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Science

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Cellular Immunology

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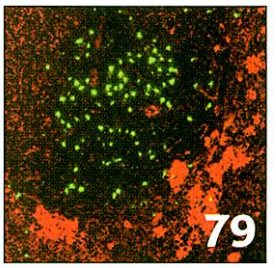
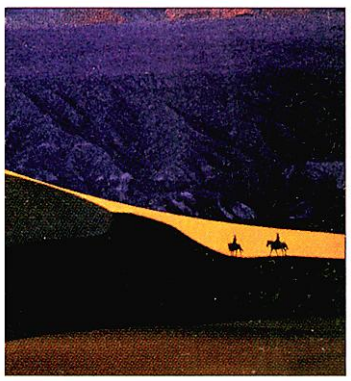


COVER Migratory capacities and effector functions of T lymphocytes are coordinately regulated during differentiation. Activated mouse CD4+ T lymphocytes (stained green) home to the T cell areas of the spleen and may be involved in secondary immune responses and immune regulation. Red indicates B cell areas stained with antibody to immunoglobulin M. A special section starting on p. 79 focuses on many aspects of cellular immunology. [Image: G. Iezzi and A. Lanzavecchia]



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Death Valley comes back to life

NEWS

RESEARCH

See also Report on p. 127.

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SCIENCE (ISSN 0036-8075) is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue, NW, Washington, DC 20005. Periodicals Mail postage (publication No. 484460) paid at Washington, DC, and additional mailing offices. Domestic individual membership and subscription (51 issues): $112 ($62 allocated to subscription). Domestic institutional subscription (51 issues): $340; Foreign postage extra: Mexico, Caribbean (surface mail) $55; other countries (air assist delivery) $90. First class, airmail, student, and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. Publications Mail Agreement Number 1069624. Printed in the U.S.A.

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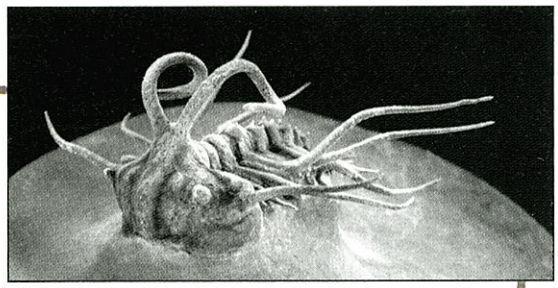

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Summary appears on page 11; full text is available online at www.sciencemag.org/cgi/content/full/290/5489/11a

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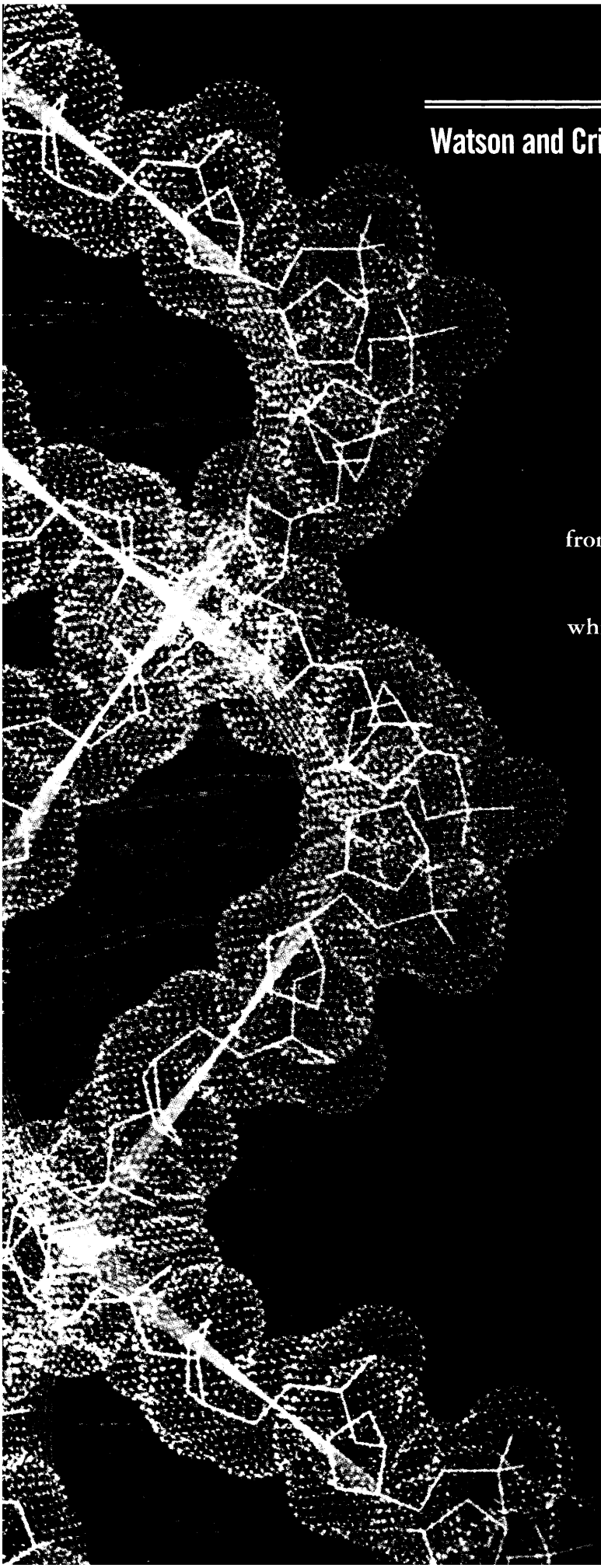

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Image: A false color scanning tunnel micrograph of a double-stranded DNA molecule taken at the Lawrence Livermore Laboratory.

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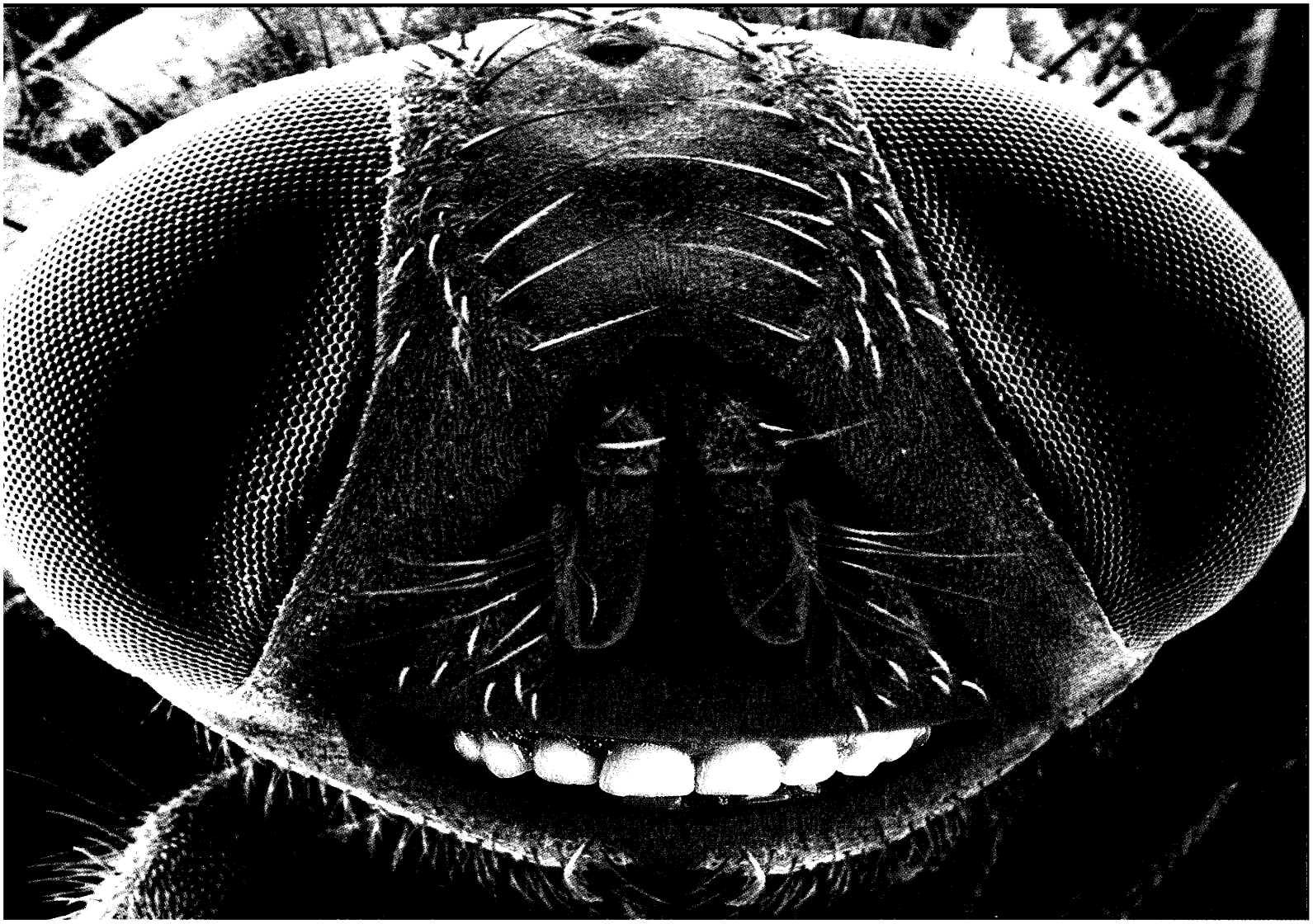

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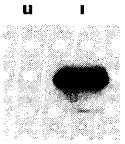

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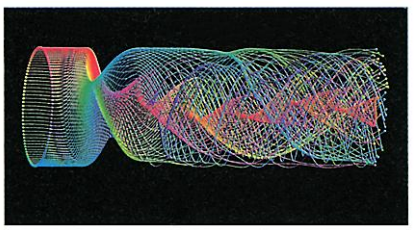
PLANETS WITHOUT ORBITS?

About 47 extrasolar planets have been detected orbiting around stars, which indicates that planets may be relatively common in the universe. Zapatero Osorio *et al.* (p. 103; see the news story by Irion) have used optical and near-infrared imaging and spectroscopy to image and determine the temperature of several young, low-mass objects (5 to 15 Jupiter masses and 1 to 5 million years old) in the nearby stellar cluster around σ Orionis. Because these objects are very cool (1700 to 2200 kelvin), they cannot sustain nuclear burning, which suggests that they may be planets. If they are planets, however, they are not orbiting any star. Such isolated planets would add a new challenge to planet formation models and the time scales over which planets may form.

OUT OF ORDER COMES CHAOS

Although the theory of nuclear magnetic resonance (NMR) spectroscopy makes a few critical assumptions, it is highly reliable and allows complex sequences of radio-frequency (RF) pulses to be used to produce predictable changes in magnetization. Lin *et al.* (p. 118) show that in aqueous solution,



the milieu of many protein NMR experiments, two effects, radiation damping and the dipolar field, that are normally treated separately can actually combine even after very simple RF pulses to create chaotic spin dynamics. Magnetization that should be eliminated by a pulse sequence can reappear and can be amplified by slight temperature gradients. The authors discuss how these effects can be avoided and even put to use in imaging.

MESOPOROUS PATTERNING

Most patterning of inorganic thin films involves the selective formation of the film in certain areas with other regions left empty. Doshi *et al.* (p. 107) have used in situ photogeneration of acid and photomasking to pattern different silica mesoporous phases within a continuous film. The exposed areas can form a more densely packed hexagonal phase than the unexposed regions, and continuous "gray-scale" patterning was achieved by varying the incident flux. If greater amounts of surfactant were used, the exposed areas formed a less dense tetragonal phase. Because these regions have different densities and thus different refractive indices, such films can be used for optical waveguides and gratings.

VIBRATIONALLY EXCITED ELECTRON TRANSFER

Most electron transfer reactions of interest occur in solution or condensed phases, but fundamental studies are difficult to unravel if there are competing solvent effects. Huang *et al.* (p. 111) looked at an intermediate case of vibrationally excited NO molecules scattering off of a single-crystal gold surface. The dipole of the NO molecule interacts with its image dipole in the metal, which mimics the effect solvent screening. What they find is a dramatic increase in electron transfer for high vibrational states that arise from more favorable crossings of the potential energy barrier. No such effect was seen for the same experiment performed with an insulating LiF surface.

THERMALLY ENHANCED ELECTRON TRANSFER

Electron transfer processes in proteins appear to require very precise structural arrangements, and thermal motions might be expected to decrease reaction rates. Balabin and Onuchic (p. 114; see the Perspective by Schulten) show that rather than being disturbed by them, proteins can use thermal motions to their advantage. Electrons can explore a web of pathways, some of which may occur in protein conformations far from equilibrium. Because of the quantum nature of electron motion, constructive and destructive interference effects arise between pathways that may dynamically amplify electron transfer.

WHEN NOBLE GAS MEETS NOBLE METAL

Noble gases have completely filled valence electron shells and are therefore quite unreactive. Nevertheless, a variety of compounds with covalent noble gas bonds have been made, although most of these compounds cannot be isolated. Seidel and Seppelt (p. 117; see the Perspective by Pyykkö) now show that even xenon can go for the gold—in this case, by combining with a square planar gold complex that could be crystallized and that was stable up to –40°C. In solution, the compound was even stable at room temperature under a xenon pressure of 10 bars.

NEUROPATHIC PAIN KILLER

Peripheral nerve damage can lead to neuropathic pain, which is intense, persistent, and difficult to treat with presently available drugs. Boucher *et al.* (p. 124) present evidence that GDNF, but not other neurotrophic factors, can prevent the development of neuropathic pain and could also help revert already established neuropathic pain states. The effects of GDNF are caused by a reduction of spontaneous activity in myelinated sensory afferents. The underlying mechanism is a readjustment of voltage-gated sodium channel expression in dorsal root ganglion neurons.

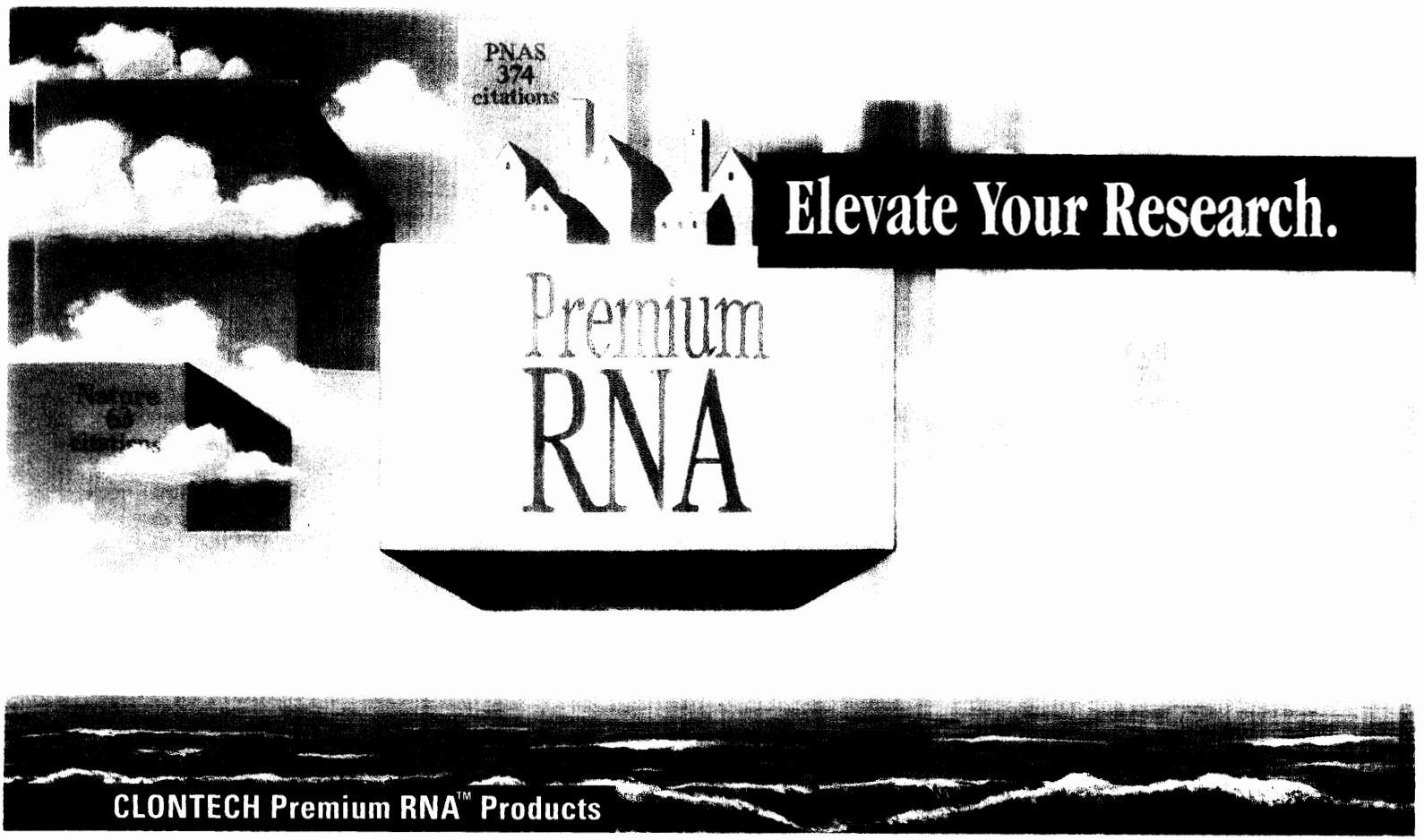
HAVING THE NERVE TO GO ON

In the nematode *Caenorhabditis elegans*, mutations that disrupt the signaling pathway of the insulin-like receptor *daf-2* dramatically extend the animals' life-span and cause the accumulation of large amounts of fat. By selectively expressing normal versions of the mutated insulin-like receptors only in certain tissues, Wolkow *et al.* (p. 147) pinpoint the nervous system as responsible for this pathway's effect on life-span and the muscles as the site that controls the metabolic alterations. The authors suggest that defects in the *daf-2* pathway allow overexpression of free-radical scavenging enzymes, which protects neurons from oxidative damage and allows them to secrete life-prolonging neuroendocrine signals.

A SENSE OF SPACE

T cells have acquired the ability to respond to the physical space in which they exist, as can be seen when they divide to fill lymphoid organs that are empty or contain only a few lymphocytes. Such homeostatic expansion is held in check when the space is fully occupied, and in this case, naïve T cells survive in a steady state. Seddon *et al.* (p. 127) examined the requirement of $p56^{lck}$, a tyrosine kinase critically associated with T cell receptor signaling and T cell development. By switching off $p56^{lck}$ in mature naïve T cells, they made the surprising observation that although this signaling molecule was necessary for homeostatic expansion, it was not required for T cell survival.

CONTINUED ON PAGE 11



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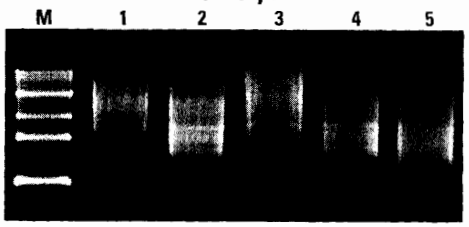

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 9

CANCER: THE PROXIMITY EFFECT

Chromosomal rearrangements between the *RET* gene and other distant loci are common in radiation-induced thyroid tumors and has been seen in children exposed to environmental radiation after the Chernobyl incident. What mediates these reciprocal and illegitimate rearrangements between sequences that are often very far apart in the linear DNA sequence? Nikiforova *et al.* (p. 138; see the Perspective by Savage) show that the *RET* gene and the *H4* gene, with which it often recombines in these tumors, are in close physical association in the nuclei of human thyroid cells. The formation of this chimeric gene product is known to cause cancer in mice.

DETERMINING FAT CELL FATE

Adipose tissue serves as the body's site for energy storage and expenditure. A fair amount is known about the gene functioning in adipocyte differentiation; however, we are lacking knowledge of the players involved in early adipogenesis. Tong *et al.* (p. 134) used a fruit fly model system to identify two vertebrate GATA factors that, like their homologs in *Drosophila*, function in adipose tissue. The proteins GATA-2 and GATA-3 hold differentiating cells in the preadipocyte stage and hence regulate the preadipocyte to adipocyte transition. Several mouse models of obesity display a reduction in adipose expression of GATA-2 and GATA-3. Because GATA factors function in adipose tissue in both the fly and mouse, these proteins may serve as appropriate targets for obesity studies and therapy.

MAKING AN UNKIND CUT

In Alzheimer's disease, the accumulation of β-amyloid peptide in the brain results from the cleavage of its precursor protein by the membrane-associated aspartic protease memapsin 2 (β-secretase). Hong *et al.* (p. 150) have determined the crystal structure of the protease domain of memapsin 2 complexed with an inhibitor at a resolution of 1.9 angstroms. Although the hydrogen bonds involving the inhibitor backbone resemble those of other aspartic proteases, contacts with inhibitor side chains are different, and the inhibitor backbone has an unusual bent structure. These features may facilitate rational design of drugs that specifically inhibit memapsin 2.

TARGETING ANXIETY

Benzodiazepines are widely used drugs that enhance inhibitory GABAergic neurotransmission in the central nervous system. This pharmacological profile causes both anxiolytic and sedative effects. In an attempt to better understand the enormous heterogeneity of $GABA_A$ receptors Löw *et al.* (p. 131; see the news story by Helmuth) selectively tried to silence specific receptor subunits. They discovered that the α2 subunit of the $GABA_A$ receptor mediates the anxiolytic action of benzodiazepines. This finding could lead to the development of new drugs for the treatment of anxiety without the side effects of sedation or motor impairment.

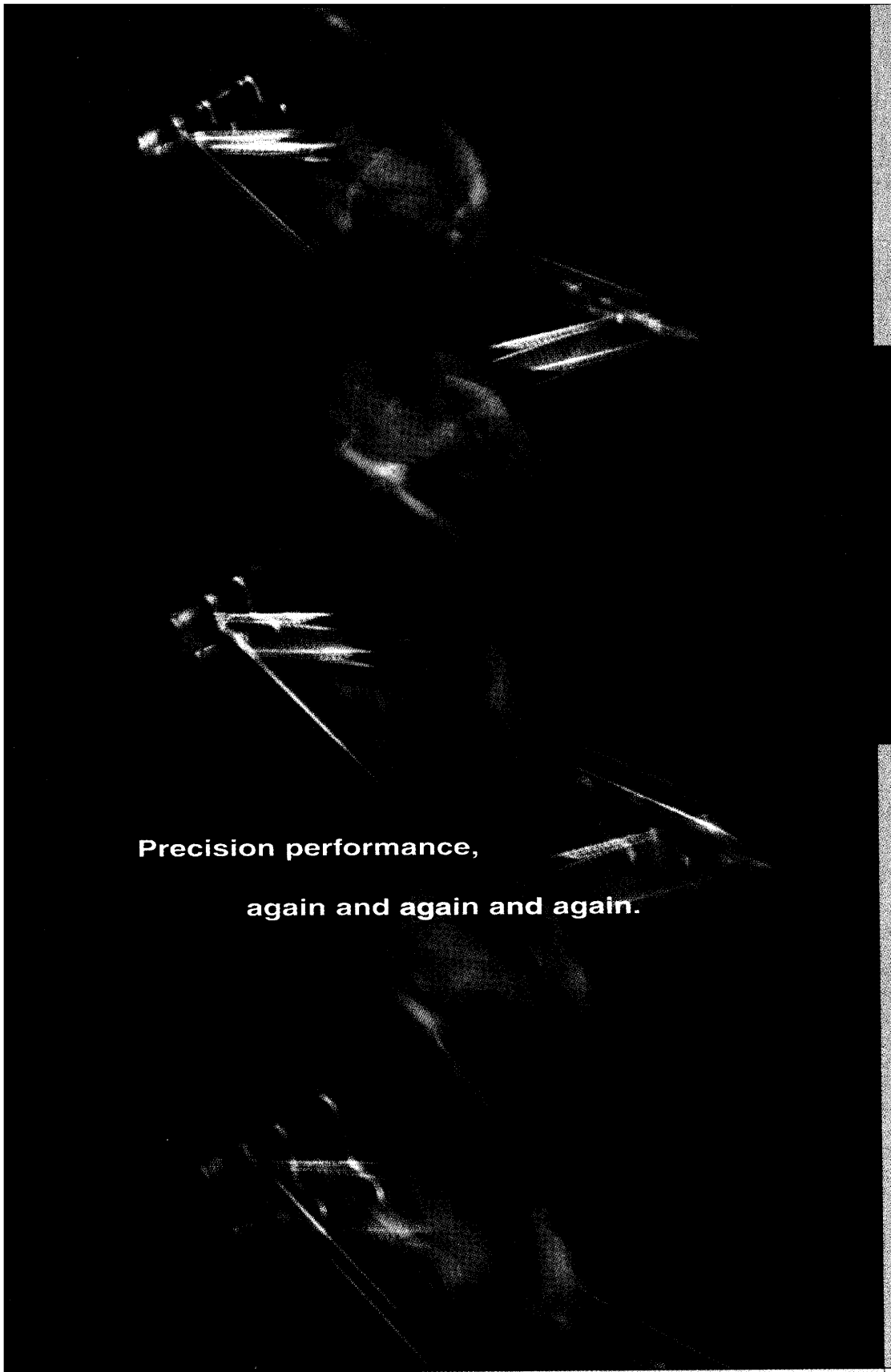
TECHNICAL COMMENT SUMMARIES

Assessing the Mechanisms That Give Rise to Autoimmunity

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/290/5489/11a

Kouskoff *et al.* (Reports, 31 March, p. 2501), using a transgenic (Tg) mouse model, showed that challenge with a self-mimicking foreign antigen could break B cell self-tolerance in a manner independent of T cell help, and thereby identified "a potentially important mechanism" for autoimmune reactions. Zinkernagel, in a comment, draws attention to previous work from his lab, not cited by Kouskoff *et al.*, that concluded that against "highly repetitive, identical polymeric determinants, B cells are not tolerant and react in a TI-1 [T-independent type 1] fashion without an obvious polyclonal activator," whereas "against monomeric antigens, B cells strictly and exclusively react in a T cell–dependent and linked fashion." Zinkernagel concludes that "instead of the still unproven mimicry hypothesis," these results suggest that "antigen patterns plus absence or presence of T cell help play the principal roles in regulating B cell responsiveness."

Nemazee *et al.* express regret at their failure to cite this previous work, but nonetheless argue that Zinkernagel's contention that immune tolerance does not occur at the B cell level "cannot be generalized without denying a large body of direct evidence to the contrary." And, while recognizing the limitations of antibody Tg mice, Nemazee *et al.* stress that such experiments also allow determinations that "are difficult or impossible to make in a polyclonal model." Thus, they conclude, "our results provide novel mechanistic insight that complements other types of studies."



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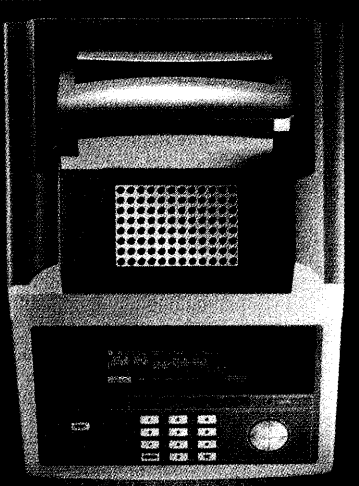

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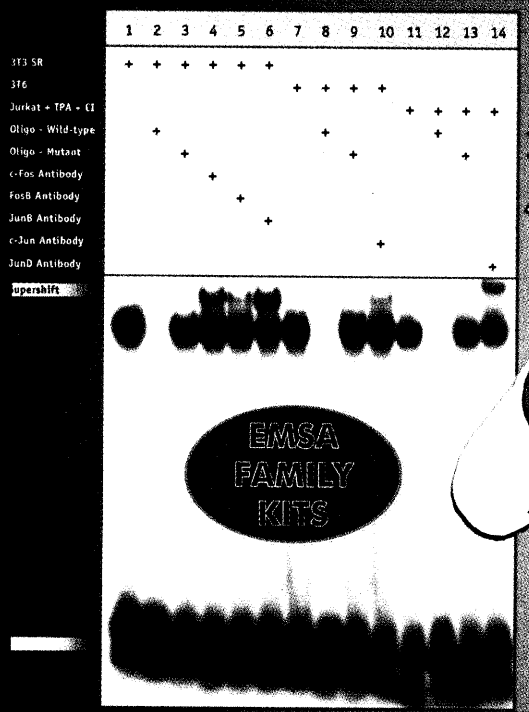

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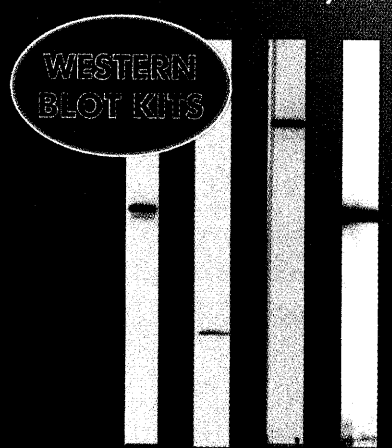

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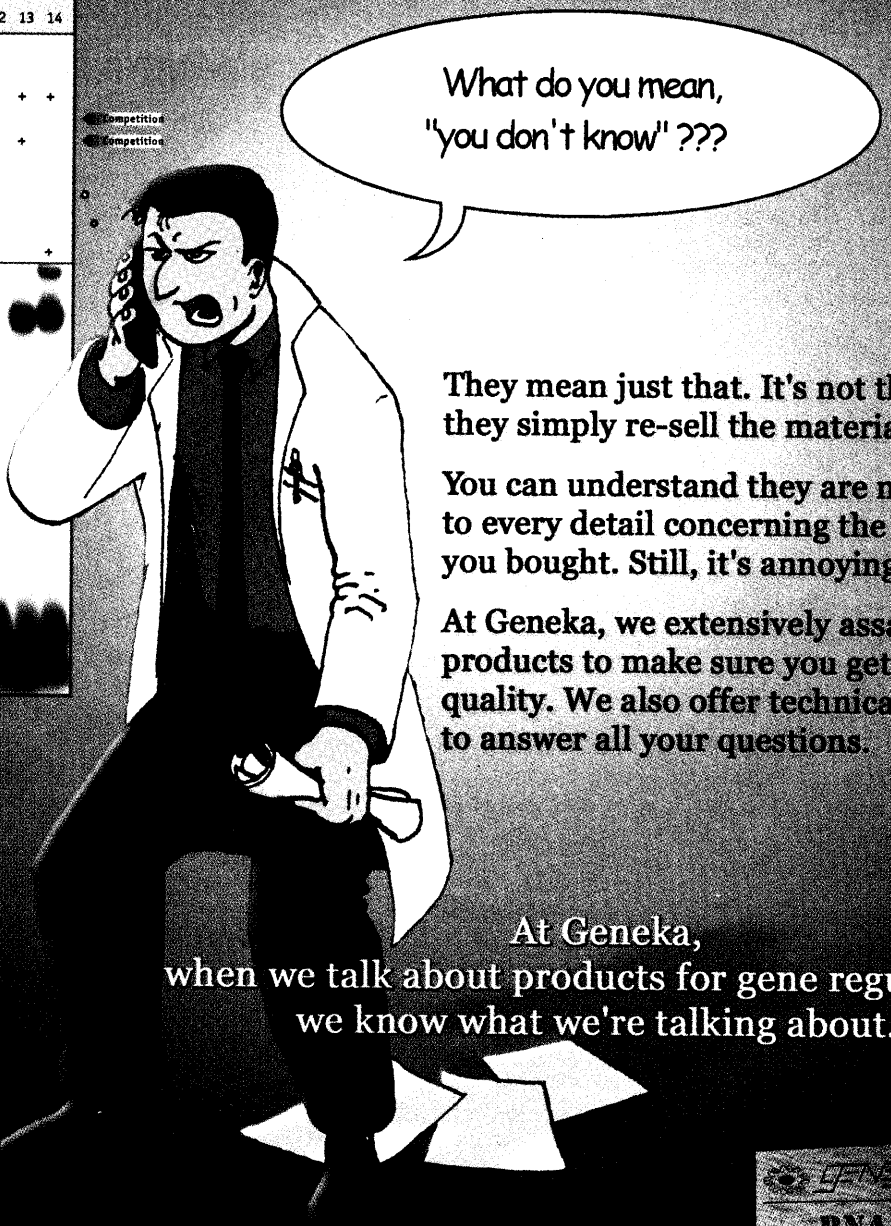

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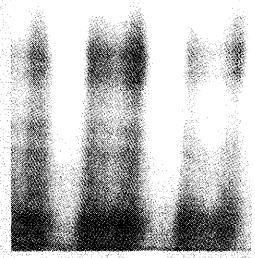

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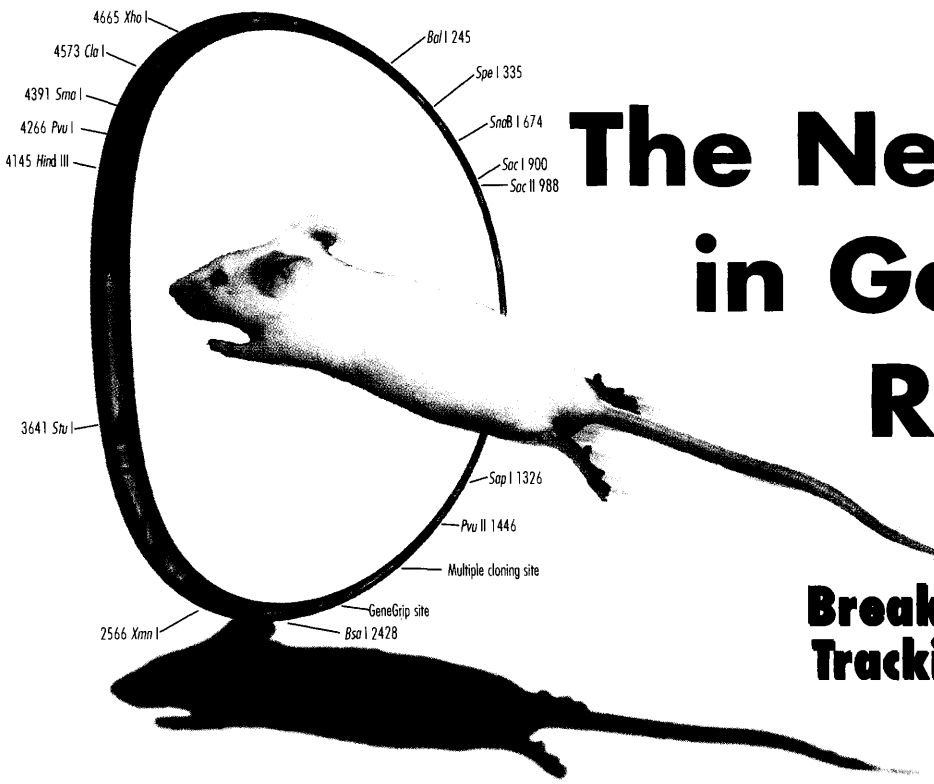

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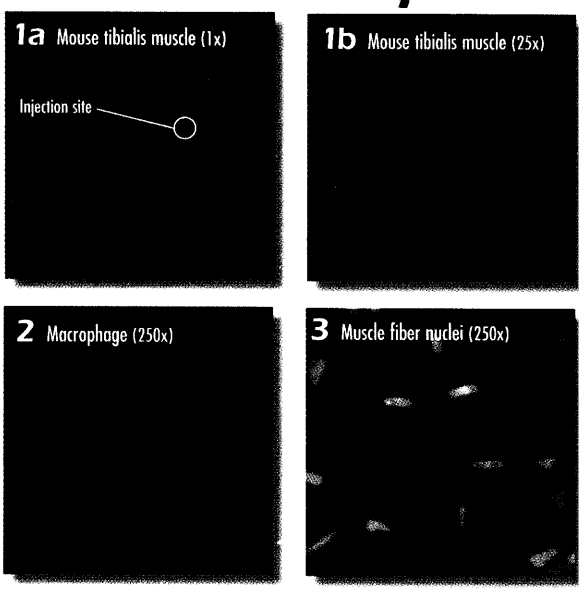

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[1]Dupuis, M., et al., *J. Immunol.* 2000, 165:2850–2858.

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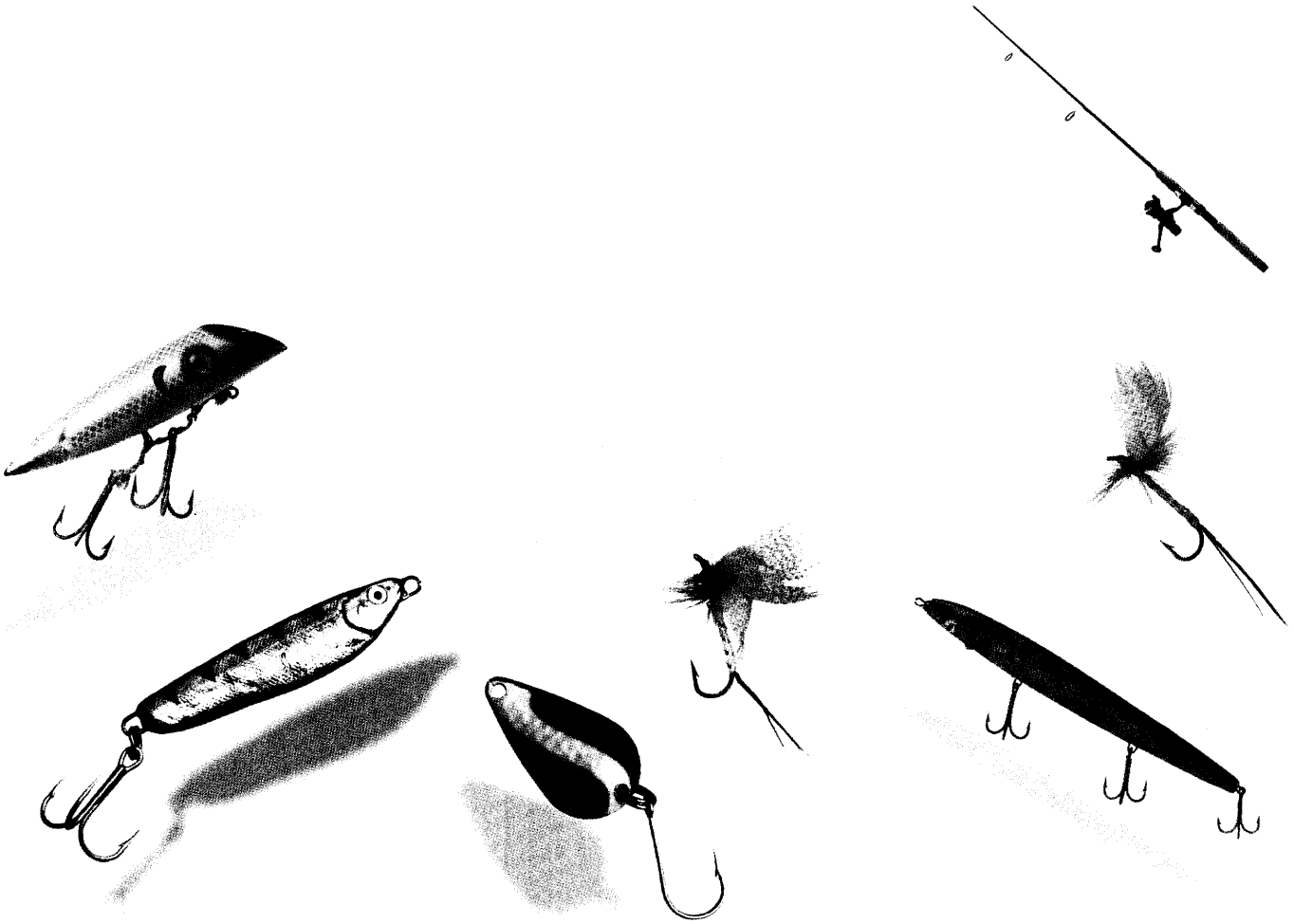

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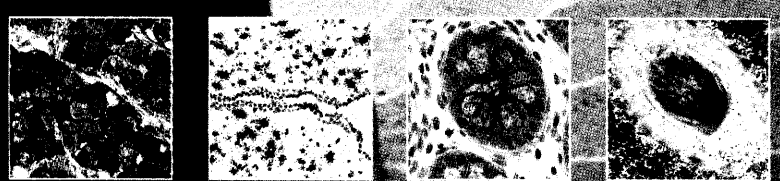

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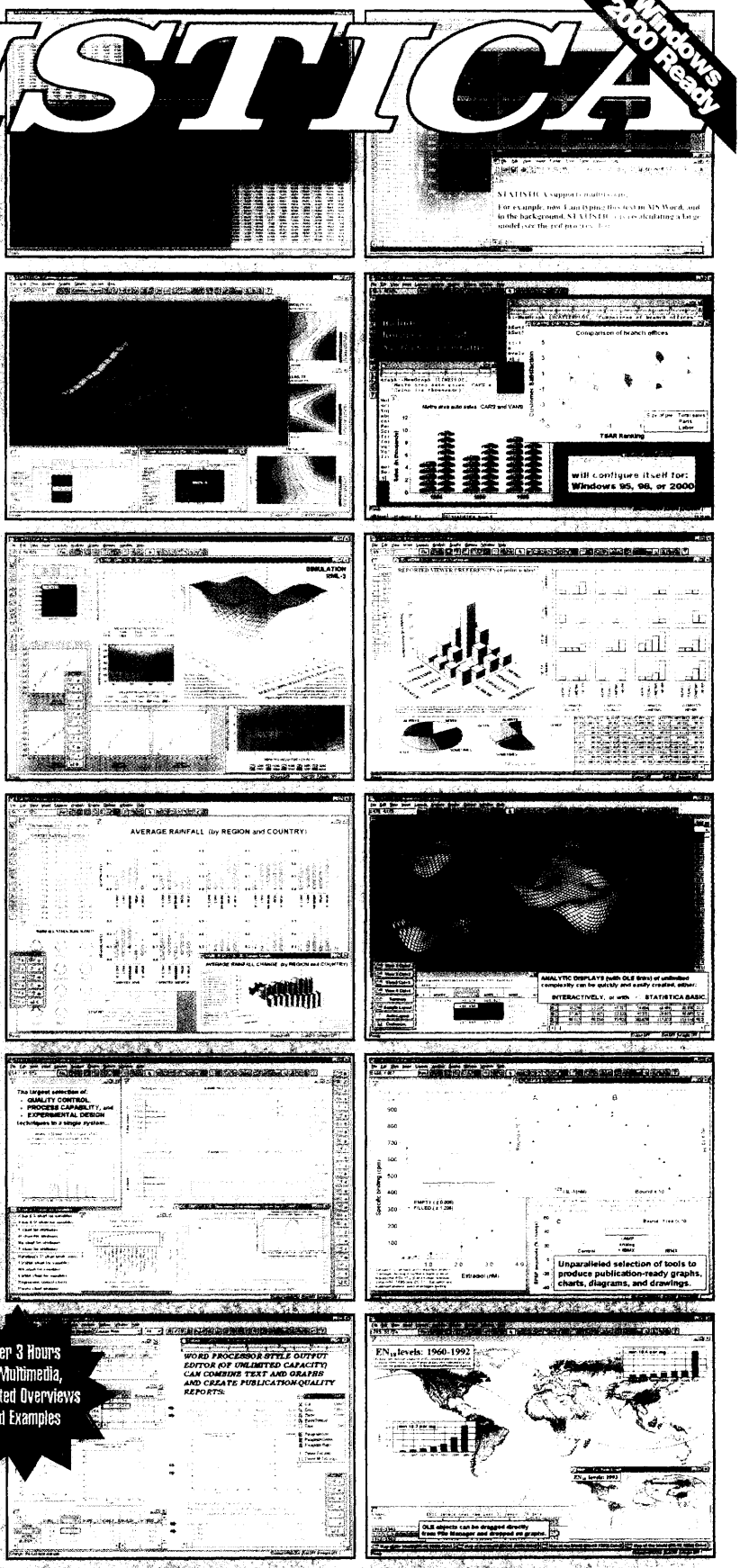

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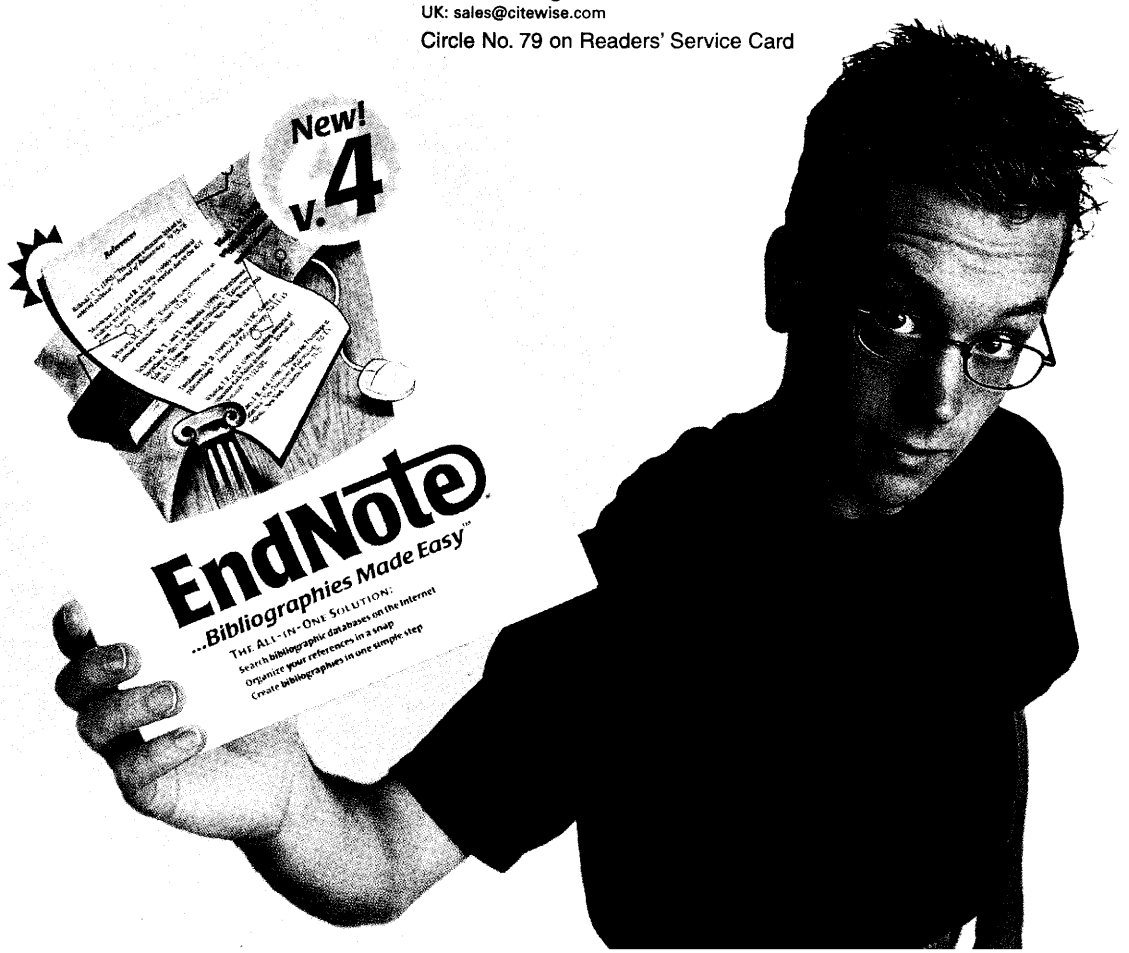

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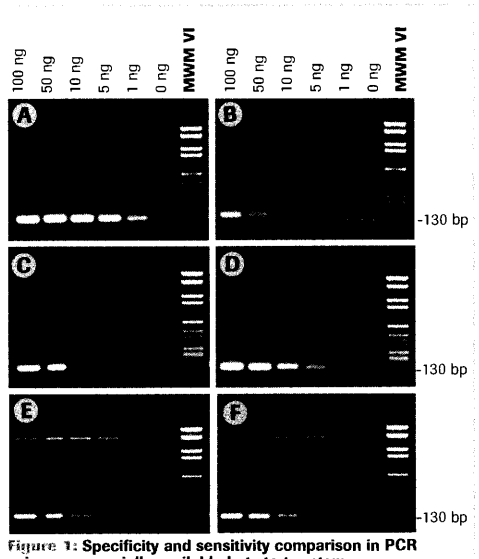

Figure 1: Specificity and sensitivity comparison in PCR using commercially available hot start systems.

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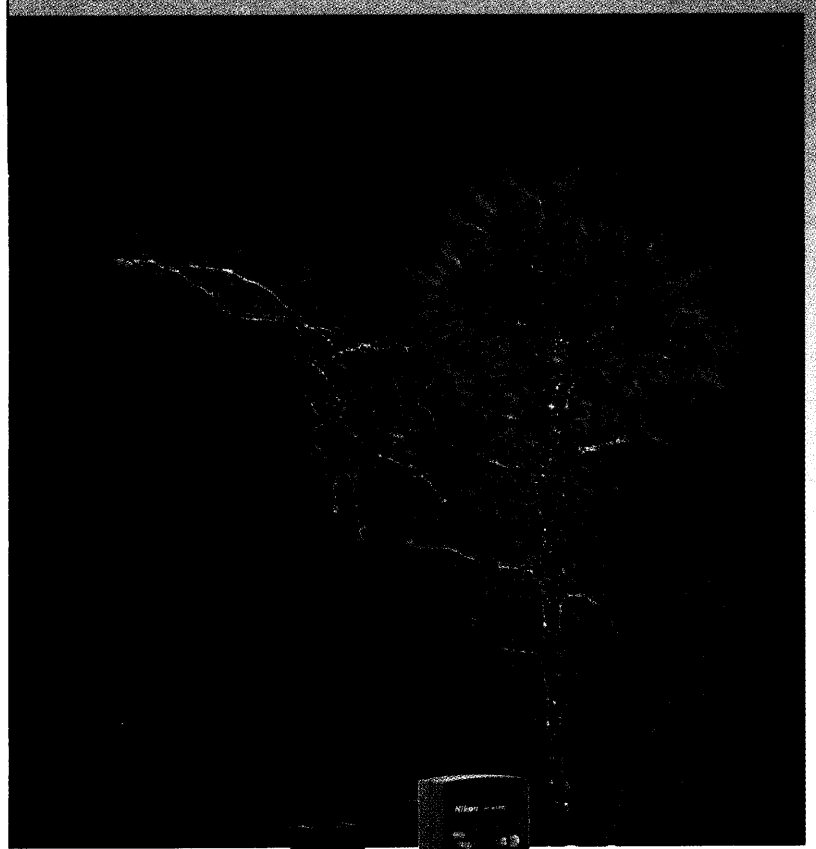

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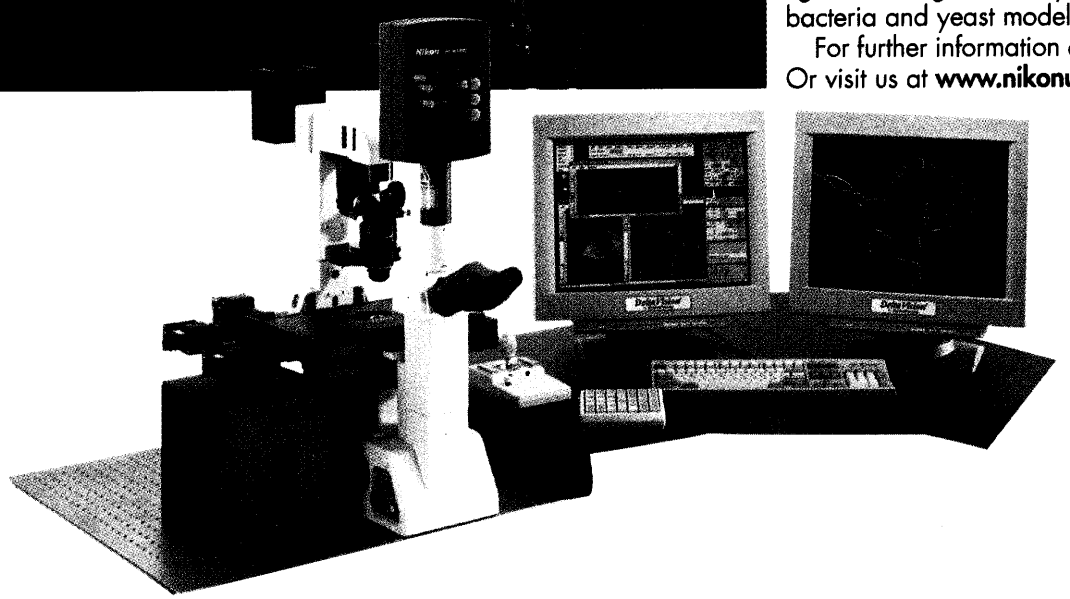

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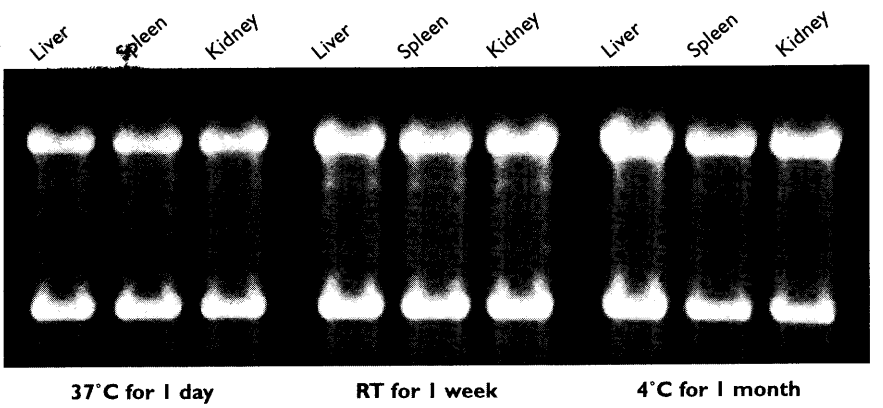

Figure 1a. Quality of RNA isolated from Tissue Stored in RNA*later*™ Solution. Fresh mouse tissues were dissected and stored in RNA*later*™ at 37°C for 1 day, room temperature for 1 week, or 4°C for 1 month. RNA was isolated using TRI Reagent® (MRC) and analyzed using denaturing agarose gel electrophoresis.

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Fig.1. Fluorescent sequencing results of a 100 bp pUC18 PCR fragment sequenced with a -20 Fwd primer using the DYEnamic ET Terminator Cycle Sequencing Kit (Amersham Pharmacia Biotech). Data generated for USB by Cleveland Genomics (clevelandgenomics.com), a research service company. PCR clean-up performed with: (a) ExoSAP-IT; (b) a column designed for PCR clean-up. Base miscalls in (b) are due to inherently low yields of short PCR products when using columns.

Fig. 2. Autoradiograms of a 20.7 kb Lambda PCR fragment sequenced with MBL202 Fwd primer using USB's Thermo Sequenase Radiolabeled Terminator Cycle Sequencing Kit. PCR clean-up performed with: (a) ExoSAP-IT; (b) a column designed for PCR clean-up.

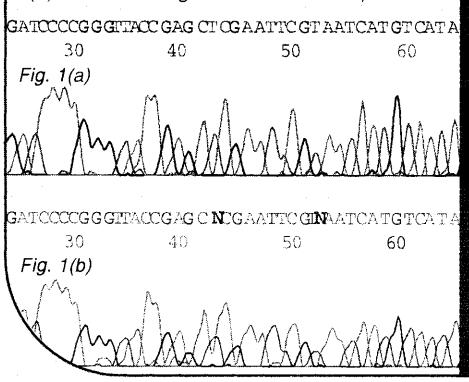
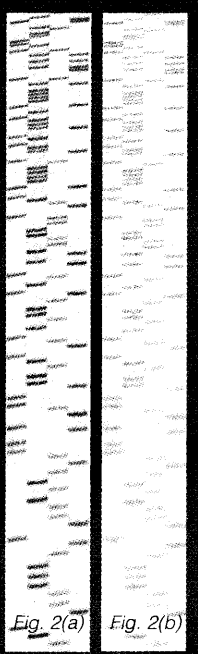


Fig. 1(a)

Fig. 1(b)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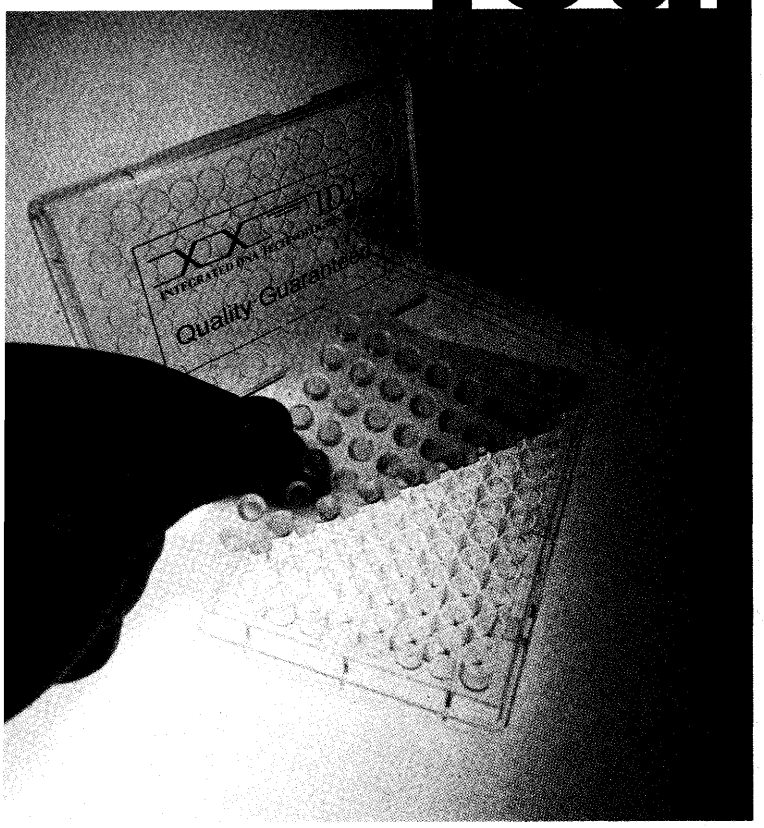

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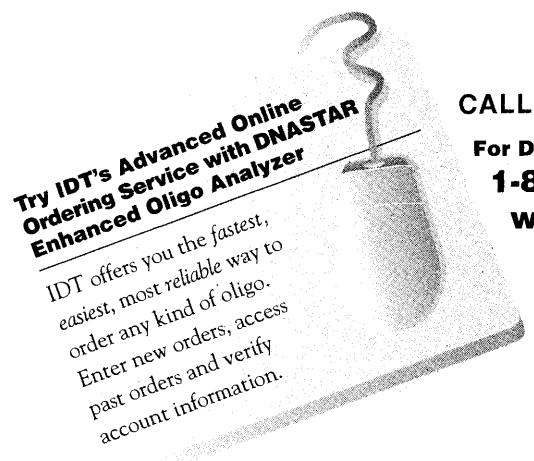

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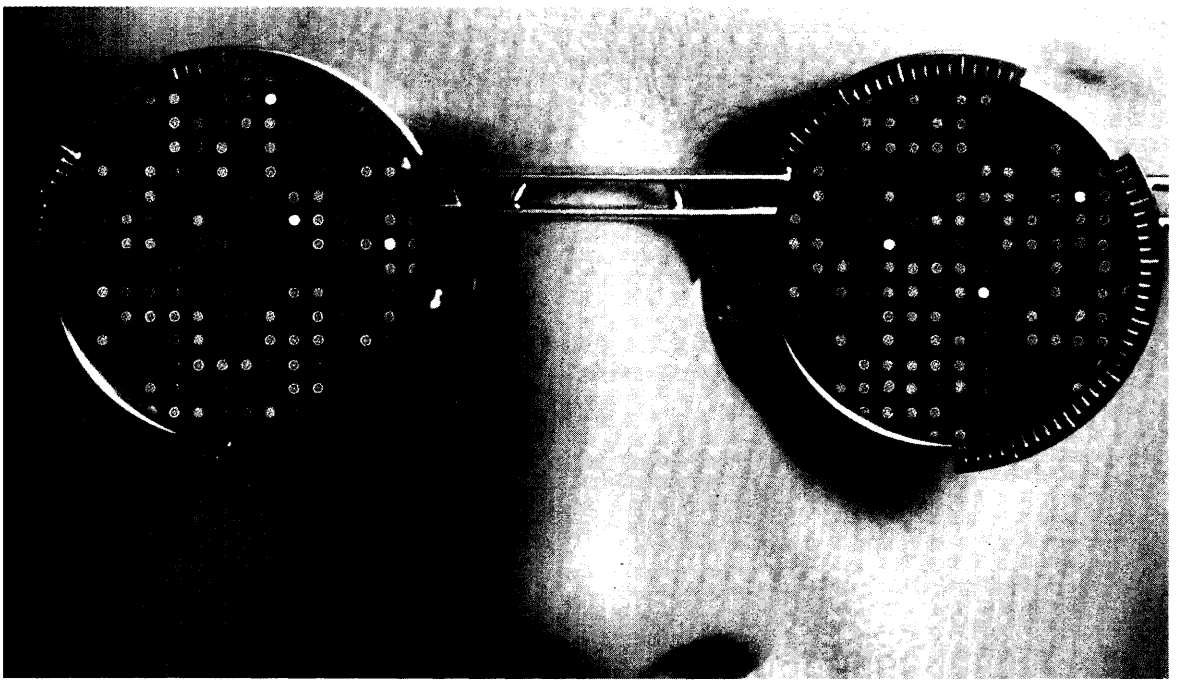

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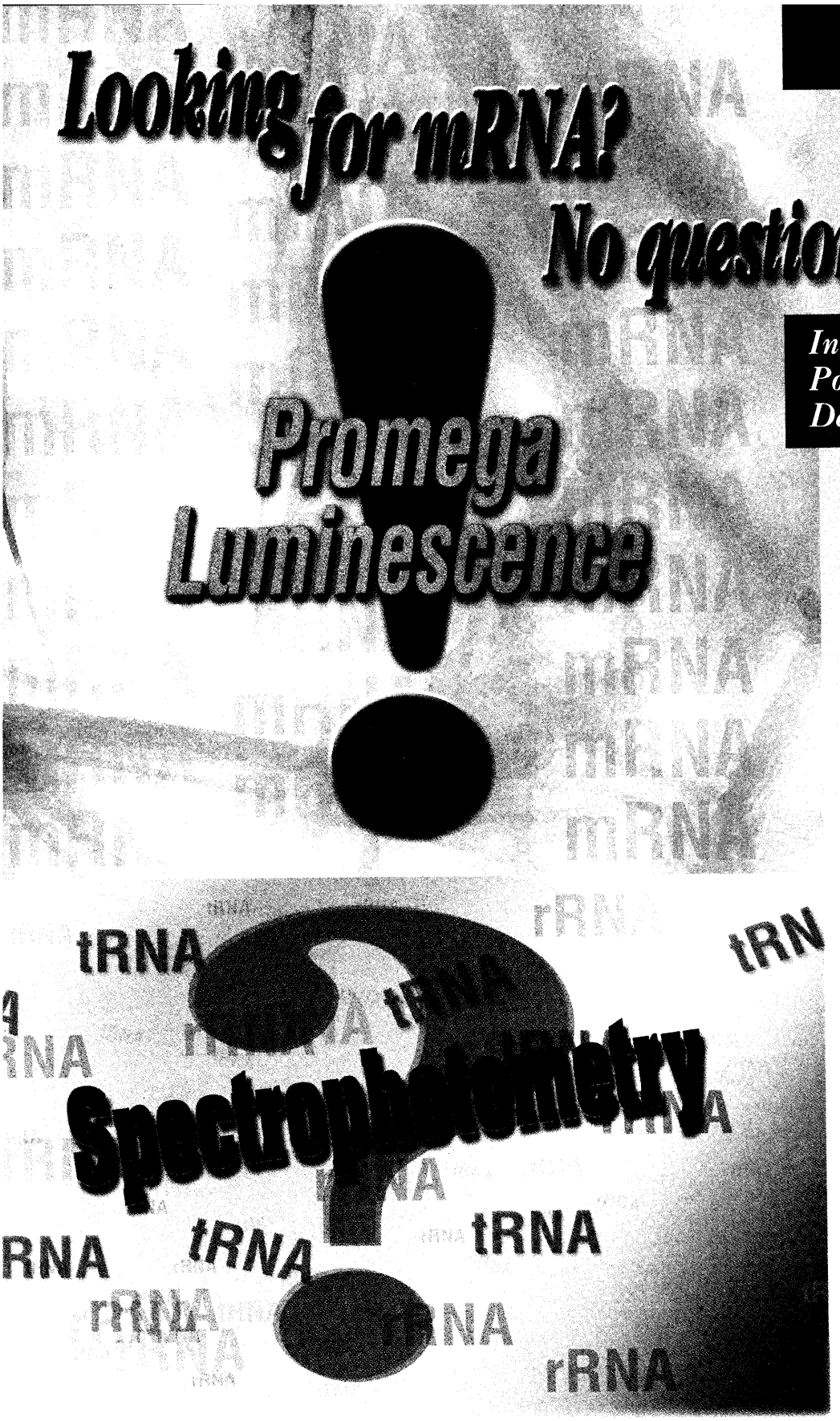

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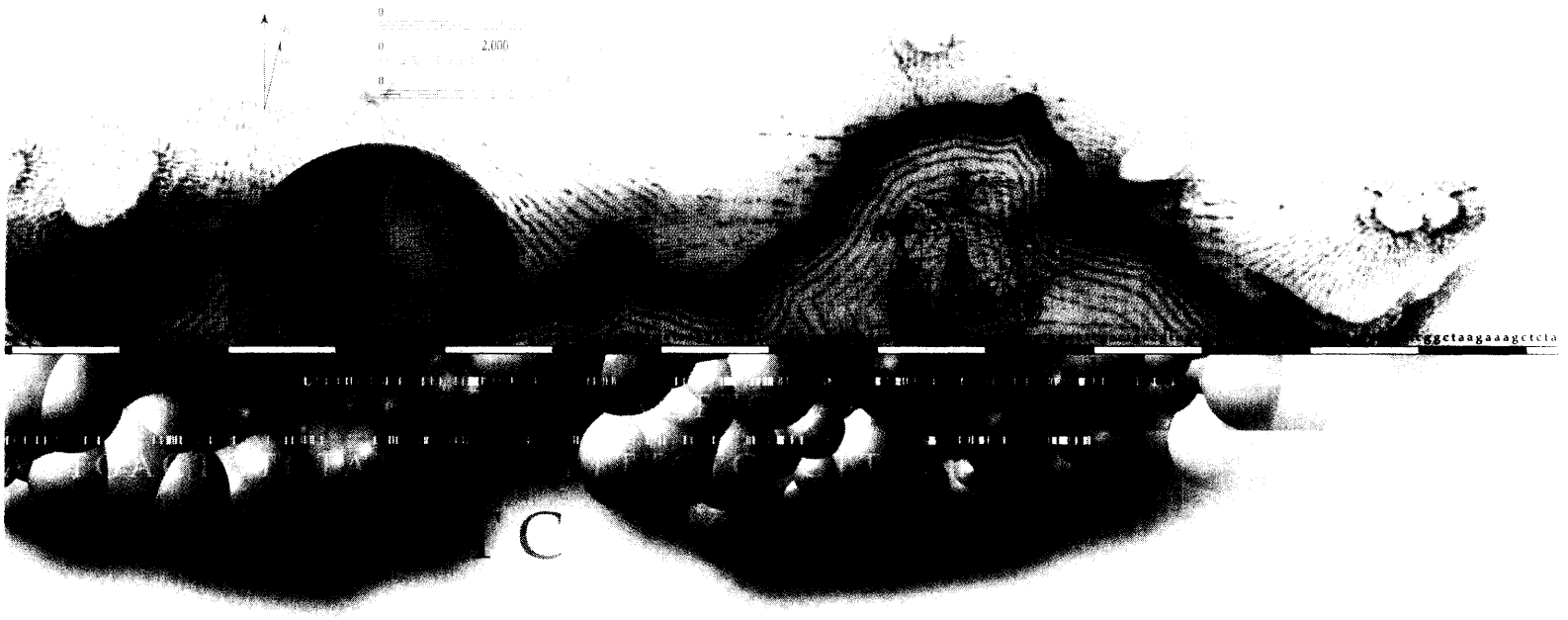

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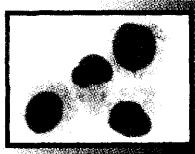

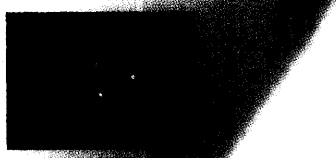

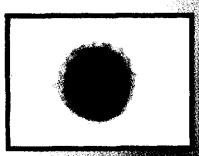

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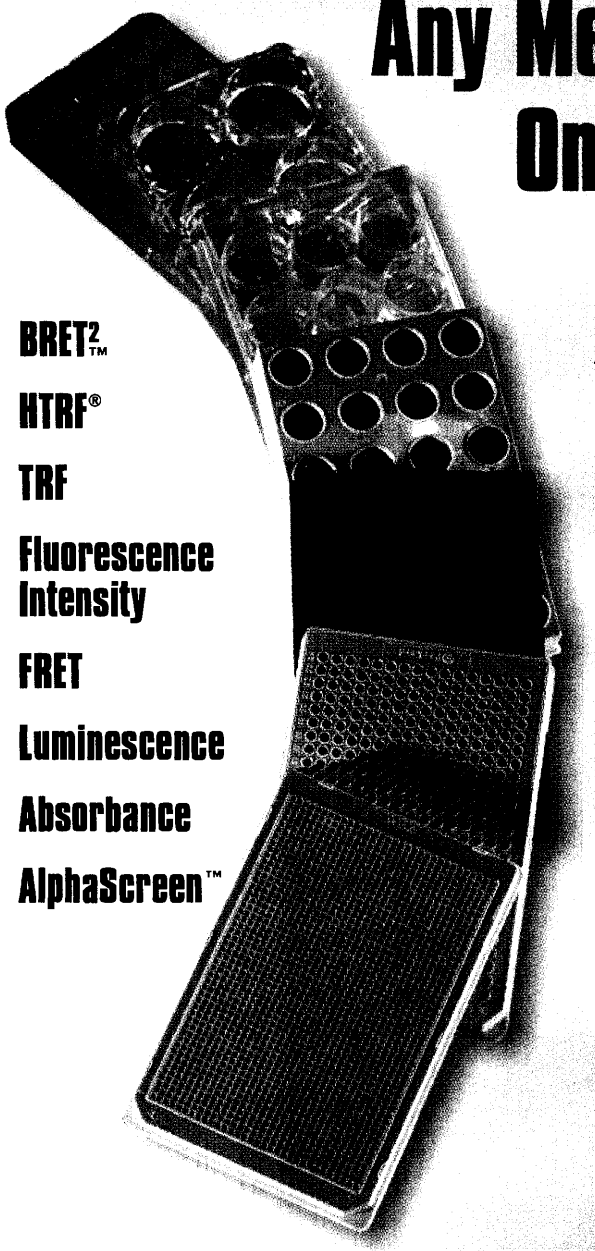

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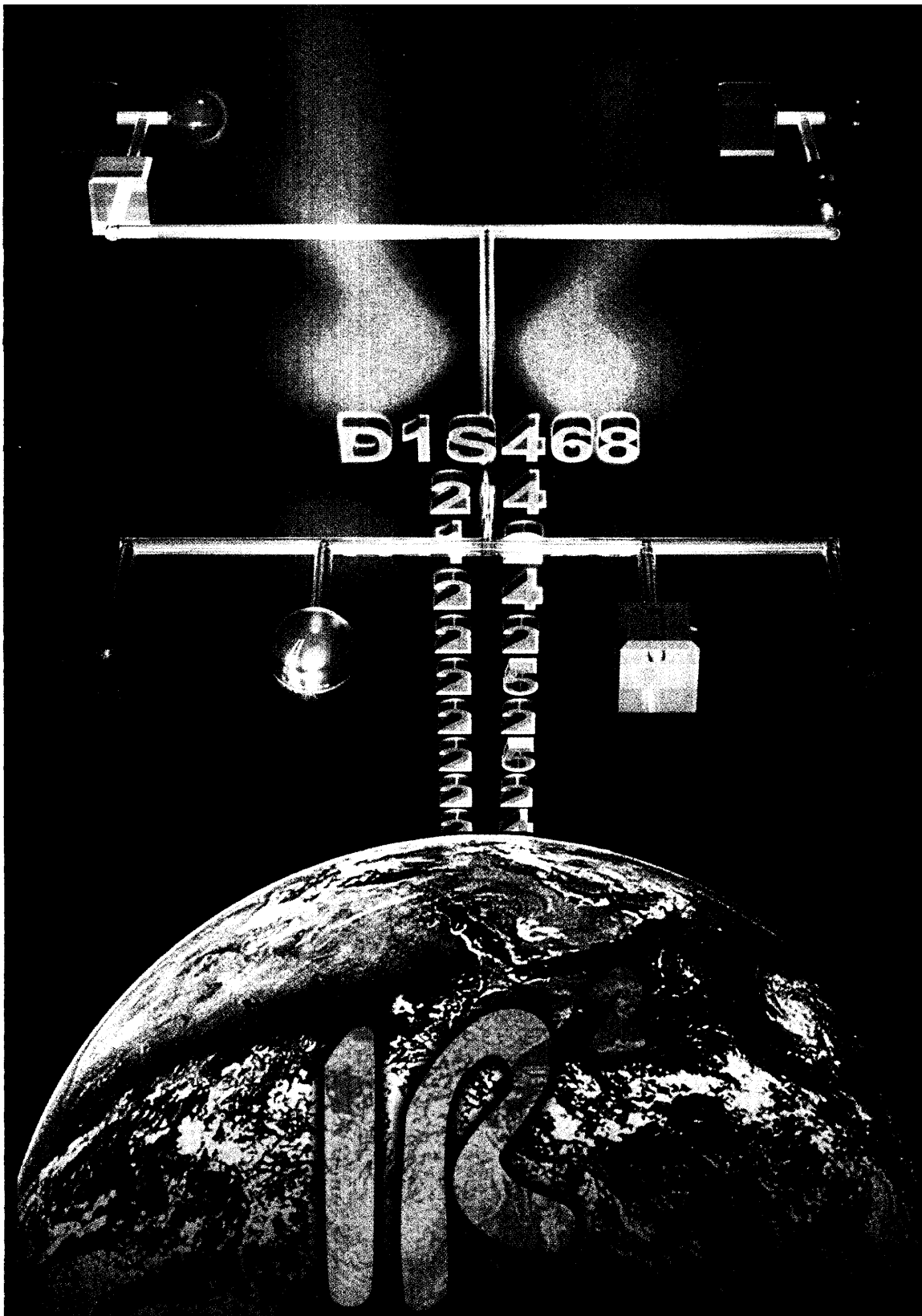

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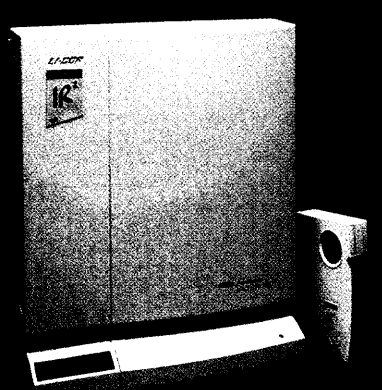

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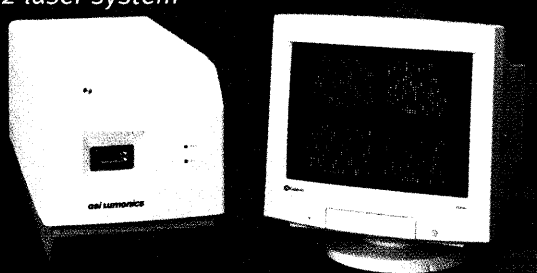

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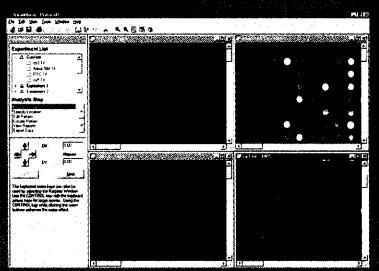

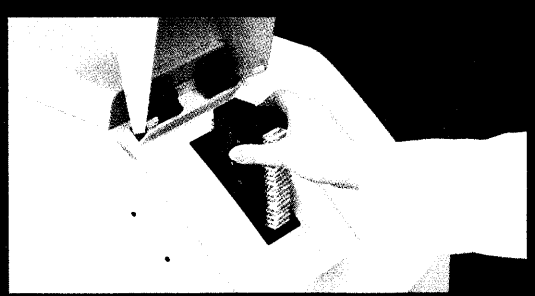

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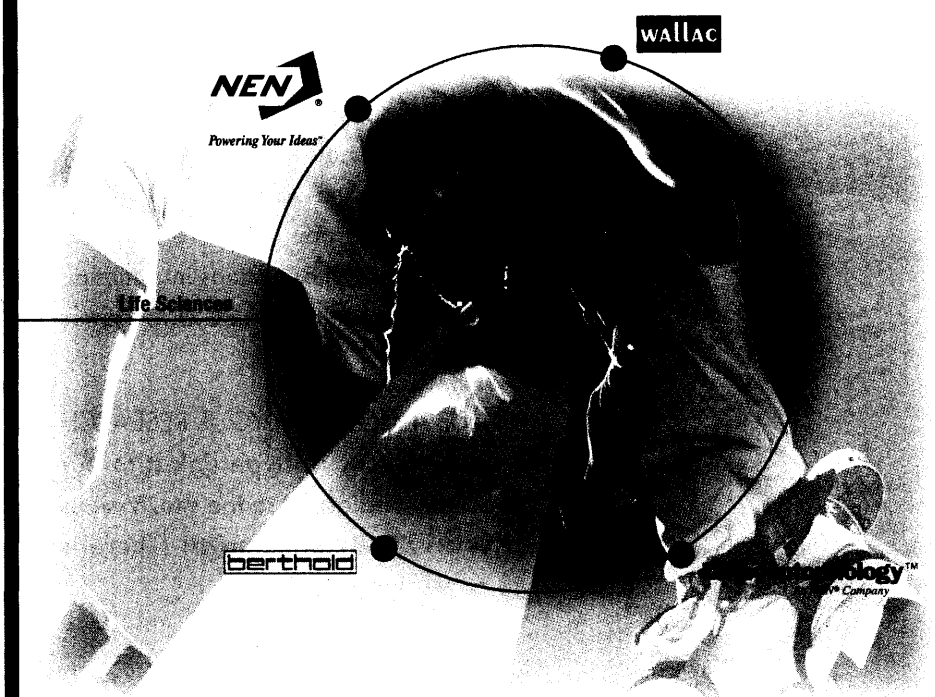

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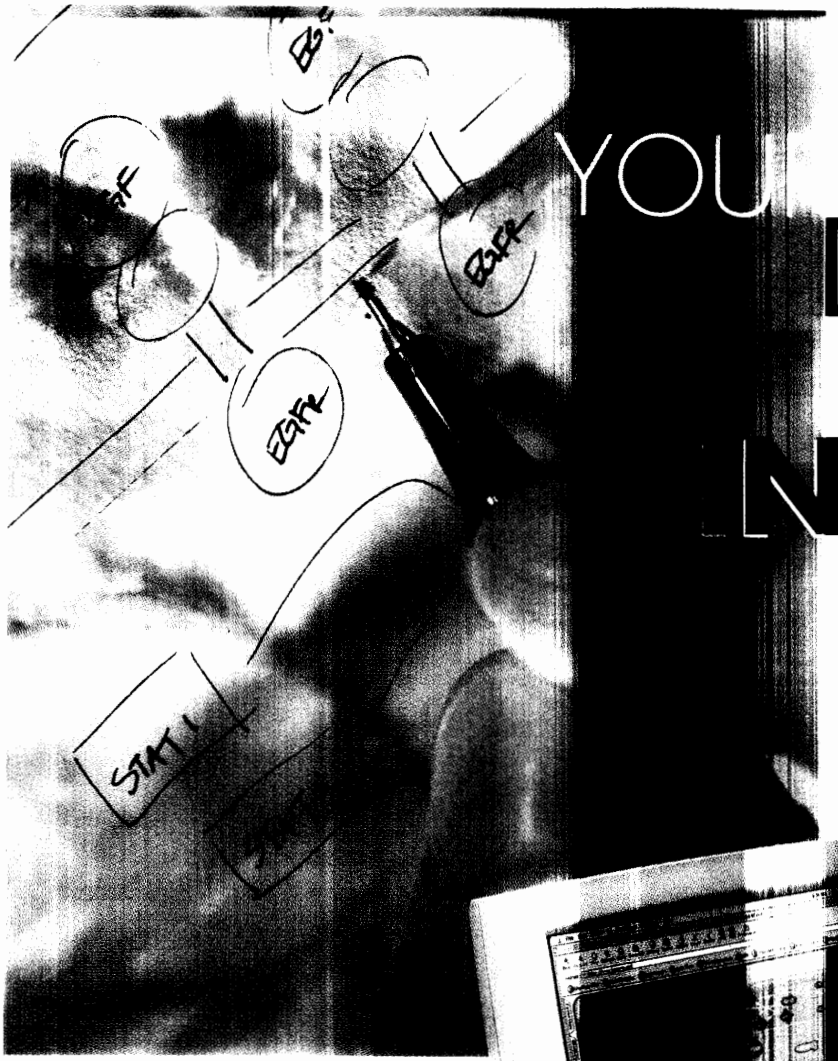

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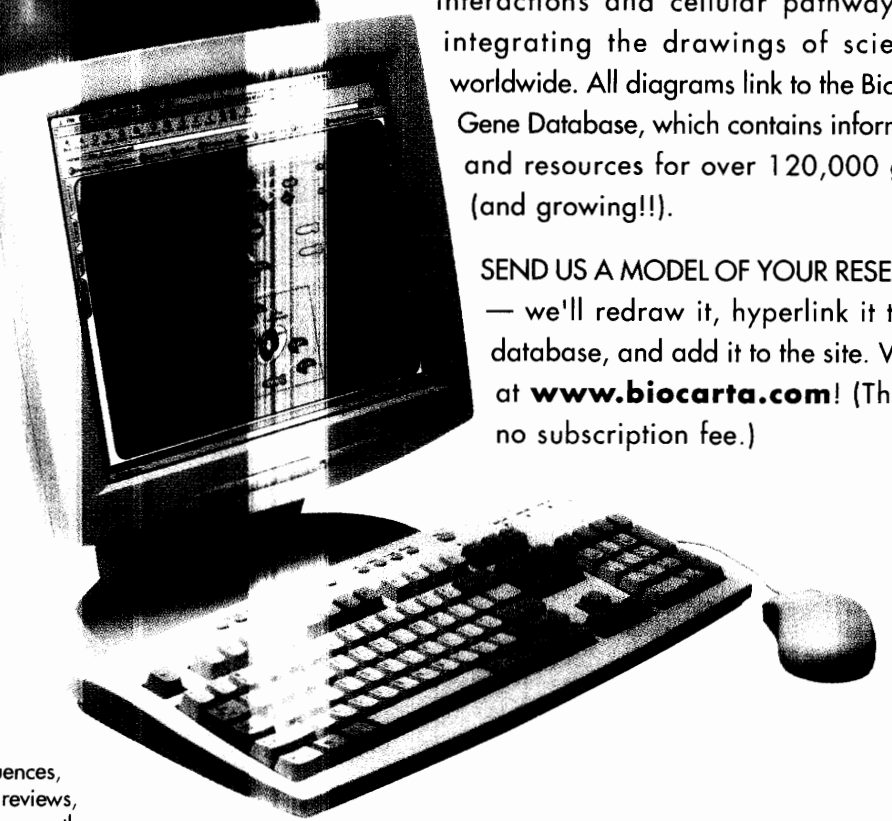

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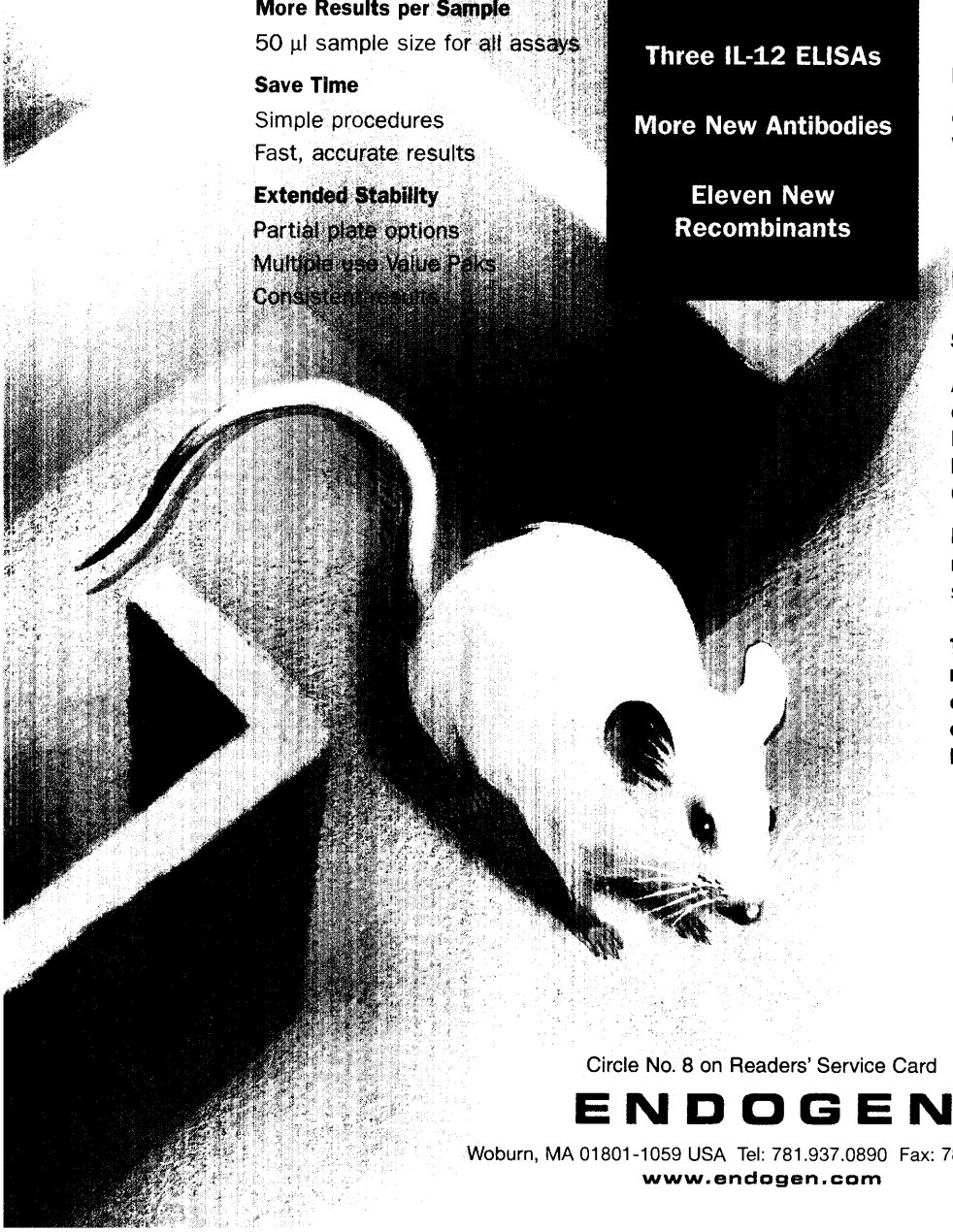

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ABSTRACT DEADLINE
October 16
2000

Program in Progress

As the secrets of the human genome unravel, we are poised to take advantage of a wealth of new information and technological advances to prevent and cure cancer. Stanley J. Korsmeyer and the Program Committee are developing an exciting program for the 92nd AACR Annual Meeting. The meeting is focused on the highest quality fundamental and translational cancer research. The following partial list of topics provides examples of areas that will be addressed during the meeting. The latest scientific breakthroughs and the translation of these findings into new therapies in the clinic as well as novel strategies for prevention will be presented under each of these topics.

Perspectives on the Human Genome and Cancer
Gene Expression Profiling
Human Cancer Genetics
Animal Models
Small Molecules for Molecular Targets
Molecular Targeted Cancer Therapeutics
Tumor Suppressor Genes and Therapeutics
In Vivo Imaging
Subcellular Trafficking
Adhesion Molecules
Extracellular Matrix
Protein Degradation, Ubiquitin, and Proteasome
Angiogenesis
Cell Cycle
DNA Repair Mechanisms
Cellular Senescence
Antibody-based Therapeutics
Molecular Diagnostics and Detection
Chromatin and Nuclear Organization
Molecular Approaches to Population Studies
Prevention of Breast Cancer: Molecules to Clinical Trials
Nervous System Tumors
Hypoxia and Cancer
Stem Cell Biology
Prostate Cancer
Behavorial Genetics
Studies in Cancer Survivors
Chromosomal Translocations in Hematopoietic Malignancies: Causation to Therapeutics
Viruses in Cancer
Transcription Factors in Cancer
Signal Transduction
Proteins That Inhibit Cell Cycle Kinases
Modification of ras Proteins
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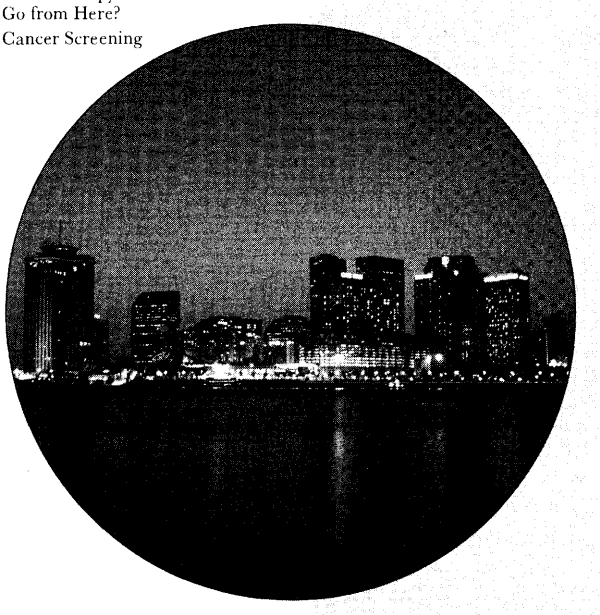
Proteomics
Signaling in Benign Breast Disease
Jak STAT Signaling
Apoptosis
Drug Resistance Mechanisms
Etiology of Adult Leukemias
Genomic Instability
Cancer and the Microenvironment
The p53 Family
Genetic Imprinting
Bioinformatics
Mechanisms of Carcinogenesis
Antisense Strategies
Breast Cancer
Gene Regulation
Telomerase and Cancer
Treatment of Intraepithelial Neoplasia
Gene-Environment Interactions
Gene Therapy: Where Do We Go from Here?
Cancer Screening



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The NCI Cooperative Human Tissue Network (CHTN) provides normal, benign, pre-cancerous and cancerous human tissue to the scientific community for basic and developmental studies in many areas of cancer research. Contact the CHTN website at: http://www-chtn.ims.nci.nih.gov, or Ms. Marianna Bledsoe, NCI, (301) 496 - 7147; e-mail: mb80s@nih.gov.

The NCI Clinical Trials Cooperative Groups have banked tumor specimens from large numbers of uniformly treated cancer patients with a variety of malignancies. Each group has a review process for research proposals. If proposals receive favorable reviews, specimens with clinical, treatment and outcome data can be made available to researchers through collaborative arrangements. These banked specimens are most useful for clinical correlative studies on uniformly treated patient populations. Contact the NCI Human Specimen and Data Information System website at: http://www.specimens.ims.nci.nih.gov, or the NCI Tissue Expediter, (301) 496-7147; e-mail: tissexp@mail.nih.gov.

The Cooperative Family Registry for Breast Cancer Studies (CFRBCS) provides biological specimens with associated family history, clinical, demographic and epidemiologic data from participants with a family history of breast cancer, breast/ovarian cancer, and their relatives. The CFRBCS's repository is particularly suited to support interdisciplinary and translational breast cancer research. Contact the CFRBCS website at: http://www-dccps.ims.nci.nih.gov/CFRBCS, or Dr. Daniela Seminara, NCI, (301) 496-9600; e-mail: seminard@epndce.nci.nih.gov.

The NCI Cooperative Breast Cancer Tissue Resource (CBCTR) can provide researchers with access to over 9,000 cases of formalin-fixed, paraffin-embedded primary breast cancer specimens, with associated pathology and clinical data. The collection is particularly well-suited for validation studies of diagnostic and prognostic markers. Contact CBCTR's website at: http://www-cbctr.ims.nci.nih.gov, or Ms. Sherrill Long, Information Management Services, Inc., (301) 984-3445; e-mail: sherrill@ims.nci.nih.gov.

The AIDS and Cancer Specimen Bank (ACSB) provides qualified researchers with tissue, cell, blood and fluid specimens, as well as clinical data from patients with AIDS and cancer. The specimens and clinical data are available for research studies, particularly those that translate basic research findings to clinical application. Contact the ACSB website at: http://www.cancernet.nci.nih.gov/amb/amb.html or http://acsb.ucsf.edu, or Dr. Ellen Feigal, NCI, (301) 496-6711; e-mail: ef30d@nih.gov or Dr. Jodi Black, e-mail: jb377x@nih.gov.

Each of the resources listed above has an established review process for specimen requests and/or requirements that must be met for access to specimens. Additional details may be obtained from the resource websites and/or resource contacts.

The NCI Breast Cancer Specimen and Data Information System can provide additional information on breast cancer tissue resources (http://www-napbc.ims.nci.nih.gov).

Other human specimen resources for cancer research may be available through collaborative arrangements. **Contact the NCI Tissue Expediter, (301) 496 - 7147; e-mail: tissexp@mail.nih.gov.**

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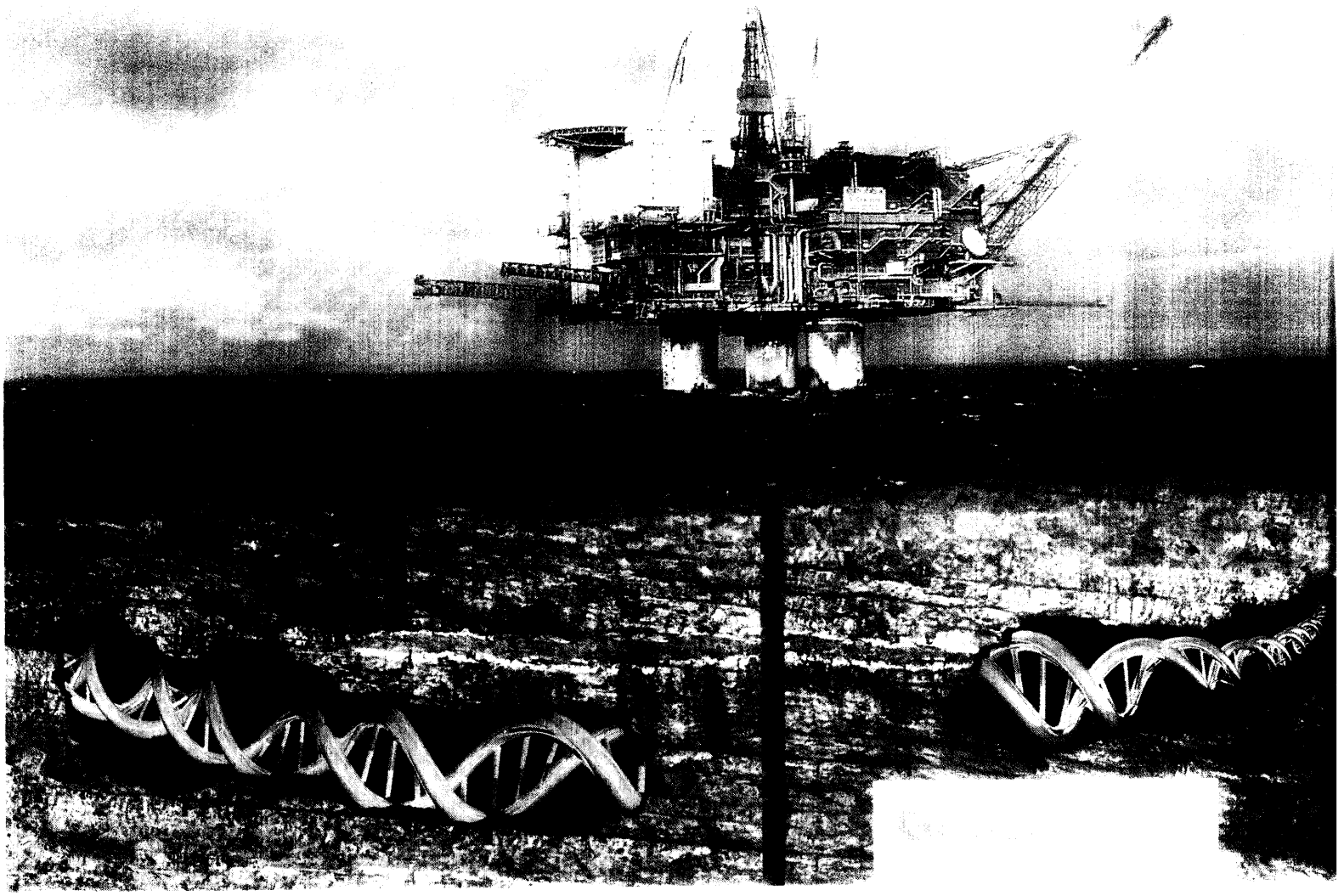

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