2 July 1999

Science

Vol. 285 No. 5424
Pages 1–156 $8

INSIDE
HEPATITIS C
News Coverage & Reports

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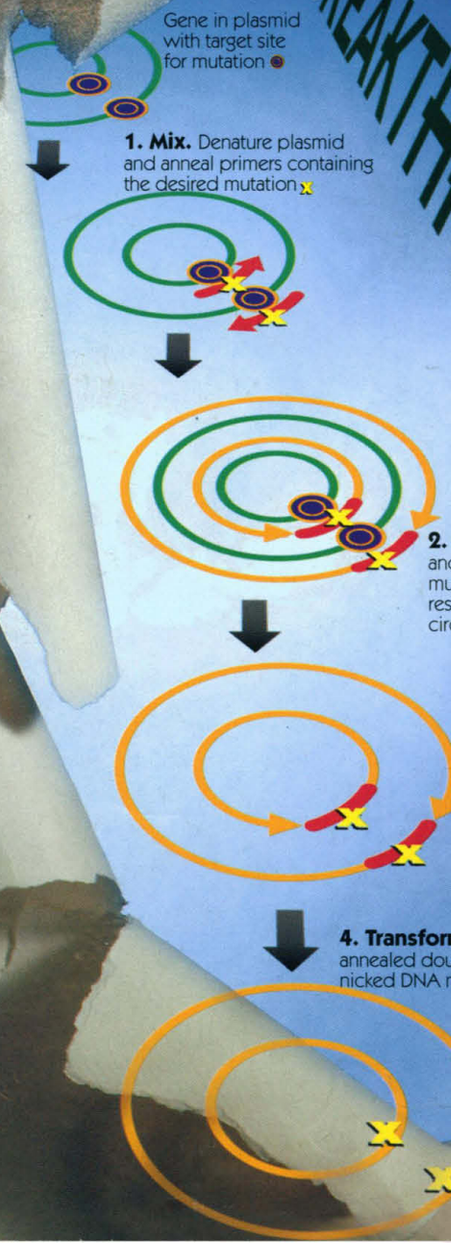

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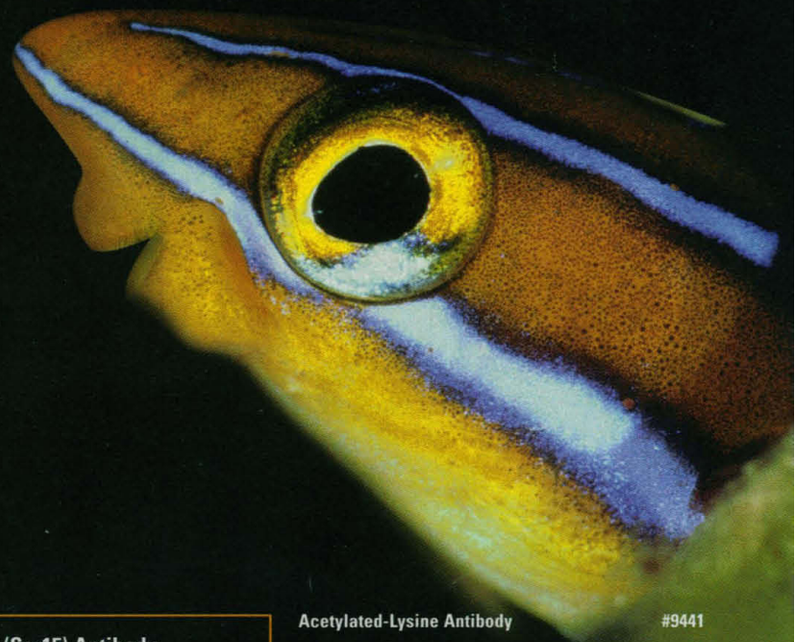
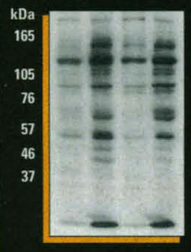
CELL SIGNALING

DNA Damage/Protein Acetylation

FOR ANALYSIS OF p53 PHOSPHORYLATION & LYSINE ACETYLATION



Acetylated-Lysine Antibody

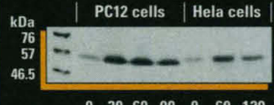


Western analysis of extracts from TSA treated COS cells using Acetylated-Lysine Antibody (A) and MAPK Antibody (B).

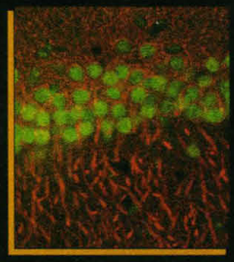
Increase in p53 acetylation of UV treated 293 cells detected by IP using p53 Antibody followed by Western blotting using Acetylated-Lysine (A) and p53 Antibodies (B).

Increase in Histone acetylation of NIH/3T3 cells treated with 5 mM sodium butyrate for 24 hours detected by Western blotting using Acetylated-Lysine Antibody.

Phospho-p53 (Ser15) Antibody



Western analysis of cell extracts from PC12 cells or Hela cells treated with UV using Phospho-p53 (Ser15) Antibody.



Confocal image of double immunostaining for Phospho-p53 (Ser15) Antibody (green) and propidium iodide (red) in rat hippocampus CA1 region from tissue section of 15 minutes of transient cerebral ischemia followed by 3 hours of reperfusion. Yellow represents overlay of red and green. (Provided by Dr. Bingren Hu, Queens Medical Center, Hawaii.)

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Phospho-MAPK Antibody Sampler	#9910
p53 (S15)	#9284
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VOLUME 285 2 JULY 1999 NUMBER 5424

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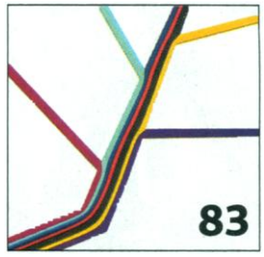

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26
A virus on the rise

NEWS

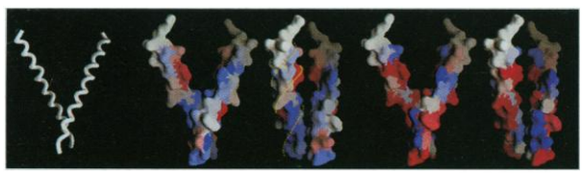
NEWS OF THE WEEK

NEWS FOCUS

RESEARCH

RESEARCH ARTICLE

REPORTS



73
Helix rotation leads to K^+ channel activation

DEPARTMENTS

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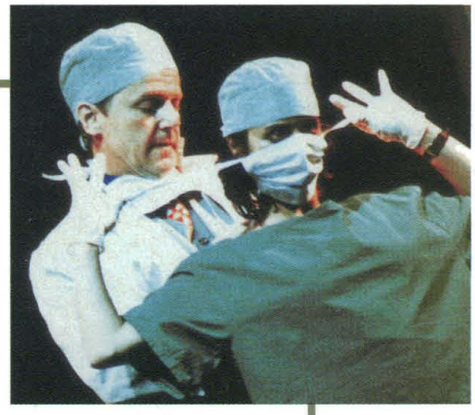


53

Giving reproduction a helping hand

EDITORIAL

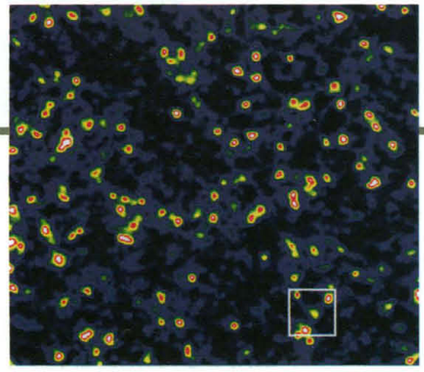
LETTERS

ESSAY

BOOKS *ET AL.*

PERSPECTIVES

REVIEW



88

Scattering centers in superconductors

TECHNICAL COMMENTS

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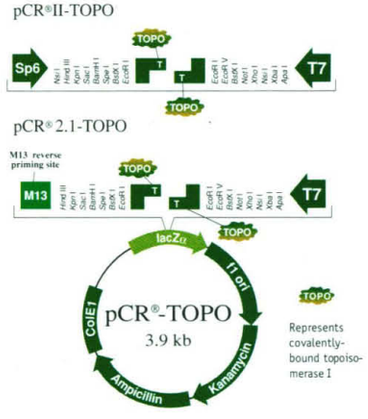

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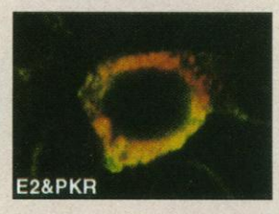
EXPLORING HCV REPLICATION

With an estimated 170 million people infected worldwide, hepatitis C virus (HCV) has emerged as a major public health problem. One of the greatest barriers to HCV research has been the lack of a reliable cell culture system for studying viral replication (see the news story by Cohen). Lohmann *et al.* (p. 110) have produced selectable RNA replicons from the HCV genome and found that these RNAs replicate stably and to high levels in transfected human hepatoma cells. This experimental system should allow detailed molecular studies of the HCV life cycle and testing of new antiviral therapies. At present, interferon (IFN) is the most common therapy for HCV, but many viral isolates are resistant to it. Taylor *et al.* (p. 107) show that the HCV envelope protein E2 contains a sequence identical to the phosphorylation sites in the IFN-inducible kinase PKR and the translation initiation factor eIF2α, a target of PKR. In cultured cells, E2 inhibited the kinase activity of PKR and blocked its ability to suppress protein synthesis and cell growth. Thus, the E2-PKR interaction may be one of the strategies by which HCV circumvents IFN's antiviral function.



VERY OLD AGES

Determining the age of sedimentary rocks and correlating rock packages globally is critical for accurately evaluating the pace of evolution and extinction and determining global-climate and sea-level changes. Dating has been problematic in the absence of interbedded volcanic rocks, and particularly troublesome for Precambrian samples where few index fossils are available. In many cases, ages are not known to better than tens of millions of years during the Phanerozoic and to better than hundreds of millions of years in the Precambrian. McNaughton *et al.* (p. 78; see also the Perspective by Whitehouse) show that xenotime, an early diagenetic mineral in many sedimentary rocks, can provide accurate uranium-lead ages from Precambrian to Quaternary rocks. They specifically dated a Precambrian sandstone in Australia to 1704 million years ago.

THE REMAINS OF CANYON DIABLO

The iron meteoroid, Canyon Diablo, hit Earth about 50,000 years ago and created Meteor Crater, Arizona. The area around the crater is littered with both meteorites, bits of unmelted iron, and spheroids, blebs of melted iron. Schnabel *et al.* (p. 85) measured the concentration of nickel-59, a nuclide produced by cosmic rays, and found a lower concentration in the spheroids than in the meteorites. This low concentration is consistent with the spheroids being shielded from some cosmic ray exposure and with most of their melting occurring during atmospheric entry, and suggests that the spheroids were probably derived from a depth of 1.3 to 1.6 meters inside the meteoroid.

PINNING DOWN QUASIPARTICLES

In superconductors, electrons condense into Cooper pairs and move freely throughout the material. If the material is defective, the pairs can be broken as they come into contact with the scattering centers and form quasiparticles. Such scattering effects in the high-temperature superconductors have been predicted theoretically but have so far remained elusive to experimental verification. Hudson *et al.* (p. 88; see the Perspective by Atkinson and MacDonald) used scanning probe microscopy to show that even far below the superconducting transition temperature, there are many such atomic-scale scattering centers. This result also confirms the *d*-wave nature of the superconducting gap.

WORKING IN TIGHT QUARTERS

Microfabrication of ever smaller devices, such as microanalytical systems or microreactors, poses significant technical challenges. Kenis *et al.* (p. 83; see the cover and the news story by Hellemans) address one challenge, namely, how to pattern the insides of small capillaries in a spatially localized manner. The method exploits the laminar flow properties of multiple liquid streams to induce chemical reactions at the desired place. For example, a thin silver wire was grown in the capillary, as well as a functioning three-electrode system inside an elastomeric channel.

HYDROGEN STORAGE IN CARBON NANOTUBES

The great promise of hydrogen as an energy carrier for batteries and fuel cells has been limited by difficulties in storing it for consumer use. Chen *et al.* (p. 91) report that carbon nanotubes intercalated with lithium or potassium can adsorb up to 20 weight % hydrogen at ambient pressures and moderate temperatures (200° to 400°C). The energy densities, nearly half that of gasoline, are much greater than those achieved by metal hydrides or cryoadsorbents.

CAUGHT AT LAST

Identifying and characterizing short-lived chemical species can be very challenging, although mass spectrometry techniques have ameliorated the situation significantly. However, for radical species, extra tricks are needed. Cacace *et al.* (p. 81) demonstrate how neutralization-reionization mass spectrometry can be used to demonstrate the existence of the radical hydrogen trioxide and estimate its lifetime. This molecule has been implicated in atmospheric processes but has not been identified before.

ION CHANNEL GATING AND PERMEATION

Two fundamental processes underlie the function of an ion channel in biological membranes: permeation, the selective translocation of ions across the membrane, and gating, the access control of ions to the permeation pathway. Recently, the structure of an ion channel, the KcsA potassium channel, was determined. Roux and MacKinnon (p. 100) used electrostatic modeling methods to describe the permeation of K^+ ions through this channel, and Perozo *et al.* (p. 73) used site-directed spin-labeling and electron paramagnetic resonance spectroscopy to determine the conformational changes involved in gating of the KcsA channel (see the Perspective by Zagrovic and Aldrich).

TIGHT REGULATION OF Mg^{2+}

Magnesium reabsorption in the kidney is mediated primarily by paracellular transport (passage of solutes between cells), a process about which little has been known. Simon *et al.* (p. 103; see the Perspective by Wong and Goodenough) studied families with an inherited disease associated with massive magnesium loss and calcium loss and identified the causative gene as *paracellin-1* (*PCLN-1*). The *PCLN-1*

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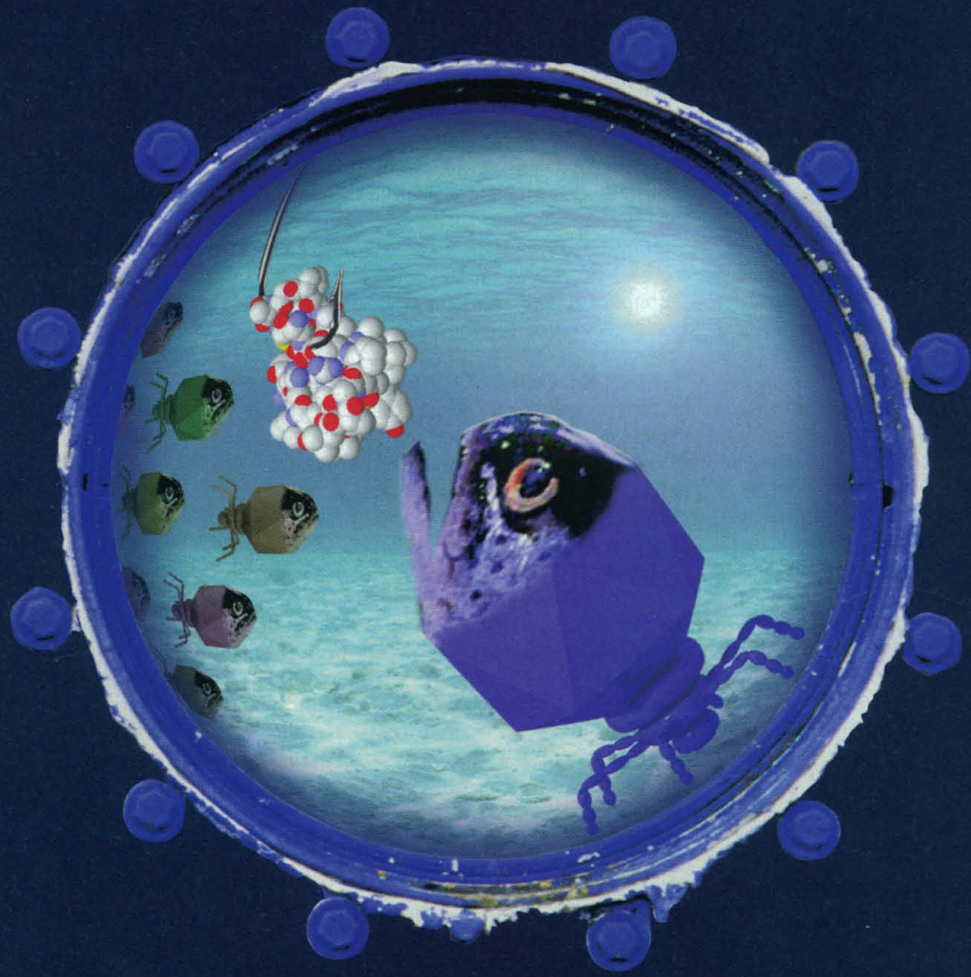

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gene encodes a putative transmembrane protein, paracellin-1, with sequence homology to a family of tight junction proteins, the claudins. Paracellin-1 specifically localized to tight junctions in the kidney segment implicated in magnesium reabsorption.

IP_6 AND mRNA TRANSPORT

The enzyme phospholipase C (PLC) hydrolyses phosphatidylinositol (PtdIns) to produce diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). The latter is a signaling molecule that causes release of calcium from intracellular stores. The roles of more phosphorylated inositols like IP_6 are less well understood. York *et al.* (p. 96) identified mutations in yeast that were lethal in combination with a mutant allele of the gene *GLE1*, which encodes a protein that functions in export of messenger RNA (mRNA) from the nucleus. Among the genes isolated, one encoded a PtdIns-specific PLC and another encoded an inositol polyphosphate kinase that promotes conversion of IP_5 to IP_6. The results presented indicate that generation of IP_6 is required for proper nuclear export of mRNA and raise the possibility that such export responds to cellular signaling mediated by inositol polyphosphates.

BRINGING REGULATORS TOGETHER

Information continues to accumulate on the importance of scaffolding proteins that bring together components of intracellular signaling pathways. Westphal *et al.* (p. 93) describe a signaling complex that associates with the *N*-methyl-D-aspartate (NMDA) receptor (a neuronal receptor for the neurotransmitter glutamate that functions as a regulated ion channel). They find that a scaffold protein called yotiao binds to the receptor and also to a regulatory protein kinase and protein phosphatase. Type 1 protein phosphatase 1 (PP1) in the receptor complex is constitutively active and acts to inhibit channel activity of the receptor. The adenosine 3′,5′-monophosphate (cAMP)-dependent protein kinase (PKA) is also present in the complex but is only activated after stimuli that increase intracellular concentrations of cAMP. Activation of PKA apparently overrides the inhibitory signal from PP1 and leads to increased current flow through the receptor. Thus, yotiao localizes enzymes with opposing regulatory influences in direct proximity to their substrate, the NMDA receptor.

A POSITIVE APPROACH TO B CELLS

B and T cells are lymphocytes, each cell carrying one antigen receptor that is randomly generated. Although it is known that T cells go through two selection processes, one positive and one negative, to produce the final repertoire of receptors, similar selection processes in B cells have been more difficult to study. It is known that they must pass a negative selection hurdle, as most autoreactive B cells are weeded out. However, human serum contains "natural autoantibodies." Hayakawa *et al.* (p. 113) devised a system to test if a self-antigen could positively select for B cells by promoting their survival. They found that B cells specific for the self-antigen were dependent on the presence of that antigen for their accumulation and the production of autoreactive antibodies.

TECHNICAL COMMENT SUMMARIES

Selection Against Susceptibility to HIV-1

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/285/5424/11a

M. Carrington *et al.* (Reports, 12 Mar., p. 1748) found that "the extended survival of 28 to 40 percent of HIV-1–infected Caucasian patients who avoided AIDS for ten or more years can be attributed to their being fully heterozygous at the [human leukocyte antigen (*HLA*)] class I loci, to their lacking the AIDS-associated alleles *B*35* and *Cw*04*, or to both."

C. Wills comments that, "if only one or a few alleles at HLA were to confer resistance to a disease, then during an epidemic, these alleles would sweep through the population (that is, individuals with these alleles would be more likely to survive). This process would reduce HLA polymorphism. Instead, at least in this case, a few alleles confer susceptibility and the majority confer resistance....This resistance occurs without destroying the genetic variation [of the major histocompatibility complex (MHC)] that is essential for defenses against other diseases."

In response, S. J. O'Brien and M. Carrington agree that this "frequency-dependent selection occurs" in the case of HIV-1, and state that "how more susceptible alleles operate" is not clear, but may be resolved by "newly available reagents and technologies."

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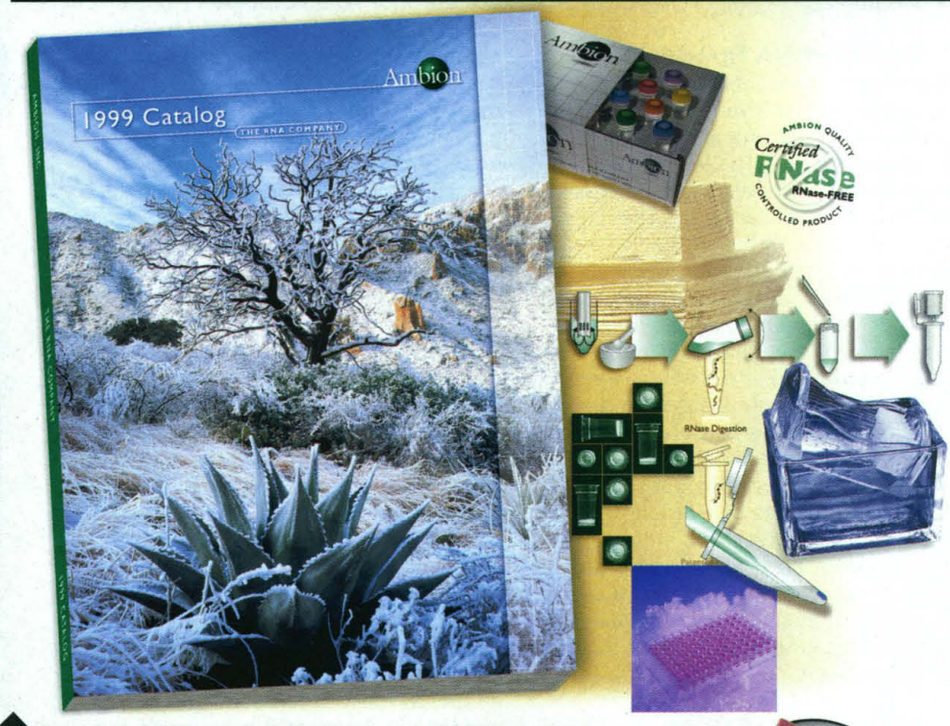

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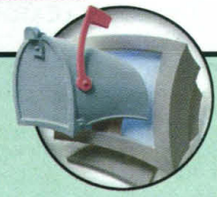

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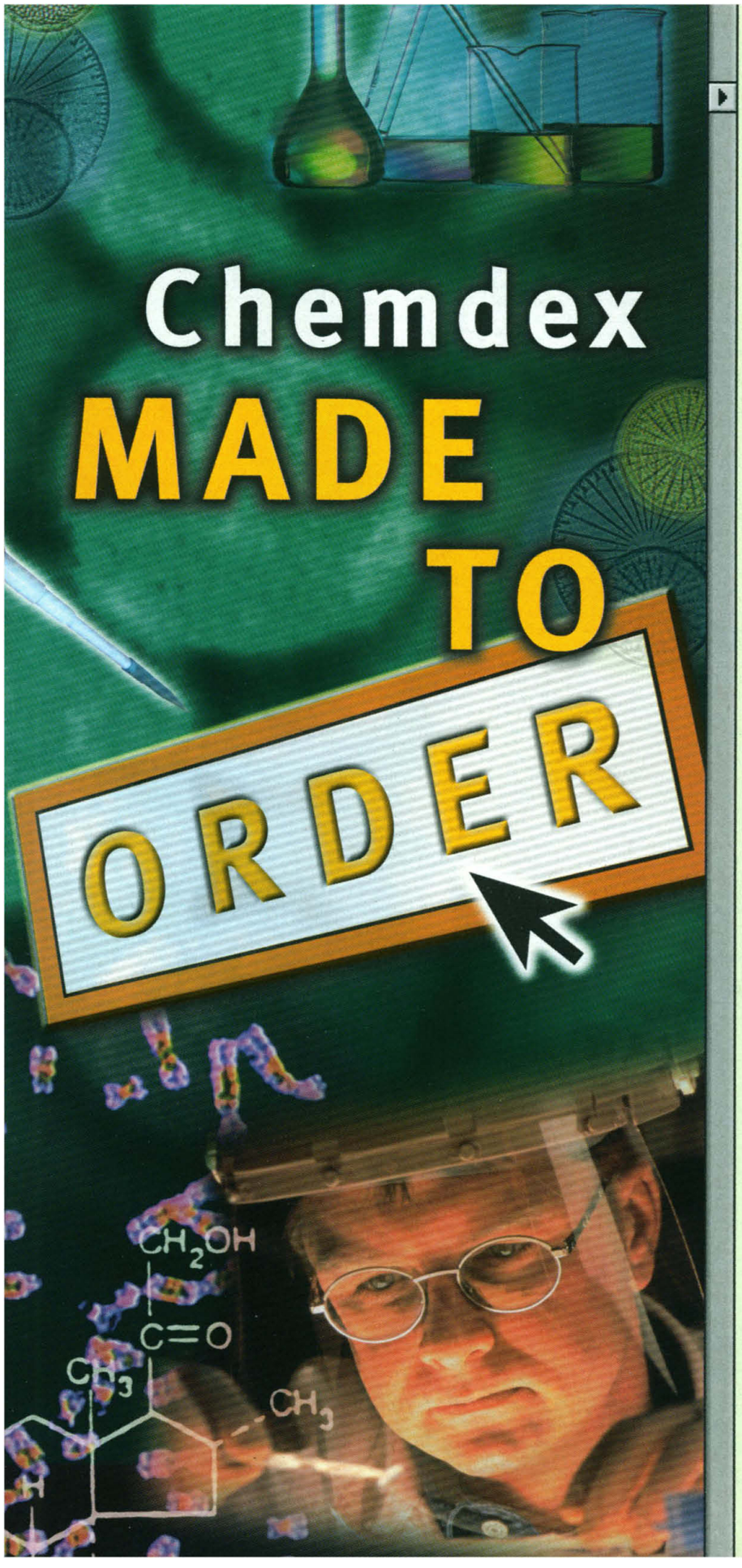

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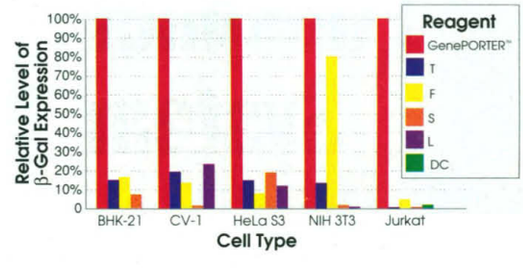

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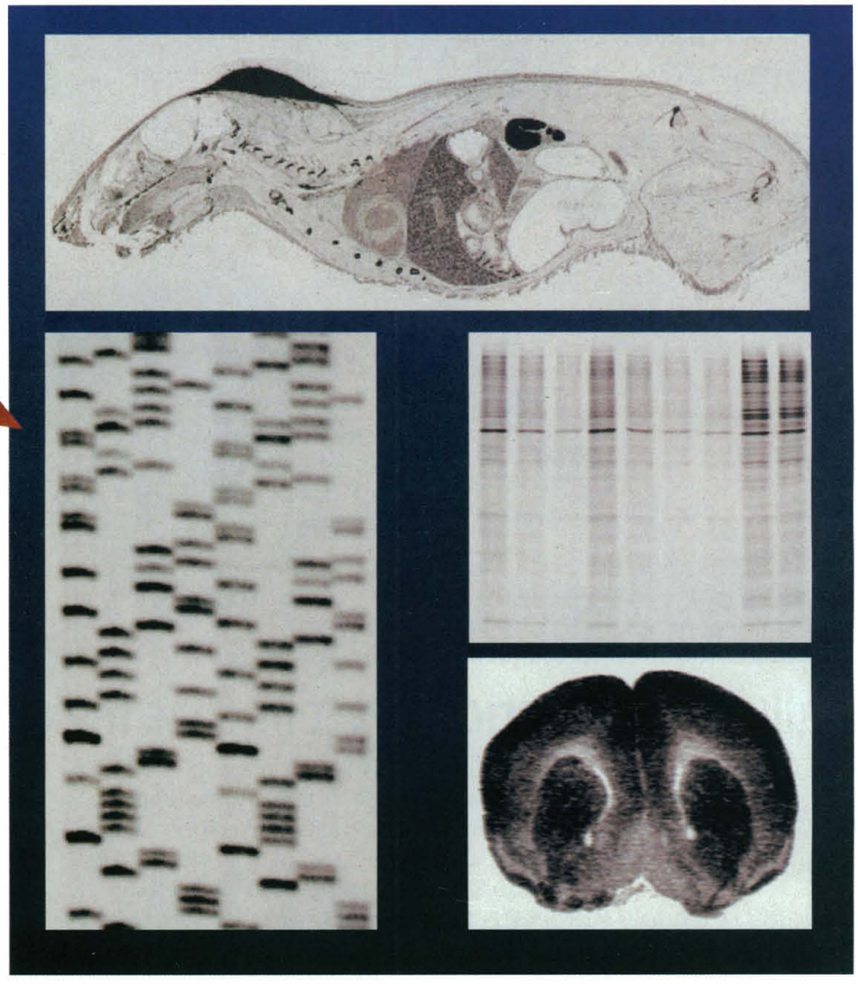

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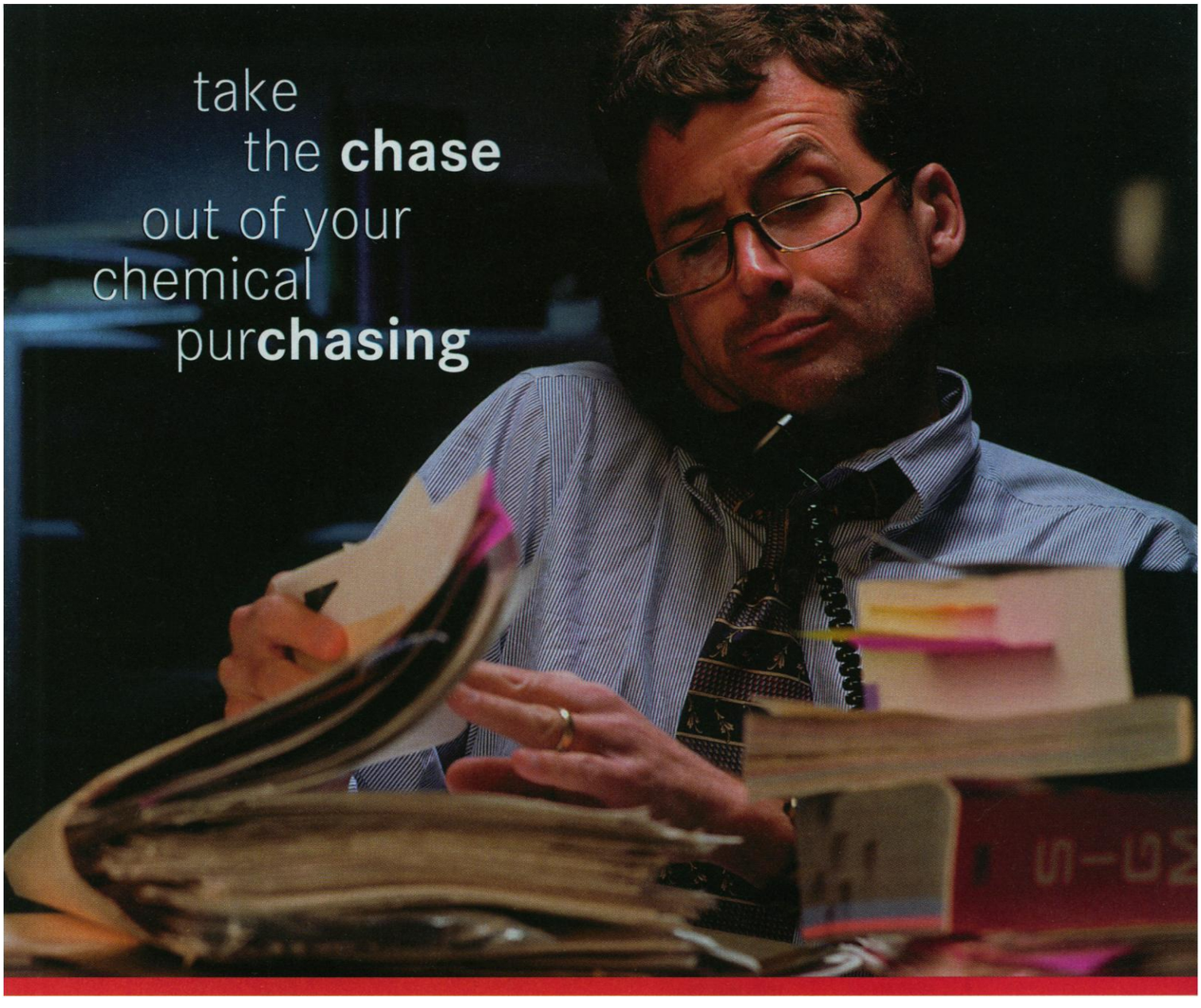

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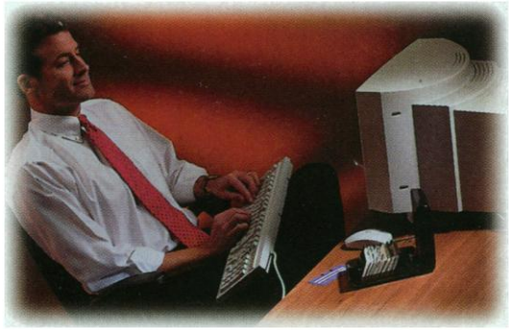

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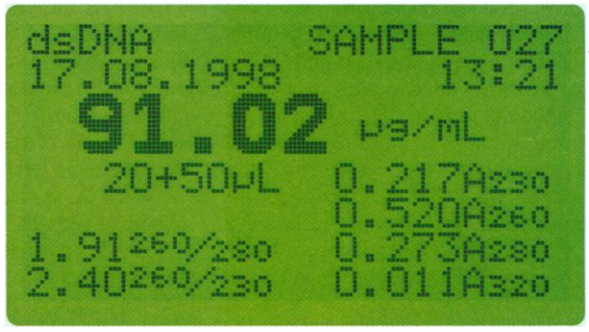

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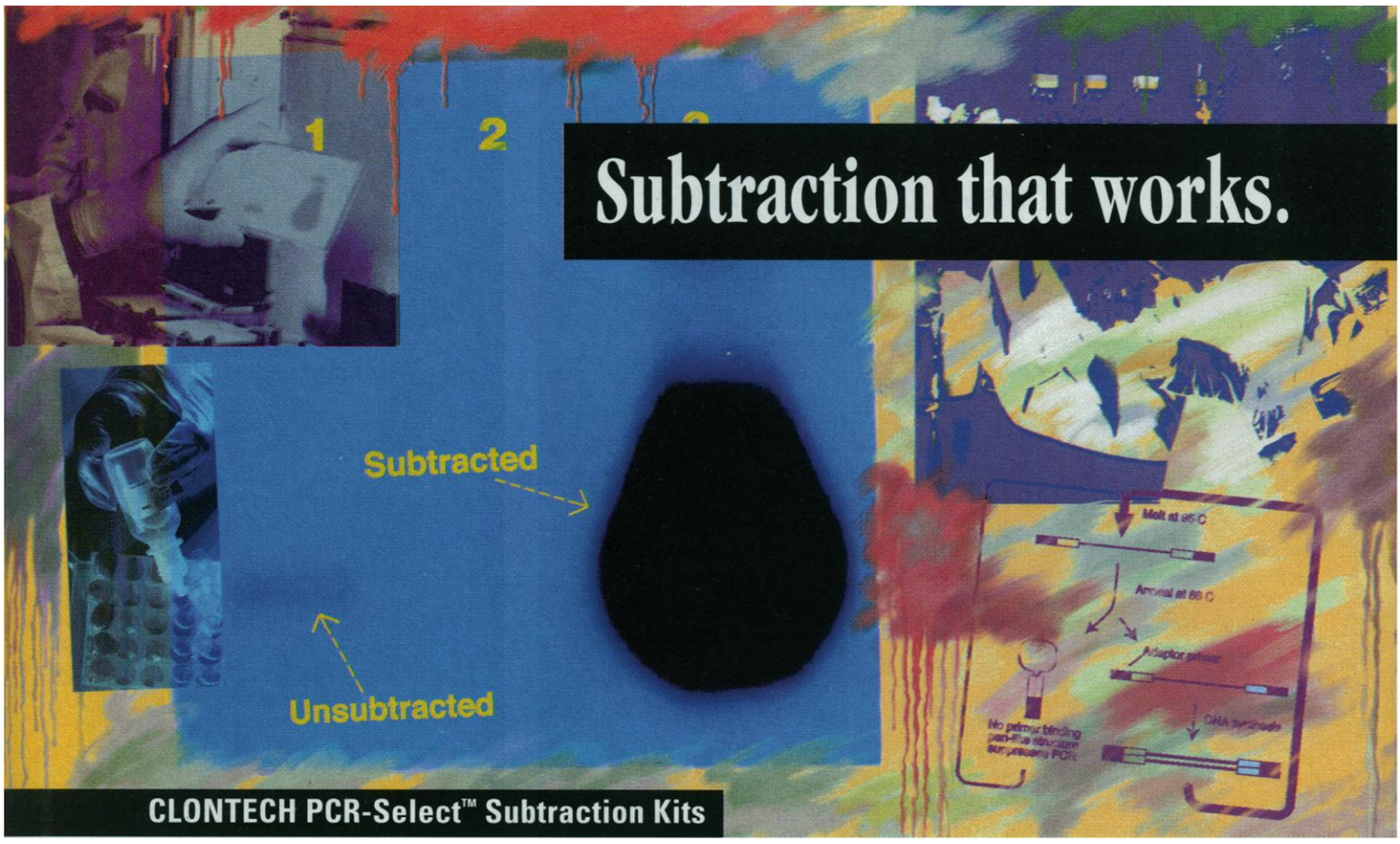

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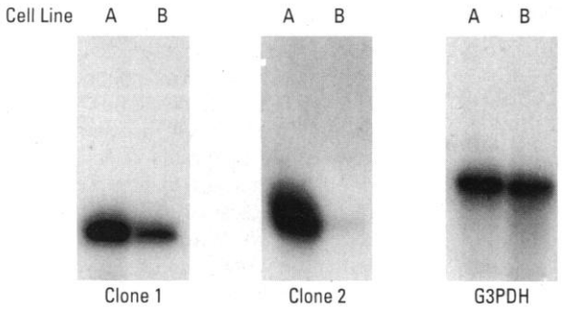

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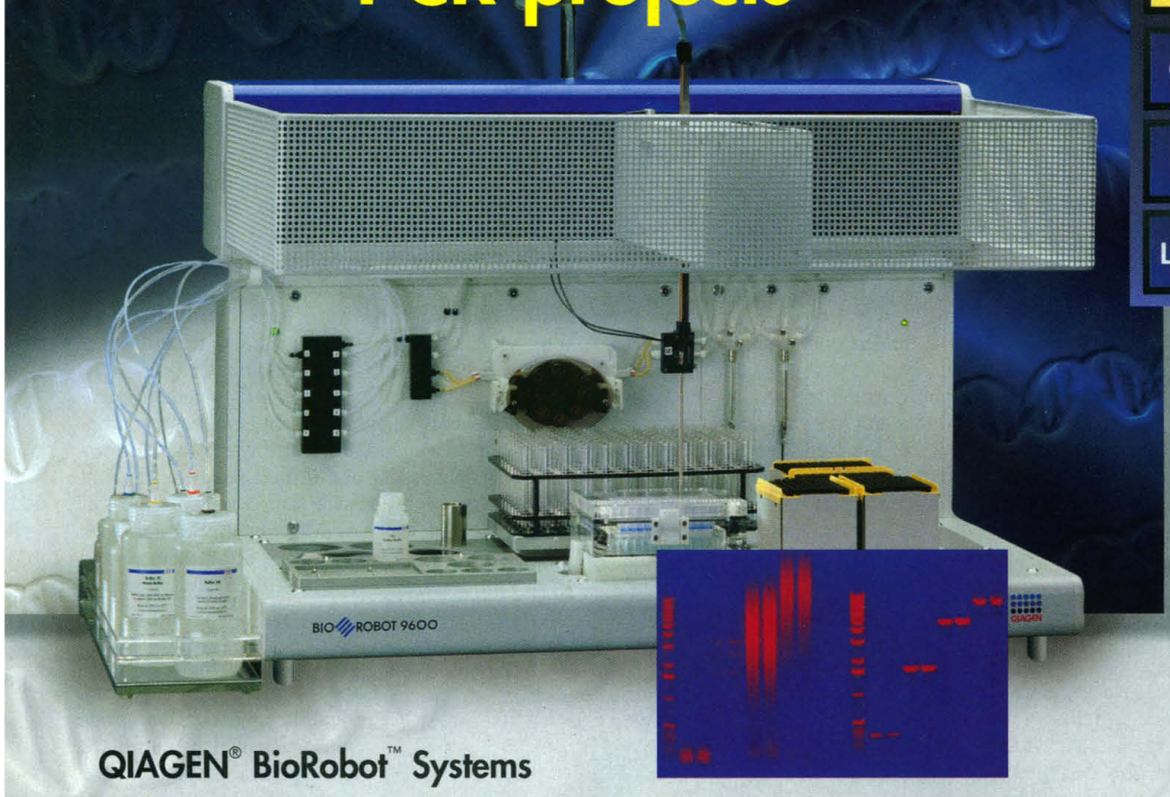

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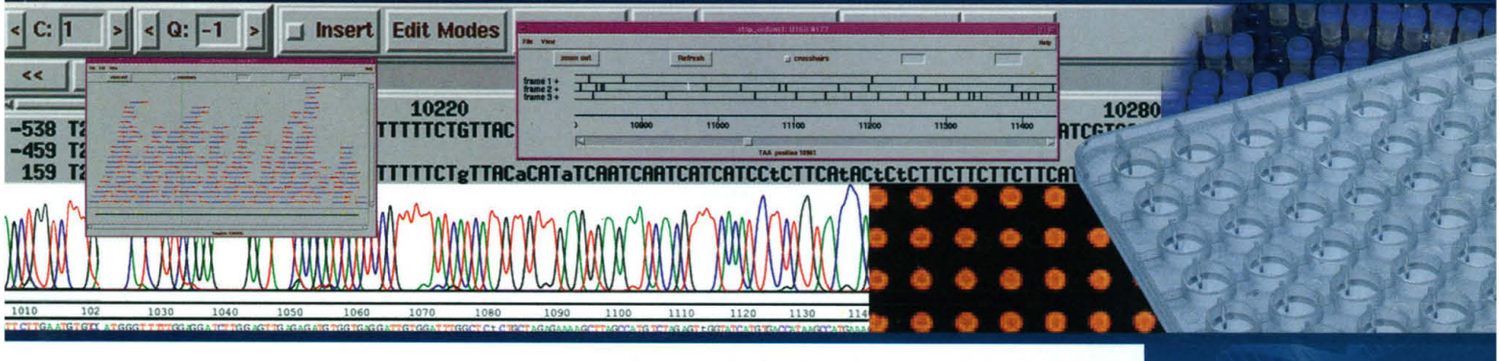

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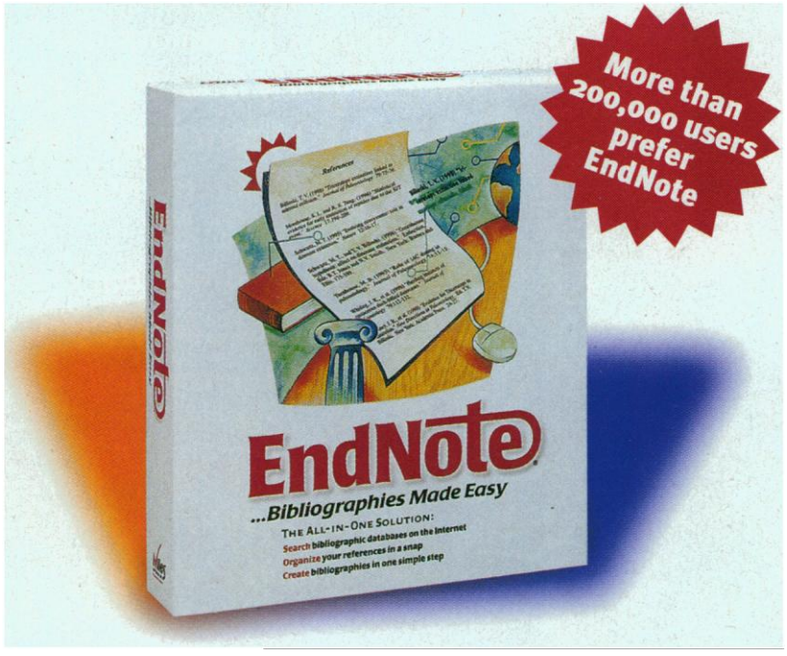

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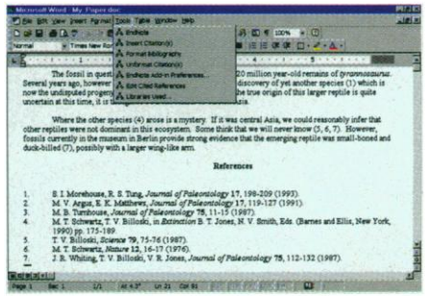

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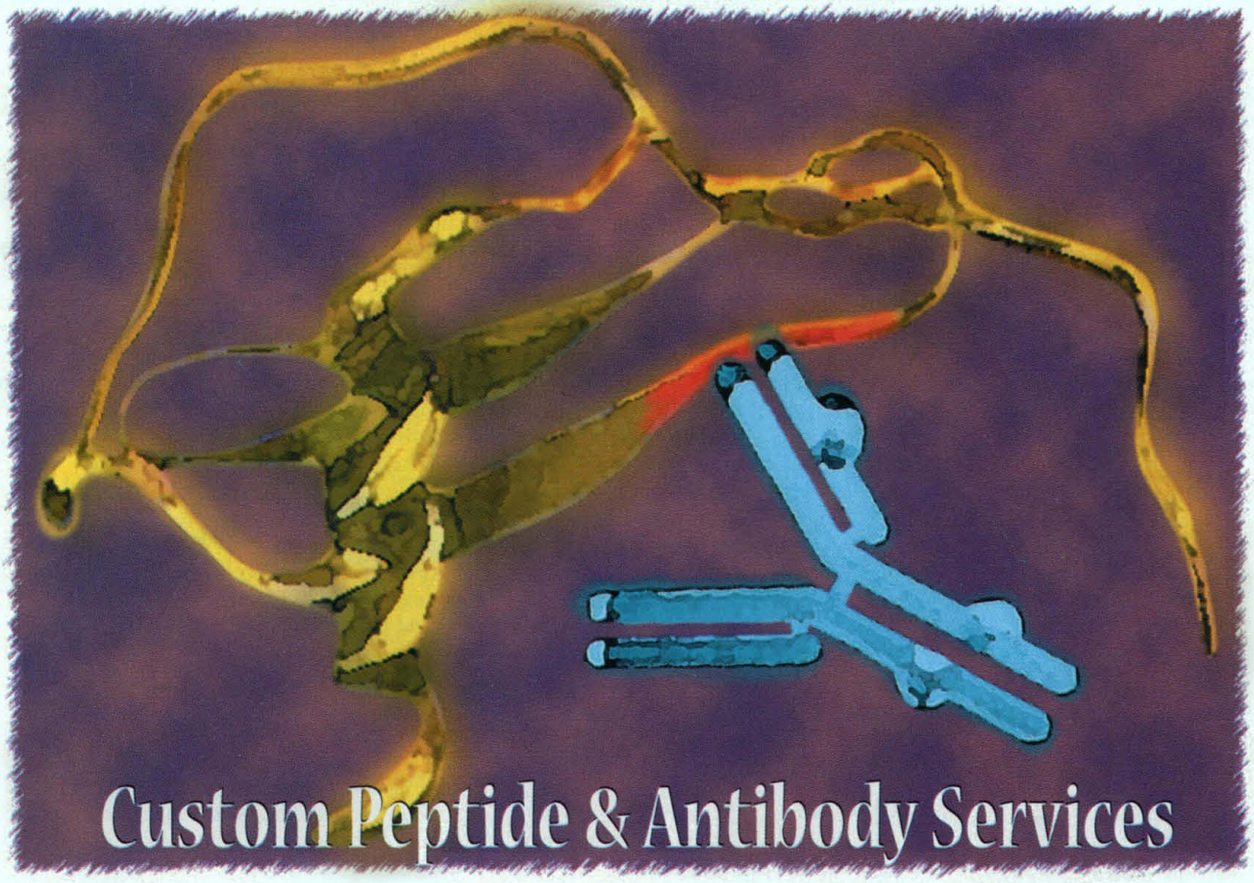

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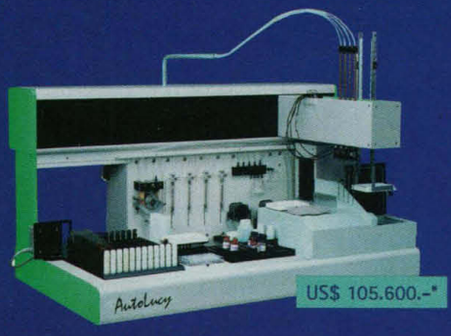

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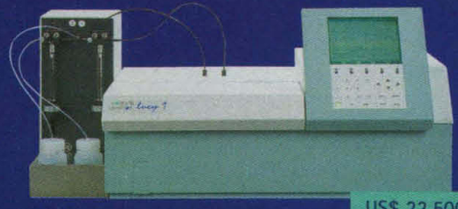

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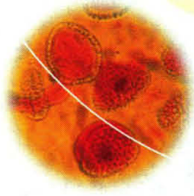

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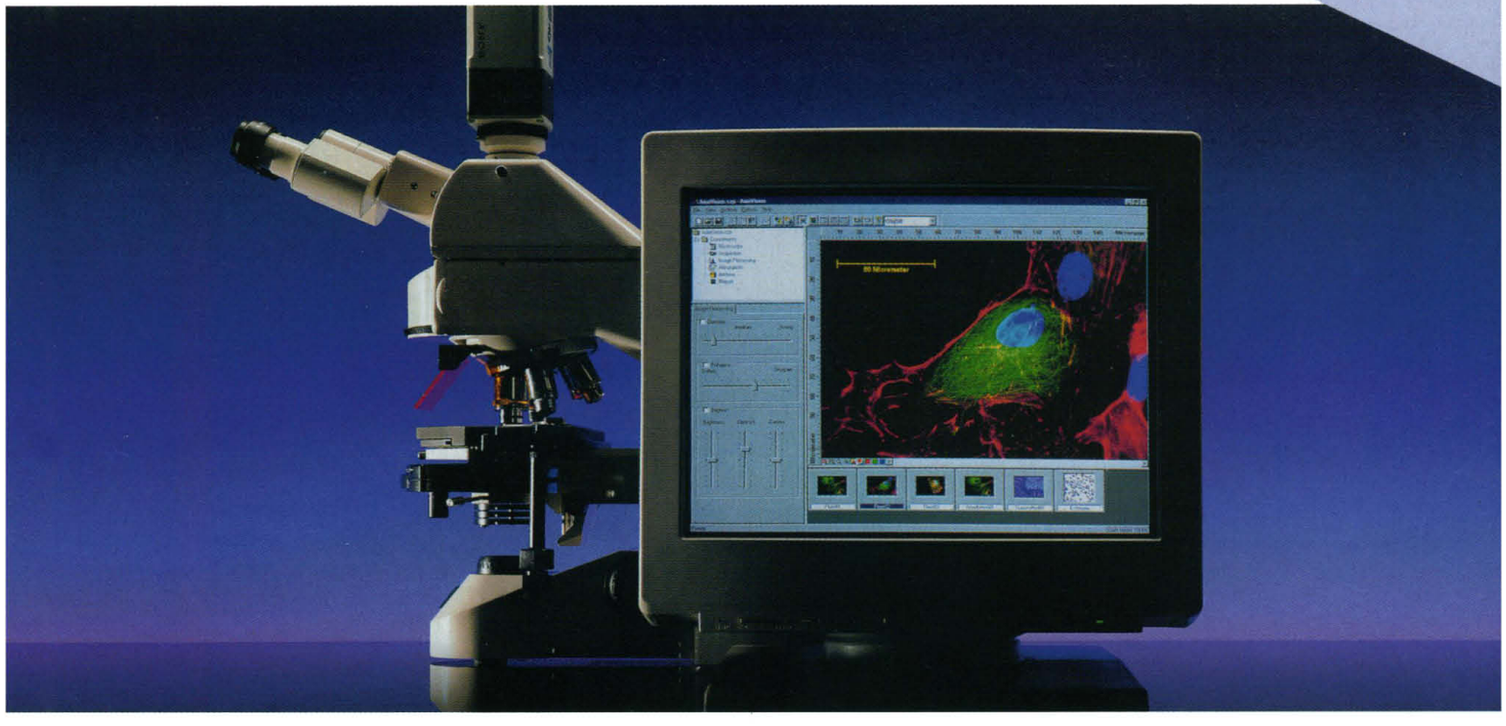

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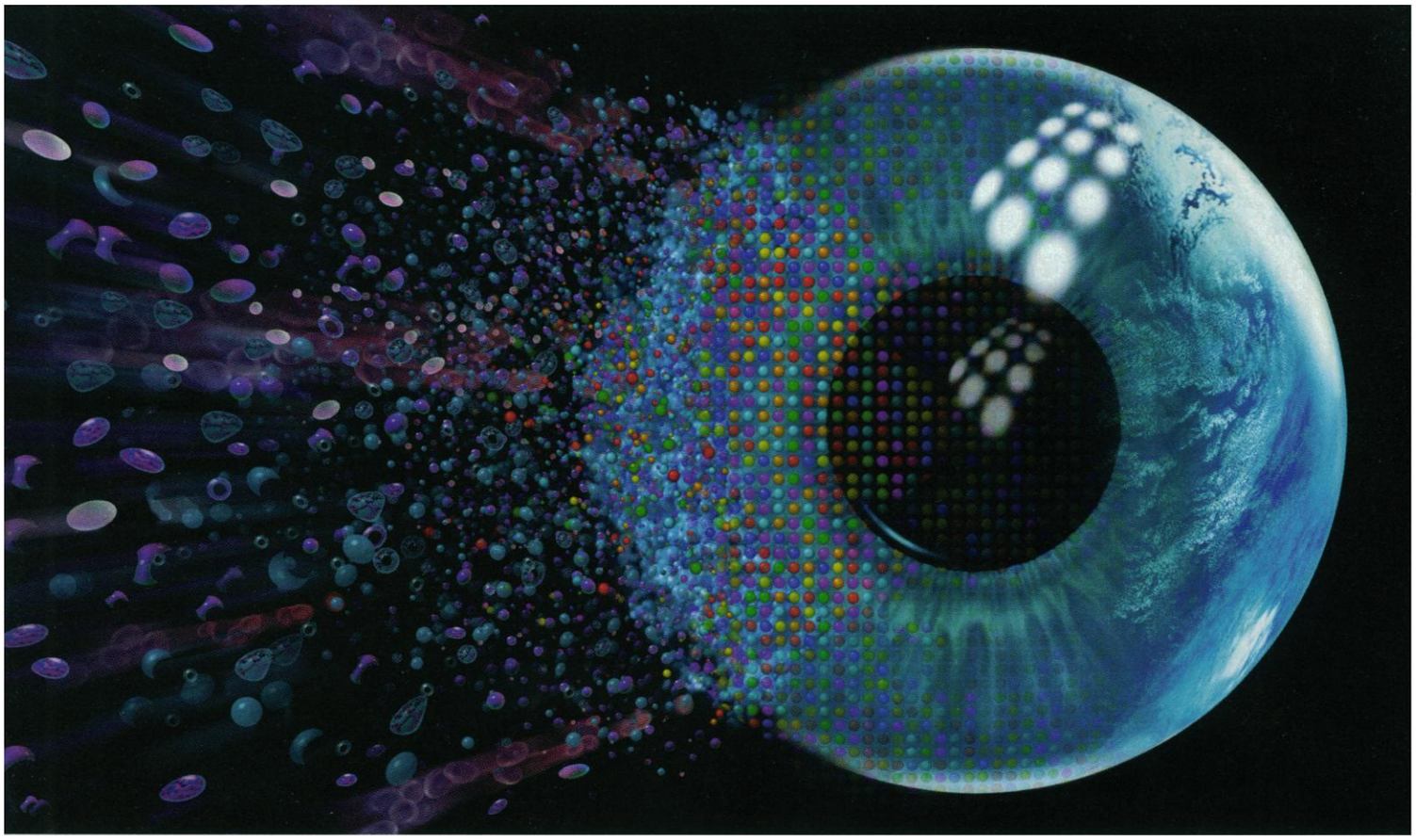

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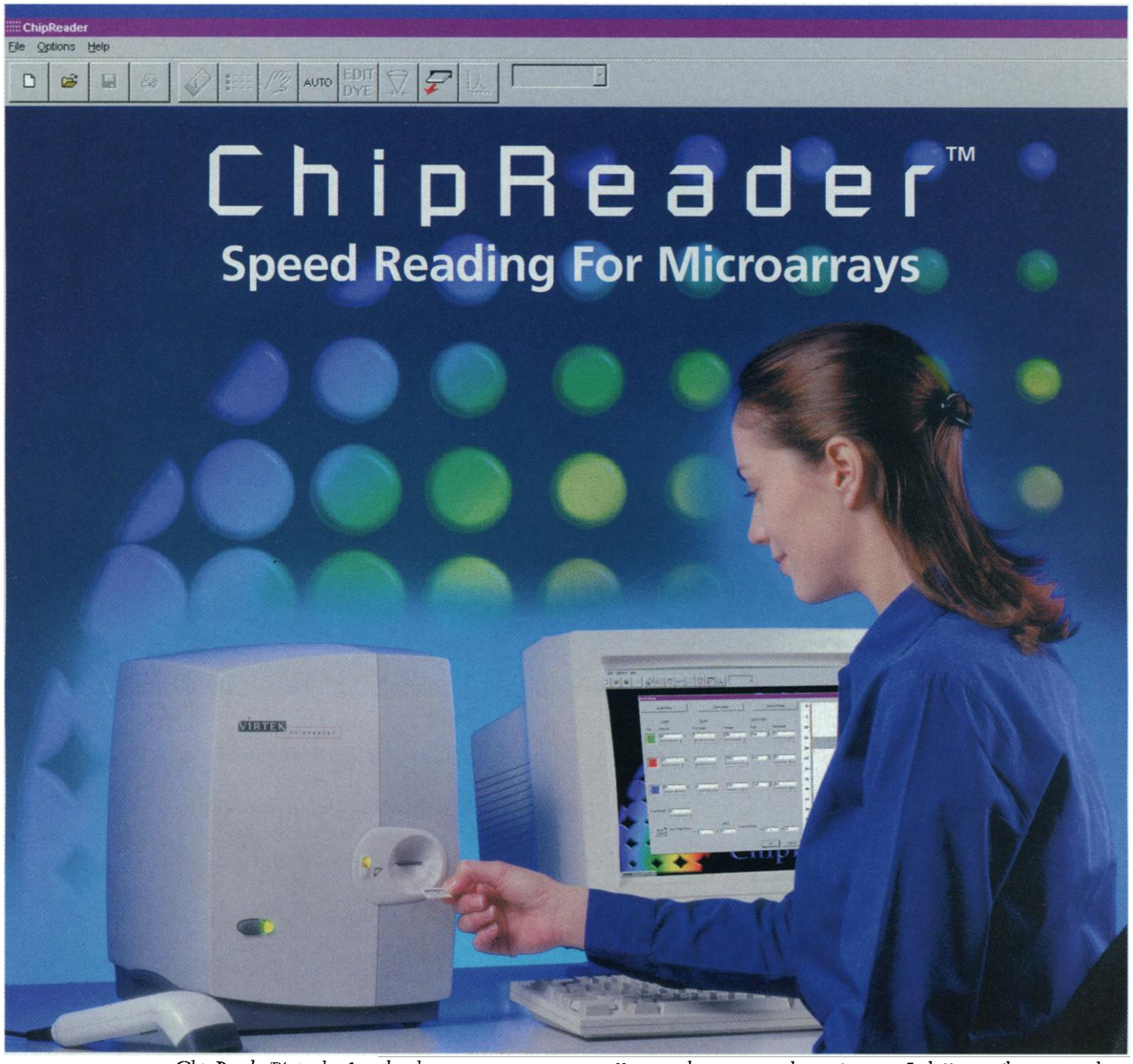

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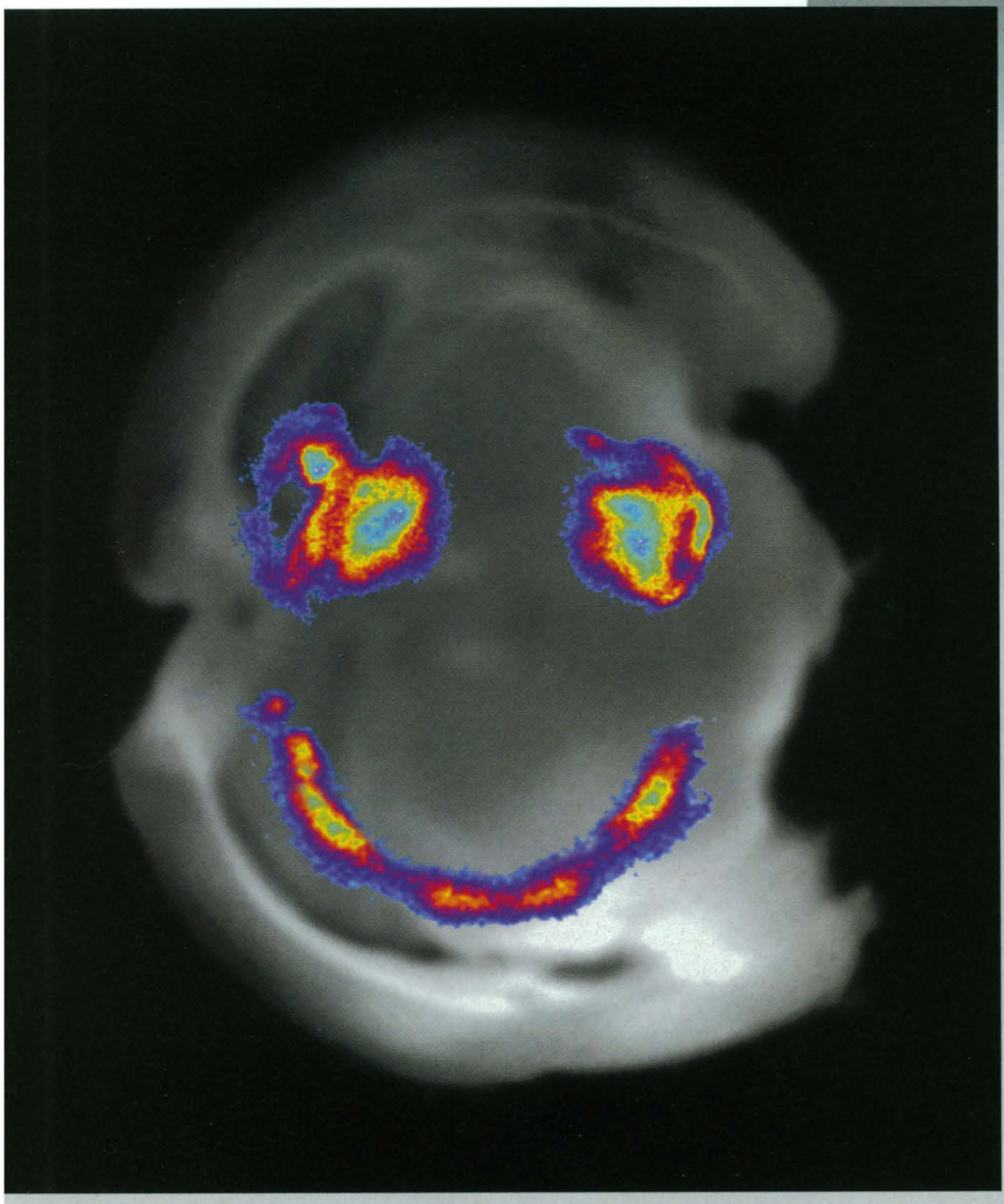

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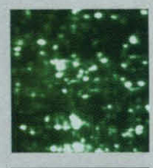

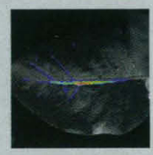

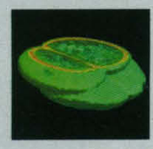

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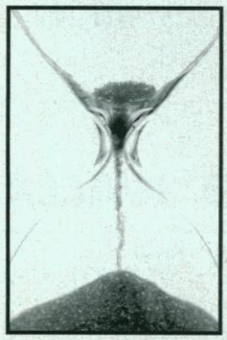

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