7 June 2002

Science

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Pages 1753–1916 $9

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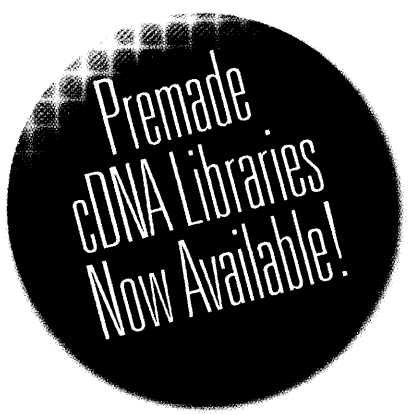

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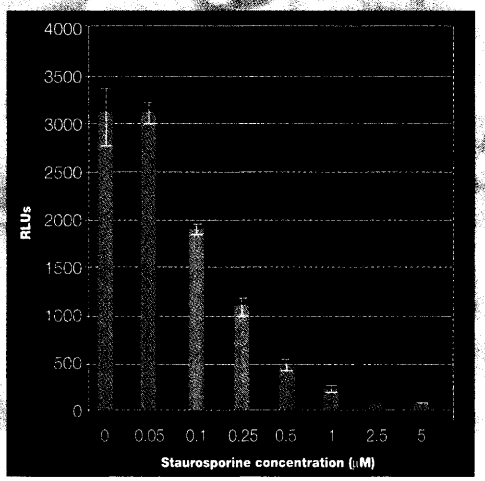

Fig 1. The cytotoxic effect of staurosporine on rat hepatocytes (out of cryopreservation) determined by ATP bioluminescence using the ViaLight HS assay kit. The results are the means ± SD for triplicate measurements.

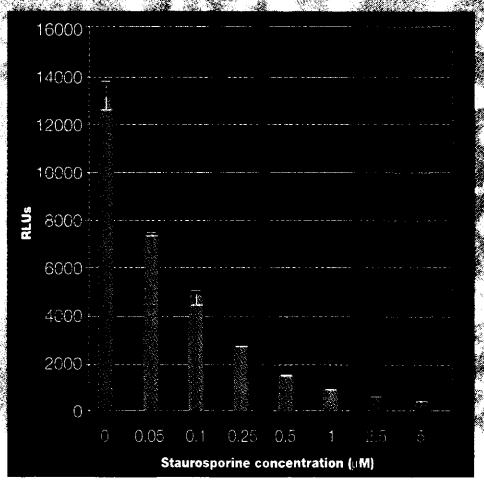

Fig 2. The cytotoxic effect of staurosporine on human hepatocytes (out of cryopreservation) determined by ATP bioluminescence using the ViaLight HS™ assay kit. The results are the means ± SD for triplicate measurements.

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Science

Volume 296 7 June 2002 Number 5574

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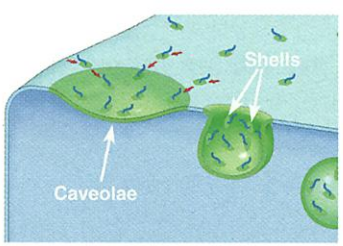

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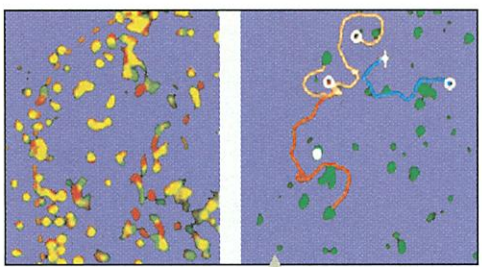
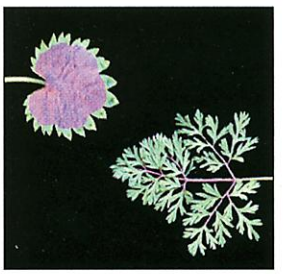


1873

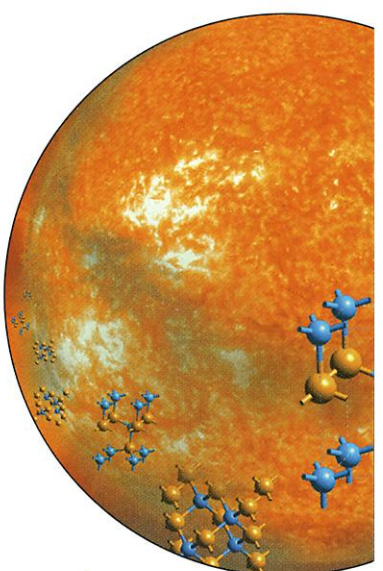
The immune system in action

REPORTS



COVER 1858

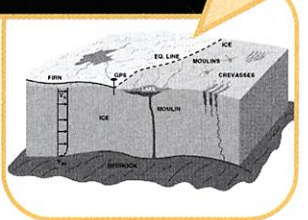
A time series of leaf development for two members of the Apiaceae family—anise (left) and carrot (right). Differences in blade growth (magenta) and marginal growth (cyan) result in final leaf forms that are simple in anise but dissected in carrot. Recent evolution of leaf form included such changes in secondary morphogenesis. [Image: T. E. Goliber, S. Kessler, N. R. Sinha]



1852

Structural simplicity of stardust

New on *Science* Express Top to bottom effect



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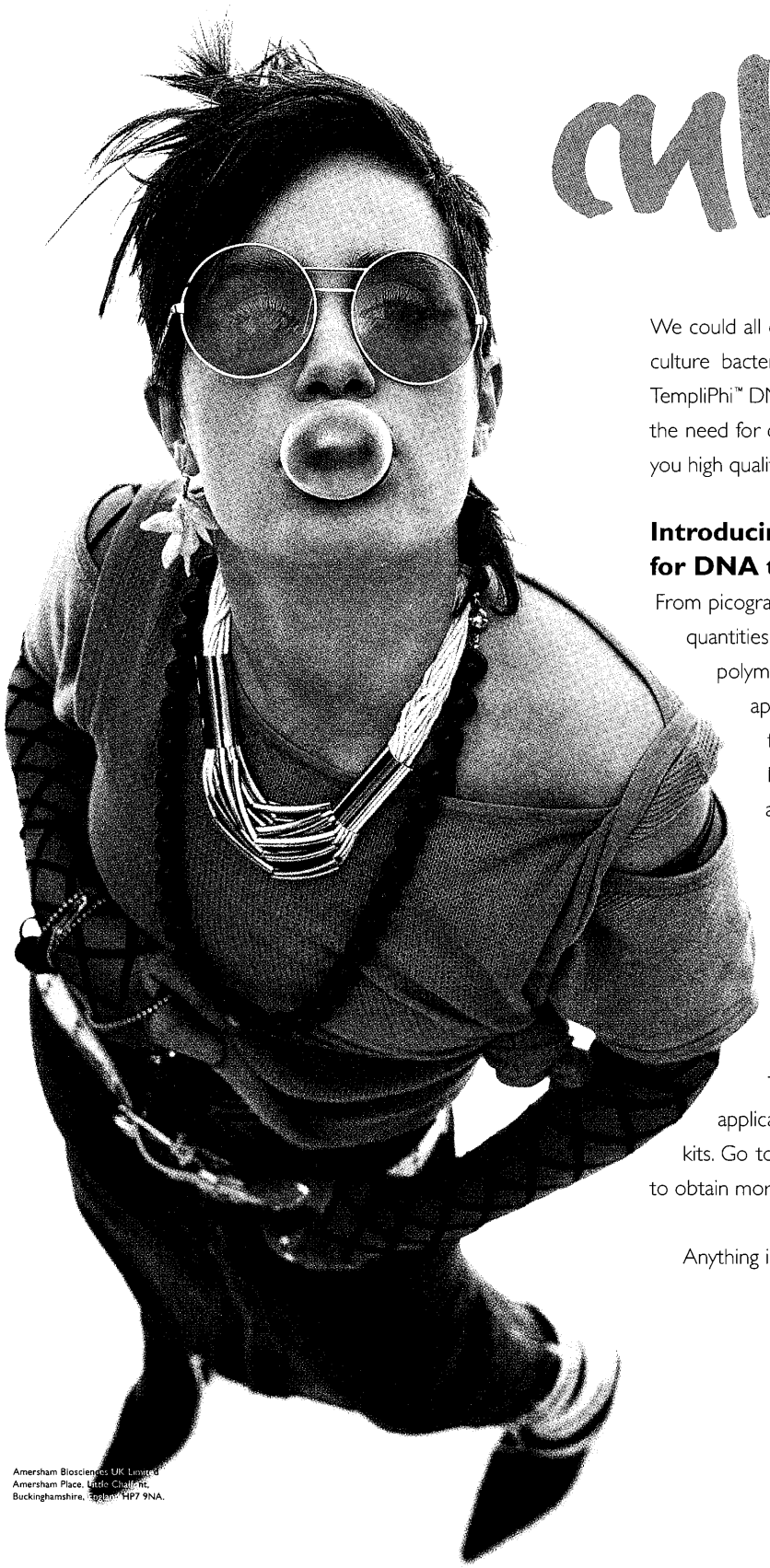

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CONTENT HIGHLIGHTS AS OF 7 JUNE 2002

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SCIENCE EXPRESS

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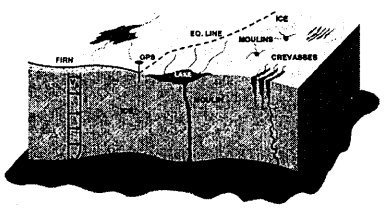
Surface Melt–Induced Acceleration of Greenland Ice-Sheet Flow H. J. Zwally *et al.*

The speed at which some parts of the Greenland ice sheet flow increases during summer because of rapid migration of surface meltwater to the ice-bedrock interface.



Covariation of Synaptonemal Complex Length and Mammalian Meiotic Exchange Rates A. Lynn *et al.*

Variations in male germ cell recombination rates correlate with length of the synaptonemal complex.

Role of Formins in Actin Assembly: Nucleation and Barbed End Association D. Pruyne *et al.*

The mechanism for forming unbranched actin cables is clarified.

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career resources for scientists

GLOBAL: Careers in the Forensic Sciences Edited by L. McKarney

Scientists from a wide range of backgrounds explain how they began working in forensics.

UK: Self-Help Advice for Postdocs P. Gardner

The fledgling Cambridge postdoc association strives to make its voice heard.

NETHERLANDS: Science or Technology? S. Oomes

After a number of job interviews, an academic's thoughts turn entrepreneurial.

GERMANY: Germany's Top 20 Universities E. von Ruschkowski

The Humboldt Foundation reveals a surprising ranking of Germany's Top 20.

GRANTSNET: June News K. Cottingham

Federal forensics funding; two Gates Cambridge Scholars; and the latest biomedical funding news.

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Booby Trap C. Aschwanden

Cancer gene spurs production of DNA-assaulting chemicals that alert and defuse rescue molecules.

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Rrm protein jump-starts idle DNA copying equipment.

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Perspective: KSR—A Regulator and Scaffold Protein of the MAP Kinase Pathway T. Raabe and U. R. Rapp

Organizing specific signaling complexes through adaptors.

Protocol: The Slice Overlay Assay—A Versatile Tool to Study the Influence of Extracellular Signals on Neuronal Development F. Polleux and A. Ghosh

A method for culturing dissociated cells over cortical slices to study differentiation and axonal and dendritic patterning signals.

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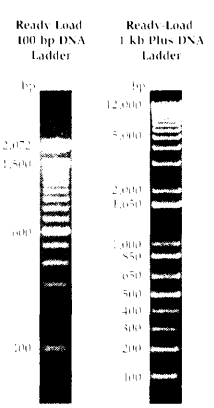

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THIS WEEK IN Science

edited by Phil Szuromi

Equal to the Task

Reversible processes make the thermodynamist's life simpler, but the experiments can require a lot of waiting. In 1997, Jarzynski derived a remarkable equality that relates the work done in irreversible processes to the equilibrium, or reversible, free energy difference of the system, no matter how far from equilibrium the irreversible paths might go. The catch, however, is that the more irreversible the paths measured, the larger the number of trials that must be performed to achieve a reasonable standard deviation. Liphardt *et al.* (p. 1832; see the Perspective by Egolf) now report an experimental verification of Jarzynski's equality, based on hundreds of stretches of a single molecule of RNA between its folded and unfolded conformations.

1838 Off in a Shot

Scanning probe methods should make it possible to map out the full series of steps that occur during the desorption of molecules from surfaces. However, desorption often occurs at temperatures where molecular diffusion is rapid, especially when recombination of species precedes desorption, and these diffusion events obscure the picture. Dürr *et al.* (p. 1838) used a single-shot laser pulse to locally heat hydrogen molecules on a Si(001) surface to accelerate desorption but not diffusion of nearby sites. During conventional heating of this system, the pair of hydrogen atoms that escaped came from the same dimer, and the two dangling silicon orbitals formed a π-like bond. However, after the laser-pulse experiment, the dangling bonds were paired on adjacent dimers. Desorption may be occurring through an interdimer reaction, which would now agree with known mechanisms for the adsorption process.

And in Brevia ...

An analysis of molecular data by Paxinos *et al.* (p. 1827) indicates that the nene, or Hawaiian goose, lost much of its genetic diversity during the expansion of the Polynesian population on the islands.

Getting a Grip on Stem Cells

A stem cell's microenvironment, or niche, is important, both for localizing the stem cell as well as for providing cues for replenishing the stem cell supply or directing the cell down a specific developmental pathway. Song *et al.* (p. 1855) examined how germline stem cells in the *Drosophila* ovary are maintained in their niche. E-cadherin–mediated cell adhesion is involved in recruiting the germline stem cells to the niche and anchoring them to the neighboring cap cells, thus keeping the germline cells from differentiation. Similar adhesion mechanism may exist in other stem cell microenvironments.

Big Bad Flood Basalts

The Siberian Traps flood basalt province in Russia occurred near the Permian-Triassic boundary, and this volcanism, which would have released gases such as sulfuric acid and carbon dioxide, could account for the major extinctions during this period. Reichow *et al.* (p. 1846; see the Perspective by Renne) determined the age and chemistry of borehole samples of basalts from the western Siberian Basin and found that the western basalts correlate with the Siberian Traps flood basalt province to the east. This new correlation doubles the extent and thus the potential environmental impact of the Siberian flood basalts.

Closing the Loop in Neuroprosthetic Control

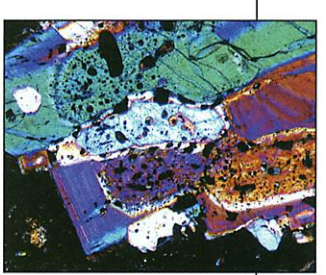
Neuroscientists have tried to control the movement of prosthetic arms or hands by signals from motor cortex neurons. These studies have largely been open-loop, in that subjects could not see the movement that was commanded by their cortex. Taylor *et al.* (p. 1829; see the Perspective by König and Vershure) developed a closed-loop paradigm in which subjects have visual feedback of their brain-controlled movements and found that movement tasks could be performed with much higher accuracy. The pool of motor neurons from which recordings were made also retune their directional selectivity during training. This finding enables brain-controlled virtual movements with nearly the same accuracy, robustness, and speed as normal arm movements.

Colloidal Control of Fluid Flow

In microfluidic systems a number of tools have evolved to control the flow and mixing of the fluid streams. Most of these, however, depend on some intrinsic property of the fluids and surfaces, such as electrokinetic pumping, or combinations of hydrophilic and hydrophobic surfaces. Terray *et al.* (p. 1841; see the Perspective by Burns) add a generic set of tools to the toolbox, by showing that colloidal particles can be used to create pumps and valves with dimensions of just a few micrometers. The pumps are controlled by an optical trap, which cycles through a preprogrammed pattern to control each colloidal particle that makes up the pump. The valves can be either passive or actively controlled with optical trapping.

From Sulfide to Ore

Economically valuable concentrations of copper (Cu) and gold (Au) ore deposits are produced by hydrothermal alteration of intermediate to acidic, silica-rich igneous rocks. Halter *et al.* (p. 1844) used highly sensitive mass spectrometry to measure the concentrations of Cu and Au in primary melt inclusions in minerals from the Bajo de la Alumbrera Mine in Argentina. These results indicate that the metals were initially concentrated in a sulfide melt and then released and concentrated in the ore deposits by secondary hydrothermal alteration.



Can't Leaf Without Them

The shape of plant leaves has been of value in considering the evolutionary relationships between plants. Simple and complex

CREDITS: (TOP) PAXINOS *ET AL.*; (BOTTOM) HALTER *ET AL.*

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leaves, without and with lobes and divisions, are found through multiple plant taxa. Bharathan *et al.* (p. 1858; see the cover) have analyzed the expression of *KNOXI* homeobox genes in the shoot apical meristems from plants of a variety of taxa. The pattern of KNOXI expression is different in meristems that will give rise to primary simple and complex leaves. KNOXI expression patterns also reveal that some seemingly simple leaves are secondary evolutionary refinements of previously complex leaves.

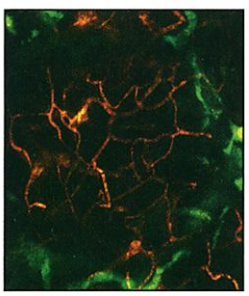
Assessing CNS Axon Regeneration

Neurons of the central nervous system (CNS) are much less able to repair themselves after damage than are neurons of the peripheral nervous system. The causes might lie with the differences in environment and type of surrounding glia, or with the neurons themselves. Goldberg *et al.* (p. 1860; see the Perspective by McKerracher and Ellezam) have isolated retinal ganglion cells (RGCs), which form part of the CNS, from the rat to study their ability to regenerate axons. RGCs isolated from embryonic rats showed a much greater capability for axon regeneration than did RGCs from early postnatal rats. The diminishing capacity for axonal regeneration correlated with developmental times at which the RGC axons would normally have reached their targets and switched from axonal growth to dendrite elaboration. The switch in growth mode was not related to intrinsic cell age but, rather, arose from signals from neighboring retinal cells.

Animated Immunity

Our current understanding of the complex cellular interactions required for immune responses has come largely from in vitro manipulation or from snapshots of events within fixed tissues. Three reports now describe real-time analysis of immune cell responses within living tissues (see the Perspective by von Andrian). Using two-photon technology to compare migration of T and B cells within organized lymphoid tissue, Miller *et al.* (p. 1869;) observed that T cells roam considerably further and at faster rates than B cells. This explorative behavior shifted toward focused clustering upon inclusion of antigen. Stoll *et al.* (p. 1873) used modified single-photon confocal imaging to investigate interactions of naïve T cells with antigen on dendritic cell (DC) in lymph nodes. Extended periods of connection, with the formation of immune synapses and eventual departure of activated T cells, were observed in the presence of antigen-loaded DCs. Bousso *et al.* (p. 1876) used two-photon imaging to study thymocyte interactions with thymic stromal cells in a reaggregated thymic organ culture. Recognition events that resulted in positive selection of thymocytes promoted thymocyte motility and increased the duration of thymocyte–thymic stromal cell contacts.

Form But No Function



Lymphatic vessels have been detected within tumors by immunostaining, but the role of these structures in tumor cell metastasis has been debated. Applying rigorous functional assays to a mouse model of metastasis, Padera *et al.* (p. 1883; see the Perspective by Gershenwald and Fidler) show that although the central regions of the tumors stain with molecular markers for the lymphatic system, the vessels there are nonfunctional. Metastasis appears to occur solely through lymphatic vessels at the tumor margin, a distinction that may have important implications for cancer therapy.

CREDIT: PADERA *ET AL.*

Oxygen in the Cell

The cellular response to oxygen—or the lack of it—is important in diseases such as cancer, cardiovascular disease, and stroke. Min *et al.* (p. 1886) have gained insight into an interaction that is key to this response by determining the structure at 1.85 angstroms resolution of a 20-residue peptide from the hypoxia-inducible transcription factor (HIF) bound to a von Hippel–Lindau tumor suppressor (pVHL)–ElonginB–ElonginC complex. The structure shows that hydroxyproline plays a central role in the specificity and affinity of the interaction and binds at a site in pVHL that is a hotspot for tumorigenic mutations. The structure could provide a basis for designing drugs that could help treat cardiovascular disease and stroke.

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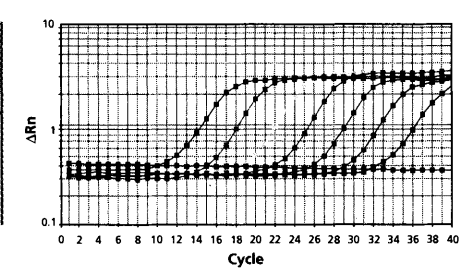
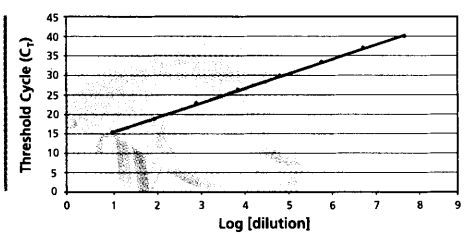
Quantitative PCR (qPCR) performed on pBac-2cp. Initial template copy number was 10^6, diluted 10-fold in subsequent wells. Threshold cycles (C_T) determined using the ABI PRISM 7700 Sequence Detection software.



Linearity of pBac-2cp ten-fold dilutions with SYBR Green JumpStart Taq ReadyMix



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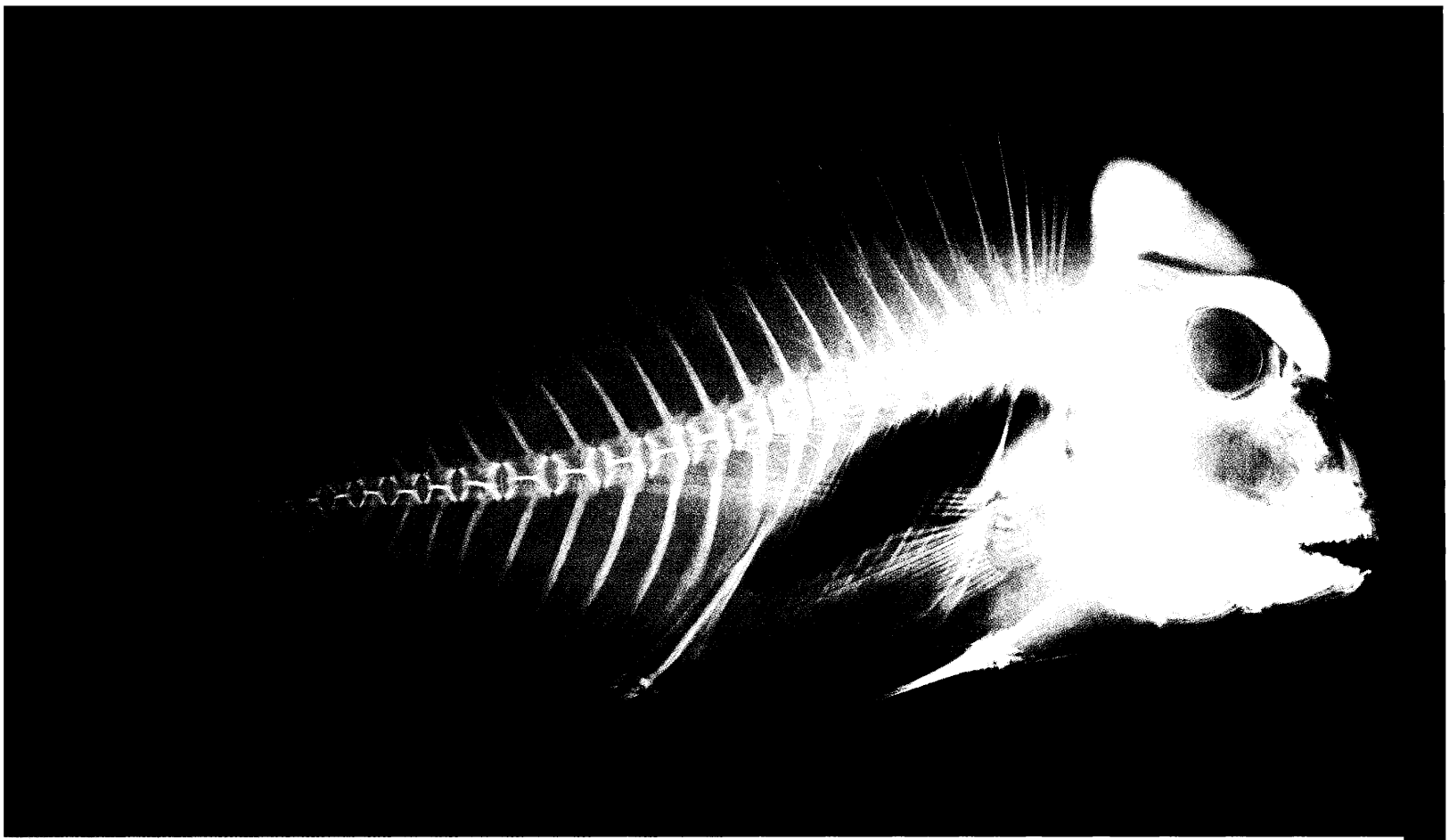

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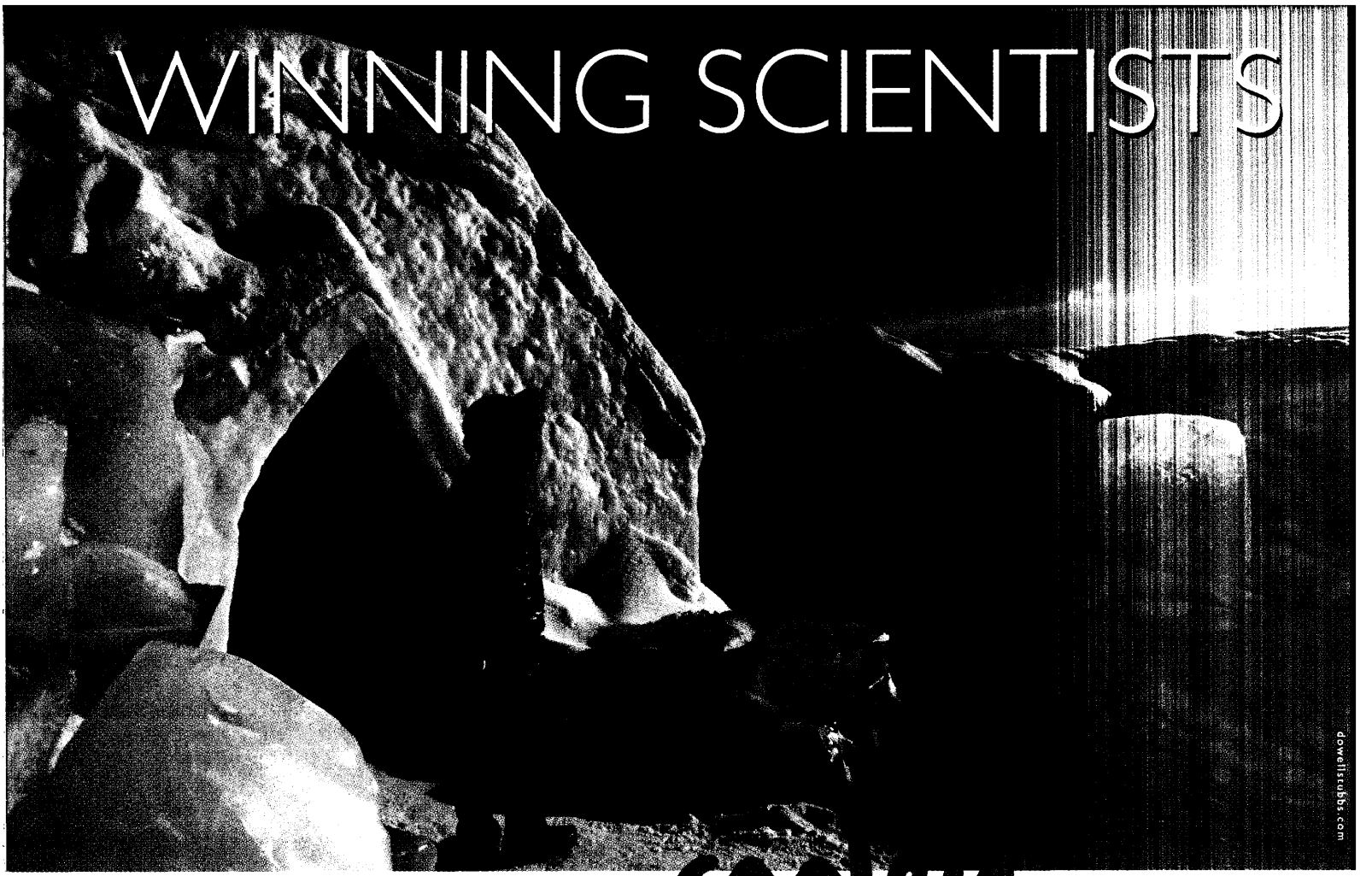

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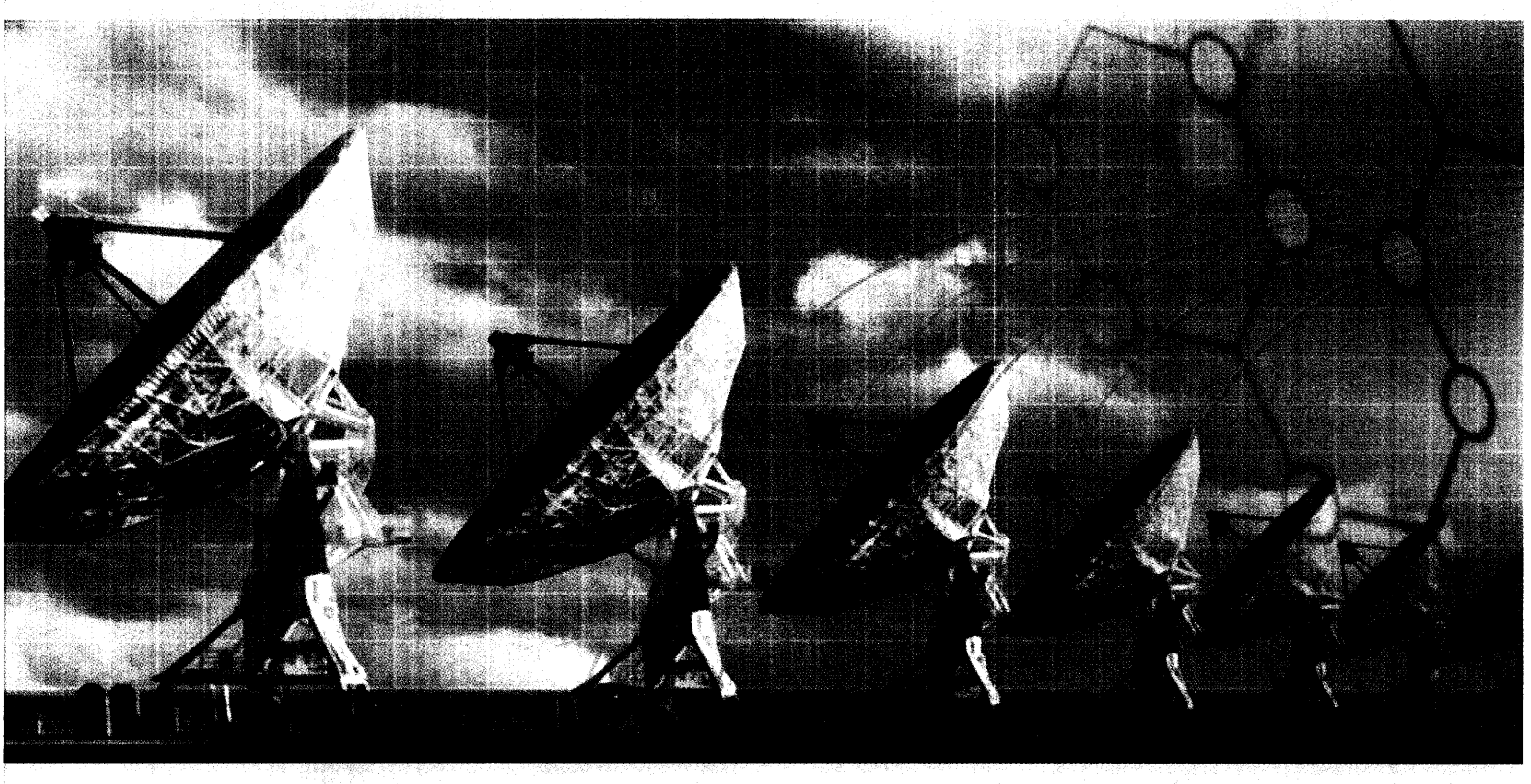

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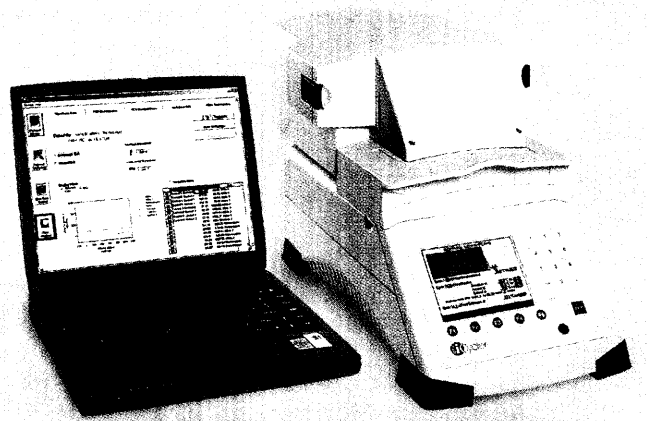

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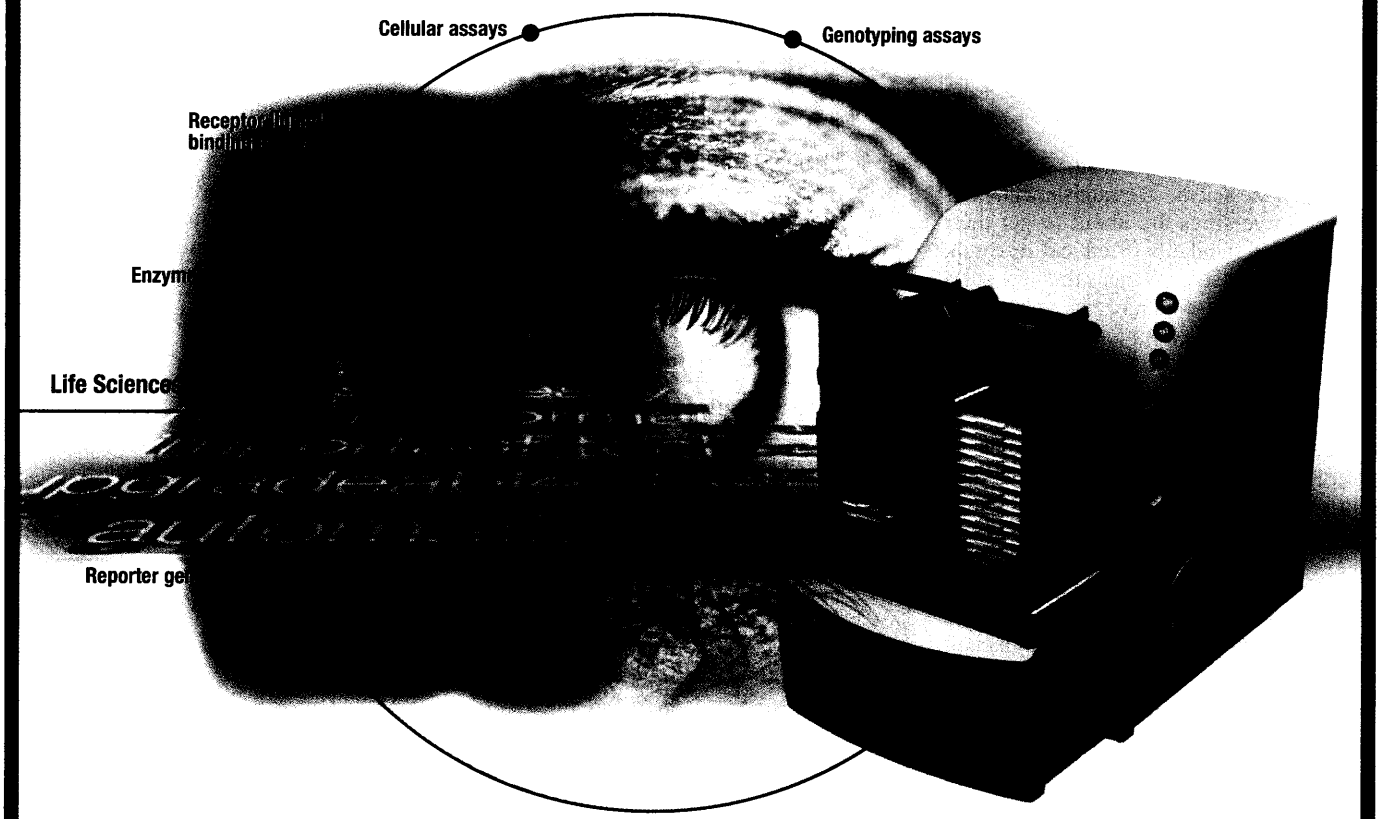

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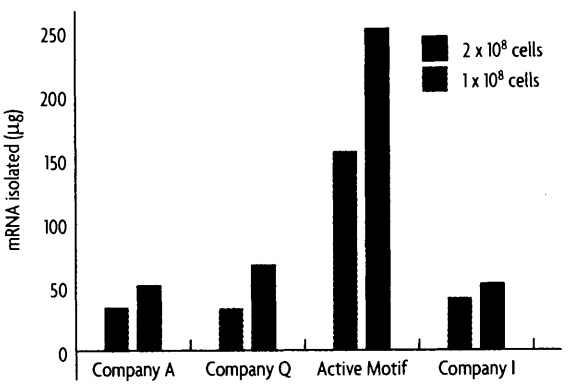

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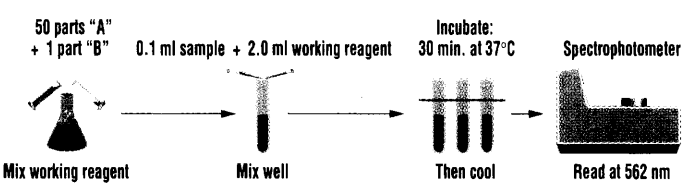
U.S. Patent # 4,839,295

1. Smith, P.K., *et al.* (1985). Measurement of protein using bicinchoninic acid. *Anal. Biochem.* **150,** 76-85.



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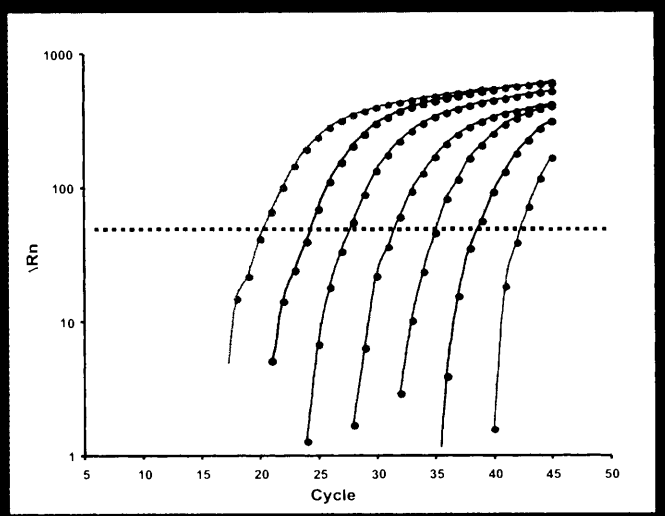

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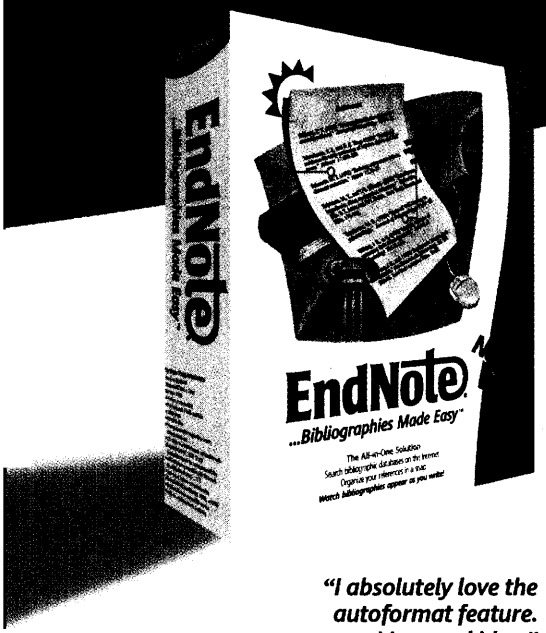

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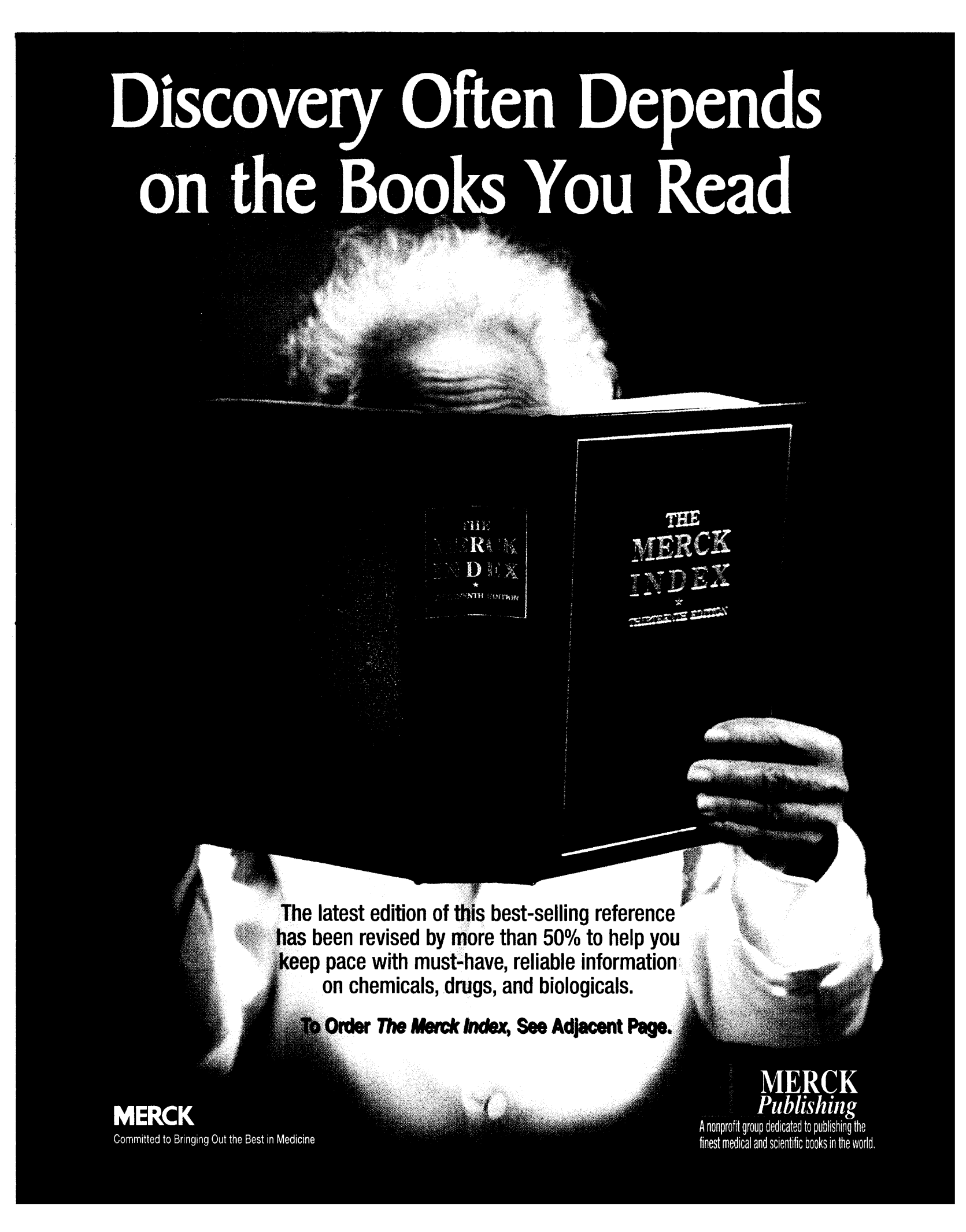

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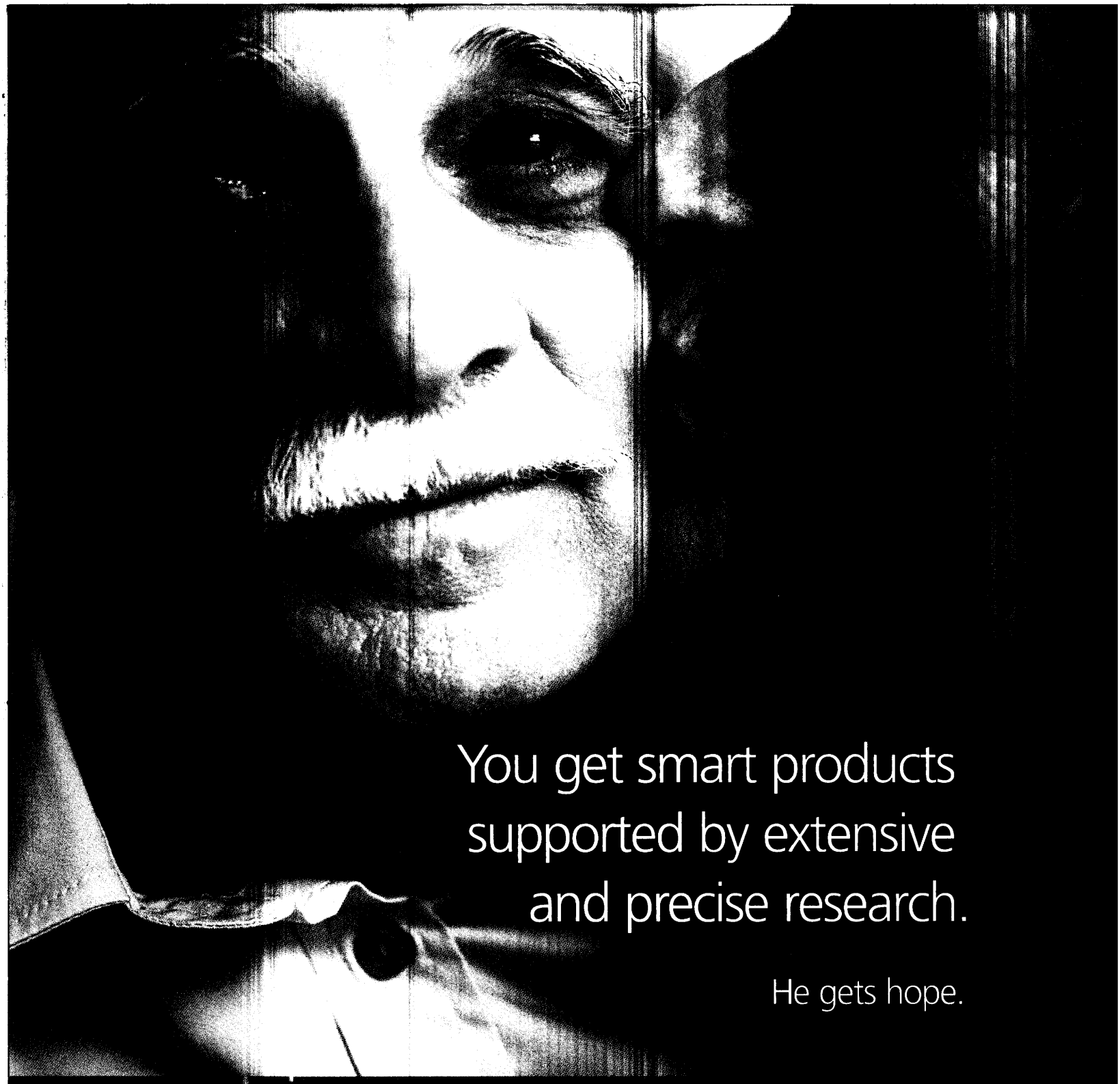

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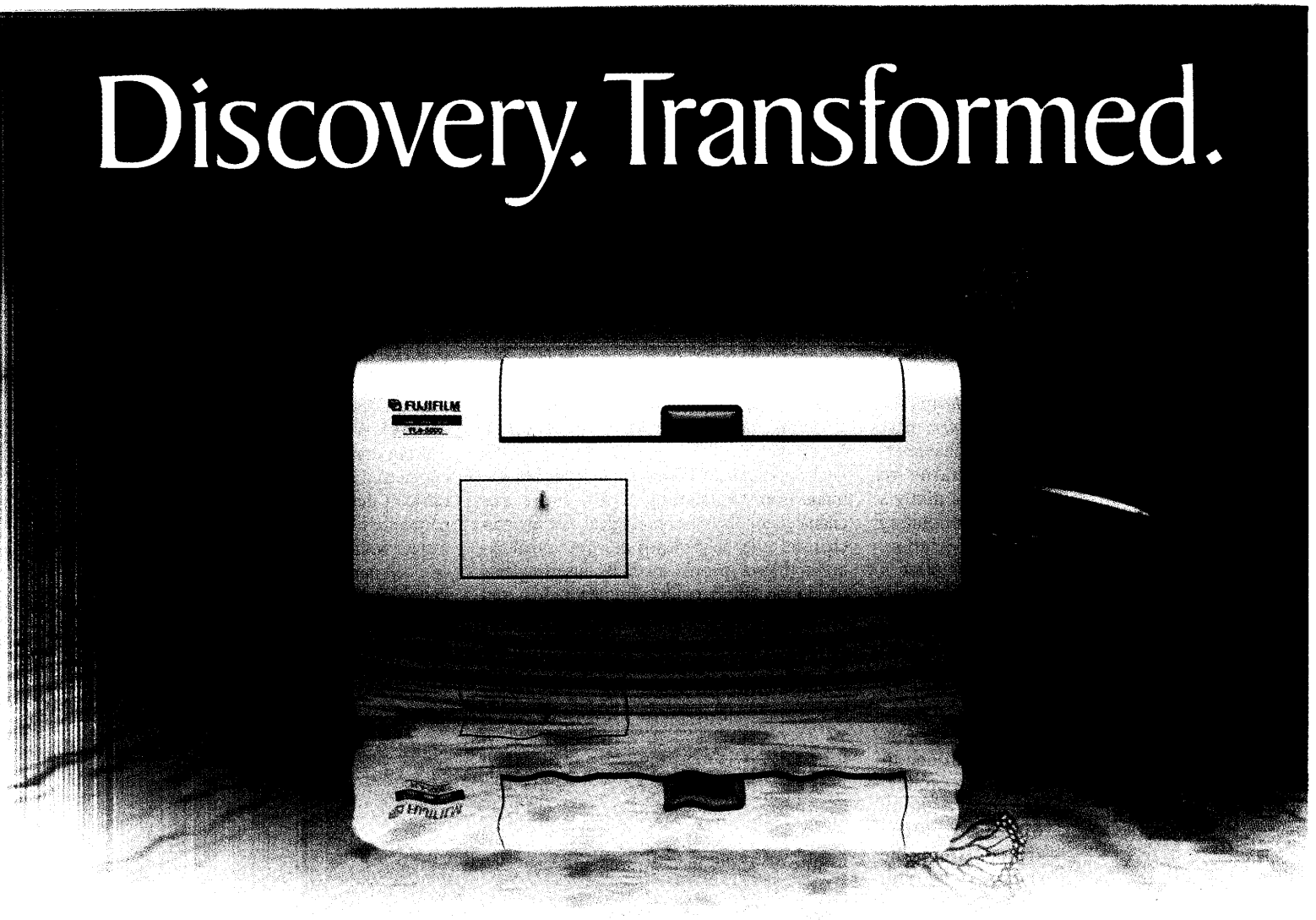

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FAMRI ANNOUNCES THE SECOND YEAR CLINICAL RESEARCH AWARDS

In October 1991, Miami attorneys, Stanley and Susan Rosenblatt, brought a class action suit against the tobacco industry seeking damages on behalf of flight attendants and their survivors, for the diseases and death that have been caused by their exposure to secondhand tobacco smoke in airline cabins. The October 1997 settlement, after four months of trial, among other substantial benefits to class members, established an endowment fund of $300 million that has supported a not-for-profit research foundation, the Flight Attendant Medical Research Institute (FAMRI). The Mission of FAMRI is to sponsor scientific and medical research for the early detection, treatment, and cure of diseases and medical conditions associated with exposure to secondhand tobacco smoke. FAMRI is governed by a Board of Trustees with the majority of flight attendants. A Medical Advisory Board of highly qualified, internationally recognized clinical scientists, chaired by former United States Surgeon General Julius Richmond, M.D, and a Lay Advisory Board of dedicated concerned citizens assist the Governing Board in decision-making. FAMRI has contracted the American Institute of Biological Sciences to conduct the peer review of proposals for the three clinical research awards detailed below. More information about FAMRI and the awards, including the Requests for Applications will be available on the web at: http://www.famri.org after May 1, 2002. Other communications and queries should be directed to: Beth Kress, FAMRI Executive Director, 201 S. Biscayne Blvd., Suite 1310, Miami, FL 33131. E-mail famri@bellsouth.net; phone, 305-379-7007; fax, 305-577-0005.

YOUNG CLINICAL SCIENTIST AWARD (YCSA)

The purpose of the FAMRI YCSA is to help prepare and support new clinical investigators with a M.D. or Ph.D. as they begin their careers as independent researchers. The program is limited to the development of young researchers in smoking-related disorders. FAMRI is particularly interested in helping to provide the bridge between the clinic and the laboratory for the critical translation of basic research findings into diagnostic and therapeutic approaches. The YCSAs are being offered to two groups of scientists: research fellows and junior faculty members.

CLINICAL INNOVATOR AWARD (CIA)

FAMRI established the CIA to stimulate novel medical and clinical scientific research studies on the effects of exposure to secondhand tobacco smoke. While considerable government and non-government funding is available to support established mainstream biomedical research projects, funds for high-risk projects are generally quite limited. With the CIA, FAMRI hopes to foster innovative breakthroughs and creative collaborations. The CIA is available to clinical investigators with a M.D. or Ph.D.

CENTER OF EXCELLENCE (CoE)

FAMRI's CoE will be the centerpiece to linking physicians and scientists from various discipl multidisciplinary programs in patient care and research. The aims of FAMRI's Centers of Excellence are to enhance the knowledge base relating to exposure to second hand tobacco smoke, to serve as a new source for more effective approaches to detection, diagnosis, and therapy for diseases associated with such exposure, and to serve as principal deliverers of medical advances to those suffering from such exposure, especially flight attendants. FAMRI has developed this award program on an institutional basis, striving for comprehensive research plans, including the entire range of research endeavors from basic to clinical research, as well as community outreach.

FAMRI does not support individuals who
or institutions that are currently receiving funds from the tobacco industry or its affiliates.
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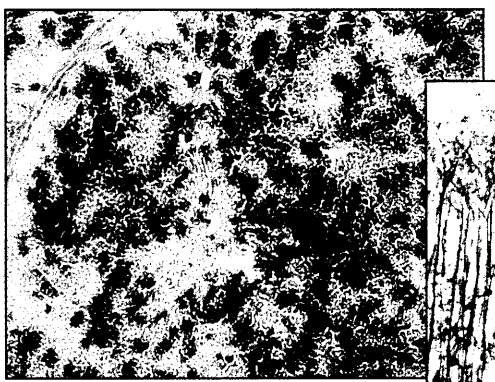
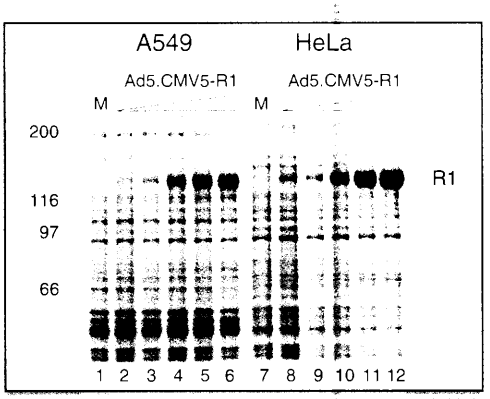


Liver[1]

Neurons[2]

...and protein over-expression in mammalian cells...



Gel Analysis[3]

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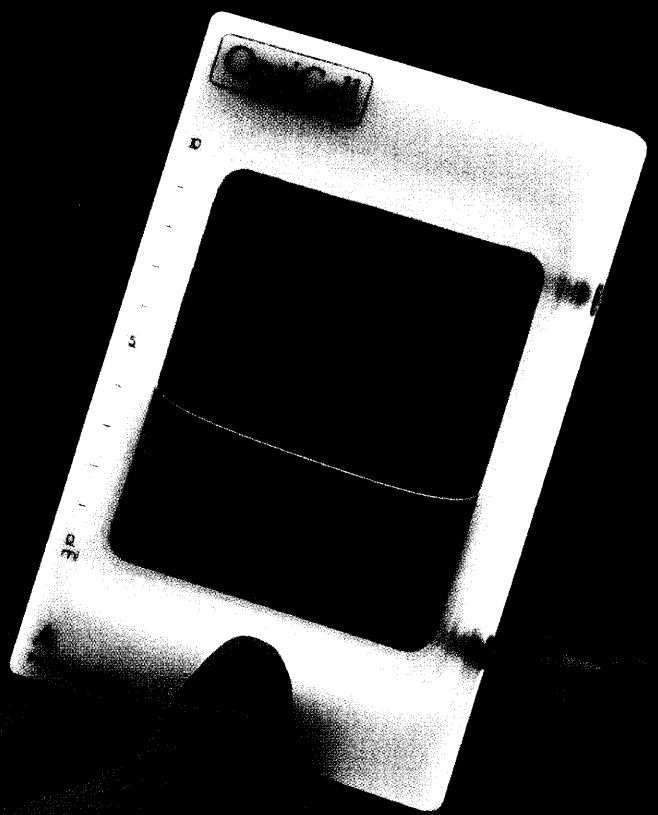
1) Adult Balb/c mouse was injected in the retro-orbital vein with Ad5.CMV-LacZ. Courtesy of Andrea Amalfitano, Clinical Genetics, Duke University, Durham, North Carolina, USA.
2) Adult male Lewis rat was injected into the mid striatum with Ad5.CMV-HSV1tk. Cells illustrated are cortical pyramidal neurons retrogradely labeled from the injection site. Courtesy of Adam Zermansky, Maria G. Castro and Pedro R. Lowenstein, Gene Therapeutics Research Institute, Cedars-Sinai Medical Center and University of California at Los Angeles, Los Angeles, CA, USA.
3) Coomassie blue stained gel of total proteins produced in A549 (lanes 1-6) and HeLa (lanes 7-12) cells infected with Ad5.CMV5-R1 (lanes 2-6, 8-12). Cells were mock infected (lane 1 and 7) or infected at MOIs of 50 (lane 2, 8), 100 (lane 3, 9), 200 (lane 4, 10), 400 (lane 5, 11), and 800 (lane 6, 12). Recombinant R1 production is 30-35% TCP at the highest MOI tested. Courtesy of Bernard Massie, Biotechnology Research Institute, Montreal, Quebec, Canada.



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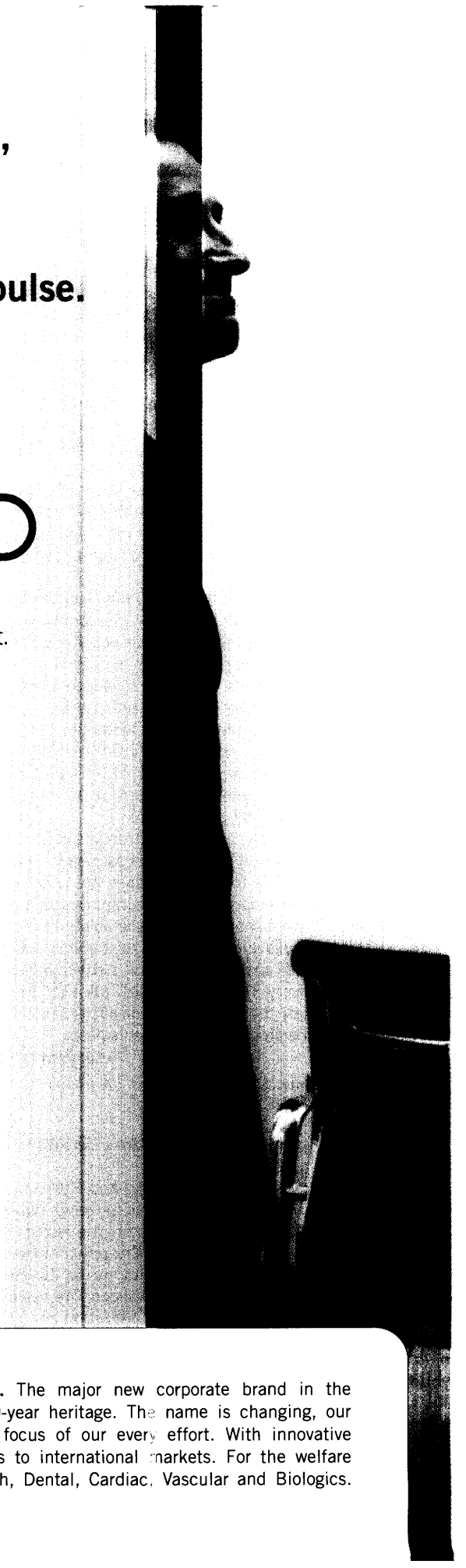

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