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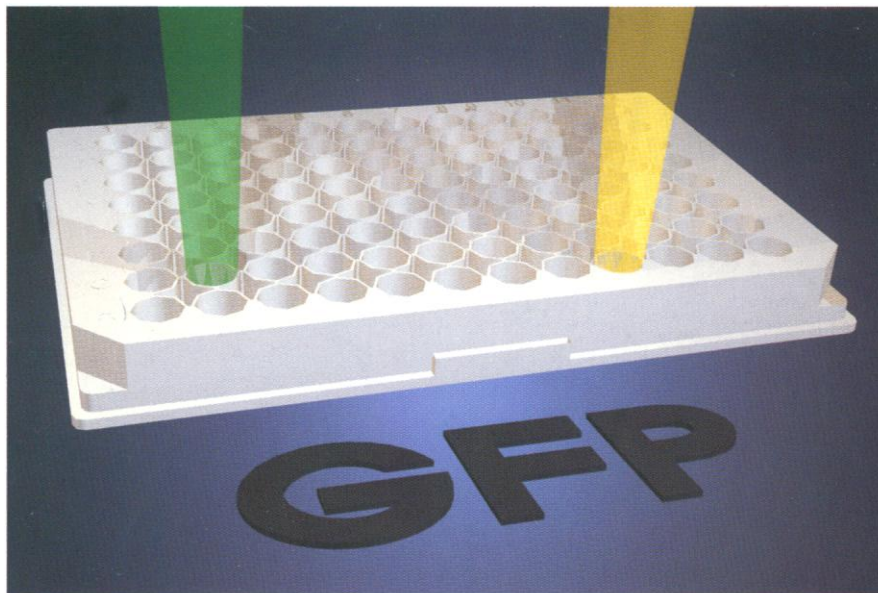
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INSIDE

Advances
in Aging
Research

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- Multiplex (dual reporter) assay capability

Nondestructive, real time promoter assays in microplates



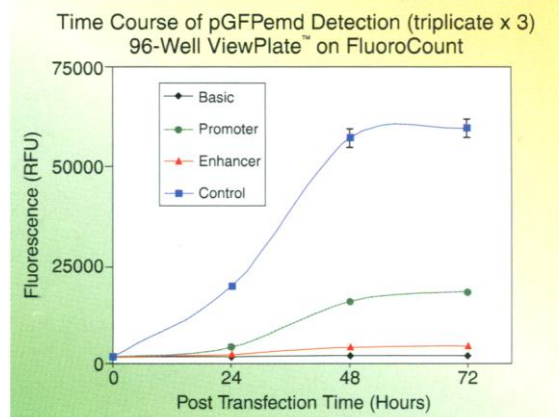
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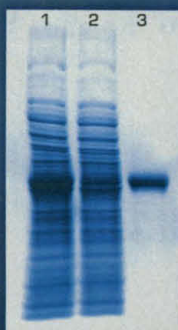
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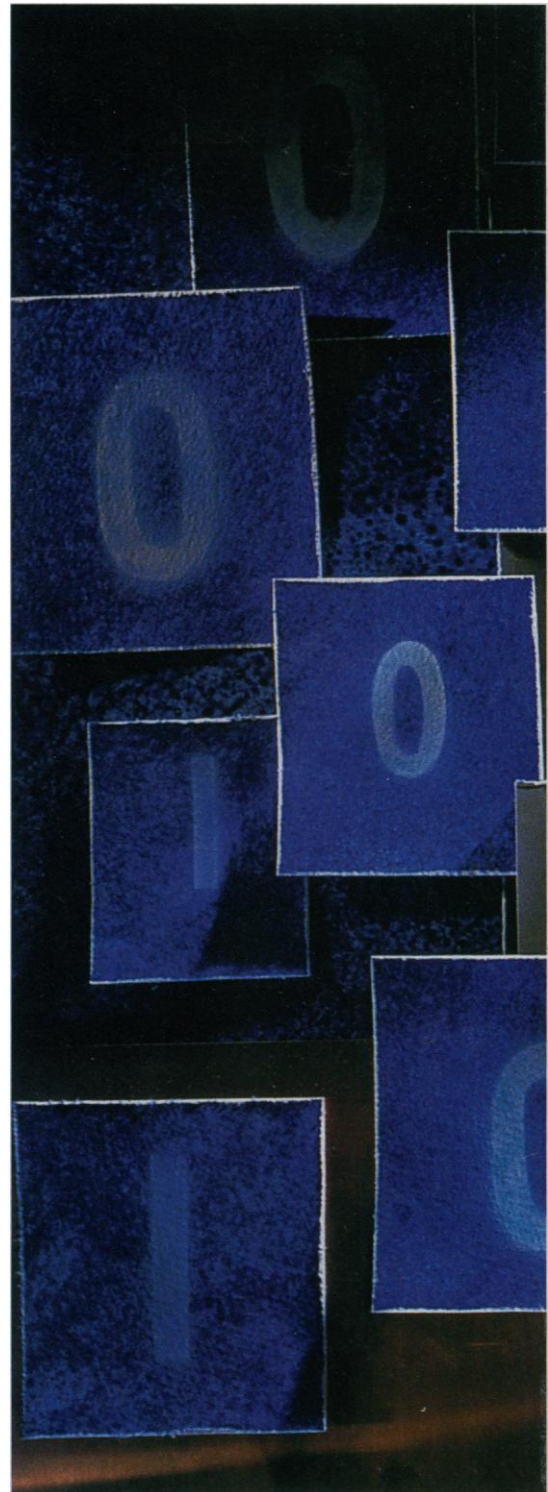
But what if we just turned the problem on its head?

What if we had a drug that could flow freely throughout the body without affecting normal tissue, and then “turn on” only when and where it was needed? And what if it only required a low-power, non-thermal red light for activation?

This is the vision of PhotoPoint™, a dramatic new medical procedure being developed by Miravant. It may give medical practitioners a high degree of selectivity and control in a minimally invasive procedure.

PhotoPoint may have application for a wide range of conditions ranging from cancers to eye diseases, and is now being tested in preclinical and clinical studies in the U.S. and internationally.

We’ll be telling you more about PhotoPoint in the months to come. Stay tuned.



PhotoPoint has potential to selectively target a range of abnormal tissues in the body, such as diseases like cancer or retinal abnormalities.



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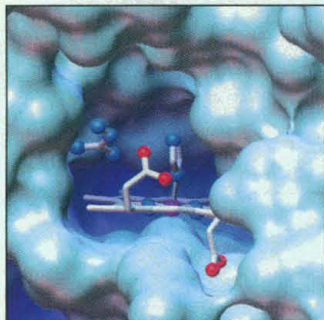


Targeted cells are destroyed by an interaction between the drug and the light, with minimal known side effects. PhotoPoint, now in clinical trials, is being developed as an outpatient procedure.

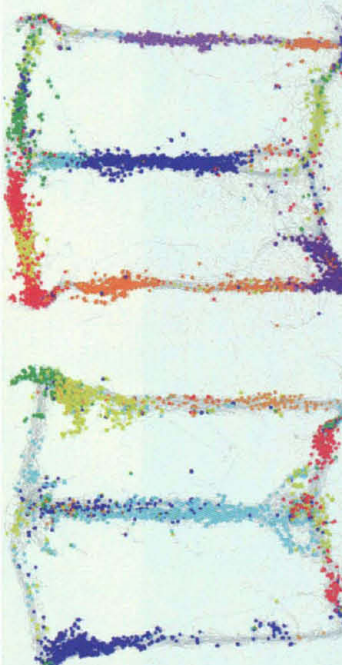
Learn more about PhotoPoint™ and Miravant (Nasdaq: MRVT) at www.miravant.com, or call toll-free at 888-685-6788. The company's products require U.S. Food and Drug Administration approval before marketing.



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389 & 425
Handling hemes



412
Aging memories

NEWS & COMMENT

- Backlash Disrupts China Exchanges **376**
Panel Sets Out Cuts Under Tight Budget **377**
Senate Hears Testimony Supporting OAM **378**
U.S.-India Pact to Plug Data Gap **379**
Glaxo to Close Top-Ranked Institute **379**
Population Research Center Launched **380**
Rocky Mix Suggests Wet Early Mars **380**
Questions Still Roil the Waters as MBL Charts New Course **381**

RESEARCH NEWS

- Patterning Electronics on the Cheap **383**
Researchers Find Signals That Guide Young Brain Neurons **385**
The Balance of Power in Ancient Ireland **386**
Two Spacecraft Track the Solar Wind to Its Source **387**
Turning Up the Heat in the Corona **387**
Terribly Tiny Transistor Unveiled **388**
Biologists Catch Their First Detailed Look at NO Enzyme **389**
Biodiversity in a Vial of Sugar Water: Natural Selection's Capricious Ways **390**

PERSPECTIVES

- A Missing Link? LTP and Learning **401**
D. Johnston
Neocortical Neurons: Where Do They Come From? **402**
A. Lumsden and M. Gulisano
Lensing by Triton's Atmosphere **403**
W. B. Hubbard
Crystal Gazing: Structure Prediction and Polymorphism **404**
G. R. Desiraju

ARTICLES



ADVANCES IN AGING RESEARCH

- Genetics of Aging **407**
C. E. Finch and R. E. Tanzi
Life and Death of Neurons in the Aging Brain **412**
J. H. Morrison and P. R. Hof
The Endocrinology of Aging **419**
S. W. J. Lamberts, A. W. van den Beld, A.-J. van der Lely

RESEARCH ARTICLE

- The Structure of Nitric Oxide Synthase Oxygenase Domain and Inhibitor Complexes **425**
B. R. Crane, A. S. Arvai, R. Gachhui, C. Wu, D. K. Ghosh, E. D. Getzoff, D. J. Stuehr, J. A. Tainer

DEPARTMENTS

THIS WEEK IN SCIENCE

361



EDITORIAL

The New Gerontology
J. W. Rowe

367

LETTERS

369

Global Choices: R. W. Nichols • Coelacanth Catches: C. S. Churcher; W. E. Bemis and A. M. Simons • Allometric Scaling Laws in Biology: C. A. Beuchat; J. Kuikka; Response: J. H. Brown, B. J.

Enquist, G. B. West • Corrections and Clarifications

SCIENTESCOPE

375

RANDOM SAMPLES

391



BOOK REVIEWS

399

Why We Age and Between Zeus and the Salmon, reviewed by B. Charlesworth • Vignettes • Browsers

TECH.SIGHT

497

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COVER

Scanning electron micrograph of the nematode *Pristionchus pacificus* (~1 millimeter long). Ventral epidermal cells differ in fate among nematode species. In *Caenorhabditis elegans*, these cells fuse with the epidermis, whereas in *P. pacificus*, the homo-

gous cells die of apoptosis. Genetic analysis in *Pristionchus* indicates that this evolutionary alteration is driven by different intrinsic properties of the epidermal cells. See page 452. [Image: J. Berger, A. Eizinger, R. J. Sommer]



REPORTS

Volatile Compounds in Archaeological Plant Remains and the Maillard Reaction During Decay of Organic Matter

R. P. Evershed, H. A. Bland, P. F. van Bergen, J. F. Carter, M. C. Horton, P. A. Rowley-Conwy

Ferric Iron Content of Mineral Inclusions in Diamonds from São Luiz: A View into the Lower Mantle

C. McCammon, M. Hutchison, J. Harris

Triton's Distorted Atmosphere

J. L. Elliot, J. A. Stansberry, C. B. Olkin, M. A. Agner, M. E. Davies

Response of the African Monsoon to Orbital Forcing and Ocean Feedbacks in the Middle Holocene

J. E. Kutzbach and Z. Liu

Direct Observation of Cooling of Heme Upon Photodissociation of Carbonmonoxy Myoglobin

Y. Mizutani and T. Kitagawa

DNA Solution of the Maximal Clique Problem

Q. Ouyang, P. D. Kaplan, S. Liu, A. Libchaber

Direct Visualization of Individual Cylindrical and Spherical Supramolecular Dendrimers

S. D. Hudson, H.-T. Jung, V. Percec, W.-D. Cho, G. Johansson, G. Ungar, V. S. K. Balagurusamy

The Homeotic Gene *lin-39* and the Evolution of Nematode Epidermal Cell Fates

A. Eizinger and R. J. Sommer

Phosphorylation of Sic1p by G₁ Cdk Required for Its Degradation and Entry into S Phase

R. Verma, R. S. Annan, M. J. Huddleston, S. A. Carr, G. Reynard, R. J. Deshaies

CDC20 and CDH1: A Family of Substrate-Specific Activators of APC-Dependent Proteolysis

R. Visintin, S. Prinz, A. Amon

Forward and Backward Propagation of Dendritic Impulses and Their Synaptic Control in Mitral Cells

W. R. Chen, J. Midtgard, G. M. Shepherd

Mediation of Classical Conditioning in *Aplysia californica* by Long-Term Potentiation of Sensorimotor Synapses

G. G. Murphy and D. L. Glanzman

Inhibition of Phosphatases and Increased Ca²⁺ Channel Activity by Inositol Hexakisphosphate

O. Larsson, C. J. Barker, Å. Sjöholm, H. Carlqvist, R. H. Michell, A. Bertorello, T. Nilsson, R. E. Honkanen, G. W. Mayr, J. Zwiller, P.-O. Berggren

Interneuron Migration from Basal Forebrain to Neocortex: Dependence on *Dlx* Genes

S. A. Anderson, D. D. Eisenstat, L. Shi, J. L. R. Rubenstein

Regulation of Gliogenesis in the Central Nervous System by the JAK-STAT Signaling Pathway

A. Bonni, Y. Sun, M. Nadal-Vicens, A. Bhatt, D. A. Frank, I. Rozovsky, N. Stahl, G. D. Yancopoulos, M. E. Greenberg

Peripheral and Cerebral Asymmetries in the Rat

N. P. LaMendola and T. G. Bever

TECHNICAL COMMENTS

Cannot Earthquakes Be Predicted?

M. Wyss; R. L. Aceves and S. K. Park; Response: R. J. Geller, D. D. Jackson, Y. Y. Kagan, F. F. Mulargia



434

Lower mantle diamonds

■ Indicates accompanying feature

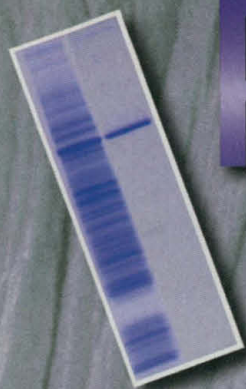
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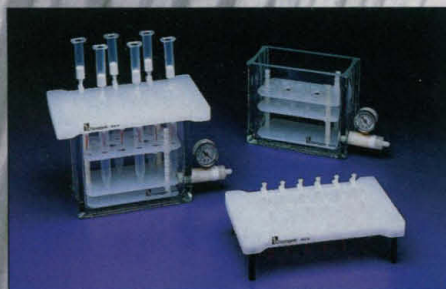
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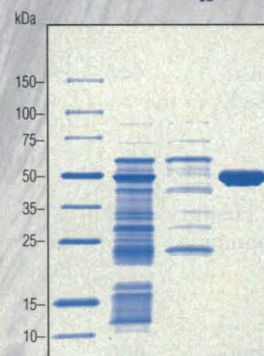
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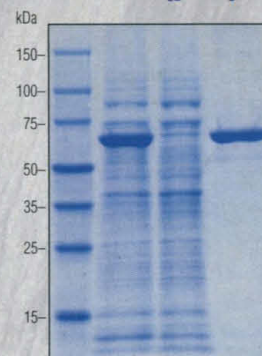
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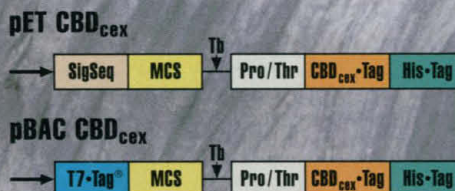
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Elution

E. coli (pET)



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Ancient clues to soil formation

The chemical reactions that begin the degradation of organic matter in soils and sediments, and thus fix carbon, have been difficult to identify. It has been thought that the classic Maillard reaction was involved, in which



sugars and amino acids combine to form compounds with a higher molecular weight (and aromatic by-products that produce the odors of cooked foods). Evershed *et al.* (p. 432) have now identified a characteristic by-product of the Maillard reaction in preserved plant materials at an archaeological site in Egypt.

Developing DNA computing

Computing with DNA molecules is massively parallel, and for certain mathematical search problems, the time needed to find an answer grows only linearly in time with problem size, rather than exponentially with a more typical Turing computer. Ouyang *et al.* (p. 446) incorporated molecular biology methods into a DNA computing algorithm for solving the maximal clique problem (for a given set of vertices and edges, a clique is a set of vertices where each vertex is connected to every other vertex by an edge). Connections in a six-vertex network were represented by DNA sequences, and selective digestion and amplification steps eliminated all but the largest cliques. The authors discuss the need for better algo-

Synthesizing NO signals

Nitric oxide (NO) participates in physiological functions as diverse as blood flow regulation, neurotransmission, and the immune response. Crane *et al.* (p. 425; see the news story by Wickelgren, p. 389) present the crystal structure of the oxygenase domain of nitric oxide synthase (NOS), which catalyzes the addition of an OH group (derived from O₂) to a guanidino nitrogen of arginine. A comparison of this heme-containing structure to those of the cytochrome P-450 family reveals how the dissimilar fold and heme environment of NOS mediate a similar mechanism. The orientations of the inhibitors imidazole and aminoguanidine provide a template for drug design.

rithms; the amount of DNA needed increases exponentially, and this method would be impractical for networks with more than about 40 vertices.

Triton's tempests

Voyager 2 showed that the nitrogen-rich atmosphere of Triton, a moon of Neptune, is dynamic, with evidence of seasonal variations in winds and clouds. Elliot *et al.* (p. 436; see the Perspective by Hubbard, p. 403) observed stellar occultations of Triton's atmosphere from Earth-based telescopes, and in 1995 the Infrared Telescope Facility in Hawaii was situated so that a "central flash," or partial focusing of starlight by Triton's atmosphere, could be seen. They deduce that the middle atmosphere of Triton is distorted from a sphere, an effect that may be caused by supersonic zonal winds or a distorted internal mass distribution.

Modeling monsoons

Atmospheric climate models have typically been used with sea-surface temperature prescribed as a boundary condition, but this approach makes investigations of phenomena such as the monsoon rains, for which the atmosphere and oceans are coupled, problematic; simulations, particularly of past climate in equatorial regions, could not always be reconciled with paleoclimate data. Kutzbach and Liu (p. 440)

used a combination of an ocean and atmospheric model, forced by orbital variations, to examine the behavior of the climate of the equatorial Atlantic Ocean 6000 years ago. The coupled model agrees with the paleoclimate data and implies that monsoon rains were about 20 percent heavier then.

Cell cycle steps

Two reports focus on molecular events that accompany the cell cycle. Identifying the substrates of the cyclin-dependent protein kinases (Cdks) has proven difficult. Verma *et al.* (p. 455) examined molecular control of the transition from the G₁ phase of the cell cycle to S phase (when DNA synthesis occurs) in budding yeast. They found that G₁-Cdks directly phosphorylate Sic1p, an inhibitor of S phase-Cdks. This phosphorylation triggered ubiquitination and consequent degradation of Sic1p, thus relieving inhibition of the S phase-Cdk. Thus, phosphorylation of Sic1p appears to be a central regulated event that controls the transition from G₁ phase to S phase. Visintin *et al.* (p. 460) enhance our understanding of how the protein degradation machinery acts on the right targets at the right time. Two proteins in budding yeast, Cdc20 and Cdh1, act as substrate-specific activators of the anaphase-promoting complex, which degrades target proteins to allow segregation of chromosomes and

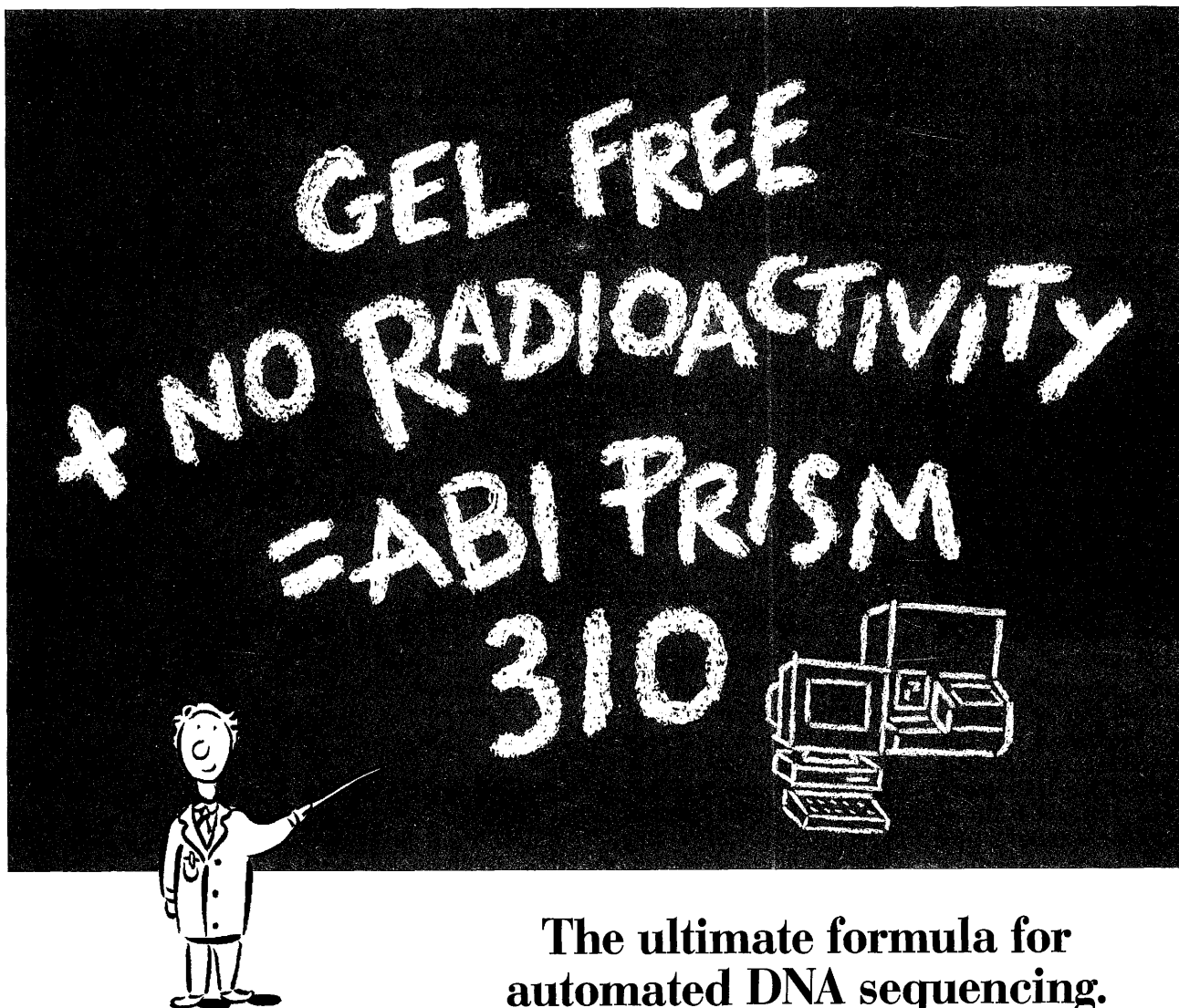
exit of the cell from mitosis. It appears that the activity of the proteolytic machinery is finely tuned by proteins like Cdc29 and Cdh1 so that appropriate targets are degraded at the correct time during the cell cycle.

Insulin signaling

The role of inositol hexakisphosphate (InsP₆) in insulin-secreting cells has been explored by Larsson *et al.* (p. 471). InsP₆ inhibited activity of protein phosphatases 1 (PP1), 2A (PP2A), and 3 (PP3). The inhibition of the phosphatases can in turn help sustain phosphorylation of voltage-gated L-type calcium channel or an associated protein, which leads to increased open probability of the channel, influx of calcium into the cell, and insulin release. Indeed, application of InsP₆ did increase calcium currents through L-type channels in cultured cells. Exposure of the cells to increased concentrations of glucose transiently increased the intracellular concentration of InsP₆. Thus, InsP₆ may contribute to stimulus-secretion coupling in pancreatic β cells.

Brain sources

The vertebrate brain arises from a complex pattern of cell proliferation, cell migration, and folding from what begins as a simple tube. Although previous indications had been that the cells of the neocortex, the complex surface layer of higher vertebrate brains, was formed by proliferation of cells within the neocortical primordium, Anderson *et al.* (p. 474; see the Perspective by Lumsden and Gulisano, p. 402) show that neocortical cells arise from a combination of cells proliferating nearby and cells migrating in from a subcortical zone. The compartments of the mature brain may be less isolated during development.



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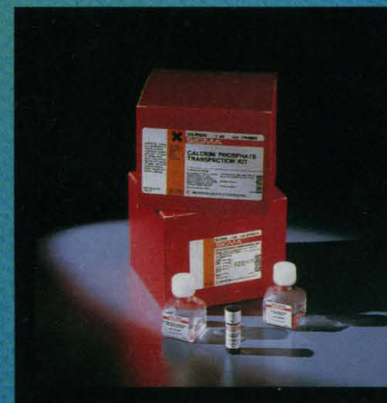
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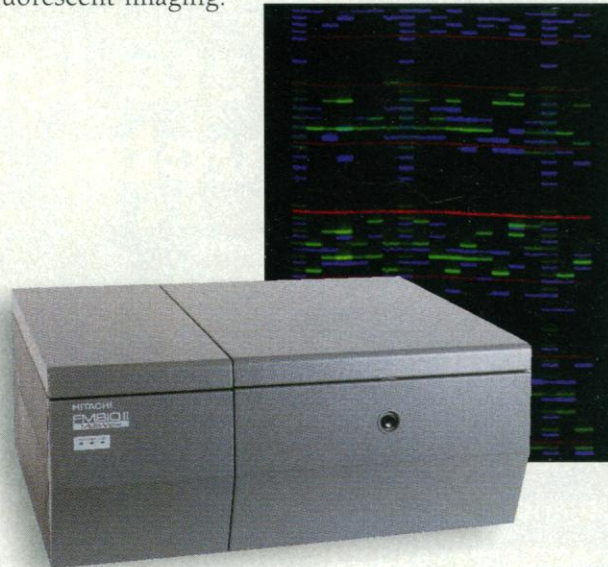


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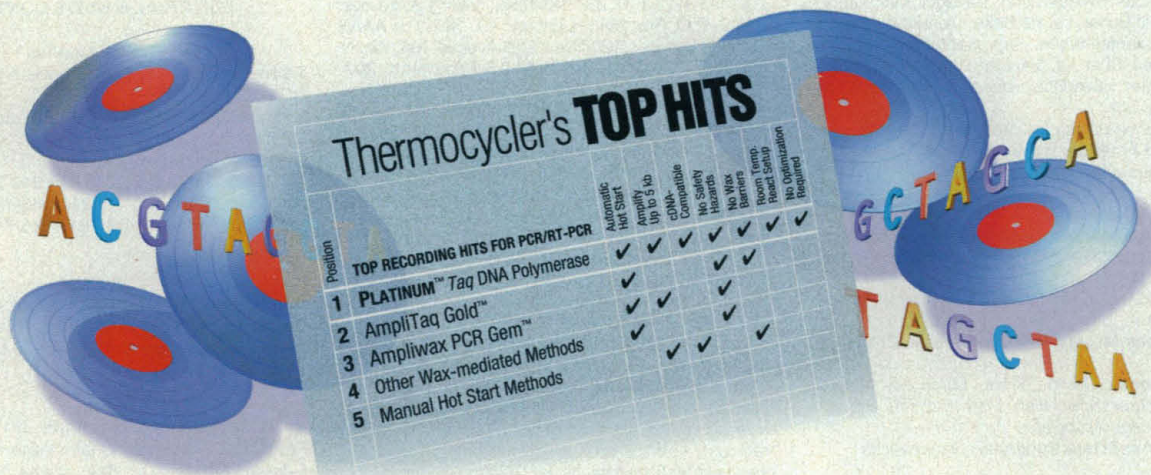
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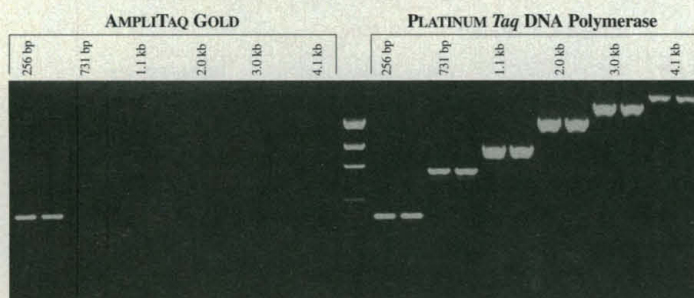
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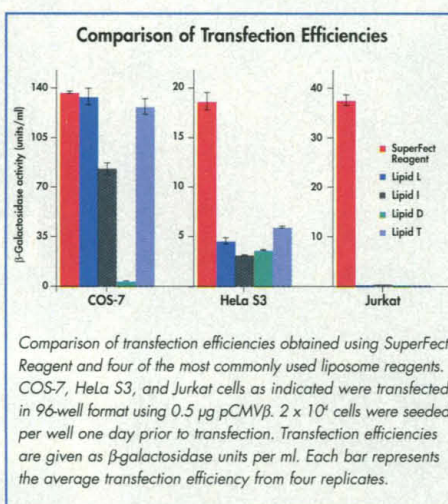
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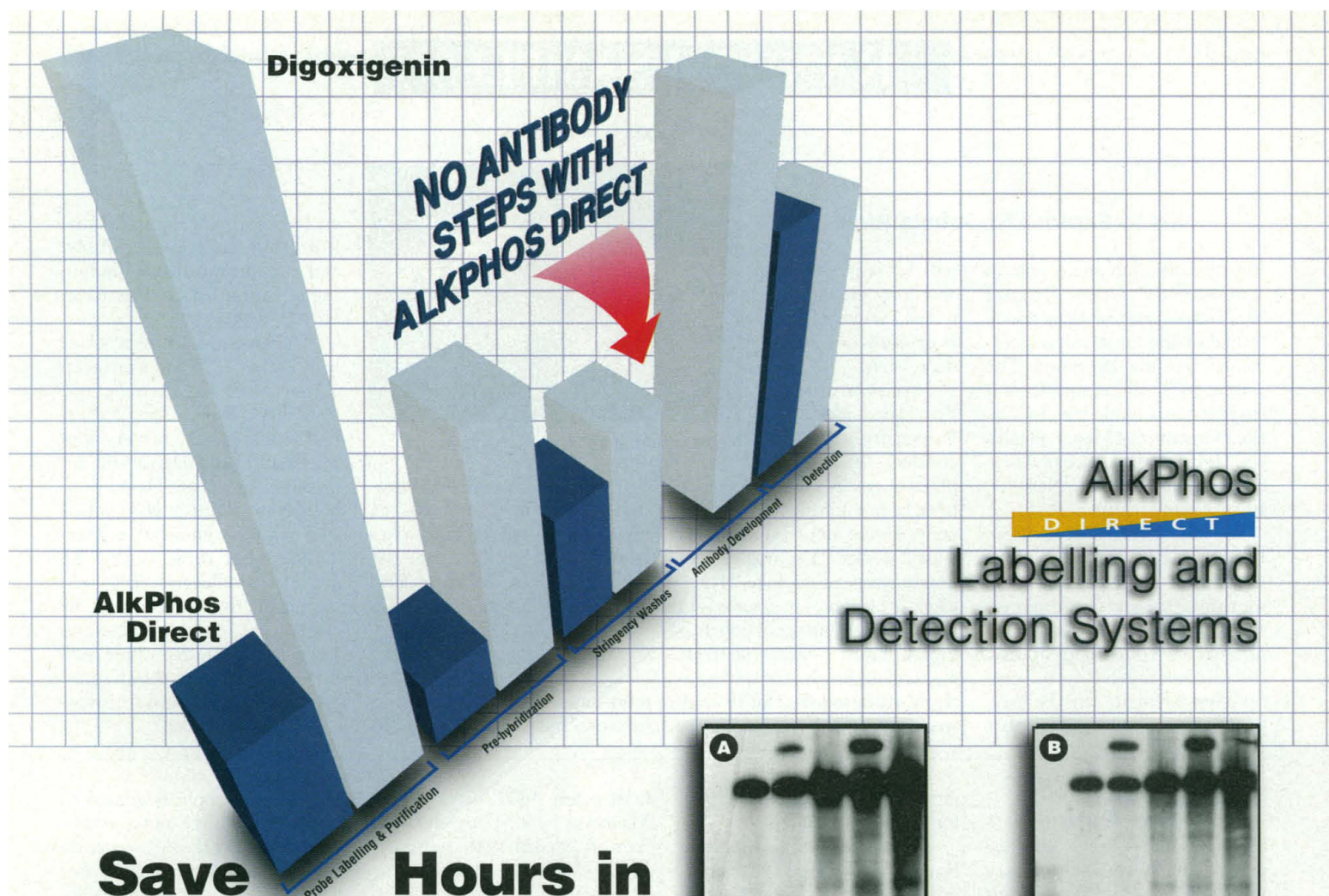
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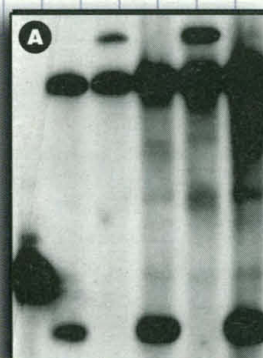
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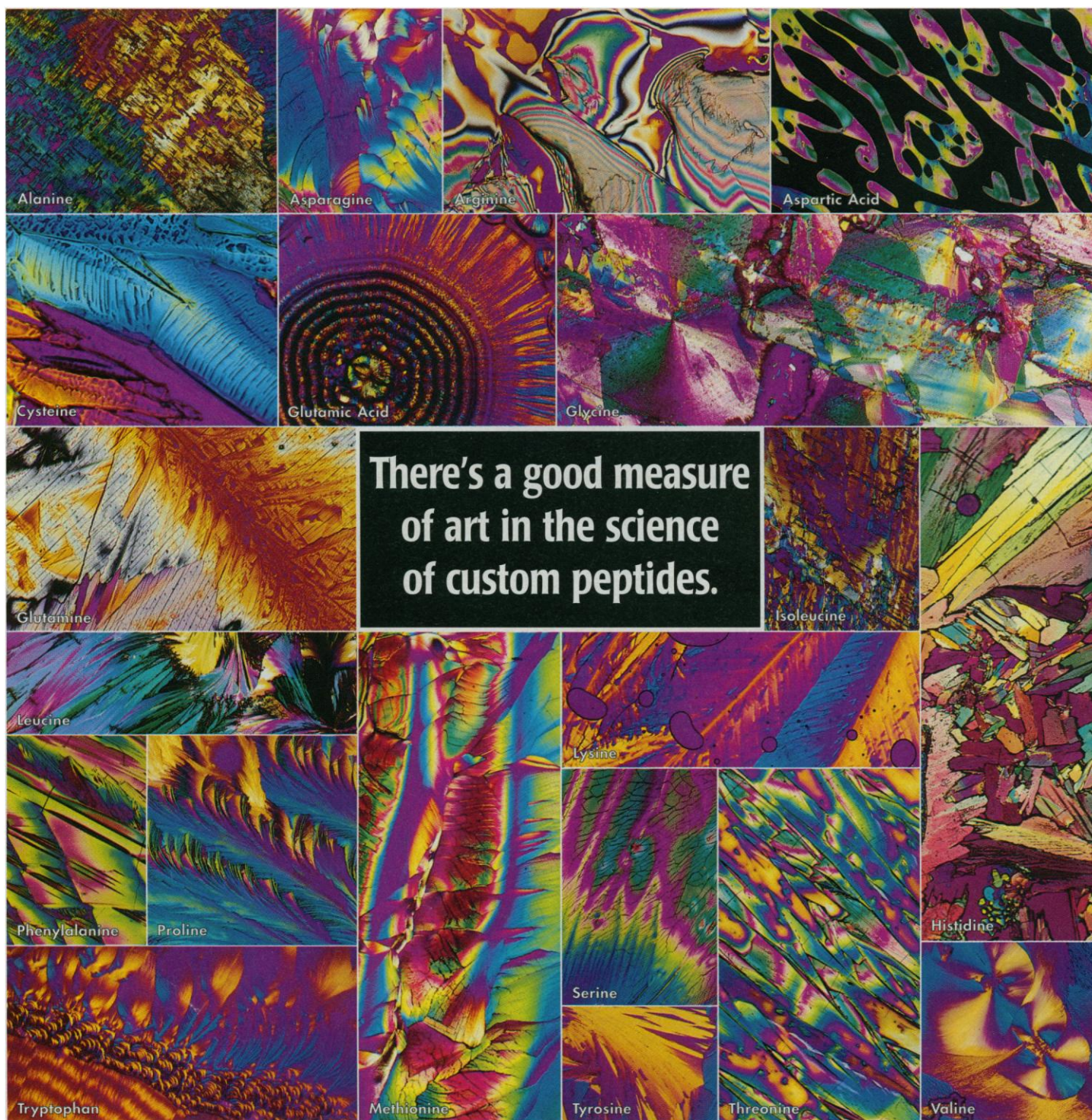
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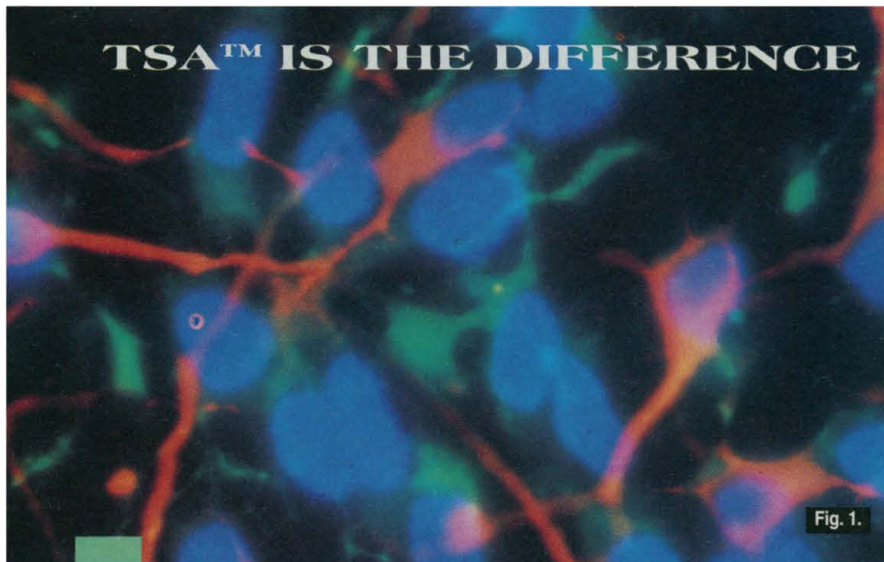


Fig. 1.

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Fig. 1. Multicolor detection using TSA-Direct.
Courtesy of Kevin Roth, M.D., Washington University
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Fig. 2

a. Standard fluorescent detection.



b. TSA-Enhanced fluorescent detection.



c. Standard chromogenic ISH.



d. TSA-Enhanced chromogenic ISH.



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Figs. 2 a-b. Fluorescent detection of chromosome centromere probes in metaphase spreads.
Figs. 2 c-d. *In situ* chromogenic detection of oxytocin in rat brain tissue sections.

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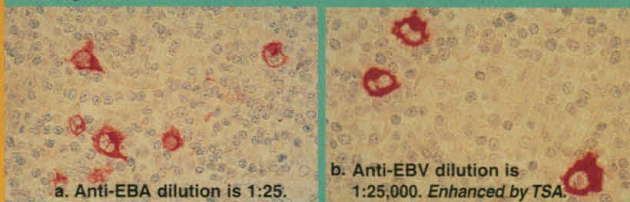
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Fig. 3



a. Anti-EBA dilution is 1:25.

b. Anti-EBV dilution is 1:25,000. Enhanced by TSA.

Figs. 3 a-b. IHC of EBV antigen in Hodgkin's Lymphoma of mixed cellularity.
Courtesy of R. Von Wasielewski and S. Gignac, Pathologisches Institut der
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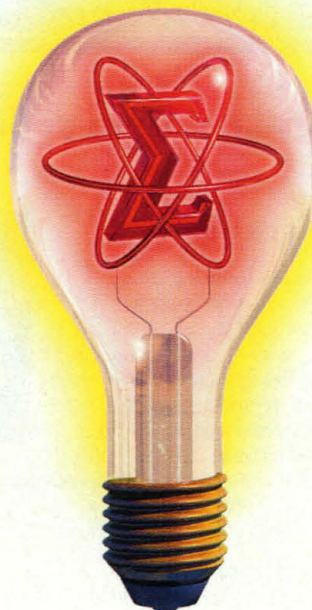
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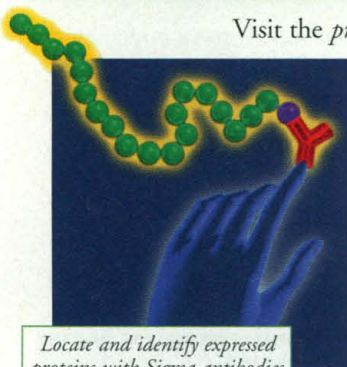


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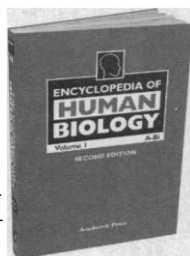
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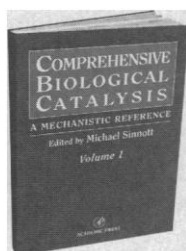
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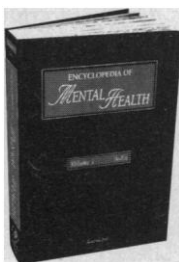
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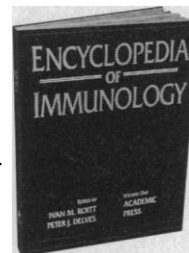
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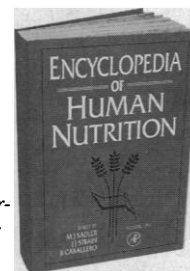
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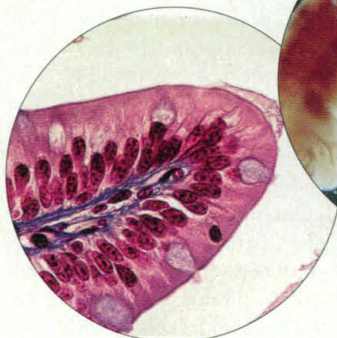
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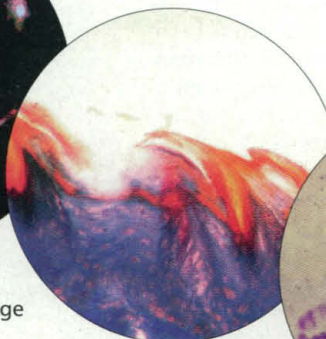
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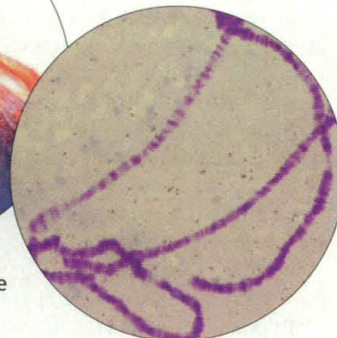
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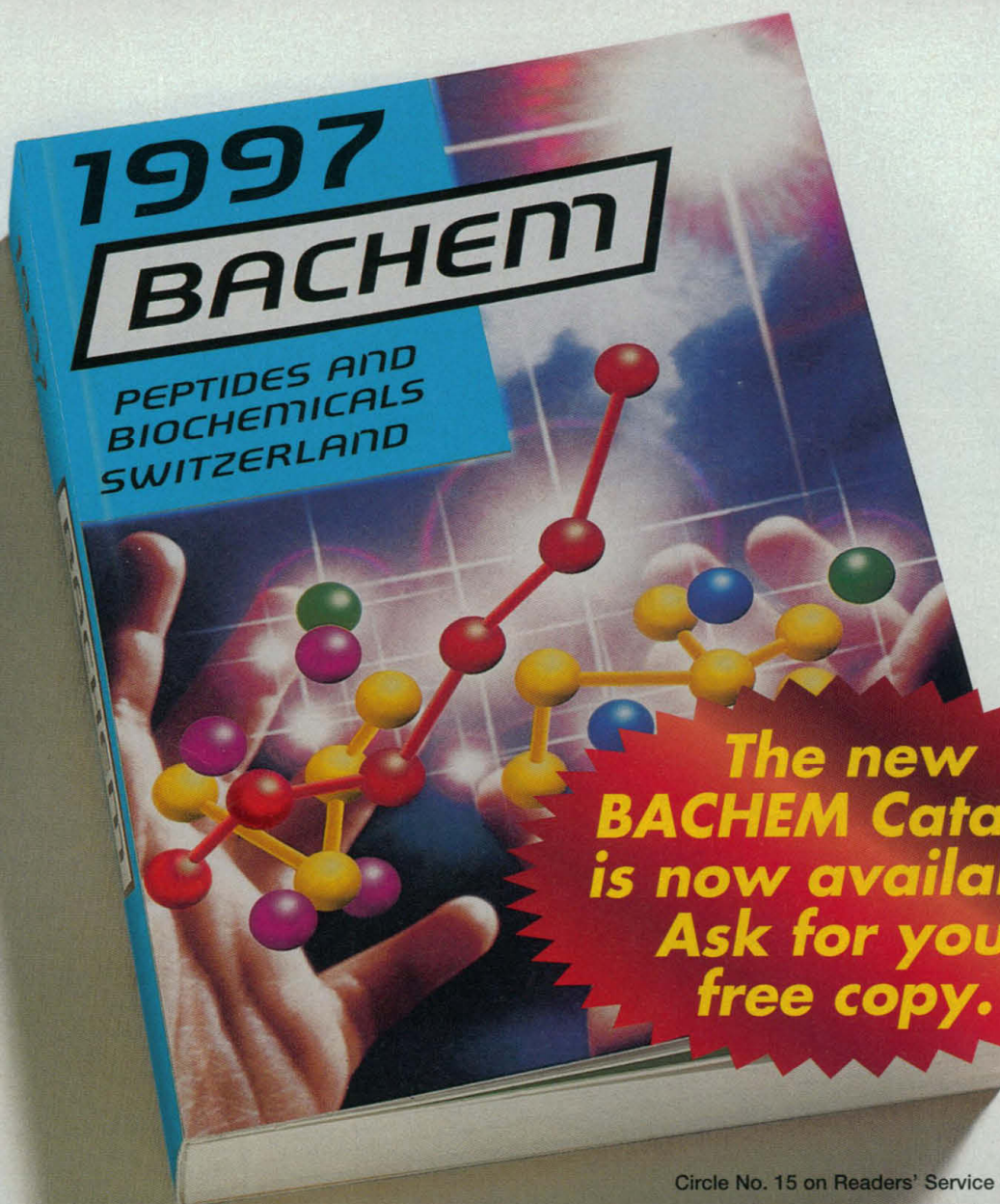
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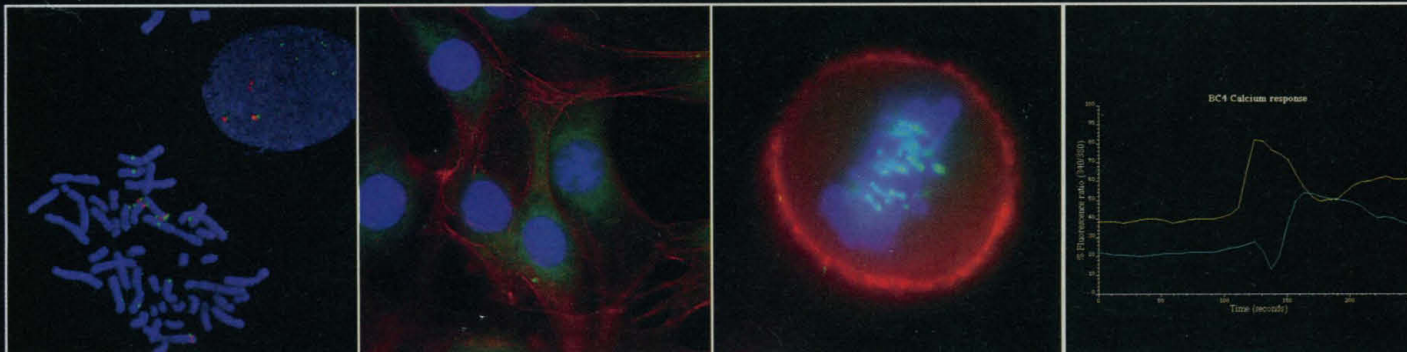
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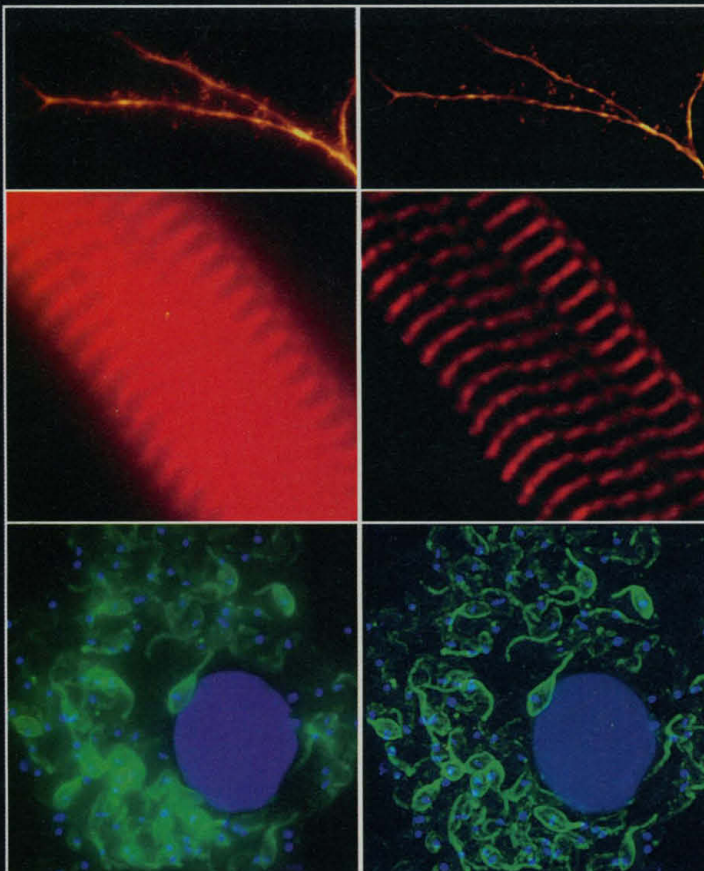
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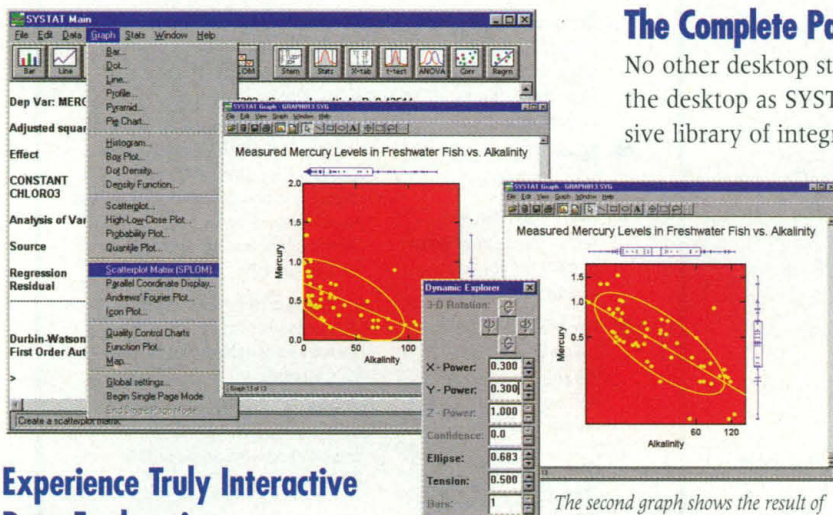
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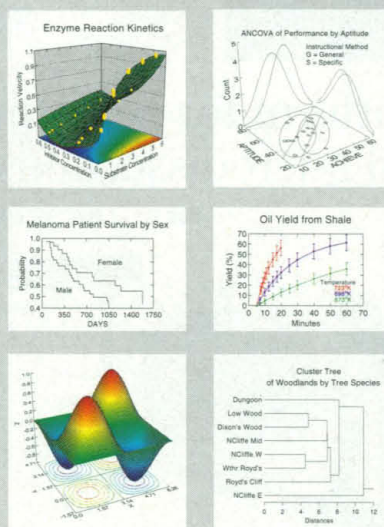
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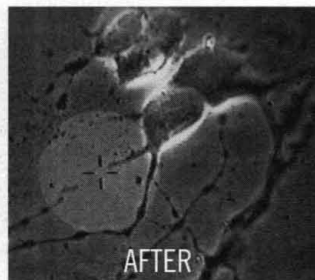
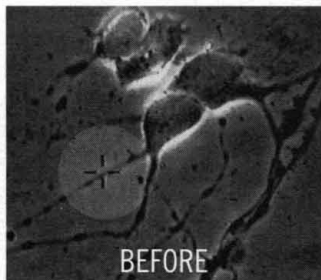
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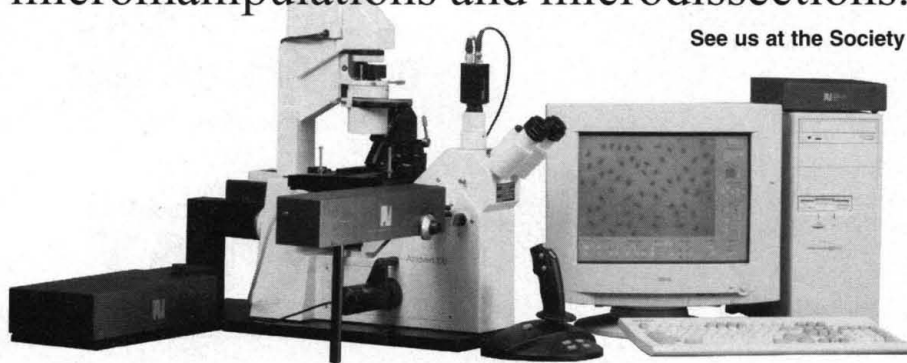


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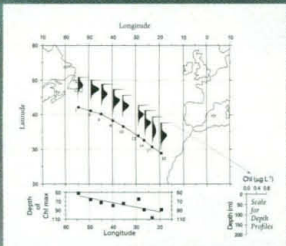
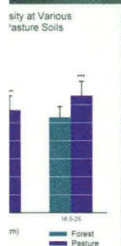
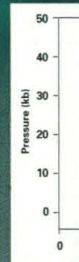
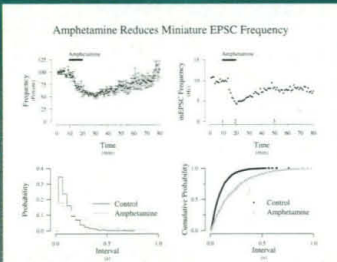
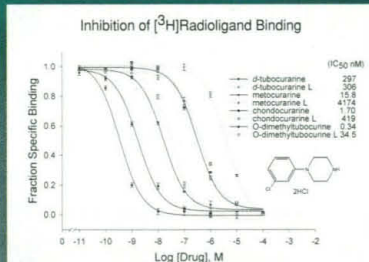
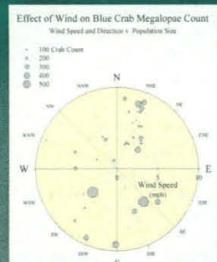
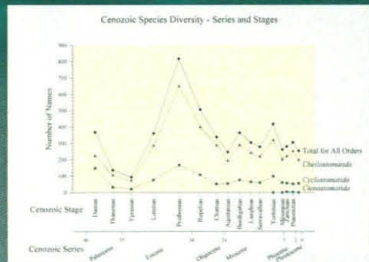
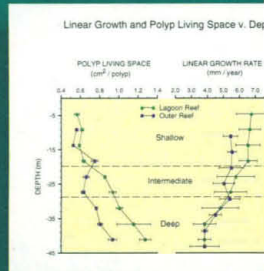
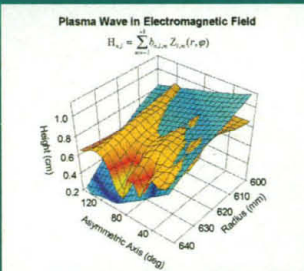
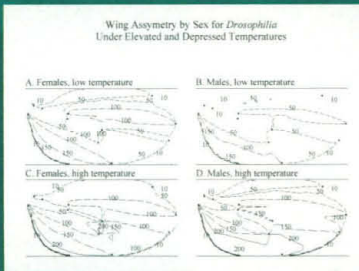
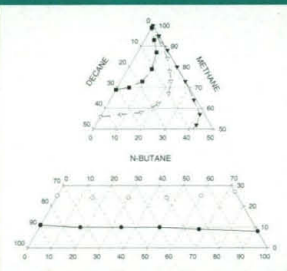
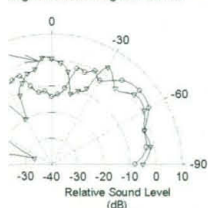
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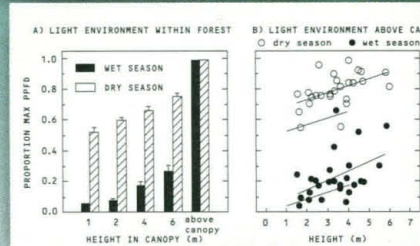
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