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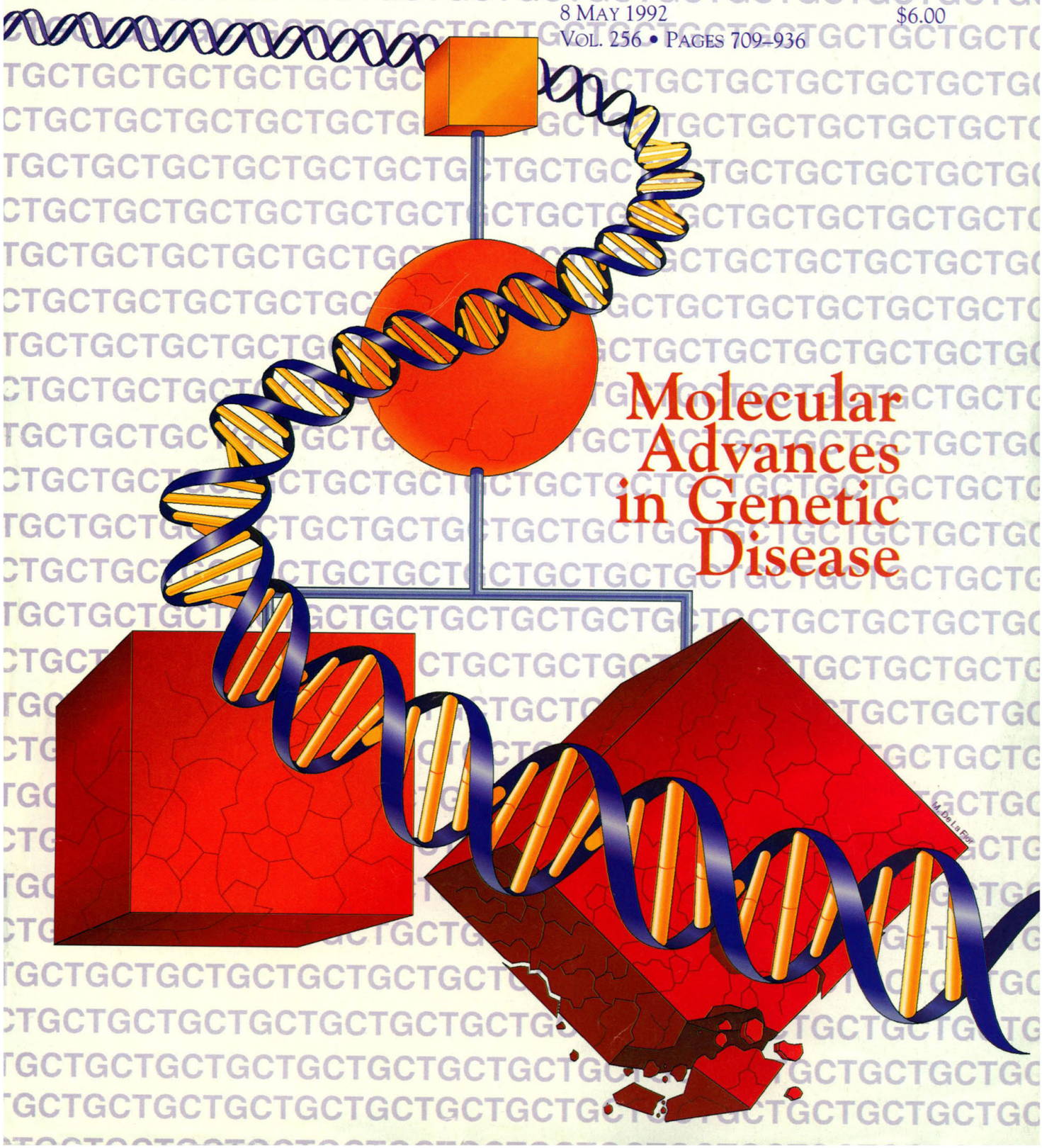
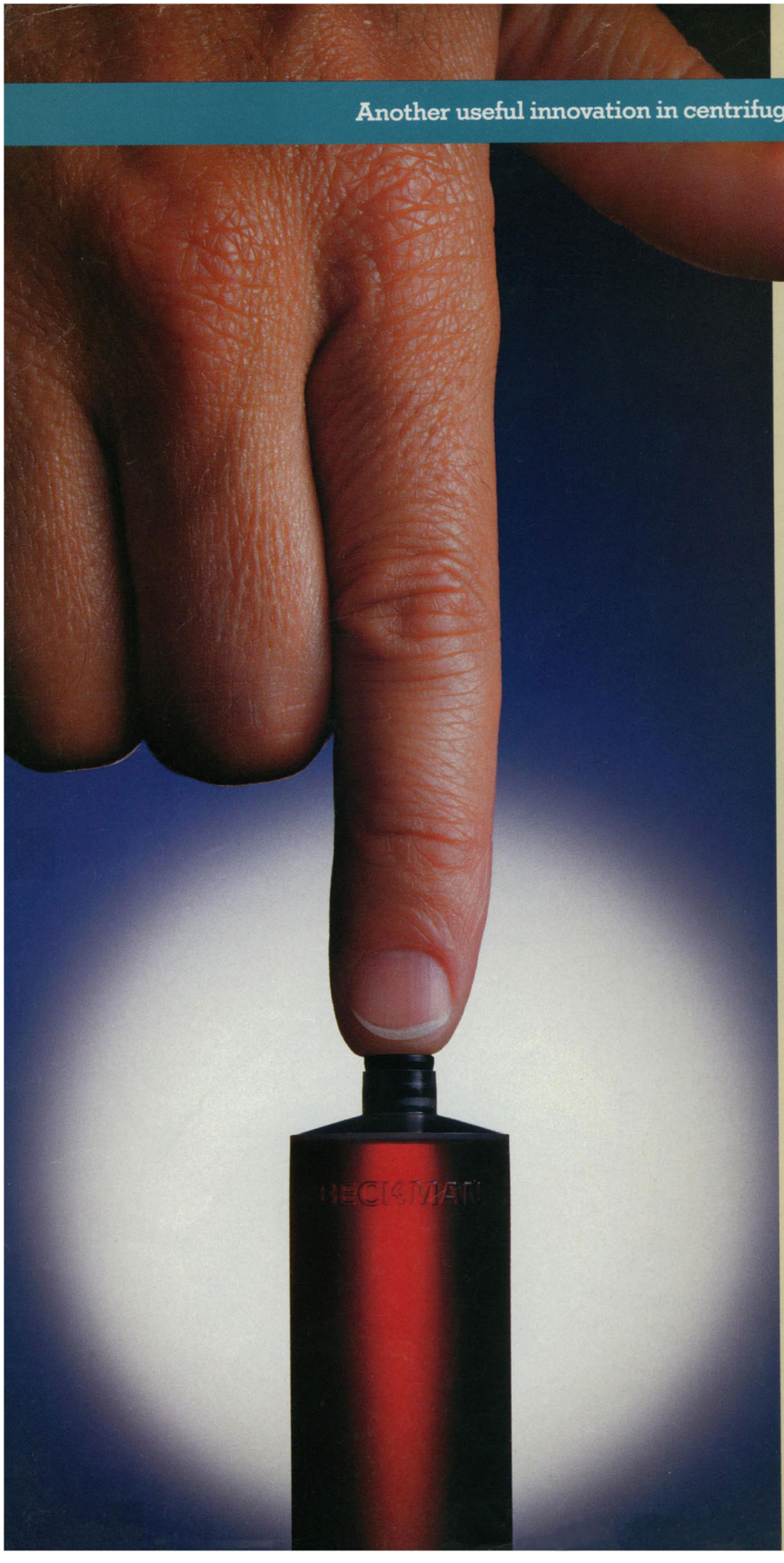


Molecular Advances in Genetic Disease



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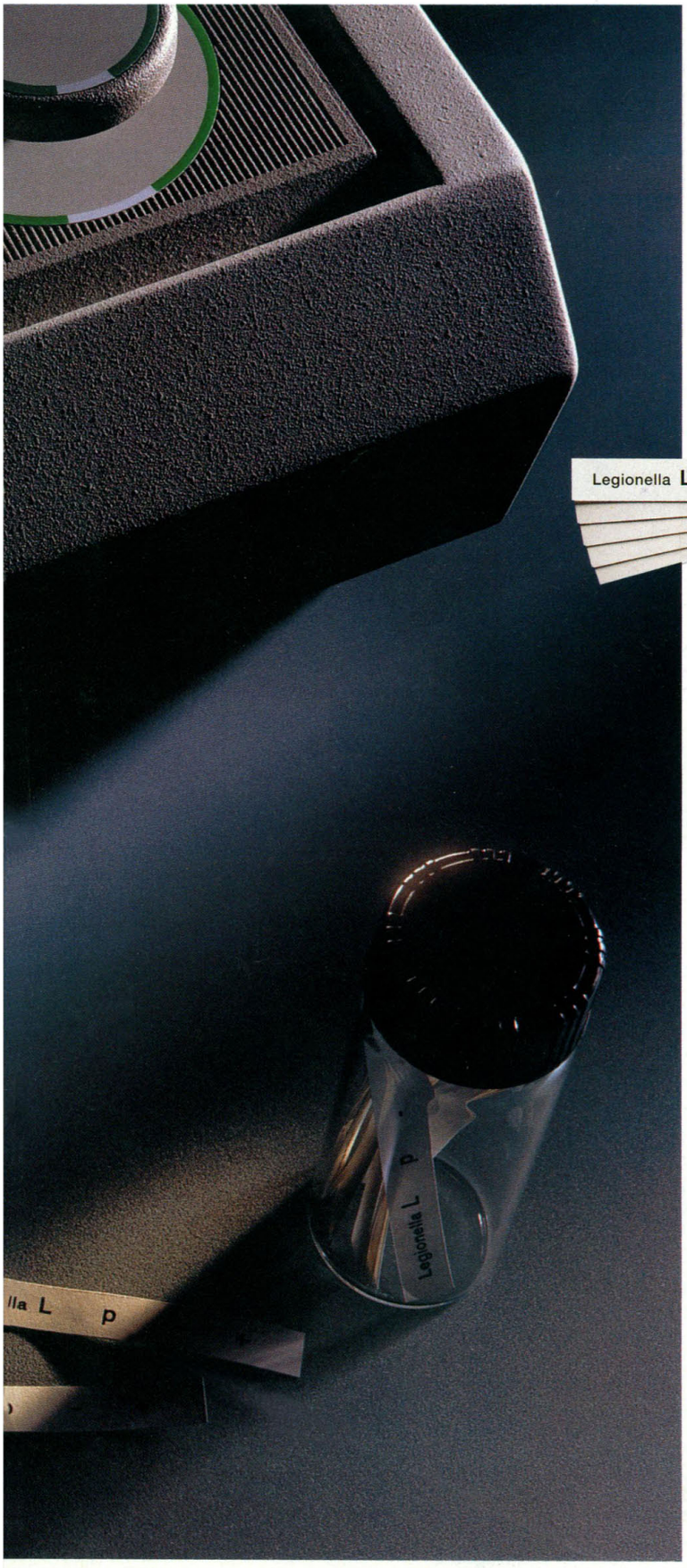

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SCIENCE

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833 How ewes recognize their offspring

NEWS

MOLECULAR ADVANCES

BIOTECH SPECIAL REPORT

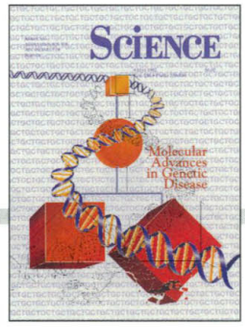
ARTICLES

PERSPECTIVES

DEPARTMENTS

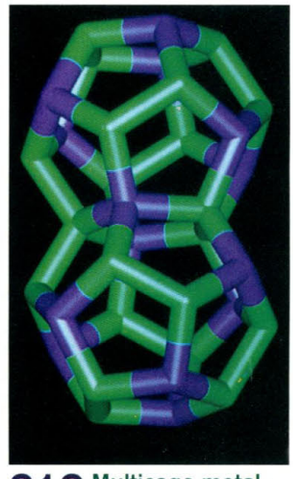
COVER

Pedigrees describe the inheritance of genetic disorders in related individuals. The cover shows a rendition of the pedigree of myotonic dystrophy, a human genetic disease. Between generations, an unstable nucleotide triplet (GCT) is amplified, shown here by increasing symbol size. Individuals who carry larger amplifications are more severely affected, represented by greater intensity of color and more cracks (see page 784). A series of News Reports and Articles focuses on recent advances in the exploration of molecular aspects of disease. See the Editorial and pages 766 to 813. [Illustration: Mike A. De LaFlor]



REPORTS

TECHNICAL COMMENTS



818 Multicage metal-carbon clusters

◩ Indicates accompanying News story or Perspective

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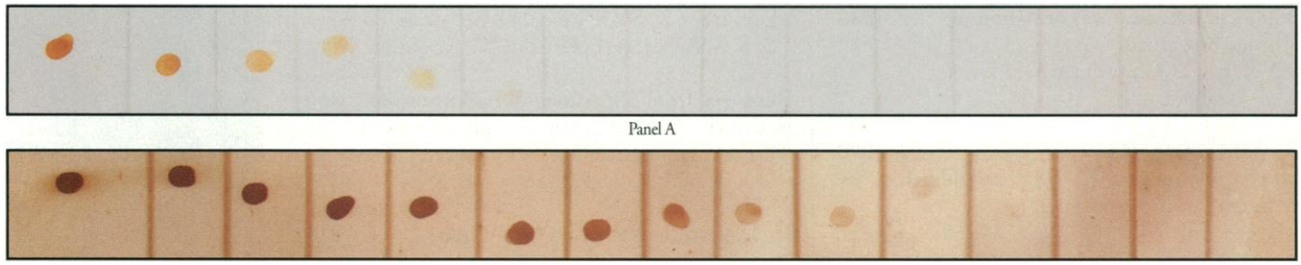

Panel A

Panel B

Two-fold serial dilutions of Rabbit IgG were spotted onto Du Pont's PolyScreen PVDF transfer membrane (1 µL aliquots starting at 1 µg/mL). Spots were then detected using AntiRabbit-IgG-HRP and DAB, either unamplified (Panel A) or with Du Pont's BLAST amplification systems (Panel B).

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References: (1) Bobrow M, *et al. Journal of Immunological Methods.* 1991; 137:103-112. (2) Bobrow M, *et al. Journal of Immunological Methods.* 1989; 125:279-285.

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DU PONT

edited by PHIL SZUROMI

Magic numbers and multicages

Metallo-carbohedrenes, cage-like molecules of transition metals and carbon, can form higher multiple connected cages. Mass spectroscopy studies by Wei *et al.* (p. 818) revealed "magic numbers," that is, truncations in the intensity of spectral features as a function of mass. They found evidence for double cages ($Zr_{13}C_{22}$ and $Zr_{14}C_{21}$, the latter of which also coincides with $Zr_{14}C_{23}$), triple cages ($Zr_{18}C_{29}$), and quadruple cages ($Zr_{22}C_{35}$). This series is unusual; for example, magic numbers for clusters of Ta and C also correspond to the formation of close-packed cubic structures rather than cages.

Brominated buckyball

Reaction of C_{60} with liquid bromine might have yielded numerous bromine derivatives, but Tebbe *et al.* (p. 822) report the formation at room temperature of a yellowish-orange product, $C_{60}Br_{24}$. An x-ray study reveals that the bromine ligands are arranged in a highly symmetrical fashion so that the molecule displays the rare point group symmetry of T_h. The 24 added bromine atoms are bonded to sp^3 carbon atoms, and the remaining carbon atoms form 18 double bonds. The addition of more bromine atoms would lead to crowding of the bromine atoms.

Signaling through GAP

The guanosine triphosphatase–activating protein GAP can inactivate the guanine nucleotide–binding protein Ras by promoting conversion of the active (guanosine triphosphate–bound) form of Ras to the inactive (guanosine diphosphate–bound) form. Schweighoffer *et al.* (p. 825) present results that indicate that GAP also functions to transmit signals to the biochemical pathways activated by Ras. Their experiments with a truncated form of GAP suggest that the NH_2-terminus of GAP is required to modulate the activity of the enzymes (or effectors) that are controlled by Ras.

Function of p53

The p53 protein is a tumor suppressor that has sequence-specific DNA binding activity and contains a domain that can activate transcription when attached to the DNA binding domain of another protein. The encoding gene for p53 has been found to be mutated in a variety of human cancers. Kern *et al.* (p. 827) show that normal p53 activates the expression of a gene that has a p53 DNA binding site and that activation correlates with the ability of p53 to bind DNA. Cancer-causing forms of p53 do not activate transcription and inhibit activation by normal p53. Thus, oncogenic forms of p53 may promote tumor formation by interfering with normal p53-mediated activation of genes involved in growth inhibition.

Scent for ewe

As in many species, a selective bond based on smell is formed between a ewe and her offspring shortly after birth due to a change in the mother's processing of olfactory signals. Kendrick *et al.* (p. 833) made electrophysiological recordings from ewes before and after they gave birth. Before birth lamb odors had little effect on neurotransmitter release or electrical activity, and no cells responded preferentially to lamb odors as compared to other odors such as those from food. After birth the number of mitral cells (the principal cells of the olfactory bulb) that responded to lamb odors increased, and some cells responded preferentially to the ewe's own lamb. There were also indications of an increased efficacy of glutamate-evoked release of the neurotransmitter γ-aminobutyric acid.

Functional expression

Ion channels often have multiple subunits, and the expression of functional channels often requires the expression of more than one subunit type. Voltage-sensitive sodium channels initiate and propagate action potentials; the channels' α subunits from rat brain have been previously cloned and expressed, but channels containing only α subunits inactivate more slowly the sodium channels in neurons. Isom *et al.* (p. 839) have cloned and expressed the β_1 subunit of rat brain sodium channels. They find that coexpression of the β_1 subunit with the α subunit leads to properties more representative of the wild-type channel, including increasing the peak sodium current, speeding up inactivation, and shifting the voltage dependence to more negative potentials.

Hearing words and music

Listening to a song requires processing of both the lyrics (distinguishing elements of speech or phonemes) and the music (distinguishing pitches). Zatorre *et al.* (p. 846) used positron emission tomography to map out the lateralization in the brain of these two aspects of speech, phonetic structure, and pitch discrimination. Studies in human volunteers revealed processing of phonetic structure by the left-hemisphere side of Broca's area, which is usually associated with articulation. This result is consistent with the motor theory of speech, which holds that decoding speech requires access to information in the brain on making the sound. Pitch discrimination activated the right prefrontal cortex, which is also involved in other auditory functions.

Parkinson's drug

Parkinson's disease results from degeneration of neurons in a specific region of the brain, the substantia nigra pars compacta. Currently available treatments can help, but do not clearly stop, the disease process. Schneider *et al.* (p. 843) investigate the effect of treatment with G_{M1} ganglioside on experimental parkinsonism. Monkeys were treated first with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which acutely induces behavioral and cognitive deficits similar to those caused by Parkinson's disease. When treated with G_{M1}, such monkeys recovered most of their motor function and apparently all cognitive function. Their brains showed greater dopamine levels and innervation than did brains of monkeys that received only MPTP.

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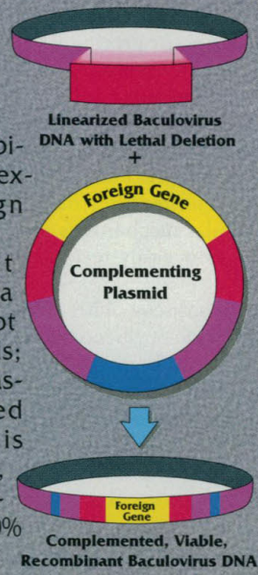

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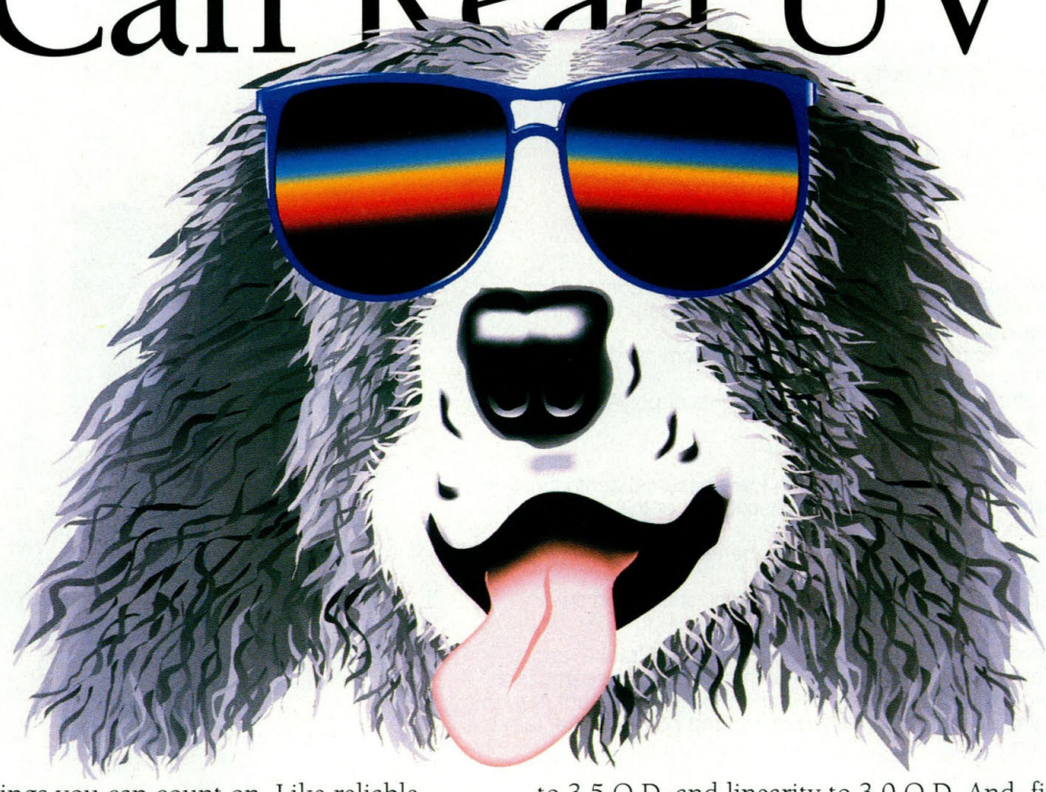

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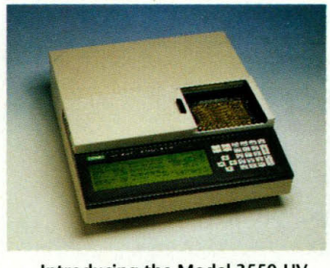

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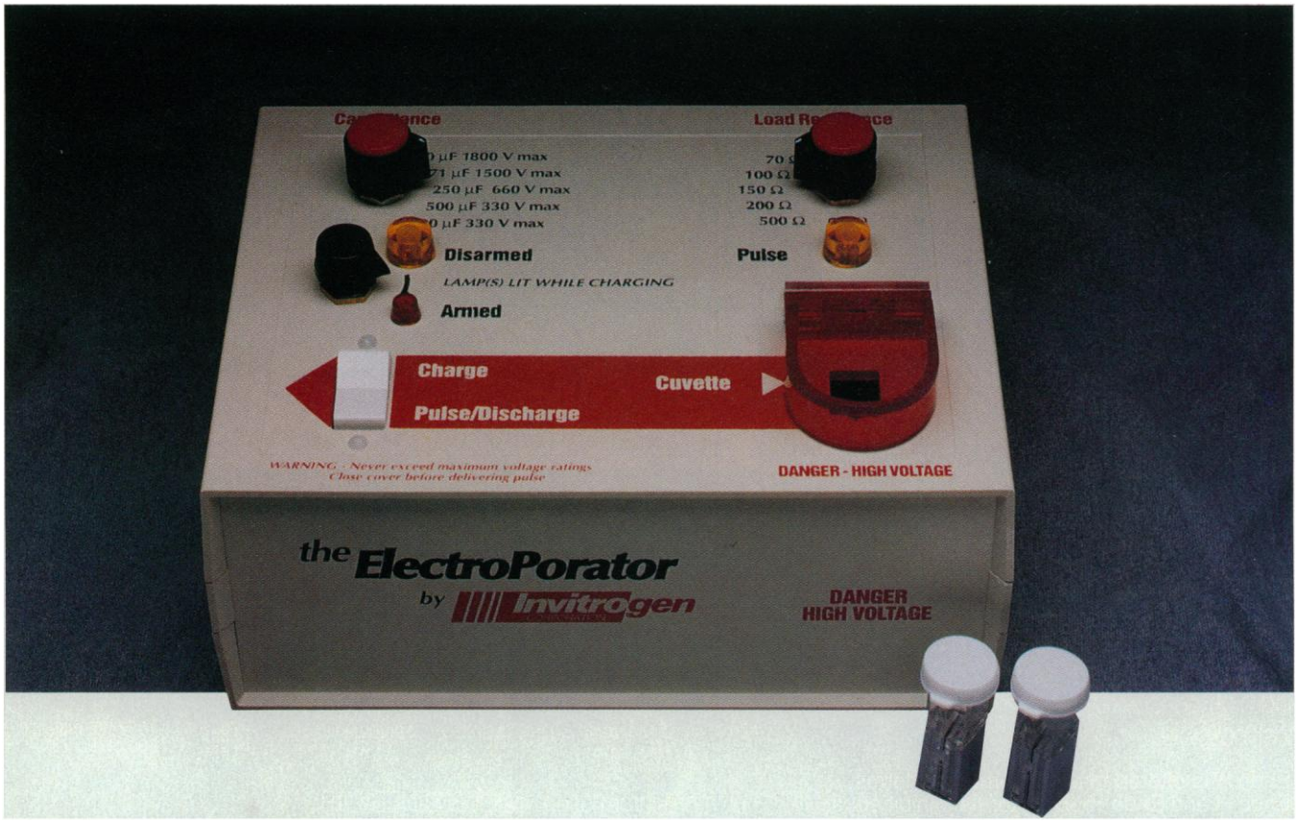

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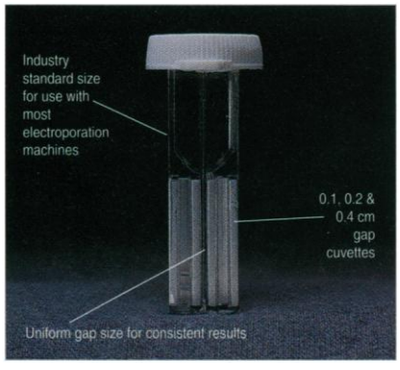

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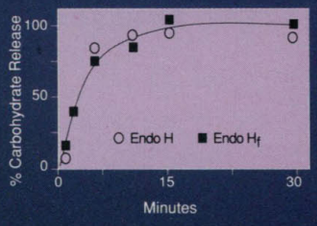
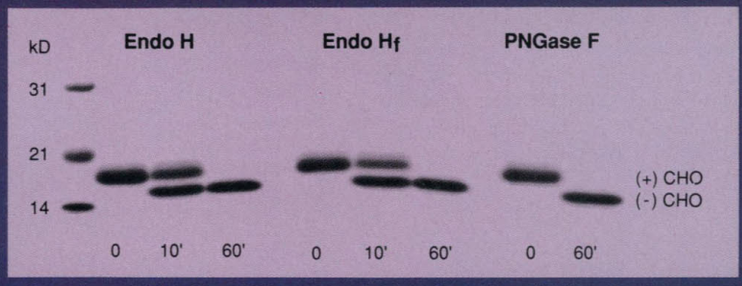


60 mg of RNase B was incubated with 3,000 units of Endo H or Endo H_f under standard assay conditions. Aliquots were removed at various time points and measured for released carbohydrate. (Dubois et. al [1956] Anal. Chem. 28, 350-356).

MOBILITY SHIFT ANALYSIS



1 unit of Endo H, Endo H_f or PNGase F was incubated per 10 µg of RNase B under standard assay conditions. At various time points, aliquots were removed and analyzed on a 10-20% SDS-gel for carbohydrate (CHO) release. 1 unit is defined as the amount of enzyme required to remove all of the carbohydrate from 10 µg of RNase B at 37° C in 1 hour.

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PNGase F		Endo H		Endo H_f	
Recombinant peptide: N-glycosidase F		Recombinant Endoglycosidase H		Recombinant protein fusion of Endoglycosidase H and maltose binding protein	
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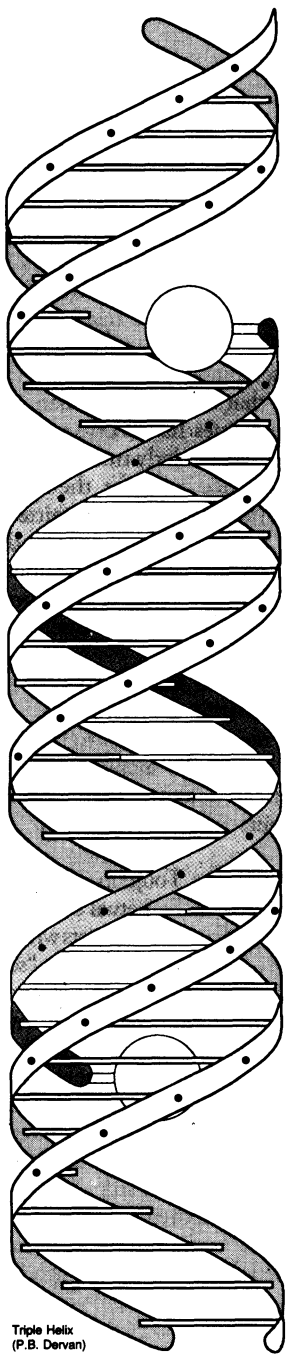

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- ✧ Electrical Measurements of Mammalian Cells in Culture
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- ✧ Protein Structure Determination

For complete details regarding the scientific program, registration, abstract submission, or exhibits, call 202-326-6461 or fax your request to 202-289-4021.

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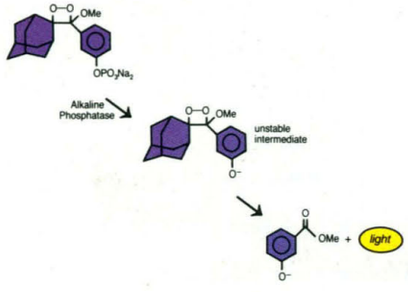
New information identifies ideal techniques for nonradioactive labeling and detection.

Scientists reluctant to incorporate nonradioactive labeling and detection into their research techniques have historically accused nonradioactive products of lacking sufficient levels of sensitivity. However, recent technological advancements — chemiluminescent detection, to be exact — have allowed select products to meet or exceed the sensitivity levels achievable with ^{32}P labeling and detection.

Those products, part of the Genius™ System with Lumi-Phos™ 530 from Boehringer Mannheim, guarantee detection of 0.1 pg of target nucleic acid in less than one hour. In addition, they allow detection of single-copy genes in human DNA in less than 30 minutes when used in Southern blotting techniques.



Molecular structure of the active ingredient in Lumi-Phos 530

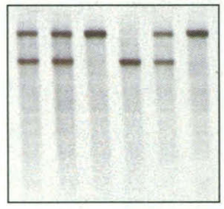
The Genius products rely on the very same procedures already used for radioactive labeling, yet provide results not just hours earlier, but *days* earlier.

Results can be recorded on X-ray film and, because the chemiluminescence lasts more than 48 hours, multiple exposures are possible. Those films can be easily scanned and quantified by densitometry.

Southern blotting: single-copy gene detection in 30 minutes

The accepted wait for accurate single-copy gene detection using ^{32}P labeled probes has always been one to three days. Now identical results can be achieved in 30 minutes with the Genius System and its chemiluminescent substrate.

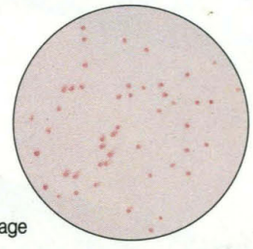
In addition, the probes are stable, allowing researchers to reuse them multiple times without relabeling. Furthermore, Southern blots developed with the Genius System can be repeatedly stripped and reprobed using the same procedures as the older radioactive method.



Human genomic Southern blot (RFLP) showing chemiluminescent detection of single-copy genes following a 2.5 minute X-ray film exposure

Library screening: positive colonies visible in one hour

Using probes labeled with the Genius System, researchers are detecting positive colonies and plaques within one hour versus the overnight exposures required with radioactive techniques.

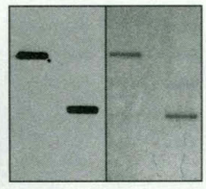


Colorimetric detection of recombinant lambda gt 10 phage

Because the Genius System can use DNA, RNA or oligonucleotide probes, many research needs can be met with a single system. Probe labeling utilizes the same techniques currently employed to prepare radioactive probes, and multiple filters can be processed simultaneously.

Dot blots: guaranteed results in under one hour

With exposure times reduced from overnight to 30-60 minutes, critical answers are relayed quickly, helping research progress as soon as possible.



Comparison of slot blot hybridizations using Genius-labeled oligonucleotide probe (left panel, 60 minute film exposure) and ^{32}P-labeled probe (right panel, overnight film exposure)

Performance is guaranteed as the Genius System products are function tested in dot blot (also referred to as slot blot) assays.

The unique digoxigenin-labeled probes are stable for at least one year and can be reused multiple times, offering savings in terms of the time and money normally spent relabeling decayed radioactive probes. By using the same probe, experimental variables are reduced and reproducibility between experiments is provided.

0.1 pg DNA Guaranteed

Technique-specific information and bibliography available upon request

To receive additional information about the Genius System products, their applications and specifications, or to receive a bibliography of publication references, call Boehringer Mannheim at **800-428-5433**.

If you would like to speak directly with a specialist about your individual research needs, call **800-262-4911**.

Genius™ System

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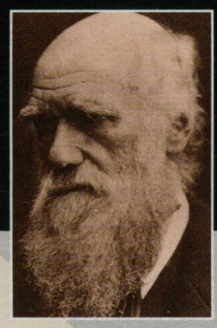

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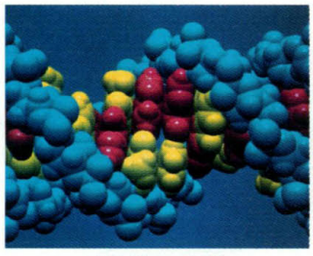
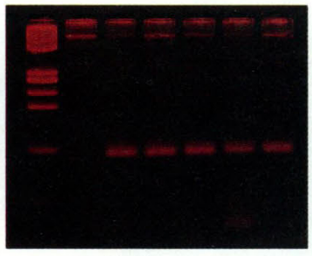
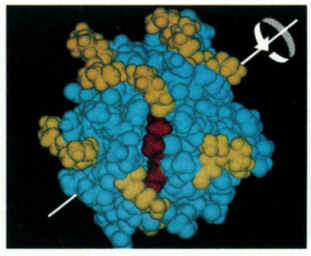


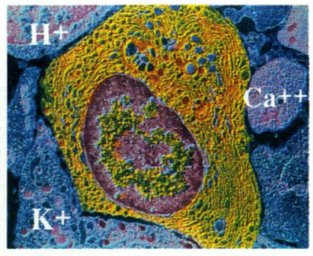
DNA Quantitation



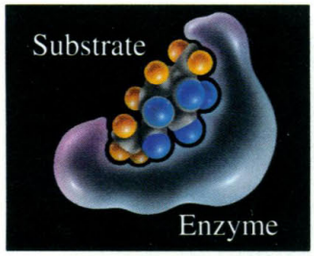
Gel Scanning



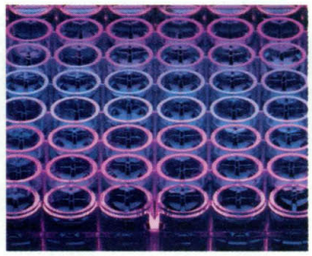
Macromolecular Anisotropy Measurements



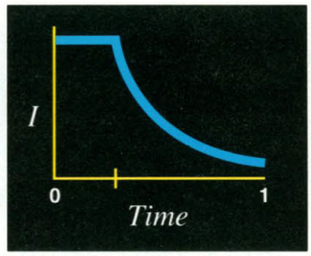
Intracellular Ion Determinations



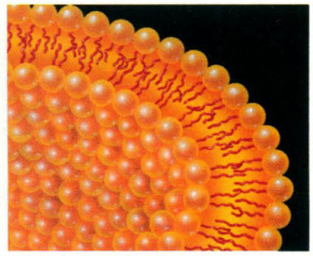
Enzyme Kinetic Analysis



Microplate Assays



Stopped-Flow Kinetic Analysis



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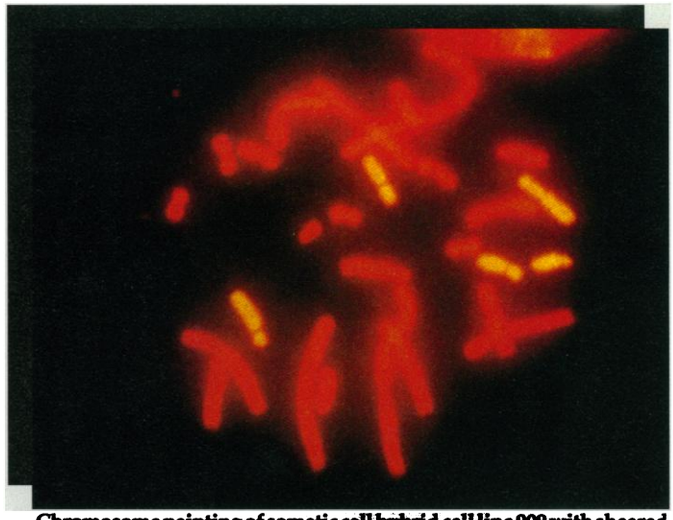

Chromosome painting of somatic cell hybrid cell line 909 with sheared total human DNA labelled with dUTP-digoxigenin detected by anti-digoxigenin-FITC. Data show the labeling of human chromosomes 5, 6, 8, 14 and X.

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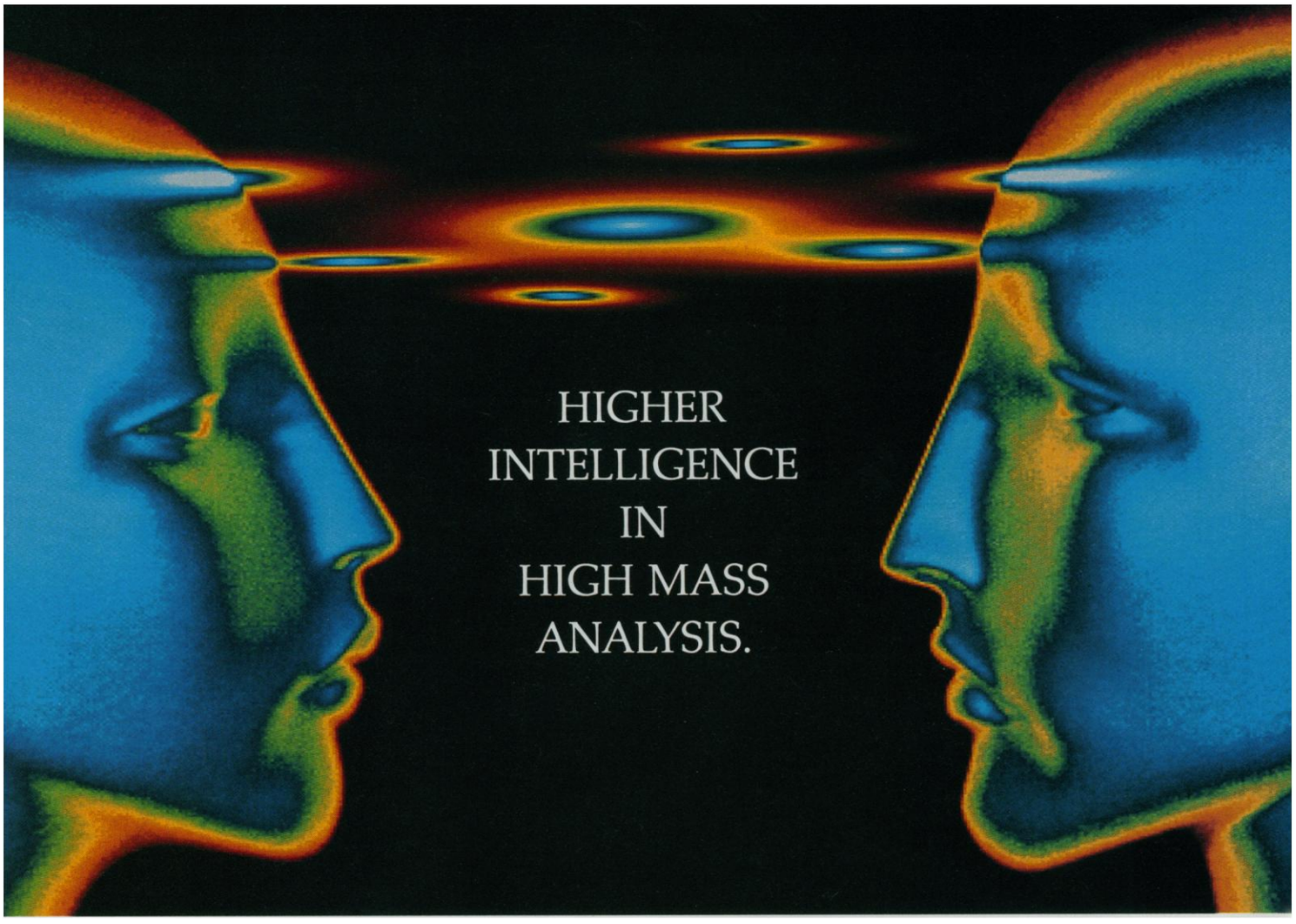

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Tentative Program

Mapping
(Thursday, 15 October, 8:30am–noon)
Bertrand R. Jordan (chair), *INSERM-CNRS*
Jean Weissenbach, *CNRS, Inst. Pasteur*
Daniel Cohen, *Ctr. d'Etude du Polymorphisme Humain*
Malcolm Ferguson-Smith, *Cambridge Univ.*
Cassandra L. Smith, *Univ. of California, Berkeley*
Yoshihide Hayashizaki, *Natl. Cardiovascular Research Inst.*

Human Genetic Diversity
(Thursday, 15 October, 4:00pm–7:00pm)
P. Fasella (chair), *Comm. of European Communities*
L.L. Cavalli-Sforza, *Stanford Univ.*
A. Piazza, *Univ. of Torino*
Alec J. Jeffreys, *Univ. of Leicester*
Kenneth Kidd, *Yale Univ. School of Medicine*
Svante Paabo, *Univ. of Munich*
Julia Bodmer, *Imperial Cancer Research Fund*

Applications of the Human Genome Project
(Friday, 16 October, 8:30am–noon)
Jean Dausset (chair), *Ctr. d'Etude du Polymorphisme Humain*
John Hardy, *St. Mary's Hospital Medical School*
Francis Collins, *Univ. of Michigan*
Yusuke Nakamura, *Japanese Fdn. for Cancer Research*
Hans-Hilger Ropers, *Univ. of Nijmegen*
Ulf Landegren, *Univ. of Uppsala*

Contributed Papers
(Friday, 16 October, 4:00pm–7:30pm)
Howard M. Cann (chair), *Ctr. d'Etude du Polymorphisme Humain*
Speakers will be chosen from poster session abstracts.

Model Organisms
(Saturday, 17 October, 8:30am–noon)
George Carle (chair), *Univ. of Nice*
Marc van Montagu, *Univ. of Ghent*
Piotr Slonimski, *CNRS*
John Sulston, *MRC Lab of Molecular Biology*
Steven Tanksley, *Cornell Univ.*
Eric Lander, *Whitehead Inst.*
Michael Ashburner, *Cambridge Univ.*

cDNA Sequences & Intellectual Property
(Saturday, 17 October, 4:00pm–7:30pm)
Lennart Philipson (chair), *EMBL*
J. Craig Venter, *Natl. Inst. of Health*
Kenichi Matsubara, *Osaka Univ.*
Rebecca Eisenberg, *Univ. of Michigan*
Charles Auffray, *Inst. d'Embryologie du CNRS*
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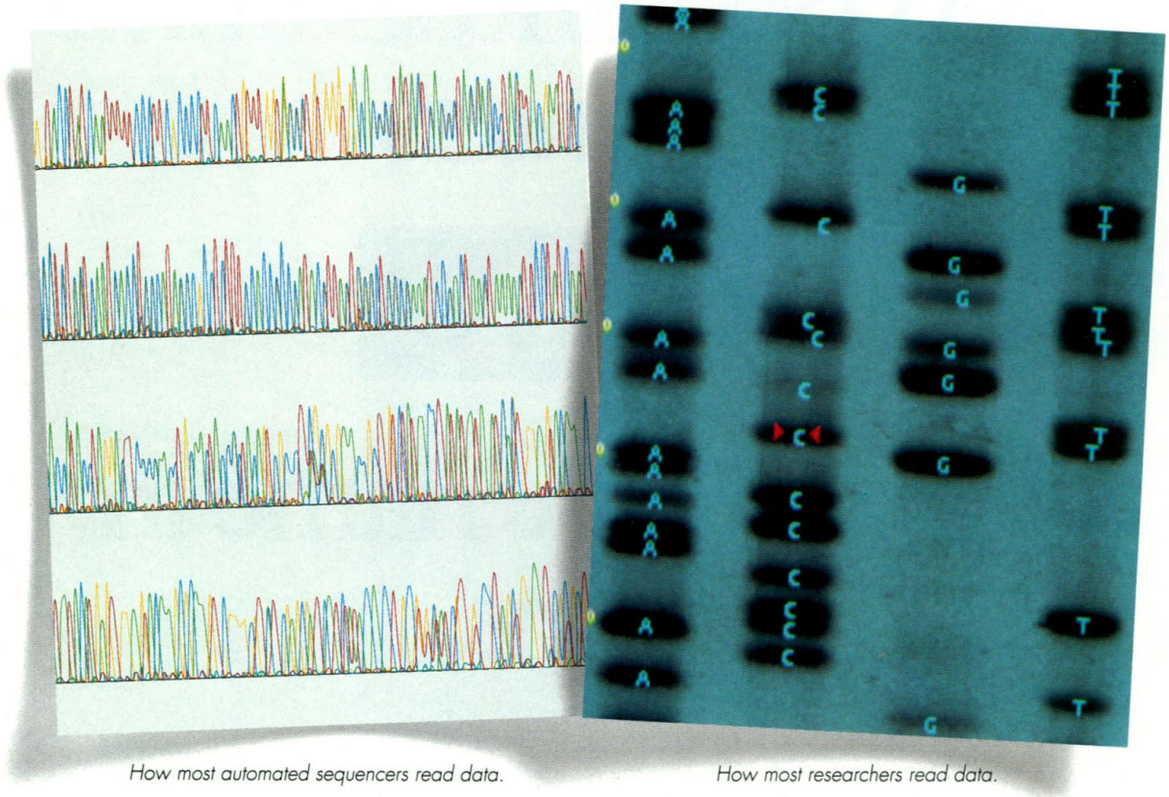

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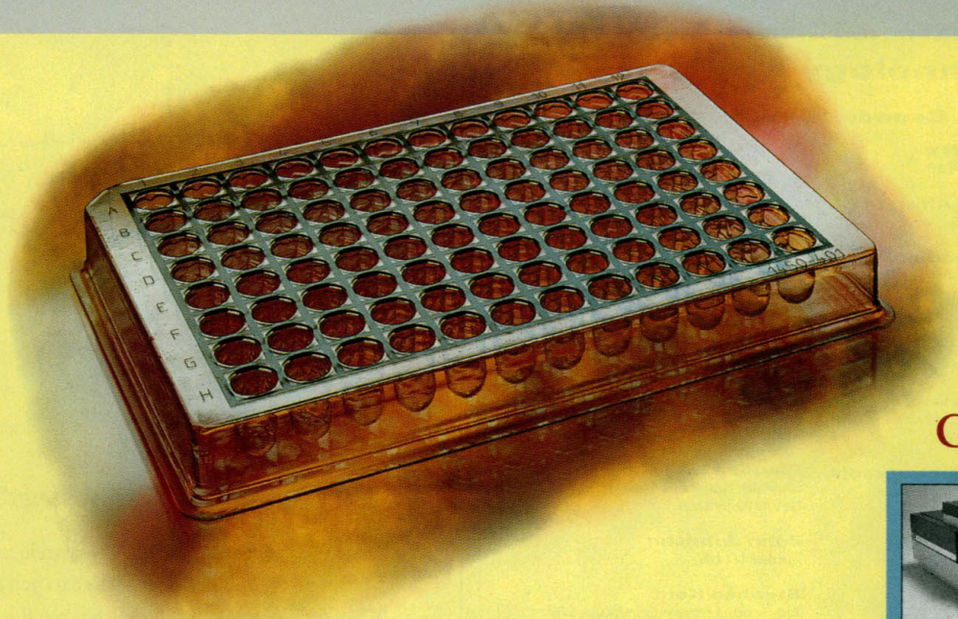
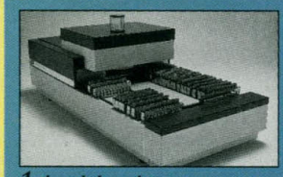


The Company.



1st rack-based counters - RackGamma (LKB-Wallac, 1975), RackBeta™ (1977)

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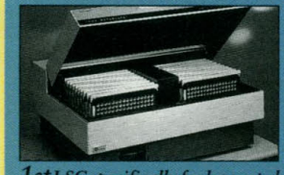

1st LSC specifically for harvested samples -Betaplate (Wallac,1986)

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PROGRAMME
The programme includes a three-track approach:

BIO-SCIENCE:
discussion of leading edge research on ribozymes; antisense; genomics; protein structure and function; protein design; growth factors; lipids; and glycobiology.

BIO-TECH:
discussion of protein synthesis; expression systems; adsorption of proteins to solid surfaces; nucleic acid sequencing; RFLPs; miniaturized biosensors; drug delivery systems; use of oligonucleotides, peptides and Mabs for identification; and carbohydrate-related technologies.

BIO-BUSINESS:
discussion of different approaches to investment in biotechnology by financial companies; a hands-on workshop on how to pitch to the financial community; sessions on intellectual property and patent law; regulations (health, safety and field testing); taking your company abroad; shaping your corporate structure; and a look into the future - biotechnology and the quality of life.

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Attention: Doris Ruest

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INTERNATIONAL HUMAN FRONTIER SCIENCE PROGRAM

REQUEST FOR APPLICATIONS

Research Grants / Fellowships / Workshops 1993

The Human Frontier Science Program (HFSP) aims to promote, through international collaboration, basic research to elucidate the complex mechanisms of living organisms, including man. Applications are invited for the support of research grants, fellowships and workshops in the areas set out below. The program distributed about $13 m on new awards this year and aim to spend a similar amount in 1993.

Research Areas of the HFSP

(A) Basic research for the elucidation of brain functions

1. Perception & Cognition
2. Movement & Behaviour
3. Memory & Learning
4. Language & Thinking

(B) Basic research for the elucidation of biological functions through molecular level approaches

1. Expression of Genetic Information
2. Morphogenesis
3. Molecular Recognition & Responses
4. Energy Conversion

Research Grants : Grants for basic research carried out jointly by research teams in different countries. The principal applicant must be from one of the eligible countries*.

Fellowships : Long-Term *(up to 2 years),* **Short-Term** *(up to 3 months)* ; Fellowships for researchers from the eligible countries who wish to do research in foreign countries, or for researchers outside the eligible countries who wish to do research in one of the eligible countries.

Workshops : Grants for international workshops organized by researchers from the eligible countries.

* *The eligible countries for the current year are Canada, France, Germany, Italy, Japan, Switzerland, U.K., U.S.A. and non-summit EC member countries. (Details in the guidebook).*

Application Deadline : September 30, 1992

For Research Grants and Long-Term Fellowships, the awards will be announced in April 1993. Applications for Short-Term Fellowships and Workshops can be submitted throughout the year.
Guidebooks and Application forms may be obtained upon written request by using the address form below. Please indicate which program activity you are interested in.

Guidebooks and application Forms for Research Grants & Long-Term Fellowships will **not** be available after September 1, 1992.

Please use the form below to request information (please print).

Name :

Institute :

Address :

Check squares to indicate which program you are interested in.

- ☐ **Research Grant**
- ☐ **Long-Term Fellowship**
- ☐ **Short-Term Fellowship**
- ☐ **Workshop**

Request to be sent to: *H.F.S.P.O., Tour Europe, 20 place des Halles, 67080 STRASBOURG CEDEX FRANCE*
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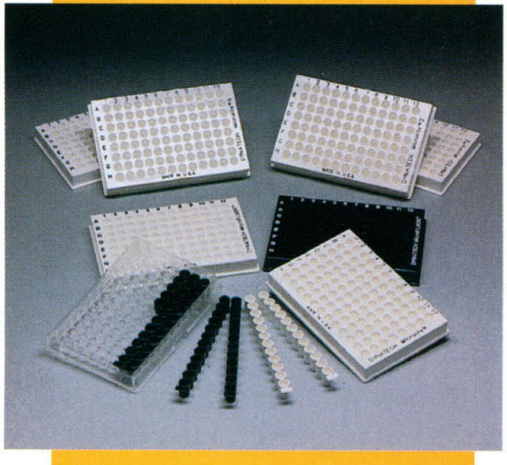

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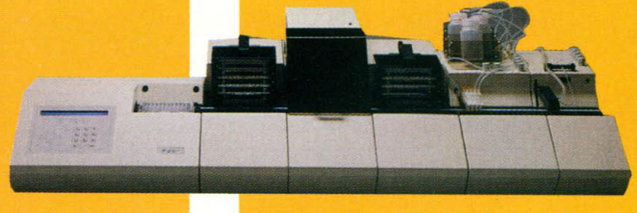

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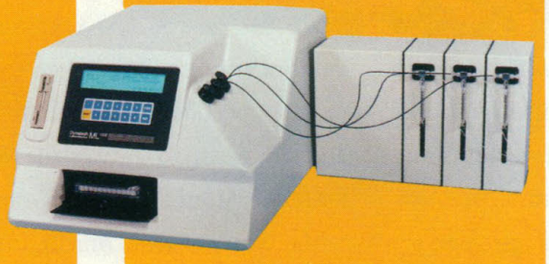

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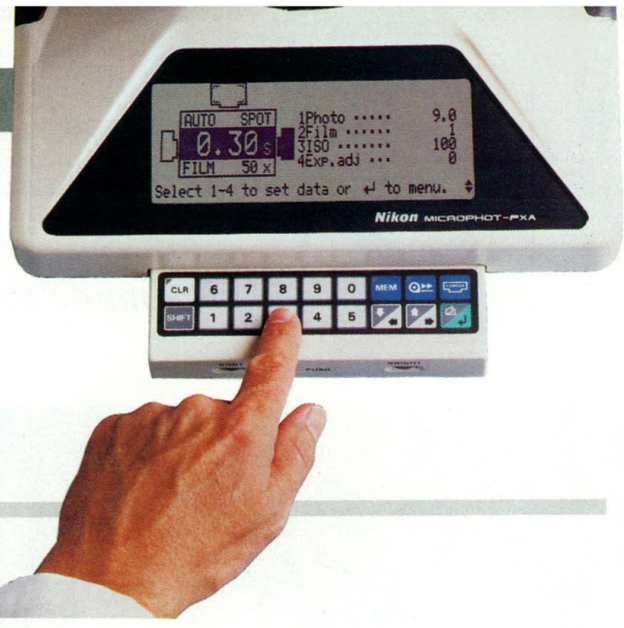

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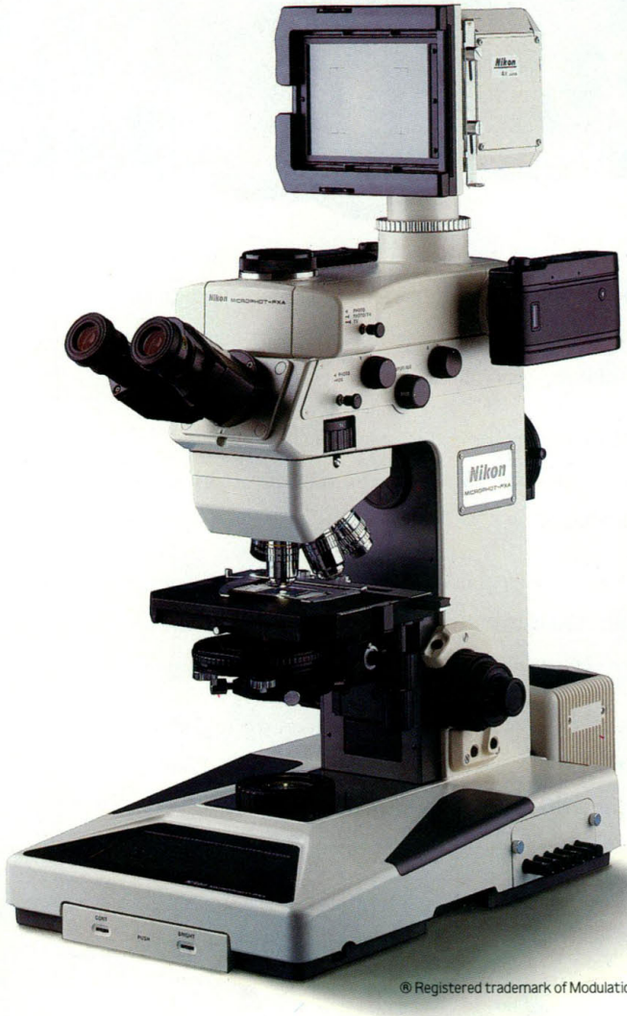

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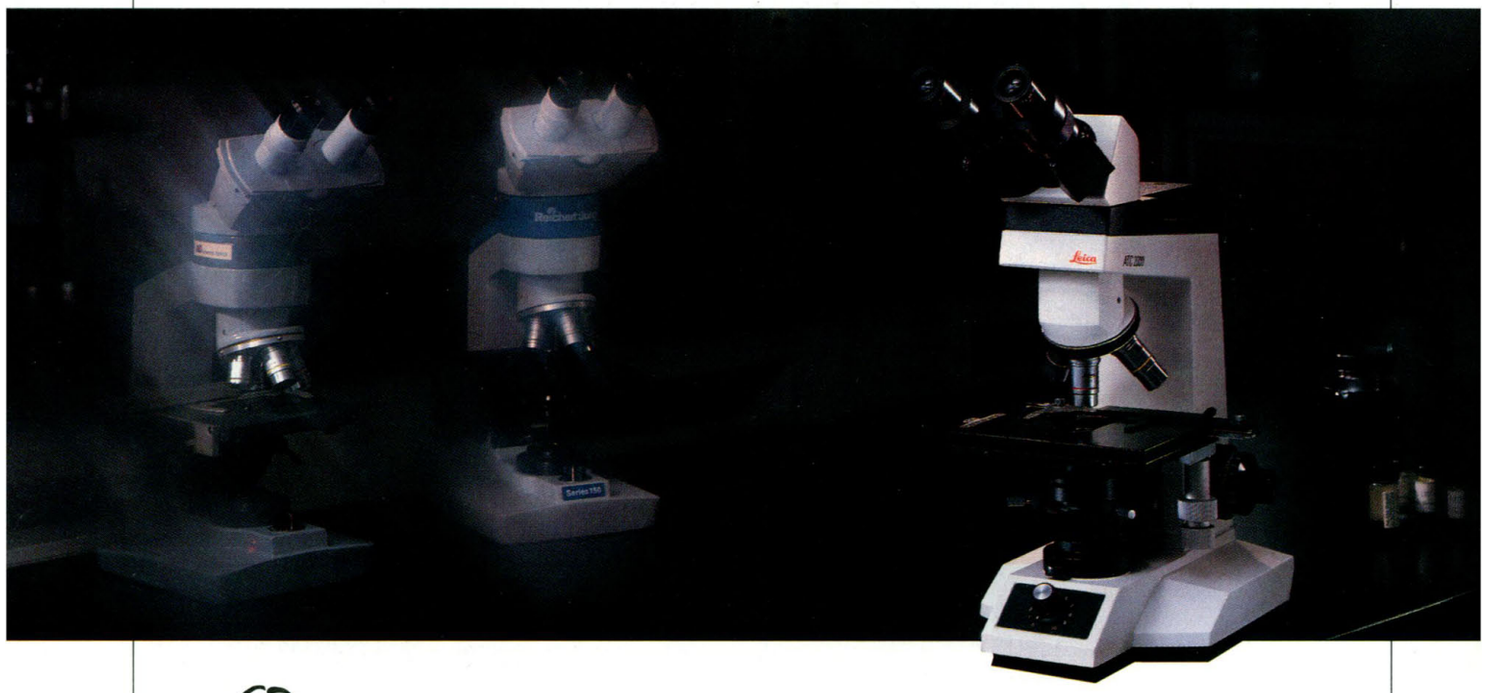

The Series 150 microscope had a good life. It was part of fine companies...including American Optical, Reichert-Jung and Leica. And for more than 20 years, it has been the standard for microscopy in teaching laboratories. But good things can become better...

Introducing the new ATC™ 2000 microscope.

The ATC 2000 has all the features you've come to expect—all-metal construction, a spring-loaded nosepiece that prevents damage to objectives and slides, an ultra-positive focusing system for smooth focusing without lag and override and a fixed stage and focusing nosepiece for sample stability.

While the ATC 2000 Advanced Teaching Microscope will fit right in with your existing microscopes, its performance will quickly make it stand out. It has an expanded 20mm field-of-view, a standard field diaphragm to maximize illumination performance, a reverse nosepiece to make slides more accessible and optional phase contrast capabilities.

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It's not easy to let go of a classic...unless you're getting another classic in return. Leica has designed the ATC 2000 to establish a new standard in performance, features and durability—a microscope that will be the standard for the next generation.

For more information about the ATC 2000 contact Leica Inc., 111 Deer Lake Road, Deerfield, IL 60015, telephone 1-800-248-0123 or fax 708-405-0147.

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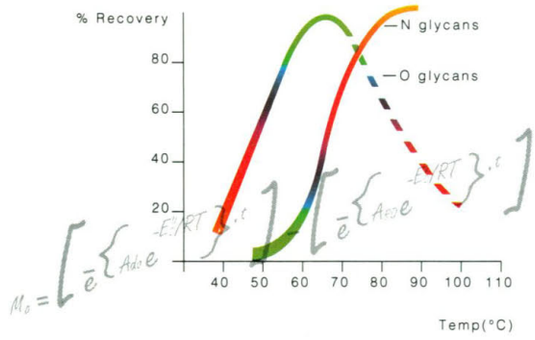

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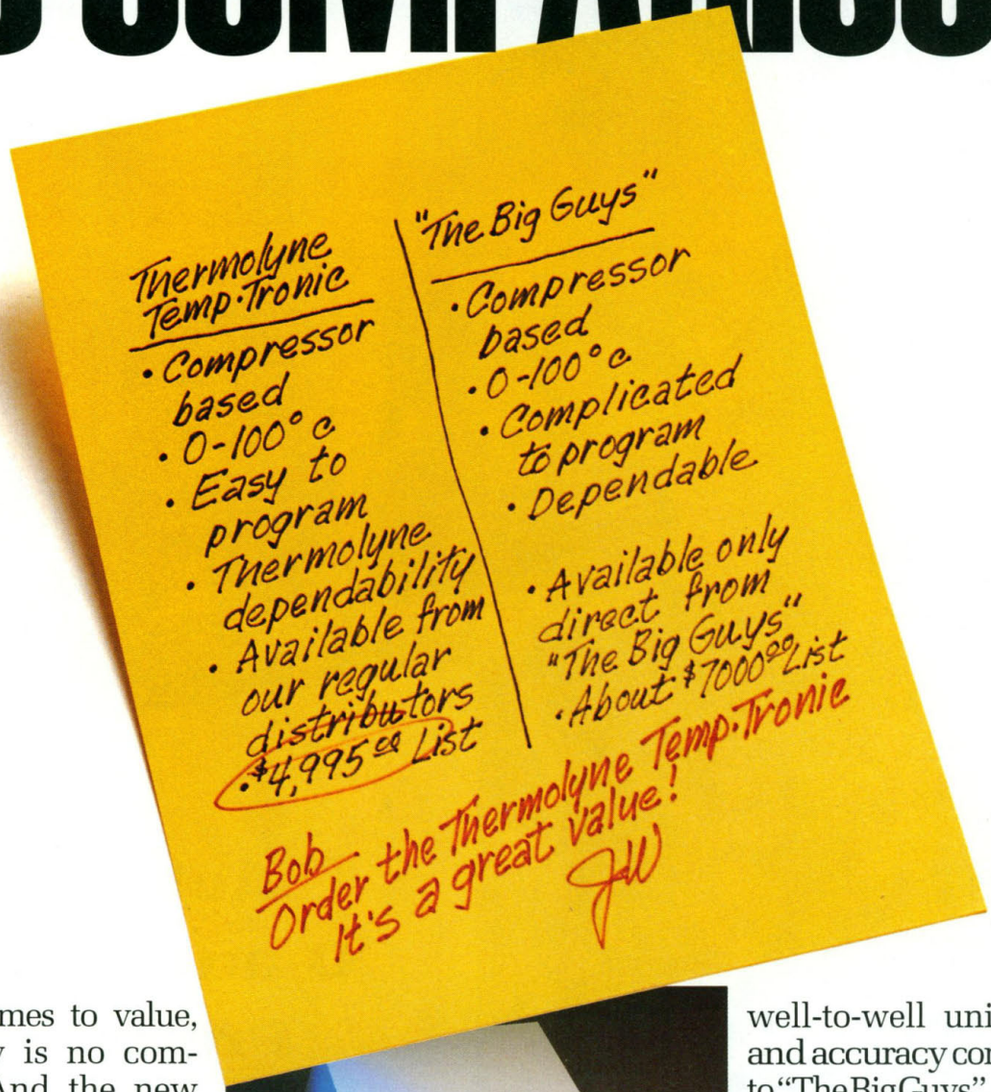
When choosing a thermal cycler, there's NO COMPARISON



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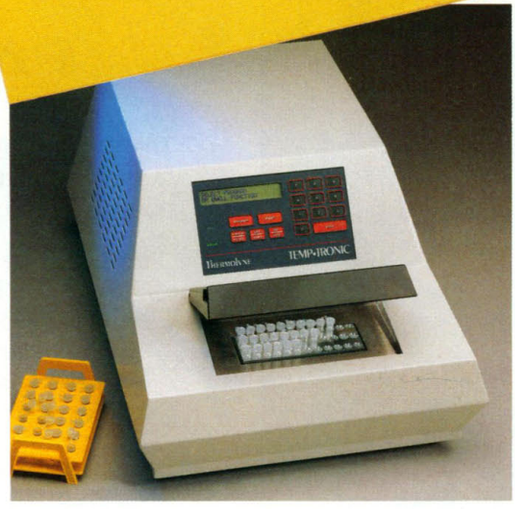

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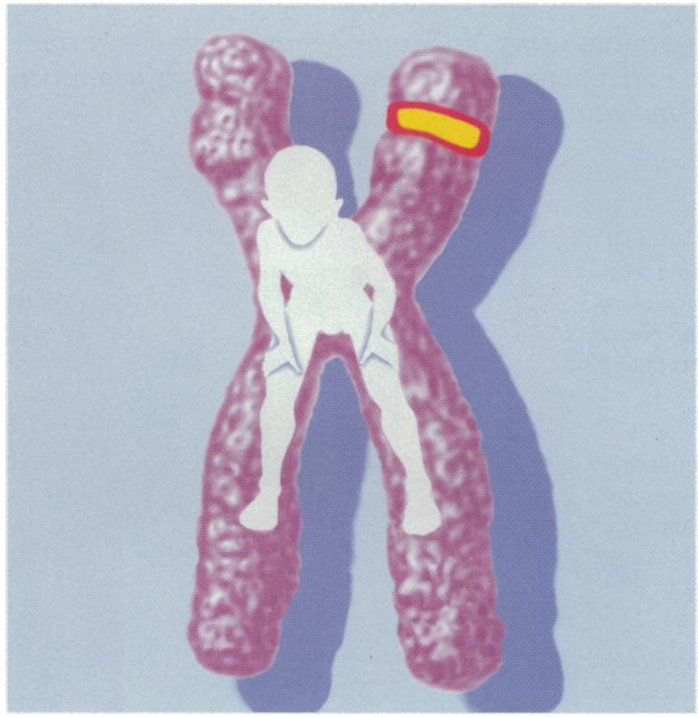
Gene Navigator™ detects DNA rearrangements in Duchenne muscular dystrophy.



Introducing the perfect tool for mapping chromosomal DNA and YAC clones.

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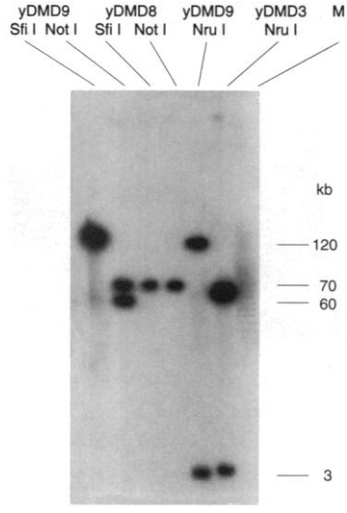
Gene Navigator extends the DNA separation window, without extending separation difficulty. This system, together with unique markers from Pharmacia, reveals finer distinctions that other systems miss.

Gene Navigator mapping system has made PFGE both simple and accurate. Optimal running procedures are provided by Pharmacia, along with a comprehensive line of enzymes and buffers, which ensure reliable, reproducible results. Extensive customer support increases performance and minimizes downtime.



Autoradiograph of Sfi I, Not I, Nru I digested DMD YAC clones hybridized with pBR 322 DNA. DNA was separated on Gene Navigator (M=markers).

To learn more about how Gene Navigator can increase both the speed and accuracy of your research, contact your local Pharmacia representative.

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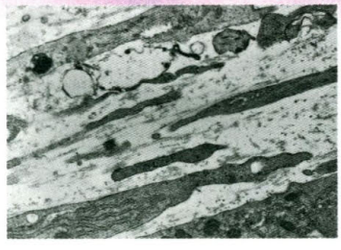
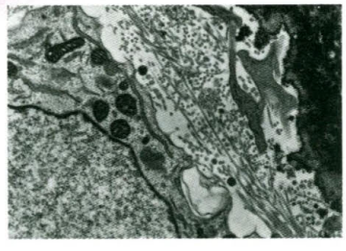


Electron micrograph of chick calvarial cells cultured in 10% chicken serum-supplemented medium. These cells remain undifferentiated, depositing a matrix characterized by a sparse fibrous component and no mineralization.



Chick calvarial cells grown for 10 days in 10% Nu-Serum IV-containing medium. Note the extracellular matrix showing collagen fibers characterized by the typical banding pattern.

Photos courtesy of Drs. Warren Ramp and Richard Dillaman.

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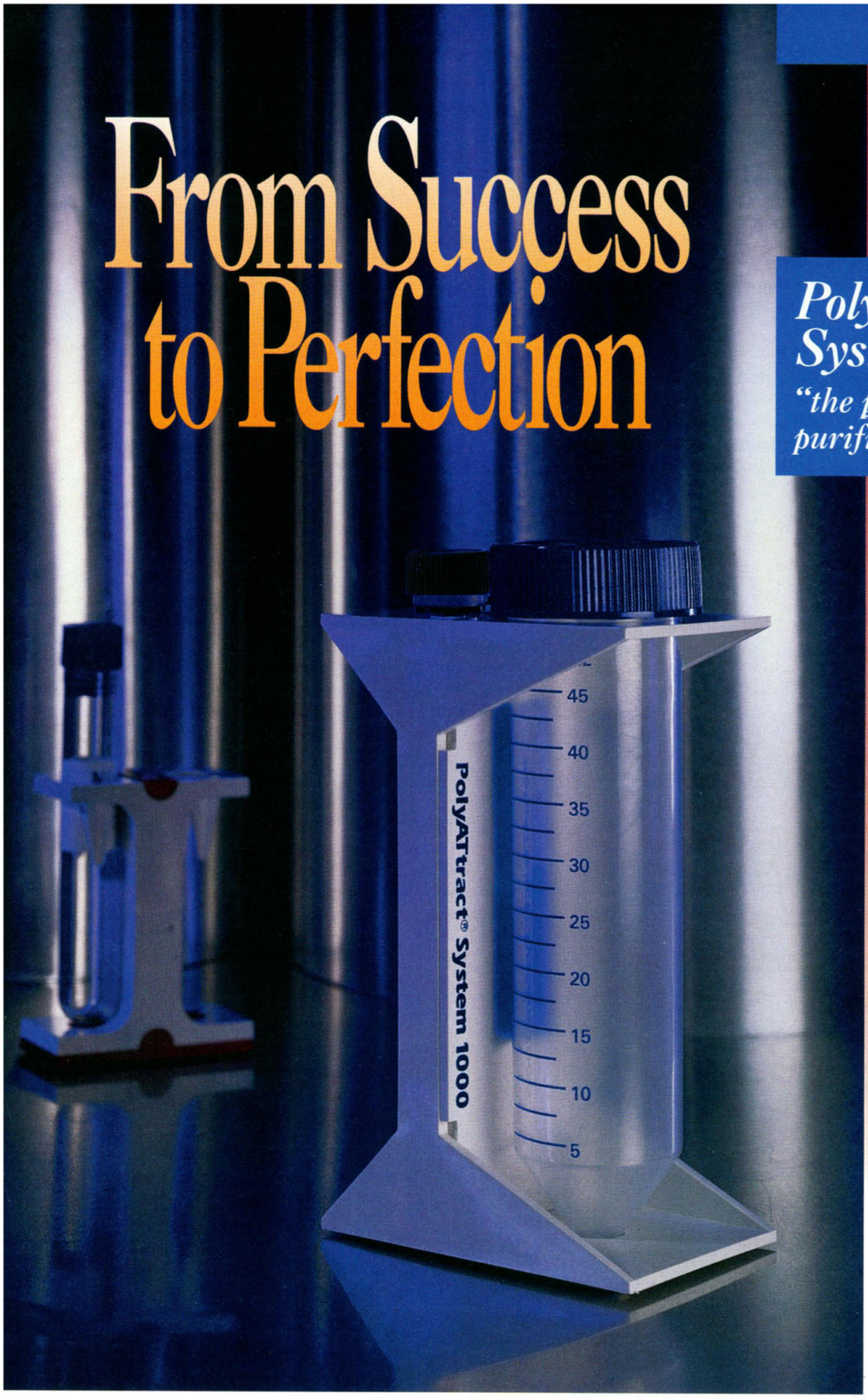

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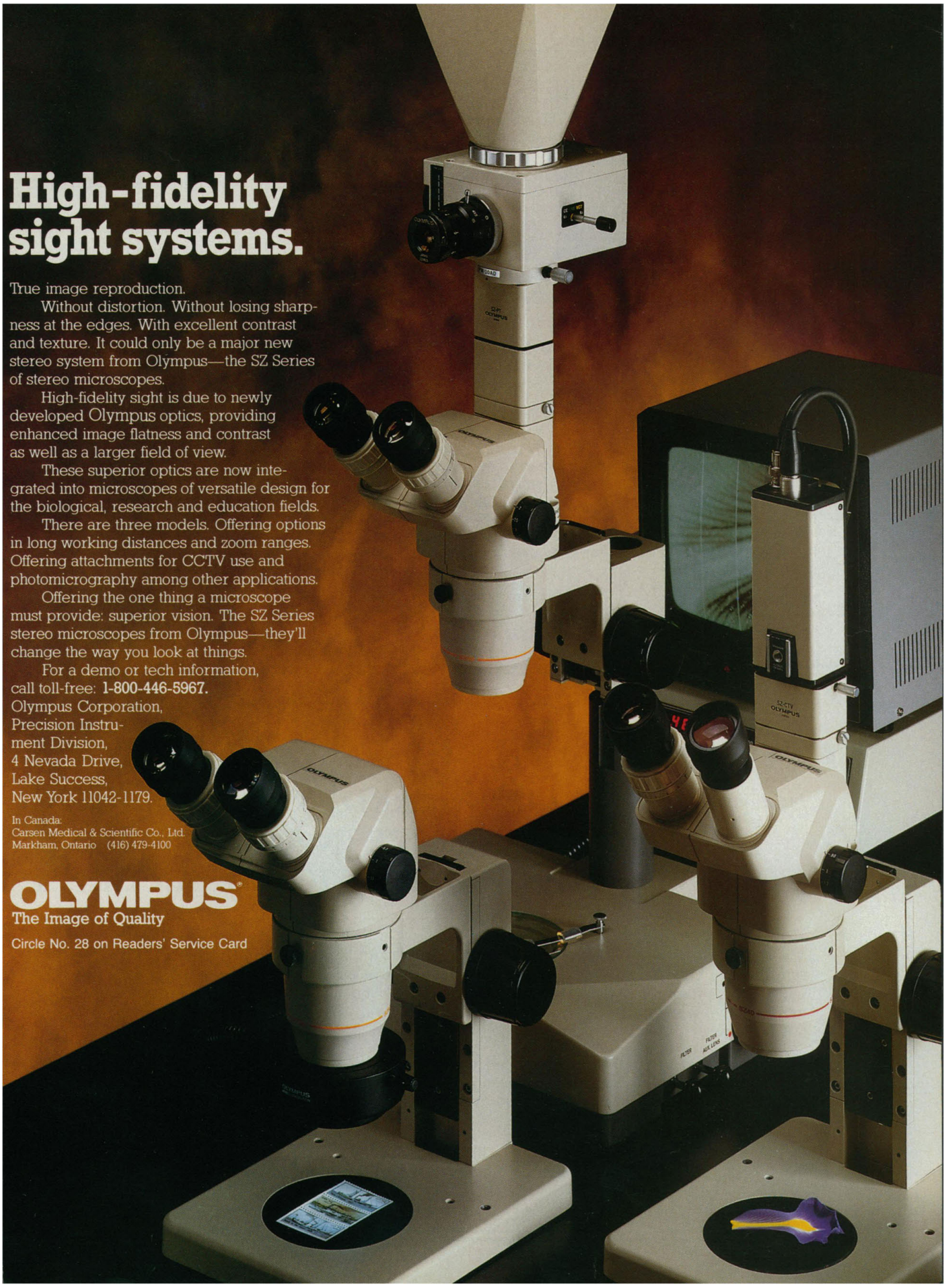
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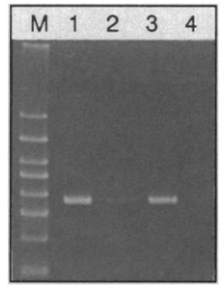

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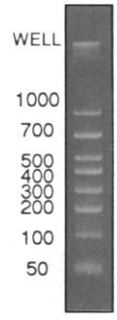

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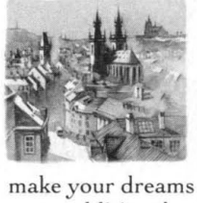

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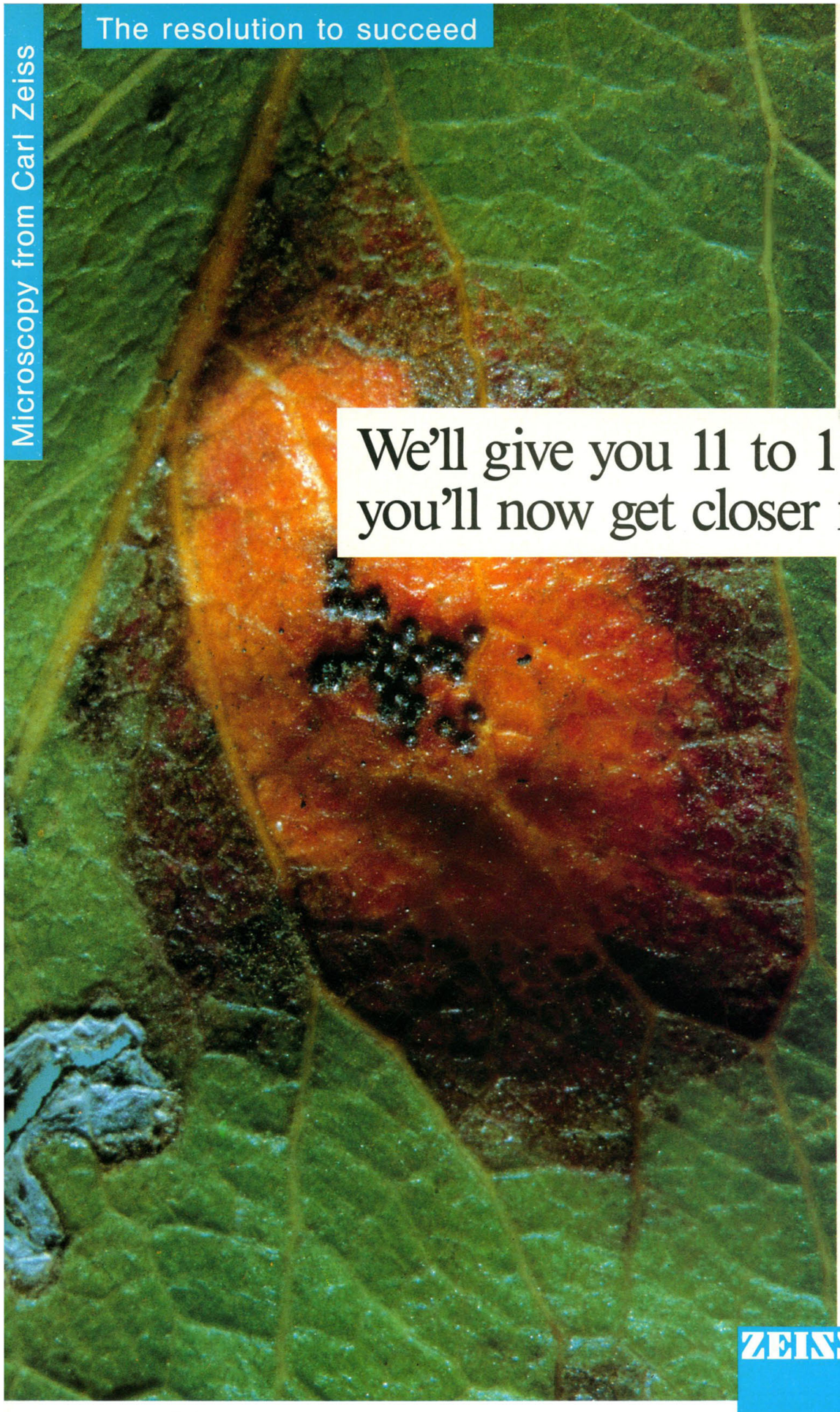

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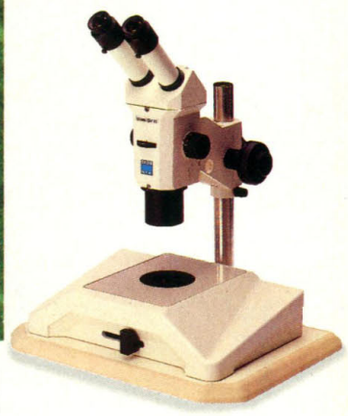

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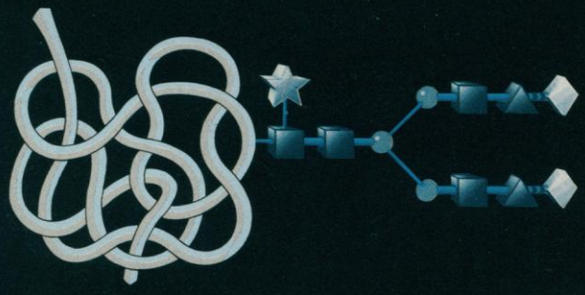

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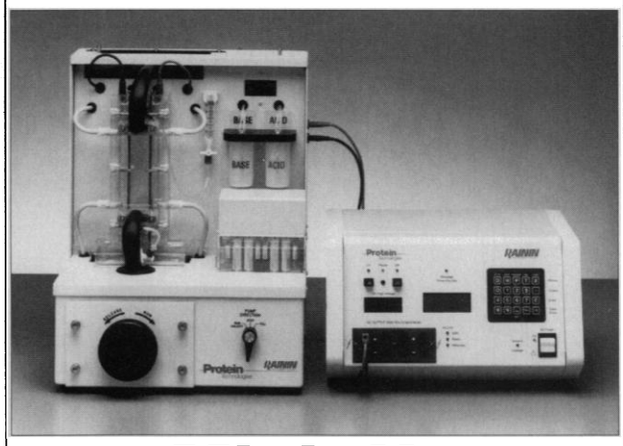

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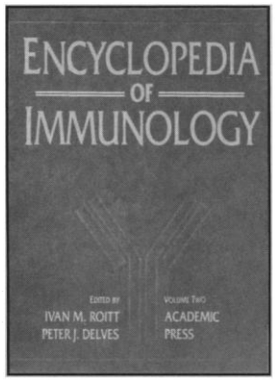

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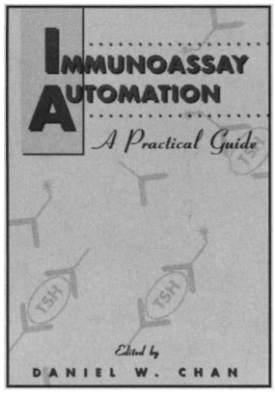

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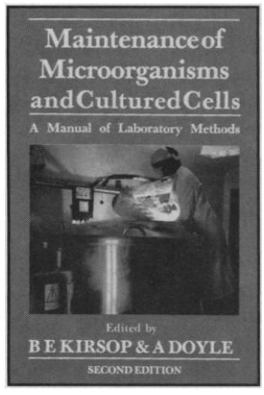

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