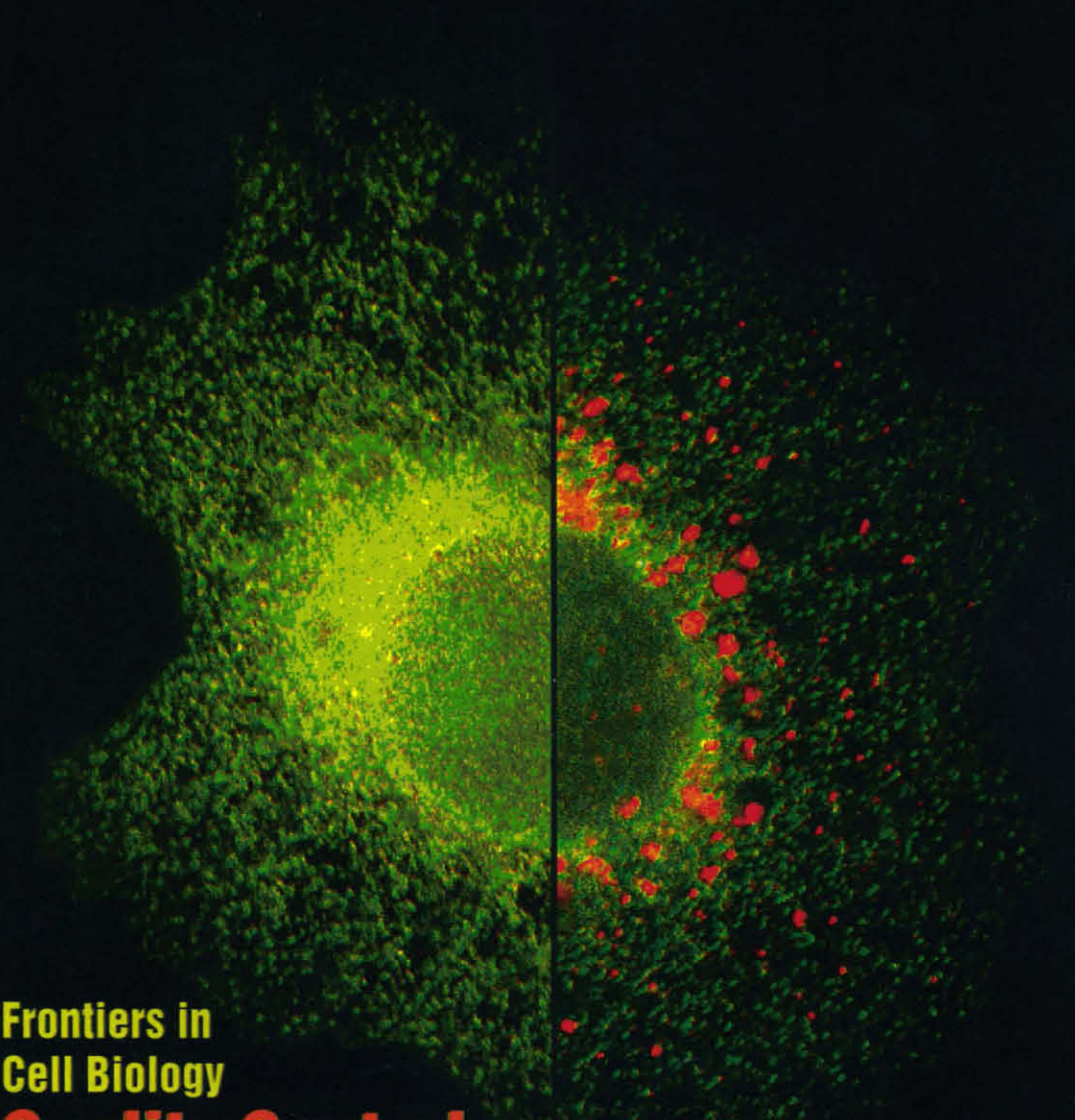


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Frontiers in
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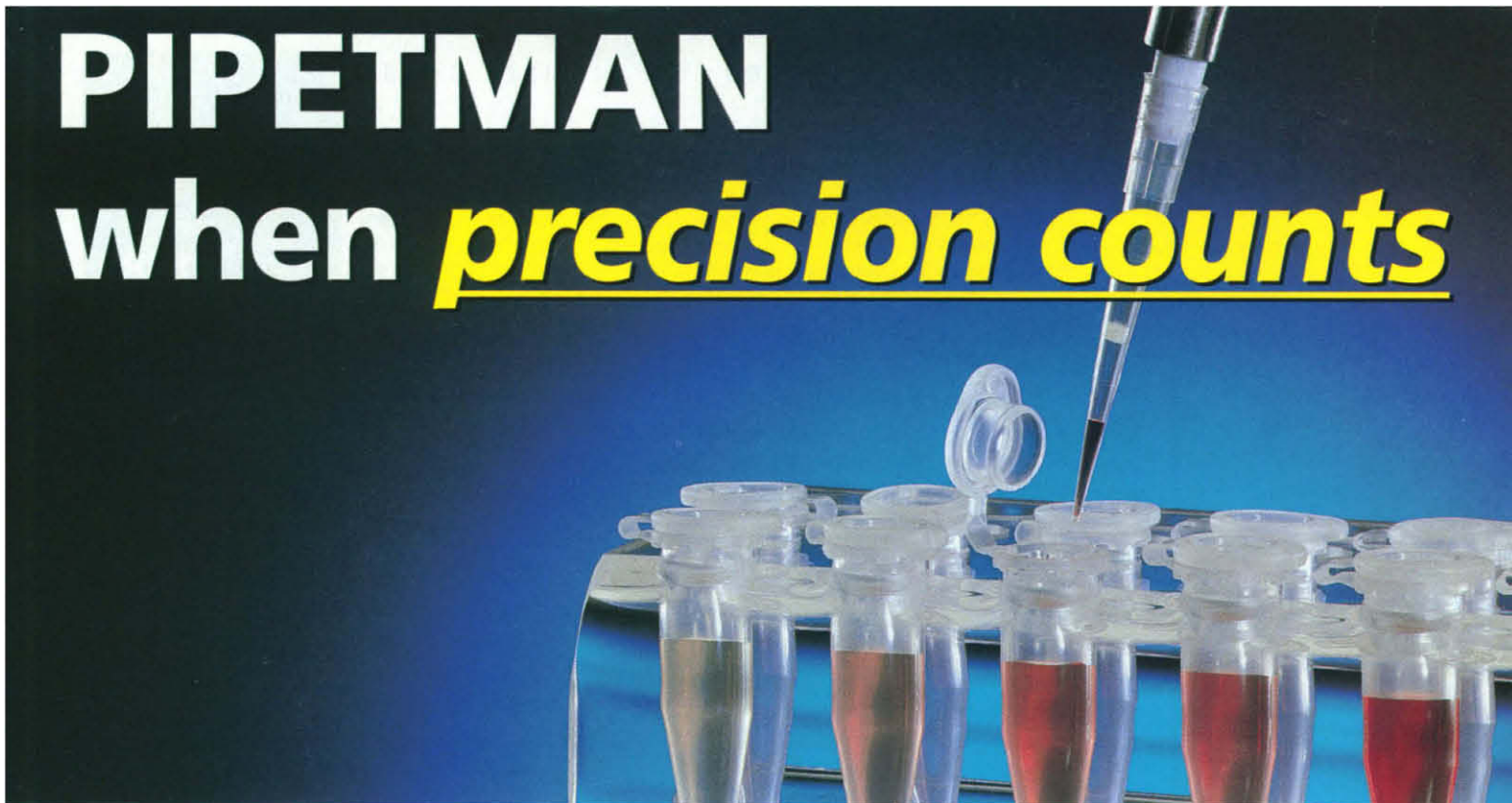
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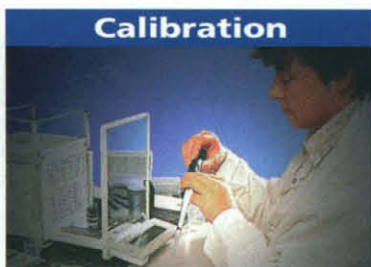
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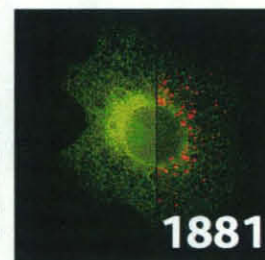


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COVER The yellow area (left) shows a red-stained misfolded protein colocalizing with a green-stained molecular chaperone in the endoplasmic reticulum (ER) (image width, ~12 μm). After a shift from 39.5° to 32°C, the protein folds properly, passes quality control, leaves the ER, and enters vesiculotubular clusters (red spots on the right) en route to the cell surface. This special issue looks at quality control mechanisms in the cell, beginning on p. 1881. [Image: Anna Mezzacasa and Ari Helenius]



1836

The bottom line

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- 1822 **ASTRONOMY:** Shadow and Shine Offer Glimpses of Otherworldly Jupiters
- 1823 **MOLECULAR BIOLOGY:** Member States Buoy Up Beleaguered EMBL
- ▼ 1825 **BIOMEDICINE:** Cholesterol-Lowering Drugs May Boost Bones
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- 1826 **STEM CELLS:** Rat Spinal Cord Function Partially Restored
- 1827 **PLANETARY SCIENCE:** Another 'Ocean' for a Jovian Satellite?
- ▼ 1828 **CLIMATE CHANGE:** Will the Arctic Ocean Lose All Its Ice?
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- 1829 **PALEONTOLOGY:** Fossil Opens Window on Early Animal History
- 1829 **NUCLEAR FUSION:** Europe, Japan Finalizing Reduced ITER Design

- 1831 **MICROSCOPY:** Helium Beam Shows the Gentle, Sensitive Touch

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- 1832 **EPIDEMIOLOGY:** No Meeting of Minds on Childhood Cancer
The Elusive Causes of Childhood Cancer
A Broader Push on Childhood Health
- 1835 **PLANT PATHOLOGY:** Geminiviruses Emerge as Serious Crop Threat
- 1836 **2000 BUDGET:** Thanks to NIH, R&D Ends Up With 5% Boost
- 1837 **ACADEMIC EARMARKS:** Pork Takes a Bite Out of NASA's Science Budget
- 1839 **NEUTRINO PHYSICS:** Squabbling Kills Novel Korean Telescope Project
- 1840 **COMPUTER SCIENCE:** Physicists and Astronomers Prepare for a Data Flood

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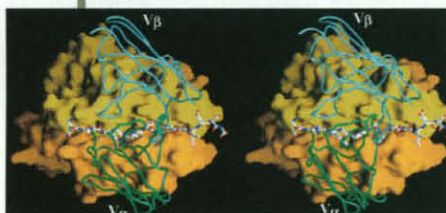
RESEARCH

RESEARCH ARTICLES

- ▼ 1913 **The Crystal Structure of a T Cell Receptor in Complex with Peptide and MHC Class II** E. L. Reinherz, K. Tan, L. Tang, P. Kern, J. Liu, Y. Xiong, R. E. Hussey, A. Smolyar, B. Hare, R. Zhang, A. Joachimiak, H.-C. Chang, G. Wagner, J. Wang
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- ▼ 1921 **Predicting the Evolution of Human Influenza A** R. M. Bush, C. A. Bender, K. Subbarao, N. J. Cox, W. M. Fitch
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REPORTS

- ▼ 1925 **Complex Shear Wave Velocity Structure Imaged Beneath Africa and Iceland** J. Ritsema, H. J. van Heijst, J. H. Woodhouse
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- ▼ 1928 **A Lower Mantle Source for Central European Volcanism** S. Goes, W. Spakman, H. Bijwaard
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1913

A T cell receptor-class II complex

FRONTIERS IN CELL BIOLOGY: QUALITY CONTROL

- 1881 **Frontiers in Cell Biology: Quality Control**

REVIEWS

- 1882 **Setting the Standards: Quality Control in the Secretory Pathway** L. Ellgaard, M. Molinari, A. Helenius
- 1888 **Posttranslational Quality Control: Folding, Refolding, and Degrading Proteins** S. Wickner, M. R. Maurizi, S. Gottesman
- 1893 **Quality Control Mechanisms During Translation** M. Ibba and D. Söll
- 1897 **Quality Control by DNA Repair** T. Lindahl and R. D. Wood
- 1931 **Transition States Between Pyramids and Domes During Ge/Si Island Growth** F. M. Ross, R. M. Tromp, M. C. Reuter
- ▼ 1934 **Global Warming and Northern Hemisphere Sea Ice Extent** K. Y. Vinnikov, A. Robock, R. J. Stouffer, J. E. Walsh, C. L. Parkinson, D. J. Cavalieri, J. F. B. Mitchell, D. Garrett, V. F. Zakharov
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- ▼ 1937 **Satellite Evidence for an Arctic Sea Ice Cover in Transformation** O. M. Johannessen, E. V. Shalina, M. W. Miles
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- 1851 Readers' Visions**
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- 1853 Peer Review Under Review** R. D. Nicholls.
State of Scientific Research at Danish Universities L. Hækkerup. **One-Size-Fits-All Role of Research Faculty** R. K. Boohar. **Response** L. M. Chalupa. **Nutraceuticals** M. Curry, A. Hazard-Daniel, H. J. Daniel. **Response** S. H. Zeisel. **Transplants from Pigs** P. Collignon. **Response** K. Paradis and G. Langford. **Corrections and Clarifications**

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- 1859 Frankenstein in the Land of *Dichter* and *Denker*** M. D. Laubichler

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- 1861 PSYCHOLOGY: *Within Reason Rationality and Human Behavior*** D. B. Caine, reviewed by P. M. Todd

- 1862 Browsings**

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- 1862 PALEOCEANOGRAPHY: Tracing Past Ocean Circulation?** F. von Blanckenburg

- ▼ **1865 GEOPHYSICS: Rising Through Earth's Mantle** J. R. R. Ritter
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- ▼ **1866 EVOLUTIONARY BIOLOGY: Predictive Evolution** D. M. Hillis
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- ▼ **1867 PROTEIN STRUCTURE: Class-Conscious TCR?** I. A. Wilson
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- 1870 Agents and IPOs: A Retrospective of My Academic Career (2000–2050)** S. H. Friedman
1872 In Touch at Last S. Shostak
1875 Wetware Performance Problems E. Bushman



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- 1943 Linking Spontaneous Activity of Single Cortical Neurons and the Underlying Functional Architecture** M. Tsodyks, T. Kenet, A. Grinvald, A. Arieli

- ▼ **1946 Stimulation of Bone Formation in Vitro and in Rodents by Statins** G. Mundy, R. Garrett, S. Harris, J. Chan, D. Chen, G. Rossini, B. Boyce, M. Zhao, G. Gutierrez
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- 1949 Requirement for B Cell Linker Protein (BLNK) in B Cell Development** R. Pappu, A. M. Cheng, B. Li, Q. Gong, C. Chiu, N. Griffin, M. White, B. P. Sleckman, A. C. Chan

- 1954 An Essential Role for BLNK in Human B Cell Development** Y. Minegishi, J. Rohrer, E. Coustan-Smith, H. M. Lederman, R. Pappu, D. Campana, A. C. Chan, M. E. Conley

- 1957 Perforin Gene Defects in Familial Hemophagocytic Lymphohistiocytosis** S. E. Stepp, R. Dufourcq-Lagelouse, F. Le Deist, S. Bhawan, S. Certain, P. A. Mathew, J.-I. Henter, M. Bennett, A. Fischer, G. de Saint Basile, V. Kumar

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- 1962 Activation Tagging of the Floral Inducer FT** I. Kardailsky, V. K. Shukla, J. H. Ahn, N. Dagenais, S. K. Christensen, J. T. Nguyen, J. Chory, M. J. Harrison, D. Weigel

- 1965 Organogenic Role of B Lymphocytes in Mucosal Immunity** T. V. Golovkina, M. Shlomchik, L. Hannum, A. Chervonsky

- 1968 Use of Chemokine Receptors by Poxviruses** A. S. Lalani, J. Masters, W. Zeng, J. Barrett, R. Pannu, H. Everett, C. W. Arendt, G. McFadden

TECHNICAL COMMENTS

Early Holocene Atmospheric CO₂ Concentrations A. Indermühle, B. Stauffer, T. F. Stocker, D. Raynaud, J.-M. Barnola; H. H. Birks, W. Eide, H. J. B. Birks. **Response** F. Wagner, W. M. Kürschner, H. Visscher, S. J. P. Bohncke, D. L. Dilcher, B. van Geel

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1931

How quantum dots get into shape

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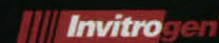
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DISCONTINUOUS PLUMES

Several volcanic regions, such as Hawaii and Iceland, are associated with hot spot plumes, but their depth of origin and thus the heat sources that lead to the formation of these plumes have been debated. Two reports show how seismic tomography, which generates an image of the variations in velocity in the mantle, can be used to try to resolve plume structures. Goes *et al.* (p. 1928) have resolved a lower mantle upwelling of hot material beneath central Europe that may be broken up into smaller upper mantle plumes. Ritsema *et al.* (p. 1925) have resolved an upper mantle upwelling beneath Iceland that does not extend into the lower mantle. They have also found evidence for a tilted upwelling in the lower mantle beneath East Africa that does not connect with the upper mantle plume-like structures that have been related to the East African Rift. In a Perspective, Ritter discusses how these discontinuous plumes may be related to upper mantle structure and crustal volcanism and rifting.

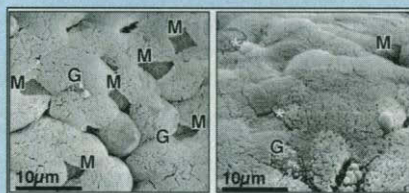
SKATING ON THINNING ICE

Sea ice is a sensitive indicator of climate change—if global climate were warming, then the amount of permanent sea ice in the Arctic should decrease. Satellite measurements and surface observations have shown that at least the areal extent of Northern Hemisphere sea ice has been decreasing for almost 50 years. Two reports present new measurements and analysis of changes in Arctic sea ice (see the news story by Kerr). Johannessen *et al.* (p. 1937) measured the areal extent of the perennial Arctic sea ice pack and found that the area of multiyear ice has decreased by more than twice as much as that of total sea ice. This change in ice cover has been accompanied by a roughly coincident decrease in ice thickness, which suggests that the heat and fresh water balances of the Arctic may be changing in significant ways. Vinnikov *et al.* (p. 1934) have examined the decrease in areal extent of sea ice. They combined five separate data sets and two independent climate models to test whether these sea ice reductions can be attributed to natural climate variations. Their model results suggest that the probability of this change being caused by natural variability is less than 2% for the last 20 years and that the decreases seen should

continue during the next century. They conclude that the observed decrease in Northern Hemisphere sea ice is probably a result of anthropogenically driven global warming.

B CELLS AND MUCOSAL IMMUNITY

The immune system that develops along the length of the small intestine consists of organized lymphoid tissue called Peyer's patches. Within these patches are M cells, which allow microbes to pass into the lymphoid tissue where they initiate an immune



response or gain a foothold for infection. Golovkina *et al.* (p. 1965) report that mice lacking B lymphocytes were deficient in M cells, and that M cells were restored by exposure to B cells. The resistance of mice with no B cells to infection by murine mammary tumor virus was found to be due to the deficiency of M cells rather than the direct lack of B cells. Thus, B cells not only participate in immune responses but are involved in the generation of the organs for mucosal immunity.

QUANTUM DOTS GROW UP

One way to self-assemble quantum dots or nanocrystals on a surface is through strain. When there is sufficient crystallographic mismatch between a thin film several monolayers thick and its underlying substrate, the resulting strain can be relieved by rearrangements that create quantum dots. For germanium-silicon dots, low-volume pyramids and high-volume domes form, but the origin of these two size distributions has been unclear. Ross *et al.* (p. 1931) used a low-energy electron microscopic technique to look at the evolution of the dots in real time. The dots begin as square-based pyramids, and proceed through a series of metastable transition states before maturing into multifaceted dome-shaped dots.

DID YOU GET THAT FLU SHOT?

The value of the annual flu vaccine is directly related to how well it can be determined which flu strain will actually predominate in the seasonal onslaught. Bush *et al.* (p. 1921; see the Perspective by Hillis) have analyzed the molecular evolution of flu strains through recent years and arrived at a means to predict more accurately which strain will emerge in the next flu season. Their process, which involves identification of codons under positive selection to change, successfully predicted in retrospective tests the flu strains for the last 8 years.

A CLASS DIFFERENCE IN WHERE YOU DOCK

The adaptive immune response is stimulated when peptides bound to major histocompatibility complex (MHC) molecules bind to T cells. Structures of T cell receptors (TCRs) in complex with peptide-MHC class I ligands have been determined. Now Reinherz *et al.* (p. 1913) present the structure of a TCR binding to a complex of a 16-residue peptide antigen and a murine MHC class II molecule (pMHCII). The authors propose that the angle of TCR-pMHCII docking will be restricted to a more "orthogonal" interaction than that seen in the class I "diagonal" mode, and that this difference in docking specifies the preferential binding of pMHCI and pMHCII to CD8 or CD4 coreceptors, respectively. In a Perspective, Wilson analyzes the similarities and differences between the pMHCII and pMHCI structures, and cautions that while this work is a valuable contribution, more TCR-pMHC structures are needed to understand fully the structural basis of TCR-MHC recognition.

GOING WITH THE GROUP

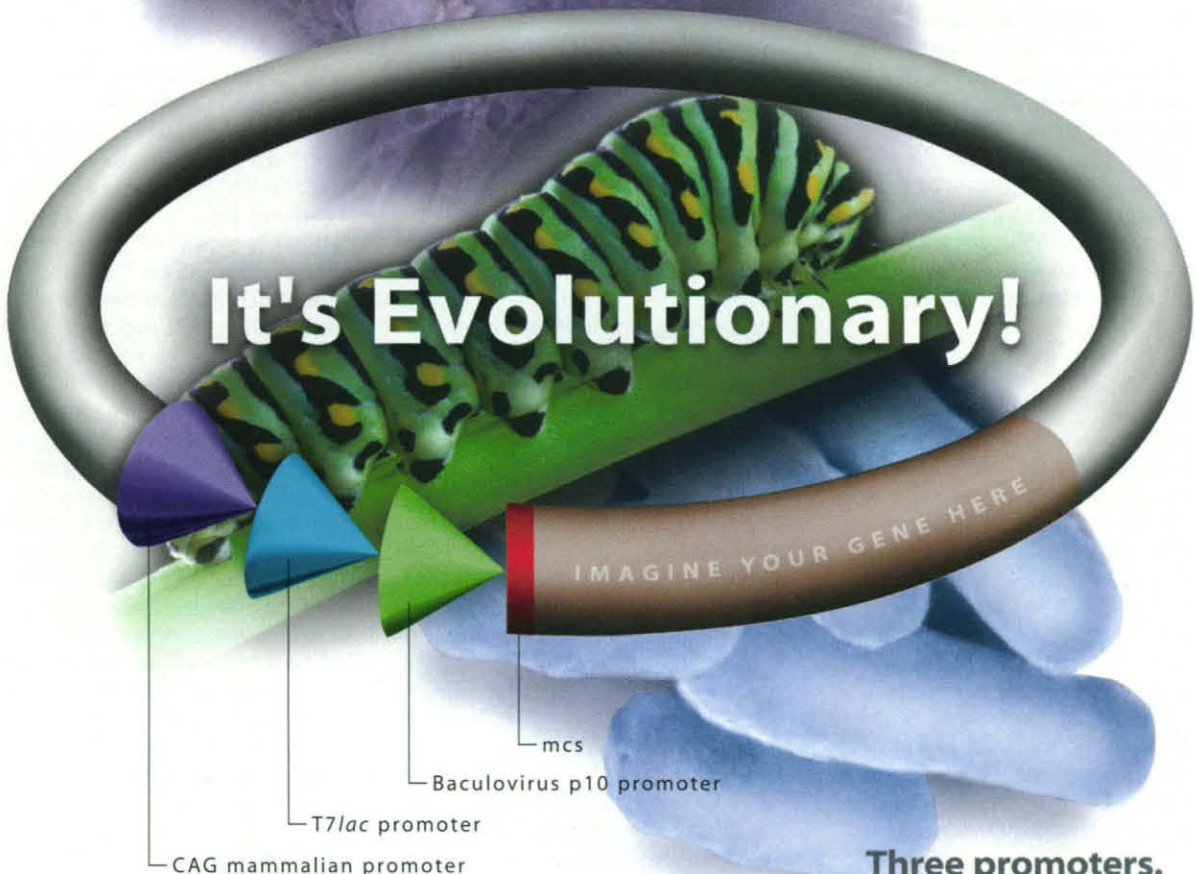
Spontaneous activity is seen during recording from a single neuron in the brain. Is this seemingly random firing simply "noise" that lacks any informational content or could it also represent some kind of meaningful signal? Tsodyks *et al.* (p. 1943) combined single-neuron recording with real-time optical imaging of a large surrounding cortical region and found that the firing of a cell depends on the overall activity pattern in the surrounding area. It appears that nerve cells are not really firing at random, but rather that they are participat-

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THIS WEEK IN SCIENCE

CONTINUED FROM PAGE 1073

ing in larger cortical activity states that seem to correspond to the functional architecture maps.

BONING UP ON STATINS

Nearly 100 million people worldwide are at risk for osteoporosis, a debilitating disease of bone loss, and this number is expected to rise as the population ages. Mundy *et al.* (p. 1946; see the news story by Vogel) show that the statins, a group of drugs commonly prescribed to lower serum cholesterol levels, also stimulate bone formation in vitro and in rodent models. This effect was associated with increased expression of bone morphogenetic protein-2, a growth factor produced by bone cells. These results raise the possibility that with optimization of dose and tissue distribution properties, the statins may have beneficial effects in the prevention and treatment of osteoporosis.

TOO MANY DOING TOO LITTLE

Familial hemophagocytic lymphohistiocytosis (FHL) is a genetic disorder that dysregulates the immune system and leads to excesses of lymphocytes, macrophages, and inflammatory cytokines. Two genetic loci have been identified and linked to the disease. Stepp *et al.* (p. 1957) identified the defective gene in the 10q21-22-linked patients as the gene coding for perforin, a protein released from cytotoxic lymphocytes to kill the target cell. This finding provides insight into the biological role of perforin as a mechanism for turning off immune responses, perhaps through the elimination of antigen presenting cells or the cytotoxic T cells themselves.

BLOCKING DEVELOPMENT OF B CELLS

Not all of the causes of genetic immunodeficiencies have been worked out. In cases in which B cells are lacking in the periphery, the Btk protein kinase signaling pathway is suspect, as it has turned out to be critical for B cell activation and development. Minegishi *et al.* (p. 1954) have characterized the defect in a patient that had normal Btk. The mutation responsible in this case was the BLNK adaptor protein, which coordinates signaling from the B cell antigen receptor by binding to various kinases, lipases, and adaptors. Pappu *et al.* (p. 1949) generated mice deficient in BLNK and report that these mice have the same defect—a block in the development of immature B cells from the pro-B to the pre-B stage that effectively prevents maturation of B cells and antibody production.

POX ENTRY PATHWAYS

The ability of chemokine receptors to act as viral receptors is best known for the case of the human immunodeficiency virus (HIV). Lalani *et al.* (p. 1968) have now identified a receptor for a very different pathogenic virus, myxoma, a rabbit pox virus. They show that 3T3 cells can be made permissive for this virus if the cells are transfected with one of a number of chemokine receptors, including CCR1, CCR5, and CXCR4. Infection could be blocked by treatment with a chemokine or specific antibody. The authors speculate that the existence of poxviruses may have led to the selection in the human population for mutant alleles of CCR5 that would later provide resistance to HIV.

TECHNICAL COMMENT SUMMARIES

Reconciling Holocene CO₂ Records

Wagner *et al.* (Reports, 18 June, p. 1971) used measurements of stomata of fossil leaves from a peat bog in the Netherlands to infer atmospheric CO₂ levels during deglaciation and the beginning of the Holocene. They concluded that changes in CO₂ levels accompanied small climatic oscillations and suggested that CO₂ levels were high [above 300 parts per million by volume (ppmv)] in the beginning of the Holocene.

Two comments critique their second interpretation in particular. Birks *et al.* comment that other fossil leaf data and ice core data "are consistent with atmospheric CO₂ levels...at ca. 260 to 280 ppmv" and question the calibration set used by Wagner *et al.* Indermühl *et al.* provide further discussion of the discrepancy with the ice core measurements of atmospheric CO₂ levels from Taylor Dome, Antarctica.

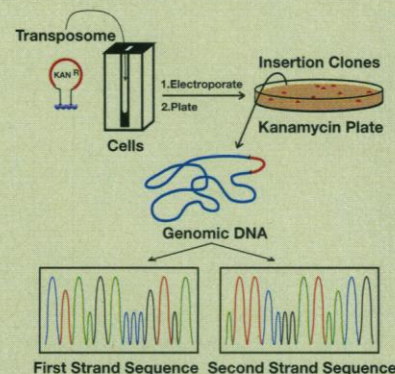
Wagner *et al.* respond that the other data from leaf stomata have low temporal resolution and may be biased by comparison of samples across latitudes, and "agree that [their] results cannot be reconciled with the ice-core records from Antarctica."

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/286/5446/1815a

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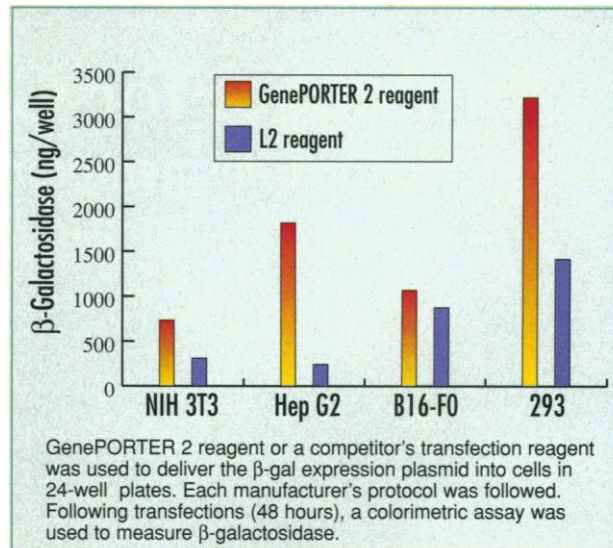
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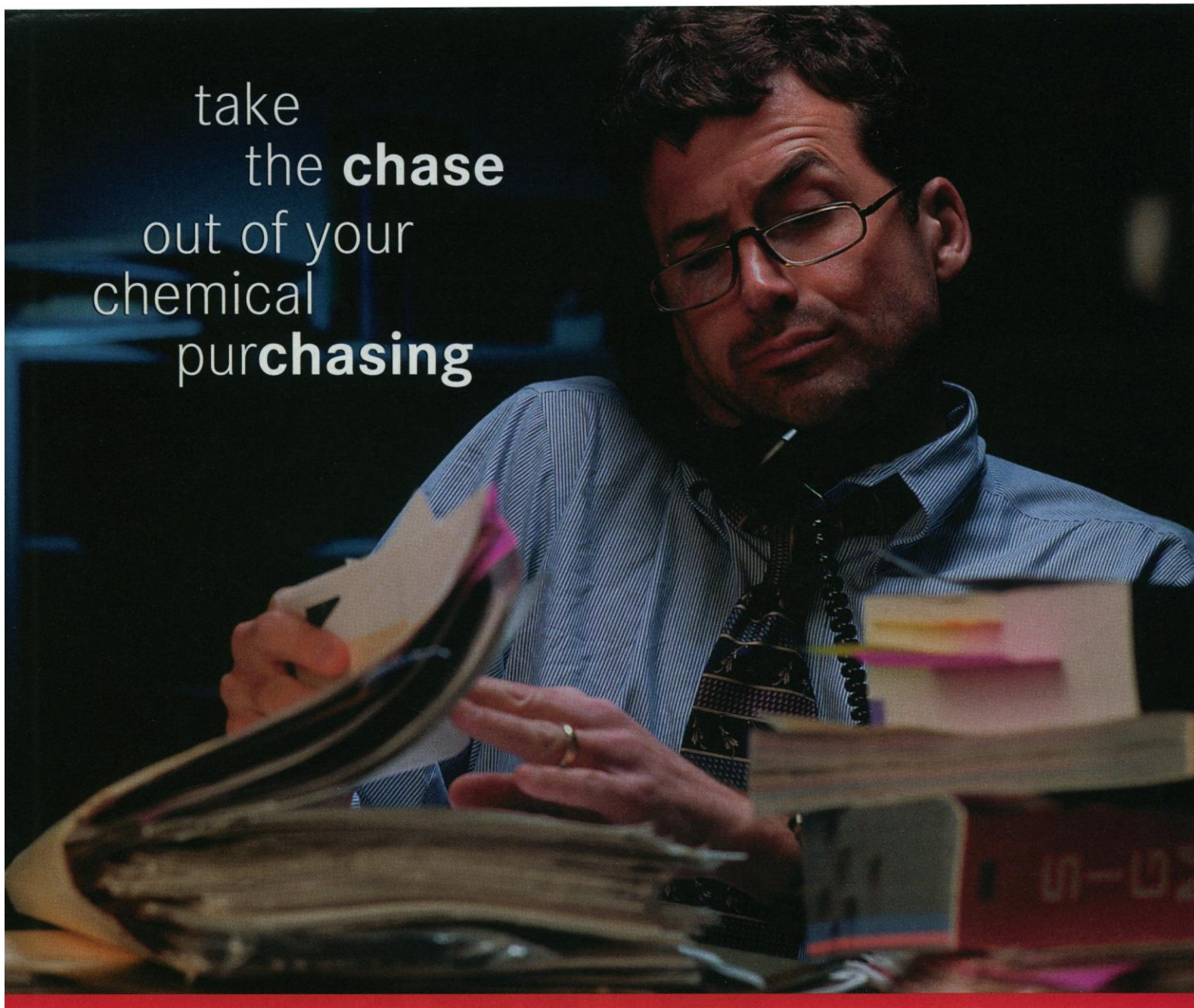


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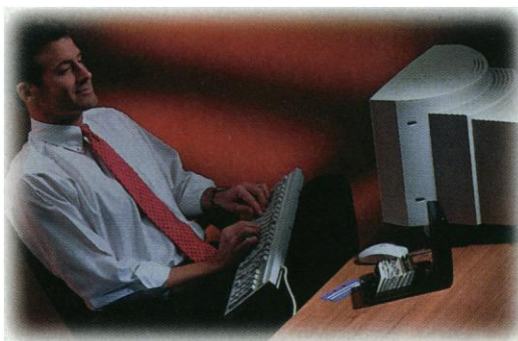
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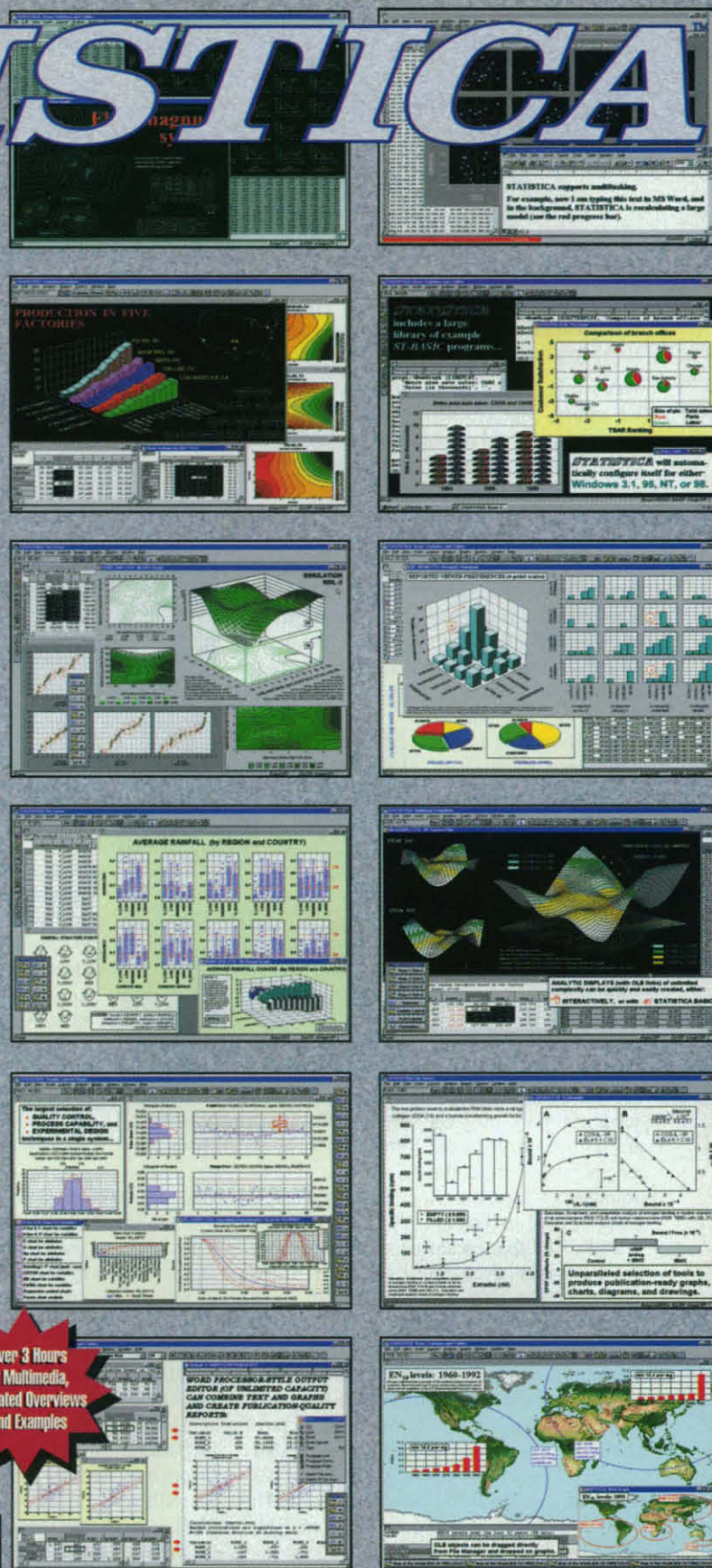
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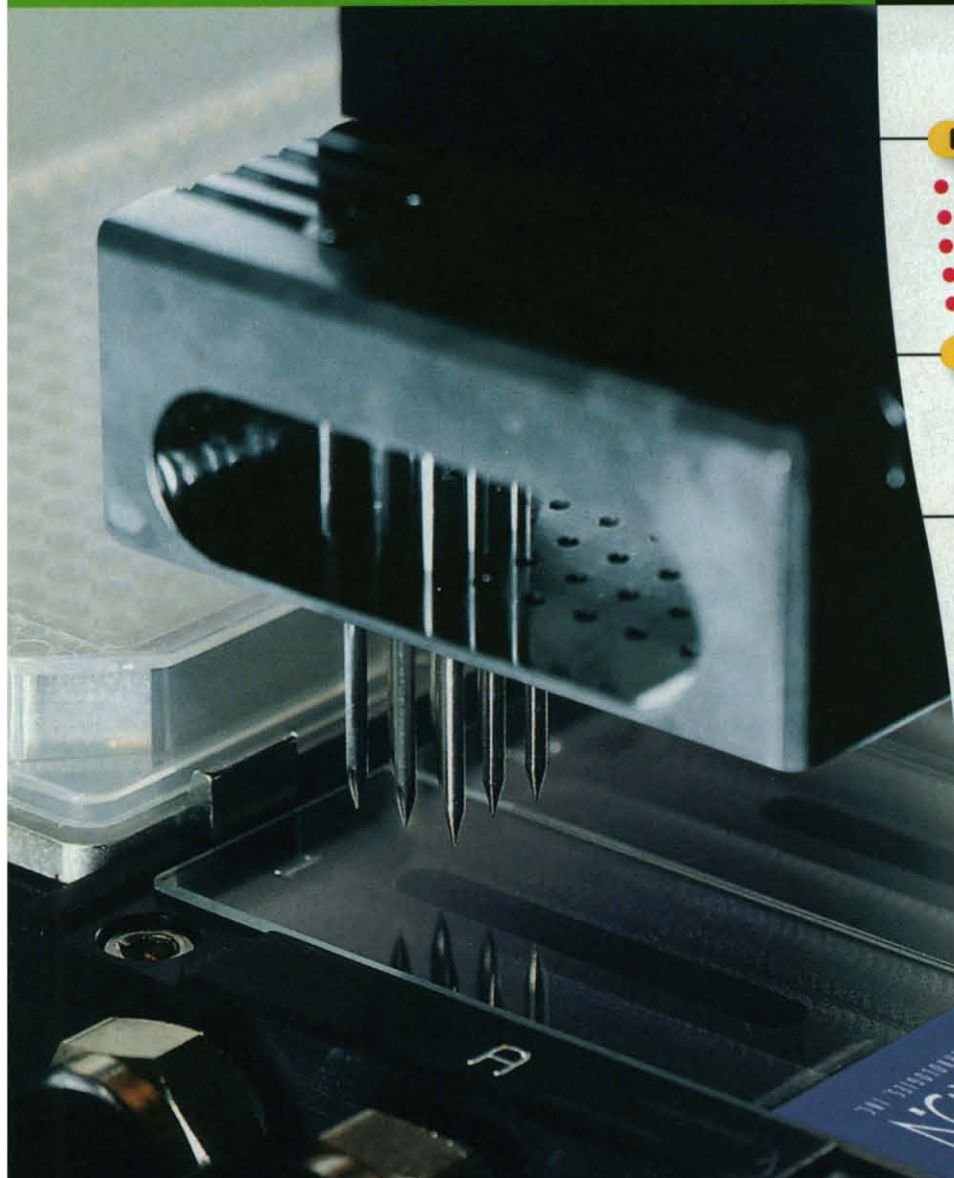
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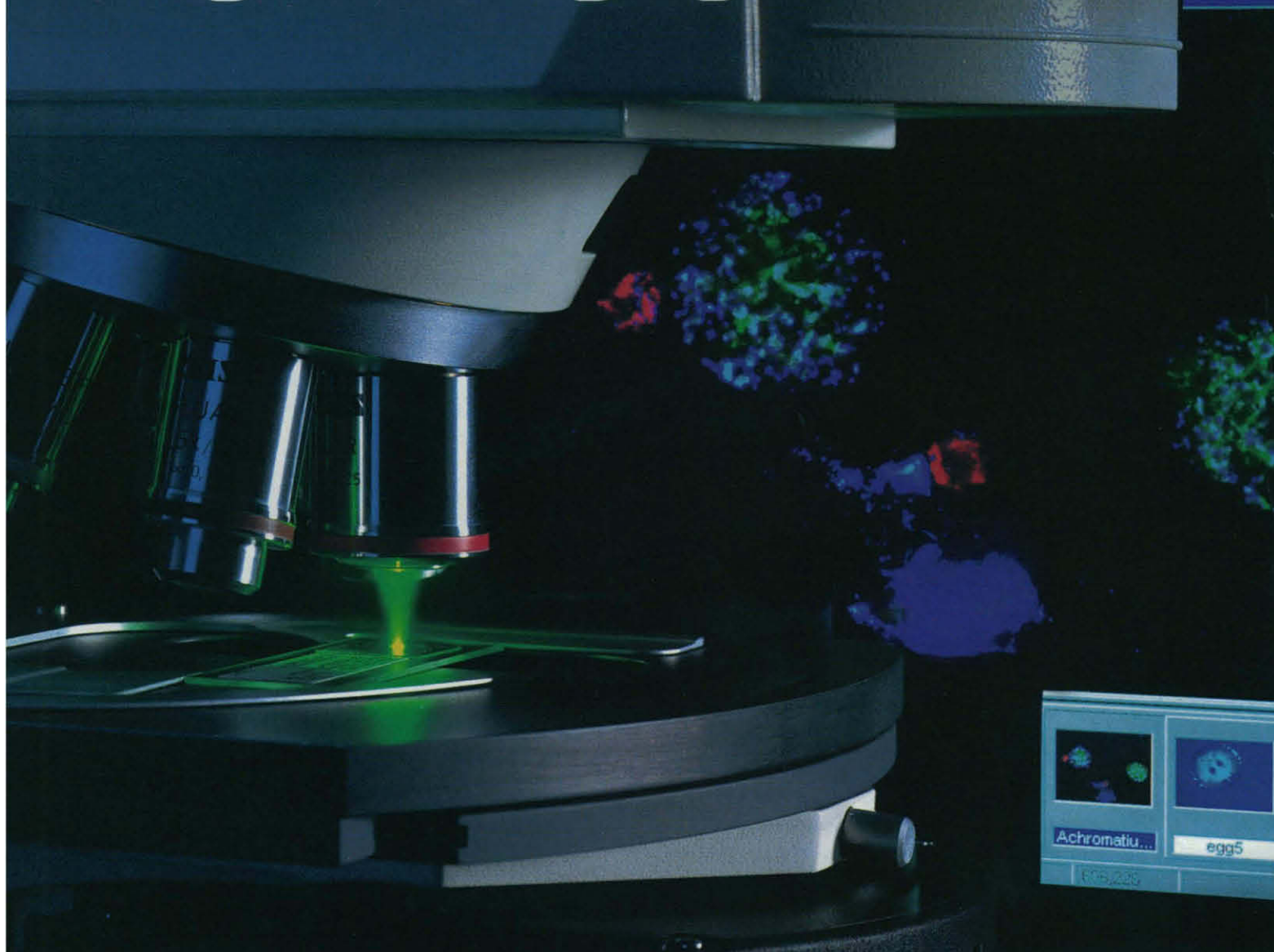


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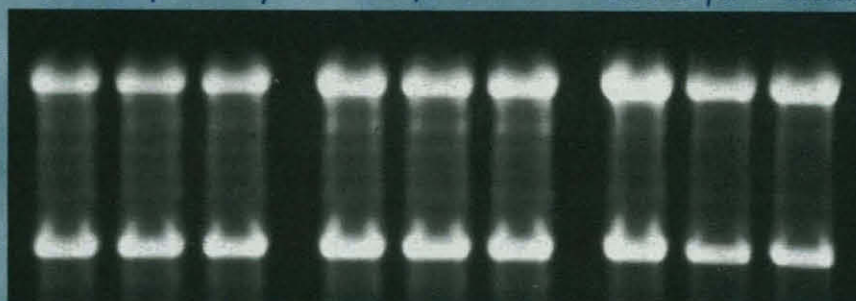
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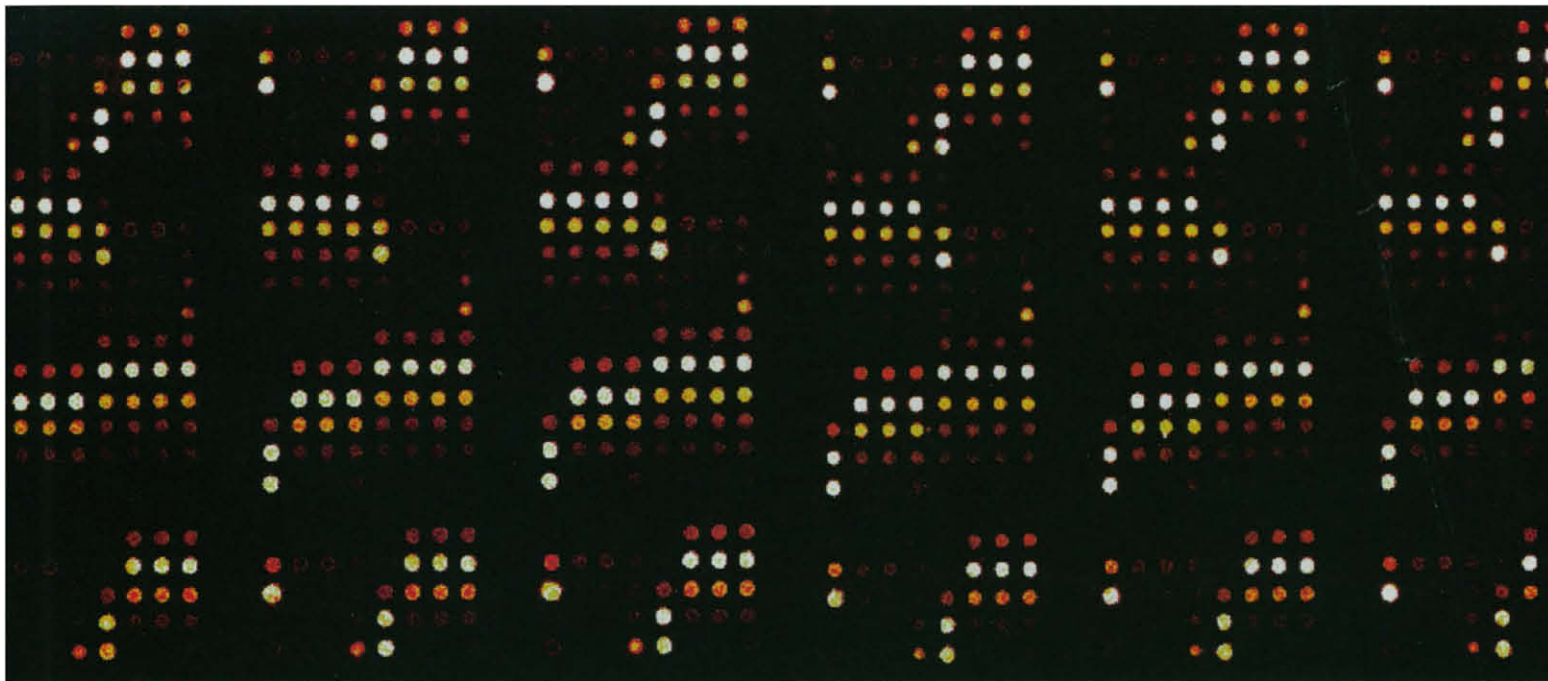
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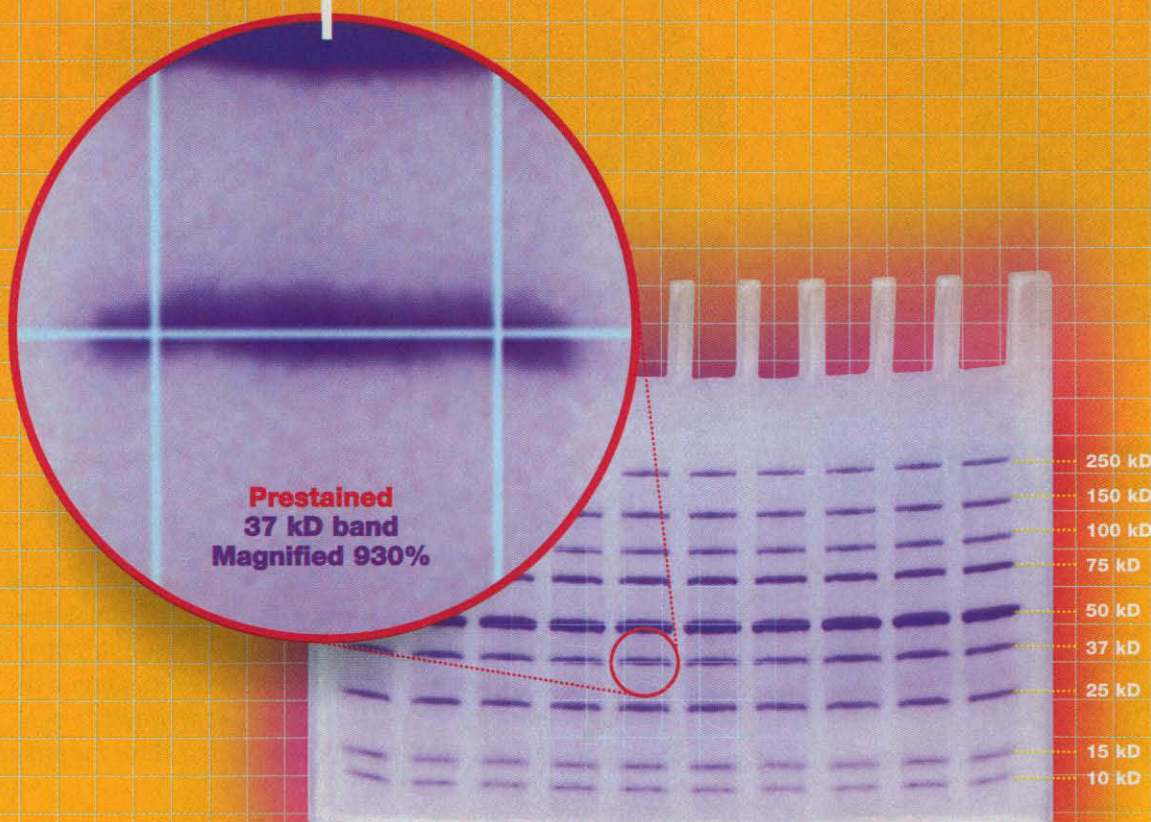
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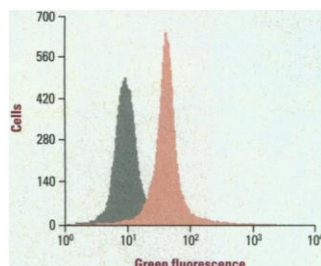
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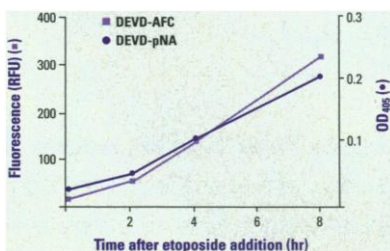


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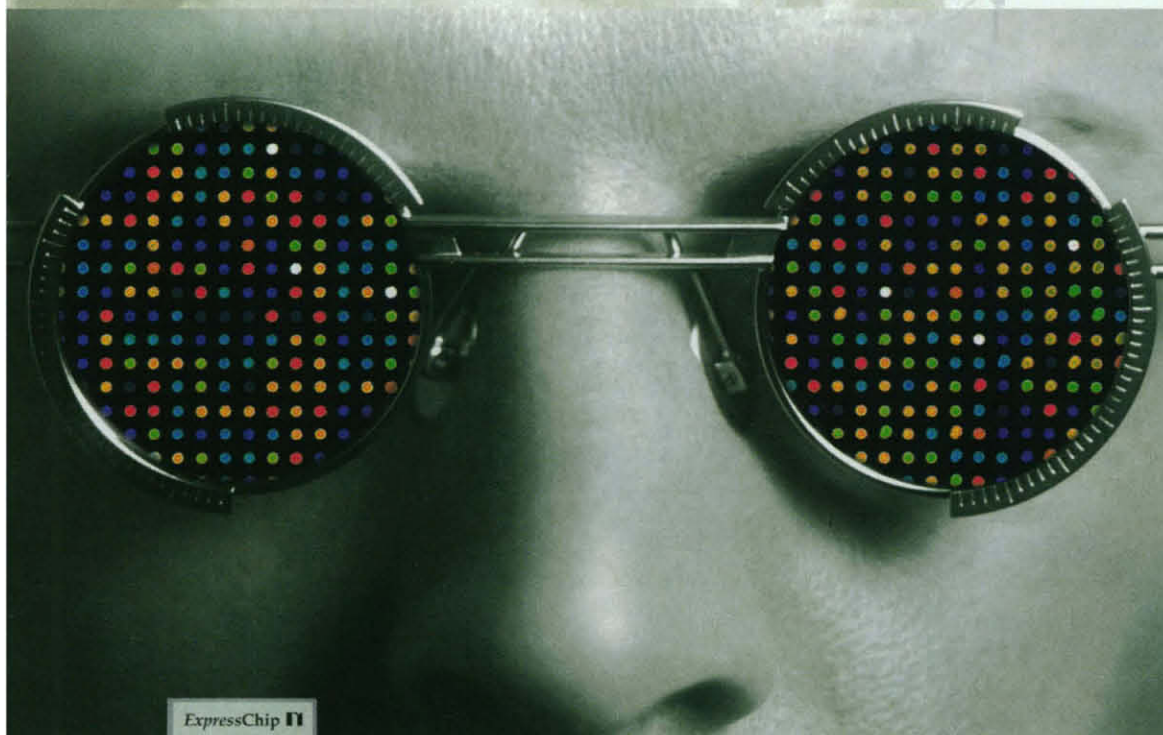
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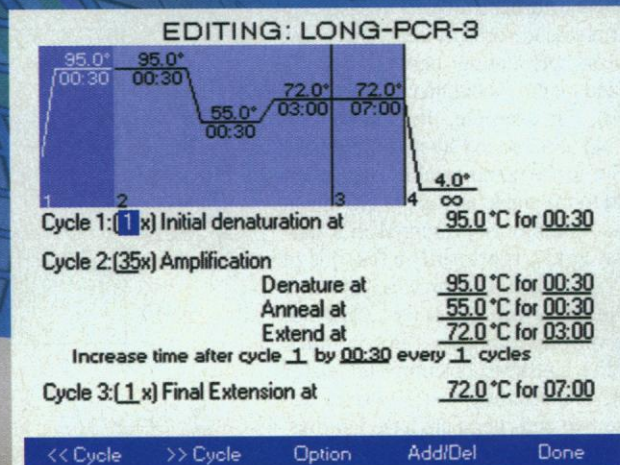


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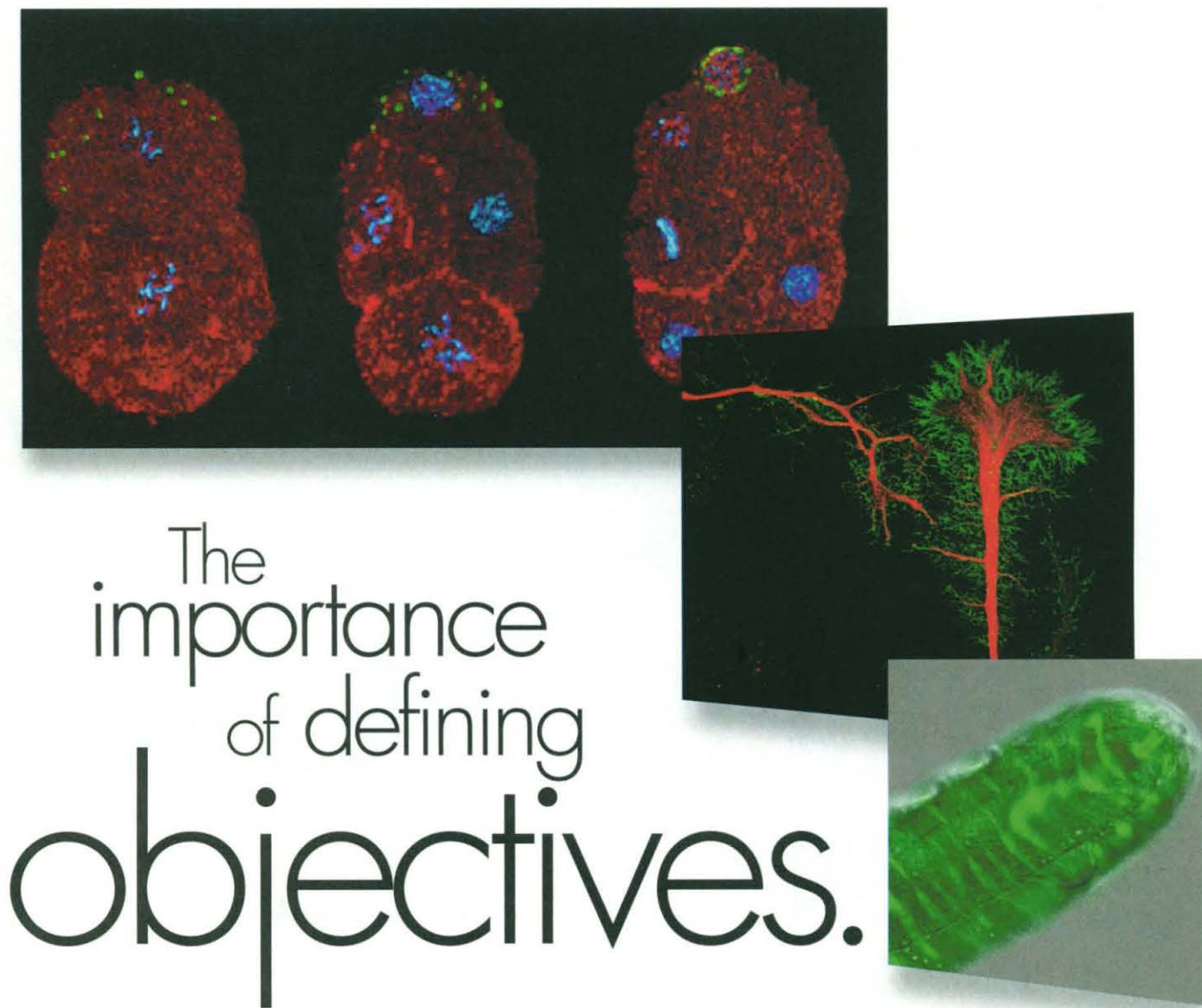
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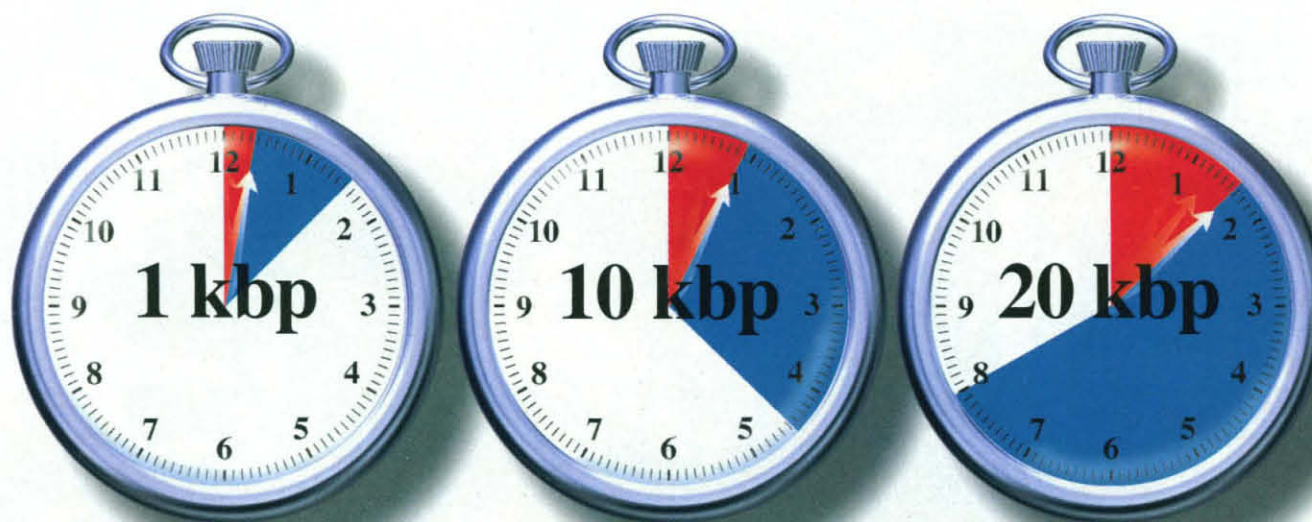
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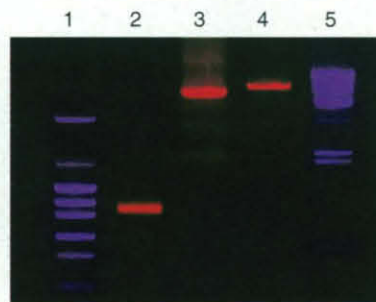
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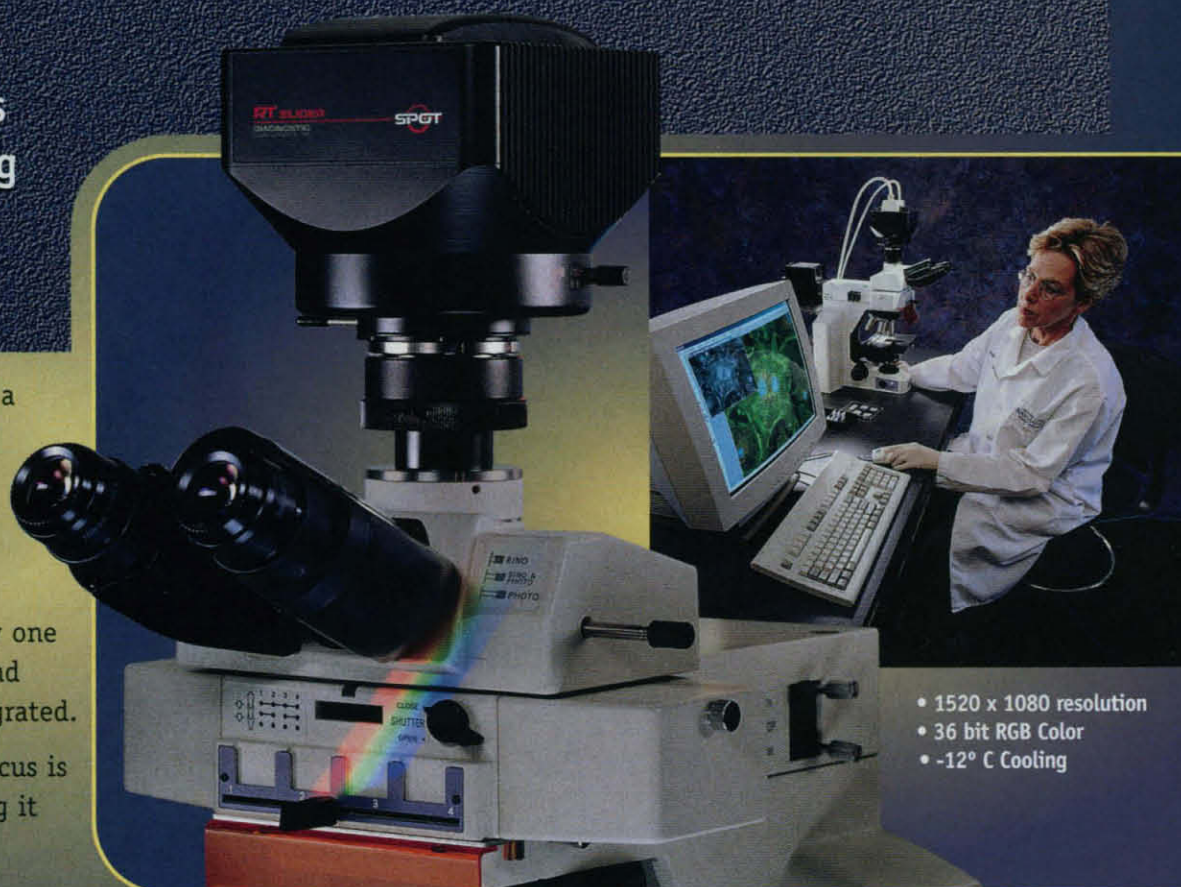
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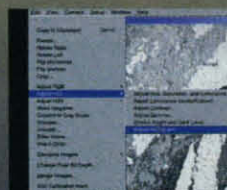
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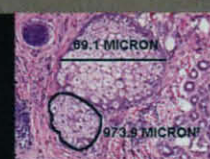
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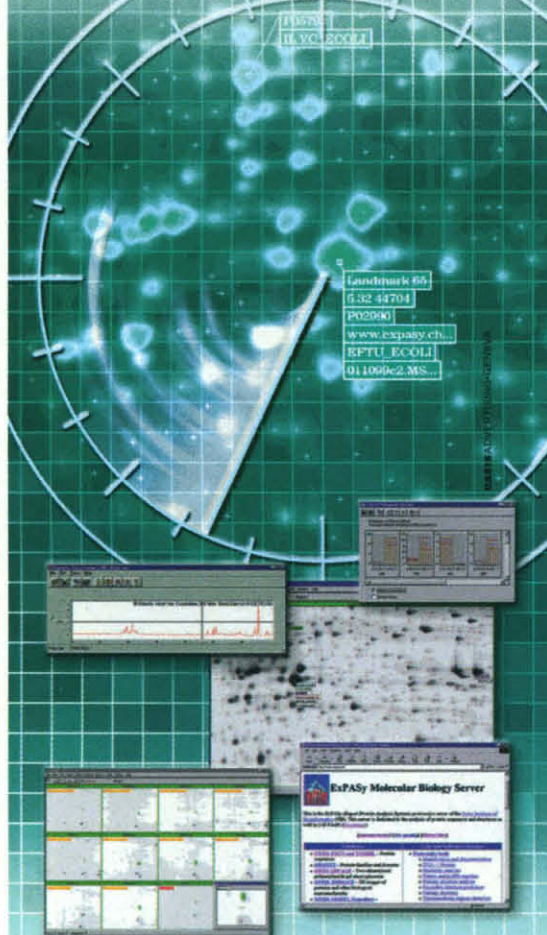
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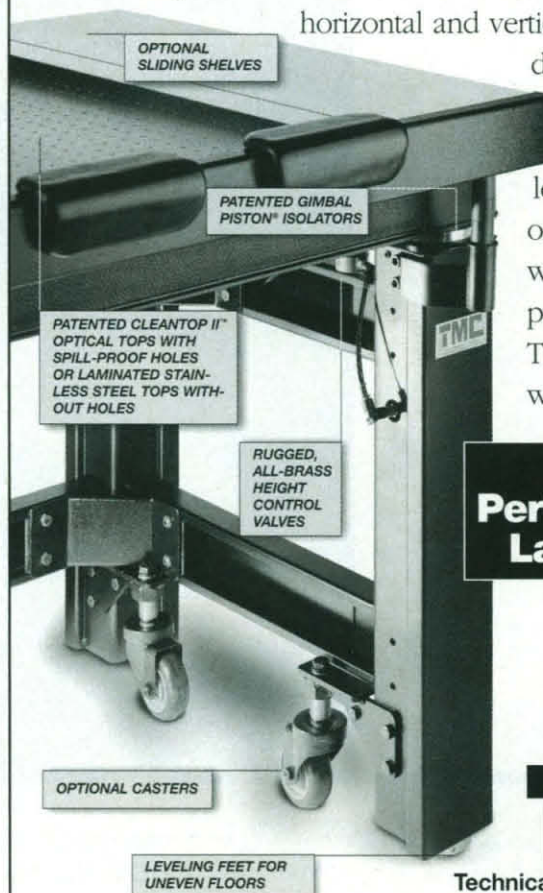
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