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SCIENCE

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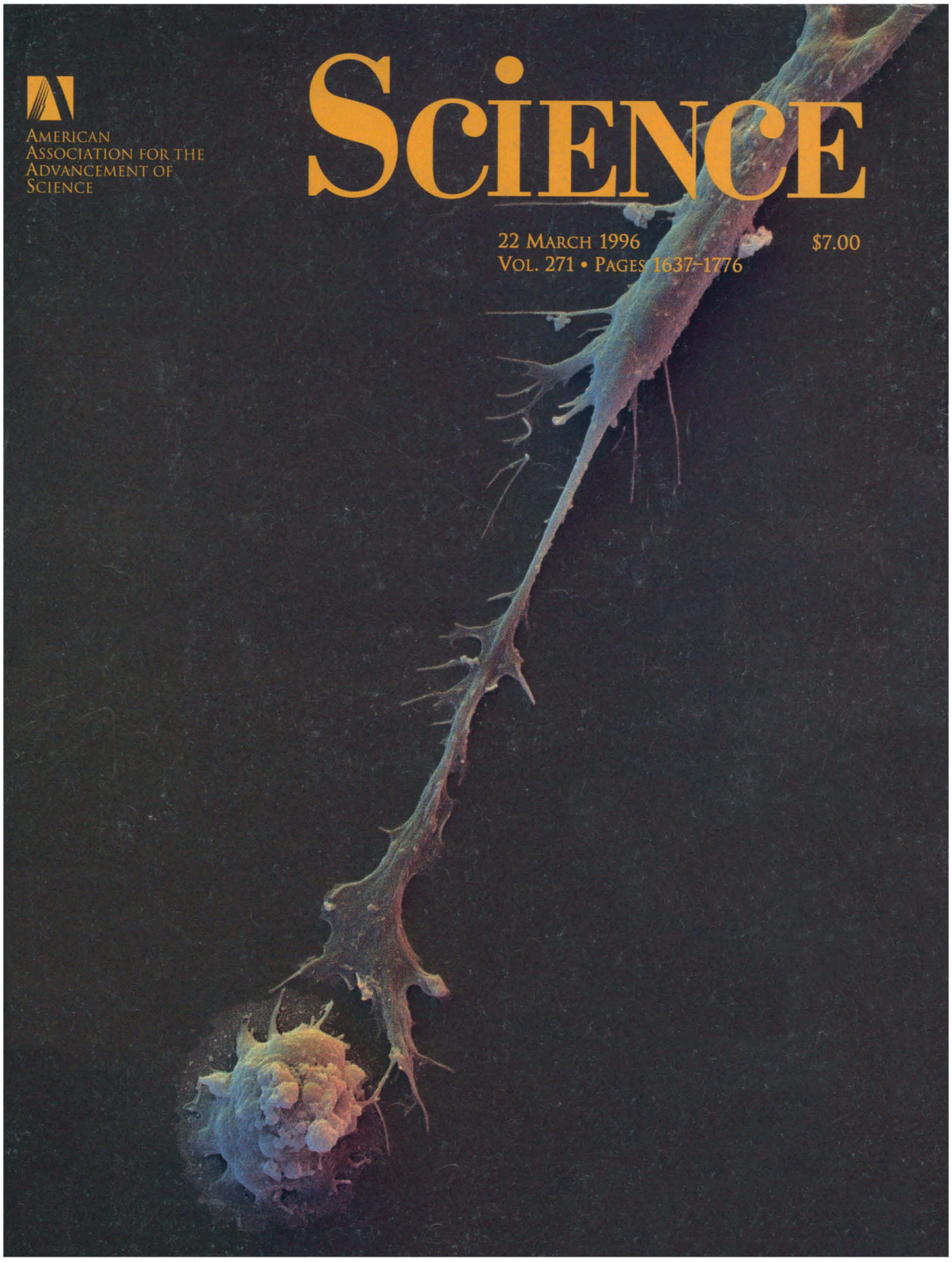

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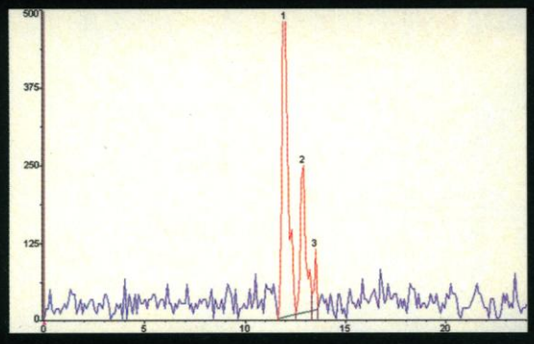

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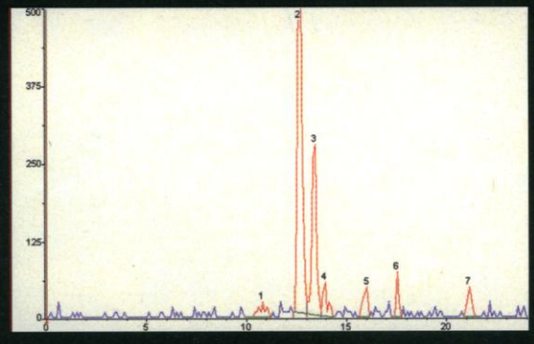

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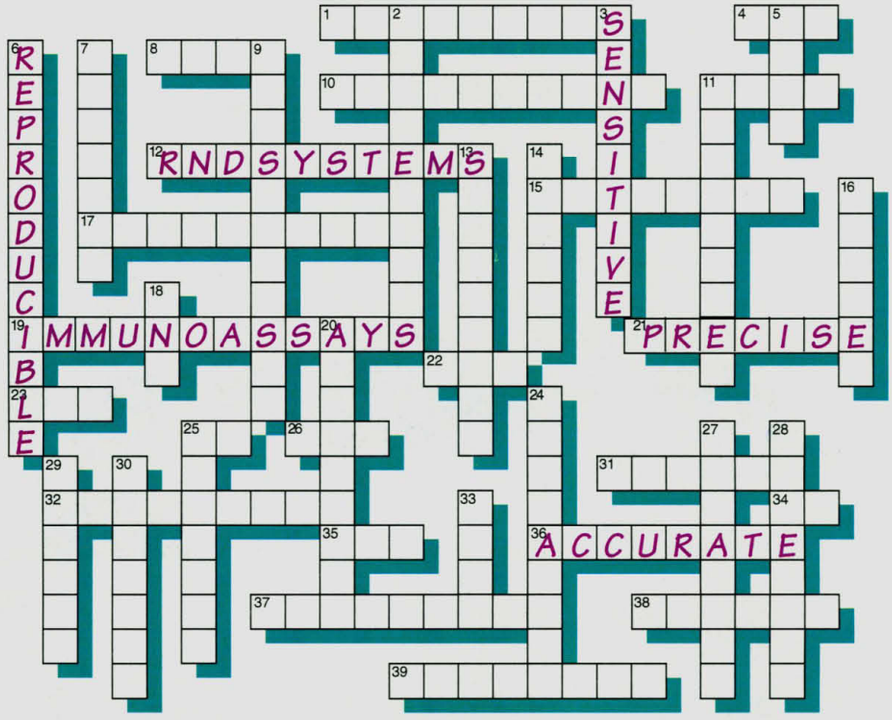

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ACROSS

1 1 of 4 specific families of CAMs
4 Abbrev. for biological response modifiers
8 Abbrev. for human anti-mouse antibody
10 R&D Systems' line of immunoassays for the measurement of cytokines
11 Basic structural and functional unit of all organisms
12 R&D Systems URL - http://www.____.com
15 Glycoprotein substance produced by B lymphoid cells in response to stimulation with an immunogen
17 Proteolytic complex with a mass of about 1,000,000
19 Tests that measure antigen or antibody
21 Successively reproducible within close specified limits
22 Abbrev. for cell-selective protein that promotes adhesion of cells
23 Abbrev. for gram negative endotoxin
25 Site on DNA lacking either purines or pyrimidines
26 Abbrev. for a detection enzyme
31 Obtained from an affinity column
32 "The Ice Man Cometh" for cells
34 Abbrev. for cluster of differentiation
35 Abbrev. for superoxide dismutase
36 In exact conformity to fact
37 Cross-linked molecules
38 Discrete portion of a molecule
39 Region of an antigen that combines with an MHC class II molecule

DOWN

2 Cell migration from the interior of small vessels into tissue spaces
3 A high level of discrimination; with 21 and 36 across, descriptive of Quantikine kits
5 Evidence ignored by Simpson jury
6 Capable of replication
7 An antigenic determinant
9 An end-to-end union or joining together of blood vessels
11 What R&D Systems is your source for
13 Substance acted upon by enzymes
14 The weight of a single hydrogen atom or a member of an outlaw gang
16 Winner who shared 1984 Nobel prize with Milstein
18 Major component of Dawkins' selfish entity
20 A molecule that serves as a homing device
24 Having a single binding site
25 A substance with which an antibody molecule or T cell receptor may bind
27 A defining example
28 Complementary binding site
29 "M" of ECM
30 A specimen of known content used together with an unknown in order that the two may be compared
33 Abbrev. for an anticoagulant that binds divalent cations

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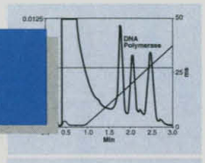

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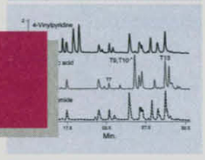

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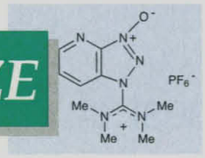

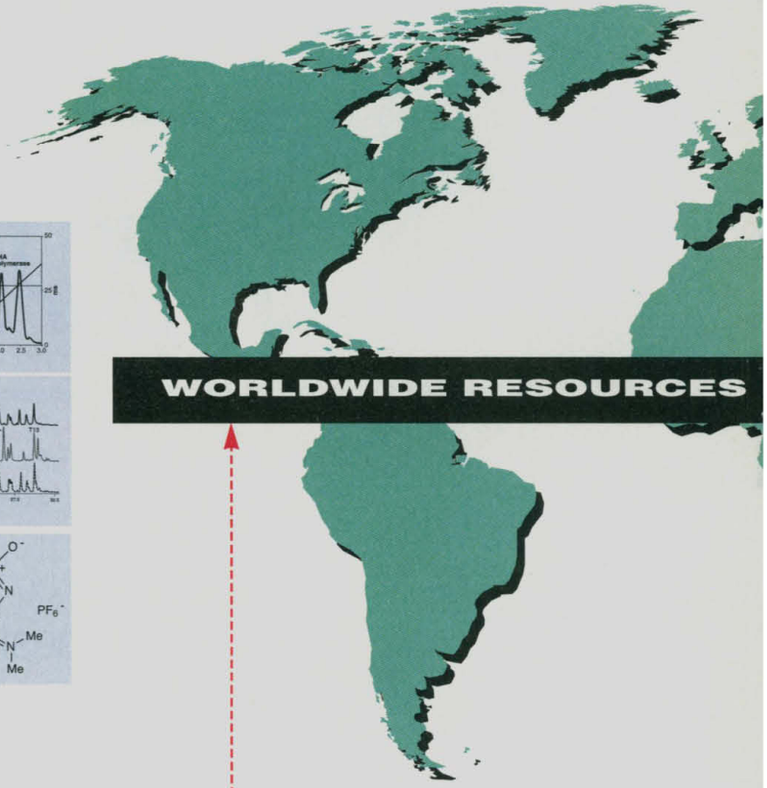

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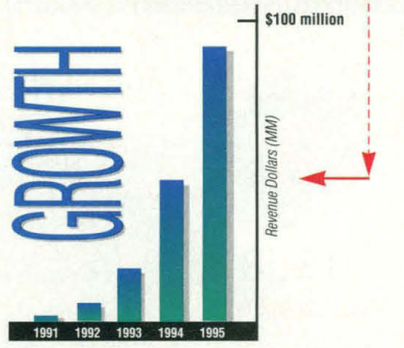

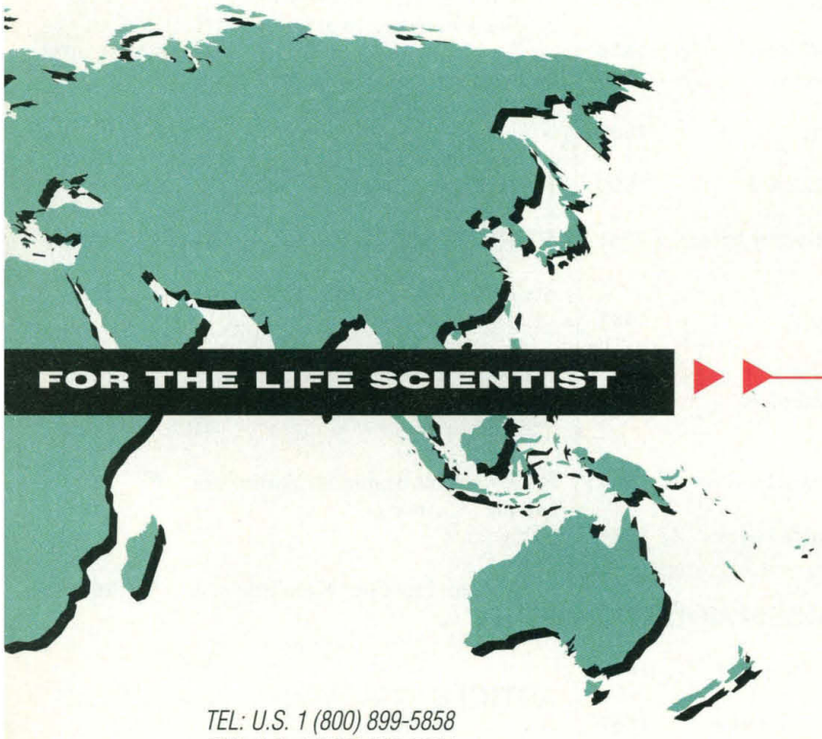

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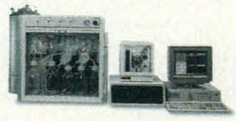

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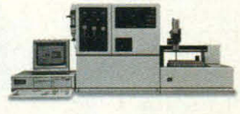

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1658
Don't bank on it

1710
Organized meanders

NEWS & COMMENT

RESEARCH NEWS

PERSPECTIVES

ARTICLE

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COVER

Dendritic cells and T cells interact to initiate an immune response. The scanning electron microscope image shows a male dendritic cell embracing a helper T cell (lower cell, ~7 μm in diameter) that recognizes the male antigen H-Y. These same dendritic cells were used to show that a newborn mouse has a competent immune system. See page 1723 and related Reports (pages 1726 and 1728) and News story (page 1665). [Cells cultured by J. P. Ridge. Image: D. Scharf, using the S.E.M. Wideband Multi-Detector Color Synthesizer]

RESEARCH ARTICLE

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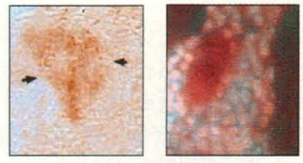

1671, 1736, & 1740

Setting the circadian clock

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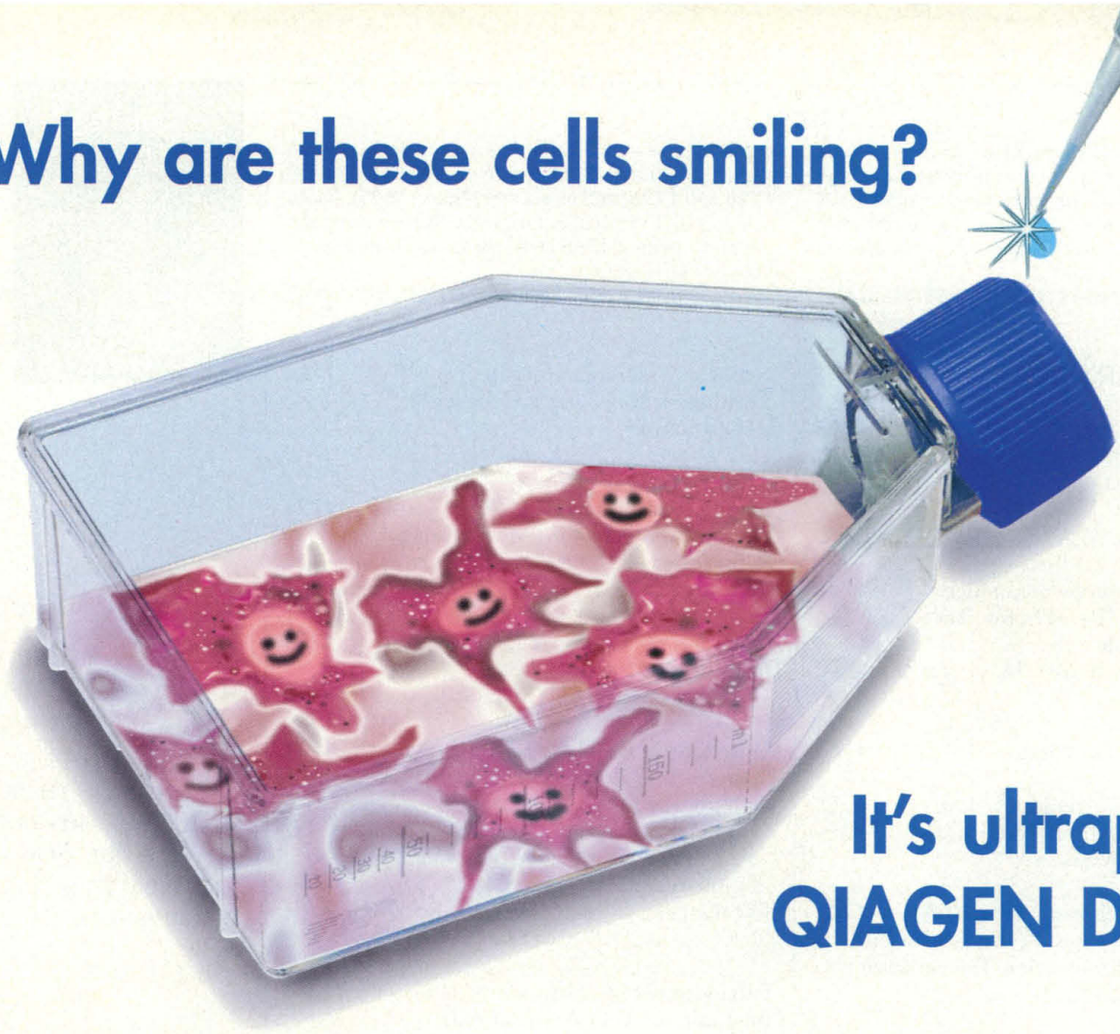

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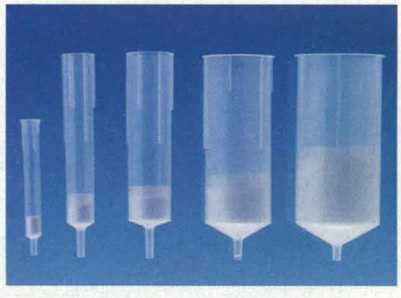

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edited by PHIL SZUROMI

In a shape of flux

Aromatic organic cations play an important role in organic chemistry, but the shape of the benzene cation, $C_6H_6^+$, has been unresolved despite numerous theoretical and experimental studies. Electronic degeneracy of the cation should lead to Jahn-Teller distortions that would normally lower the symmetry of the ground state. Lindner *et al.* (p. 1698) studied the rotational and vibrational structure of $C_6H_6^+$ in zero-kinetic-energy threshold photoionization experiments. They conclude that $C_6H_6^+$ is fluxional—its distorted isomers easily interconvert through pseudorotation, and the molecule essentially retains D_{6h} symmetry.

Keeps meandering along

The meander patterns of streams and rivers, from a small stream to a large river such as the Mississippi, appear to be similar. By using simulations of a freely meandering river and comparison with natural rivers, Stolum (p. 1710) suggests that planforms of meandering rivers may oscillate between two states. In one, the meander pattern is ordered and sinuosity is low, in the other it is chaotic. Both can occur on the same river. Clusters of migrating cutoffs induce transitions between these two states.

Singles and doubles

Recent advances in molecular detection and manipulation have led to the development of single-molecule spectroscopic and microscopic techniques that can provide detailed information about local chemical environments. In these techniques, absorption of a single photon leads to a transition from the ground to the excited state. Plakhotnik *et al.* (p. 1703) now show that simultaneous two-photon absorption on the single-molecule level is possible. This nonlinear optical interaction should open the way to nonlinear single-molecule scanning microscopy.

Young but not necessarily tolerant

Neonatal animals show much less of an immune response when challenged by antigens than do adults. Three reports indicate that neonatal T cells are not more easily tolerized by antigens than are adult T cells but generate responses that may have been mistaken for tolerance (see the news story by Pennisi, p. 1665). Ridge *et al.* (p. 1723; see cover) show that challenge of newborn T cells with nonself spleen cells also exposes the T cells to inappropriate antigen-presenting cells (APCs) that lead to a tolerizing response; exposure to professional APCs, however, leads to their activation. Sarzotti *et al.* (p. 1726) show that for a viral antigen, low doses lead to a cytotoxic T lymphocyte response but that high doses lead to a nonprotective type 2 cytokine response. Forsthuber *et al.* (p. 1728) show that the response to a foreign protein in mice (hen egg lysozyme) is not tolerization but a T helper 2 response.

Epilepsy gene

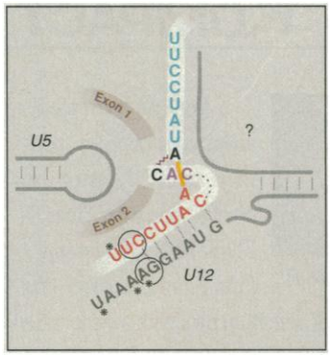
Mutations in a gene on chromosome 21 have been linked to progressive myoclonus epilepsy (Unverricht-Lundborg type, or EPM1). Pennacchio *et al.* (p. 1731; see the news story by O'Brien, p. 1672) found mutations in the gene encoding cystatin B, a protease, in cells from affected patients. These occurred at a 3′ splice site and a stop codon site and were associated with decreased levels of messenger RNA expression.

Tumor immunotherapy

T cell activation depends on the outcome of competing stimulatory and inhibitory signals, and Leach *et al.* (p. 1734; see the Perspective by Pardoll, p. 1691) have used such signaling to develop a new approach to enhancing the immune response to tumors. They blocked the inhibitory signals with an antibody to the appropriate T cell–surface receptor, named CTLA-4. Mice with established tumors, which were fatal if left untreated, mounted strong antitumor responses when treated with the antibody to CTLA-4. These responses were sufficient to clear tumors and to induce immunity to rechallenge.

Mending your RNAs

Most pre–messenger RNA introns begin with the dinucleotide GU and end with the dinucleotide AG. Recently, a minor class of introns beginning with the dinucleotide AU and ending with AC has been recognized. Because splicing of introns requires pairing between the intron and small nuclear RNAs (snRNAs), it was proposed that splicing of the minor intron class would involve different snRNAs than does splicing of the major class. Hall and Padgett (p. 1716; see the Perspective by Mount, p. 1690) have now found that the U12 snRNA, of previously unknown function, is required to splice the minor class.



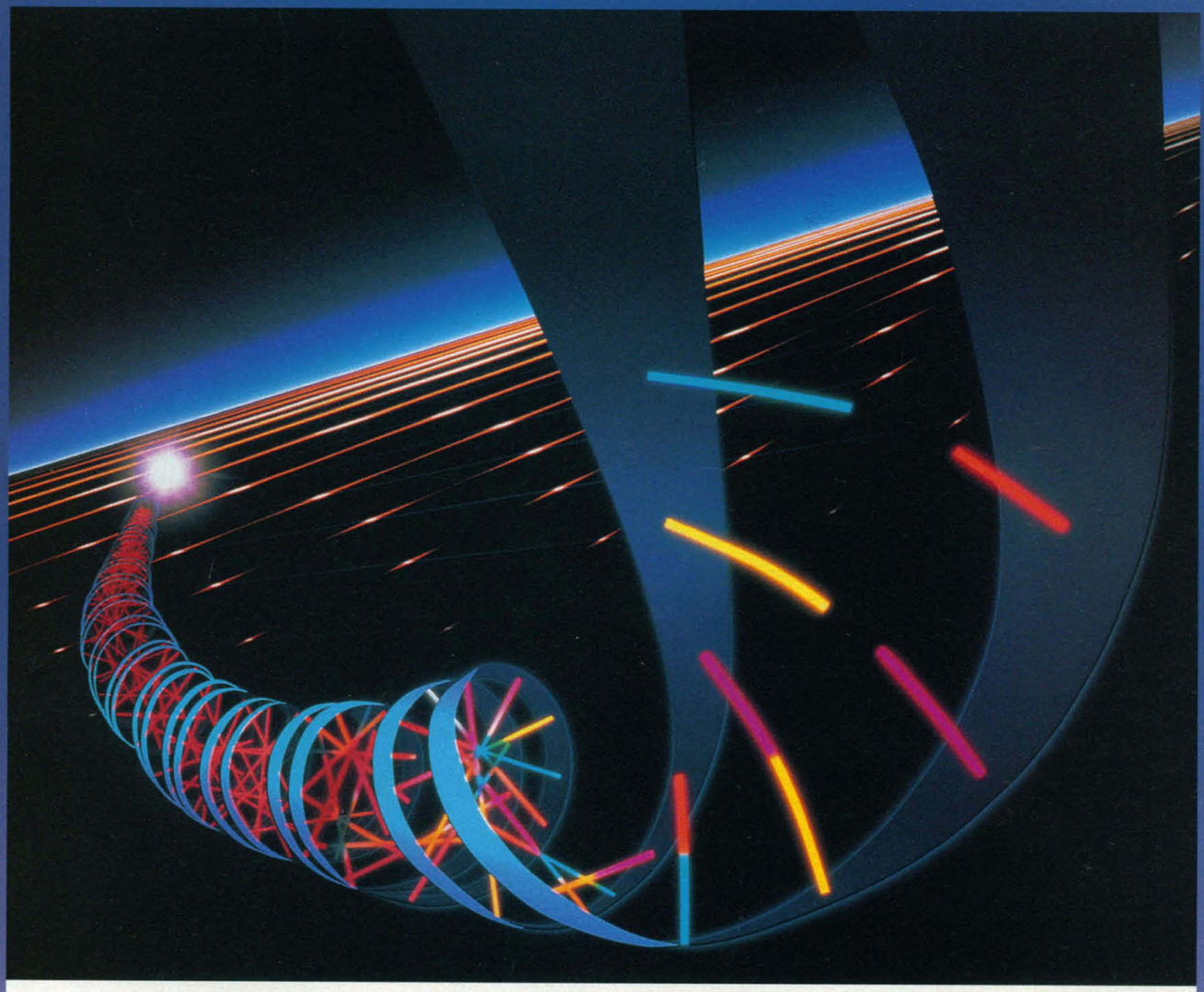
Resetting the clock

In *Drosophila*, the products of the *period* (*per*) and *timeless* (*tim*) genes form the core of the circadian clock. Two reports show how light interacts with this system to reset the clock, a process necessary for keeping organisms in tune with their environment (see the news story by Barinaga, p. 1671). Myers *et al.* (p. 1736) and Lee *et al.* (p. 1740) found that light causes a rapid degradation of the TIM protein, which disrupts the PER-TIM complex and advances or delays the circadian clock.

Centrosome surplus

Centrosomes are major microtubule-organizing centers in eukaryotic cells and play an important role in mitotic fidelity by ensuring balanced chromosome segregation. Centrosomes normally duplicate once per cell cycle. Fukasawa *et al.* (p. 1744) show that cells deficient in the tumor suppressor protein p53 accumulate multiple copies of functional centrosomes, which results in unequal segregation of the chromosomes. This finding suggests that p53 may help maintain genomic stability through regulation of centrosome duplication.

SHIMADZU



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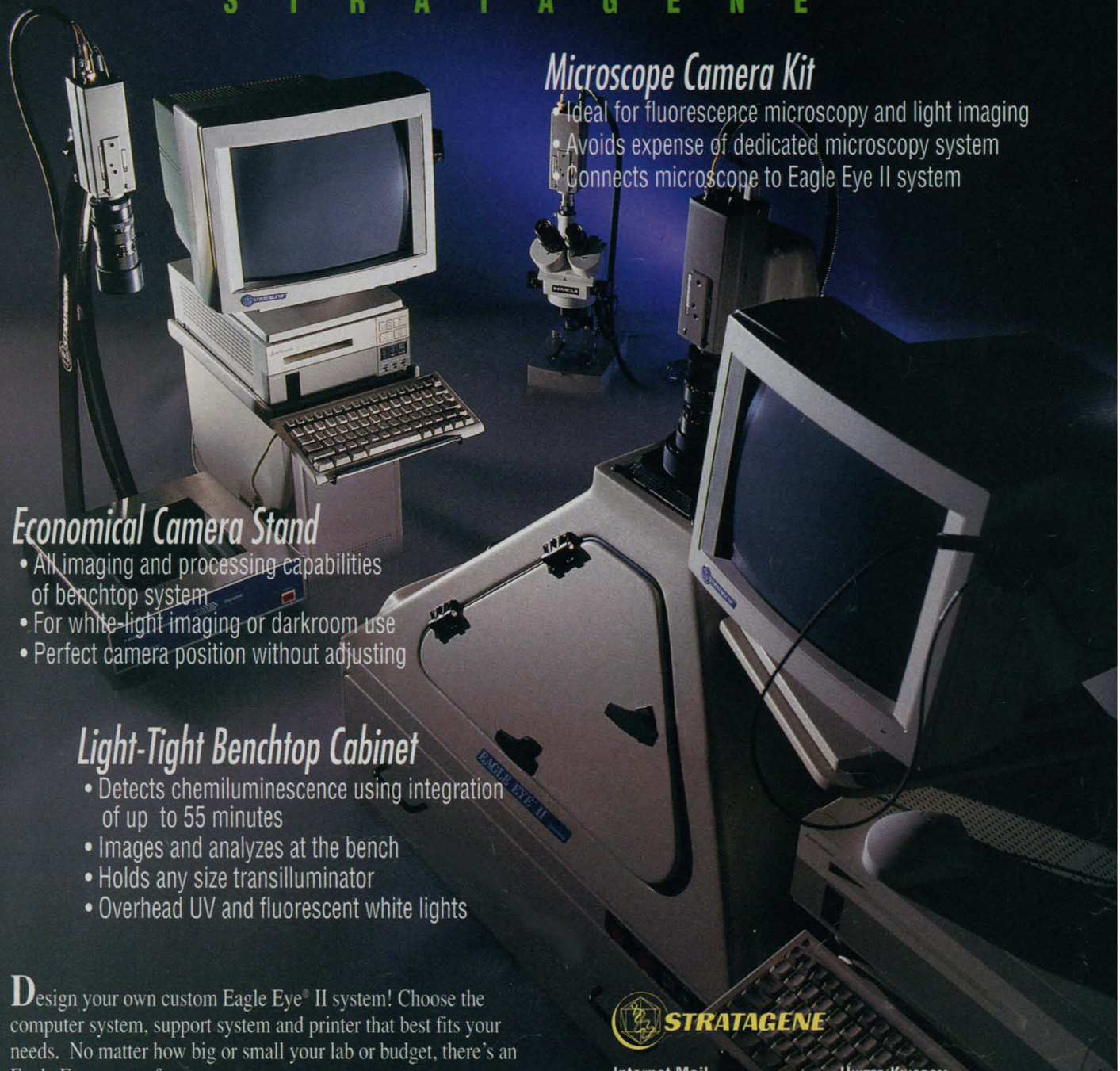

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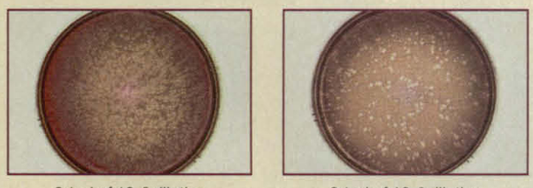

0.1ml of 10^{-5} dilution
Plaques: Too numerous to count

0.1ml of 10^{-6} dilution
Plaques: $>2.5 \times 10^9$ pfu/ml

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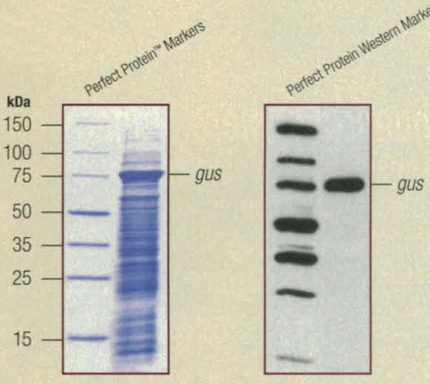

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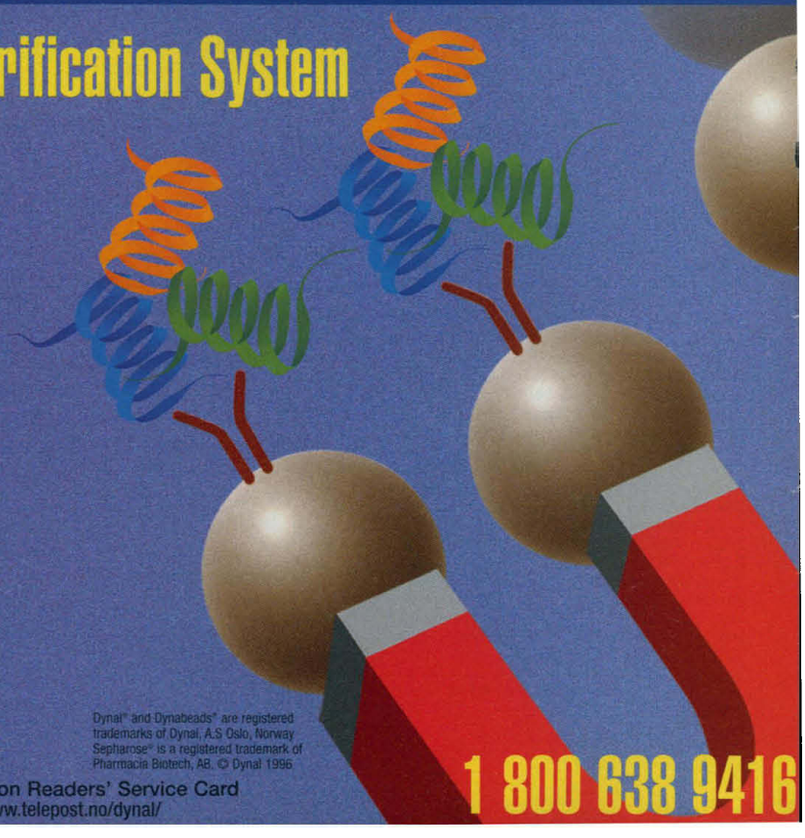

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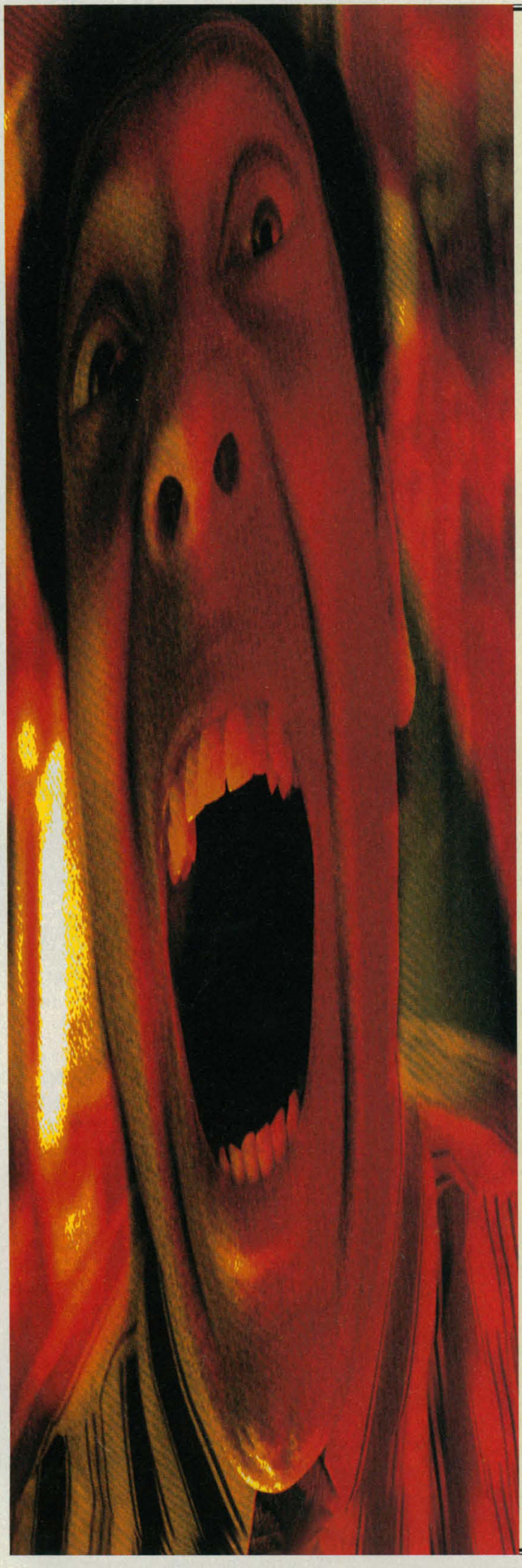

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1. Bernard, P. *et al.* (1994) *Gene* **148**: 71-74.

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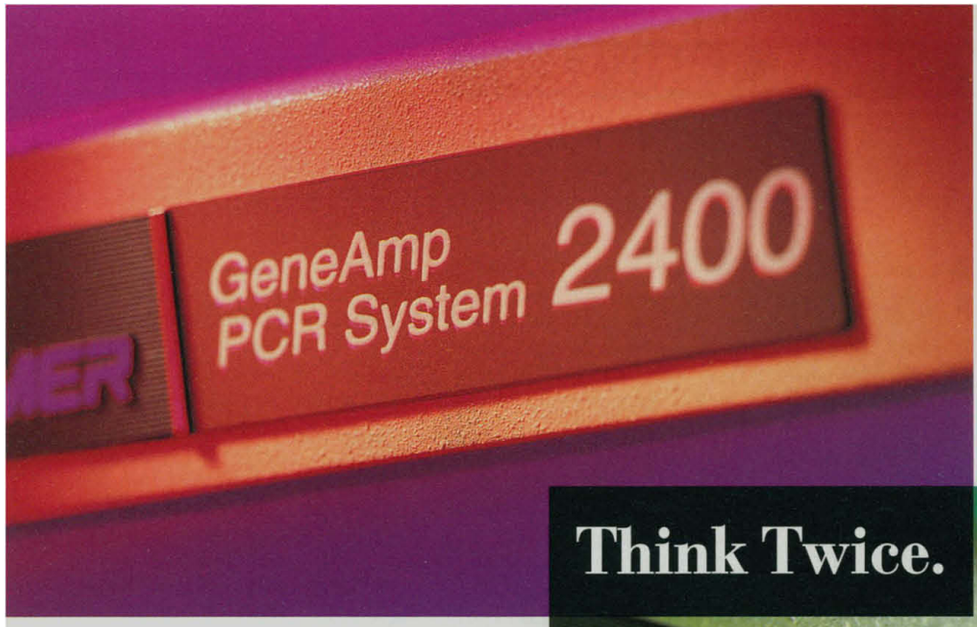

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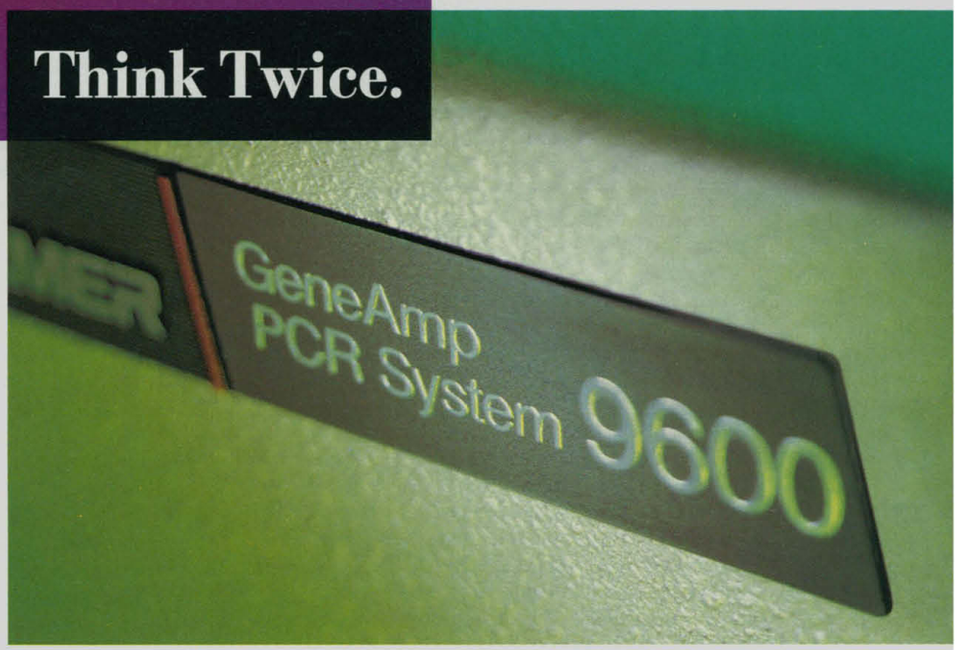

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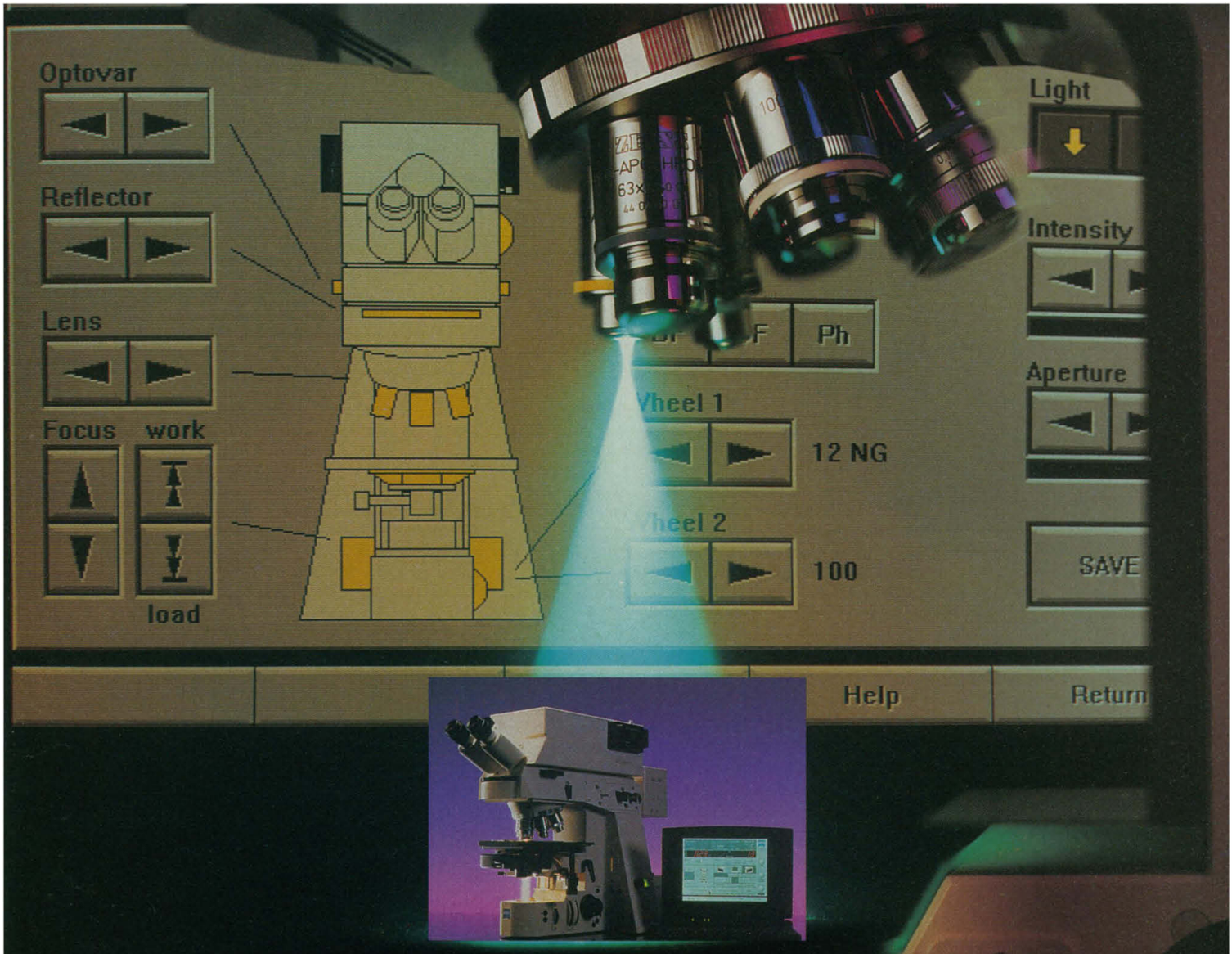

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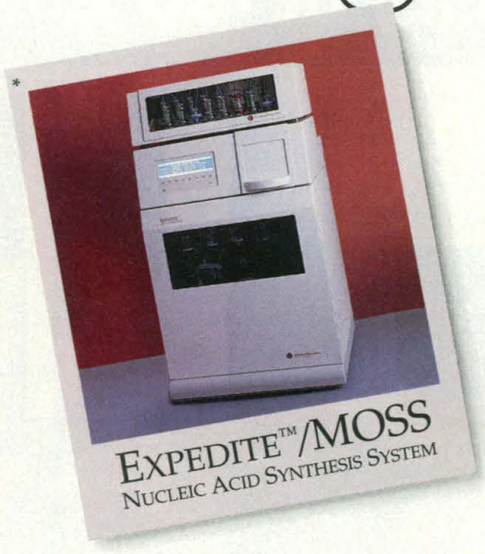

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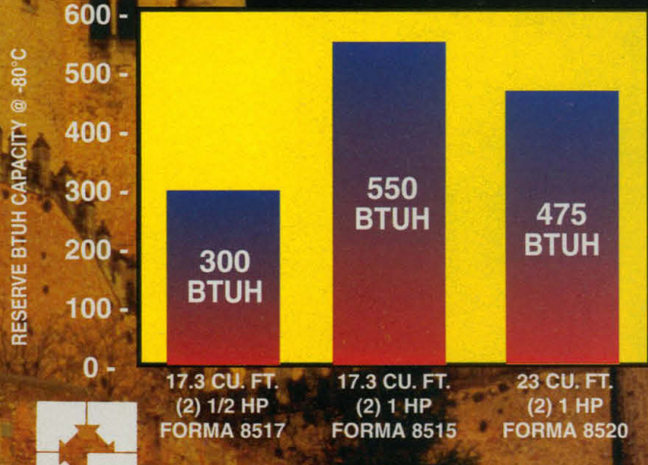

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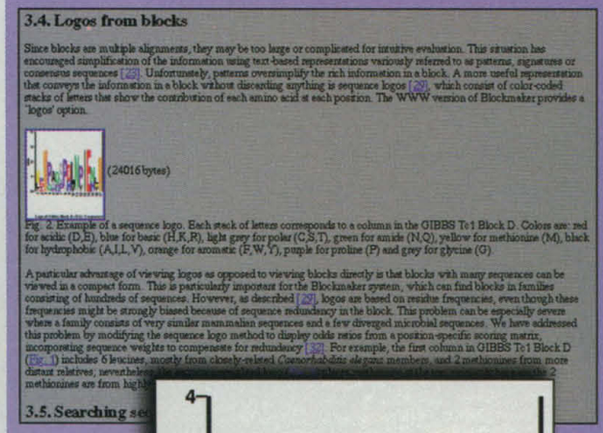

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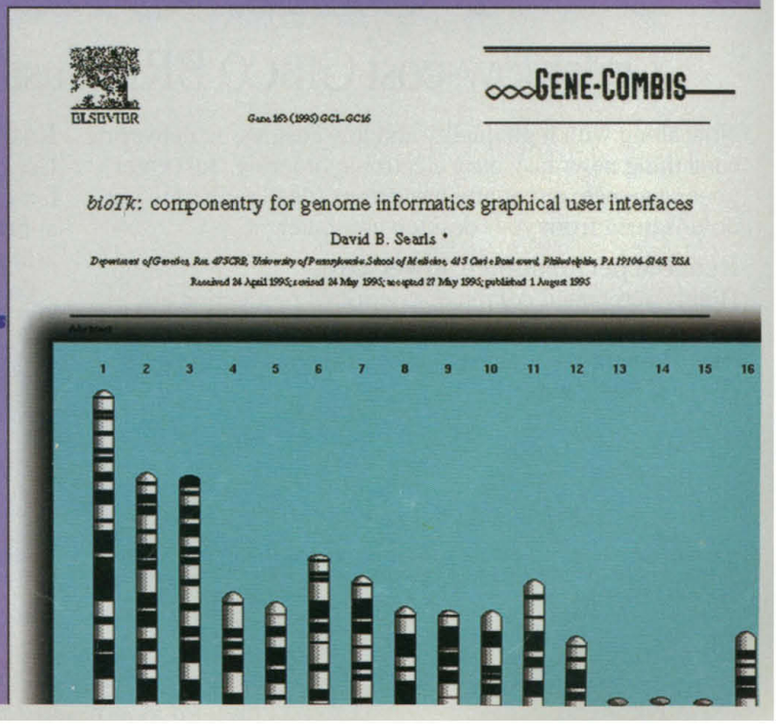

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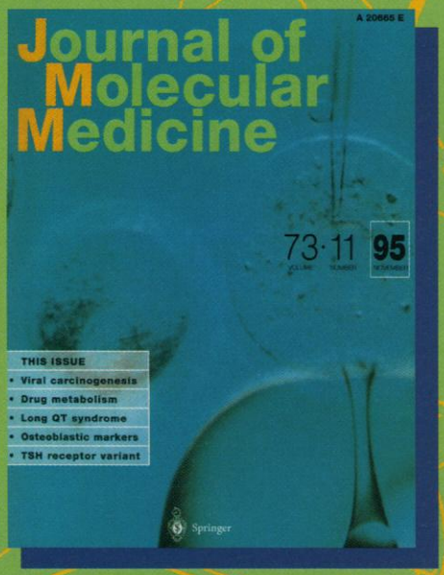

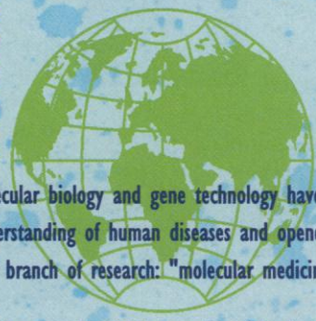

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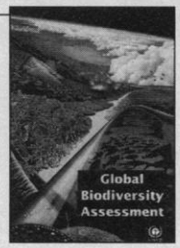

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Enrico Di Cera

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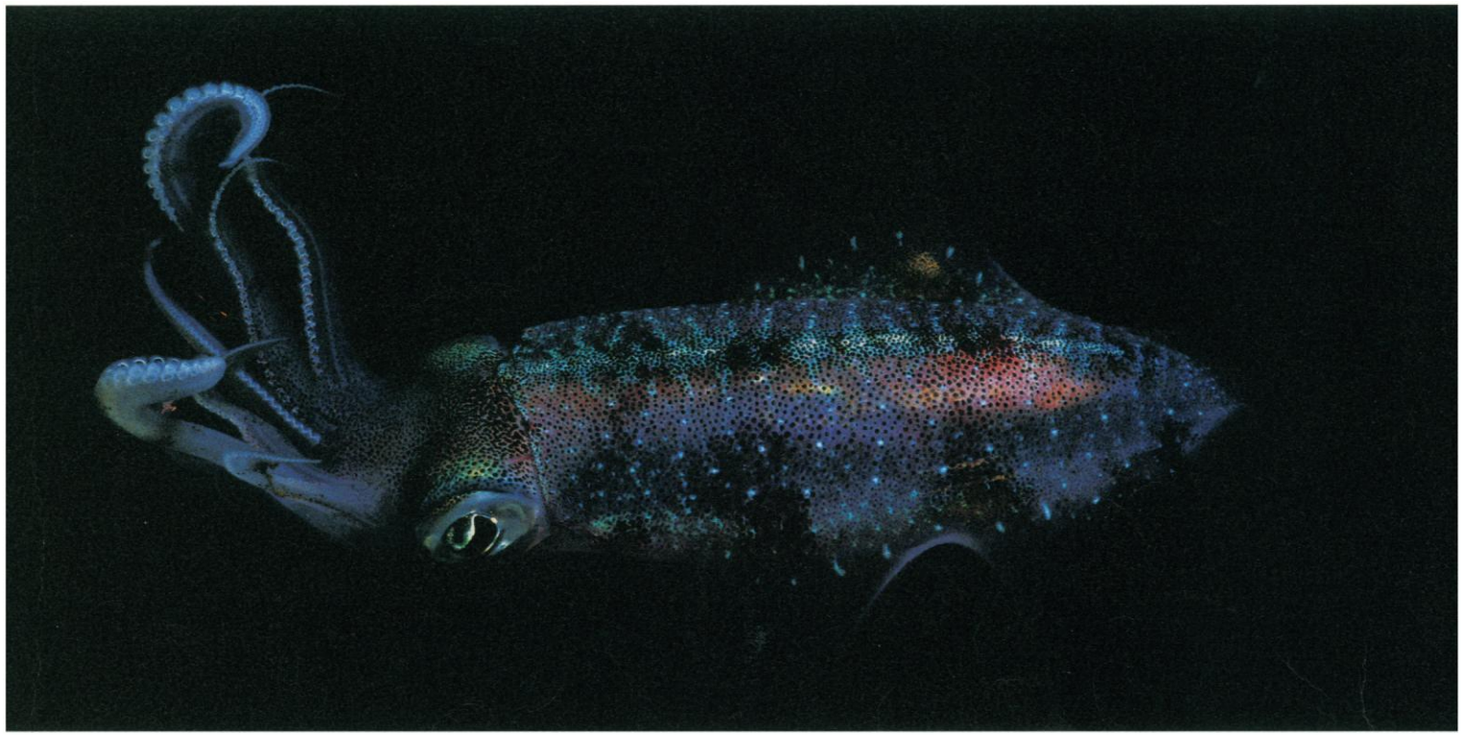

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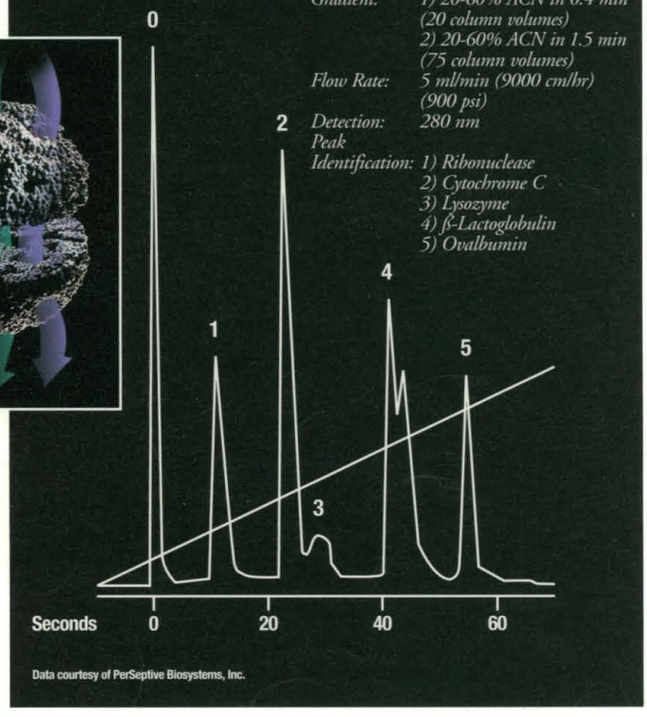
60 second/75 column volume gradient



Column: *POROS R2/M (2.1 mmD/30 mmL) (0.1 ml column volume)*
Eluent: *0.1% TAFA/ACN*
Gradient: *1) 20-60% ACN in 0.4 min (20 column volumes) 2) 20-60% ACN in 1.5 min (75 column volumes)*
Flow Rate: *5 ml/min (9000 cm/hr) (900 psi)*
Detection: *280 nm*
Peak Identification: *1) Ribonuclease 2) Cytochrome C 3) Lysozyme 4) ß-Lactoglobulin 5) Ovalbumin*

Data courtesy of PerSeptive Biosystems, Inc.

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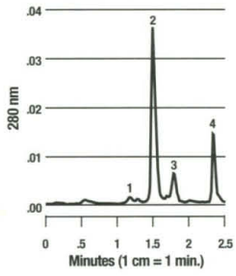
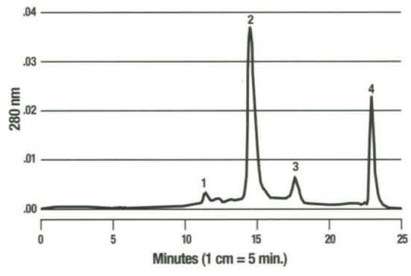


Column: *POROS HQ/H column 4.6 x 50 mm*
Sample Volume: *100 µl*
Flow Rate: *3060 cm/hr (8.5 ml/min)*
Buffer A: *20 mM Tris/bis-Tris propane, pH 7.0*
Buffer B: *20 mM Tris/bis-Tris propane, 500 mM NaCl, pH 7.0*
Gradient: *0-40% B in 11 column volumes, 40-100% B in 4 column volumes*
Peak Identification: *1) Transferrin 2) Anti-TSH 3) Anti-IgE 4) ß-Galactosidase*

Column from Leading Competitor
Strong Anion Exchange



Column: *Competitor 5 mm x 50 mm*
Sample Volume: *100 µl*
Flow Rate: *306 cm/hr (1 ml/min)*
Buffer A: *20 mM Tris/bis-Tris propane, pH 7.0*
Buffer B: *20 mM Tris/bis-Tris propane, 500 mM NaCl, pH 7.0*
Gradient: *0-40% B in 11 column volumes, 40-100% B in 4 column volumes*
Peak Identification: *1) Transferrin 2) Anti-TSH 3) Anti-IgE 4) ß-Galactosidase*

Data generated by Boehringer Mannheim.

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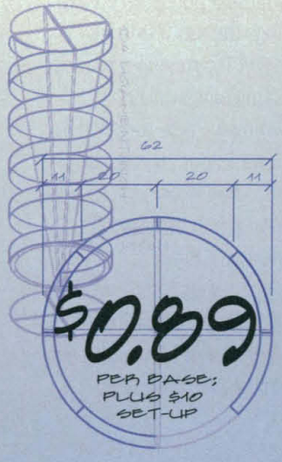

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Chances are
we've helped your business.
(Even if you've never owned a Macintosh.)

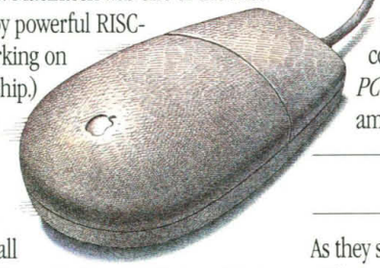
Back in 1984, a young company named Apple Computer did a rather remarkable thing. It introduced a new way of computing. A new way of getting things done.

A new way named Macintosh.®

Sure, personal computers had been around for a while. But never before had one computer so completely, so instantly, changed the landscape of the possible.

Making the extraordinary ordinary.

In the 12 years since, Apple® innovations have continued to redefine what people can do with a personal computer. They've also found their way into some of our competitors' PCs and operating systems. For example, the plug-and-play technology we brought to market in 1987 is just now becoming a reality for other PC makers. Macintosh was one of the first affordable desktop computers to employ powerful RISC-based microprocessors. (We're now working on the fourth-generation PowerPC™ RISC chip.) And we're still the only company in the world making a computer that runs both the Mac™ OS and Windows.*



More than a few of the things that seem standard on a personal computer today were pioneered by Apple.

As a result of these Apple innovations, ordinary people can sit down at all kinds of PCs and actually get some work done. Of course, if they sit down at a Macintosh, they can build 3-D graphics. Use virtual reality in very real ways. Videoconference across continents. Collaborate with colleagues on the far side of the corporate campus. Build interactive sites on the World Wide Web. And more. That's the Mac advantage.

People do know the difference.

Today, 56 million people do their work the Macintosh way. Some in school. Some at home. And, when you look at the numbers from recent studies, quite a few in business. We command a 47% share of the U.S. commercial publishing market. And 76.2% of the color pre-press market. And though our dominance in graphics-related businesses may not shock you, consider this: we have a 50% share of the chemical, pharmaceutical, biotechnology, scientific and engineering computing markets.

And then, there's the fact that Macintosh brand loyalty is the highest of any PC in the world: 90% of Macintosh customers buy a Mac the next time around. Which leads people like Andrew Laham, MIS Director at the law firm Fleming, Hovenkamp & Grayson, to say, **"***There would be a major crisis if we had to do without Macs. In fact, there would be an open revolt.***"** Indeed, if the mail we've received lately is any indication, more than a few CFOs out there would revolt, too, if their companies didn't use Macintosh computers.

"NASA saved $800,000 a year on maintenance alone when we replaced their legacy system with a Macintosh system," says Steve Monteith, a member of the Research Triangle Institute TechTracS Team.

And if you replace a Windows system with a Mac? According to a recent study by the Gartner Group, you'll save 25% on support costs. And there's more. *PC World* magazine—that's right, we said *PC World*—ranked Apple as one of the best for reliability and service among all makers of personal computers.

See the future. Turn on a Mac.

As they say, you can't simply rest on your laurels. So what's next? Let's start with Copland, our upcoming operating system.** Copland won't just change the look of the Macintosh desktop; it will incorporate an entirely new technology called OpenDoc® that will change the way you think about computers. (Sound like hype? Check out *InfoWorld*—they named OpenDoc the winner of the 1995 Landmark Technology Award.)

And then there are the 53 new software patents we were awarded in 1995, patents on everything from wireless communication, power management and manufacturing systems to data encoding, data compression and encryption. That's more than enough innovation to bring another generation, or three, of intelligent business tools to market.

The kinds of tools that keep your productivity up. Your costs down. The kinds of tools that keep your people motivated to push the limits. To challenge the unknown. To discover the unexpected. And bring it to market. You know, the same things we keep doing with Macintosh. Year after year.

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