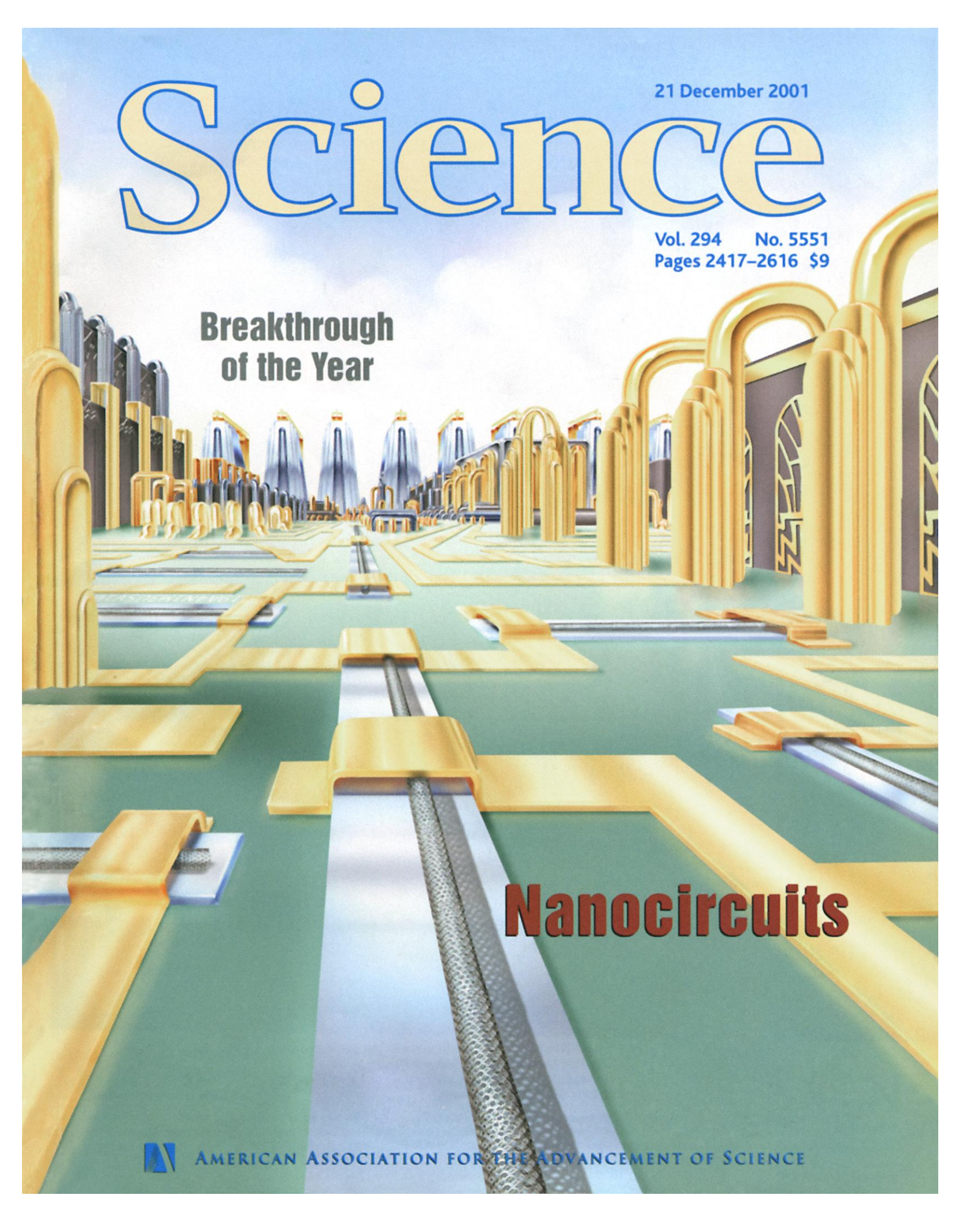




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21 December 2001

Vol. 294 No. 5551
Pages 2417–2616 \$9

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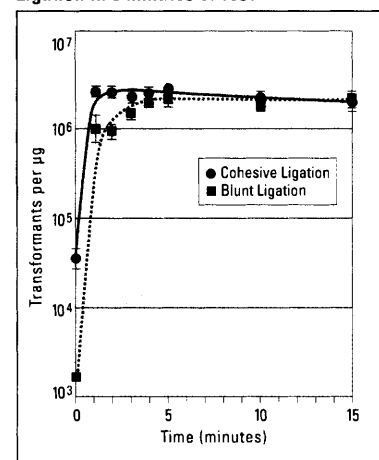
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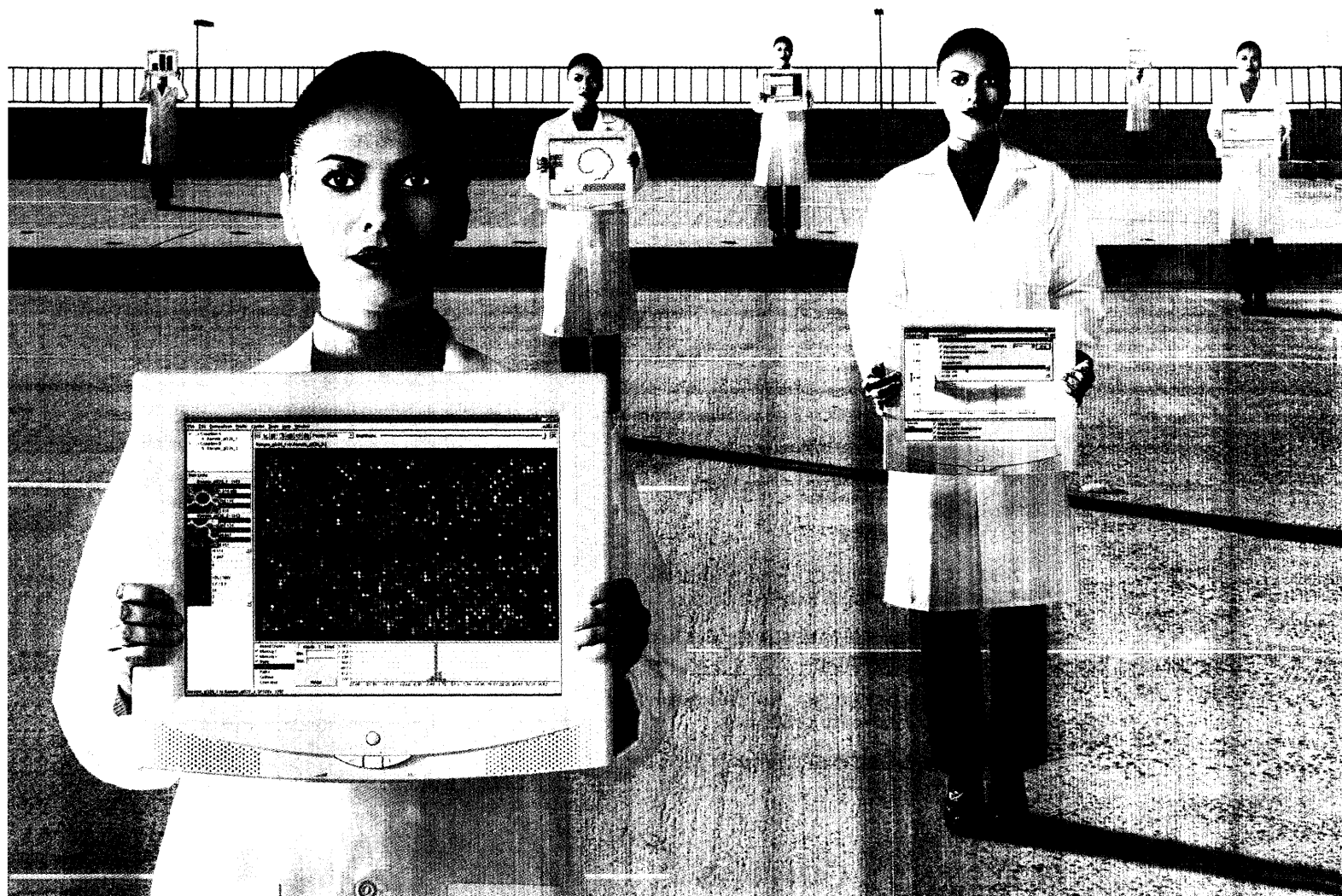
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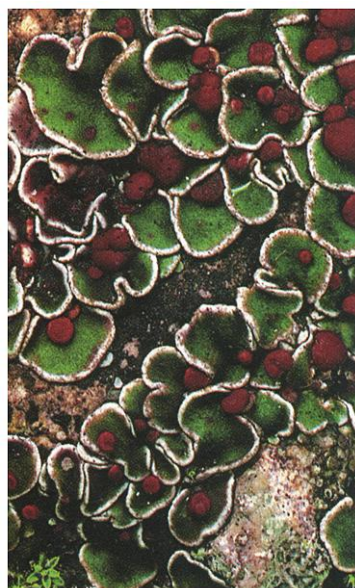
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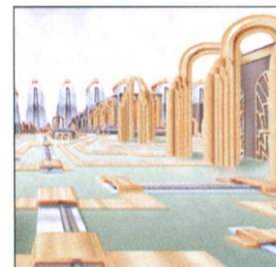
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- ▼2511** **Regulation of Daily Locomotor Activity and Sleep by Hypothalamic EGF Receptor Signaling** A. Kramer, F.-C. Yang, P. Snodgrass, X. Li, T. E. Scammell, F. C. Davis, C. J. Weitz

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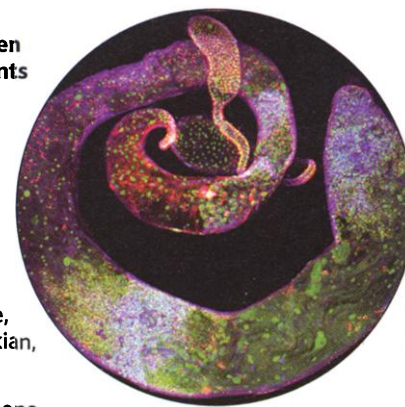


COVER 2442

A bright new world of nano-circuitry may now be possible, thanks to recent advances in molecular electronics. In 2001, researchers went beyond basic nanodevices by wiring up the first molecular-scale electronic circuits. See the Breakthrough of the Year special section, beginning on page 2442, and the Editorial on page 2429. [Illustration: C. Slayden]

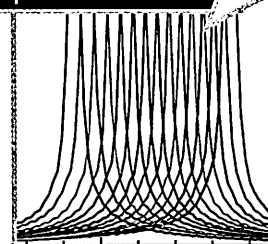
2546

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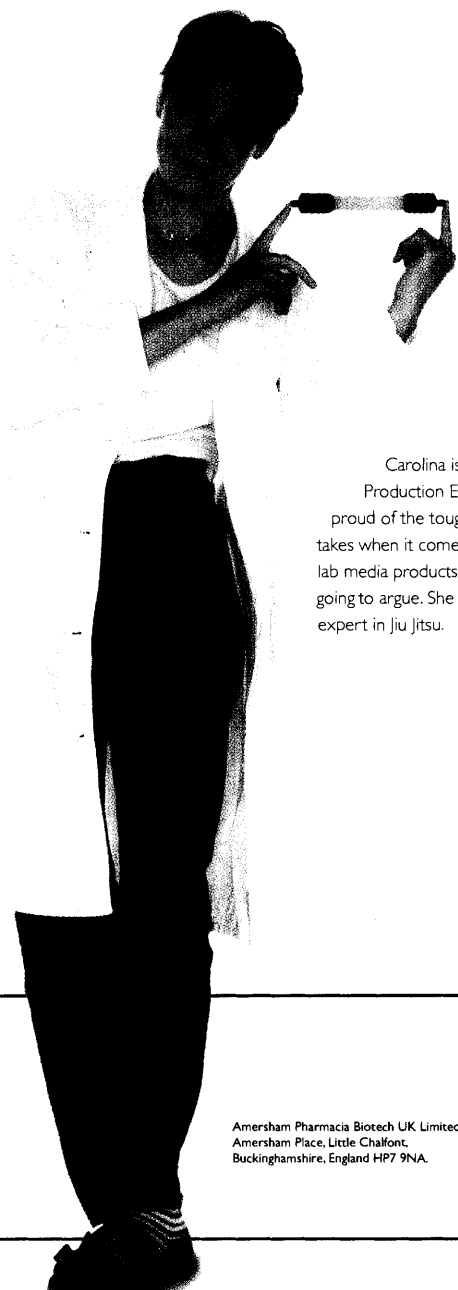


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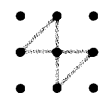
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CONTENT HIGHLIGHTS AS OF 21 DECEMBER 2001

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Continuous Wave Operation of a Mid-Infrared Semiconductor Laser at Room Temperature M. Beck *et al.*

²⁴⁵⁴ With a redesign of the semiconductor laser structure allowing efficient heat extraction, continuous-mode operation at room temperature is demonstrated.

Chaperone Suppression of α -Synuclein Toxicity in a *Drosophila* Model for Parkinson's Disease P. K. Auluck, H. Y. E. Chan, J. Q. Trojanowski, V. M.-Y. Lee, N. M. Bonini

Chaperones can protect from the neurodegeneration induced by high levels of α -synuclein in the Parkinson's model fly.

Modulation of NMDA Receptor-Dependent Calcium Influx and Gene Expression Through EphB Receptors M. A. Takasu, M. B. Dalva, R. E. Zigmond, M. E. Greenberg

Activity-independent developmental signals appear to modulate activity-dependent signaling by a neurotransmitter during development of the central nervous system.

TECHNICAL COMMENTS

In Silico Mapping of Mouse Quantitative Trait Loci

Grupe *et al.* (Reports, 8 June 2001, p. 1915) described a novel computational algorithm for prediction of chromosomal locations of quantitative trait loci (QTLs) in mice. In a comment, Chesler *et al.* suggest that the algorithm does not work when an important strain, CAST/Ei, is omitted, and express concerns that, though the method "does not appear to be a viable alternative to current QTL methodology," it could jeopardize funding for, and attention to, conventional QTL studies. Separately, Darvasi comments that the new method "is not of practical use for most relevant cases of QTL mapping" because of the large numbers of strains required for the correct calculations. Usuka *et al.*, in response, identify a potential error in the implementation of their method by Chesler *et al.*, and state that their method "should markedly increase interest in and productivity from mouse genetic research," including conventional QTL studies. Further, they argue that Darvasi's calculations are not applicable to their computational method and that "every new source of QTL information is valuable."

The full text of these comments can be seen at
www.sciencemag.org/cgi/content/full/294/5551/2423a

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career resources for scientists

Canada: Eye on Science—New Journal Targets High School Students L. McKarney

The University of Toronto Press is trying a new experiment in publishing: November saw the release of a science journal for students in grades 7 to 12.

US: Seeding Postdoctoral Innovators—A Program for Scientist-Teachers H. E. Macalister

The SPIRE program takes UNC-Chapel Hill postdocs to new places to provide them with a full portfolio of professional preparation for academic careers.

Singapore: Environmental Science and Engineering—An Outlook on R&D (Part II) T. Yugarani

Following last week's discourse on clean water, we focus this week on air and water pollution.

UK: Hey Big Spender! P. H. Dee

Having won his postdoc research grant, our *Yours Transferredly* columnist explains how and why he's spending every penny with care.

UK: From Bacteria to Balance Sheets—A First Post-Ph.D. Job I. Dutta

What to do when you don't want to stay in research? Chartered accountancy may not be the obvious choice, but it really does offer opportunities to use your Ph.D. skills.

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Working Out the Kinks R. J. Davenport

Fly enzyme reverses protein damage, extends life-span.

Survivor! S. Hechtel

Examples from many branches of the tree of life hint that elements of hard-core survival tactics might slow normal aging.

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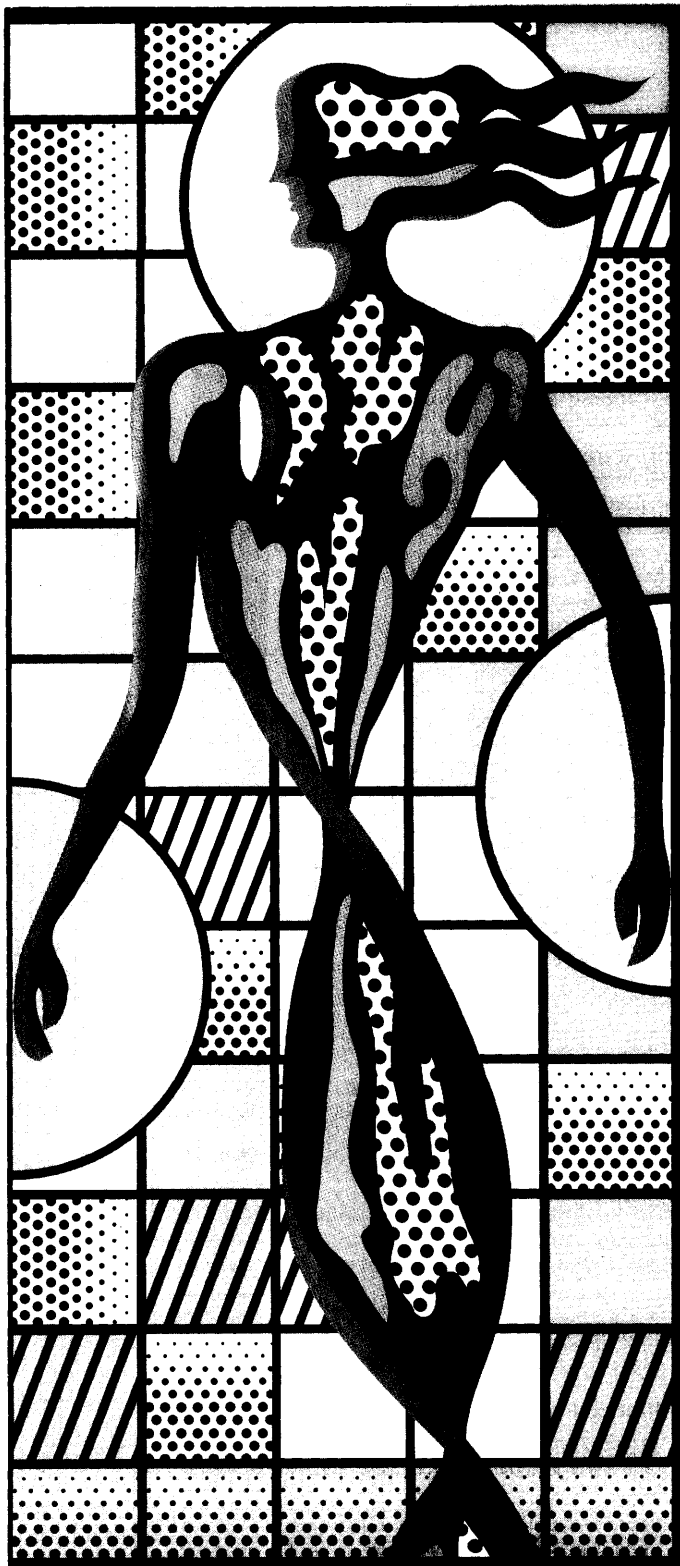


Illustration inspired by the art of Roy Lichtenstein (1923–1997).

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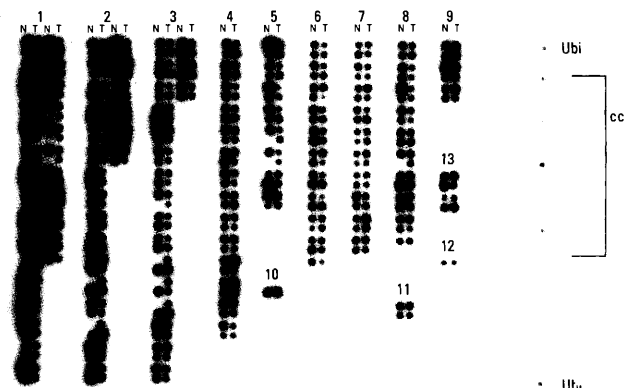


Figure 1. The Cancer Profiling Array demonstrates tissue-specific expression of gelsolin. The Cancer Profiling Array was hybridized with a radiolabeled probe for gelsolin. Hybridization signals were detected by phosphorimaging. Significant up regulation is clearly present in tumor samples from breast, uterine, and ovarian tissues. Numbers in columns indicate tissue types. 1: breast. 2: uterus. 3: colon. 4: stomach. 5: ovary. 6: lung. 7: kidney. 8: rectum. 9: thyroid gland. 10: cervix. 11: small intestine. 12: pancreas. 13: prostate. N = normal. T = tumor. Ubi = ubiquitin cDNA. cc = cancer cell line cDNAs.

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THIS WEEK IN Science

edited by Phil Szuromi

Our Fair Share?

A study by Vitousek *et al.*, 15 years ago, based largely on extrapolations from limited field-based studies, estimated that humans co-opt about 42% of the global terrestrial production. Rojstaczer *et al.* (p. 2549; see the Perspective by Field) now provide an update based on recent, mainly satellite-based surveys and an error analysis. They reach a similar conclusion through this different methodology, but caution that the uncertainties are still very large for several key parameters, namely, the productivity of agricultural land and the biomass of secondary forests.

Black Holes and Growth Spurts

The excessive luminosity of active galactic nuclei (AGNs) has been attributed to a period when black holes at their core were accreting the bulk of their mass. Page *et al.* (p. 2516) studied the x-ray flux of AGNs where their luminosity peaks (those with redshifts from about 1 to 3). They assign the emission to dust from starburst activity, which reflects star formation, in the bulges of the galaxies. Starburst activity and the period of major growth of the black holes appears to be coeval, which suggests that the source materials for rapid star formation and black hole growth should be similar. Thus, galaxy morphologies in the bulge and the center developed at the same time in a relatively hyperactive universe.

Exciting Landings on Surfaces

When a molecule adsorbs on a surface, bond formation releases energy. Generally it has been assumed that for low-energy bonds (less than half an electron volt), this energy is dissipated as heat (vibrations in the surface, or phonons), and that electronic processes are unimportant. Gergen *et al.* (p. 2521; see the Perspective by Auerbach) now show that adsorption of water, nitric oxide (NO), nitrous oxide (NO₂), and even xenon onto a polycrystalline silver film all produce electron-hole pairs that can be observed with a low-barrier Schottky diode. This finding not only revises the conventional model of chemisorption but also suggests new possibilities for sensors.

Exotic Behavior with Sheets

Low-transition-temperature (T_c) superconductors, in which the superconductivity is described by an electron-phonon coupling mechanism, generally display isotropic pairing of the electrons in momentum space—they are said to exhibit s-wave symmetry. However,

2524 Reasons to Transfer

The Marcus cross relation allows the rate of electron transfer between different species to be systematized in terms of equilibrium constants (ground-state energetics) and self-exchange rates. Hydrogen atom (H) transfers (an electron plus a proton) are radical reactions that exhibit wide variations in rates for similar driving forces. Roth *et al.* (p. 2524) now show that the rates of a wide variety of H-transfers obey a Marcus cross relation, and compounds that show slow electron or proton transfer often undergo slow H-transfer.

And in Brevia ...

A previously unknown species of large squid, up to 7 meters in length and with distinctive morphology, has been sited by Vecchione *et al.* (p. 2505) in four deep-ocean basins.



Analysis of the tiny marine organism *Oikopleura dioica* by Seo *et al.* (p. 2506) reveals the smallest genome found so far for a chordate, part of the lineage that gave rise to the vertebrates and ultimately humans.

2559; see the Perspective by Frey) offer crystallographic evidence that the free-radical intermediate in the degradative reaction catalyzed by pyruvate:ferredoxin oxidoreductase contains a partially localized electron after decarboxylation of the pyruvate has occurred but before oxidation is complete. Twisting of the thiazole ring during catalysis greatly reduces its aromaticity and prevents complete delocalization of the lone electron.

A Syringe in Action

Projections from bacteria have been predicted to play a role in the export of specific proteins and DNAs during conjugation and pathogenesis. However, a direct demonstration of such a role has been lacking. Jin and He (p. 2556) have now directly visualized the extrusion of a protein from the Hrp pilus of *Pseudomonas syringae*. The immunogold labeling protocol used will help to provide unambiguous answers in other systems where similar questions remain open.



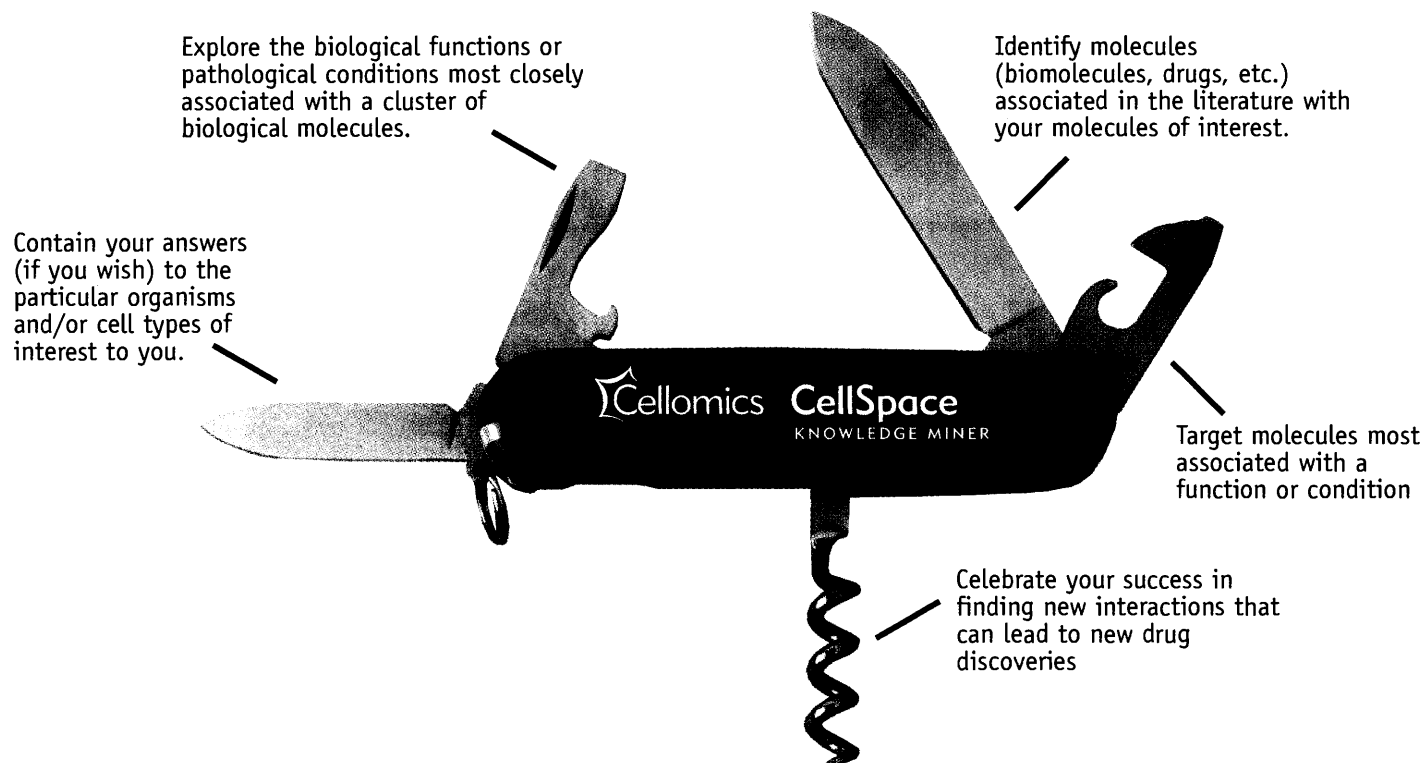
Walk, Don't Walk

Signals from a circadian clock in a region of the mammalian brain called the suprachiasmatic nucleus (SCN) must somehow be translated into the rhythmic behavior of processes such as locomotion and rest. Kramer *et al.* (p. 2511; see the news story by Barinaga) show that neurons in the SCN secrete transforming growth factor- α (TGF- α) that acts on cognate receptors in the hypothalamus to inhibit locomotion in hamsters. Expression of

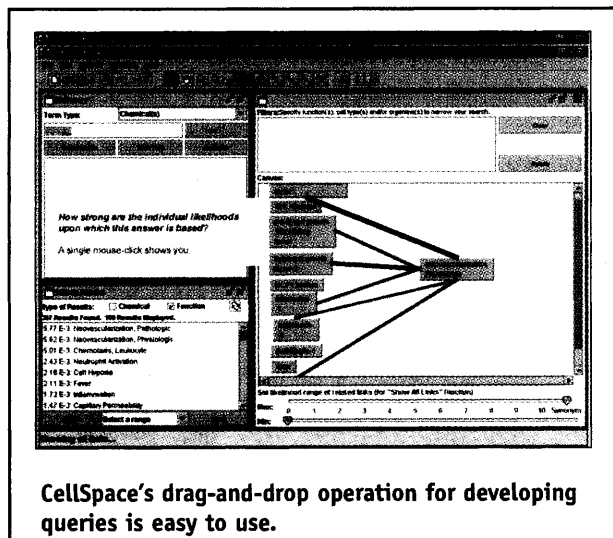
er, like some of their high- T_c cuprate cousins, a few low- T_c superconductors have revealed a more complex pairing symmetry. One mechanism put forward to explain this apparent discrepancy has been additive contribution of several Fermi surface sheets. Yokoya *et al.* (p. 2518) used an ultrahigh-resolution angle-resolved photoemission technique that could resolve different Fermi-surface sheets in such a superconductor (2H-NbSe₂) and confirmed that the underlying mechanism is s-wave pairing.

A New Twist on Aromaticity

Thiamine diphosphate, a cofactor in many enzymatic reactions, contains a thiazole moiety that can yield a nucleophilic carbanion at the C-2 position. Chabrière *et al.* (p.



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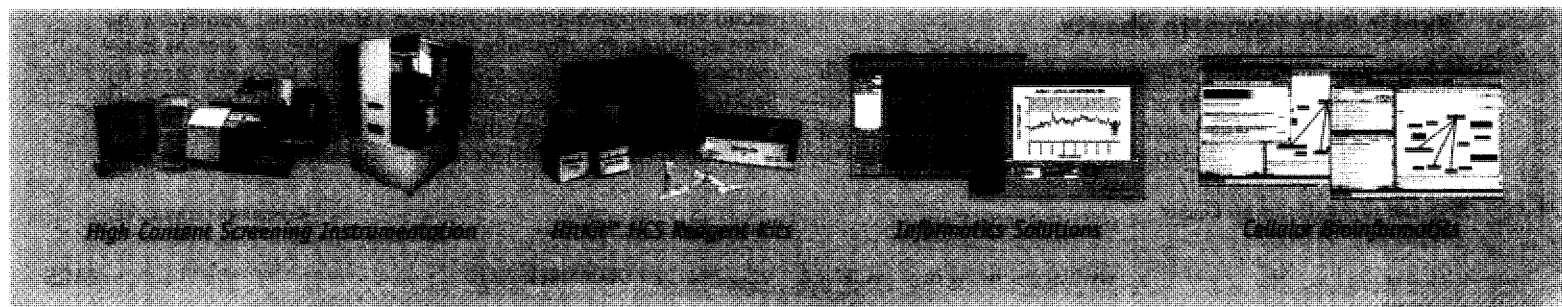
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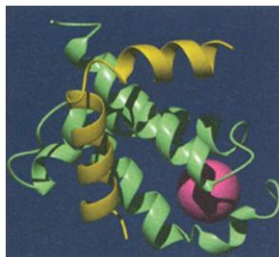
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TGF- α is correlated with cycles of locomotion and rest. Hence, secretion of factors that act locally in the brain is one mechanism by which the clock exerts its cyclic effects.



Transcription and Cofactor Methylation

In order to access DNA that is packaged into nucleosomes, histone-modifying factors come into action to allow subsequent DNA transcription. Xu *et al.* (p. 2507; see the Perspective by Nishioka and Reinberg) now show that the histone methyltransferase CARM1 also has a nonchromatin substrate and acts in two separate but coordinated ways to influence gene expression. With *in vitro* chromatin templates, CARM1 acts positively to stimulate nuclear receptor transcription. However, the factor can block transcription by methylating the coactivator CBP at an amino acid that interferes with the action of CREB. Thus, CARM1 potentiates transcriptional activation by retinoid receptors whereas it can block cAMP (adenosine-3',5'-monophosphate) signaling and allow for cross-talk between the two signaling pathways. **X**

interferes with the action of CREB. Thus, CARM1 potentiates transcriptional activation by retinoid receptors whereas it can block cAMP (adenosine-3',5'-monophosphate) signaling and allow for cross-talk between the two signaling pathways. **X**

The End-Joining Justifies the Screen

A genome-wide screen in yeast for mutants defective in nonhomologous end-joining (NHEJ), a form of genetic recombination critical in immunoglobulin rearrangement, double-strand break repair, and yeast mating type-switching, has been performed by Ooi *et al.* (p. 2552). Thousands of these mutants were analyzed at one time with a functional assay in which cells were transformed by linear or circularized plasmids containing a selectable marker. One of the genes identified as being involved in NHEJ, *NEJ1*, interacts with the amino-terminal end of a homolog of a human protein that protects cells against cancer. **X**

From Stem to Sperm

A pair of studies sheds light on the molecular mechanism and the spatial organization of a signaling pathway that regulates stem cell fate in the testis of fruit flies (see the Perspective by Wasserman and DiNardo). A group of somatic cells located at the testis apex (the hub) is surrounded by stem cells that can generate sperm. When needed by the fly, a stem cell can divide asymmetrically to yield a daughter stem cell and a cell that will subsequently differentiate into a mature sperm. Tulina and Matunis (p. 2546) and Kiger *et al.* (p. 2542) now show that the hub sends regulatory signals from the JAK-STAT signaling pathway in order to maintain these stem cells in an undifferentiated state. When this pathway is defective, cells begin to go through spermatogenesis. A better understanding of how stem cells are maintained and directed down different paths of differentiation should prove useful in medical applications.

Genetic Clue to Prostate Cancer

Prostate cancer affects one in eight men and causes 32,000 deaths each year in the United States alone. About half of these cancers show allelic loss at chromosome 10p15. Nara *et al.* (p. 2563) find that one of the genes mapping to this region, *KLF6*, encoding a Kruppel-like putative transcription factor, is mutated at high frequency in sporadic prostate tumors. Transient expression of wild-type *KLF6*, but not *KLF6* containing tumor-associated mutations, slowed the growth of prostate cancer cells in culture, an effect mediated through the cell-cycle regulatory protein p21/WAF1. These features of *KLF6* suggest that it functions as a tumor suppressor gene in prostate cancer.

Useful Information in the Neighborhood

How is information distributed over populations of neurons? Cortical neurons with selectivity for similar stimulus features can be found close to each other. Reich *et al.* (p. 2566; see the Perspective by Richmond) simultaneously recorded from single neurons in primary visual cortex and found that the responses of nearby neurons are only correlated to a relatively small degree. Simple averaging strategies, such as population histograms, imaging, or field potentials, are suboptimal and vastly underestimate the information processing that is occurring, even at such an early stage in sensory processing.

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The Human Frontier Science Program (HFSP) supports basic research with emphasis placed on **novel, innovative and interdisciplinary** approaches to basic research which involve scientific exchanges across national boundaries. HFSP previously supported 2 scientific programs focused on neuroscience and molecular biology. With the dissolving of boundaries separating traditional biological fields, and the need to involve disciplines outside biology in life sciences research, these separate programs have been unified into a **single program on complex mechanisms of living organisms** by the HFSP Board of Trustees. Henceforth, a single committee will review all grant applications, while a second committee will review all long-term fellowship applications. Both committees are composed of internationally-leading scientists.

CALL FOR LETTERS OF INTENT TO APPLY FOR A RESEARCH GRANT FOR AWARD YEAR 2003

The new HFSP research grant program places special emphasis on the involvement of other disciplines such as chemistry, physics, mathematics, computer science and engineering in projects within the general areas of neuroscience and molecular approaches to biological functions. Significant new ideas, techniques and discoveries often arise at the boundaries between traditional disciplines. To stimulate novel, daring ideas and innovative approaches, preliminary results are not required in research grant applications. Applicants are expected to develop new lines of research through the collaboration; projects must be distinct from applicants' other research funded by other sources. HFSP supports only international, collaborative teams, with an emphasis on encouraging scientists early in their careers.

International teams of scientists interested in submitting applications for support must first submit a letter of intent online via the HFSP web site. The guidelines for potential applicants and further instructions are available on the HFSP web site (www.hfsp.org).

Research grants provide support for basic research (*up to 3 years*) carried out jointly by research teams in different countries. The principal applicant must be from one of the member countries* but co-investigators may be from any country. Preference is given to intercontinental teams. The size of the team should normally be 2 – 4 members with not more than one member from any one country.

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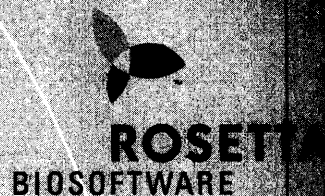
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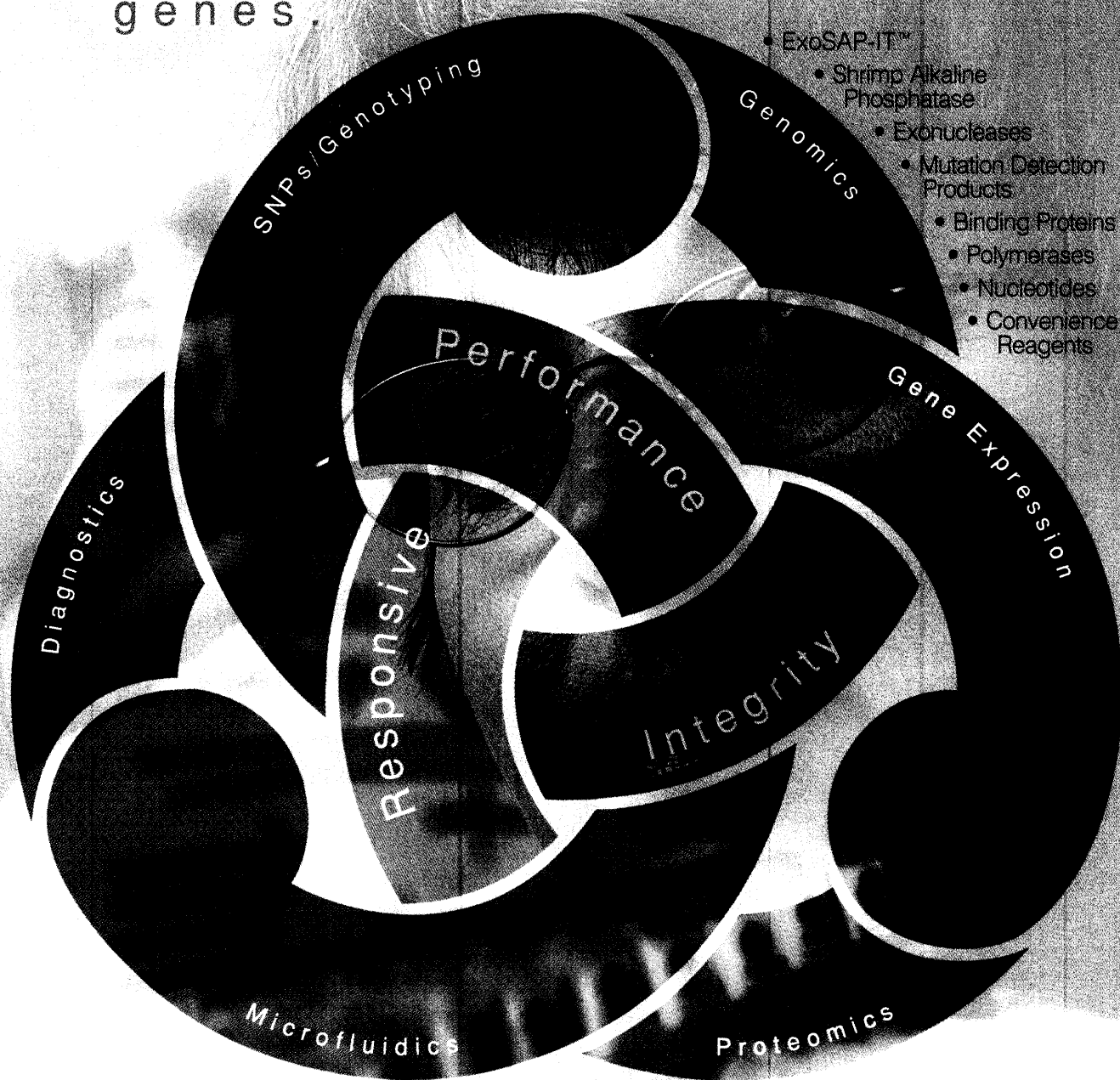


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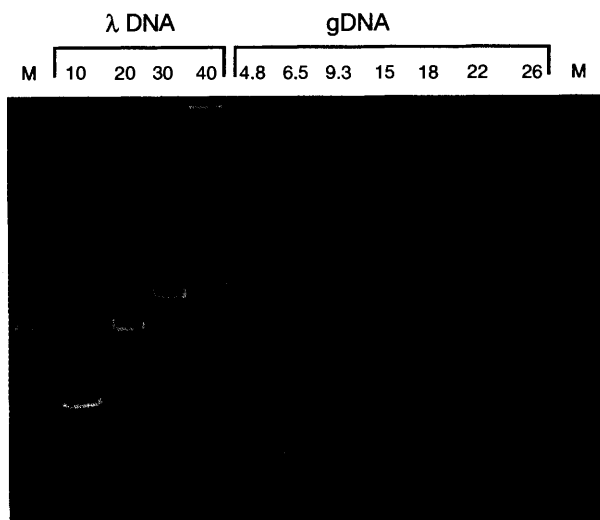
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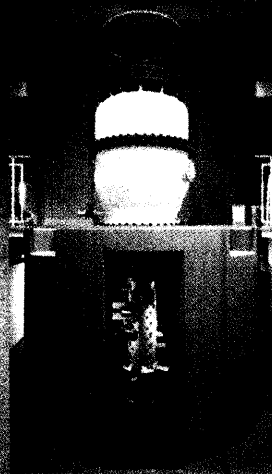
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With support from the CREST[®] program of the JST[™], the University of Tokyo and Hitachi Ltd. have achieved a breakthrough in ultra-high-voltage electron microscopy. This new 1-MeV holography electron microscope allows not only high-spatial resolution for imaging, but also makes maximum use of the wave property of electrons as part of novel techniques for measuring electric and magnetic fields on an atomic scale, verification of quantum phenomena, and analysis of structures and functions of biological polymers.

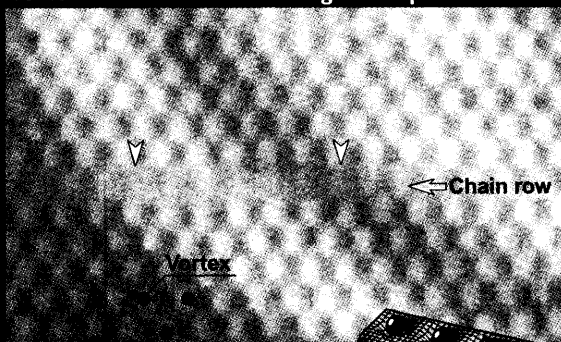
While participating in this project prods its most advanced technology in new directions, Hitachi also continues a commitment to basic research, such as findings that may someday underpin practical development of high-Tc superconductors. Hitachi hopes that the new microscope's enormous potential will enable researchers the world over to reach a clearer understanding of the nature of our world.



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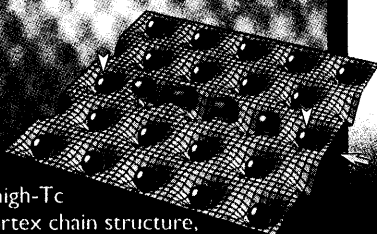
Vortex chain oscillation in a high-Tc superconductor:



Vortices show fantastic behaviors, especially in high-Tc superconductors. The vortex chain structure, a densely packed row of vortices which appears in the oblique magnetic field, is one of them.

The 1-MeV holography electron microscope reveals a dynamic aspect of such vortex chains. The Lorentz micrograph (top) shows vortices in $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_{8+x}$, including a chain. While the normal vortices form triangular lattices and appear as bright and dark contrasting pairs, several vortices in the chain row (between the arrows) are faded. Have these vortices really disappeared? Image analysis suggests that they may be thermally oscillating at high frequency, and blurring the image (see illustration above).

To learn more, see the paper by Matsuda et al. in *Science* Vol. 294, No. 5549, 7 December 2001.



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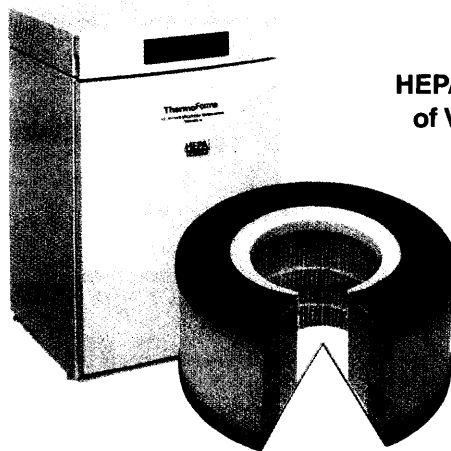
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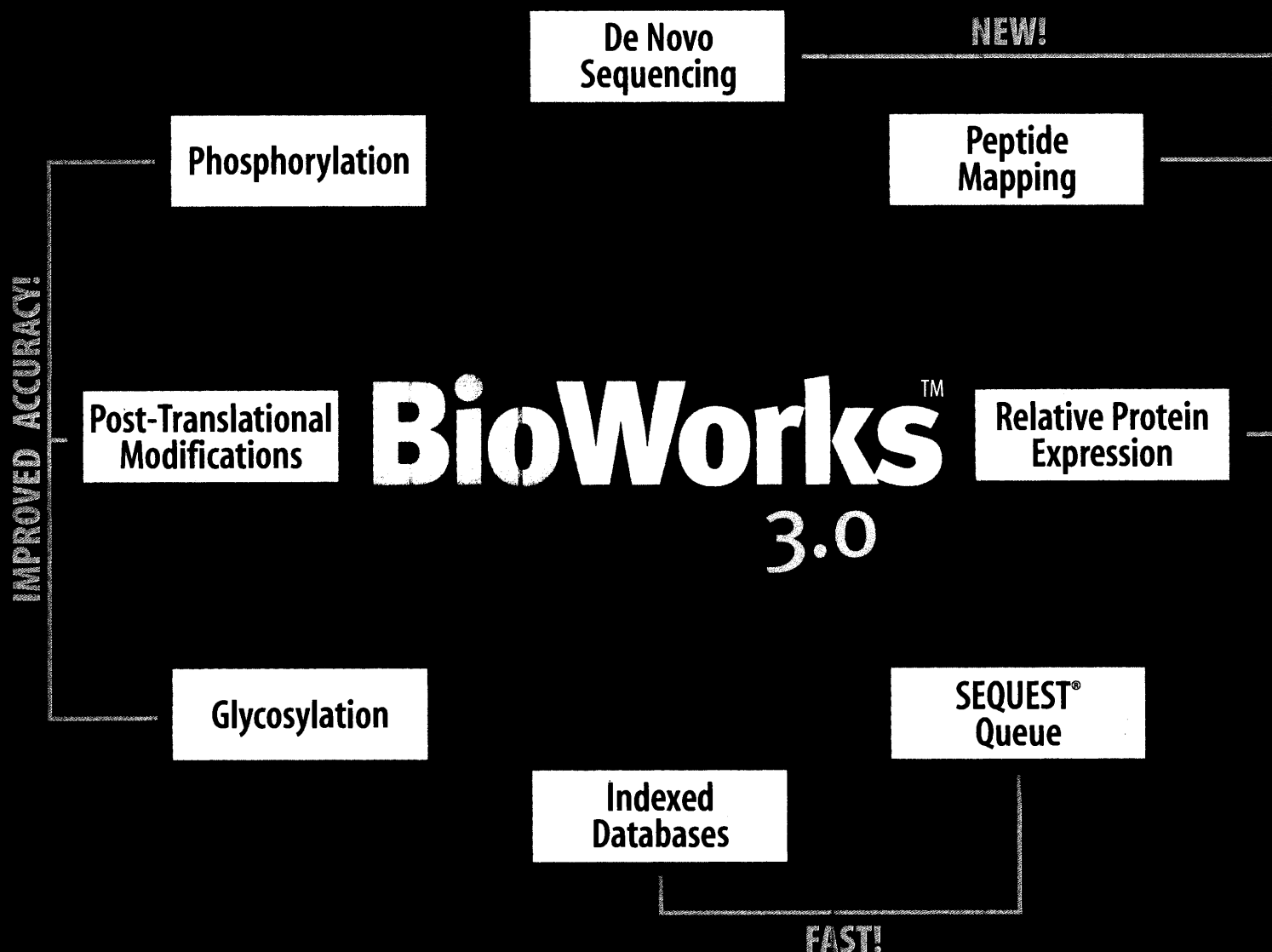
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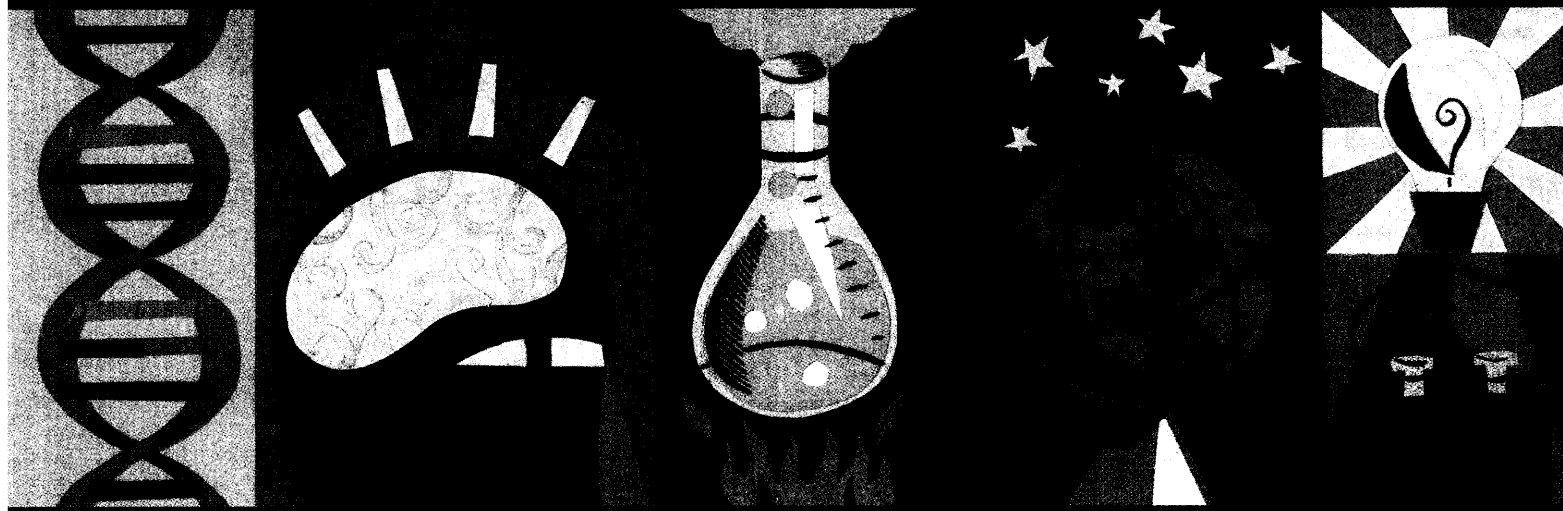
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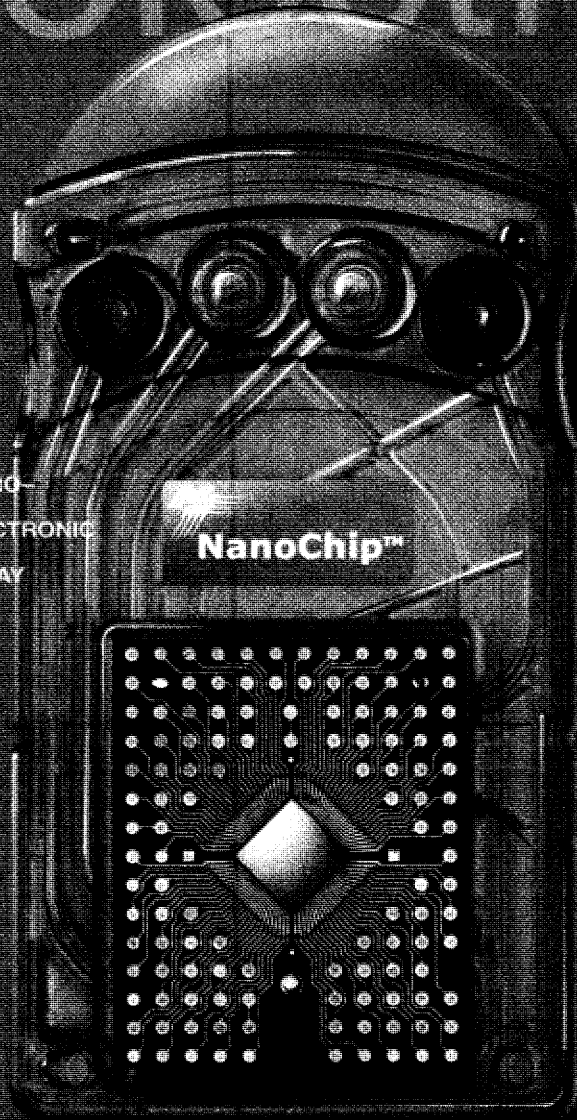
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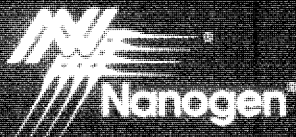
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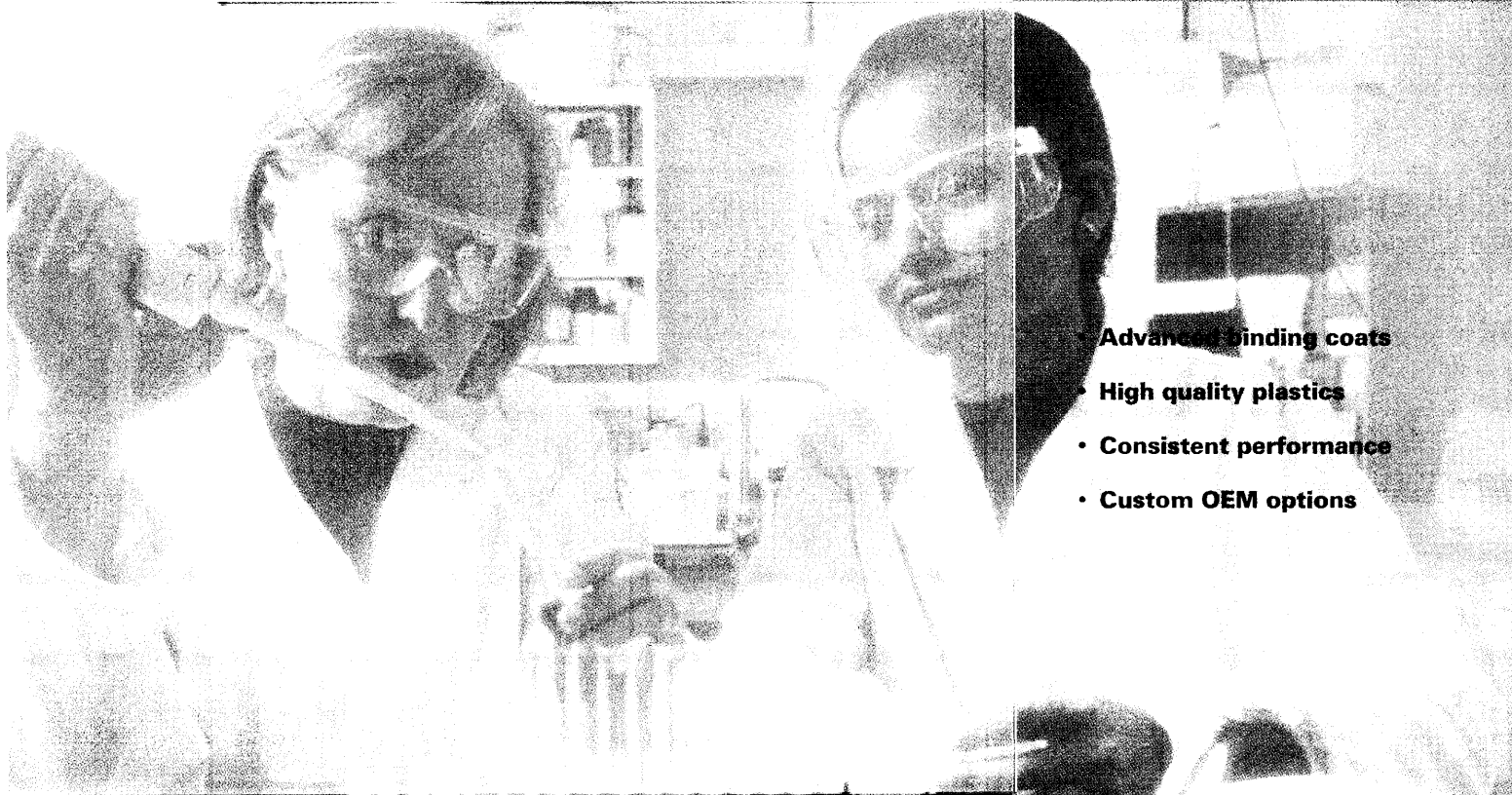
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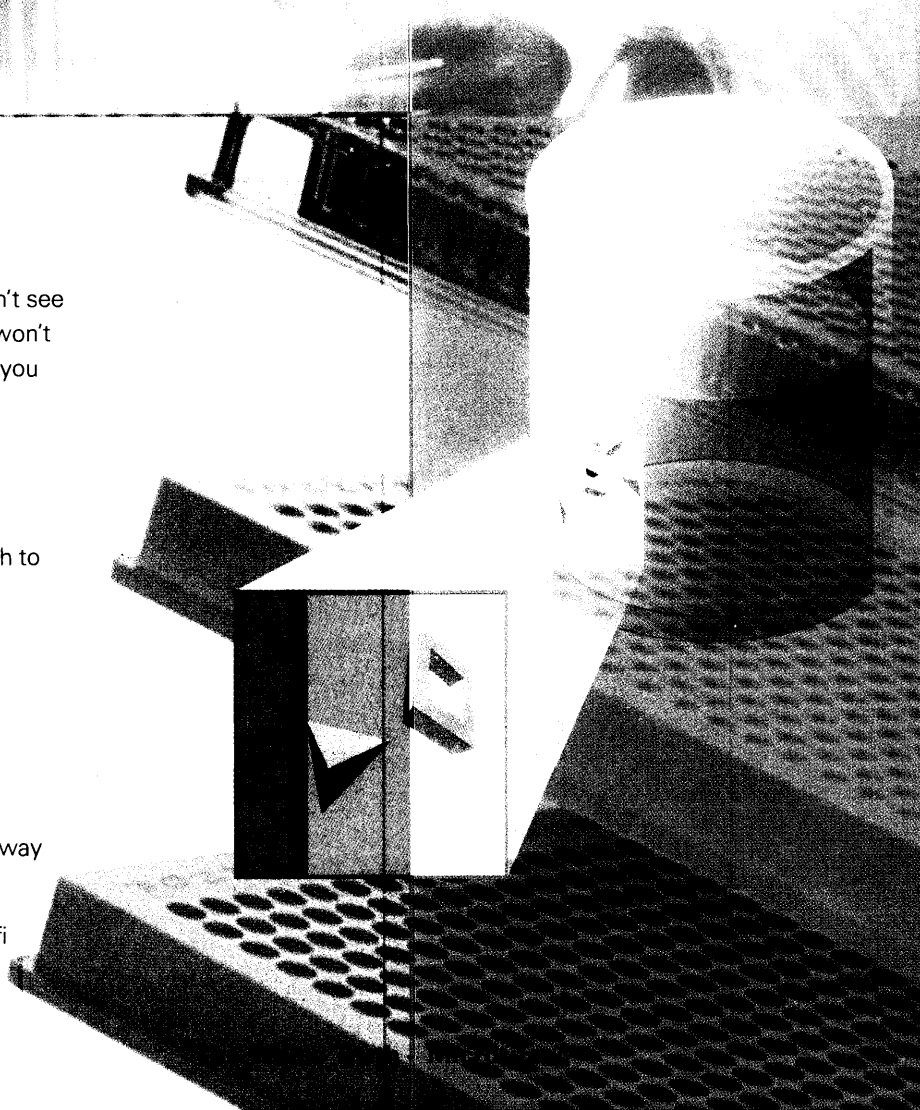
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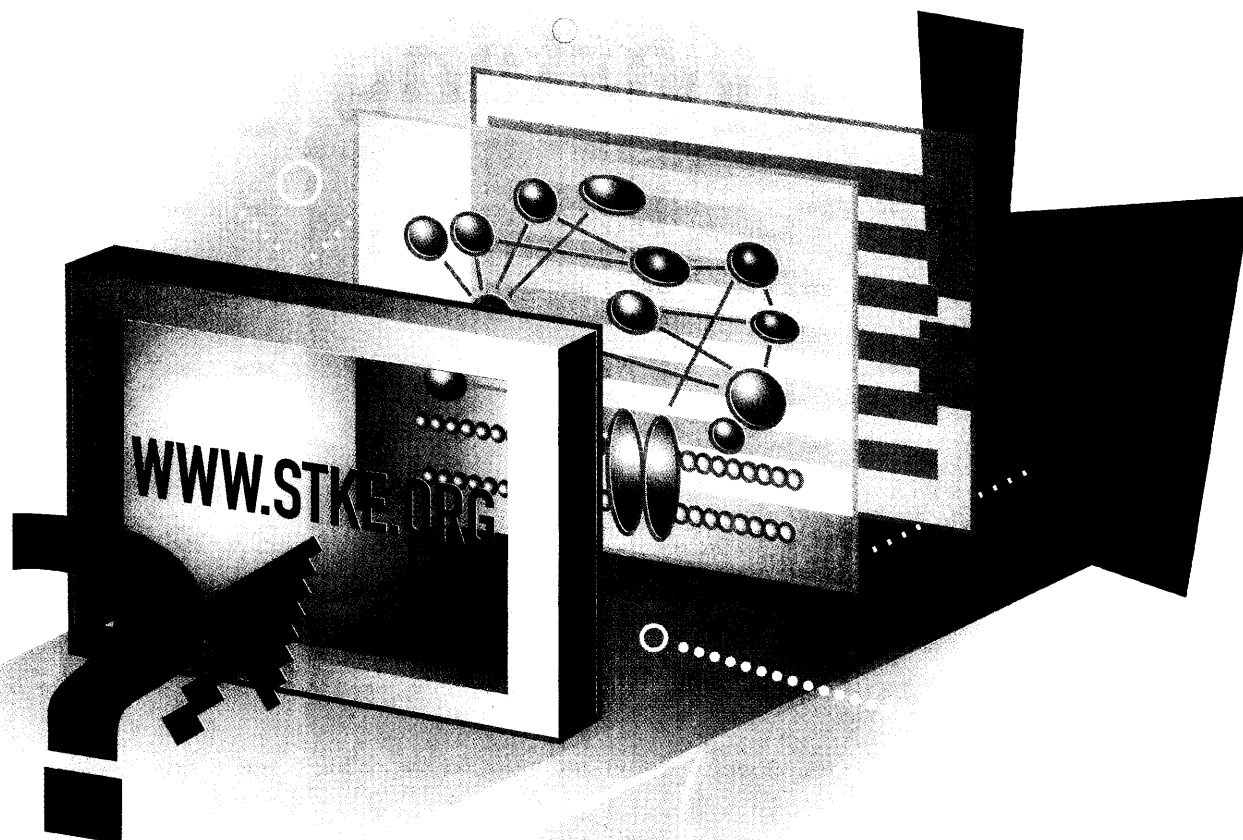
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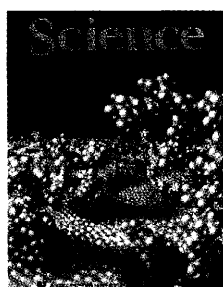


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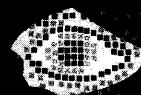
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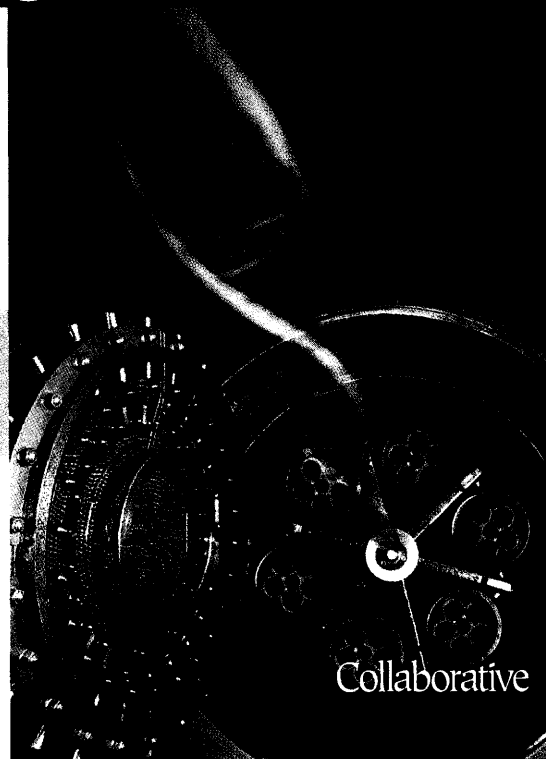
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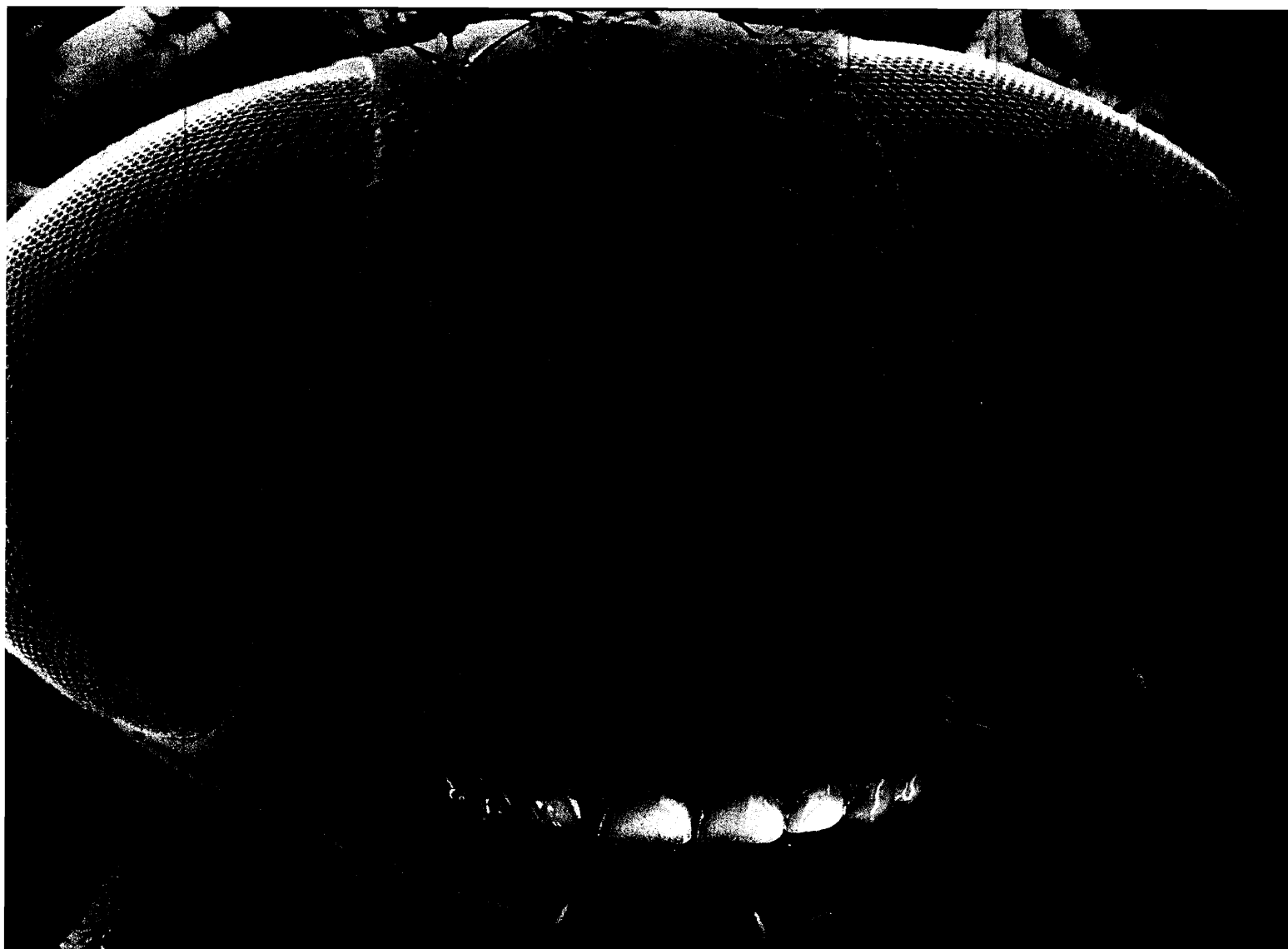
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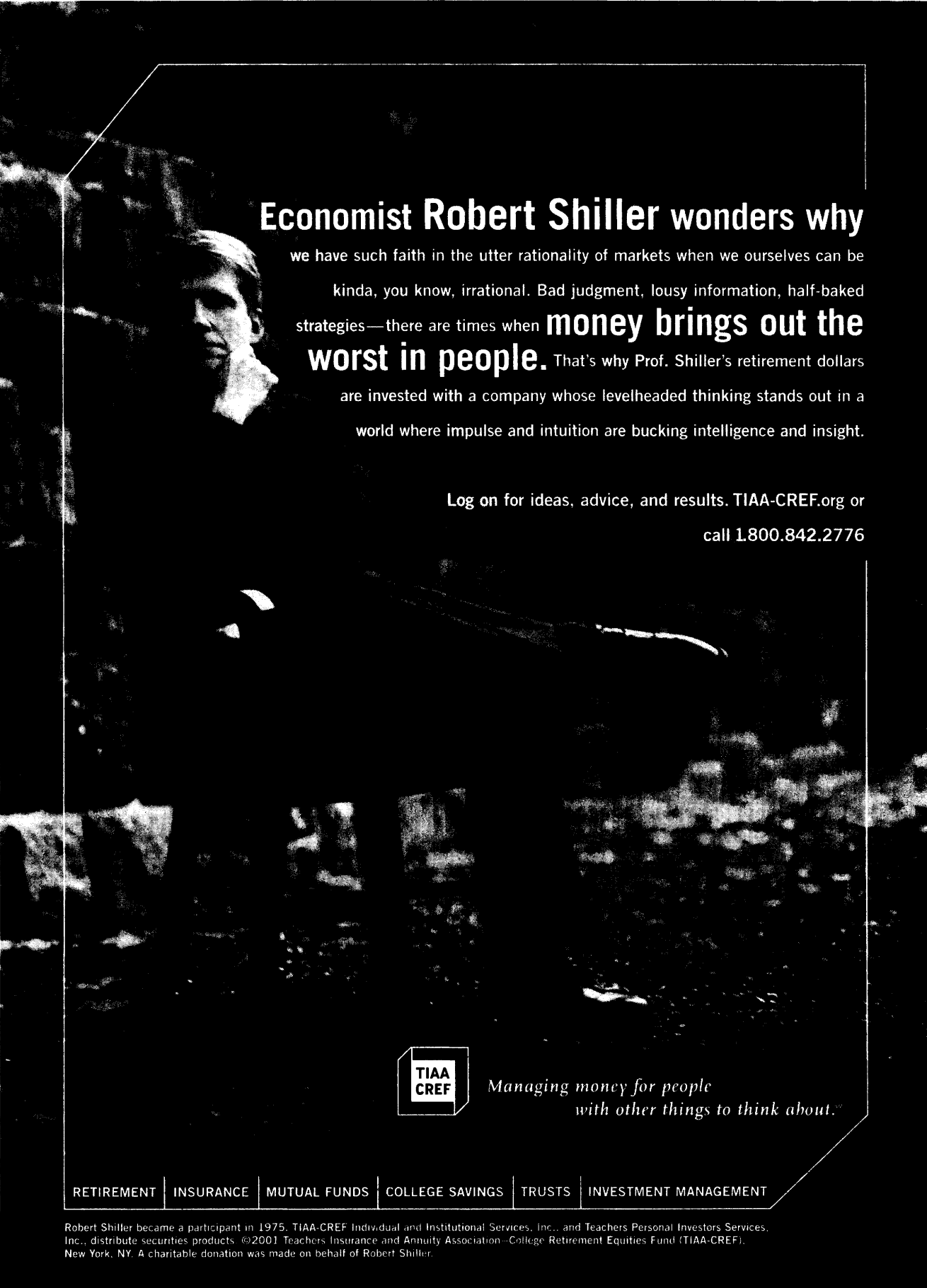
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