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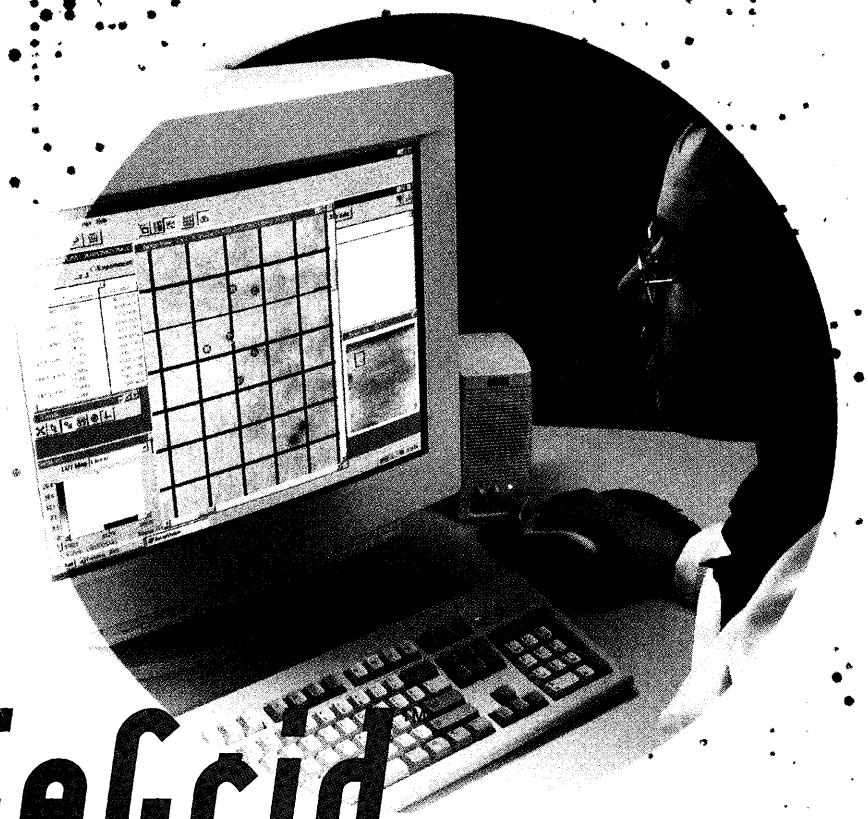

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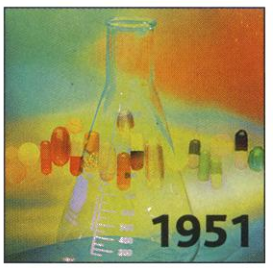

COVER Recent scientific advances in fields ranging from genomics to combinatorial chemistry are poised to revolutionize drug discovery, with added benefits for health care. A special section starting on page 1951 looks at how these chemical and biological advances are leading to new approaches to drug discovery. Aspects of the social and economic context of drug discovery are also discussed. [Photo illustration: Ann Elliott Cutting]

1906
Confronting an ancient scourge

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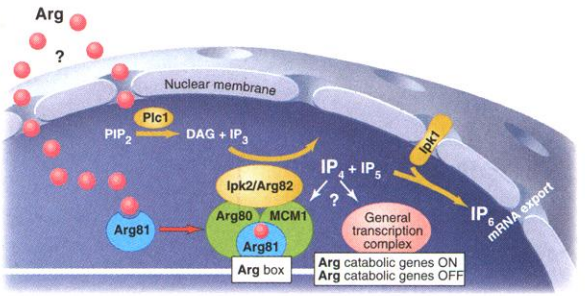
SCIENCE'S COMPASS

1937

Copycat inositol phosphates in the nucleus



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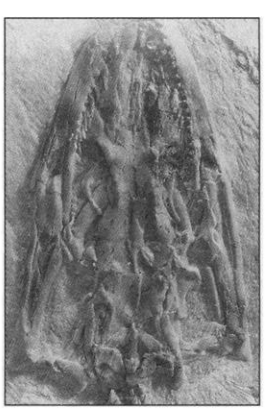

2010

Snake evolution—new fossil clues

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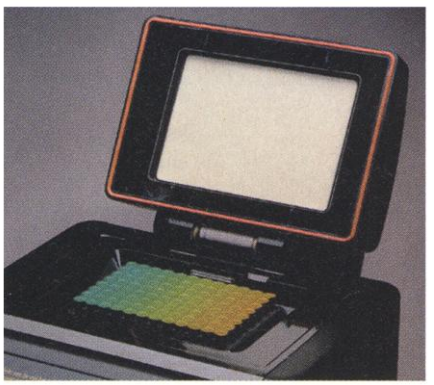
THE MJ RESEARCH NOTEBOOK

Volume IX...No. 3 *A Bulletin of Technological Advance in Molecular Biology* *Winter 2000*

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.

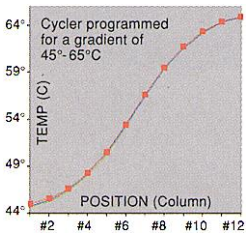
Too bad. MJ's scientific staff finds that denaturation often leads to problems. Use of a lower denaturation temperature, such as 90°-92°C, is generally recommended whenever possible. Not only does it preserve enzymatic activity for later cycles, it also reduces breakdown of fluorescent dyes in cycle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

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).

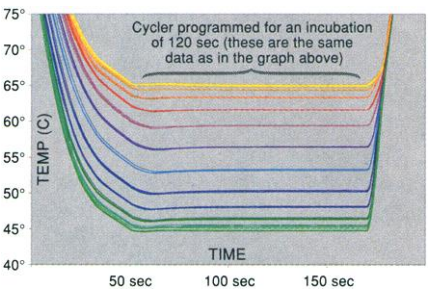
This calculator is so precise and accurate that it reports the temperatures in individual columns to within ±0.4°C of the NIST standard, making transfer of values to normal operation *very* reproducible. Just look above how reported temperatures from the gradient calculator superpose *almost perfectly*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

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.

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.

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CATALYZING C–H BOND REACTIONS

The selective activation under mild conditions of the carbon-hydrogen bonds of saturated hydrocarbons, or alkanes, as well as those of aromatic compounds, such as benzene, is the focus of two reports (see the Perspective by Jones). Transition metal complexes that activate alkanes generally do so as reagents, not as catalysts. Chen *et al.* (p. 1995) report on a rhodium complex that catalyzes the formation of linear alkylboranes (derivatized at the end of the chain) from alkanes and commercially available boron compounds in high yield. These compounds can then be converted to alcohols or amines for use in fine chemical synthesis. Most of the catalytic routes for the activation of aromatic C–H bonds are either unselective, require a particular group to present on the ring, or encounter difficulties in catalyst regeneration. Jia *et al.* (p. 1992) used a palladium complex with a weakly coordinating anion as a catalyst to insert alkynes and alkenes into aromatic C–H bonds under mild room-temperature conditions, thus forming carbon-carbon bonds. The reaction with alkynes usually produces the thermodynamically less-favored cis-substituted alkenes.

CHANGES IN IO'S EXOSPHERE

The gaseous eruptions of Io have created a broad plasma torus around Jupiter. The Galileo Orbiter made a close flyby of Io in 1995, and measurements of the ion density in the plasma confirmed that sulfur dioxide from eruptions on Io was being ionized and trapped in the torus. Russell and Kivelson (p. 1998) have analyzed new data from another close flyby of Io in October 1999, and they infer that a high density of ionized sulfur monoxide and possibly other more exotic species such as cyanogen or ionized sodium are present in a fan-shaped region extending from about 2 to 20 Io radii away from Jupiter. The authors attribute changes in the composition and shape of the ionized region since the 1995 flyby to recent eruptions from the active volcano, Pillan Patera.

SWINGING SINKS

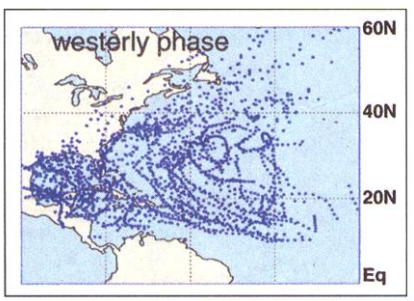
Carbon storage by natural ecosystems is a major factor in the global carbon cycle, and much recent effort has been devoted to estimating the size of such "sinks." Recent estimates have varied widely, especially for the United States, where they have ranged over an order of magnitude. Using climatic data for the past 100 years, Schimel *et al.* (p. 2004) model the effects of carbon dioxide increase and climate fluctuations on carbon storage in the United States. Their models show that the carbon sink is highly variable from year to year, and that sometimes there is actually a net efflux. Forest management and agricultural abandonment appear to contribute at least as much as climate and carbon dioxide increases do to the sink.

IRONING OUT THE PAST

Iron plays a key role in the regulation of oceanic productivity, and thus changes in paleoproductivity might be ascertained from records of the abundance and isotopic composition of iron in seawater. Zhu *et al.* (p. 2000) have created a seawater iron-isotopic curve for the past 6 million years by analyzing the ferromanganese crust of a deep-sea nodule. The correlation with lead isotopes that they observe indicates that the isotopic variations are of geological, not biological, origin.

ILL TIDINGS ON THE WINDS

Some of the most destructive hurricanes and tropical storms affecting the United States come from the Gulf of Mexico or the western Caribbean Sea. Maloney and Hartmann (p. 2002) have analyzed the record of tropical cyclones in these areas and found that the frequency of these storms is mod-



ulated by a tropical intraseasonal variation in winds called the Madden-Julian oscillation (MJO). These hurricanes are four times more likely when these wind anomalies are westerly in the eastern Pacific than when they are easterly. This correlation could be useful in improving long-range predictions of tropical cyclone activity in this region because the MJO may be forecast up to 2 weeks into the future.

MODIFYING CELL SURFACES OUTSIDE—AND IN?

The selective chemical modification of cell surfaces could be used for working out or even engineering cell-surface interactions. The few approaches that exist usually require a condensation reaction between the chemical species to be introduced (such as a dye or a receptor) and a partner formed within the cell. If such reactions are to be specific, the partners should be "abiotic," yet most "abiotic" organic chemistry is usually run in nonaqueous solvents. Saxon and Bertozzi (p. 2007) have modified the Staudinger reaction, the coupling of an azide and a phosphine, so that an amide linkage can form in water. Azides were introduced into cell surfaces by metabolism of an azidosugar, and these groups formed covalent adducts with a biotinylated triarylphosphine. It may be possible to extend this reaction to work in the intracellular environment as well.

STILL SNEAKY

The origin of snakes provides a readily perceived example of a major evolutionary transition in the vertebrates that involved extensive morphological changes associated with locomotion, feeding, and life history. Equally, it has been a subject beset with controversy in recent years and hampered by the relative poverty of the fossil record. Tchernov *et al.* (p. 2010; see the Perspective by Greene and Cundall) describe a new fossil snake with limbs from 95-million-year-old deposits near Jerusalem. This fossil, named *Haasiophis*, shows very close affinities with *Pachyrhachis*, which has been claimed as the sister-taxon of all snakes. However, the better preservation of the *Hassiophis* material indicates that these two snakes were primitive members of only the more advanced snake assemblage, the macrostomates (such as pythons and boas).

ATTACKING ASTHMA

Asthma is caused by exposure to certain substances in the environment that lead to inappropriately severe allergic reaction in the lung. These environmental antigens trigger immunoglobulin E antibodies that then activate mast cells. One of the inflammation-inducing substances released by the mast cells is prostaglandin D_2, which Matsuoka *et al.* (p. 2013) now show to cause some of the more severe symptoms of asthma. In mice in which prostaglandin D_2 has been genetically deleted, fewer T lymphocytes (which se-

CONTINUED ON PAGE 1887

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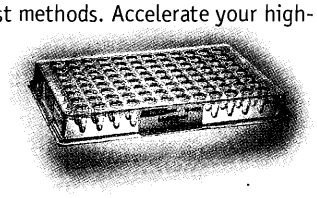

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 1885

crete T_H2 cytokines) and eosinophils accumulate in the lung, and the mice did not develop the hyperreactive airways usually characteristic of asthma attacks. Thus, prostaglandin D_2 could prove to be a new therapeutic target against asthma.

MITOCHONDRIAL DETECTION OF CANCER

Cancer therapy is most effective at early stages of the disease, so there is much interest in developing sensitive and noninvasive methods of early diagnosis. Fliss *et al.* (p. 2017) show that human tumors contain a large number of mutations in mitochondrial DNA (mtDNA) and that these mutant mtDNAs appear to accumulate at disproportionately high levels in the tumor cells. Analysis of bodily fluids such as urine and sputum revealed that the mtDNA mutations were significantly easier to detect than were mutations in *p53*, a nuclear gene. These results raise the possibility that mtDNA can serve as a powerful diagnostic marker for cancer detection.

OUTWARD BOUND

DNA replication in yeast and bacteria begins at a particular site and propagates in both directions outward. In mammalian cells, the details of the events surrounding the initiation of DNA replication have remained obscure. Abdurashidova *et al.* (p. 2023) studied the lamin B2 gene in human cell lines and found that the leading strands of each replication fork, which head in opposite directions, initiate within very few nucleotides of each other. This initiation site falls within a region that may bind a cell cycle–regulated protein complex.

TAKING IP_3 A STEP FURTHER

Activation of phospholipase C causes increased production of inositol 1,4,5-trisphosphate, a second messenger that regulates release of calcium from intracellular stores. IP_3 can be modified by further phosphorylation, but the signaling role, if any, of such molecules is unclear. Odom *et al.* (p. 2026; see the Perspective by Chi and Crabtree) report that in the yeast *Saccharomyces cerevisiae*, an IP_3 kinase (designated Ipk2p for inositol polyphosphate kinase) that can convert IP_3 to IP_5 is identical to Arg82p, a protein that participates in regulation of transcription. Arg82p functions as part of a transcriptional complex that mediates the response to changes in the extracellular concentration of arginine. Ipk2p protein, but not its kinase activity, was required for proper formation of complexes on DNA promoter elements. However, activity of the enzyme and formation of I(1,4,5,6)-P_4 was required for proper transcriptional regulation in response to extracellular arginine. Thus, signaling through inositol polyphosphates appears to be intimately associated with regulation of transcription in the nucleus.

RETINAL REGENERATION IN MAMMALS?

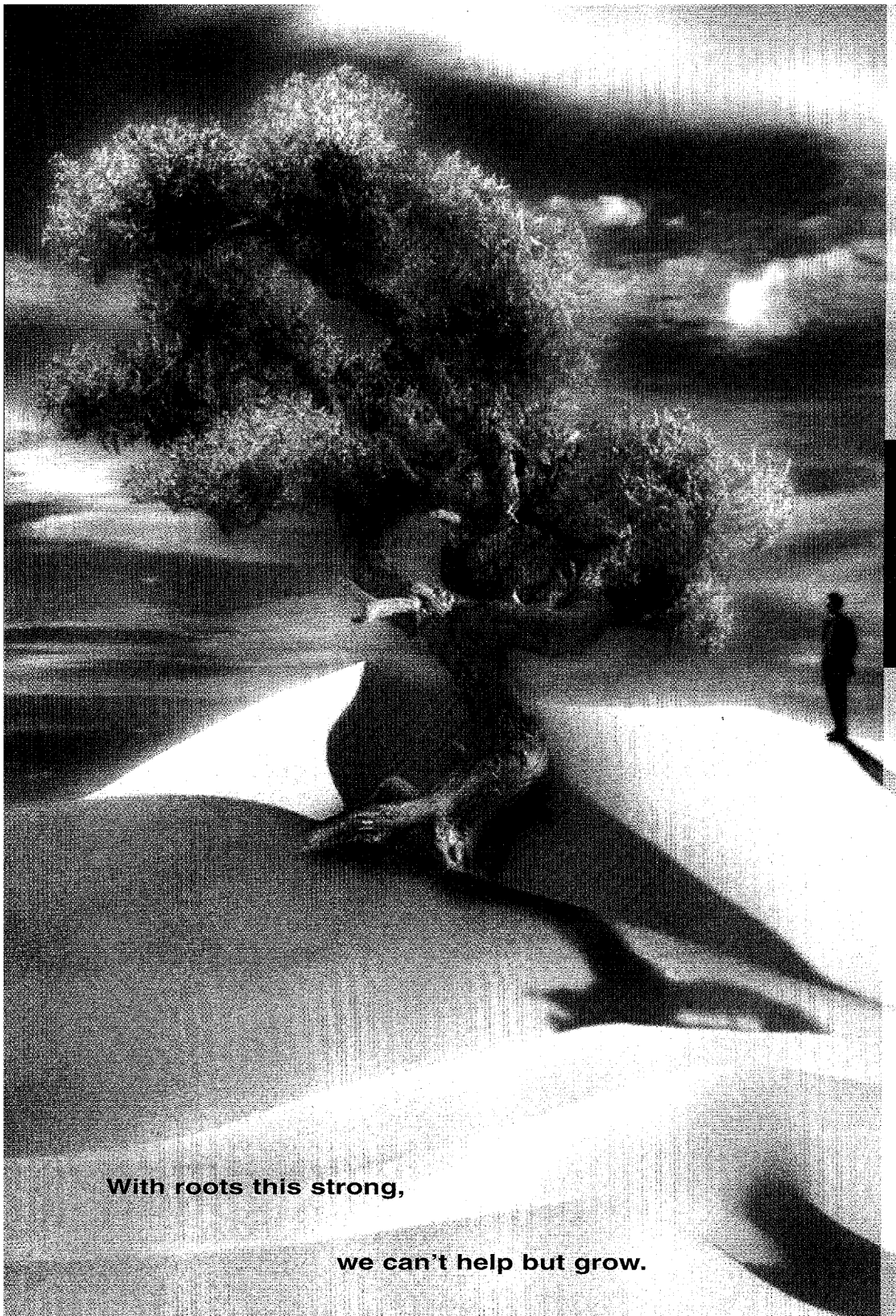
The retina in some nonmammalian vertebrates, such as fish and amphibians, can continue cellular renewal throughout life and regenerate in response to damage. These abilities are, however, lost to the mammalian retina, thus increasing the susceptibility of our vision to loss or degradation through disease. Traces of the more primitive developmental flexibility may yet exist, however. Tropepe *et al.* (p. 2032) have now found that, in mice, certain cells from the ciliary margin of the retinal pigmented epithelium function as stem cells. In culture, these cells will proliferate and will also generate differentiated neuronal cell types typical of the retina. Tremendous potential exists if this developmental flexibility can be manipulated for therapeutic benefit.

TECHNICAL COMMENT SUMMARIES

Kentucky 31, Far from Home

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/287/5460/1887a

Clay and Holah (Reports, 10 Sep., p. 1742) found that the presence of a host-specific fungal endophyte in the tall-fescue cultivar Kentucky 31 (KY-31) significantly reduced species diversity in experimental plots, and suggested that natural areas in which fescue is common and highly infected may suffer a similar loss of species richness. Saikkonen argues that these results, rather than constituting a model of endophyte-plant symbiosis, should instead be viewed as evidence of "ecosystem vulnerability to human-induced invasion" by an inbred, highly competitive exotic species. Clay and Holah respond that the experimental design of their study isolated the effect of endophyte infection from "other potentially confounding factors," and that the well-documented success of wild endophyte-infected grasses is "clearly not predicated on being either exotic or inbred."



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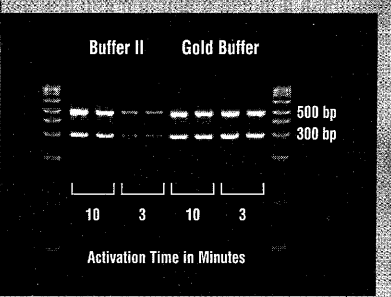

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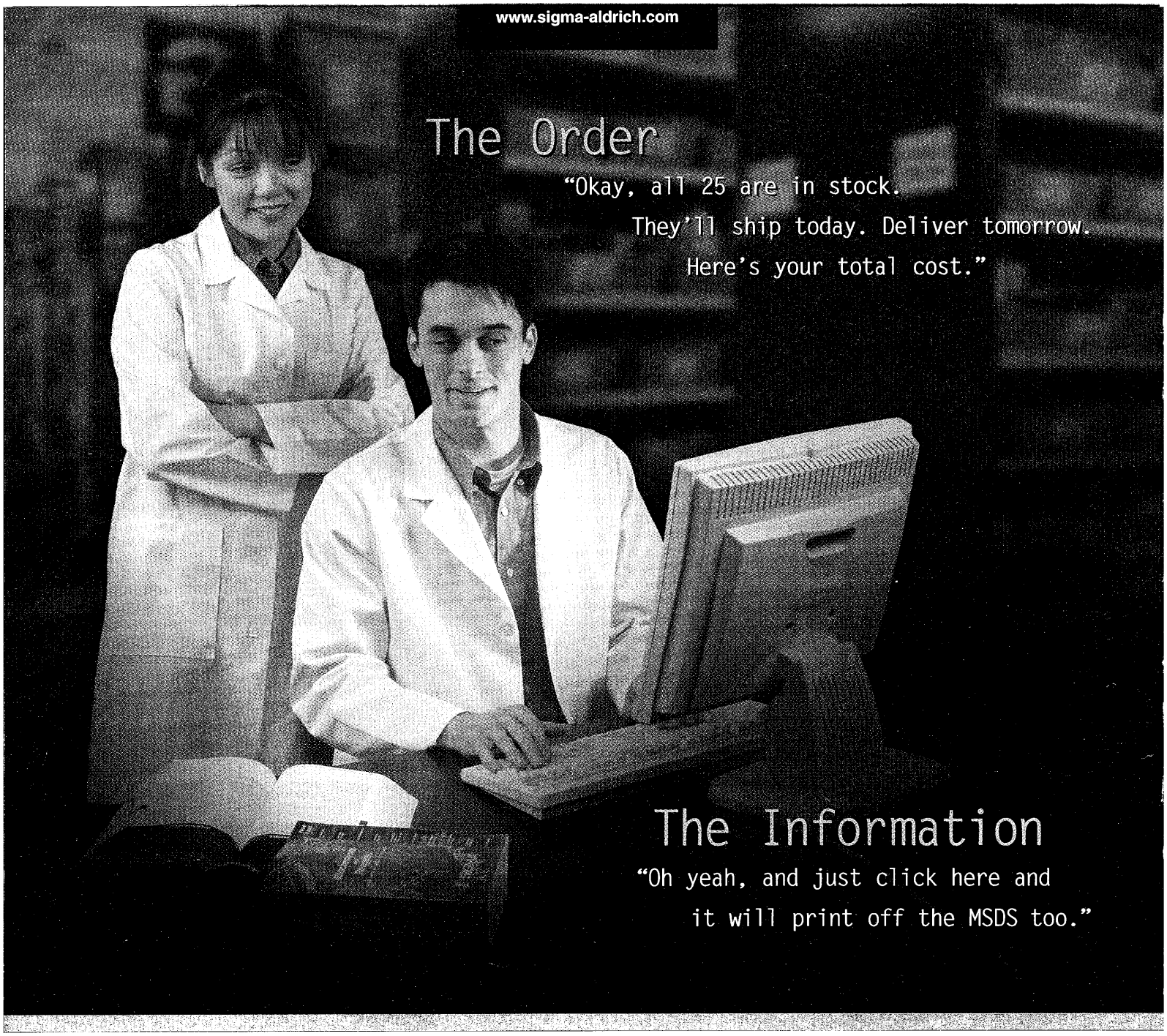

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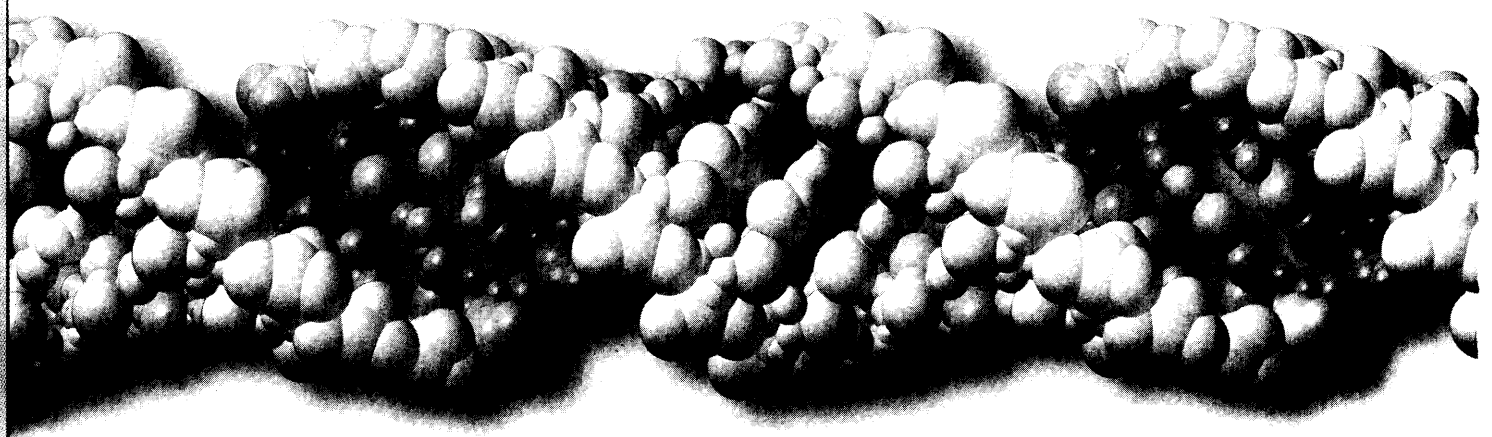

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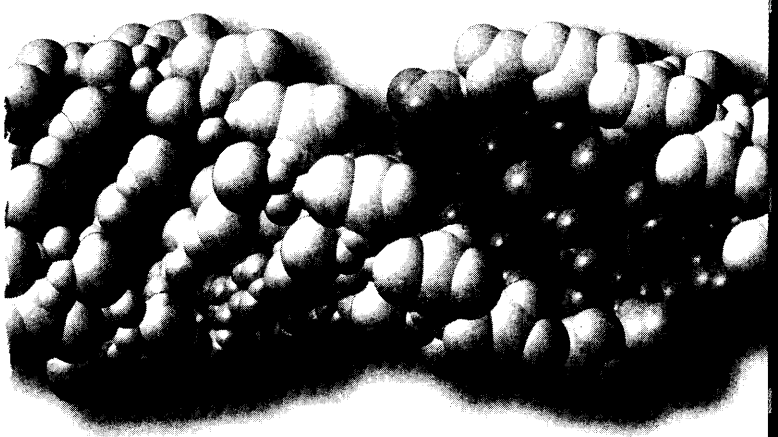

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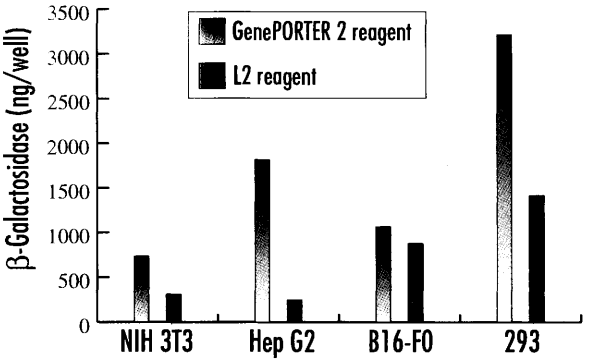

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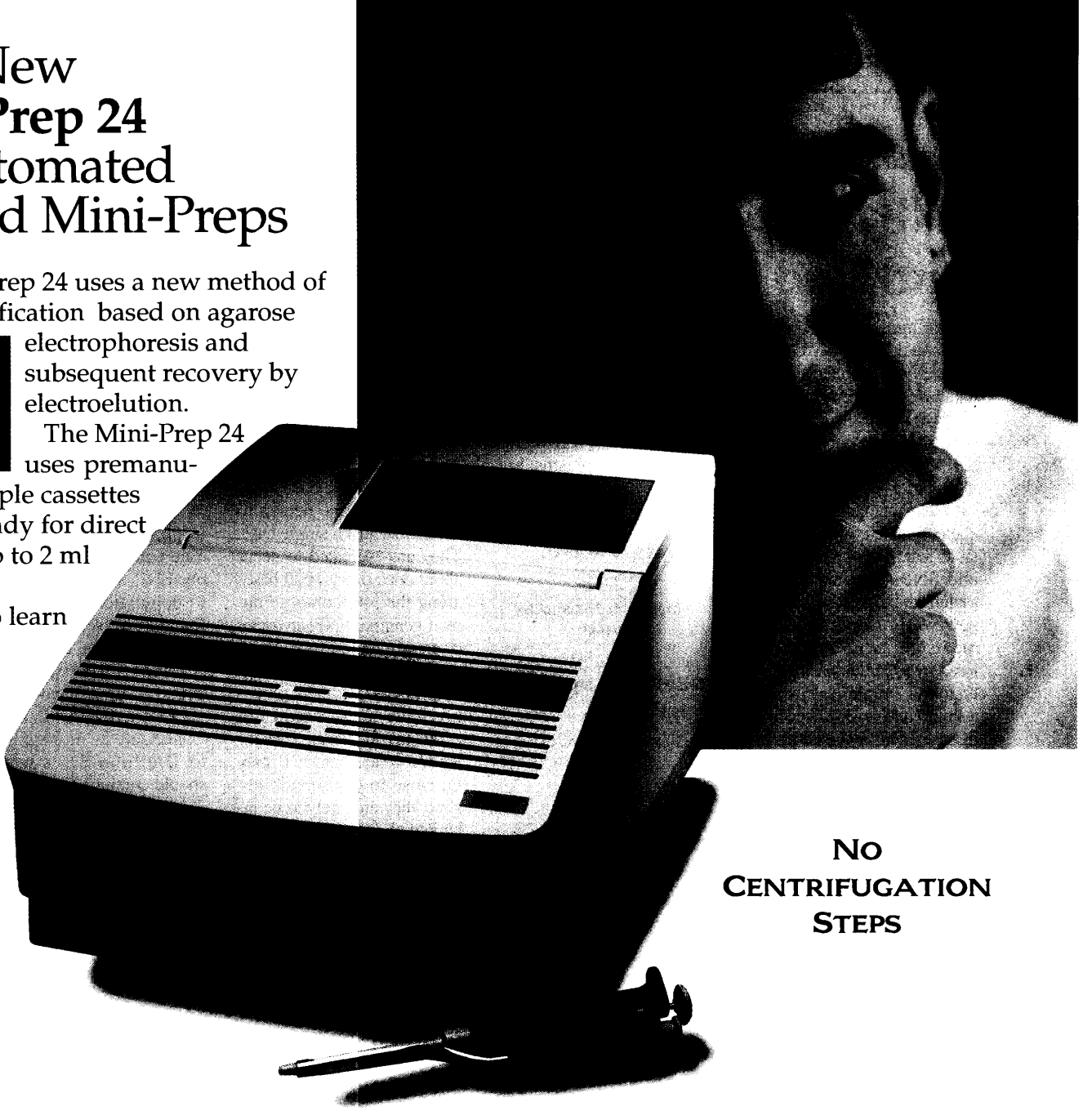

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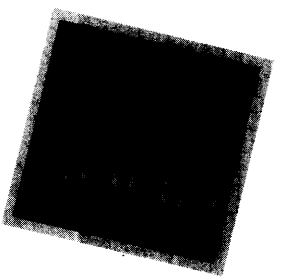

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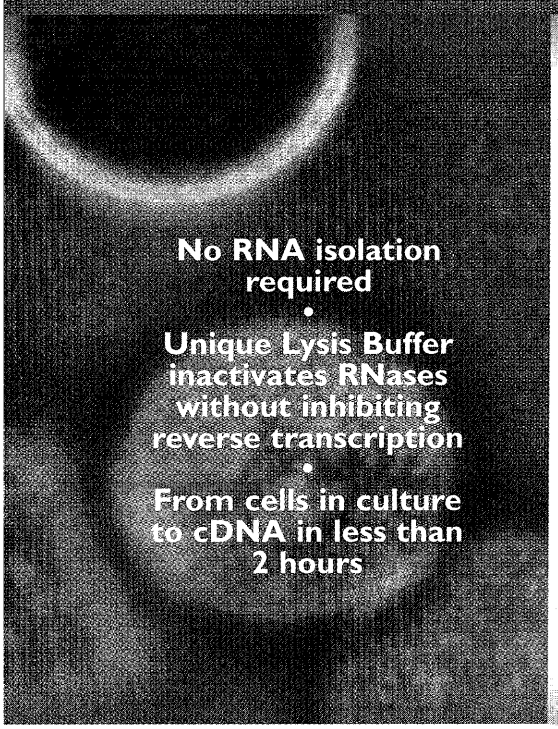

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•

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•

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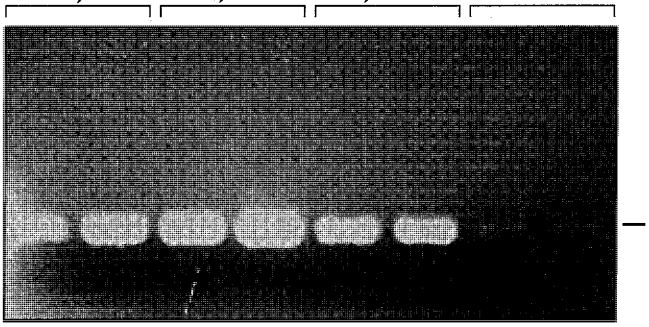
Starting Cell Number

100,000 20,000 2,000 200



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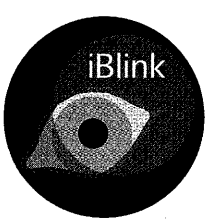

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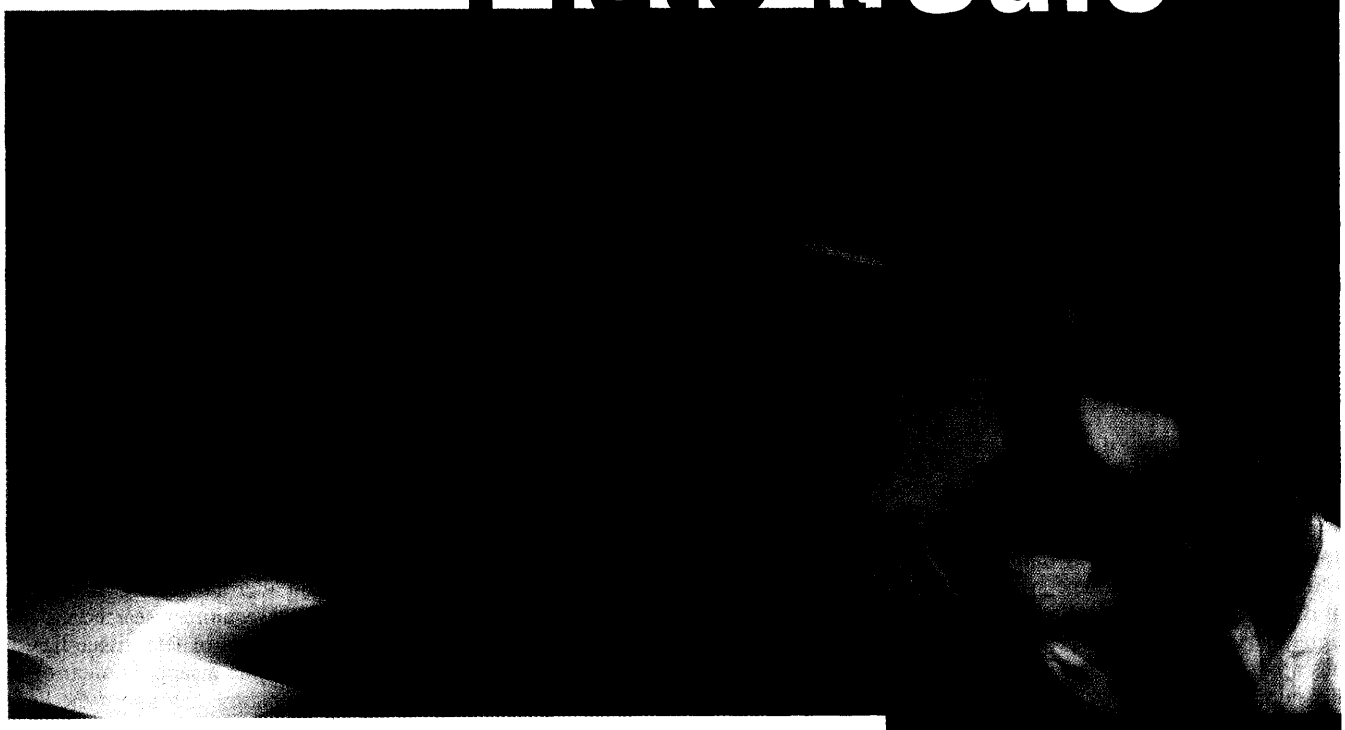

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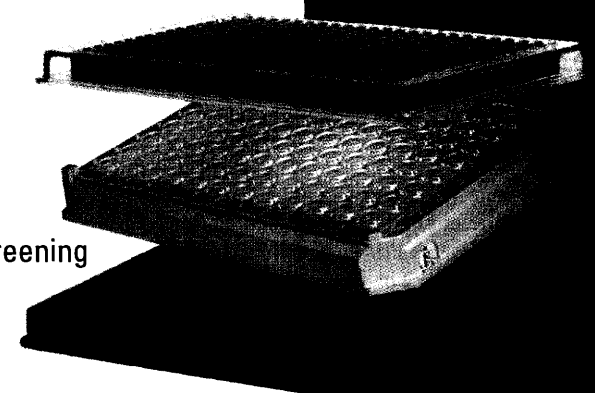

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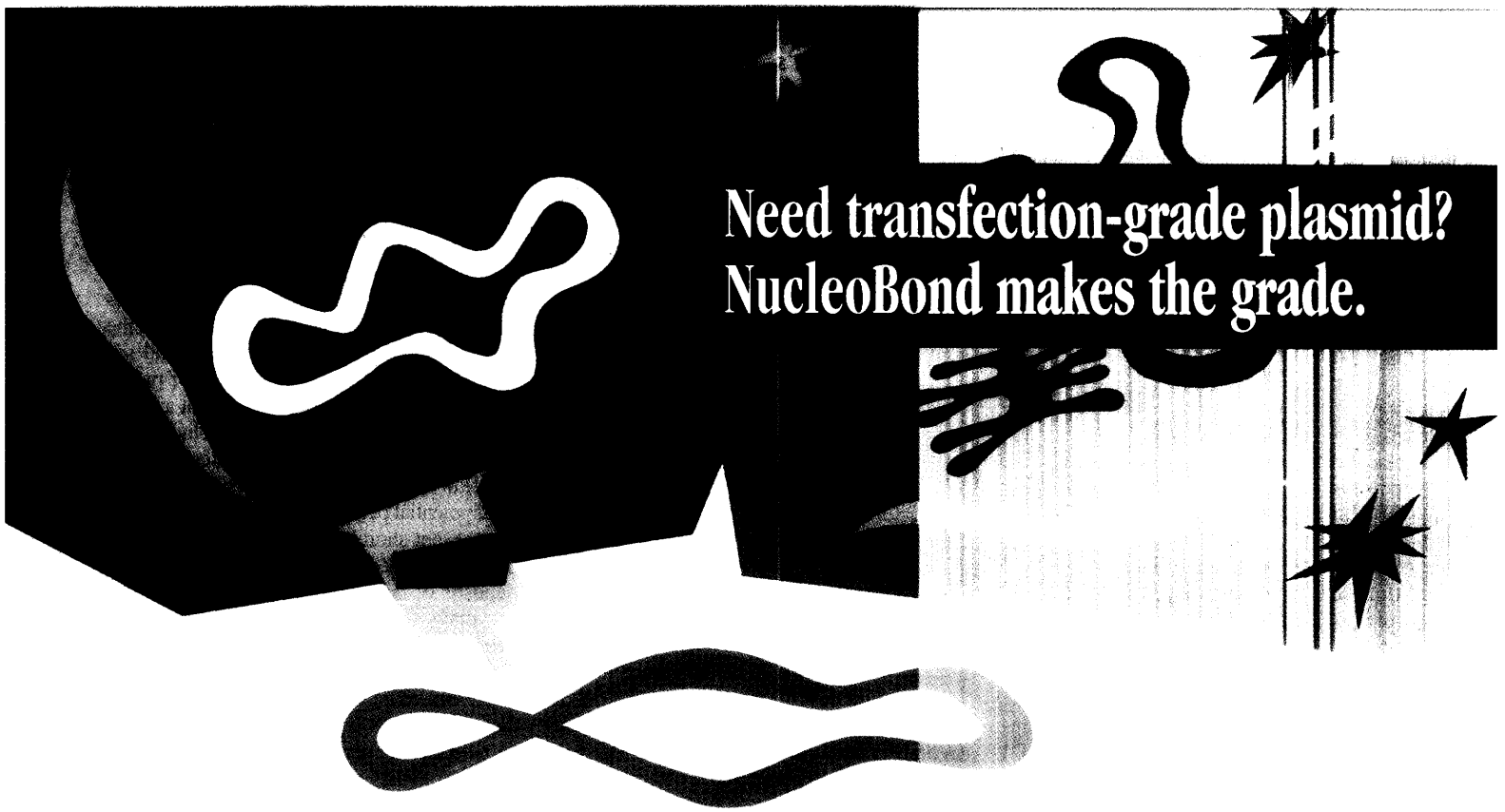

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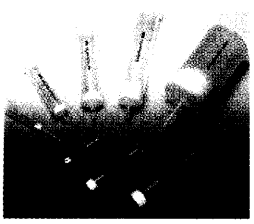

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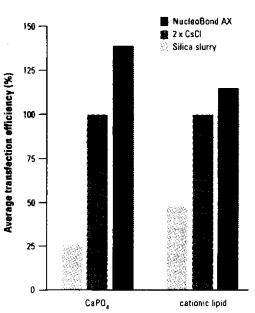

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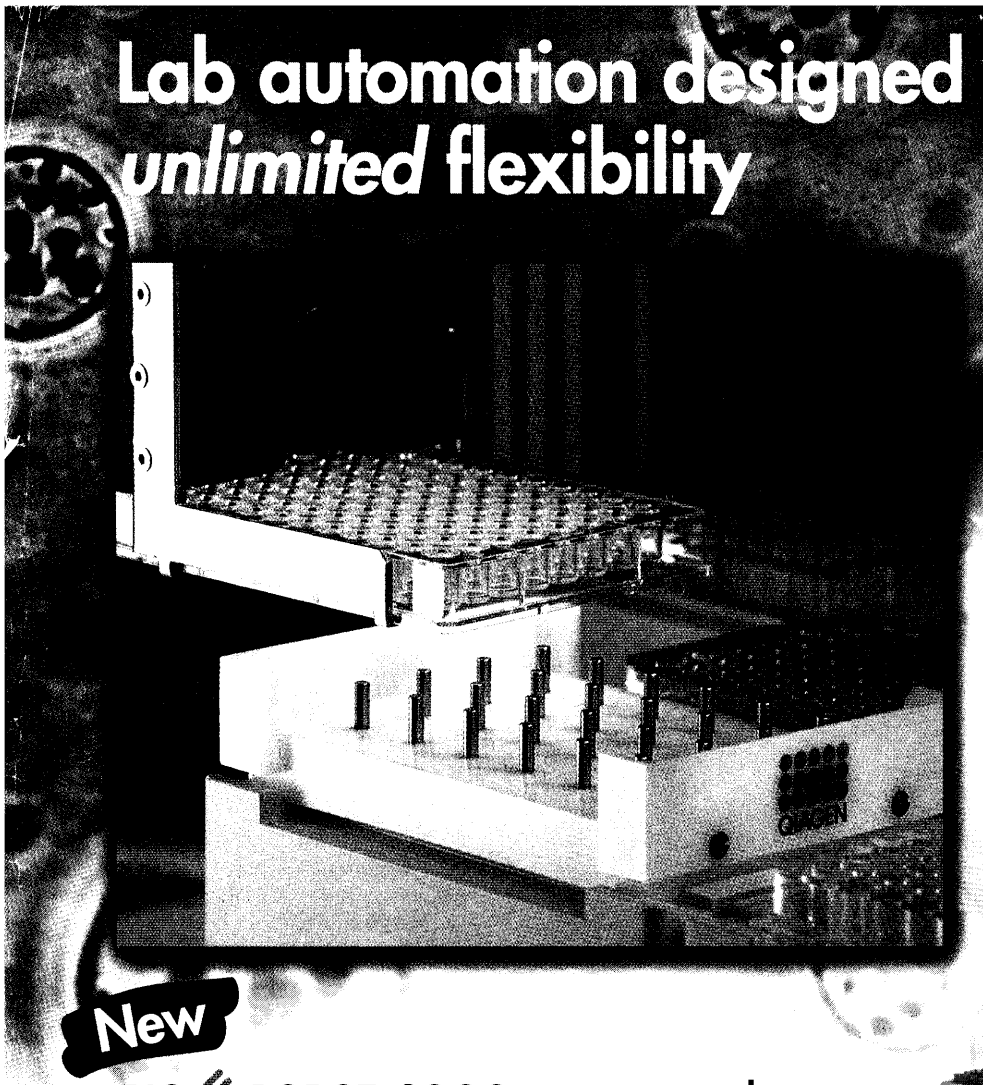

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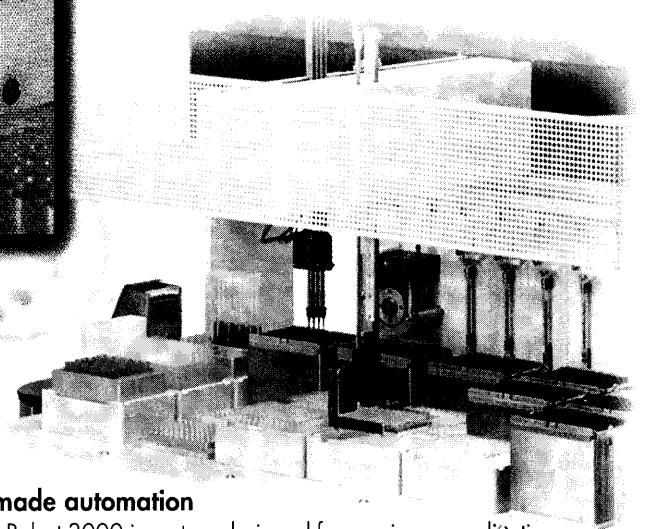

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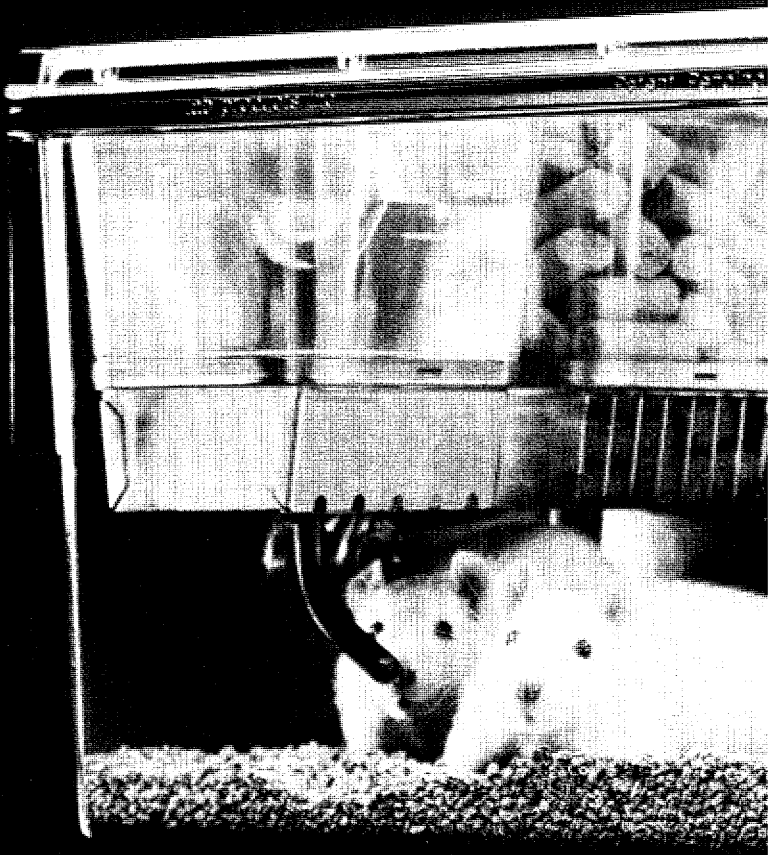
Now you can house more animals per square foot, maximize available space, streamline animal care, and greatly reduce costs. At the same time, you can insure all-critical compliance with both the Animal Welfare Act and the ILAR Guide* recommendations.

One Cage makes it possible to house all your rodents in one system. The revolutionary design features one cage with one feeder, one water bottle, one filter top (no wire bar lid required), and only One Rack™ that will accommodate 112 complete units.



Examples of how THE GUIDE* recommendations apply to the One Cage™ System

Number of animals recommended per cage based on 80 sq. inches of usable floor area, 7-3/4" interior cage height.

MICE (12-25g)	5
HAMSTERS (80-100g)	4
RATS (200-400g)	2
GUINEA PIGS (350g)	2

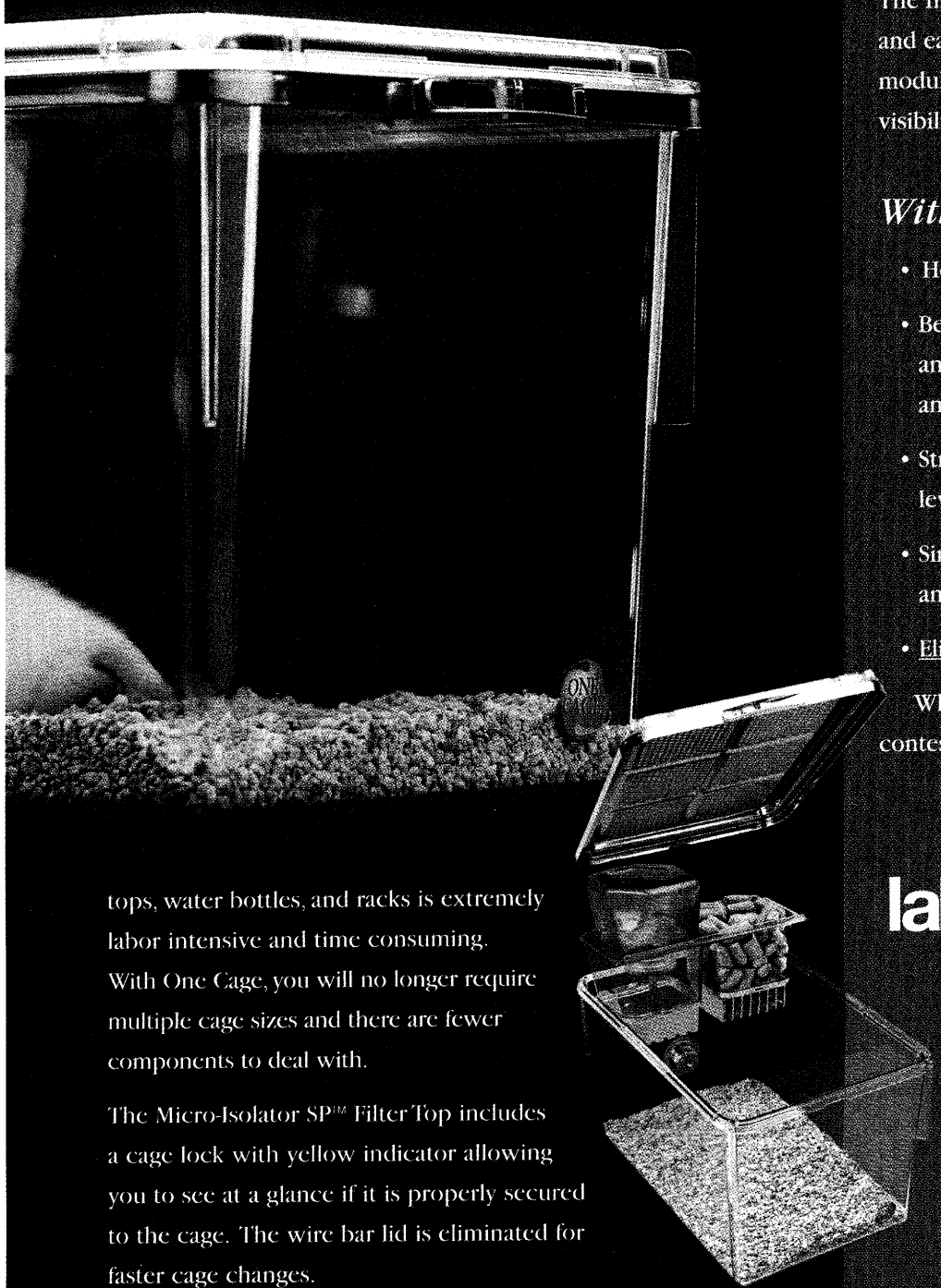
*Based on the Animal Welfare Act of 1966 as ammended 1985 and the Guide for the Care and Use of Laboratory Animals. Institute of Laboratory Animal Resources, Commission of Life Sciences, National Research Council. National Academy Press, 1996.

With One Cage, 560 mice, 448 hamsters, 224 rats, or 112 guinea pigs can be housed in a single rack. This represents up to a 273% increase in animal populations. (A facility housing 2,200 rats would require 37 racks housing 30 cages with 60 rats per rack *(based on old-style racks)*. Compare this to 10 One Cage racks housing 224 rats per rack.)

You can house more rodents in less space while meeting interior cage height and floor space requirements.

Cleaning and handling multiple cage sizes, wire bar lids, filter

e System™



The filter replacement device provides quick and easy exchange of filters. The clear plastic modular delivery system provides greater visibility of food and water for easy inspection.

With One Cage, you can:

- House more animals in less space at less cost.
- Be in full compliance with The Guide* and prepared for the arrival of new animal care policies.
- Streamline your work while improving your level of care.
- Simplify purchasing, cut down on inventory and reduce the number of turnaround units.
- Eliminate wire bar lids.

When you look at the options, there's no contest. It's One Cage.

tops, water bottles, and racks is extremely labor intensive and time consuming. With One Cage, you will no longer require multiple cage sizes and there are fewer components to deal with.

The Micro-Isolator SP™ Filter Top includes a cage lock with yellow indicator allowing you to see at a glance if it is properly secured to the cage. The wire bar lid is eliminated for faster cage changes.

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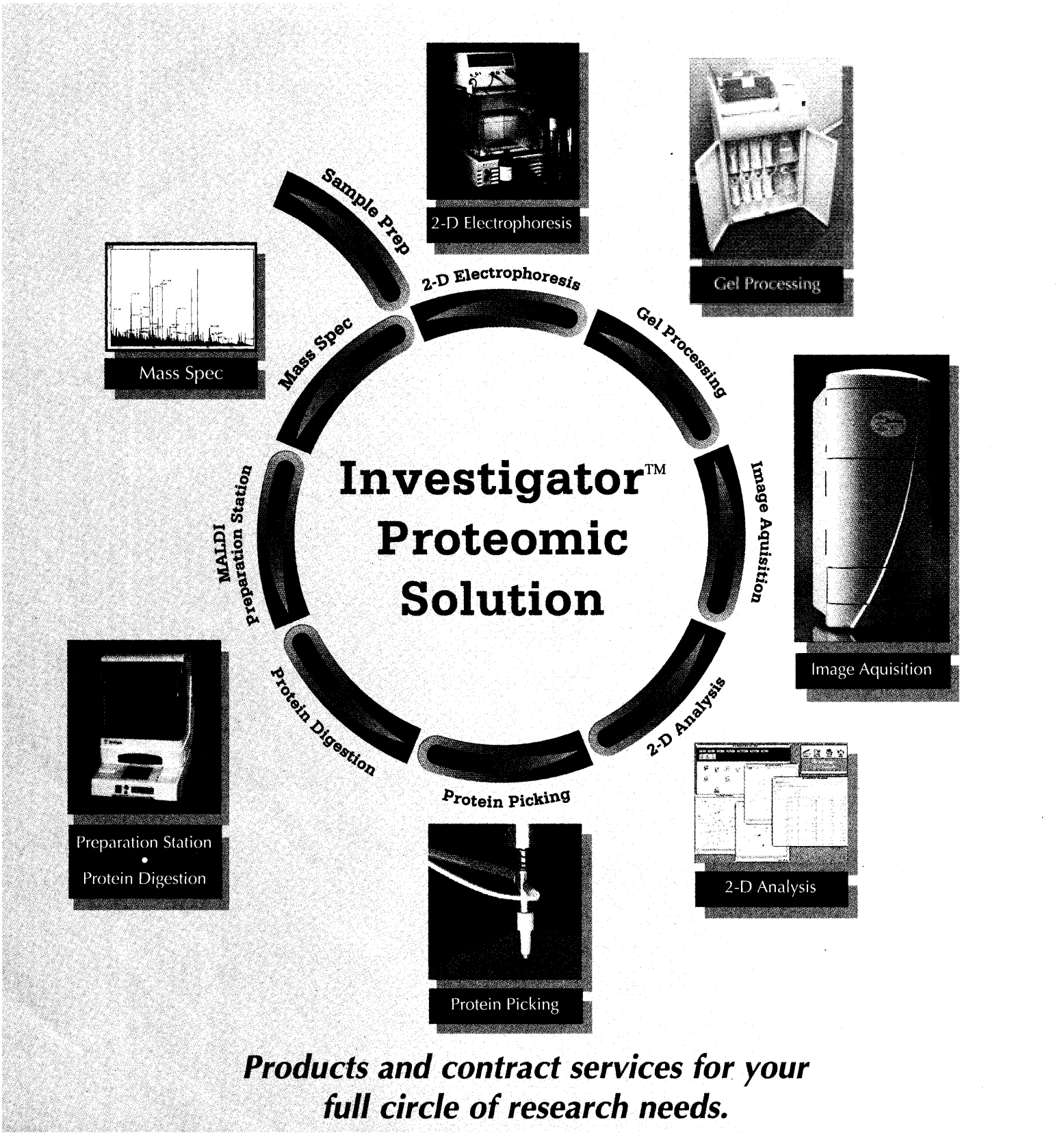

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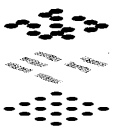

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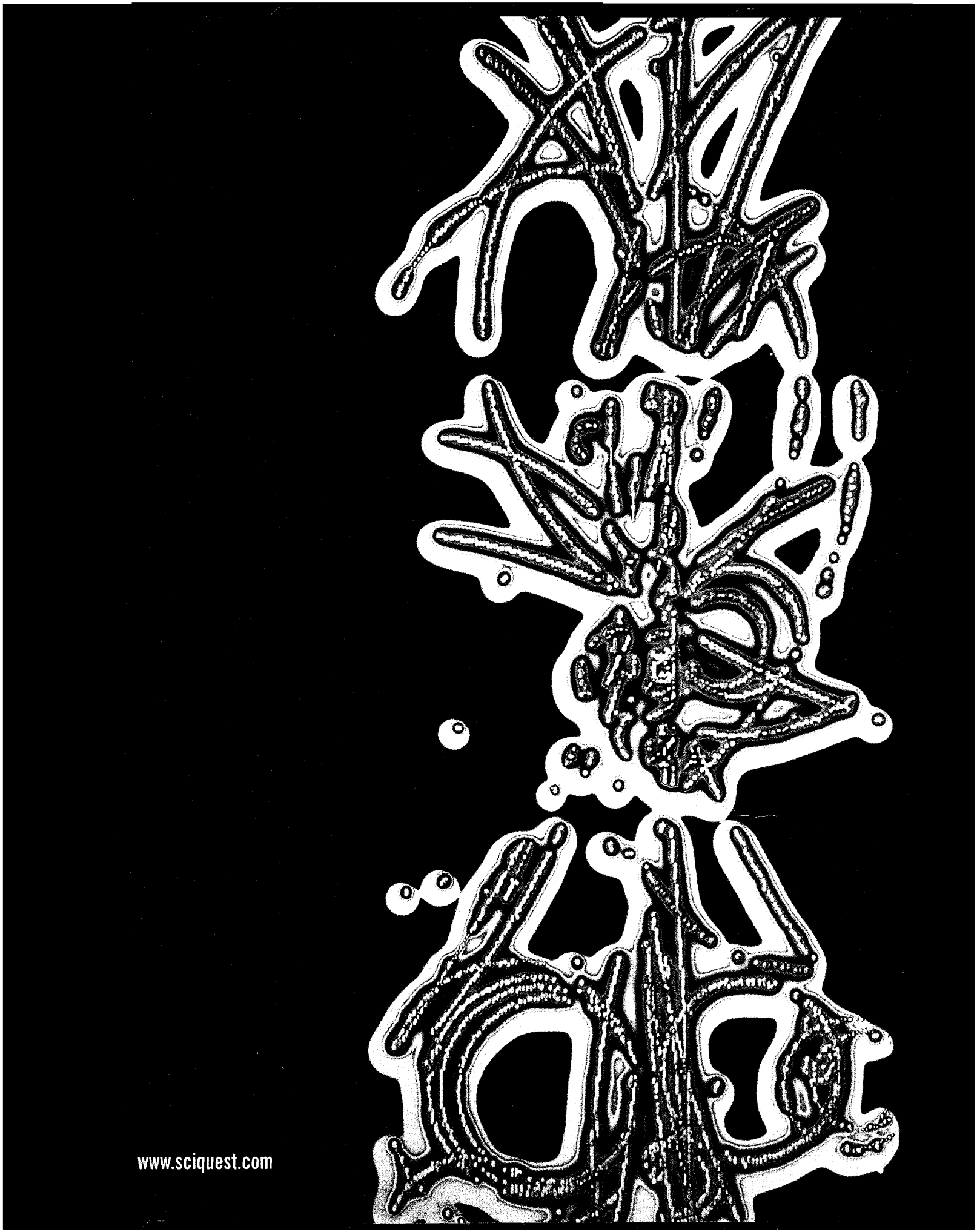

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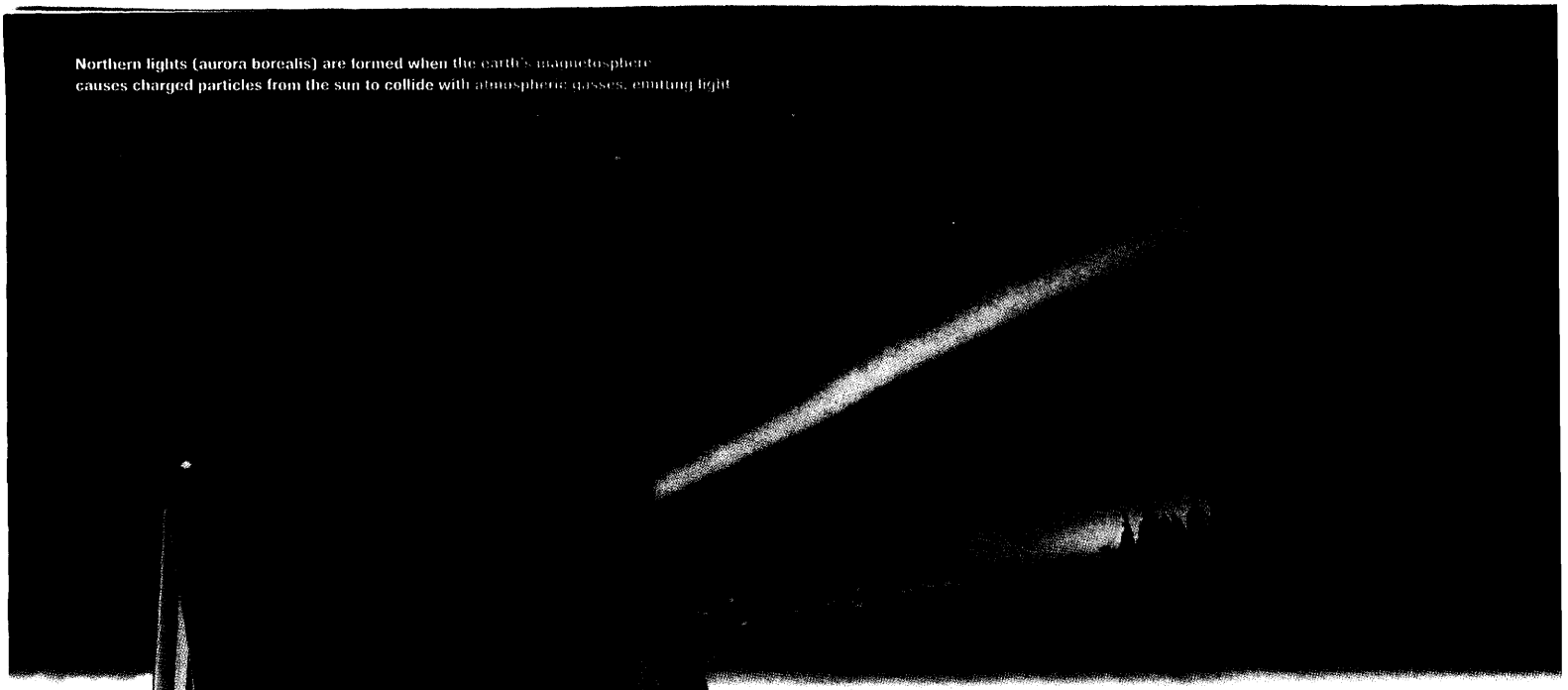

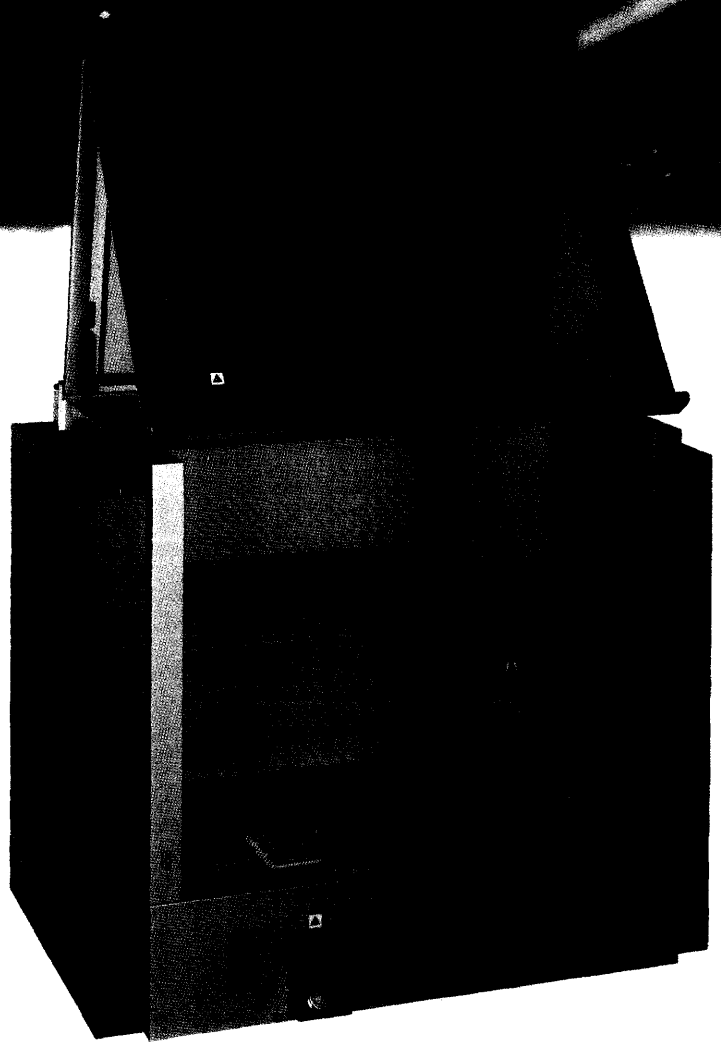

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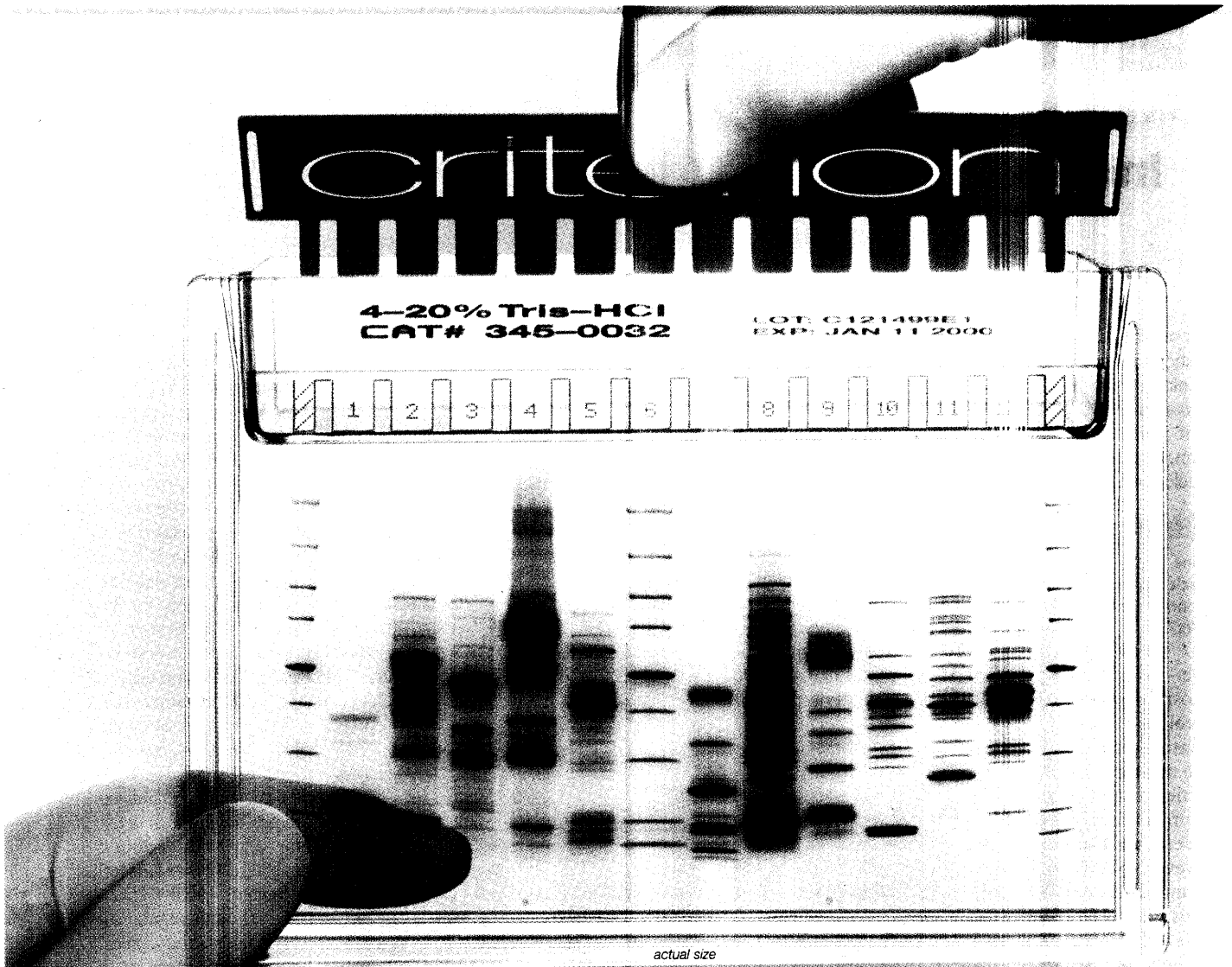

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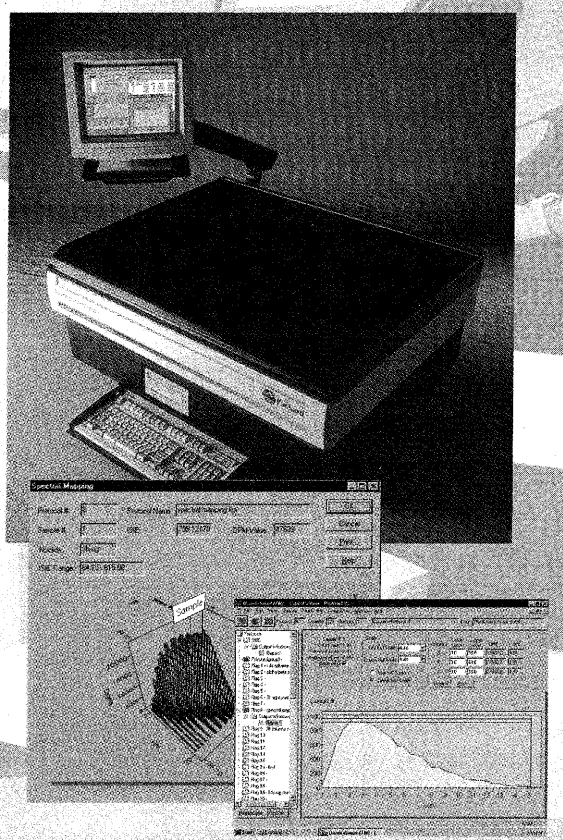

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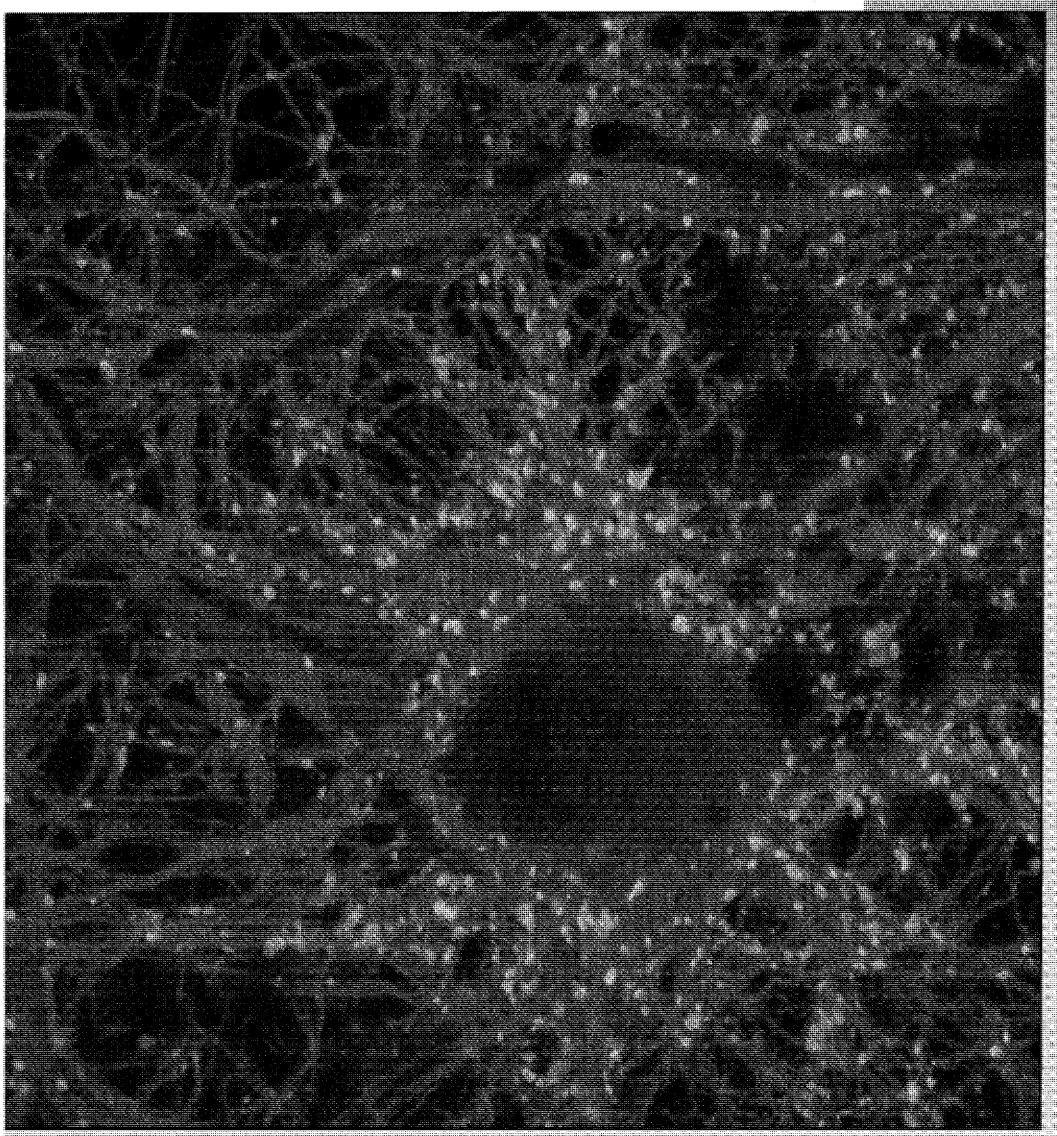

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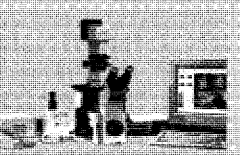

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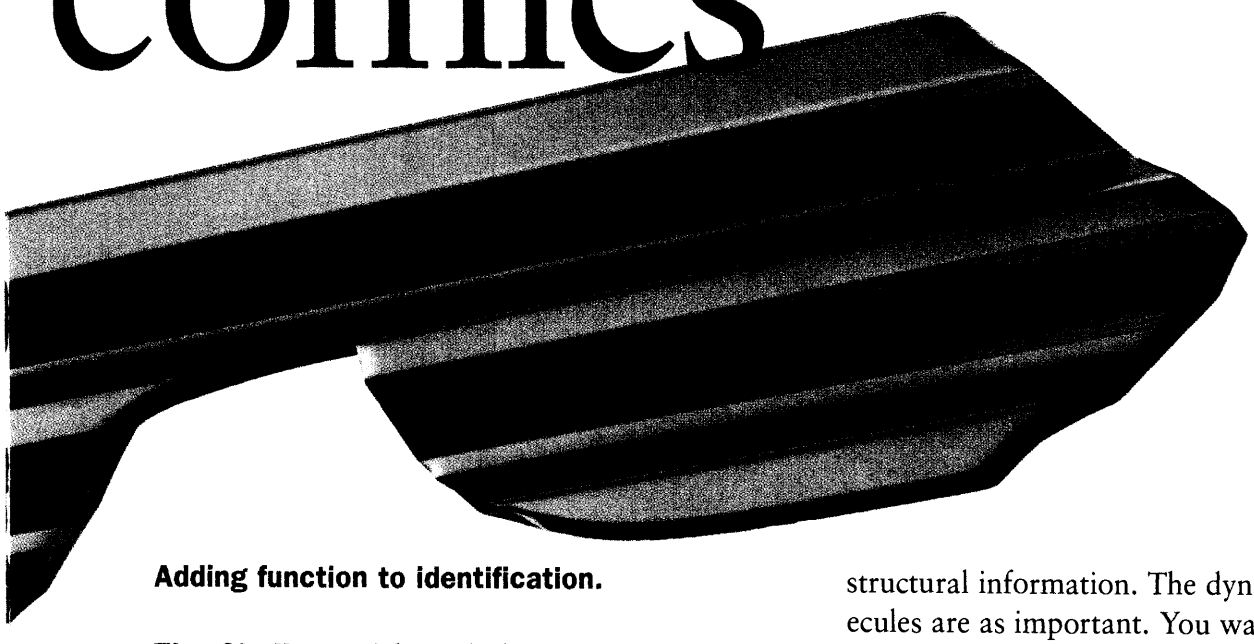

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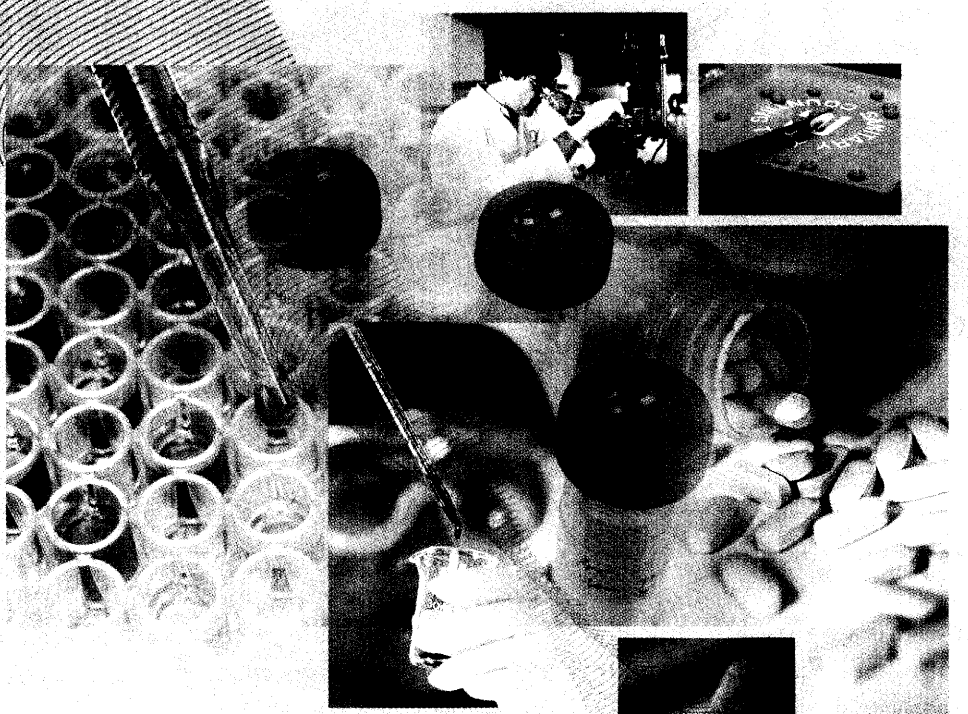

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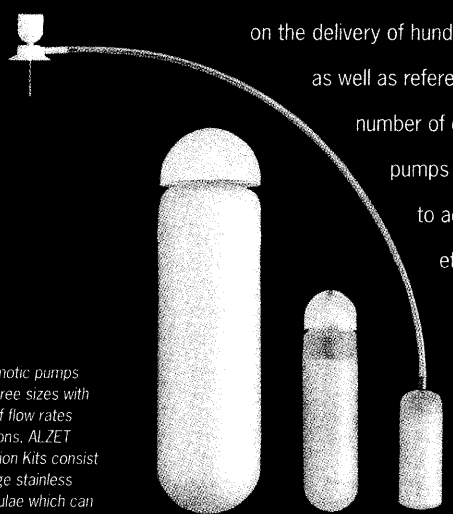

Fig. 2

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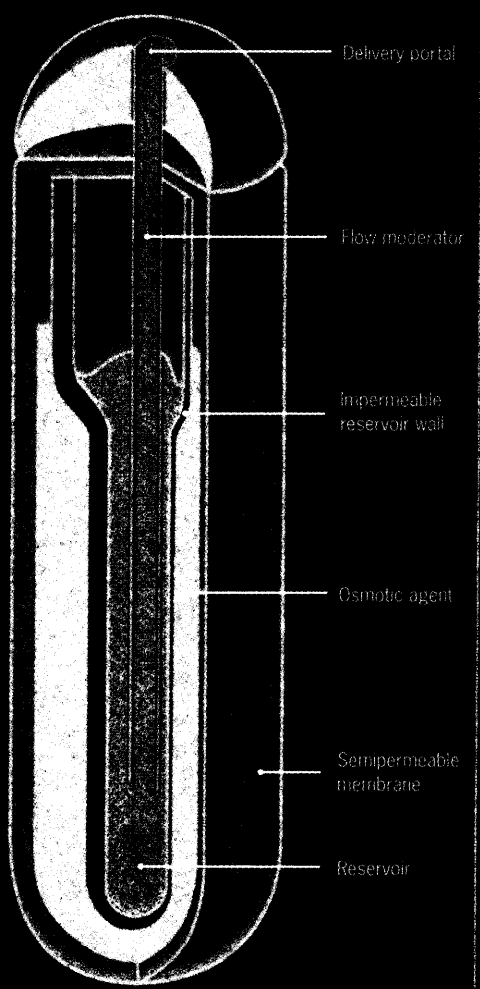

Fig. 1

The ALZET pump operates as interstitial fluid is attracted into the pump by the osmotic layer at a rate limited by the outer, semi-permeable membrane. As the osmotic layer hydrates, it compresses the flexible reservoir, which expels drug from the delivery portal of the pump.

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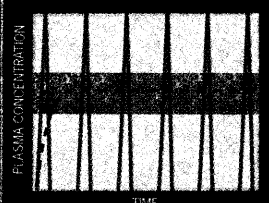

Eliminate Fluctuations in Plasma Drug Concentration

Fig. 3

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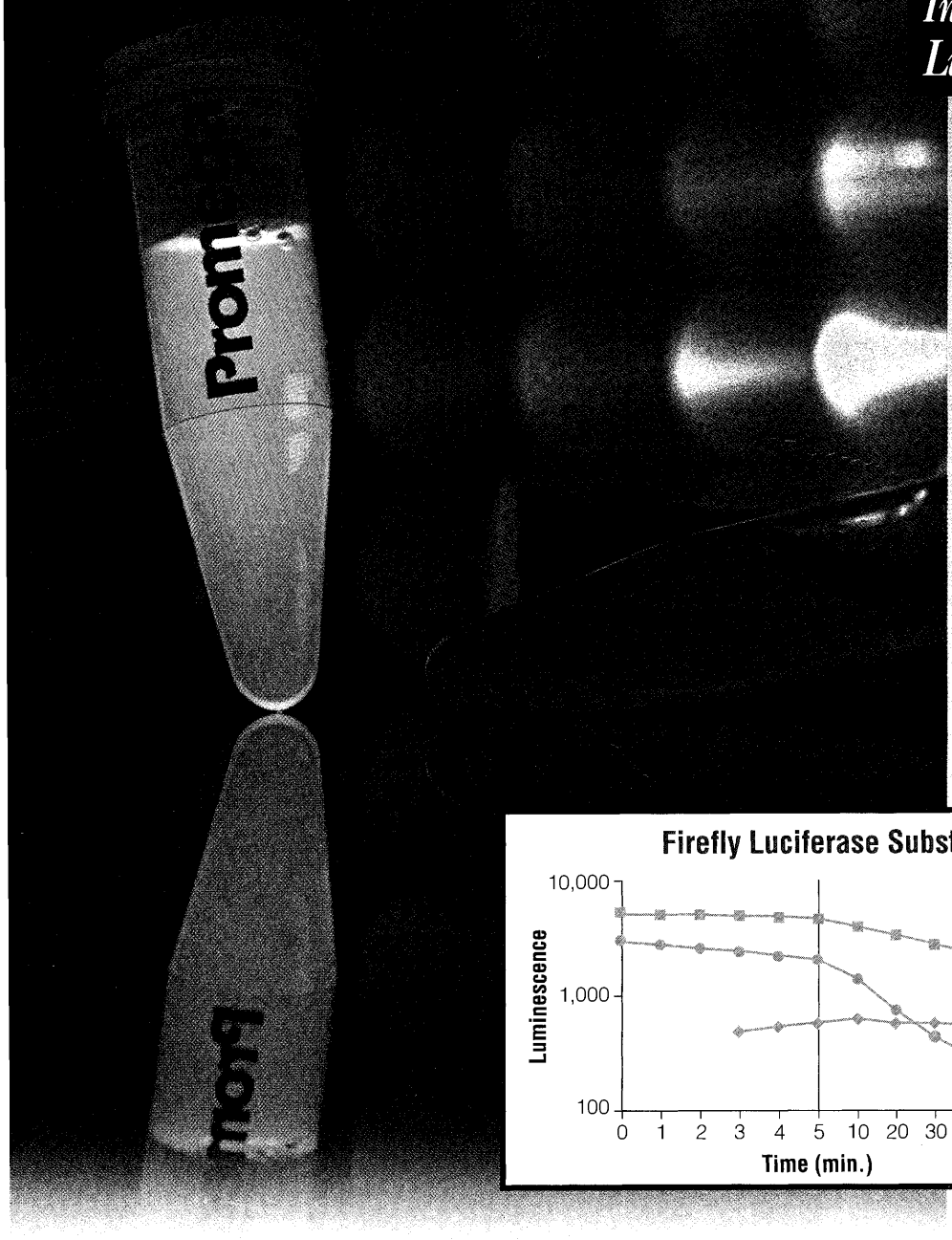

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