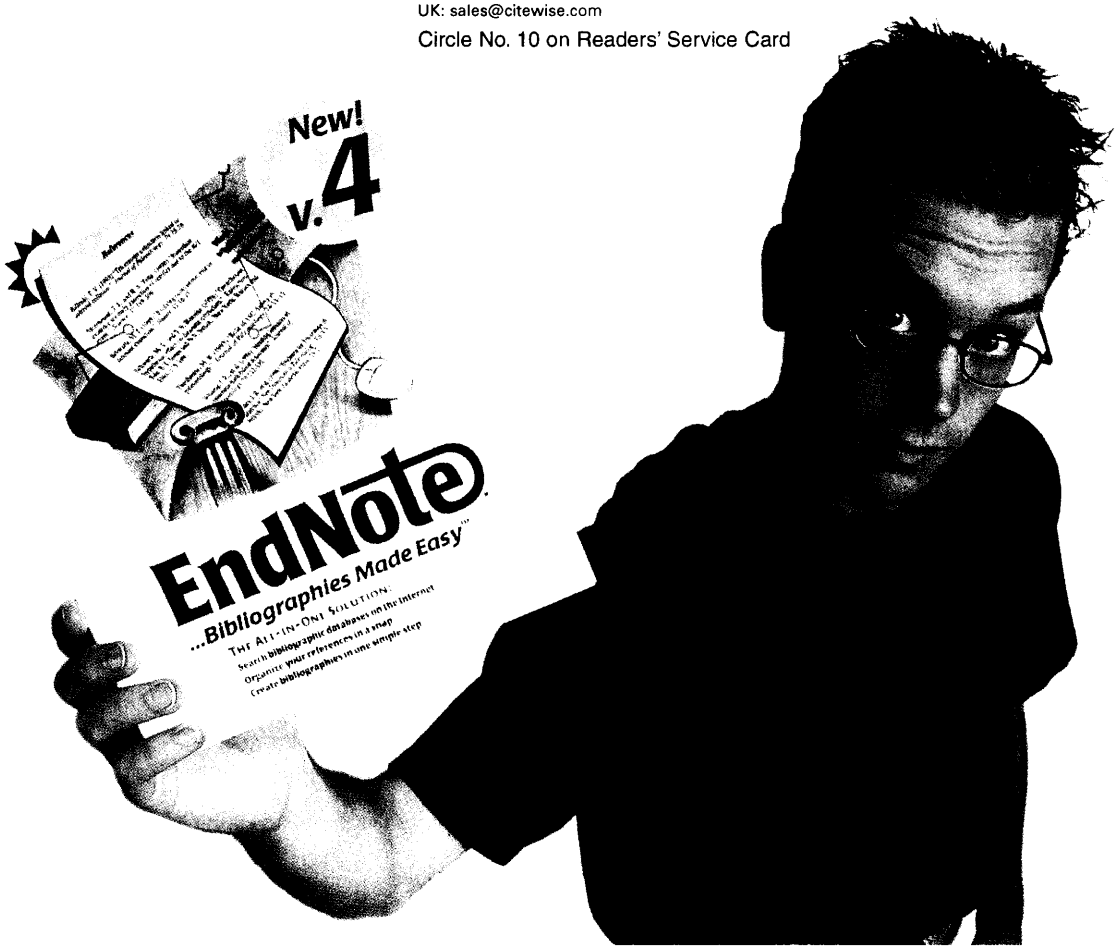

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