AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

SCIENCE

28 MAY 1993 $6.00
VOL. 260 • PAGES 1209–1396

AIDS

THE UNANSWERED QUESTIONS

Takeda

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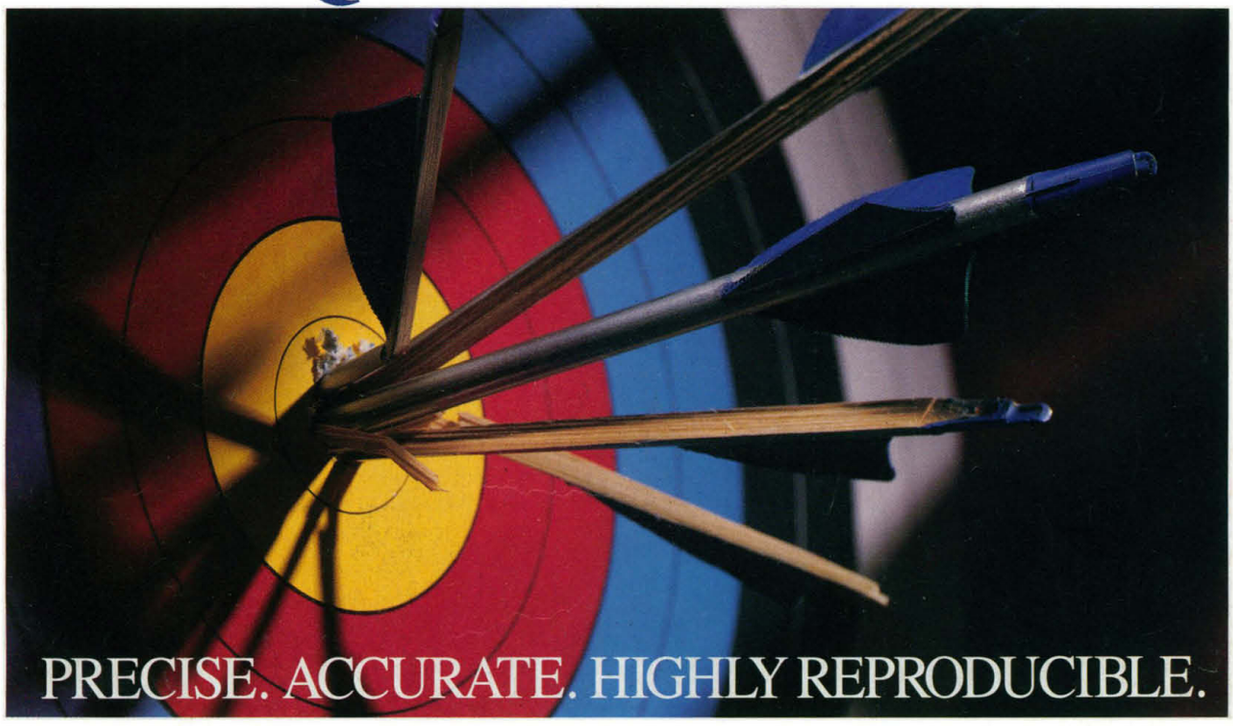

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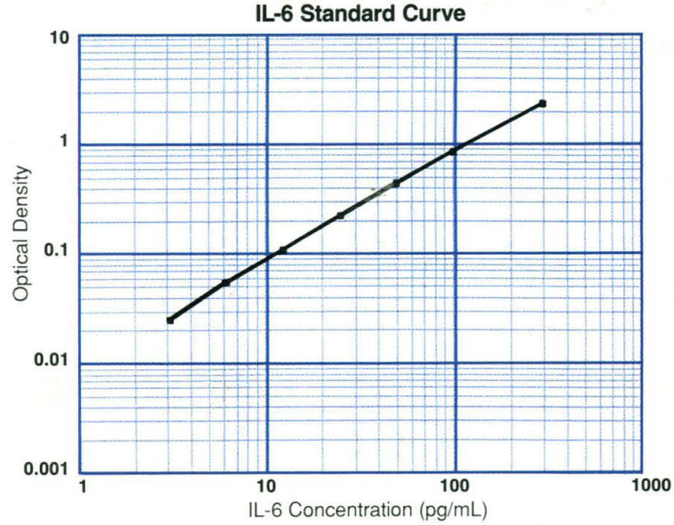

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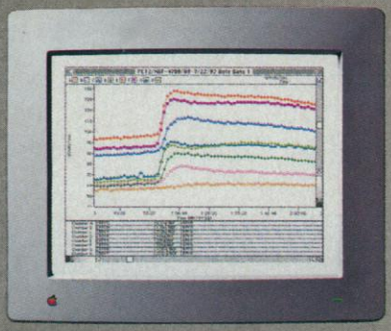
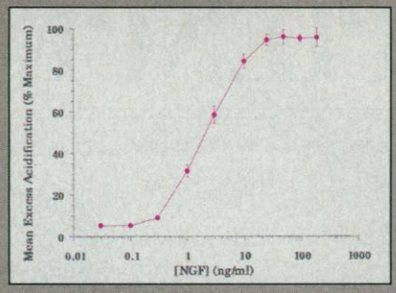
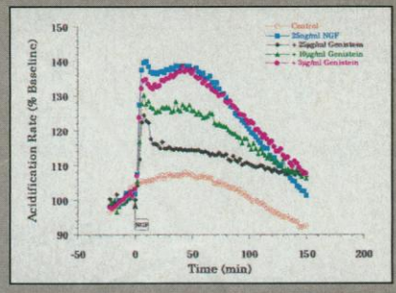
NGF



1 Real-time acidification rate data showing the response of PC12 cells to a 12 min. exposure to nerve growth factor (NGF:0.1-200ng/ml).

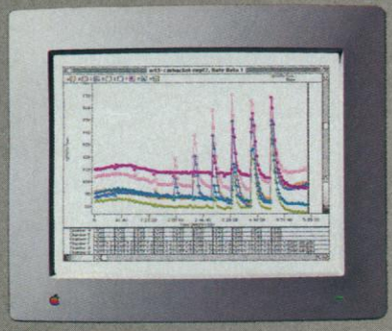


2 Dose response of PC12 cells to NGF. Each point represents data from 7 separate experiments. Calculated EC_{50} value for NGF was 1.9 ± 0.7ng/ml (~152 ± 50pM) ($\bar{x}$ ± S.E.M.).

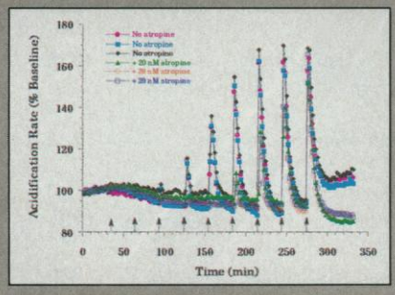


3 Dose dependent inhibition of NGF (25ng/ml) response by tyrosine kinase inhibitor, genistein (3-25μg/ml).

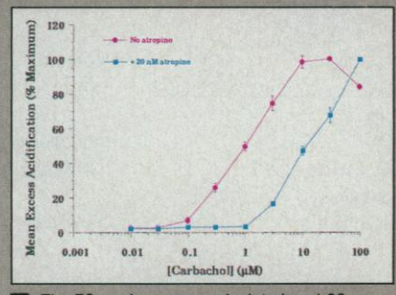
CARBACHOL



1 Real-time acidification rate data demonstrating stimulation of CHO cells transfected with muscarinic M_1 receptor. Increasing doses of carbachol (10nM-100μM) given in presence and absence of 20nM atropine.



2 Data from previous figure expressed as percentages of the basal acidification rates before initial addition of carbachol.



3 The EC_{50} values were calculated as 1.00 ± 0.08μM for carbachol alone and 11.50 ± 0.09μM for carbachol in the presence of 20nM atropine ($\bar{x}$ ± S.E.M.;n = 3).

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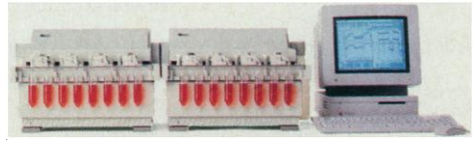

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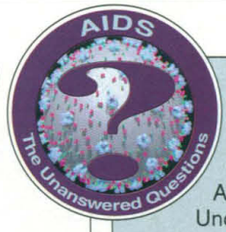
AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

1233

Fish ear stones tell age-old tales

NEWS



AIDS: THE UNANSWERED QUESTIONS

SPECIAL NEWS REPORT

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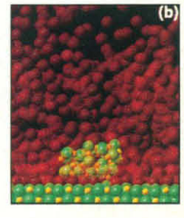
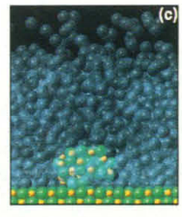
COVER

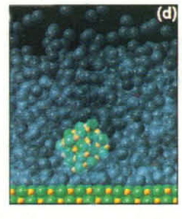
All of science is driven by unanswered questions, but in AIDS research 10 years after the discovery of the AIDS virus, there are many more questions than answers. In a special section beginning on page 1253, *Science* offers several different views of the most important questions in the field, from a survey of 150 AIDS investigators to provocative views from leading researchers. The only remaining question is: When will there be answers?

1304

Cushioned clusters







◩ Indicates accompanying feature

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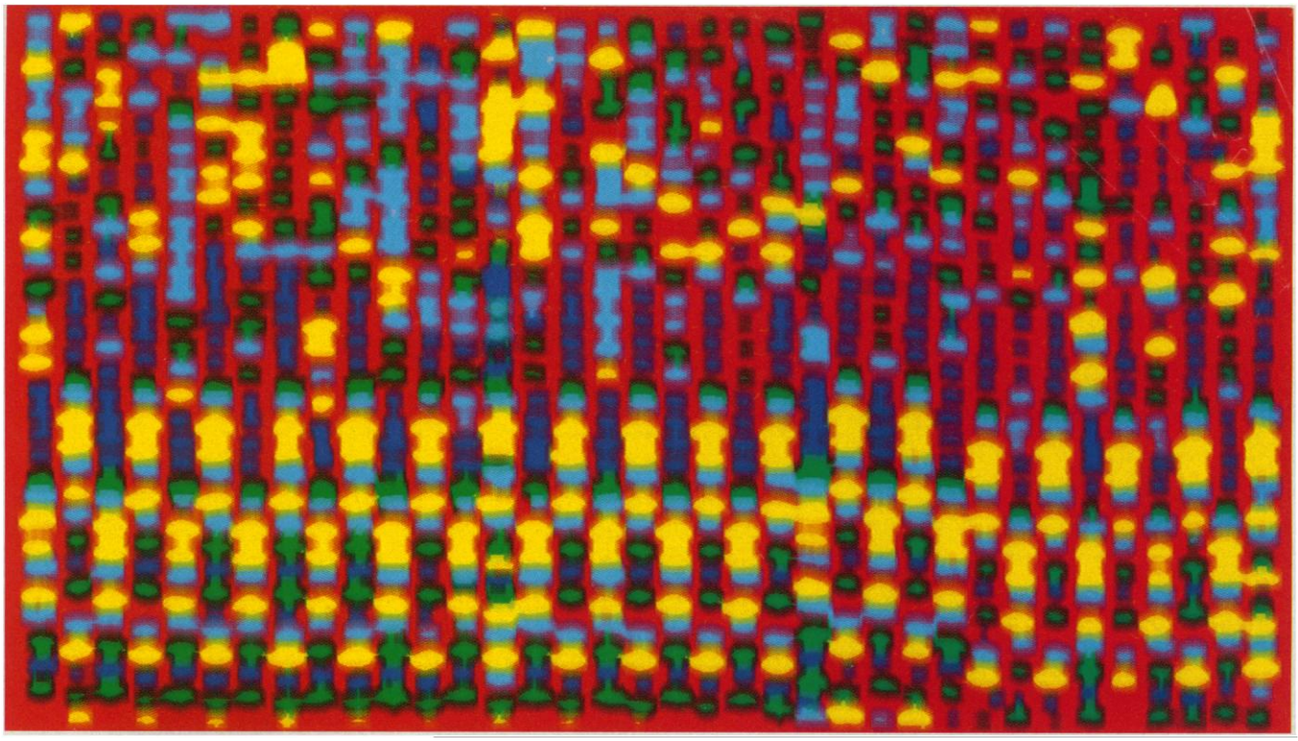
■ The American Association for the Advancement of Science was founded in 1848 and incorporated in 1874. Its objectives are to further the work of scientists, to facilitate cooperation among them, to foster scientific freedom and responsibility, to improve the effectiveness of science in the promotion of human welfare, to advance education in science, and to increase public understanding and appreciation of the importance and promise of the methods of science in human progress.



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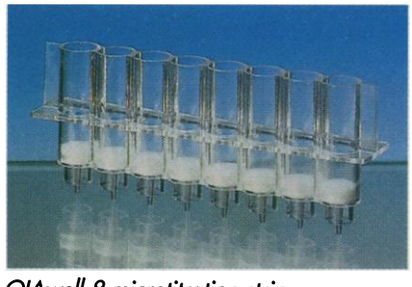

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THIS WEEK IN SCIENCE

edited by PHIL SZUROMI

Soft landings

One approach to growing materials is to consolidate nanoclusters after they are deposited onto a surface. Cheng and Landman (p. 1304) have performed numerical simulations of the dynamics of sodium chloride clusters during impact with adsorbed noble gas liquid films. For a liquid neon film, the cluster transfers energy efficiently to the cushion layer, leading to a controlled soft landing. For impacts on a higher density film of liquid argon, the cluster slows abruptly and is rapidly heated, with subsequent melting and fast cooling by argon evaporation. Such impact-processed clusters might be useful for the controlled growth of nanophase materials.

Polysaccharide synthesis

Chemical synthesis of peptides and oligonucleotides usually takes advantage of anchoring the polymer to a solid-phase support so that reactions take place at only one end of the chain. Danishefsky *et al.* (p. 1307) have developed solid-phase methods for oligosaccharide synthesis, which is complicated by the formation of stereospecific bonds at one to five hydroxyl sites. They eliminate several problems by using glycals to direct the chemistry. The glycal is epoxidized and can then glycosylate another glycal at the appropriate hydroxyl group. Failed couplings inactivate the double bond, so interior deletions are avoided.

New iron phase

Earth's liquid outer core and solid inner core are composed primarily of iron. Knowledge of the phase diagram of iron at high pressures and temperatures is key to understanding the composition and formation of the core. Saxena *et al.* (p. 1312) present experimental evidence for the existence of a previously unknown iron phase, which they call the β phase. Its structure is unknown, but it is stable at higher temperatures than the ε phase (hexagonal close-packed), which was generally thought to form the solid core.

Polycrystalline films approach natural diamond

For electronic applications under extreme conditions, diamond offers numerous advantages, but single-crystal diamond films are expensive. Plano *et al.* (p. 1310) describe how chemical vapor deposition can be used to generate lower cost polycrystalline diamond films that overcome their main limitation as a semiconductor material, namely, their low carrier mobilities. Optimization of plasma deposition conditions have allowed high growth temperatures to be used and have increased grain size and decreased impurities. The carrier mobilities and lifetimes approach that of the highest quality single crystals of natural diamond.

Tumor suppressor identified

Von Hippel–Lindau (VHL) disease is a dominantly inherited syndrome that predisposes individuals to multiple cancers, including renal cell carcinomas. Previous work has shown that the VHL gene behaves as a tumor suppressor and maps to chromosome 3p25-p26. Latif *et al.* (p. 1317; see news story by Travis, p. 1233) have now identified the causative gene by characterizing deletions in VHL families that showed coincident transmission with the disease. The VHL gene, which also appears to be disrupted in some sporadic renal cell carcinomas, is evolutionarily conserved, and encodes an acidic repeat domain found in a trypanosome surface membrane protein.

Avoiding detection

Viruses are mainly detected by the immune system through major histocompatibility complex (MHC) class I antigens, which bind to viral peptides. Many viruses reduce MHC class I expression after infection, but Howcroft *et al.* (p. 1320) show that HIV-1 dramatically decreases expression by repressing class I promoter activity. Surprisingly, deletion constructs mapped this repressive effect to a transcriptional activator, the Tat protein. Cotransfection experiments showed that the spliced, or two-exon Tat protein, effects this repression but that the one-exon Tat protein has only a minor effect.

Runaway recombination

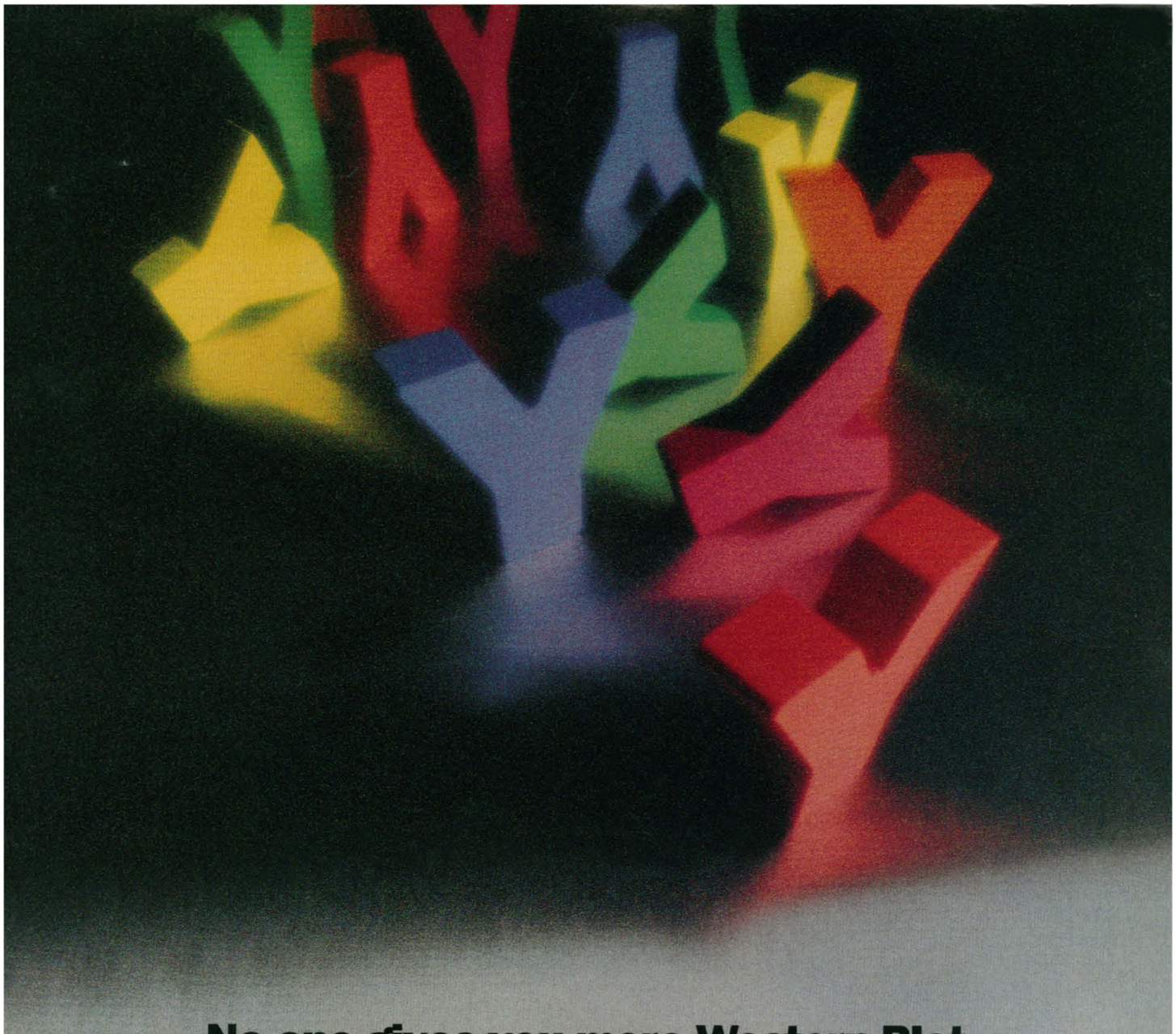
Defects in genetic recombination are thought to underlie ataxia-telangiectasia (A-T), an autosomal recessive disease characterized by neurological degeneration, immune dysfunction, and a high risk for cancer. Meyn (p. 1327) studied the rate of recombination in normal and A-T human fibroblasts. Although recombination rates were similar for both cell types for rearrangements between chromosomes, intrachromosomal recombination rates were 30 to 200 times higher for the A-T cells. One possible cause for this increase could be defects in damage-sensitive checkpoints in the cell cycle that would allow DNA replication to finish before repair processes are completed.

Free at last

The lymphoid-specific transcription factor Elf-1 participates in the regulation of inducible gene expression during T cell activation, even though Elf-1 is present in similar quantities in both resting and activated T cells. Wang *et al.* (p. 1330) find that the Elf-1 protein may be sequestered or inactivated in resting T cells by interacting with unphosphorylated retinoblastoma protein (Rb). Upon T cell activation, Rb is phosphorylated and Elf-1 dissociates.

Getting the signal

The molecules that couple hormone and growth factor receptors on the cell surface to activation of the guanine nucleotide binding protein Ras are proving to be remarkably similar in all eukaryotes. Chardin *et al.* (p. 1338) have cloned the human homolog of the son of sevenless protein (hSos), a putative guanine nucleotide releasing factor (GRF) for Ras, from *Drosophila*. They found that hSos enhanced guanine nucleotide exchange by Ras and thus appears to function as an activator of Ras. The hSos protein could substitute for the Ras-GRF CDC25 in yeast and can bind to GRB2, a so-called adaptor protein that also binds to activated growth factor receptors. All of the molecular components required to transmit an extracellular signal to Ras have now been identified.



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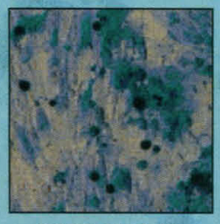
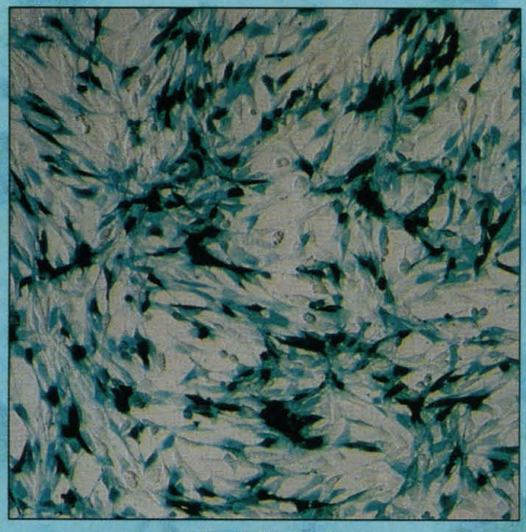


BHK-21 Cells



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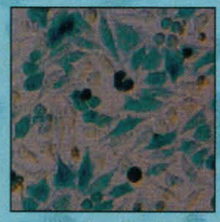
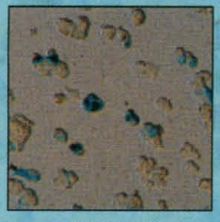
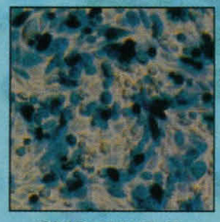


HeLa Cells



PC12 Cells



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LIPOFECTAMINE is an innovative product (patent pending) which may be used for stable or transient transfections and can be used in the presence of fetal bovine serum. It is pre-formulated so it is easy to use, and it has a long shelf life at 4°C. Best of all, LIPOFECTAMINE is from Life Technologies, the makers of LIPOFECTIN and the pioneers in transfection technology. So try LIPOFECTAMINE and watch your transfection efficiencies scale new heights. You'll even feel good about getting the blues!

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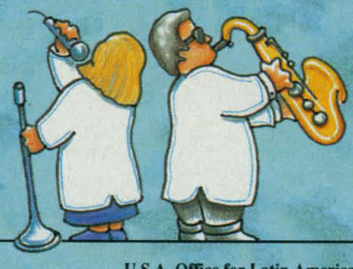

Photographs depict ß-galactosidase expression of cells transfected with pCMV ß-gal DNA and LIPOFECTAMINE Reagent.

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1. Hawley-Nelson, P., Ciccarone, V., Gebeyehu, G., Jessee, J. and Felgner, P., (1993) *Focus® 15*, in press.

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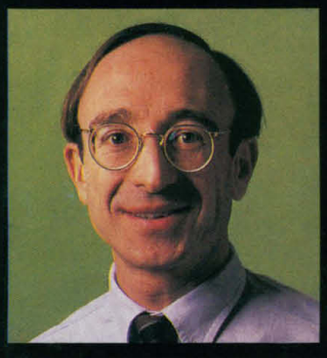
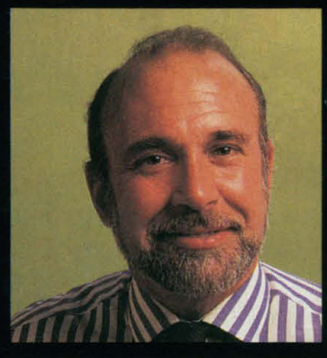
Nikon asked inverted microscope users to make a wish list.

"Our microscope is used by a number of people. I wish the height of the eyepiece tube could be adjusted for each of us."

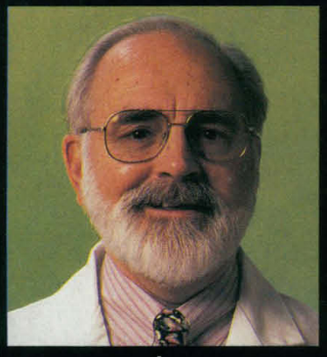


"With all the new fluorochromes available, I wish there was a quick-change multiple filter block system."

"High resolution DIC has become so much more important, I wish there was an easily set-up high N.A. DIC condenser."



"To accommodate extra-large chambers and micromanipulators, I wish there was more working distance above the stage."



"I just wish someone would design an inverted microscope with patch clamping, low-light fluorescence, IVF, confocal microscopy and other advanced applications in mind from the very start."

"I wish I had a microscope with more optical ports for simultaneous imaging."

"I'm at my microscope for hours at a time. I wish the controls were further forward so I could work more comfortably."

"For really critical specimen handling, my wish would be for a very low, very large, super stable stage."

Wish no more ...

Introducing the new Diaphot®. It's everything you've wished

Controls are far forward for maximum comfort.

Easy access to nosepiece and filters: dichroic cube fixed relative to focusing nosepiece.

0.85 and 1.4 N.A. DIC condensers for high resolution, high magnification microscopy.

Expanded space above stage and tiltable 100W illumination pillar for large specimens and micromanipulation.

Improving upon the world's finest inverted microscope was no easy task. But, after asking hundreds of users for their suggestions, we did it. The new Diaphot® features even brighter images, greater flexibility, more imaging capability, stability and comfort than its renowned predecessor, without sacrificing any of its legendary optical performance.

The new Diaphot is designed to suit applications from basic microscopy to UV fluorescence, *in-vitro* fertilization, laser scanning confocal microscopy, micromanipulation, patch clamping, microphotometry and high resolution video microscopy.

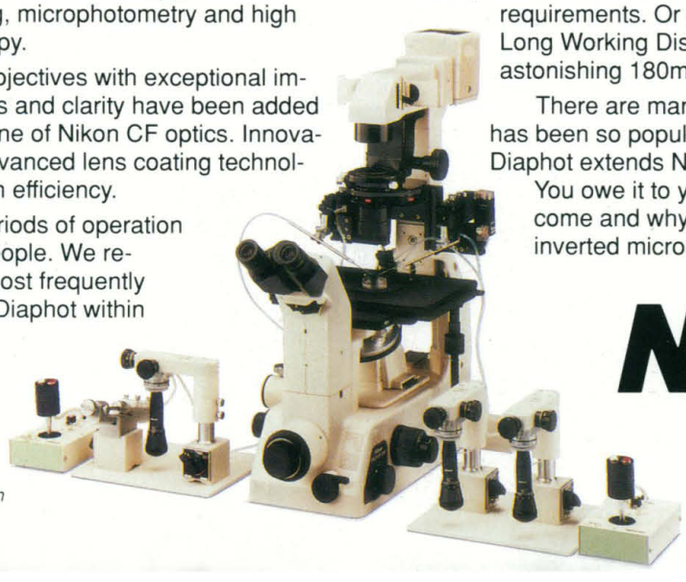
Important new CF® objectives with exceptional image sharpness, brightness and clarity have been added to the already extensive line of Nikon CF optics. Innovative optical design and advanced lens coating technology enhance transmission efficiency.

Comfort over long periods of operation was important to many people. We responded by placing the most frequently used controls of the new Diaphot within easy reach and by lowering the front and rear mounted stage for easier specimen handling and increased stability. In addition, the new Diaphot features an ergonomic height-adjustable eyepiece tube and 1μ-sensitive coaxial focusing control with refocusing preset.

The new Diaphot also addresses users' needs for versatility and expandability. A new "systems condenser" lets you select working distance, DIC prisms and phase contrast to suit your individual microscopy requirements. Or choose the new SLWD (Super Long Working Distance) condenser for an astonishing 180mm of specimen clearance.

There are many reasons why the Diaphot has been so popular for so many years. The new Diaphot extends Nikon's tradition of excellence. You owe it to yourself to see how far we've come and why the new Diaphot is the finest inverted microscope available today.

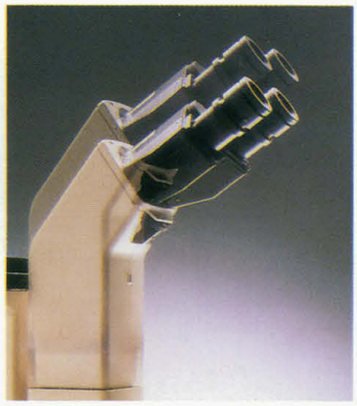
Nikon



Designed with video microscopy, patch clamp and micromanipulation in mind. The DC power supply eliminates electronic noise.

for!

Multiple image ports include side, front, and optional trinocular eyepiece tube.



Height of BT1 eyepiece tube can be adjusted for user comfort.

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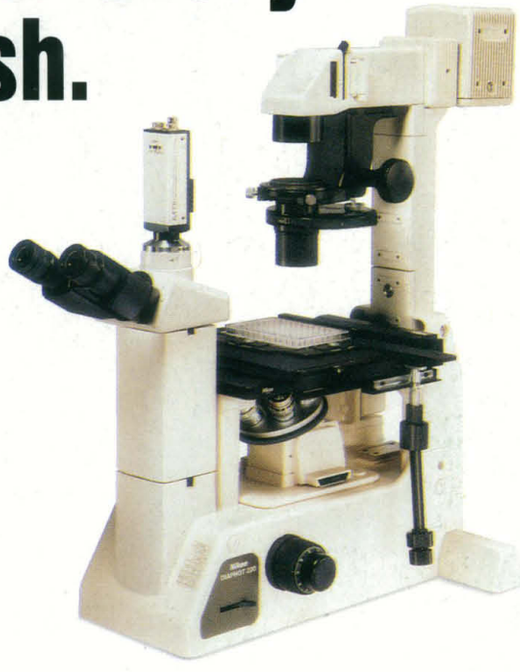
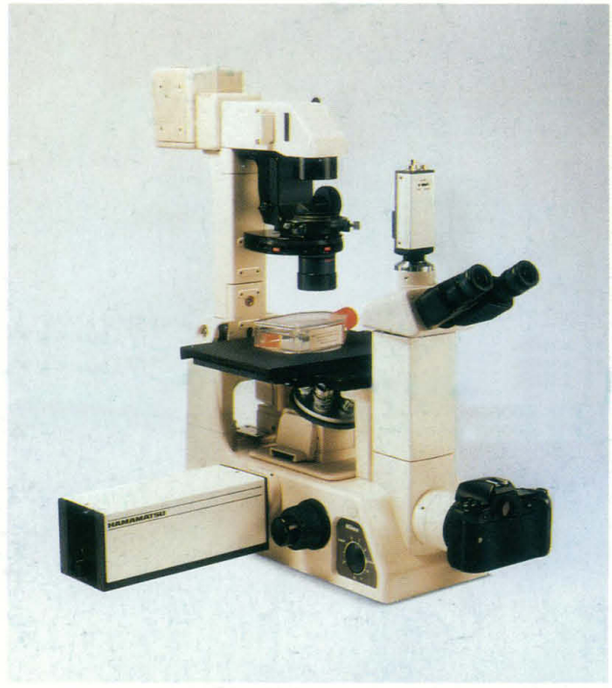
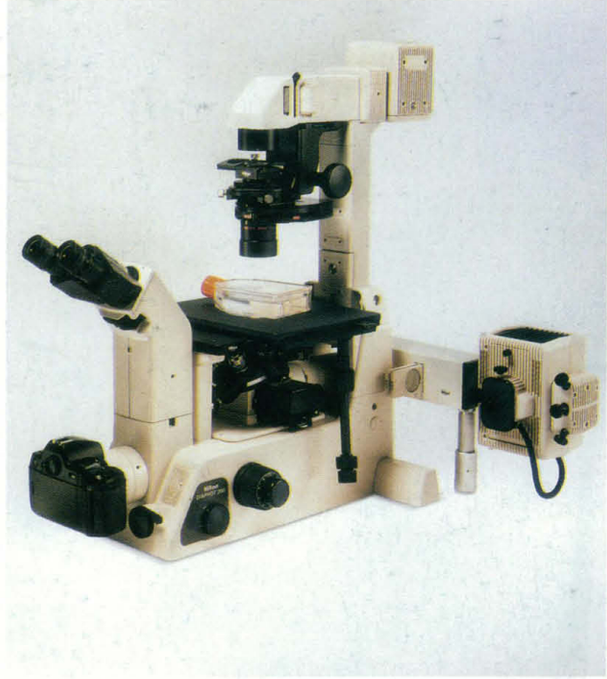


The new Diaphot microscopes, Diaphot 300 and Diaphot 200, are designed to suit the widest possible range of microscopy applications. You can customize your system for your specific needs by adding from a huge selection of CF® optics and accessories. Call today and discover how much more a new Diaphot will do for you.



With multiple optical ports, Diaphot 300 can be configured for video, microphotometry and 35 mm photomicrography simultaneously.



No other microscope can match the new Diaphot for exceptionally brilliant, high resolution epi-fluorescence over the broadest spectrum.

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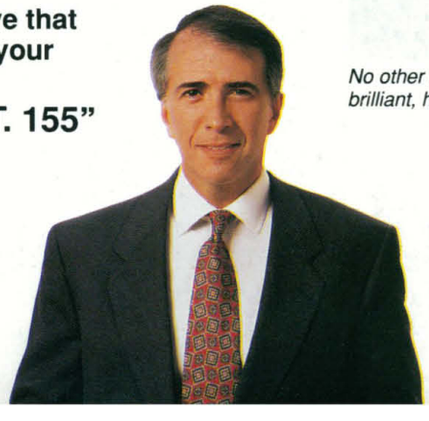

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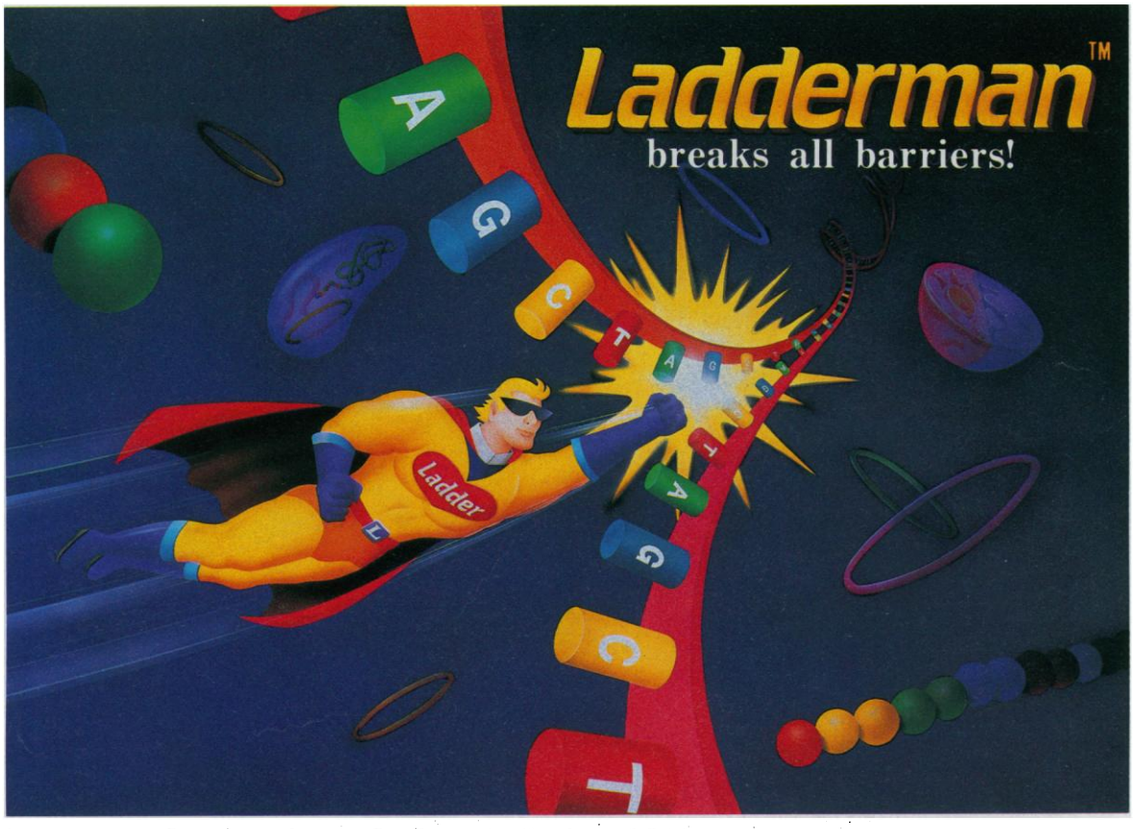

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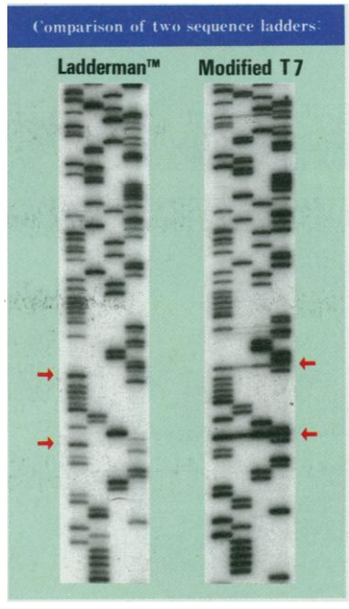

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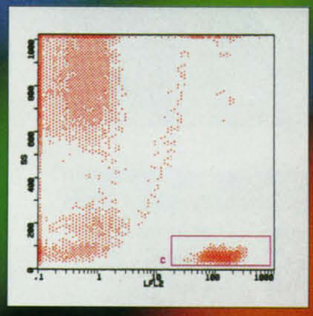

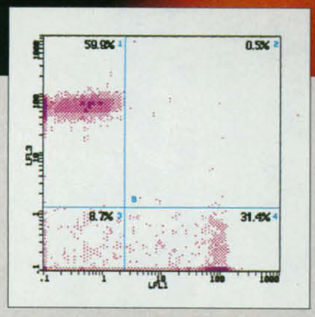

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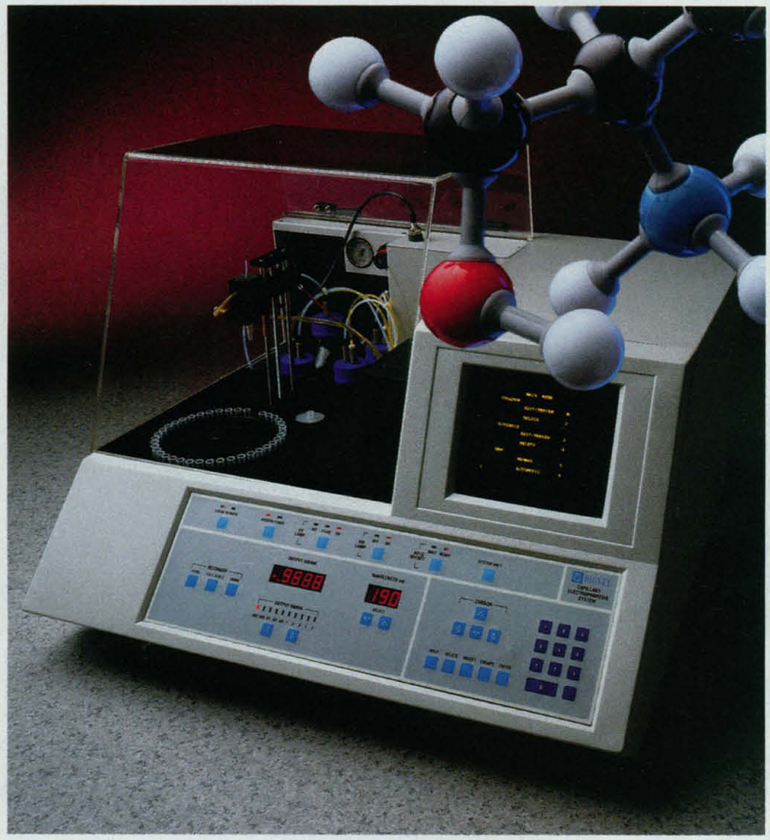
Seven precise reasons why your first capillary electrophoresis system should be a Dionex.



Get it right the first time.

Not all capillary electrophoresis systems are created equal. Which one should you get? The one that gives you the greatest flexibility and value.

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2. Three automatic sample injection methods let you match the sampling technique to the sample—*any* sample.

3. Our smart, 40-position autosampler runs your samples in *any* order. The system automatically rinses and refills vials and capillaries at each run for reproducible results. It also changes buffers—even during a run—*and* automates methods development.

4. Two detection modes are standard—UV/Vis with fiber optic-based remote cell for low noise *and* fluorescence with photo multiplier tube for femtomole sensitivity.

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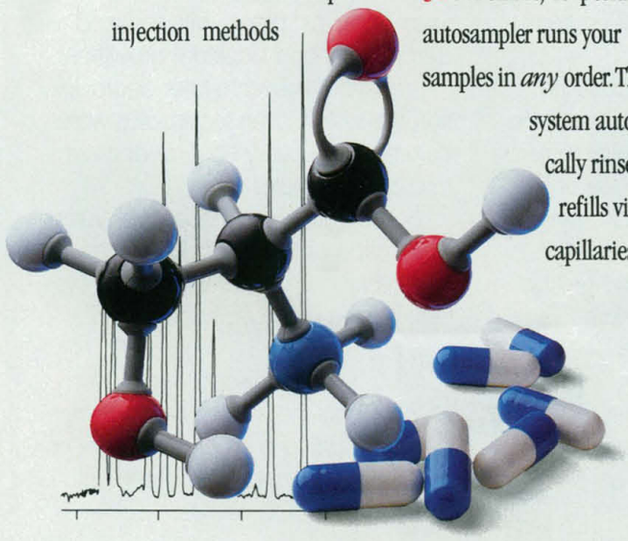
7. Committed support by *the leader* in polar and ionic separations—from applications expertise and responsive service to complete automation capabilities.



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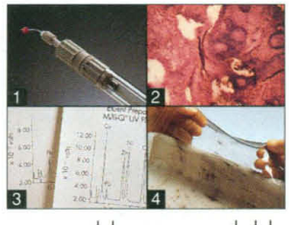
There Are Places You Expect To Find Water Hazards. Your Lab Shouldn't Be One Of Them.

Water hazards on a golf course can cost you a couple of strokes. In a lab, however, water hazards in the form of ions, pyrogens and organics can cost you months of research work.



That's why it's critical for you to have a water purification system that removes contamination instead of one that contributes to it. If you don't, you could end up like one of these facilities:

1. A lab doing protein purification with HPLC found that endotoxins in its water system contaminated proteins.

2. Organics in another facility's water system kept mammalian cells from growing in defined medium.

3. A semiconductor plant testing for copper had its chromatographic results ruined by contamination in their water system.

4. In yet another lab, phosphates being used to clean the water system got into the water used for polyacrylamide gels, rendering them useless.

In each of these cases, when the lab switched to a Milli-Q® Plus Water Purification System, all their problems disappeared.

That's because the Milli-Q Plus system delivers the highest quality water available: 1.5 liters per minute at 18 megohm and < 10ppb TOC (with RO pretreatment).

To ensure you're always getting high quality water, the system tells you when the filter module needs changing.

And unlike other systems, changing our module is easy. Instead of separate bowls, our QPAK™ purification module has an all-in-one design that takes hardly any time to change out and prevents you from ever having to come in contact with wetted surfaces.

Also, because we don't use separate bowls, the system has virtually no hold-up volume. This results in faster flush-ups, along with reduced extractables and bacterial growth.

To further prevent water degradation, the system even recirculates water automatically every hour for approximately five minutes.

So beware of less expensive water purification systems that claim to do as good a job as the Milli-Q Plus system: They may prove hazardous to your work.

For additional information about the Milli-Q Plus system, including a brochure, technical bulletins and data sheet, call 1-800-225-1380.

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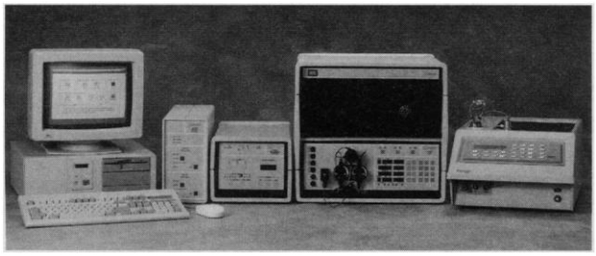
BIO-SOLUTIONS

Number 5

An Update on the State of the Art in Separations Technology

Exciting new technology for carbohydrate analysis



The GlycoStation™ features full automation, complete system control, specialized software and standards.

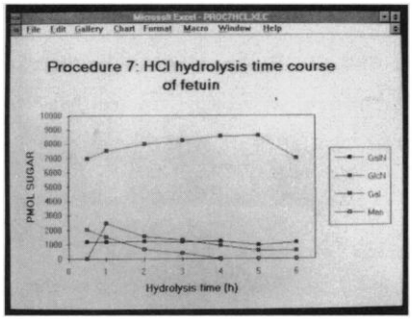
The unique GlycoStation features an interactive users' guide and intuitive software that allow new users to apply high-performance anion exchange-pulsed amperometric detection (HPAE-PAD) to carbohydrate research.

The system provides excellent resolution and sensitivity for detecting non-derivatized carbohydrates at picomole levels, and for resolving structures differing in only a single linkage position.

The GlycoStation can be fully automated, using software developed expressly for carbohydrate analysis, along with specialized analytical procedures.

The system's self-teaching user's guide and intuitive, Windows™-driven software make it possible to teach yourself carbohydrate analysis in a few weeks. Fourteen steps take you from system setup and sample prep to monosaccharide/oligosaccharide analyses. Accurate and reliable data are virtually ensured.

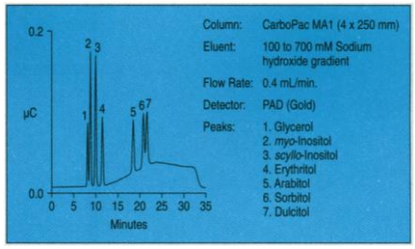
The GlycoStation is expandable with a variety of detectors and columns, including the new CarboPac® MA1 column for separating reduced mono- and disaccharides (see next column).



In addition to chromatography, the GlycoStation automatically produces easy-to-interpret graphs and charts.

A unique method for the separation of reduced carbohydrates

The CarboPac® MA1 is a high-performance anion-exchange column optimized for the separation of reduced carbohydrates commonly found in physiological fluids, reduced glycoconjugate samples and food products.



The CarboPac MA1 is optimized for reduced mono- and disaccharides. These are typical sugar alcohols found in tissues and physiological fluids.

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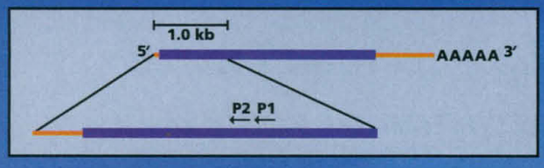
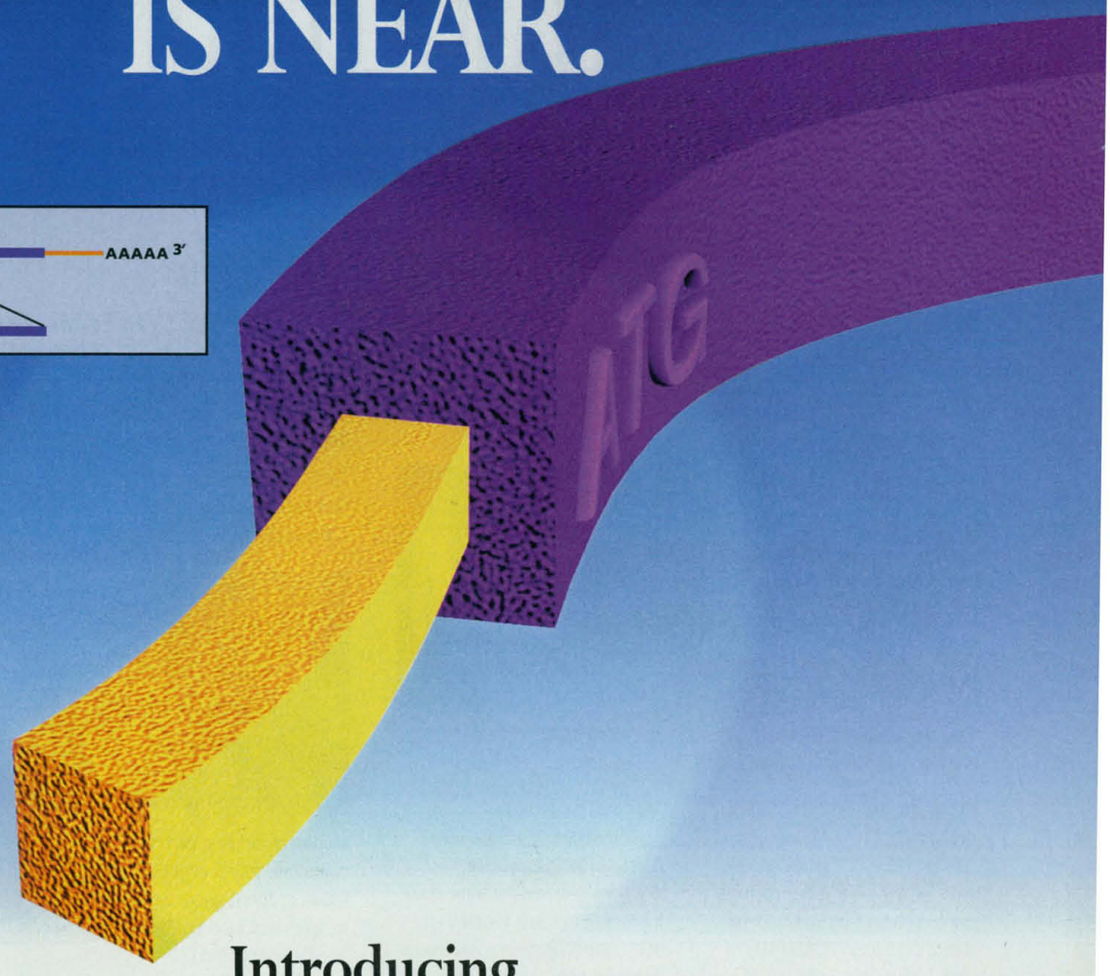


Schematic diagram of the 4.7-kb human transferrin receptor gene transcript. The locations of the nested gene-specific primers, P1 and P2, are indicated.



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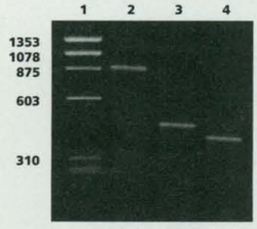

PCR amplification of the 5′ ends of the human transferrin receptor (Lane 2: 0.87 kb. Lane 3: 0.45 kb) and tissue-type plasminogen activator genes (Lane 4: 0.40 kb).

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AIDS

THE UNANSWERED QUESTIONS

If ever there were a pivotal year for AIDS research, 1993 could well be that year. It is precisely a decade since Luc Montagnier of the Pasteur Institute published the first report on the virus that is now known to cause AIDS, yet despite the high-powered arsenal of contemporary biology, there is nothing on the horizon remotely resembling a cure for AIDS. Nor is there anything like a workable vaccine.

In fact, as this special section on AIDS suggests, the more rapidly knowledge of the disease accumulates, the faster assumptions that seemed solid a year ago begin to crumble. And as solid ground disappears, scientific questions proliferate almost as rapidly as HIV itself. There are thousands of them—in vaccine work, drug research, pathogenesis studies, epidemiology, public health, and molecular biology.

To cut through that thicket of questions and focus on only the most important among them, *Science* has assembled a package combining news coverage with scientific papers. From the news team comes an overview of the crucial issues facing AIDS researchers as they were spelled out by 74 of the field's leaders in response to a survey devised by *Science*'s AIDS reporter Jon Cohen.

Offering greater depth on specific topics are six papers solicited by *Science* senior editor Barbara Jasny. In addition, the news team has previewed some of the most intriguing sessions that will be taking place at this year's International AIDS Conference in Berlin. We've also profiled four European AIDS researchers who our survey respondents told us were top contributors.

All told, we think this package offers the state of what is still very much an art: finding a way to stop HIV.

–John Benditt, Features Editor

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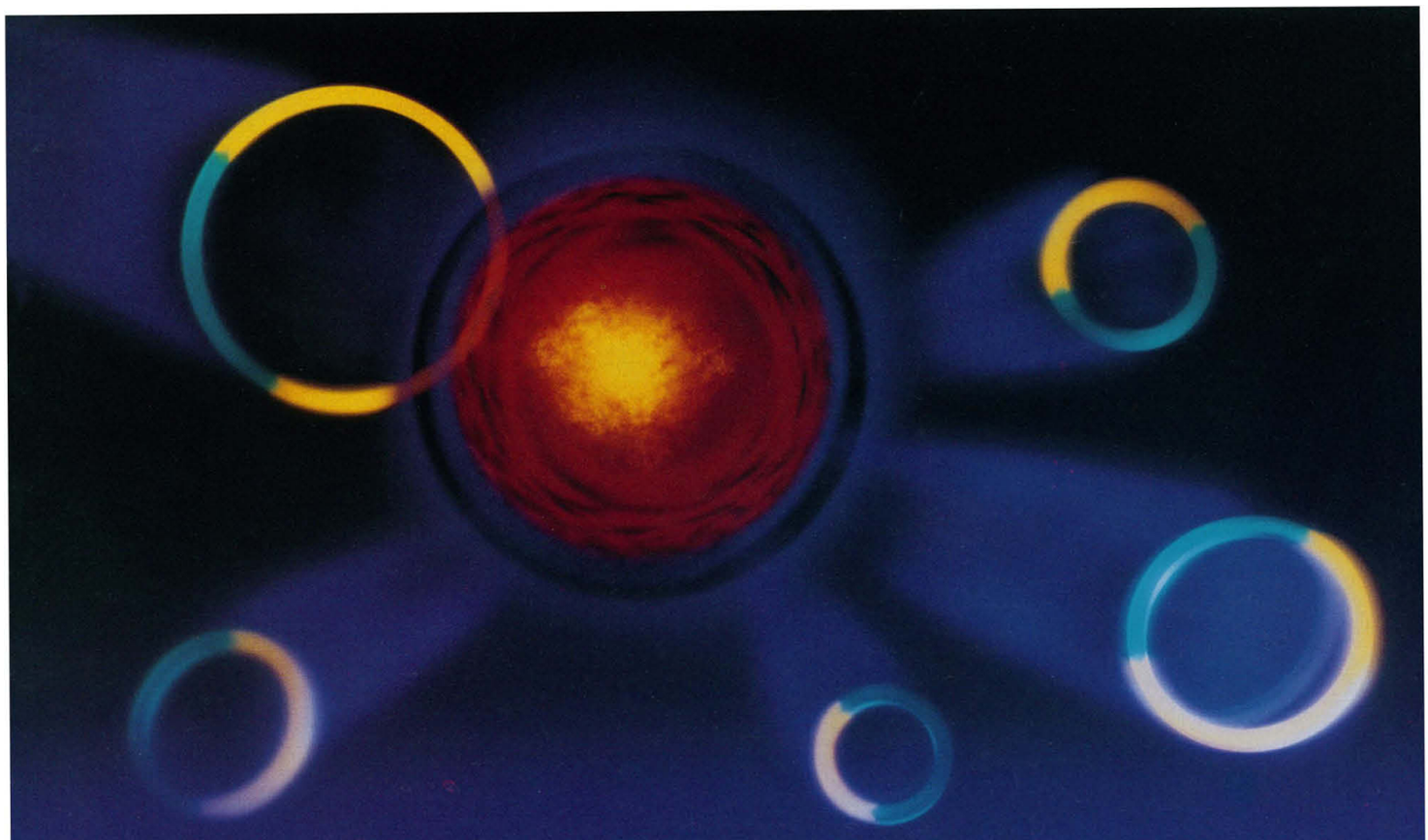

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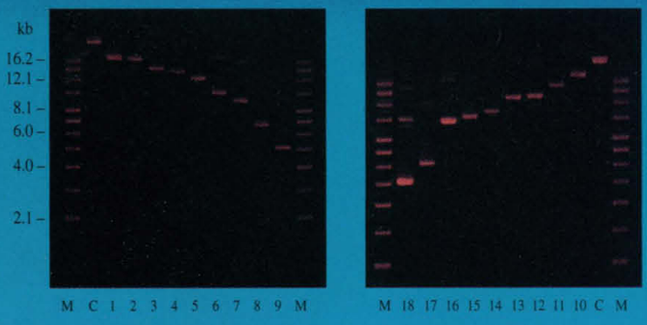

Analysis of Deletion Subclones. A 17-kb human chromosomal DNA insert in pDELTA1 (pYA50) was subjected to the DELETION FACTORY System. Representative deletion subclones recovered from sucrose/tetracycline selection *(left panel)* and from streptomycin/kanamycin selection *(right panel)* were separated by electrophoresis. Lane numbers indicate individual clones; C = pYA50, and M = GIBCO BRL Supercoiled DNA Ladder.

1. Wang, G., Berg, C.M., Chen, J., Young, A.C., Blakesley, R.W., Lee, L.Y., and Berg, D.E. *Focus® 15*, 47.

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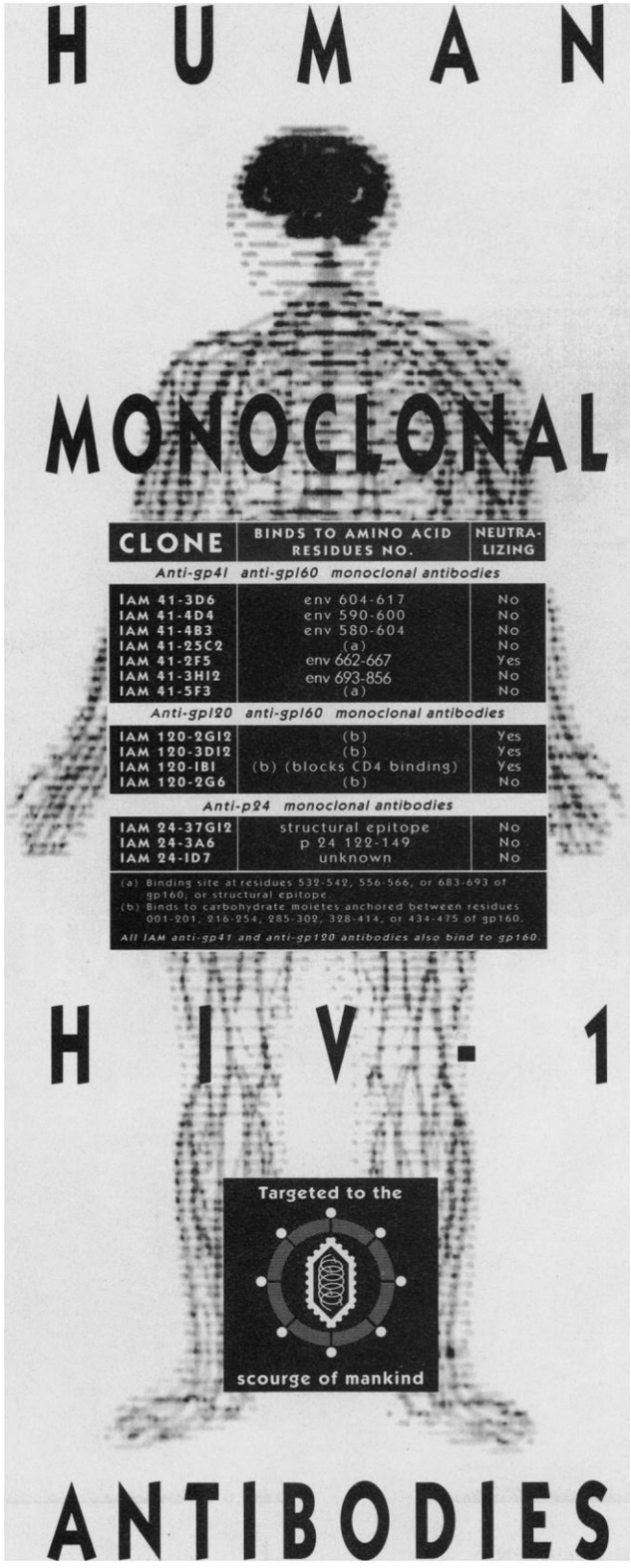

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$$pk_a = -\log k_a$$

$$E = mc^2$$

$$\frac{\partial^2\psi}{\partial x^2} + \frac{\partial^2\psi}{\partial y^2} + \frac{\partial^2\psi}{\partial z^2} + \frac{8\pi^2 m}{h^2}(E - V)\psi = 0$$

$$E = 0.76 - \frac{0.059}{2}\log_{10}\frac{(1)(1)}{(10^{-3})^2}$$

$$a^n + b^n = c^n$$

$$X_i = kP_i$$

$$\int_0^\infty \frac{a\,dx}{a^2 + x^2} = \frac{\pi}{2},\ \text{if } a > 0;\ 0,\ \text{if } a = 0;\ -\frac{\pi}{2},\ \text{if } a < 0$$

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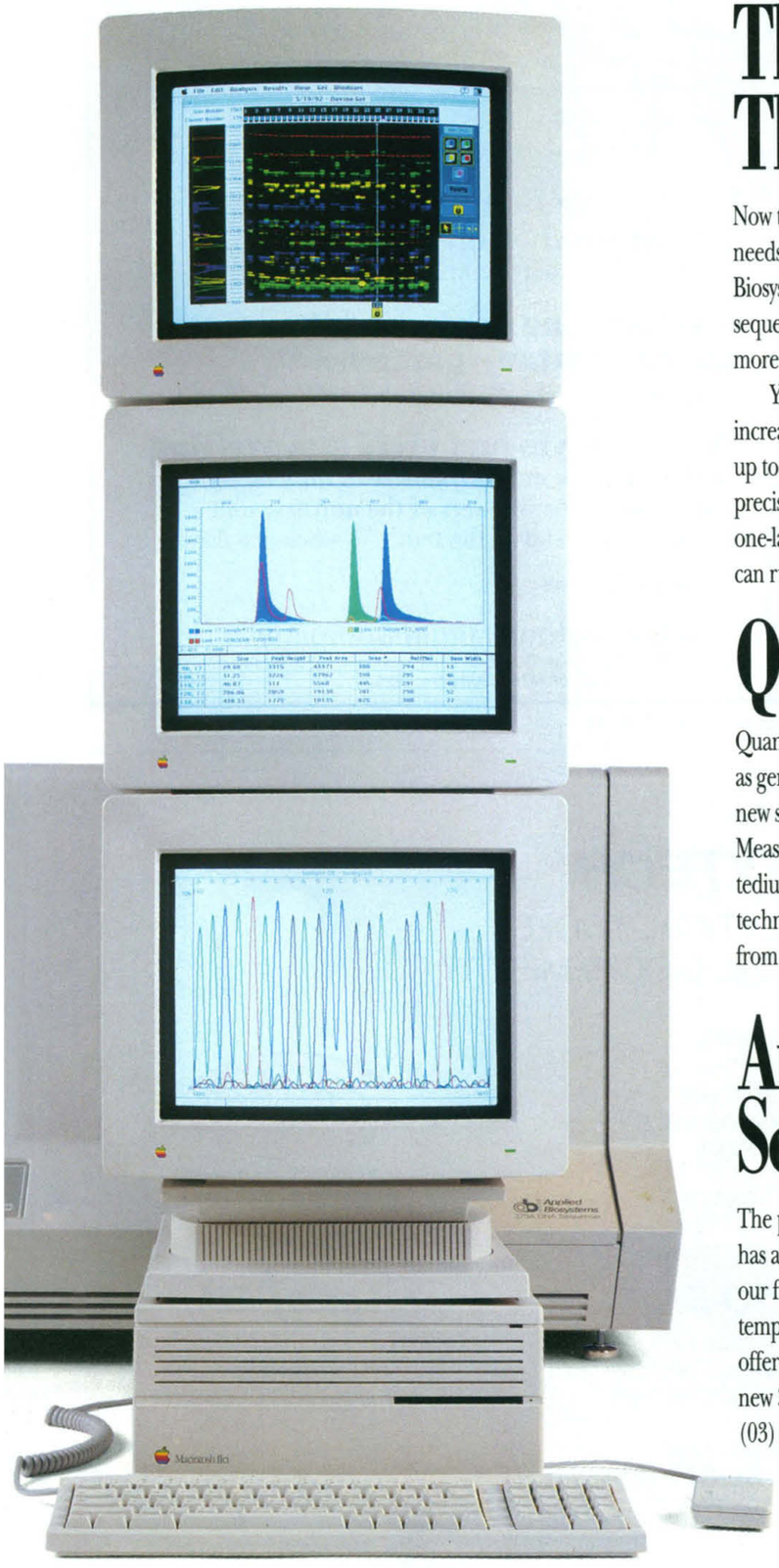

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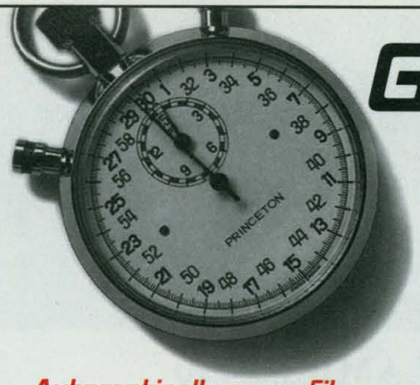

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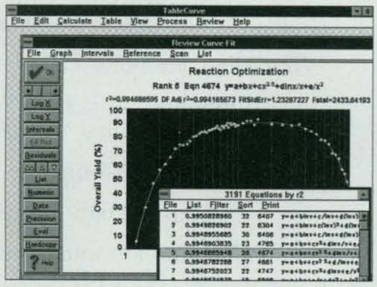

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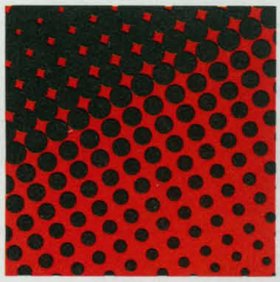

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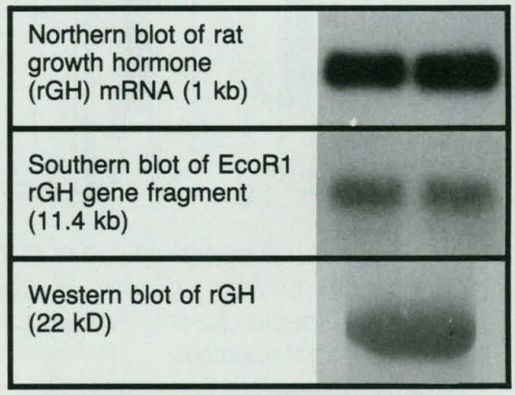

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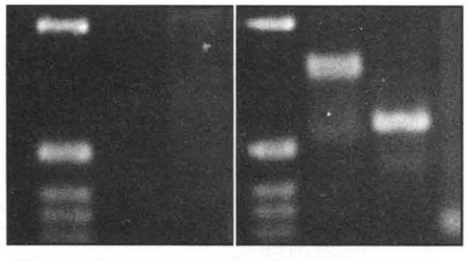

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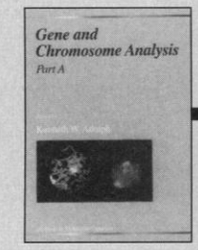

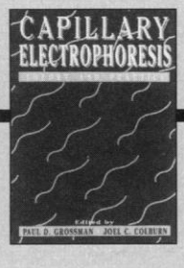

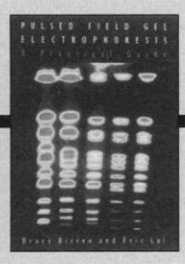

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