8 September 2000

Science

Vol. 289 No. 5485
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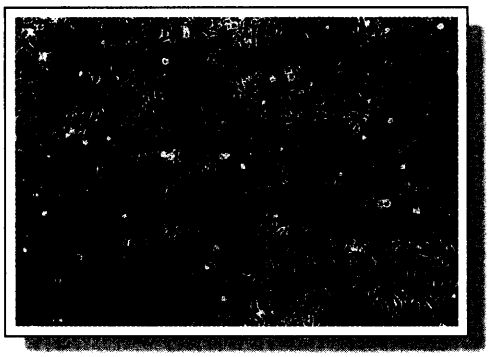

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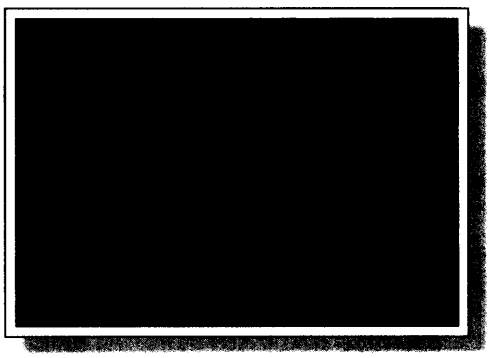

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Endothelial

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Science

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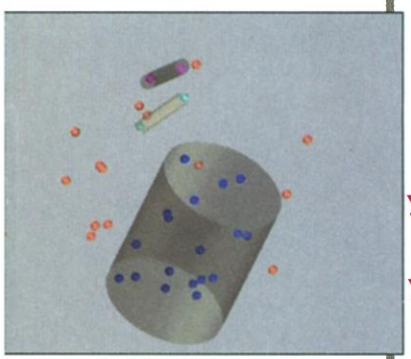
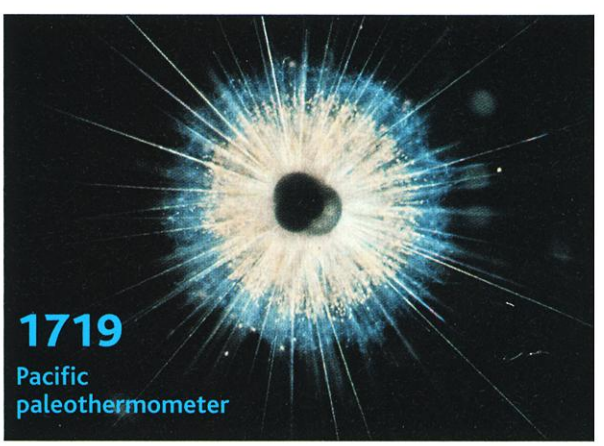
COVER *Chloroflexus aurantiacus*, a green nonsulfur bacterium (orange), growing on an agar layer with the cyanobacterium *Synechococcus* sp. (green). Anoxygenic photosynthetic bacteria, such as *Chloroflexus*, which do not produce oxygen during the process of photosynthesis, evolved millions of years before oxygenic photosynthetic bacteria, such as *Synechococcus*, which generate oxygen as a by-product of the photochemical reaction. [Photo: R. Castenholz]



1670
Cancer genes in action



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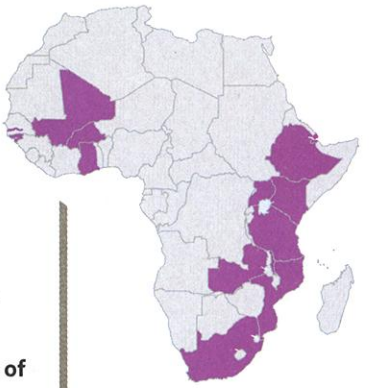


1697
Malaria futures

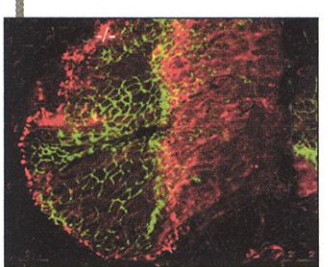
PATHWAYS OF DISCOVERY

The Incredible Life and Times of Biological Cells P. Nurse

In this month's essay, Paul Nurse recapitulates the ontogeny of one of the most important theories in the history of biology, the cell theory, and then lays out the wondrous molecular complexities and processes that he and others have discovered while studying the lives of cells.

TECHNICAL COMMENTS

Summary appears on page 1651; full text is available online at www.sciencemag.org/cgi/content/full/289/5485/1651a



1751
Distinct effects of progesterone receptors A and B

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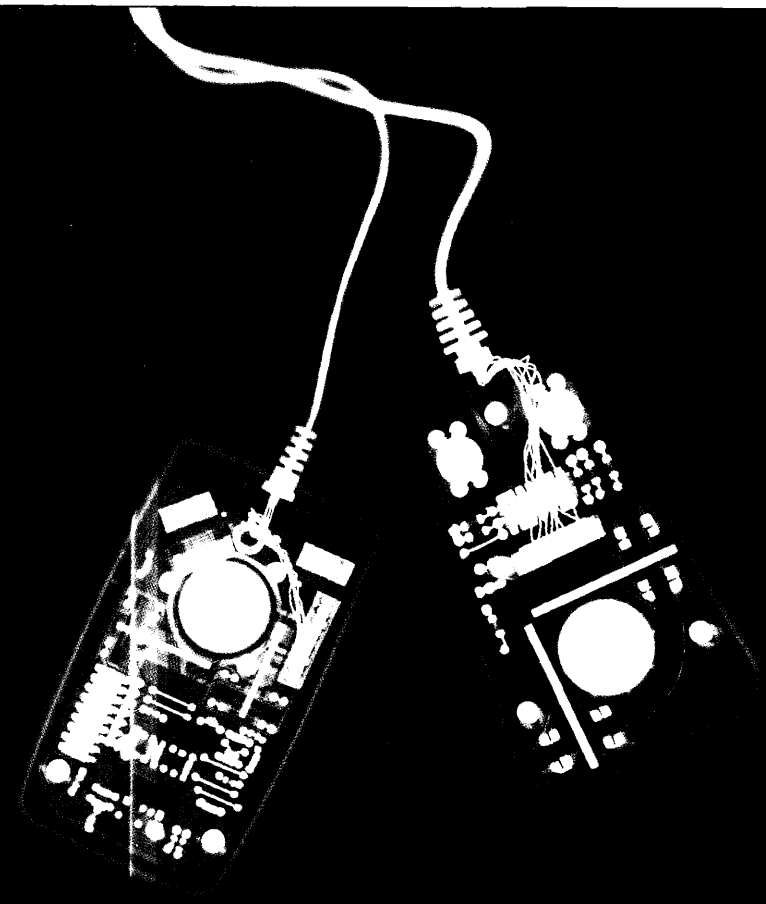

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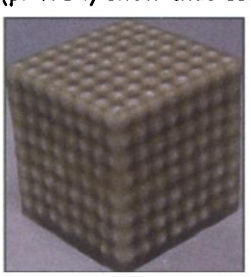
THE BIG-OCEAN CHILL

How Pacific sea surface temperatures (SSTs) have differed between glacial and interglacial periods is especially important for understanding these climate changes not only because of the Pacific's size, but because its equatorial region dominates the global tropical maritime region. Lea *et al.* (p. 1719; see the Perspective by Nürnberg) present planktonic foraminiferal magnesium-calcium and oxygen isotopic records for the past 450,000 years and show that Pacific SSTs were 3° to 5°C cooler during the glacial periods. The surface of the Pacific cooled along with Antarctic air but ahead of continental ice-sheet melting.

THIN ACOUSTIC SHIELDS

Periodic modulations in sound velocity can be used to shield sound within a certain frequency range in a manner analogous to the blocking of light by photonic band gap materials. However, the spatial modulation must be of the same order of magnitude as the sonic wavelength, which would make such structures impracticably large. Liu *et al.* (p. 1734) show that composites with



locally resonant structural units can shield sound with lattice units two orders of magnitude smaller than the relevant sonic wavelength. By varying the size and geometry of the structural units, frequency ranges over which the material acts as a sonic shield can be varied. Thus, relatively thin layers of material can be used as selective sound shields.

UPROOTED AT THE END

The end of the Permian (the Permian to Triassic or P/T boundary, about 250 million years ago) recorded the largest number of marine and vertebrate species extinctions. The cause of this massive extinction is unknown. Ward *et al.* (p. 1740; see the news story by Kerr) offer new evidence for the rapid die-off of rooted plant life in the Karoo basin of South Africa. Analysis of the change in morphology in seven stratigraphic sections indicates that the fluvial system changed from meandering rivers to braided rivers at the P/T boundary. These fluvial changes were caused by increased sedimentation related to enhanced erosion after the disappearance of rooted plants. Similar fluvial changes have been suggested at other P/T boundary sites around the world and indicate that an event such as an impact caused global-scale changes on the continents.

SKATING ON THINNER ICE

Records of the freezing and thawing of rivers and lakes have been recorded in some cases for hundreds of years and should provide another perspective on recent climate changes. Magnuson *et al.* (p. 1743) compile these records from throughout the Northern Hemisphere. Lakes and rivers consistently froze later and became ice-free earlier during the past 150 years. This pattern is consistent with a global temperature increase of about 1.2°C during the past century.

CHANNELING HEAT IN ONE DIMENSION

Potential applications in micro-electro-mechanical devices have made the issues of electron-phonon coupling and heat dissipation in carbon single-wall nanotubes increasingly important. Specific heat measurements by Hone *et al.* (p. 1730; see the Perspective by de Heer) indicate that the thermal vibrations (phonons) in the tubes are confined to one dimension. Moreover, they find that there is little coupling between the tubes in nanotube bundles, which suggests that bundles may not be so strong.

ANOMALOUS EARTHQUAKE DAMAGE

The magnitude 6.7 Northridge earthquake in 1994 caused an anomalous concentration of damage to buildings and infrastructure in Santa Monica, located about 20 kilometers south of the epicenter. Davis *et al.* (p. 1746) simulated the event and conclude that faults bounding the northwestern edge of the Los Angeles basin created acoustic lenses that focused the seismic energy to the surface at Santa Monica. Such modeling and continued simulations of complex subsurface seismic wave propagation may help in assessments of seismic hazards, particularly in tectonically active urban areas.

PURPLE IN TOOTH AND CLAW

Photosynthesis relies on chlorophyll, a light-absorbing molecule based on the porphyrin ring with a variety of modifications and additions. Xiong *et al.* (p. 1724) have sequenced genes encoding biosynthetic enzymes for bacteriochlorophyll from green sulfur and green nonsulfur bacteria. They then combined these data with similar data from other photosynthetic bacterial lineages to construct a molecular phylogeny of photosynthesis (which, of course, need not precisely replicate the phylogeny of photosynthetic organisms). They conclude that photosynthesis appeared first in the purple bacteria and relatively late in the cyanobacteria, the likely ancestor of present-day chloroplasts in plants. In a Perspective, Des Marais (see the cover) places these findings in a geochemical context.

SPLIT RESPONSE TO STEROIDS

In mammals, the receptor for the steroid reproductive hormone progesterone is encoded by a single gene, but the protein exists in two forms—progesterone receptor-A (PR-A) and PR-B—that result from alternative starting points for transcription and translation. Mulac-Jericevic *et al.* (p. 1751) describe mice in which a mutation selectively prevents expression of PR-A. Acting alone, PR-B regulated only a subset of known progesterone-responsive genes in the uterus. Progesterone normally antagonizes estrogen-induced proliferation in the uterine epithelium, yet interactions with PR-B promoted proliferation. The separation of distinct physiological functions for PR-A and PR-B raises the possibility that selective modulators of the PR isoforms could provide more specific therapeutic effects.

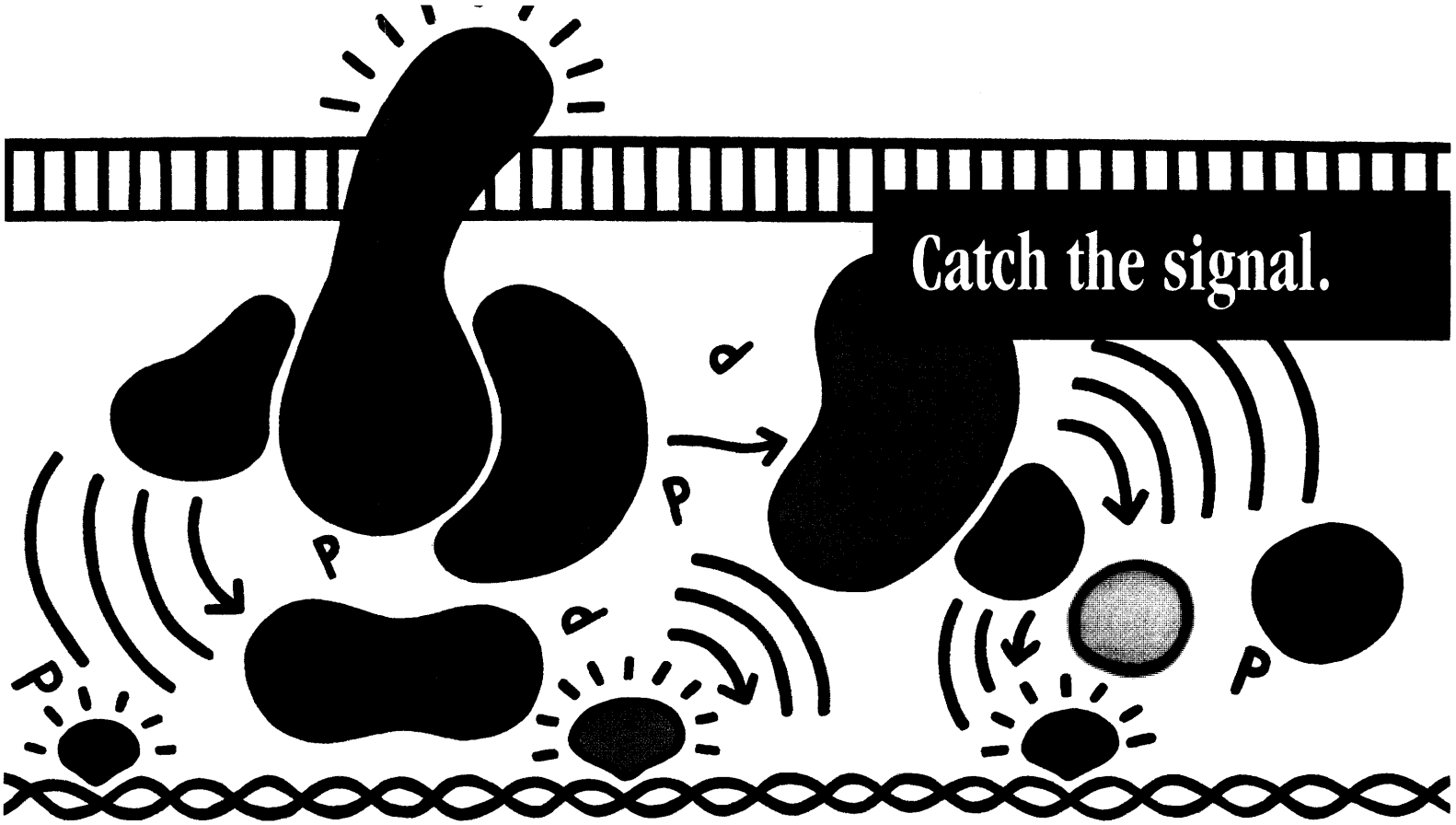
C'MON BACK!

Useful as the oligodendrocyte precursor cells are to the central nervous system, given their ability to generate a steady supply of the cells that insulate neurons, it seems they can do even better. Kondo and Raff (p. 1754; see the news story by Vogel) now show that these limited-potential precursor cells can, with treatment by a series of external growth factors, be made to "back up" through the developmental cascade. The result is a source of stem cells with greater potential than the original that can form a variety of differentiated neuronal cell types.

PROBING PROTEINS IN PACKED ARRAYS

Many assays of protein function (such as protein-protein binding) would benefit from dense arrays of correctly folded proteins on a solid substrate. MacBeath and Schreiber (p. 1760; see the news story by Service). have used a contact-printing robot to create dense arrays of immobilized proteins on glass slides. Covalent at-

CONTINUED ON PAGE 1651



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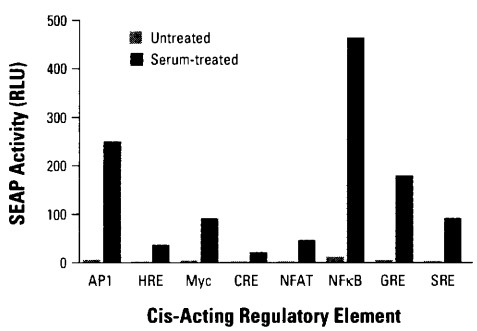

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 1649

tachment to aldehyde-derivatized glass can occur through a Schiff's base at several protein surface positions. Excess reactivity is quenched with bovine serum albumin (BSA), which also helps reduce nonspecific binding (peptide and small protein arrays were made on activated BSA monolayers). In a protein-binding assay, a single protein spot in 10,800 on a slide could be detected. Other applications demonstrated included a protein phosphorylation assay and a study of protein targets for small molecules.

MAKING THE RIGHT TAG

DNA detection by hybridization to an array of fragments has wide applications in gene analysis and medicine. Taton *et al.* (p. 1757) have found that if they use probes labeled with gold particles rather than fluorescent tags, the melting profile of hybrids between oligonucleotides and DNA fragments immobilized on a glass chip had a much steeper slope, which resulted in increased sensitivity and selectivity. With the addition of a silver deposition step, the response was sufficient to allow stain density quantification with a standard flatbed scanner.

CLIMATE AND DISEASE

The alarm has been raised that global warming will inevitably bring an increased threat of vector-borne diseases, such as malaria, to higher latitudes. In contrast, the multivariate approach used by Rogers and Randolph (p. 1763; see the Perspective by Dye and Reiter), invoking both temperature and rainfall predictions from the Hadley Centre Global Climate Model, together with knowledge of the ecology of the parasite, suggests that the gains in malaria distribution in 2050 will, in fact, be rather modest, even under extreme conditions of change. Predicted gains are into the southern United States, westward in China, southward in Brazil, and some expansion in central Asia and into Turkey; Europe would remain largely unaffected. Climate has already been thought to play an important role in cholera outbreaks. Pascual *et al.* (p. 1766) now resolve some of the complexities in cholera dynamics in Bangladesh and show that while climate plays an important role, it is not the entire story. The authors examined an 18-year disease record and found that outbreaks could be related to previous disease levels and local temperature.

THE DANGERS OF EXPANSION

Myotonic dystrophy (DM), the most common form of muscular dystrophy in adults, is caused by the expansion of CTG repeats in the 3' untranslated region of the *DMPK* protein kinase gene. *DMPK* transcripts containing expanded CUG repeats are retained in the nucleus, and it has been hypothesized that nuclear accumulation of these aberrant transcripts, rather than functional alterations of the DMPK protein, causes pathology. Mankodi *et al.* (p. 1769; see the Perspective by Tapscott) provide strong evidence for this hypothesis: They inserted CUG repeats into a gene unrelated to DM and found that transgenic mice expressing expanded CUG-containing transcripts derived from this artificial gene developed many phenotypic features of DM, whereas control mice expressing transcripts with short CUG repeats were normal. These results represent a long-sought animal model for DM.

TECHNICAL COMMENT SUMMARIES

HSV Latency-Associated Transcript and Neuronal Apoptosis

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/289/5485/1651a

Studying the latency-associated transcript (*LAT*) gene of herpes simplex virus–type 1 (HSV-1), Perng *et al.* (Reports, 25 February, p. 1500) concluded that viruses containing *LAT* block apoptosis in rabbit neurons and, thus, that *LAT* promotes survival of infected neurons after HSV-1 infection. Their experiments used a commercial antibody to test for cleaved poly (ADP-ribose) polymerase (p85 PARP), the presence of which is one indicator of apoptosis. In a comment, Thompson and Sawtell report results of tests that suggest that the antibody used by Perng *et al.* is not reactive against cleaved PARP in rabbits. Further, Thompson and Sawtell argue that in another test for apoptosis employed by Perng *et al.* to detect actual DNA fragmentation, "the signal . . . appears to be from the cytoplasm, an unlikely localization for signal originating from fragmented DNA," which they suggest should be limited to the nucleus. Thus, conclude Thompson and Sawtell, the Perng *et al.* study "provides no evidence that the HSV-1 *LAT* gene blocks virus-induced apoptosis in neurons."

Wechsler *et al.* respond with their own Western blot analysis, showing that the antibody used by Perng *et al.* "clearly . . . recognizes the rabbit-cleaved PARP p85 protein." They also present "a number of lines of evidence" to suggest that fragmented DNA can be found in the cytoplasm as well as the nucleus in apoptotic cells.

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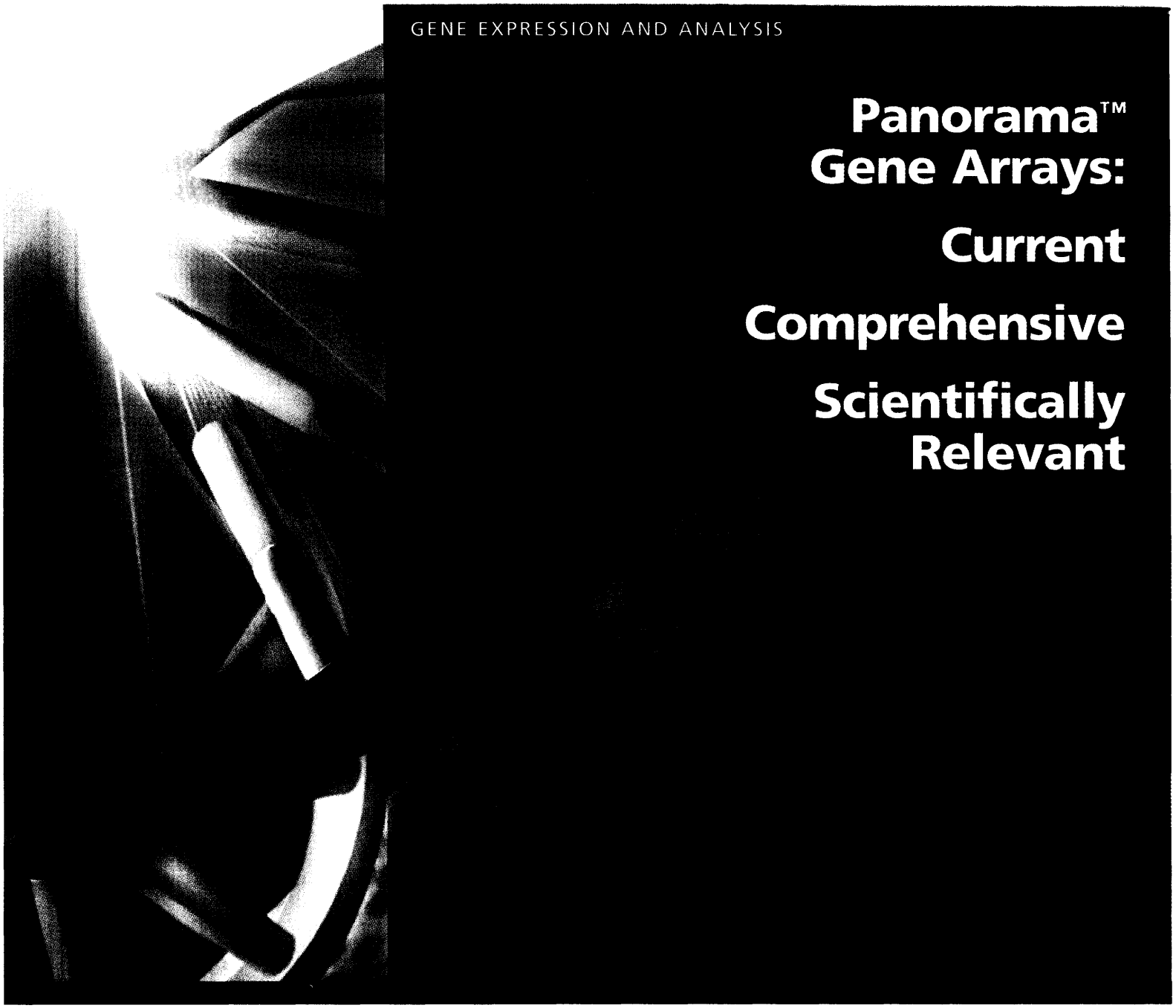

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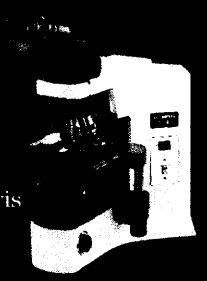

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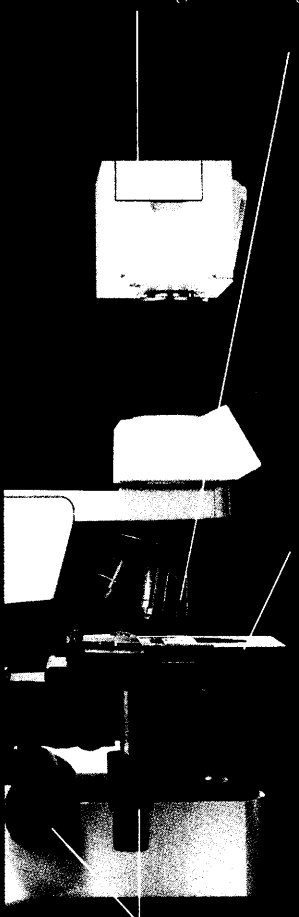
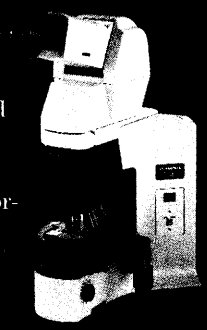


Unerringly precise-motion stage: selectable for right/left hand. Discover speed, ease, touch, comfort, and clinical accuracy.

Uncommonly easy-to-operate controls: extended fine-focus knob; forwarded-positioned illumination intensity dial; tactile X-Y control.

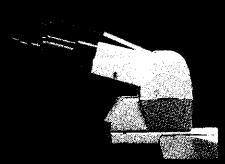
The BX45



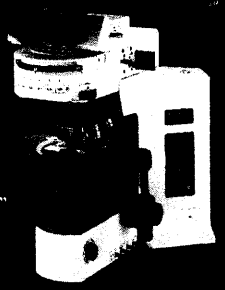
The new standard in ergonomic microscopy. A dramatic metamorphosis: innovative, intelligent, insightful design improvements specifically addressing the needs of those spending hours looking through a microscope.

The **lowest low-position stage: three inches lower** than standard microscopes, offering the promise of minimum effort and hand movement when changing specimens.

The **tilting, telescoping observation tube:** a marvel of adjustability, it can be changed to accommodate any observation position. 80mm higher and 70mm closer to the operator than a conventional tilting tube. And the eyepoint can be moved forward by 45mm and inclined from 0–25 degrees.

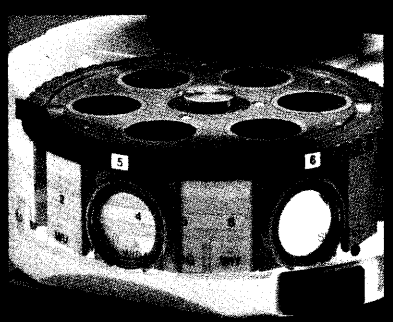


The BX51



The new standard in research microscopy. The words "new" and "standard" really don't do it justice. How about "ingenious" or "original," "paragon" or "prototypical." Prepare yourself for a higher power.

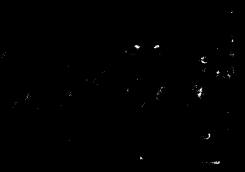
The **6-position filter cube turret:** Not 4, not 5, but 6, so single and multiband imaging of new fluorochromes and fluorescent proteins is faster, simpler and exclusively tailored.



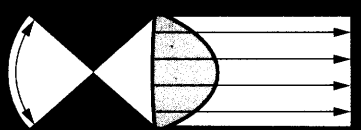
The **rectangular field stop: ours alone**. By cleverly matching the camera's field of view, only the area requiring fluorescence excitation is exposed. Which means that the surrounding areas are protected from photo bleaching.

The **fluorescence excitation balancers: another Olympus exclusive.** A continuously variable excitation bandwidth. Visualization is enhanced, differentiation of multi-labels is immeasurably improved, capturing of images is at an unheard-of level.

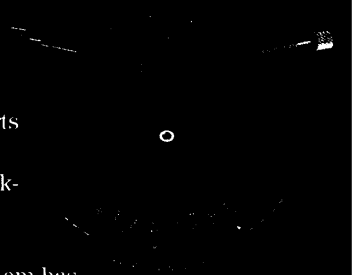
Triple Labeled Specimen (l to r):



- with prevalent FITC and Cy3
- with prevalent DAPI and Cy3
- with balanced fluorescence emission



The **aspherical collector lens:** *sui generis*, in a class by itself. Specimens appear **brighter** and **more evenly illuminated**; and achromatic performance now incorporates wavelengths from UV to IR.



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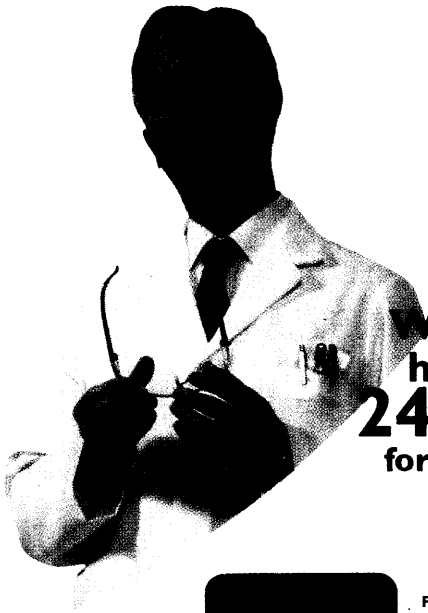

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FIG. 2 Cells are fixed

FIG. 3 CHARIOT delivery of a 10 kDa protein, labeled with lucifer yellow at the C-terminus, to the nucleus of human fibroblast (HS68) cells. Cells are not fixed. (70% transfection efficiency after 30 min. incubation)

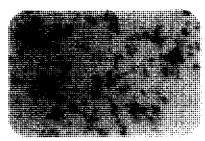

FIG. 4 CHARIOT delivery of a 119 kDa β-galactosidase protein into COS cells. Cells are fixed and stained 2 hours post-transfection. (60% transfection efficiency)

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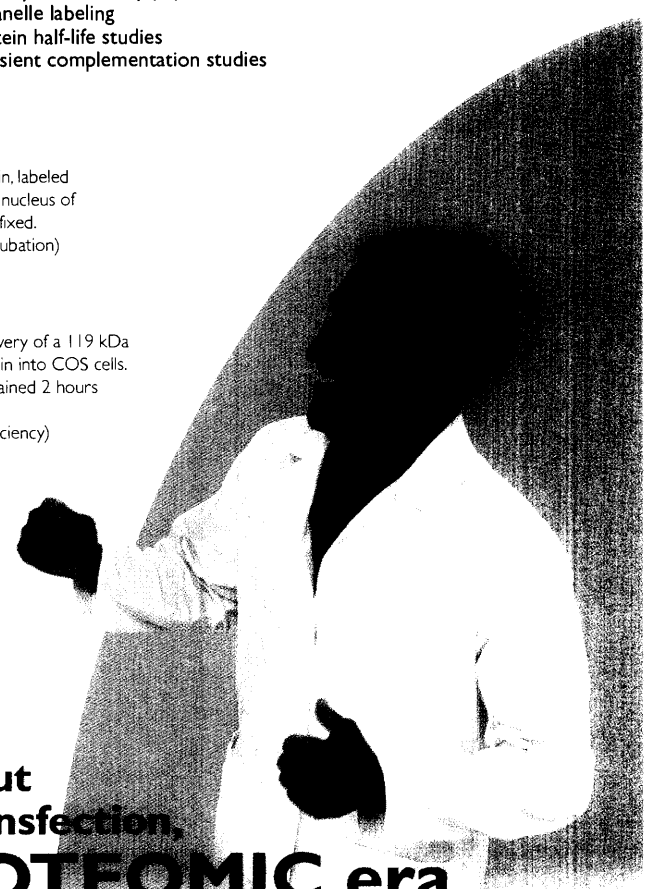

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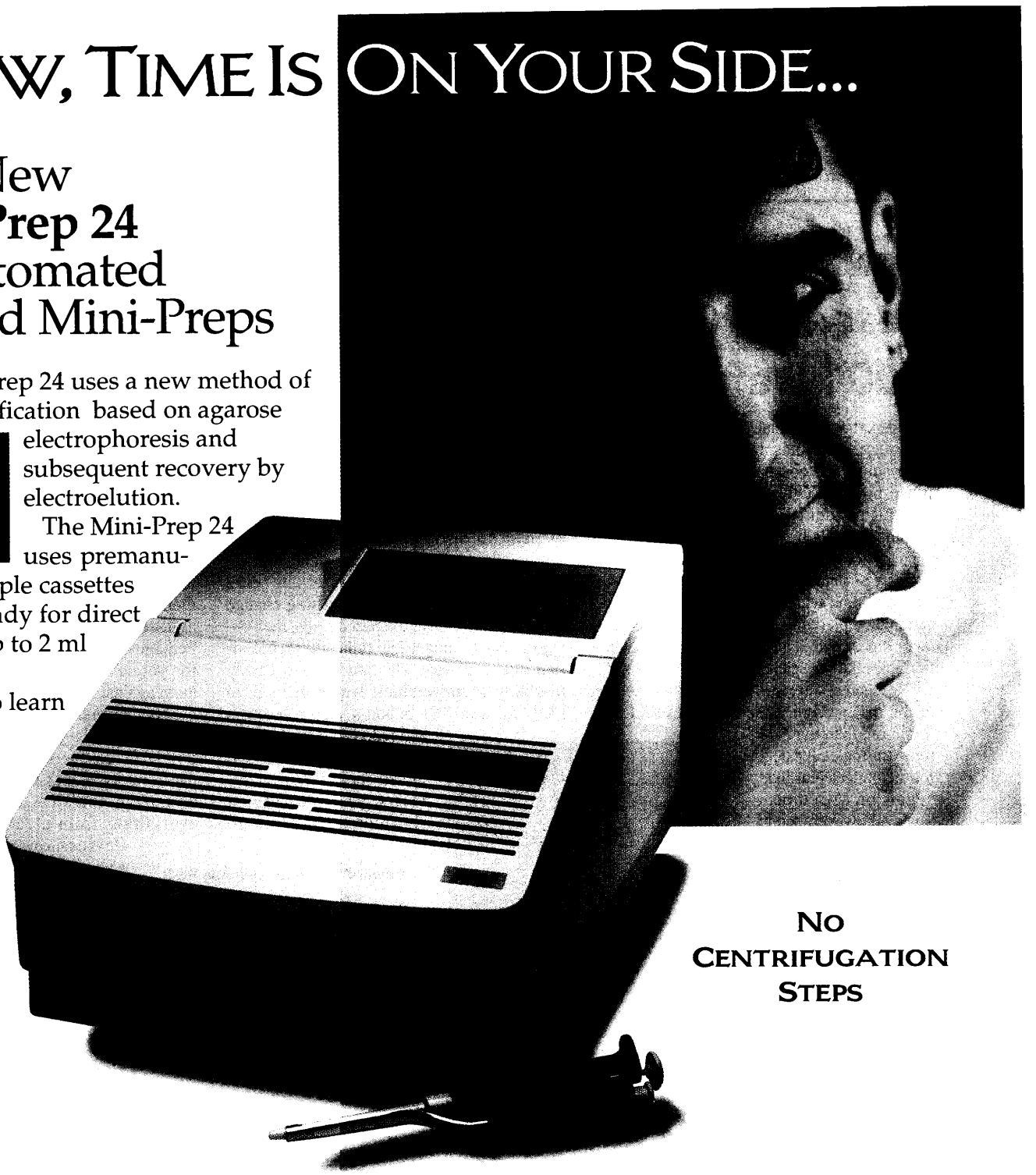

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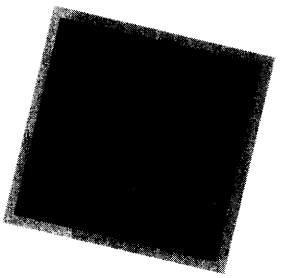

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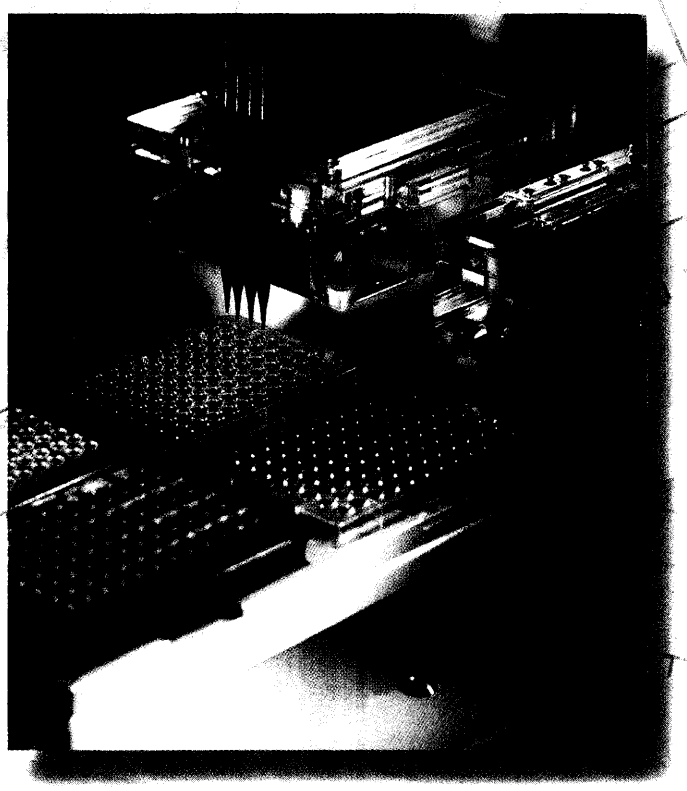

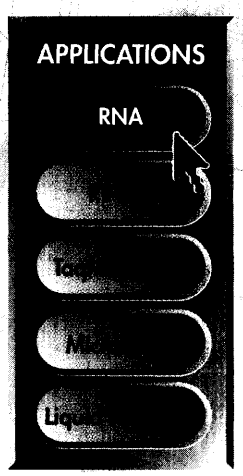

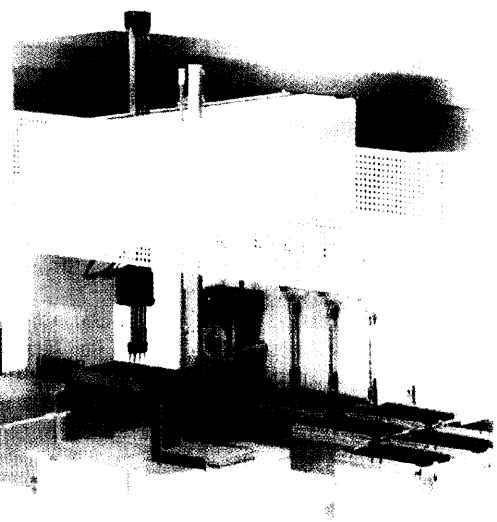

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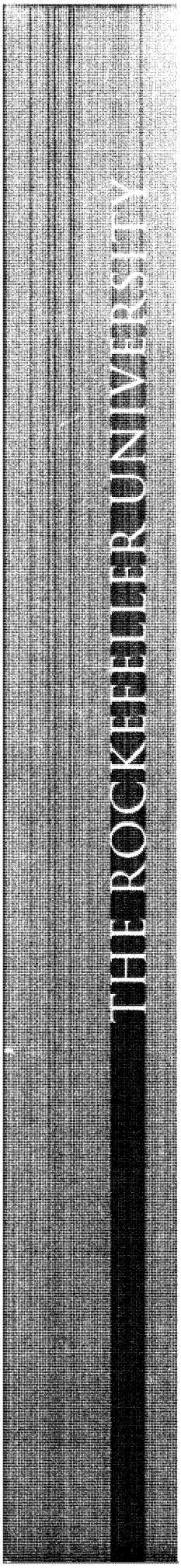

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3:45 P.M.

The Rotary Mechanism of ATP Synthase

John Walker, Nobel laureate in Chemistry
University of Cambridge

THURSDAY, NOVEMBER 9
9 A.M.–5 P.M.

Infectious Disease: **Infectious Disease and Antibiotic Resistance in the Post-genomic Era: Lessons from HIV, Hepatitis C and Tuberculosis**

Stephen K. Burley
Vincent Fischetti
Theresa Gaasterland
David D. Ho
Arnold J. Levine
John McKinney
Tom Muir
Charles Rice
Ralph Steinman
Alexander Tomasz
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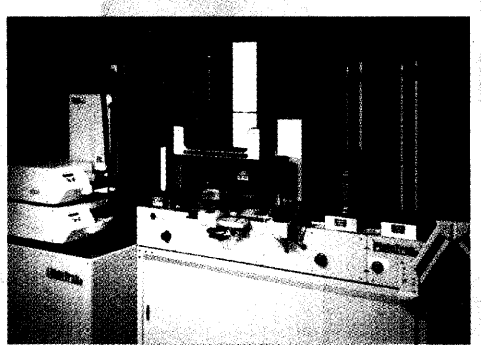

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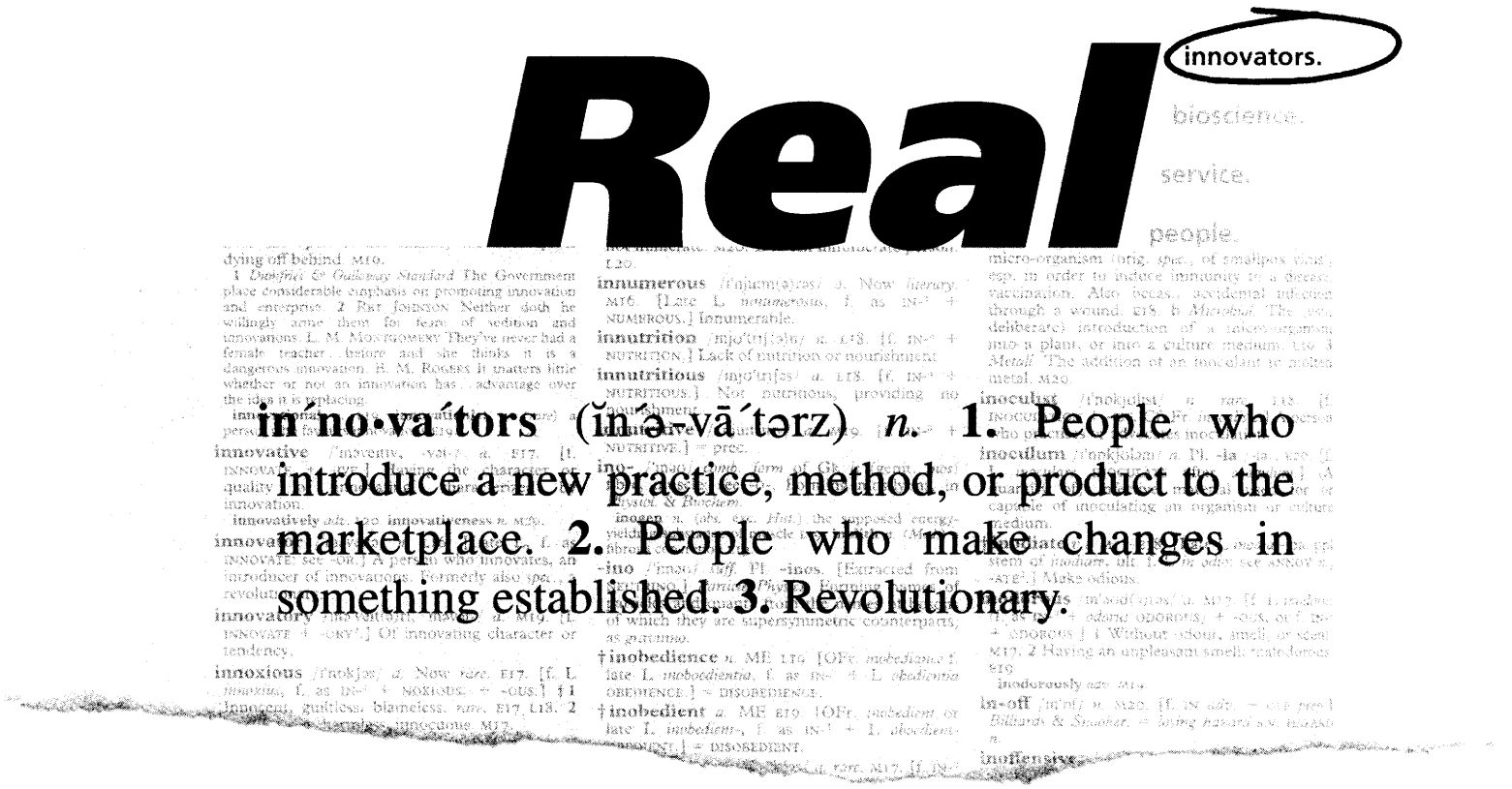

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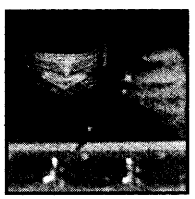

In particular, the awards program is intended to:

- Foster undergraduate research experience that enhances the understanding of the interdisciplinary relationship between biology and chemistry.
- Encourage graduate education in biology and chemistry through exposure to undergraduate research experience.
- Encourage undergraduate programs and activities that bridge chemistry and biology.

ELIGIBILITY CRITERIA

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- offer an American Chemical Society-approved BA/BS chemistry program; and
- confer an average of ten or fewer graduate degrees annually over the past five years in biology and chemistry combined.

The Program is funded by The Merck Company Foundation, a US-based, private, charitable foundation established in 1957 by Merck & Co., Inc., and administered by the American Association for the Advancement of Science, the world's largest federation of scientific and engineering societies.

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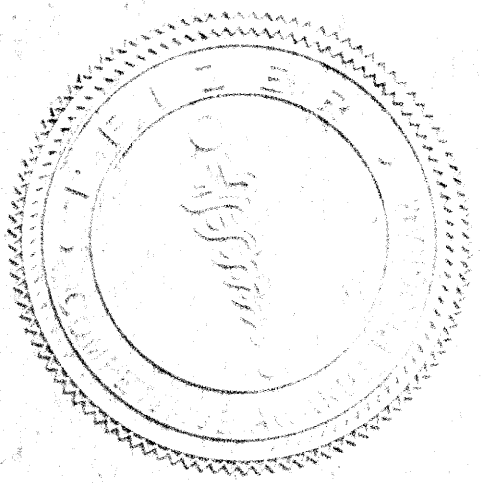
Application forms for 2001–2003 awards are mailed in early September 2000 to the President and the Chairs of the Biology and Chemistry departments of eligible institutions. The application deadline is mid-November 2000. Awards and declinations will be announced in mid-February 2001 coincident with the AAAS Annual Meeting. Send questions and requests for additional information to: **Merck@AAAS.org**



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For more information contact the local Pfizer Medical Director or Dr Patricia Walmsley at Pfizer Inc., 235 East 42 Street, NY, NY 10017 or call 212-573-2638 or e-mail doxazosinawardsprog@pfizer.com.

The winners of last year's Pfizer Competitive Awards Program

Cardiovascular Medicine

Pablo Arias
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Argentina

Paulos Berhanu
University of Colorado
Health Sciences Center
Denver, CO, USA

George Falkay
Albert Szent-Gyorgyi
Medical University
Szeged, Hungary

Manuel Labios Gomez &
Colleagues
University Hospital
Valencia, Spain

Dulcenombre Gomez-Garre
& Colleagues
Autonoma University
Madrid, Spain

Robert Hogikyan & Colleagues
University of Michigan
Medical School
Ann Arbor, MI, USA

Majid Kalani & Colleagues
Karolinska Hospital
Stockholm, Sweden

Antonio Lopez-Farre & Colleagues
Jimenez Diaz Foundation
Madrid, Spain

Kalman Toth & Colleagues
University Medical School
of Pecs, Hungary

Johann Wojta
University of Vienna, Austria

Judges: Stevo Julius, Lewis
Landsberg, and Hans Lithell

Urology

Richard K. Babayan & Colleagues
Boston University School
of Medicine
Boston, MA, USA

Michael B. Chancellor & Colleagues
University of Pittsburgh
Pittsburgh, PA, USA

Ada Elgavish
University of Alabama at
Birmingham
Birmingham, AL, USA

Natasha Kyprianou
University of Maryland
Baltimore, MD, USA

Chung Lee & Colleagues
Northwestern University
Medical School
Chicago, IL, USA

Robert M. Levin
Albany College of Pharmacy
Union University
Albany, NY, USA

Paul D. Walden
NYU School of Medicine
New York, NY, USA

E. Lynette Wilson
NYU School of Medicine
New York, NY, USA

Judges: Georg Bartsch, Claus
Roehrborn, and William Steers

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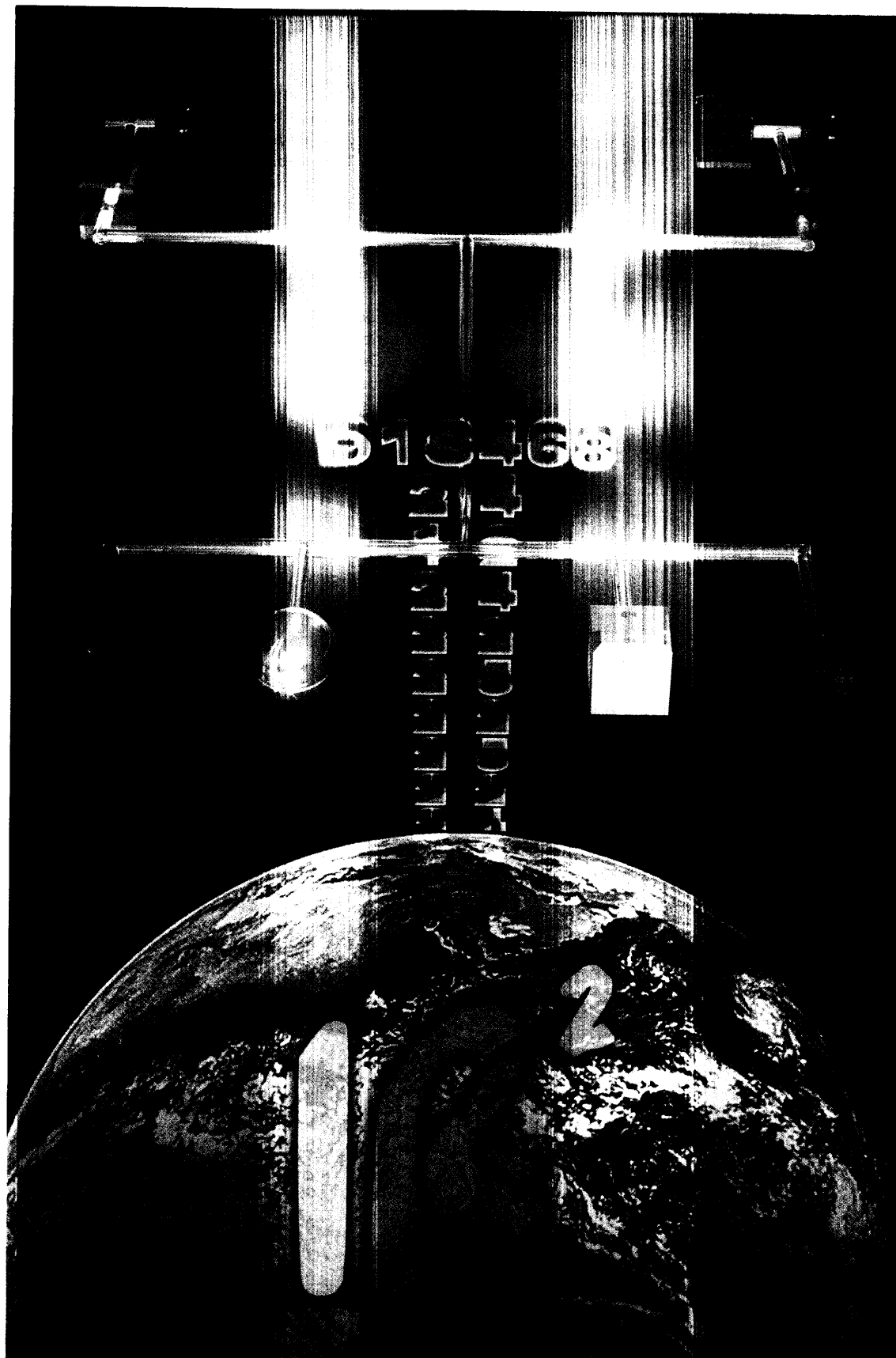

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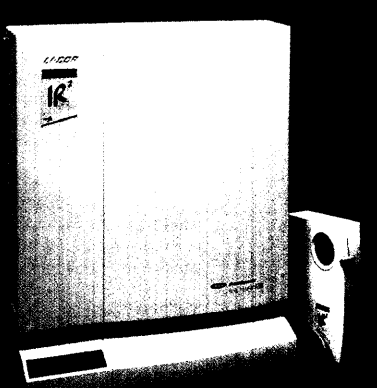

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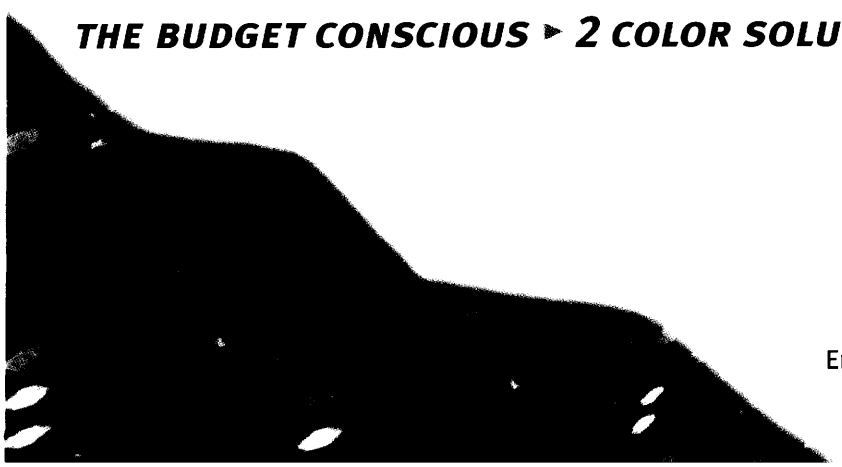

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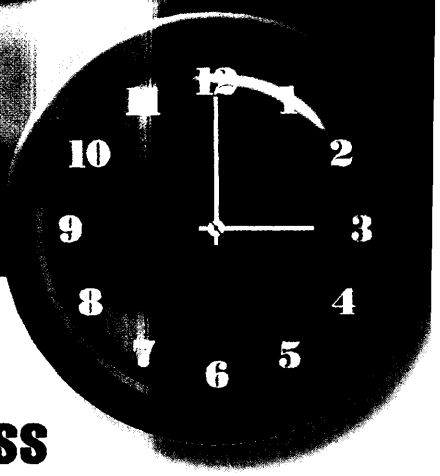

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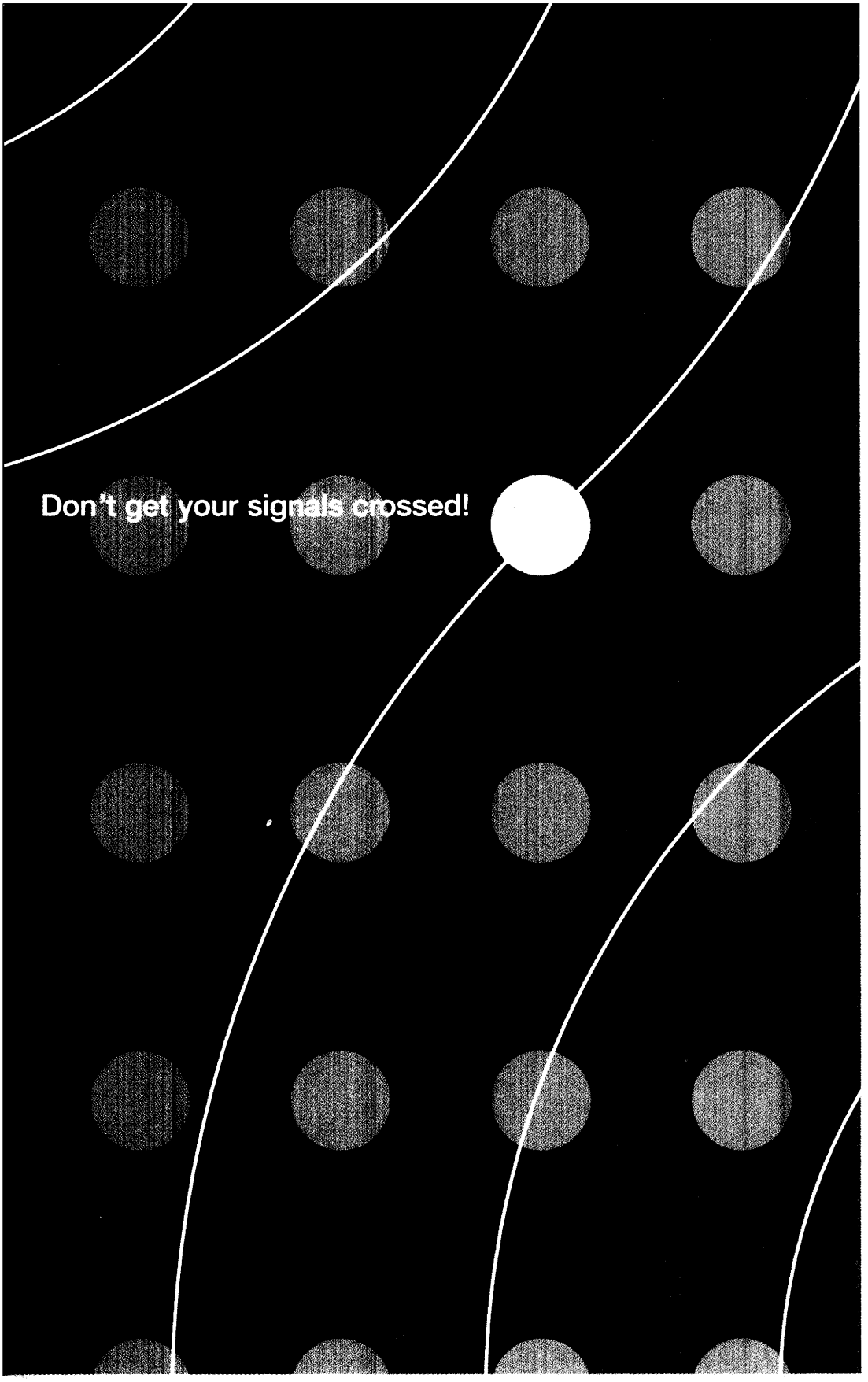

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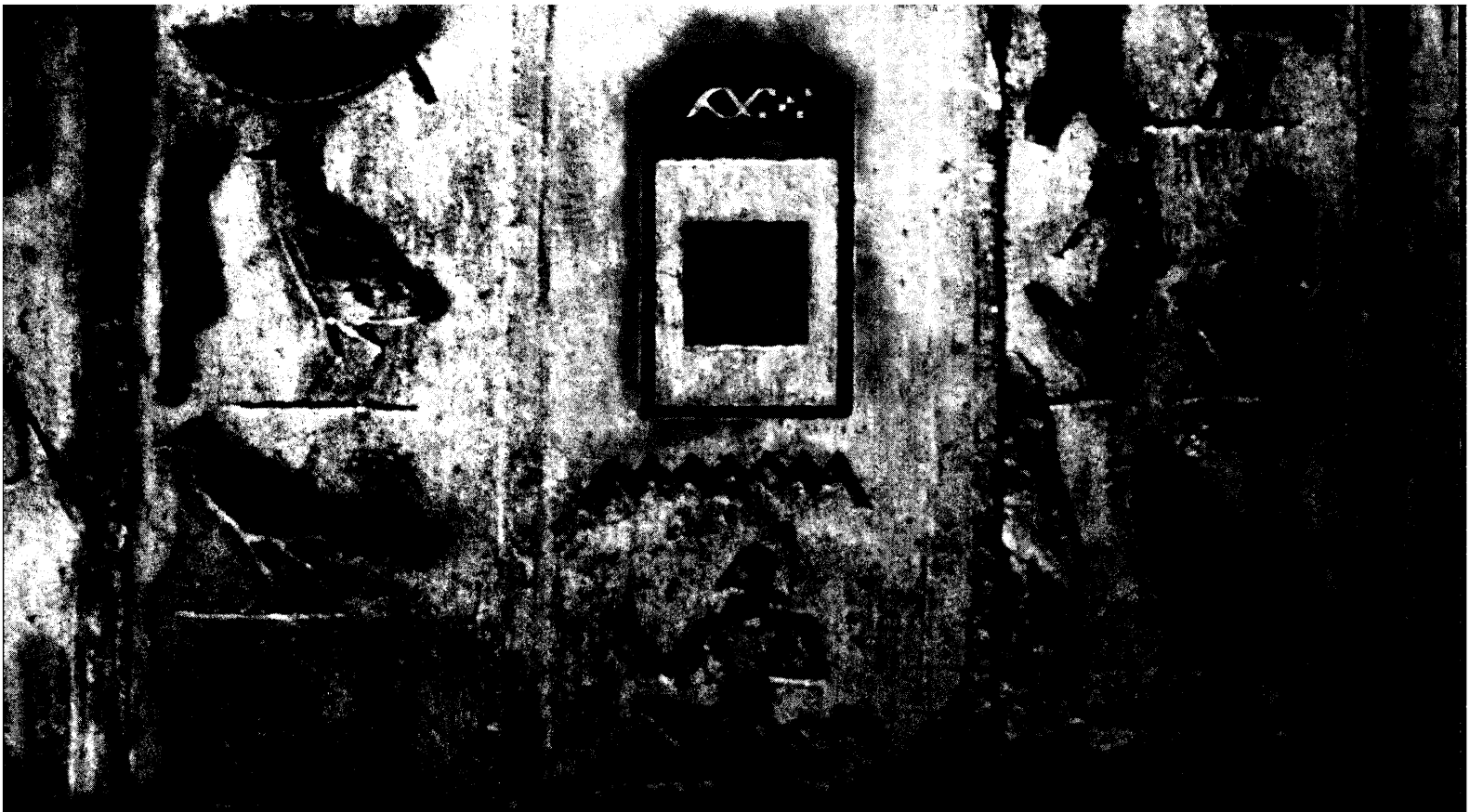

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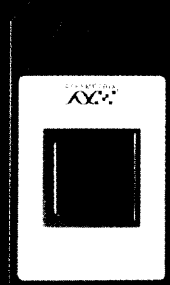

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