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Science

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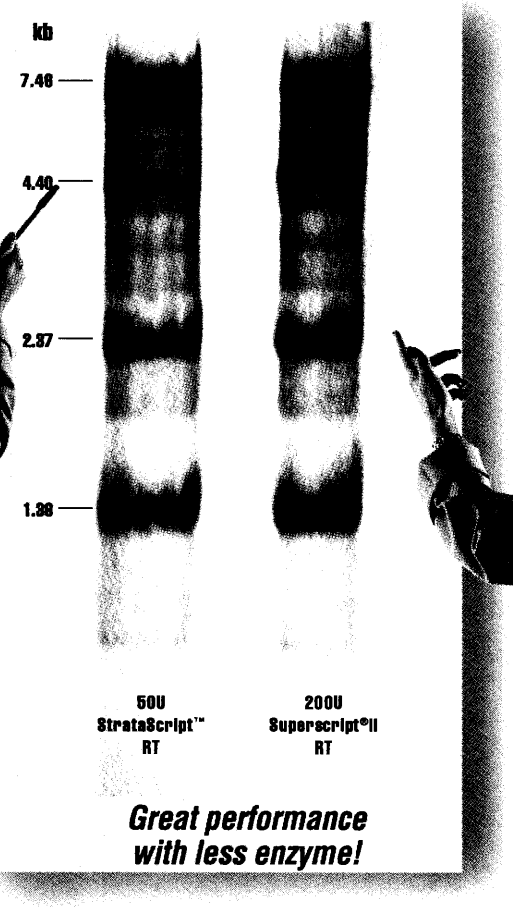

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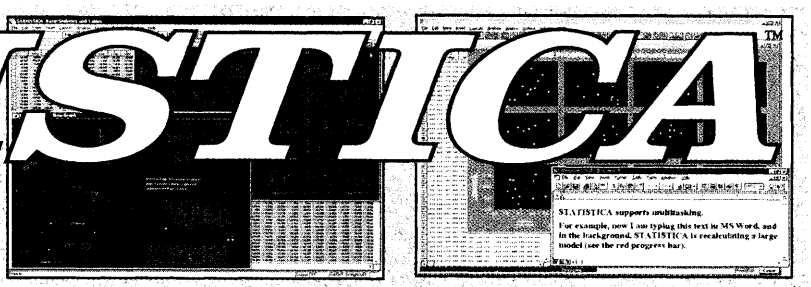

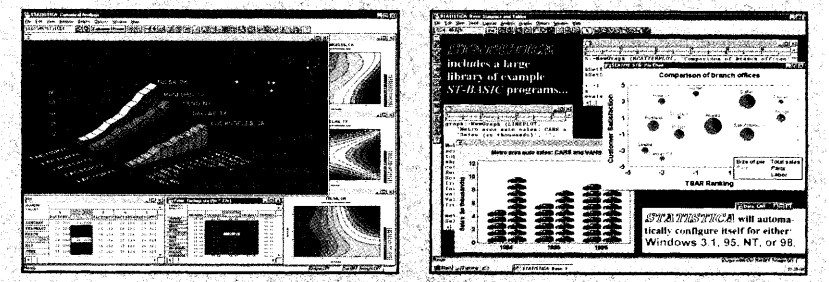

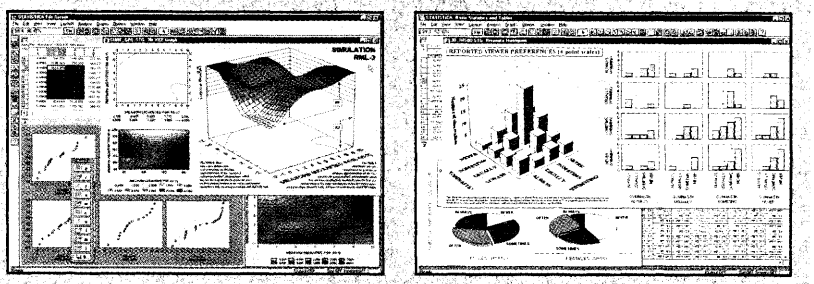

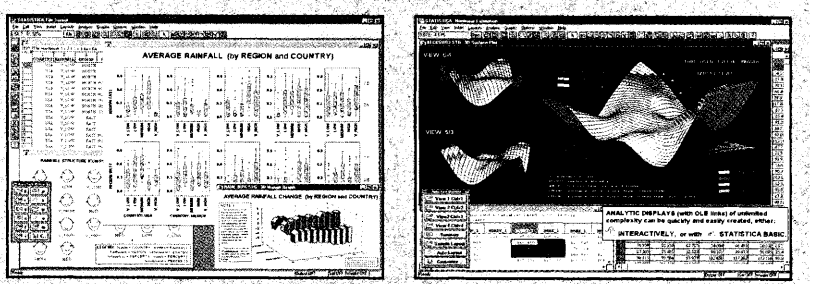

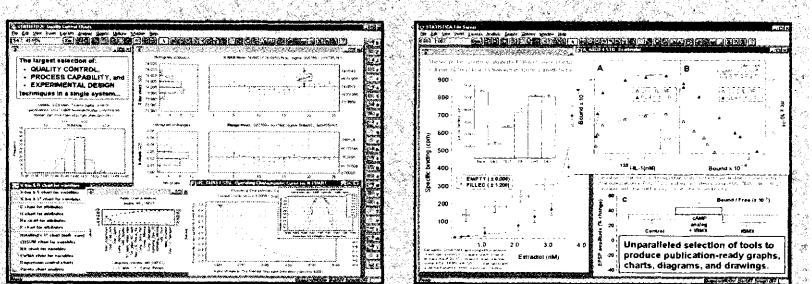

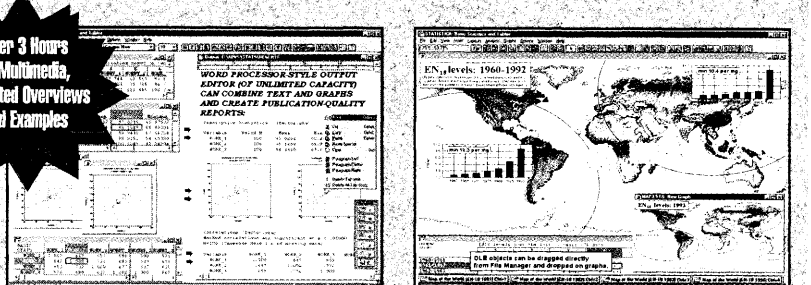

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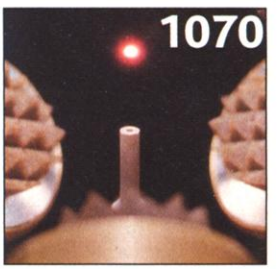

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Back to basics

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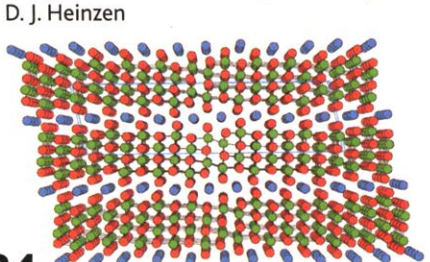

1024
Cool applications

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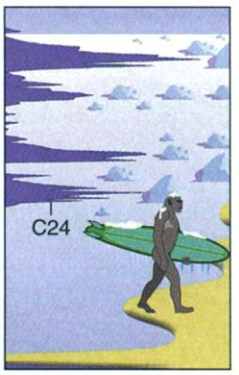


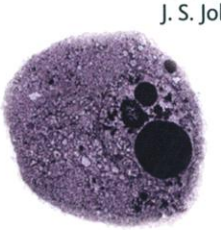
987
Climate, ~125,000 years ago

997

PATHWAYS OF DISCOVERY

Planetary Science: A Space Odyssey
David J. Stevenson

This month, David Stevenson recounts the evolution of planetary science. Not only have the field's practitioners exposed the grandeur of our local cosmic neighborhood, they've also become central to studying perhaps the most tantalizing question of all: How does life arise?



1056
How ethanol kills neurons

TECHNICAL COMMENTS

NADH Shuttle and Insulin Secretion
A. Schurr and R. S. Payne; M. J. MacDonald and L. A. Fahien. ***Response*** K. Eto, Y. Tsubamoto, T. Kadowaki

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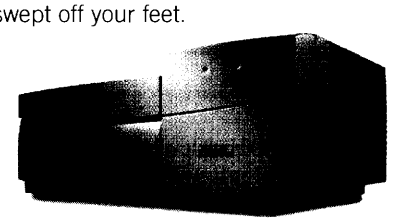

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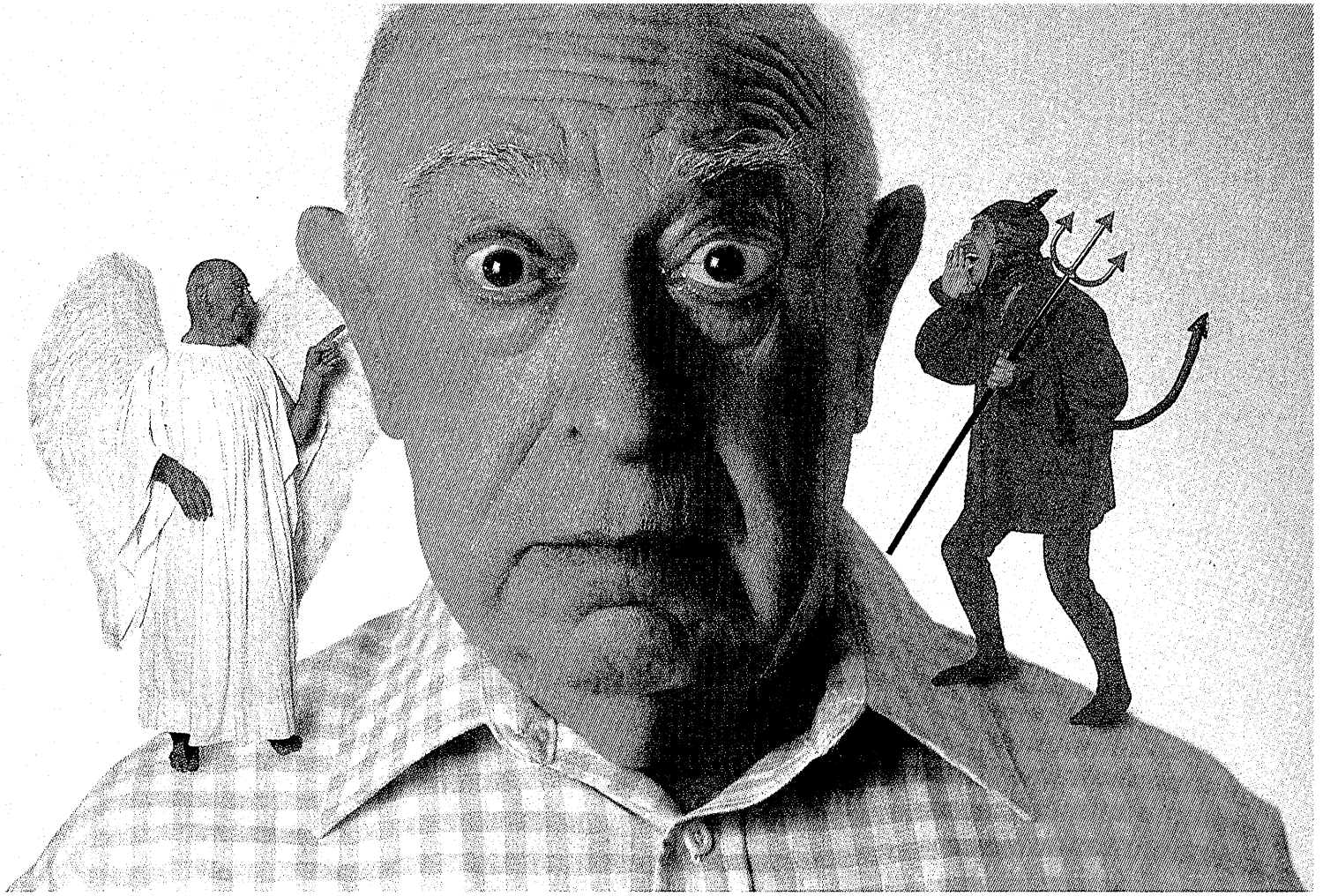

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MODELING MAGNETIC SEMICONDUCTORS

The technologically important III-V (GaAs) and II-VI (ZnTe) compound semiconductors, which are usually nonmagnetic can be made ferromagnetic by the addition of small amounts of manganese. In such materials, electronic switching might be controlled through spin interactions as well as charge. So far, the understanding of this ferromagnetism has been limited and rather phenomenological. Dietl *et al.* (p. 1019) now put the subject on a much stronger footing by proposing a theory that can describe the magnetic properties as a function of the materials' properties and the concentration of magnetic ions introduced into the system. Moreover, by extending the theory to other materials, they suggest a route for increasing the operation temperature of future magnetic devices.

ORGANIC TRANSISTORS THAT CONDUCT BOTH WAYS

Charge transport in organic semiconductors is predominantly through hole carriers (p type or p channel); conduction of electrons (n type or n channel) is usually poor. This limitation is a serious obstacle to their widespread application as a cheaper and fully complementary alternative to conventional electronics based on inorganic semiconductors. Schön *et al.* (p. 1022) now demonstrate ambipolar operation (conduction in both p-channel and n-channel modes), field-effect transistors (FETs) based on pentacene single crystals. Furthermore, the carrier mobilities at room temperature in these organic FETs are comparable to those of hydrogenated amorphous silicon, and the temperature dependence of the mobilities suggests bandlike transport.

IMAGING ANTIFERROMAGNETS

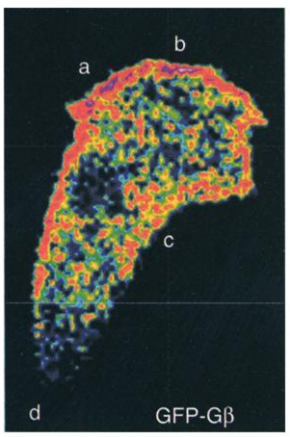
Thin layers of magnetic materials are finding more applications in storage media, and additional methods for characterizing their magnetic properties will be required. One particular problem has been determining the orientation of magnetic domains in antiferromagnetic thin films. Scholl *et al.* (p. 1014) introduce a new technique in which x-ray magnetic linear dichroism, in which the response of x-rays incident on a surface depends on the orientation of the magnetization in that layer, is combined with atom-specific photoemission electron microscopy. They can image antiferromagnetic domains in $LaFeO_3$ thin films with 20-nanometer resolution.

MAKING MOLECULES IN A BOSE-EINSTEIN CONDENSATE

Diatomic molecules have been formed in a Bose-Einstein condensate of rubidium atoms by using laser fields. Wynar *et al.* (p. 1016; see the Perspective by Williams and Julienne) took advantage of a stimulated Raman process—a close pair of atoms adsorb a photon at one frequency and emit a photon of slightly higher frequency, which drops them into an excited molecular state. This process selects for a particular rotational and vibrational state that corresponds to the frequency difference. The molecules are formed with almost no translational energy, which results in extremely narrow linewidths that facilitate the measurement of molecular binding energies with high precision.

MOBILE CELLULAR SIGNALING

Microbes seeking food and phagocytic immune cells stalking their prey rely on chemical signals, or chemoattractants, to guide their paths. Chemotactic cells can orient their anterior edge toward a stimulus gradient despite their uniform distribution of cell surface receptors. Five reports focus on the role that phosphatidylinositol 3' kinases (PI3Ks) play in chemotaxis (see the Perspective by Dekker and Segal). Hirsch *et al.* (p. 1049), Li *et al.* (p. 1046), and Sasaki *et al.* (p. 1040) describe the phenotype of mice that lack PI3Kγ, an isoform that is activated in response to G protein–coupled receptors (GPCRs). Defects in these animals show that PI3Kγ is required for a number of functions of neutrophils and T cells in vitro and in vivo. All three groups note that the inflammatory response is disrupted in several ways. Neutrophils from the mutant animals showed impaired migration and respiratory burst in response to stimulation through GPCRs. Sasaki *et al.* also found T cell activation through the T cell receptor was disrupted. Li *et al.* also generated mice lacking phospholipase C (PLC)–β2 and PLC-β3. They report that whereas PI3Kγ is required for normal production of immunoglobulin (Ig) containing the λ light chains, the PLC pathway can inhibit chemotaxis and production of Igλ$_L$. The results should enhance efforts in the development of pharmaceuticals to manage inflammation. An internal signaling gradient may accommodate such the directional chemotatic response. Jin *et al.* (p. 1034) show that in highly polarized amoeba cells, membrane-bound G protein subunits were present in a shallow anterior-posterior gradient. Servant *et al.* (p. 1037) also determined that such an internal signal gradient involves the activities of Rho family of guanosine triphosphatases and PI3K in neutrophil-like cells. Hence, signaling molecules appear to regulate an internal gradient that determines chemotactic sensitivity.



KEEPING COLD

Improved thermoelectric materials that work well below room temperature are of particular interest for electronics. Such materials, which provide cooling by converting thermal energy into electrical current, could refrigerate superconducting devices or help remove heat from transistors. Promising materials must have an unusual combination of high electrical conductivity, high thermoelectric power, and low thermal conductivity. Chung *et al.* (p. 1024; see the news story by Cho) report that $CsBi_4Te_6$, when appropriately doped, already rivals the low-temperature performance of the currently used $Bi_{2-x}Sb_xTe_{3-y}Se_y$ alloys, and several potential doping and alloying systems for $CsBi_4Te_6$ have yet to be explored.

CORE CONSISTENCY

The melting temperature of iron at the high pressures (about 140 to 330 gigapascals) of the liquid outer core has been difficult to nail down. Experiments cannot directly measure the melting temperature, and extrapolations have led to divergent results—shock wave estimates suggest higher temperatures than do static high-pressure studies. Laio *et al.* (p. 1027) have combined two theoretical approaches, first-principles calculations and molec-

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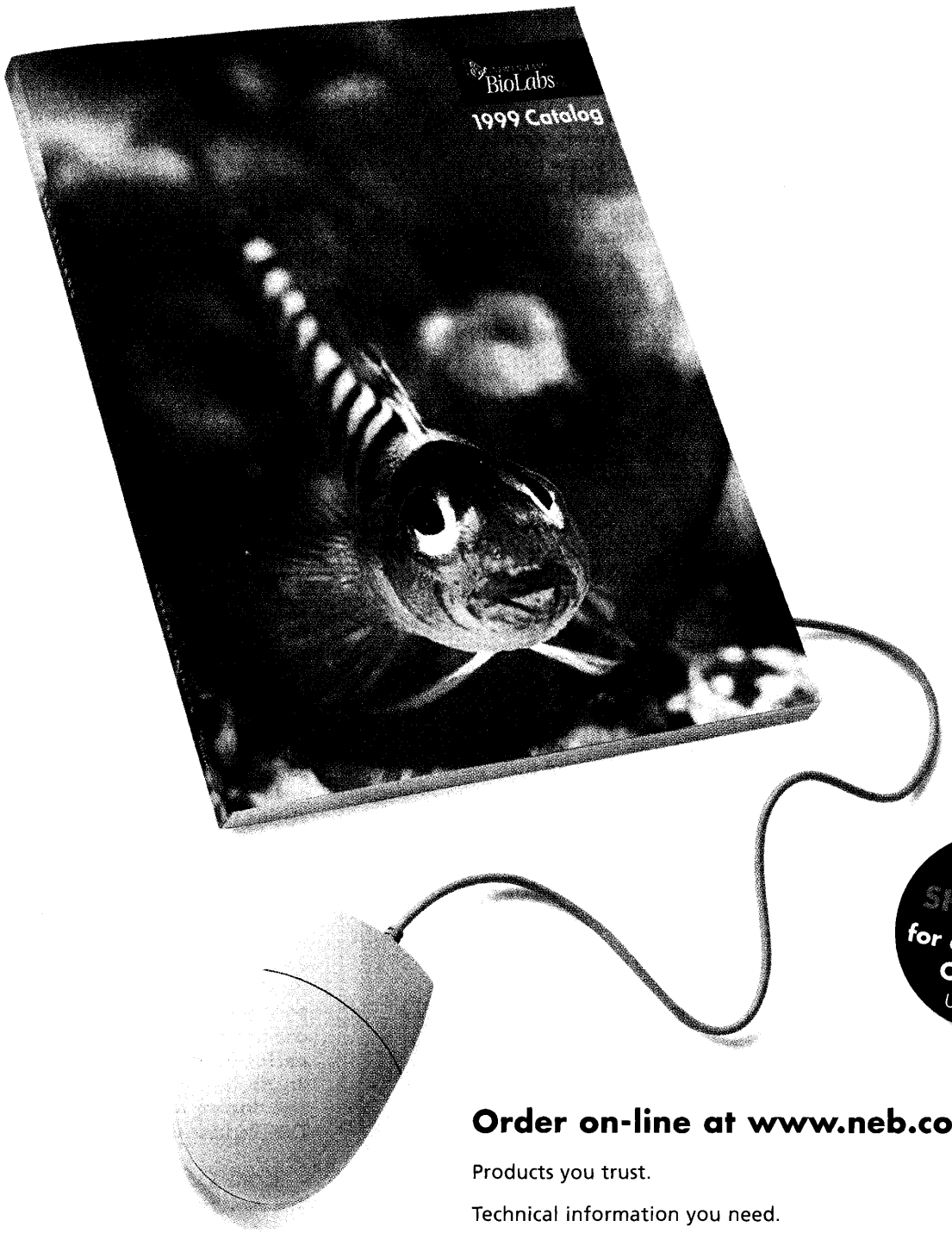

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 929

ular dynamic simulations, to determine the temperature and density of liquid iron. They calculated a melting point of 5400 ± 400 K for iron at the inner core boundary (330 gigapascals) and a density about 6% greater than the density of liquid iron at the outer core boundary (140 gigapascals). These results not only help to reconcile previous experimental results but are also consistent with seismic data.

AVOIDING NATURAL KILLER CELLS

Human cytomegalovirus (HCMV) is known to encode a series of proteins that enable it to avoid cytotoxic T cells. However, in doing so, the virus should induce natural killer (NK) cells. Tomasec *et al.* (p. 1031) found that the amino-terminal region of glycoprotein UL40 of HCMV contains a peptide identical to a cellular molecule that binds to human lymphocyte antigen–E (HLA-E). Binding results in increased synthesis of HLA-E on the surface of infected cells that acts to inhibit NK cells.

EARLY EFFECTS OF ALCOHOL EXPOSURE

Exposure of the human fetus to alcohol can result in fetal alcohol syndrome; brain mass is reduced, and subsequent neurobehavorial effects that may occur range from hyperactivity to depression and psychosis. Ikonomidou *et al.* (p. 1056; see the news story by Barinaga) studied the effects of alcohol administration on brain development in neonatal rats, which is a corresponding stage for widespread synaptogenesis to take place in rodents. They found widespread apoptosis in the forebrain that was caused by blockade of NMDA (*N*-methyl-D-aspartate) receptors and excessive activation of $GABA_A$ receptors. Transient exposure of ethanol led to the deletion of millions of neurons and can explain the reductions in brain mass.

WHAT'S NOT THROWN AWAY—ACCUMULATES

The lack of correlation between genome size and organism complexity or gene number (the *C*-value paradox) remains one of the major enigmas of molecular evolution. One recent hypothesis to explain this enigma is that differences in genome size may result from persistent differences between organisms in the rate of loss of nonessential DNA. Petrov *et al.* (p. 1060; see the Perspective by Capy) provide experimental support for this hypothesis by comparing DNA loss in two insect genera with very different genome sizes. Hawaiian crickets of the genus *Laupala* have a genome size an order of magnitude larger than that of the fruit fly *Drosophila* and eliminate nonessential DNA at a rate almost 1/40th as fast.

AN *C. ELEGANS* ANALYSIS

The sequencing of a genome is only the beginning step toward understanding the biology underlying a living organism. Hutter *et al.* (p. 989) have analyzed extracellular matrix and cellular adhesion proteins by examining the recently completed genome of *Caenorhabditis elegans*. Their studies suggest ways in which new genes and proteins arose during evolution.

TECHNICAL COMMENT SUMMARIES

NADH Shuttle and Insulin Secretion

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/287/5455/931a

Eto *et al.* (Reports, 12 Feb. 1999, p. 981) tested the role of shuttles that transport nicotinamide adenine dinucleotide (NADH) from the cytoplasm into mitochondria in coupling glucose-induced metabolism increases to insulin release from pancreatic β cells of mice. They concluded that inhibition of both the glycerol phosphate shuttle and the malate-aspartate shuttle blocks glucose-induced insulin secretion. Schurr and Payne comment that lactate derived from glycolysis in the cytoplasm could influence mitochondria if the lactate were converted to pyruvate, with concomitant generation of NADH, through the action of lactate dehydrogenase. Eto *et al.*, however, respond that the results of experiments proposed by Schurr and Payne to test this idea do not appear to support a critical role for lactate.

In a separate comment, MacDonald and Fahien point out that they and others have reported evidence that aminooxyacetate (AOA), an inhibitor of the malate-aspartate shuttle, has a more pronounced effect on rat β cells than that reported by Eto *et al.* from murine cells. They also find Eto *et al.*'s conclusion that inhibition of the shuttles does not prevent glycolysis or transport of pyruvate to mitochondria to be "biochemically impossible." Eto *et al.* reply that their results may require revision of the "prevailing hypothesis."

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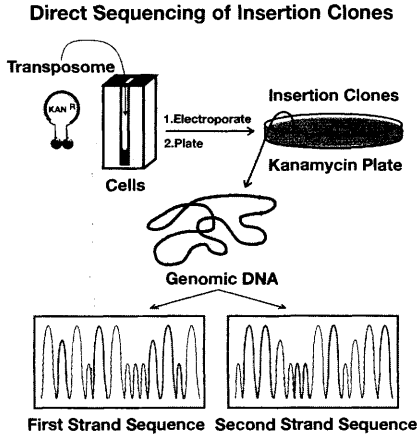

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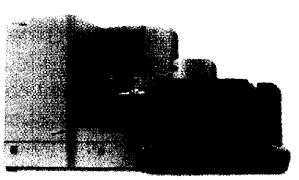

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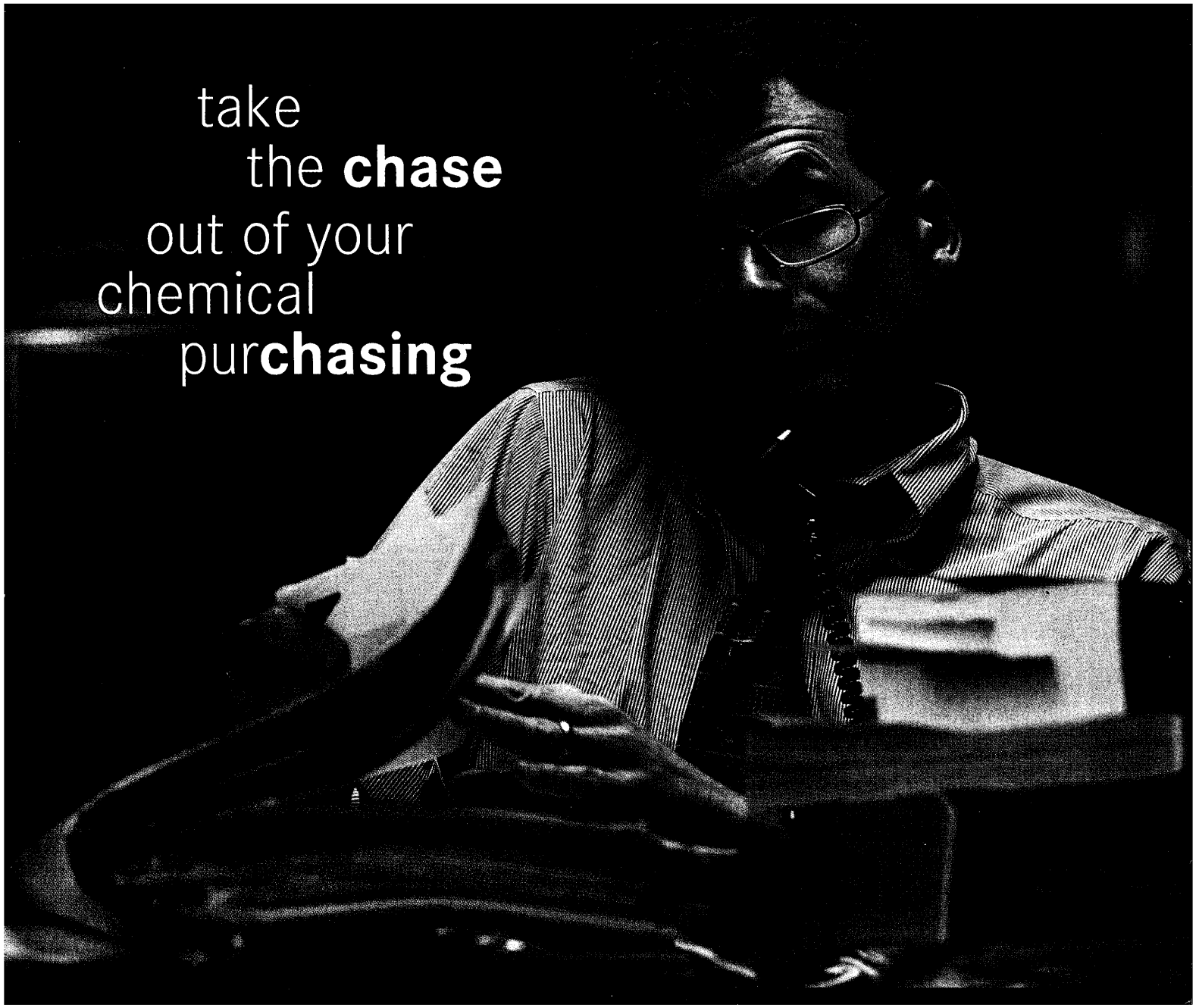

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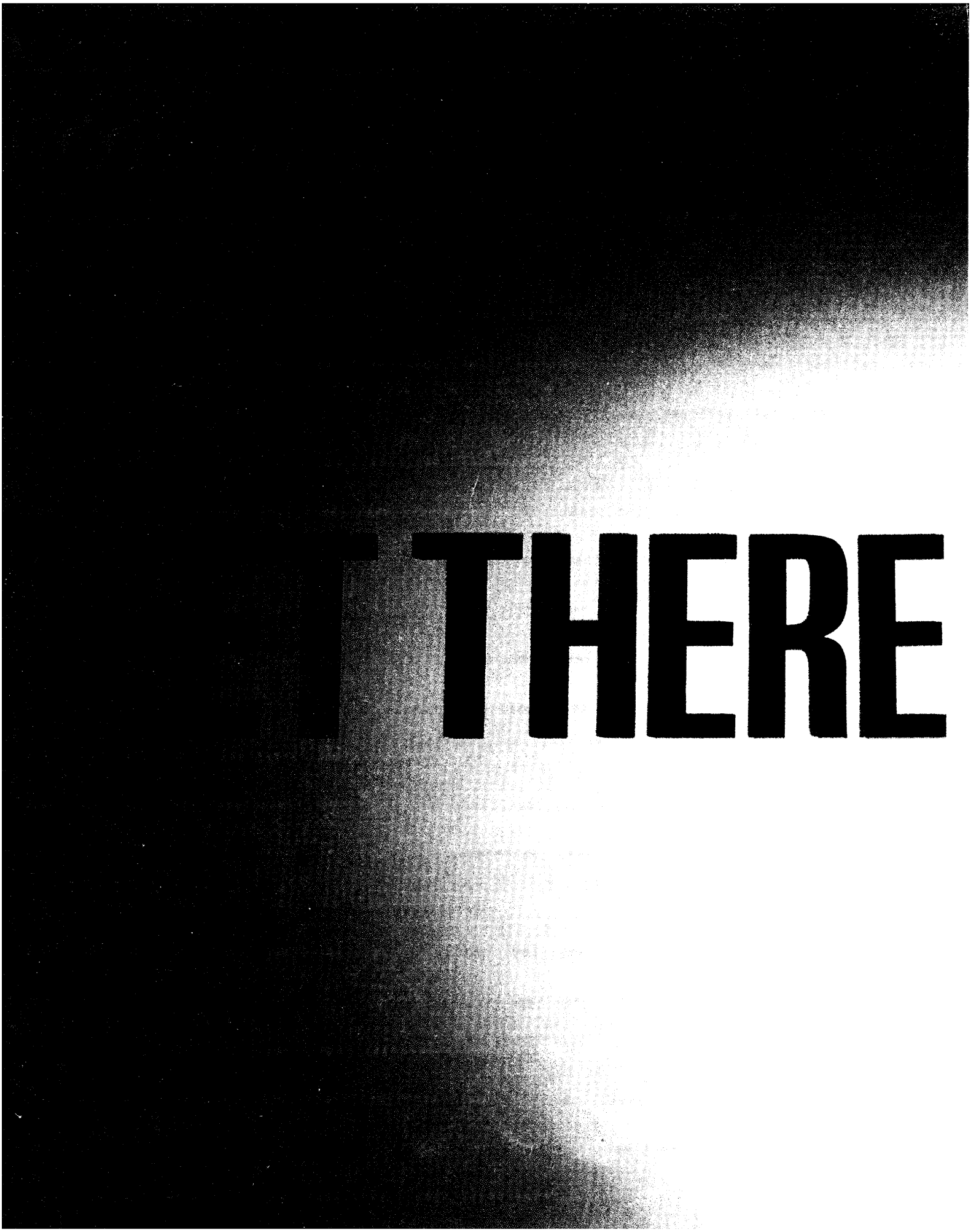
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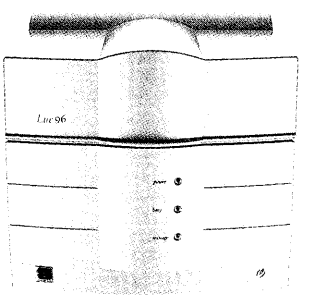

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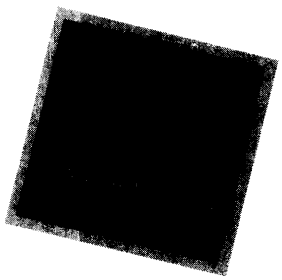

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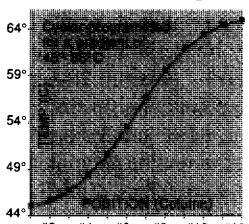
Gradient Calculator Especially Useful

Easy to Transfer "Golden" Parameters to Actual Protocols

Most researchers would agree that gradient cyclers are great in concept—but their utility is significantly compromised if an optimized protocol does not transfer well to normal, non-gradient operation. This "Achilles heel" of gradient cyclers can often be traced to imprecise knowledge of either incubation time or incubation temperature during the gradient step. Whatever technology is used, there will always be lags—often not well known—before samples reach the new temperature.

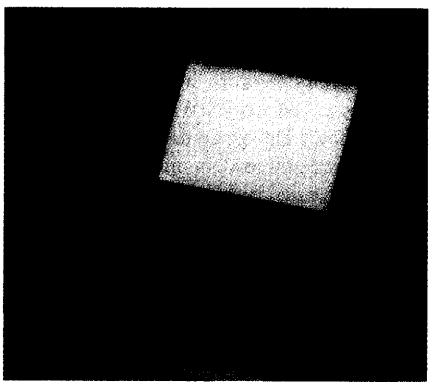
MJ has long had an excellent reputation for delivering time/temperature control with precision, so extra efforts were expended to address these issues. Thus time control includes "dynamic ramping" (see below), while temperature control incorporates a new software feature called the "gradient calculator".



Reported temps (dots) vs. independently acquired thermal data in 4 cyclers (lines).

This calculator is so precise and accurate that it reports the temperatures in individual columns to within ±0.4°C of the NIST standard, making transfer of values to normal operation *very* reproducible. Just look above how reported temperatures from the gradient calculator superpose *almost perfectly* with independent NIST-traceable data from 4 different cyclers.

NEW GRADIENT HELPS OPTIMIZE ANNEALING AND DENATURATION


DNA Engine™, with the thermal gradient shown in artificial colors from data collected by an IR camera.

Optimized Denaturations Surprisingly Important

It is well known in the biological community that DNA amplification reactions should have optimized annealing temperatures for best results. Denaturation is quite important as well—but only the savvy optimize this step.

Too bad. MJ's scientific staff finds that denaturation often leads to problems. Use of a lower denaturation temperature, such as 90°-92°C, is generally recommended whenever possible. Not only does it preserve enzymatic activity for later cycles, it also reduces breakdown of fluorescent dyes in cycle sequencing. On the other hand, higher temperatures, such as 95°-96°C, may be required for GC-rich templates from organisms such as Mycobacteria.

ALL EXISTING DNA ENGINES & TETRADS CAN BE UPGRADED

Standard Feature on New Thermal Cyclers

WALTHAM, Mass. — MJ RESEARCH is pleased to announce the introduction of an advanced gradient feature that is now standard on all DNA Engine & Tetrad thermal cyclers. This powerful new function allows precision thermal gradients as high as 24°C to be developed across 96-well blocks, at any temperature between 30° and 105°C. This greatly assists in developing robust protocols, for the optimal annealing and denaturation temperatures give strong results without lots of "ampli-schmutz" or other unwanted artifacts appearing in the gel.

Many reactions benefit from careful temperature optimization, especially sensitive ones, such as dye-terminator cycle sequencing. GC-content, length of molecule, concentration of magnesium—all these lead to differences in optimal "heat" for annealing and denaturation. This is why empirical experiments can almost always enhance even the *best* calculations for T_m.

But who wants to do a dozen runs of slightly variant protocols? Gradient cyclers make this chore much easier by allowing a dozen different incubation temperatures in a single run. The user simply selects a range of temperature, and the cycler does the rest. The optimal temperatures become obvious in the gel—with thick "meaty" bands unbracketed by artifact.

How to Get Upgrade

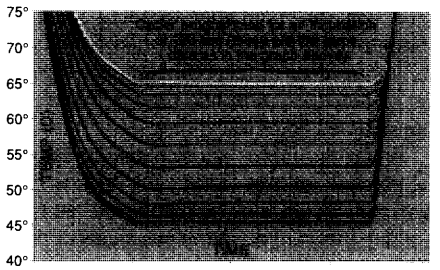
In a nutshell, visit the MJ website. For DNA Engines manufactured after 1/1/99, the gradient feature is a simple software upgrade that is provided free and can be installed by users. For older DNA Engines or Tetrads, a new logic board is also required, and this upgrade is available inexpensively from MJ or its distributors.

Precision Control of Time as well as Temp

"Dynamic Ramping" Incubates Each Sample for Same Period

In some gradient cyclers, the gradients develop gradually. When cooling to an annealing gradient, for example, the highest temperature stabilizes long before the lowest one does. This means that the time spent at incubation is different at each temperature—thus two critical parameters are being varied at the same time.

Not so with MJ cyclers. Careful engineering has led to "dynamic ramping" where each column of wells ramps at a different rate, for ramp rates are much less critical. The results are consistent incubation times column-to-column, with only temperature varying among samples.



Data from four cyclers are superposed in this graph, with each trace representing the average temperature measured in a column of wells. Note the consistency of incubation periods, the cycler-to-cycler reproducibility (each trace is made up of *four* separate lines), and the even spread of incubation temperatures between the programmed targets of 45° and 65°C.

PCR is covered by patents owned by Hoffmann-La Roche, Inc. & F. Hoffmann-La Roche Ltd. Users should obtain license to perform the reaction.

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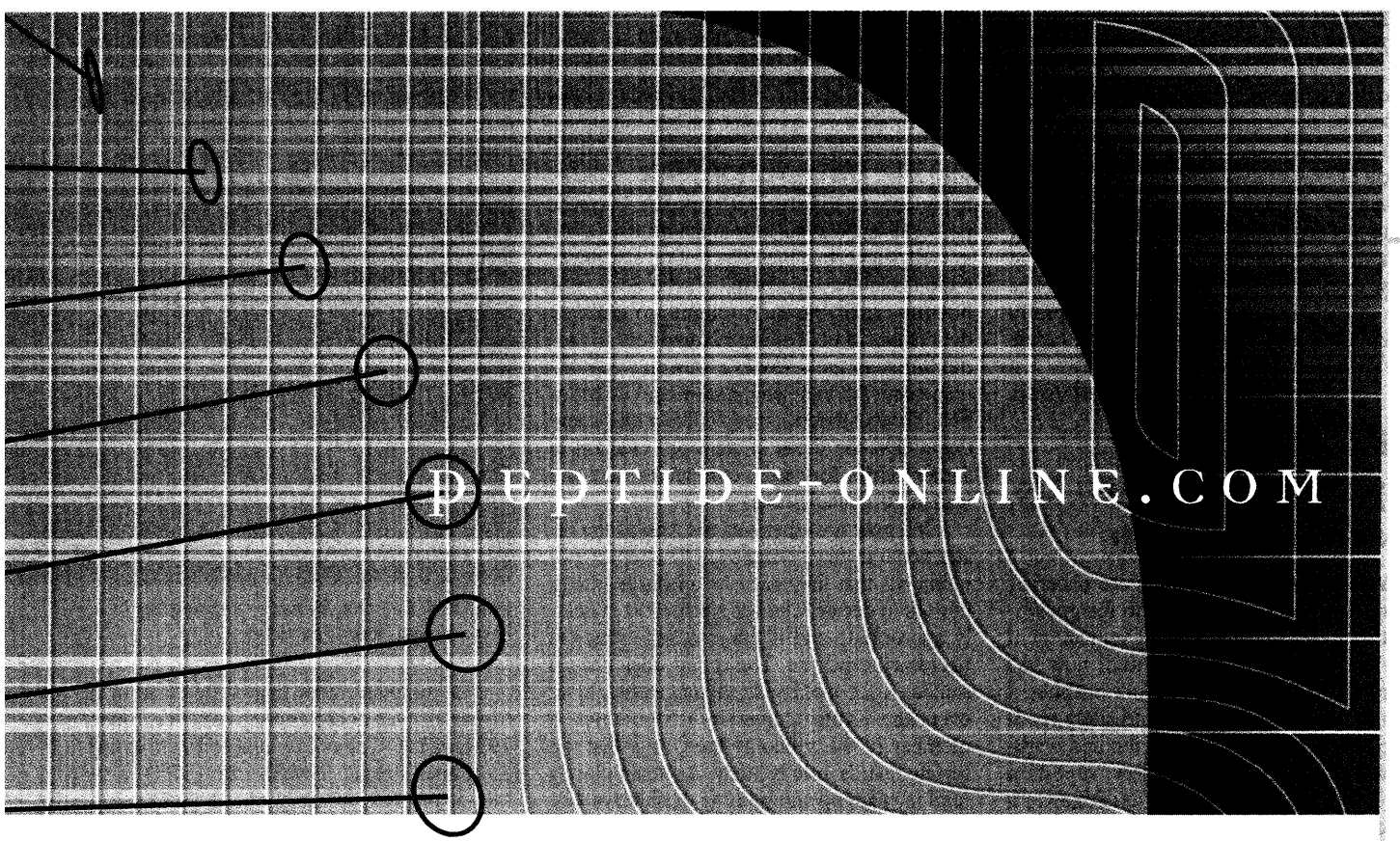

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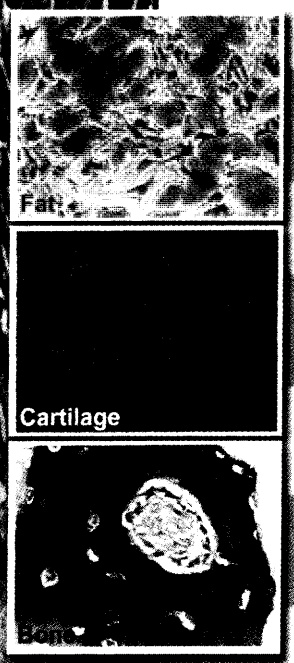

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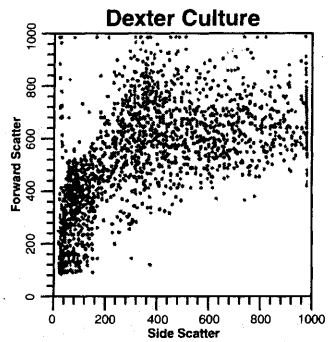

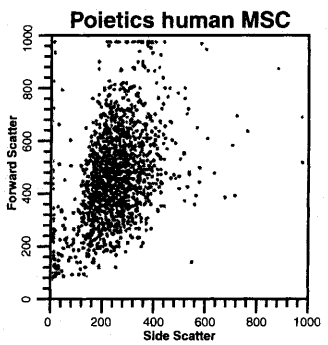

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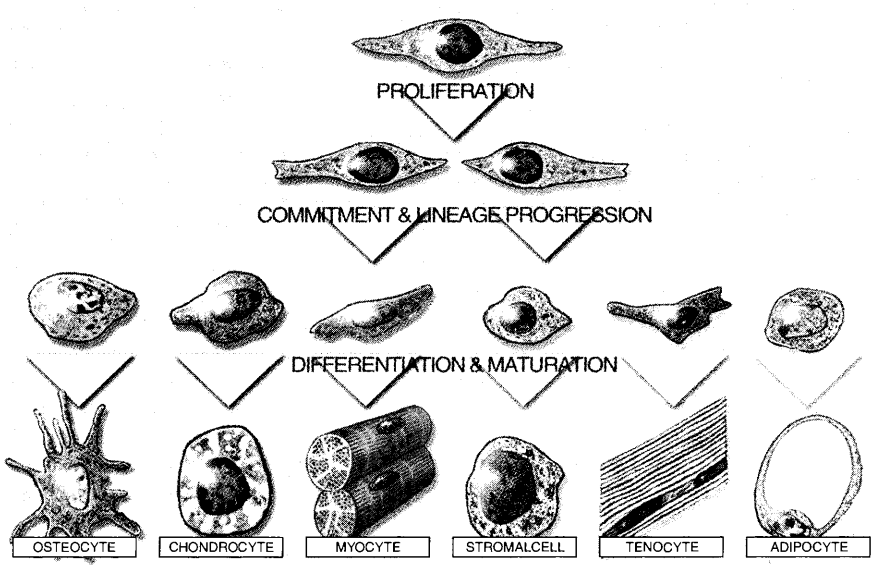

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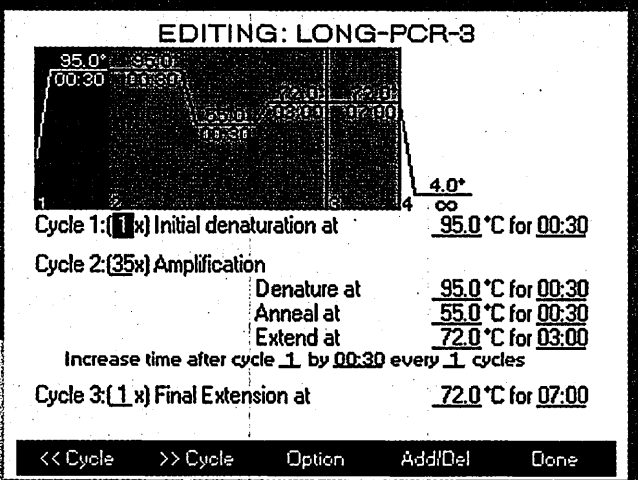

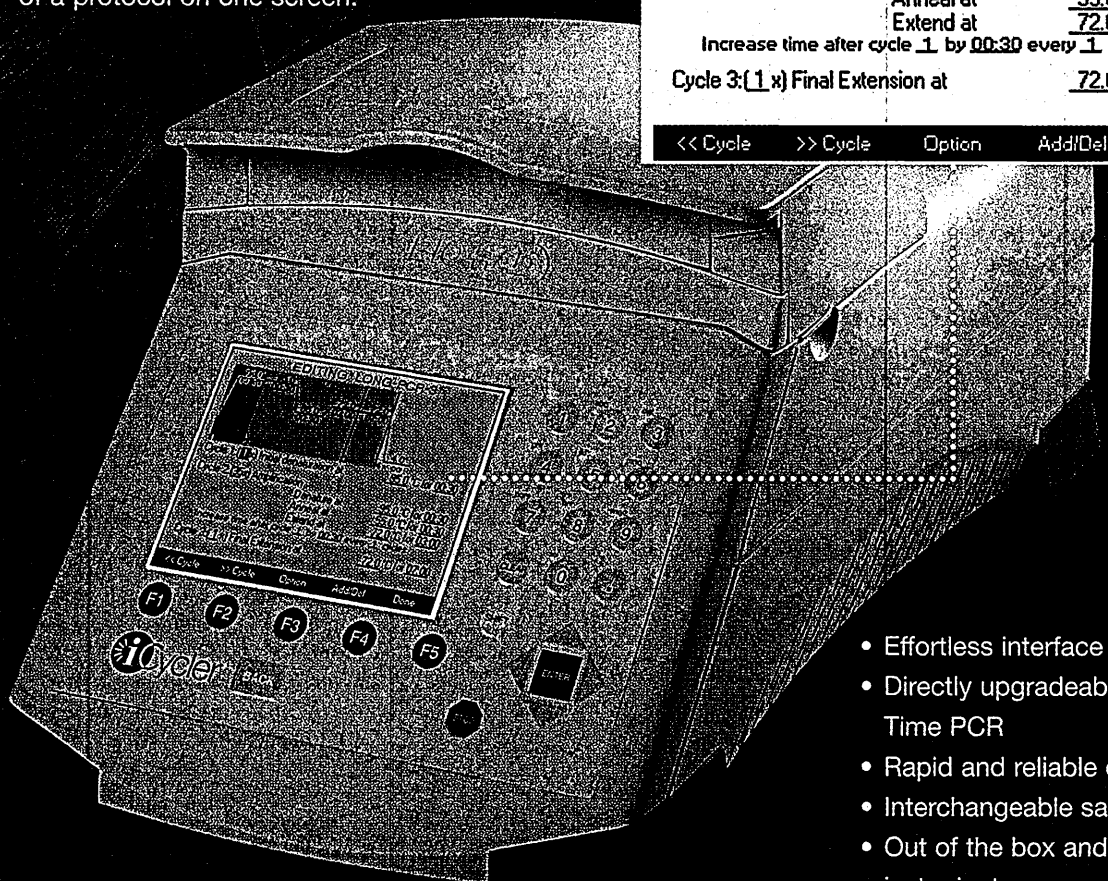

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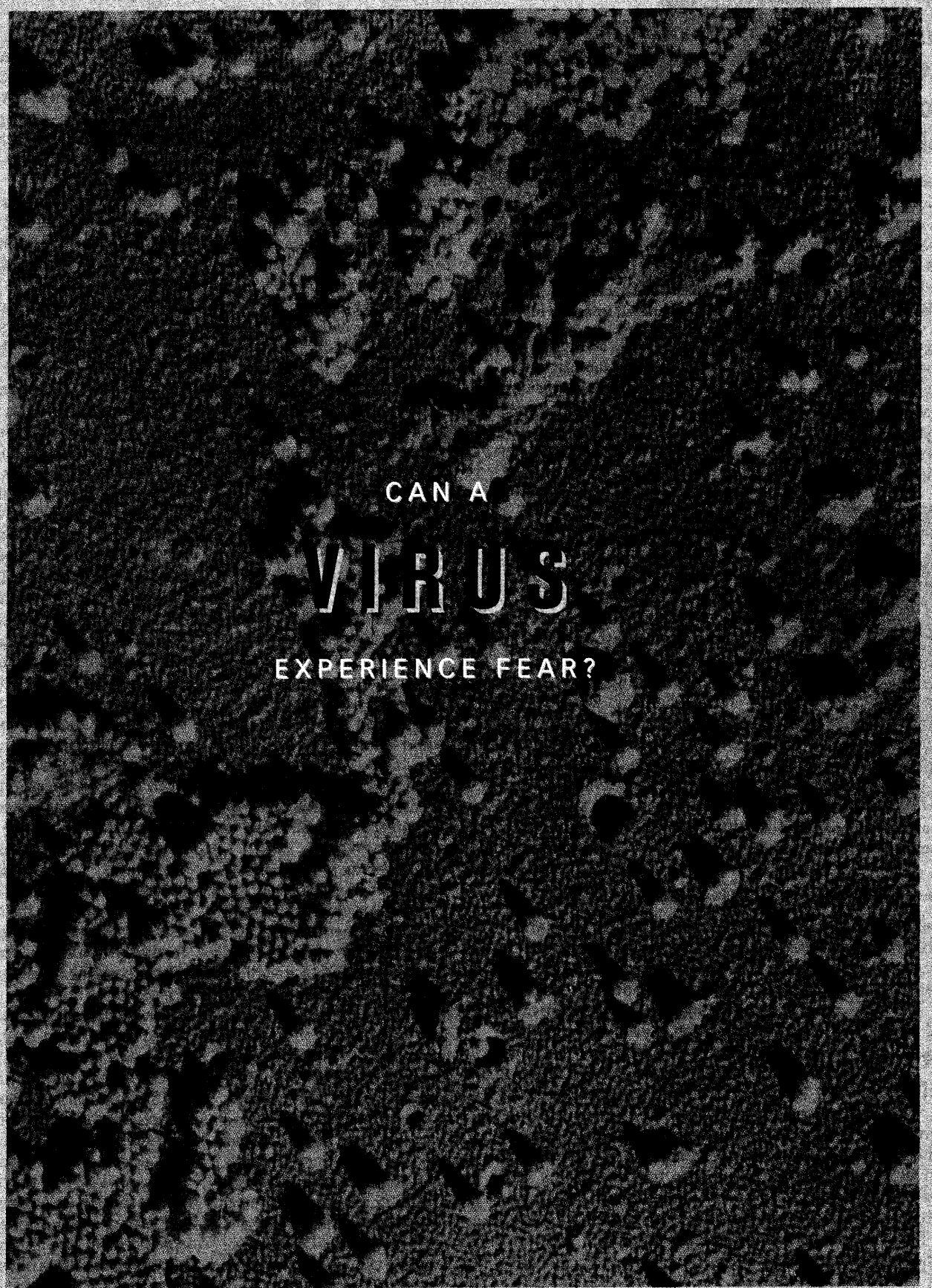
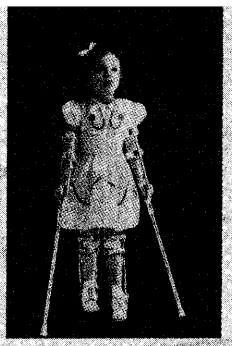


photo: Poliomyelitis Virus



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There has been no lack of heroes in this effort. Campaigns by the World Health Organization and UNICEF have immunized three-quarters of the world's children every year. Rotary International, with the support of the U.N. Foundation, has funded a vast amount of vaccine. Volunteers on foot, horseback, even camel have vaccinated as many as 100 million children in a single day. And the courage of mothers who have brought children to be immunized for the first time has helped keep polio at bay.

The eradication campaign is now in its final stage. But, as in every war, the last battle is the hardest. In 1998 there were 5,000 cases of polio detected worldwide, a ninety percent decrease over the past ten years. Reducing that number to zero will cost $500 million.

The benefits of eradicating polio are profound. Billions in immunization costs will be saved. Cease-fires to deliver immunizations could open the door to lasting peace. The culture of prevention will be in place. And the health infrastructure necessary to deliver vaccines will be ready for other epidemics.

To hesitate is to invite defeat. Polio will do anything to survive. It will not miss a single opportunity to escape. Now is the time to rid the earth of this scourge forever.

THE POWER AND PROMISE OF VACCINES

No one is safe from an infectious disease unless everyone is safe. Vaccines offer the greatest potential for improved global health. Existing vaccines have become more affordable, and delivery methods increasingly successful. At the same time, efforts are continuing to make vaccines even safer, simpler and available for a wider spectrum of diseases. Aggressive programs to develop vaccines for malaria, tuberculosis and AIDS are underway right now. Success will mean healthier lives for billions of people, and greater opportunities for entire countries.

THE BILL & MELINDA GATES FOUNDATION IS PROUD TO SUPPORT GLOBAL POLIO ERADICATION, LED BY THE WORLD HEALTH ORGANIZATION, UNICEF, ROTARY INTERNATIONAL AND THE U.N. FOUNDATION.

For a current report on polio eradication, please visit www.polioupdate.org.

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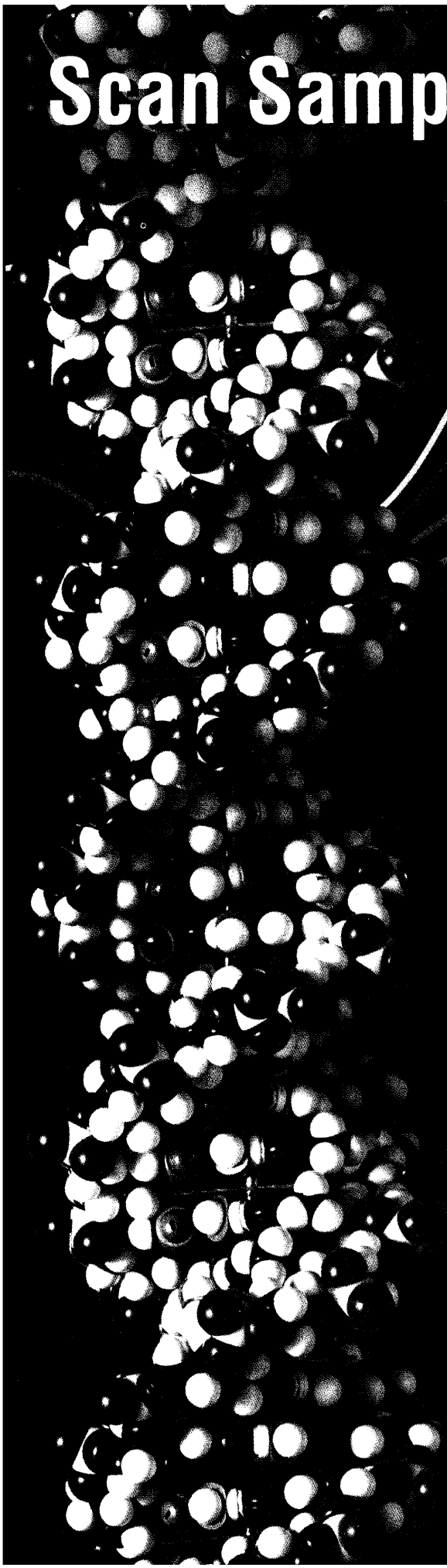
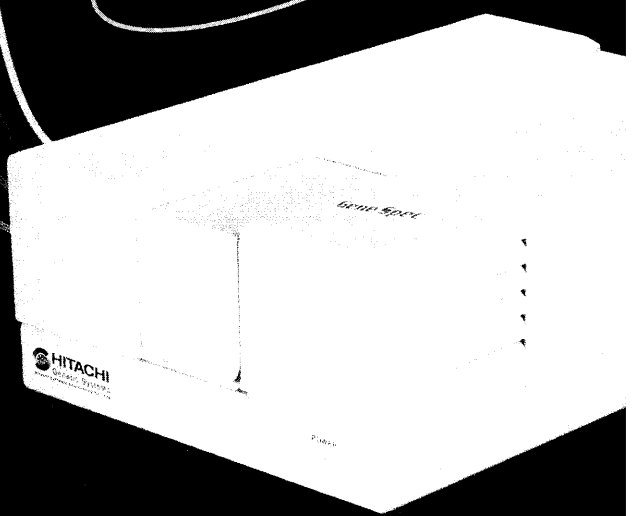


Gene Spec I



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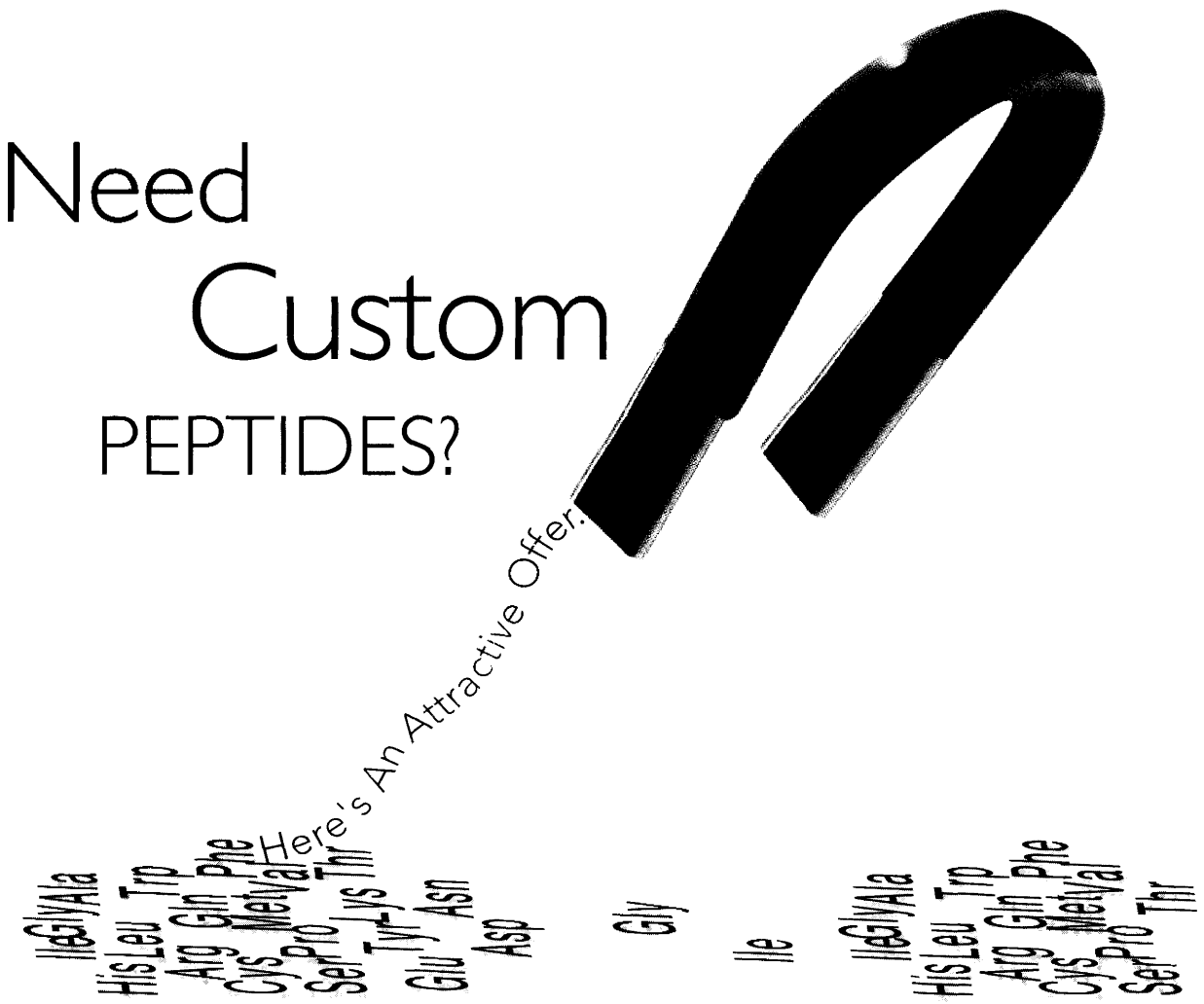

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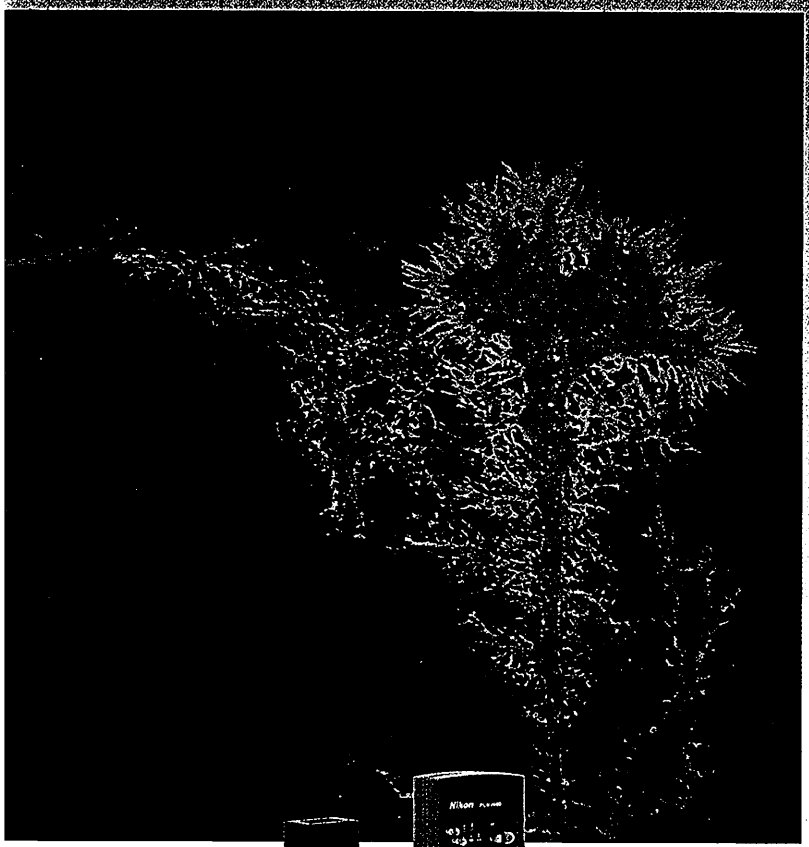

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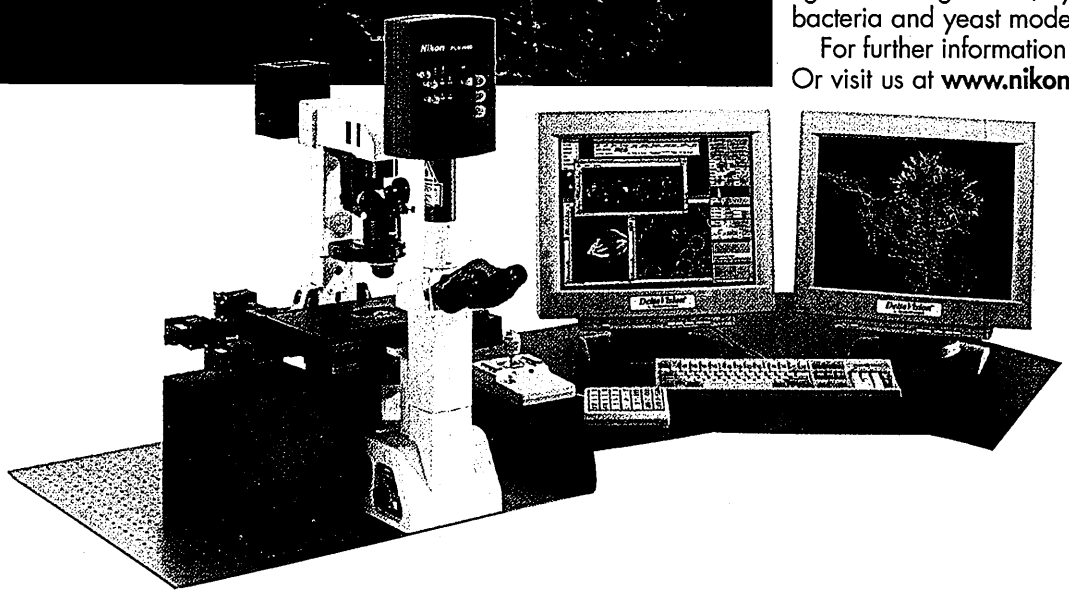

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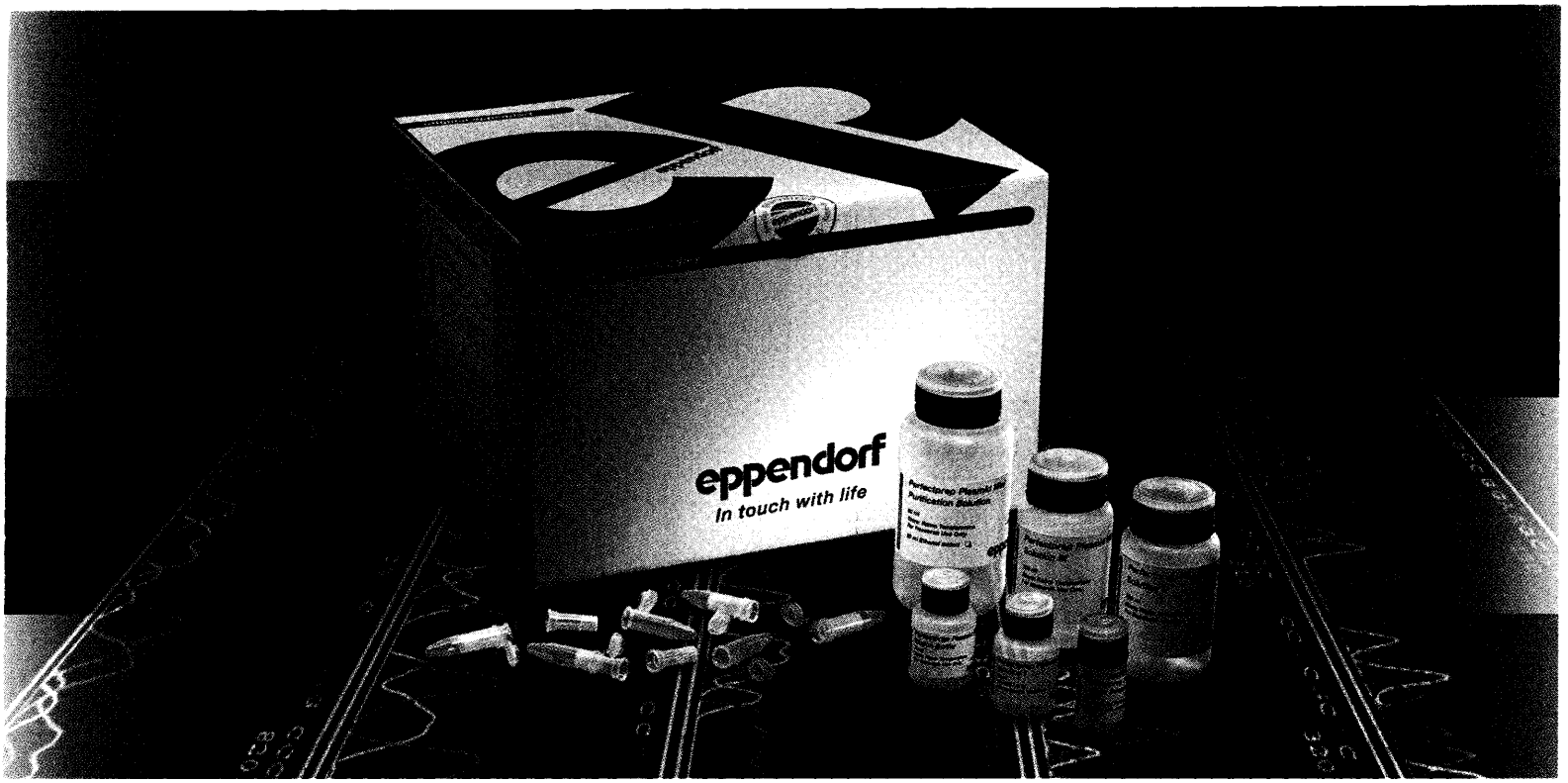

Background picture: ABI Model 377 automated fluorescent DNA cycle sequencing of pNoTA/T7™ plasmid DNA prepared by the Perfectprep method.

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Midi	10–75	120	50–600	10–100
Maxi	100–300	150	250–2,500	50–400
XL	400–800	150	2,000–6,000	200–1,000
96 Minispin	1–1.3	120	2–10	0.05–0.06

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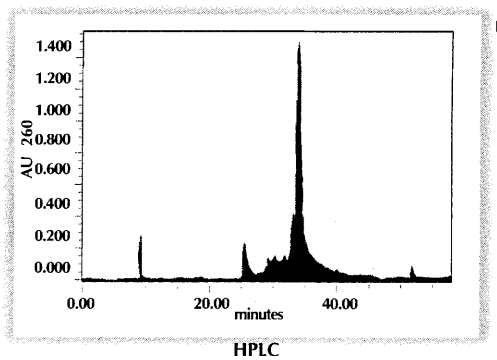

Figure 1

HPLC

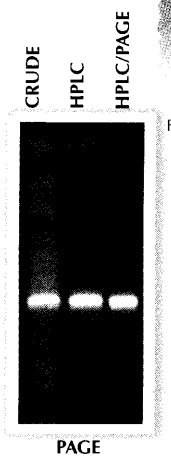

Figure 2

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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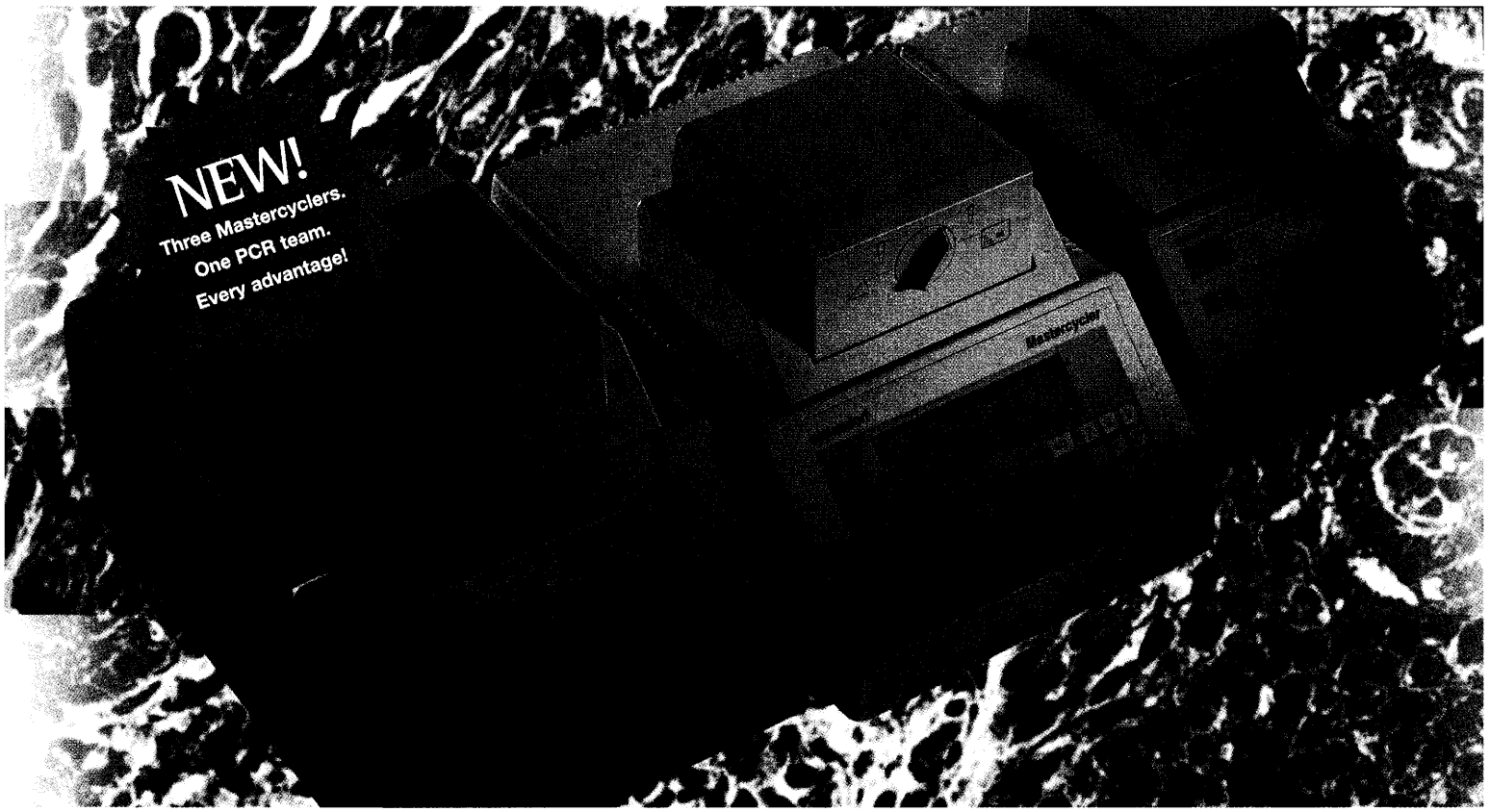

Background picture: PE squamous epithelium-CA of oral cavity, actin-in situ RT-PCR.

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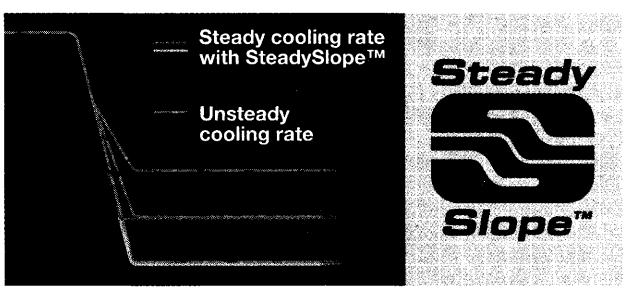

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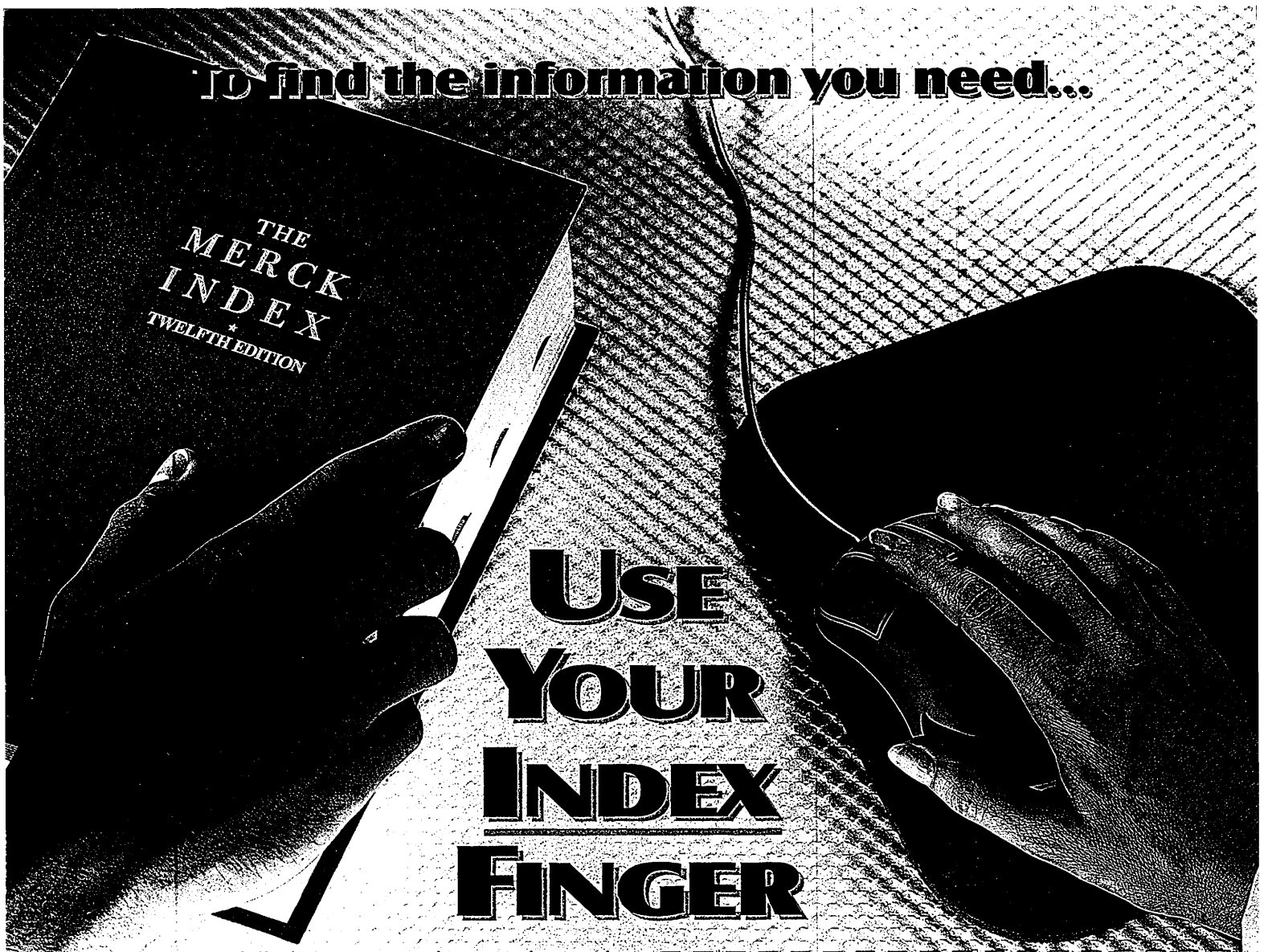

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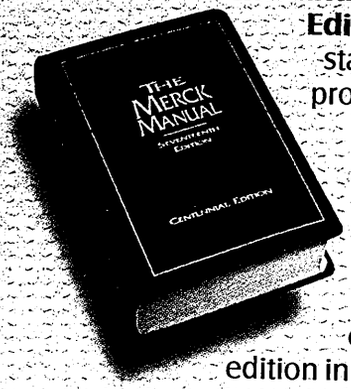

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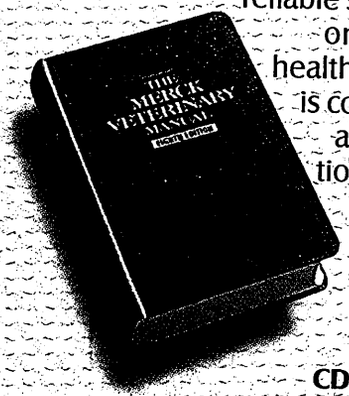

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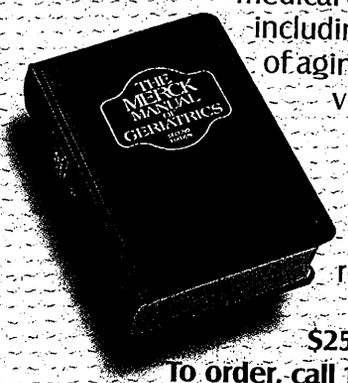

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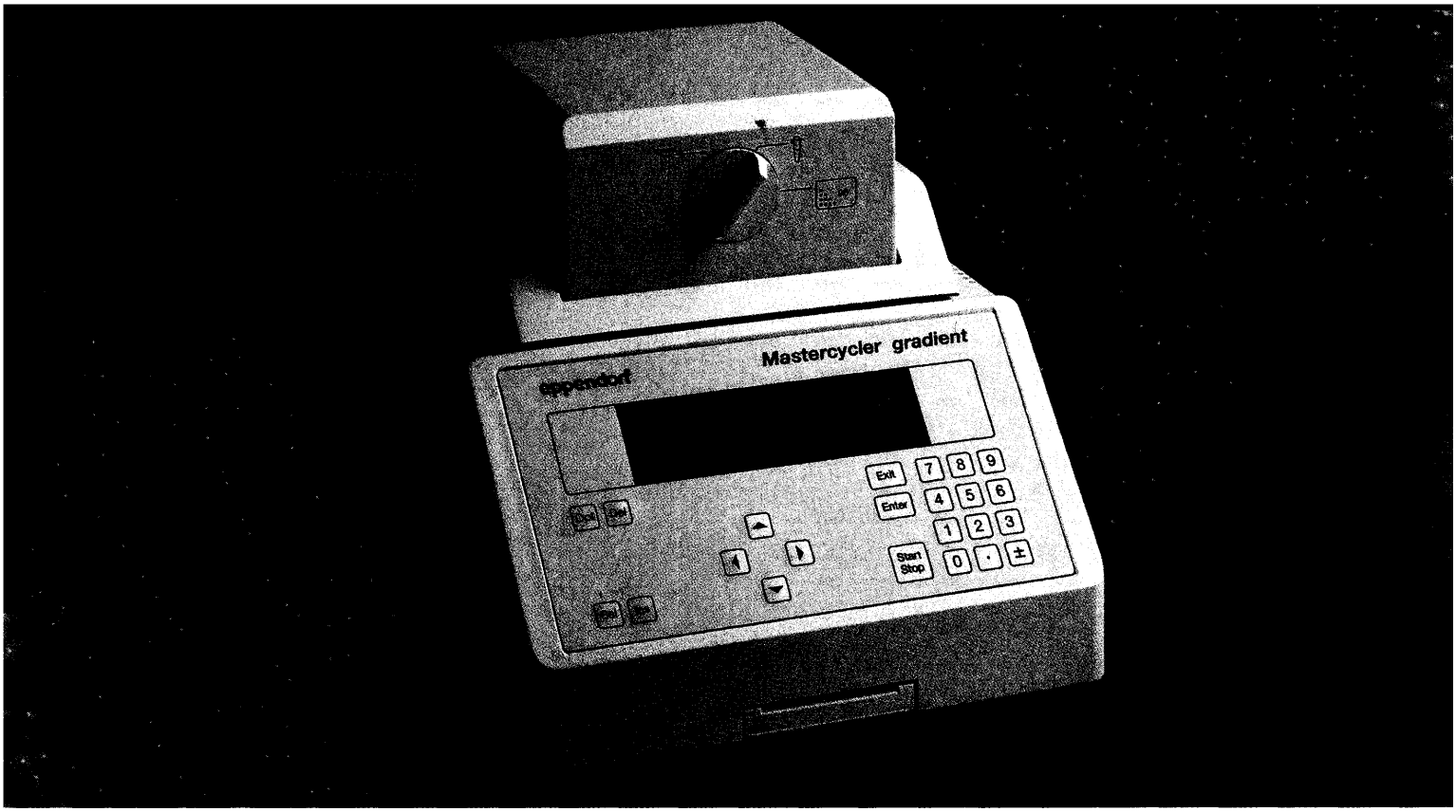

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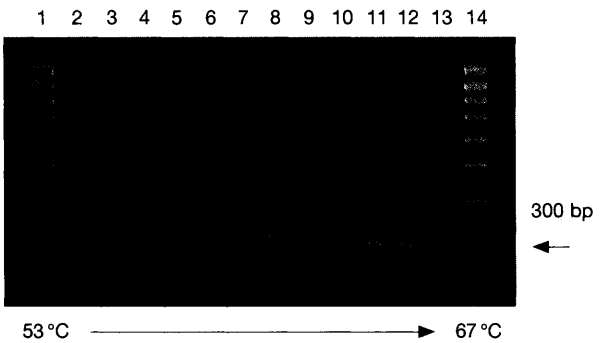

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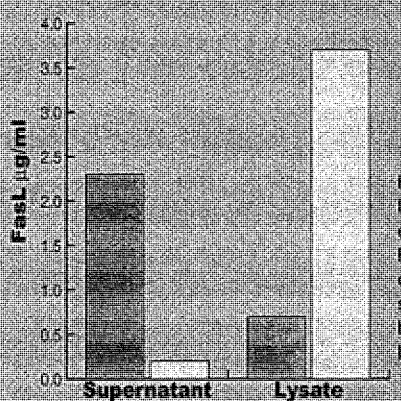

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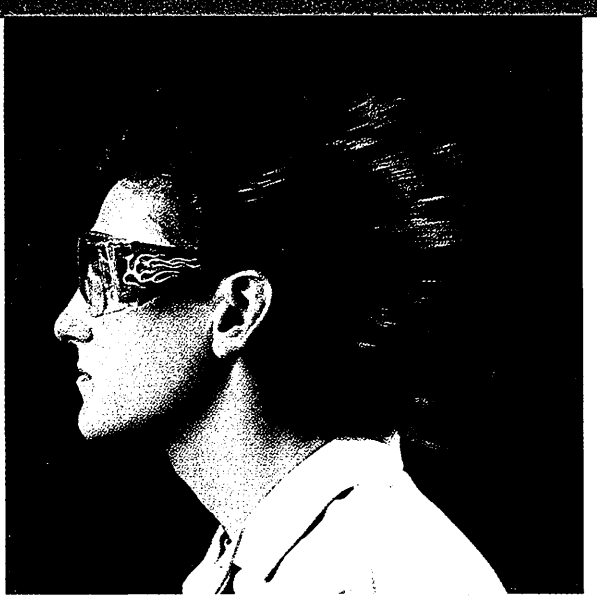

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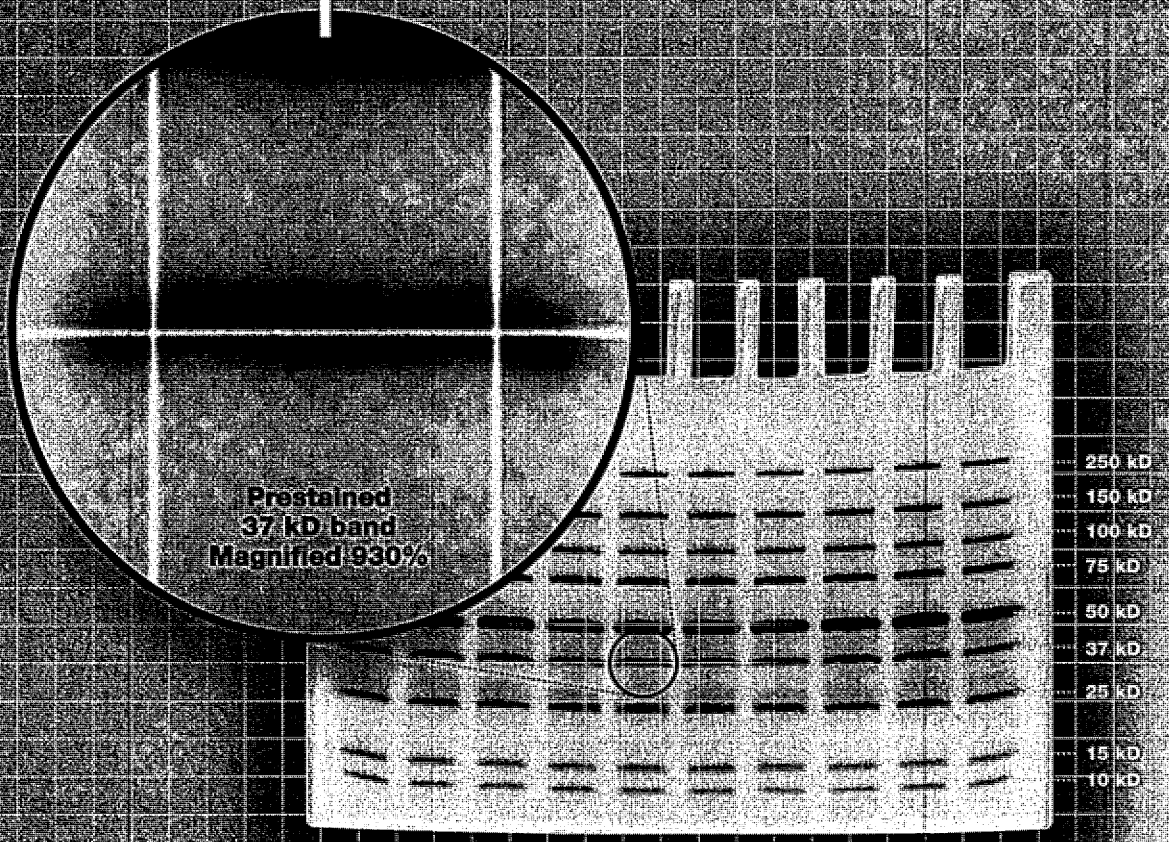

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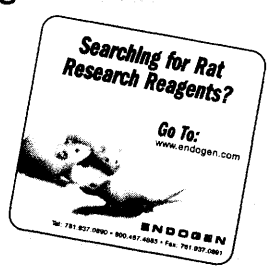

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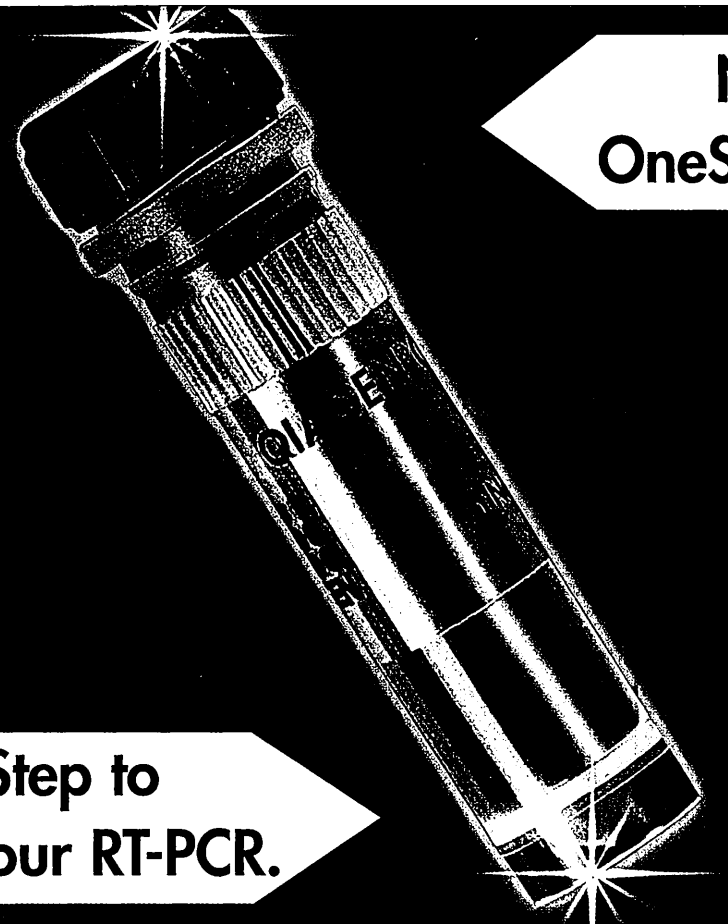

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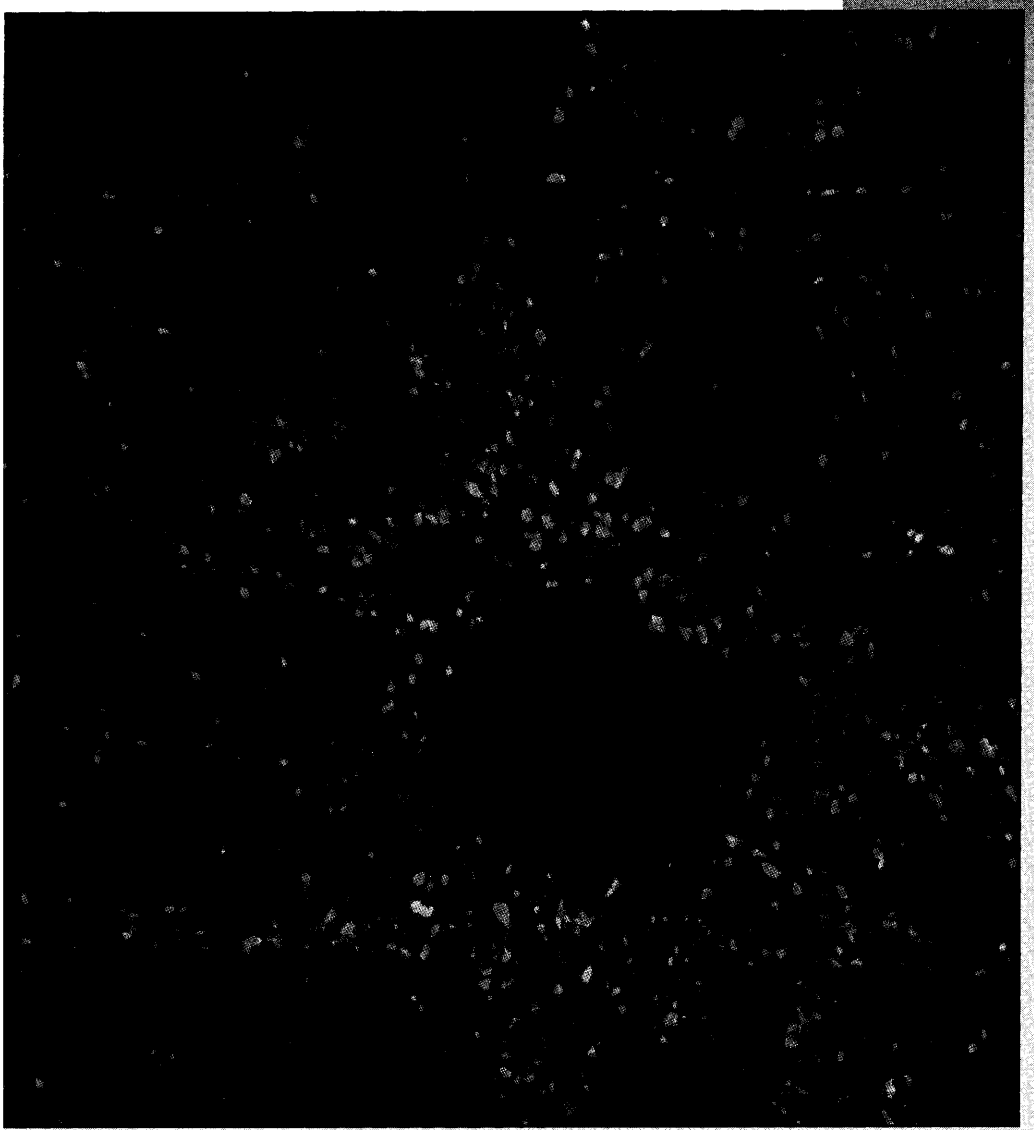

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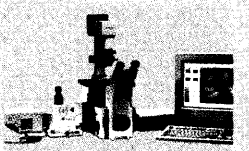

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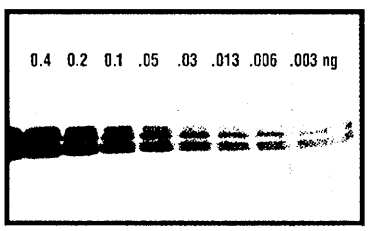

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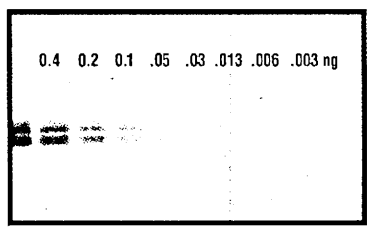

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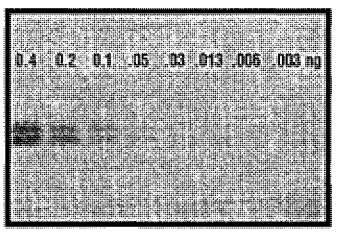
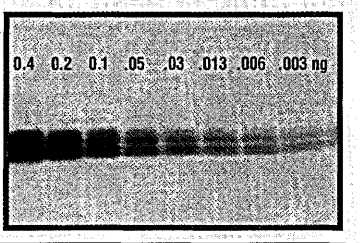
SuperSignal® West Pico Chemiluminescent Substrate

Switching to SuperSignal® West Pico Substrate from ECL™ Chemiluminescent Substrate

theirs



ours



Step-by-step Conversion Protocol	ECL™ Substrate	SuperSignal® West Pico Substrate
1. Perform standard electrophoresis and blotting.	Use their Hybond™ nitrocellulose membrane.	Use any nitrocellulose membrane.
2. Block the nonspecific sites.	Add blocking reagent, incubate and wash.	Add blocking reagent, incubate and skip the wash!
3. Add diluted primary antibody; incubate for 1 hour, then wash.	Optimization Range: **1/100-1/1,500 dilution**	→ Optimization Range: **1/500-1/5,000 dilution**
4. Add diluted secondary antibody (HRP-labeled); incubate for 1 hour, then wash.	Optimization Range: **1/1,500-1/50,000 dilution**	→ Optimization Range: **1/20,000-1/100,000 dilution**
5. Prepare chemiluminescent substrate.	Mix equal volumes of both solutions.	Mix equal volumes of both solutions.
6. Incubate the substrate on the blot.	Incubate blot with Working Solution without agitation for precisely 1 minute. It's recommended that you work quickly once ECL™ Working Solution has been added to the membrane.	Incubate blot with Working Solution with agitation for ~5 minutes. The signal lasts for hours, so take your time!
7. Expose to film.	Immediately expose to film for 1 minute.	Expose to film for 1 minute.

For detailed technical information, visit the Pierce web site at *www.supersignalwest.com*. To order, call 800-874-3723 or, outside the U.S., call 815-968-0747 for the name of your local distributor.

how easy SuperSignal® West Pico is to use?

Ordering Information

Product #	Description	Pkg. Size
34080	**SuperSignal® West Pico Chemiluminescent Substrate*** *Enough for 4,000 cm² membrane.*	500 ml
	Includes: Luminol/Enhancer	250 ml
	Stable Peroxide Buffer	250 ml

**Patent Pending*

PIERCE