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150 YEARS • 1848-1998

# SCIENCE

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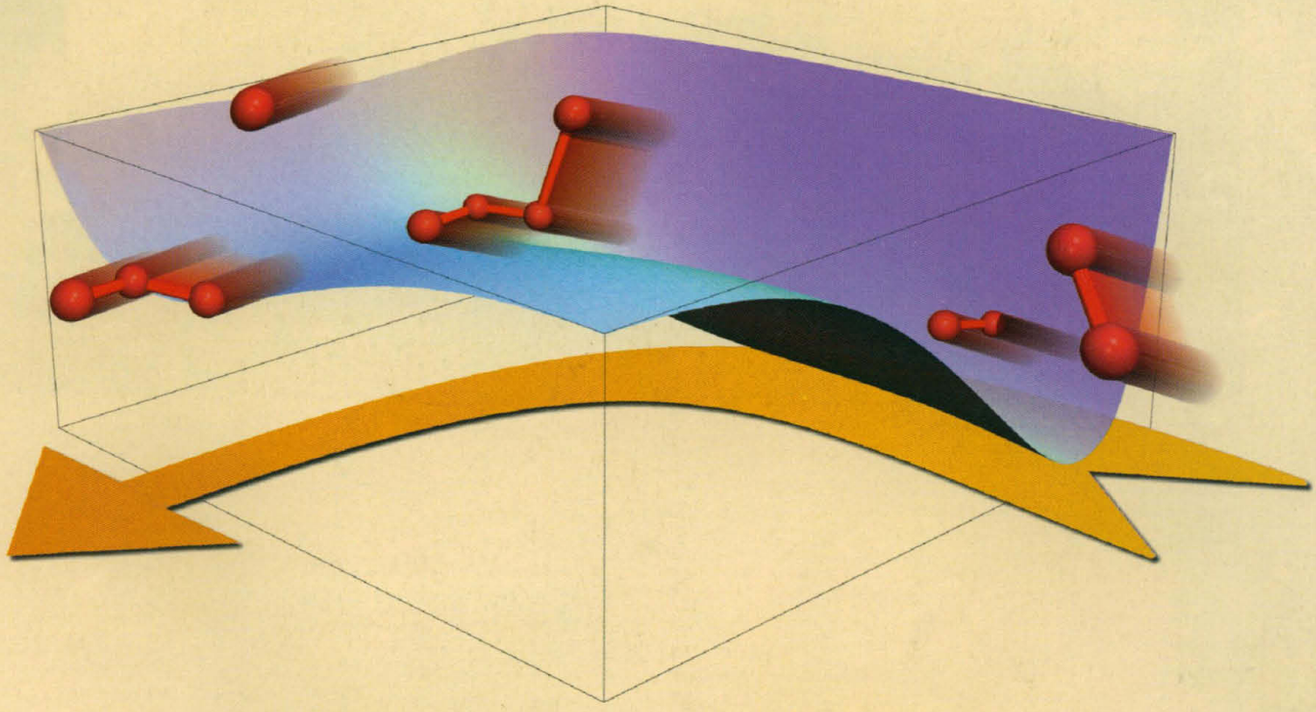

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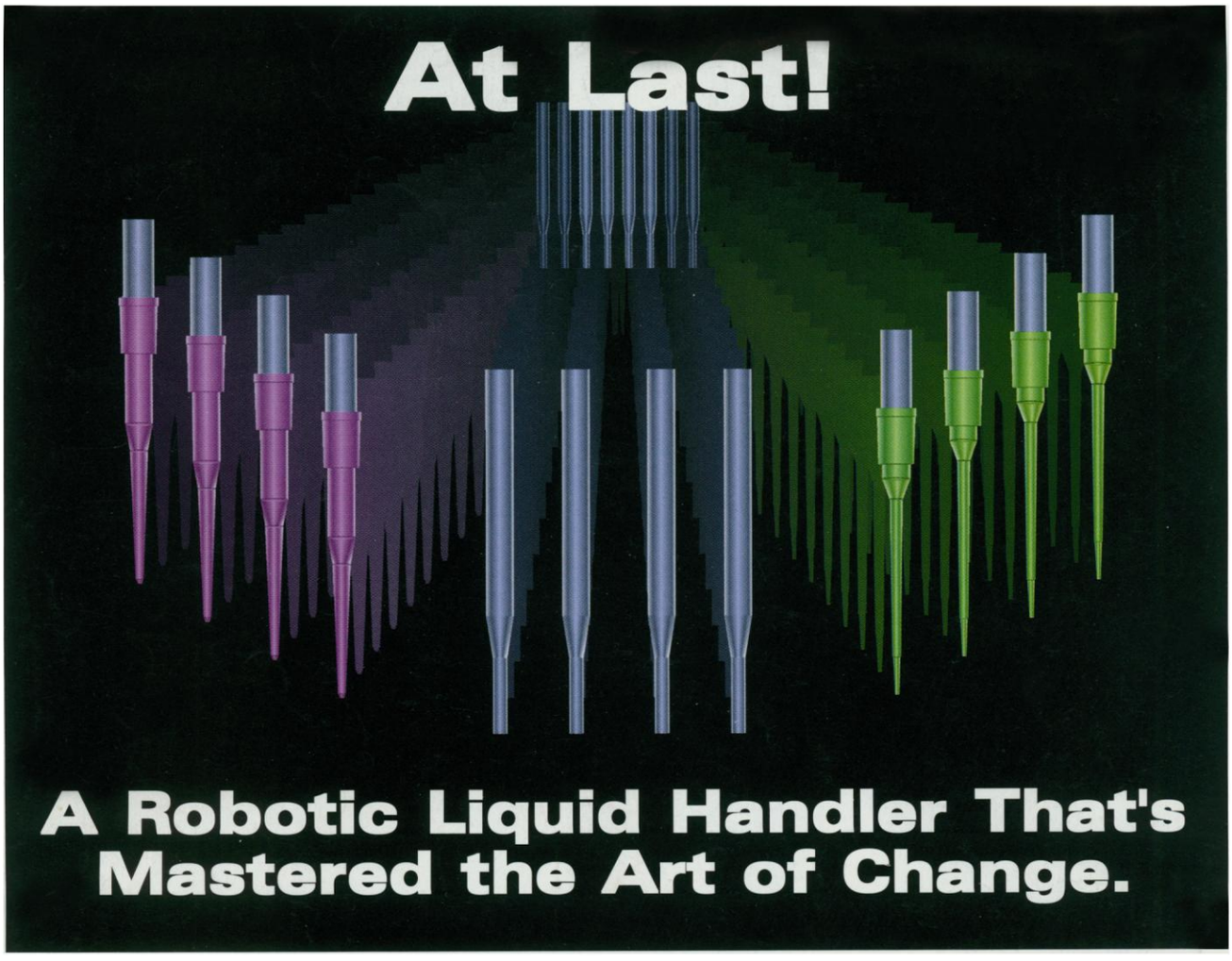


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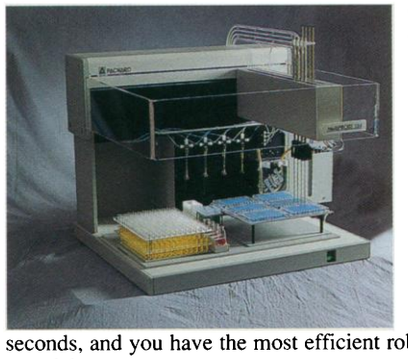

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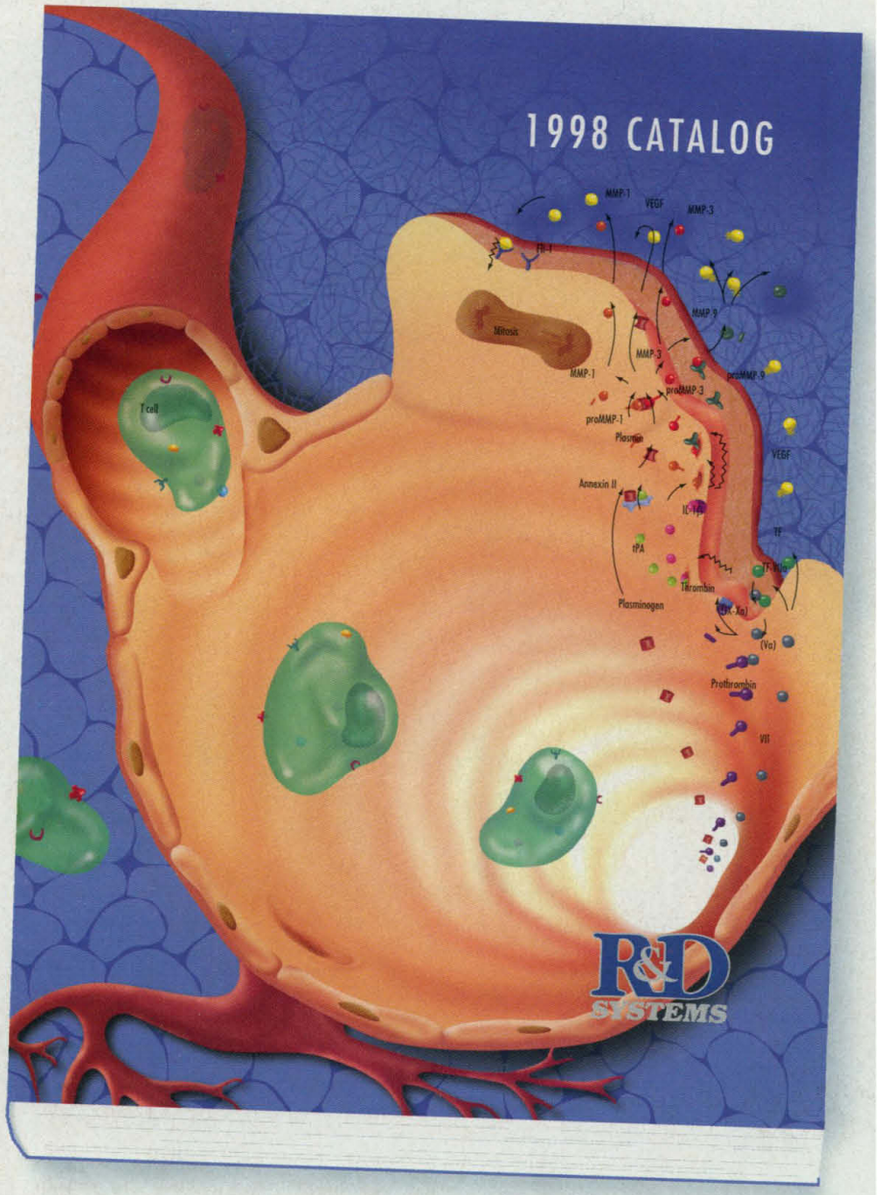


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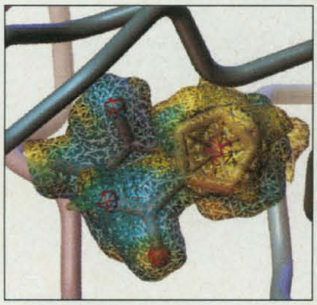
**1851 & 1915**
**Bird beginnings**



**1934**
**Insights into antibody catalysis**

## NEWS & COMMENT



## RESEARCH NEWS



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### Books and New Media



### Research



## ARTICLES

### REACTION DYNAMICS



## DEPARTMENTS





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COVER

Calculated potential energy surface for the chemical reaction $O_2 + O_2 \rightarrow O_3 + O$. This reaction is only possible if a reactant oxygen molecule has at least 25 quanta of vibrational energy. See the special section on reaction dynamics beginning on page 1875 as well as the Editorial (page 1831), News story (page 1847), and related Reports (pages 1913 and 1946). [Image: D. Lauvergnat, D. M. Benoit, D. C. Clary, University College London]




## RESEARCH ARTICLE



## REPORTS



## TECHNICAL COMMENTS



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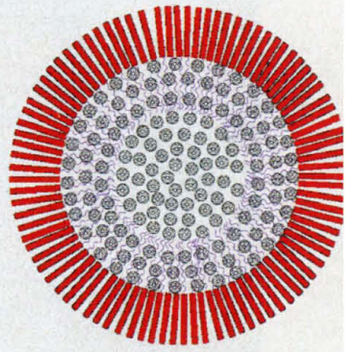
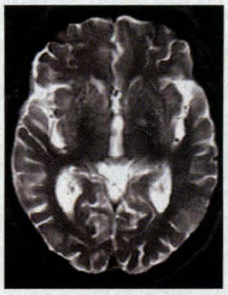
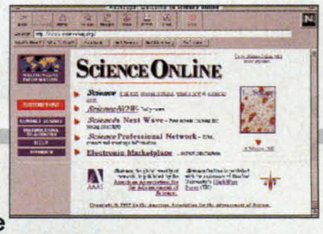


**1903**
**Polymer solutions to fullerene insolubility**



**1965**
**Tech.sight: Better brain viewing**

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edited by PHIL SZUROMI

## An early bird

The origin of birds remains uncertain; one leading hypothesis is that birds evolved from theropod dinosaurs. Forster *et al.* (p. 1915; see the news story by Gibbons, p. 1851) describe a fossil of a small bird, about the size of a raven, recovered from Late Cretaceous rocks in Madagascar. The specimen seems to have a mixture of features that are found in primitive birds and in theropod dinosaurs, including notably an enlarged sickle-shaped claw on one digit of the foot.

■

## Solvating fullerenes with polymers

Copolymers that consist of rigid rods joined to flexible coils are known to exhibit several unusual morphologies because of the different phase behavior of the two blocks. Jenekhe and Chen (p. 1903) show that poly(phenylquinoline)-block-polystyrene copolymers can form very large aggregates in solution up to 10 micrometers in diameter that have large internal cavities. These cavities can encapsulate fullerenes such as $C_{60}$ and $C_{70}$ and thus solubilize them in otherwise poor solvents.

■

## Spinning on surfaces

Molecules generally have specific positions on a surface at which the energy is lowest, and these will be their preferred binding site. If sufficient energy is introduced into the molecules, they may begin to move, for example by rotating or by moving to another nearby surface site. Stipe *et al.* (p. 1907) have used scanning tunneling microscopy to study the energy barrier to rotation of oxygen molecules on platinum surfaces by determining the rotation rate from a large number of rotation events. Insights into the coupling between electrons and nuclear motions were gained.

## Logical development

During an organism's development, gene expression rates are modulated by a complex regulatory network of DNA sequences and binding proteins in the promotor region of the gene. These regulatory elements can be organized into distinct modules, but their organization and interaction, which determine the form and function of the organism, is often unclear. Yuh *et al.* (p. 1896; see the commentary by Wray, p. 1871) performed several experiments to resolve the control of expression of a gene, *Endo16*, in the sea urchin during its development. The proximal element, module A, appears to control and integrate the effects of the other six modules. A computational model shows that the regulation can be thought of as an analog computer system in which all of the inputs to the system are regulated by this proximal element.

## Hydrogen ions in space

The reactions of the $H_3^+$ ion in space are considered to be a fundamental and efficient contributor to the production of neutral atoms and molecules. Recently, $H_3^+$ was observed in dense molecular clouds, which confirmed its abundance and importance in interstellar chemistry. McCall *et al.* (p. 1910) have now observed $H_3^+$ in the diffuse interstellar medium (ISM) toward the star Cygnus OB2 No. 12, indicating that $H_3^+$ is probably present everywhere in interstellar space. The identification of $H_3^+$ allows astronomers to estimate the physical and chemical properties of the diffuse and dense ISM. Based on their observations, the ISM between Earth and Cygnus OB2 No. 12 contains several diffuse clouds; these clouds are at about 27 Kelvin, and the $H_3^+$ present is in equilibrium with $H_2$.

■

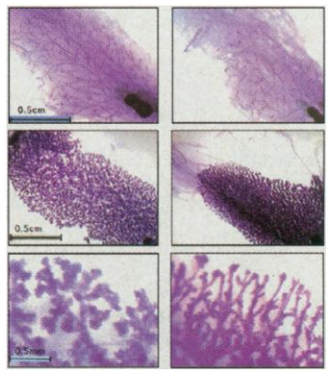
## Cave dating

The formation of caves typically reflects the interaction of geology, climate, and hydrology, but dating their formation has been difficult. Polyak *et al.* (p. 1919; see the commentary by Sasowsky, p. 1874) obtained argon-40–argon-39 dates on the formation of Carlsbad Caverns and related caves in the southern United States from alunite, a potassium-bearing mineral that formed in the alteration of clay minerals in the cave walls. The dates indicate that the caves formed from 11 to 4 million years ago, much earlier than was previously thought, and that caves at higher elevations formed first as the region was uplifted tectonically.

■

## Steroid hormone partner

To study the biological role of steroid receptor coactivator–1 (SRC-1), Xu *et al* (p. 1922) prepared mice in which the *SRC-1* gene was inactivated. When bound to their ligands, receptors for steroid hormones (such as the sex steroids that regulate sexual behavior and reproductive function) activate transcription of specific genes by forming active complexes with coactivators and



general transcription factors. The mice lacking the coactivator SRC-1 had no obvious phenotype. However, when endogenous steroids were removed by ablation of the appropriate gland, the mice showed resistance to the effects of administered progesterone, estrogen, or testosterone. Although loss of SRC-1 may be partly compensated by increased expression of the related protein TIF2, the results indicate that SRC-1 is required for full biological actions of steroid hormones in vivo.

■

## Folding clues to RNA structure

To fully understand protein or RNA function, it is necessary to elucidate the structure of these molecules. Two reports discuss how the structure of the *Tetrahymena* group I intron, a large catalytic RNA (ribozyme), can be determined by examining the RNA folding mechanism. Sclavi *et al.* (p. 1940) used synchrotron x-ray beams to conduct rapid time scale (10 milliseconds) hydroxyl footprinting to map the hierarchical folding pathway of the ribozyme's native conformation. This kinetic analysis measured the time and order of folding for the various domains within the ribozyme. Further analysis of the group I intron has been made by Treiber *et al.* (p. 1943), who examined a kinetic barrier to ribozyme folding. Although folding barriers are often thought of as those represented by misfolded intermediates, a folding intermediate stabilized by native tertiary interactions was identified.

■

## Concentrating on gene regulation

Certain genes are coordinately turned on or off during B cell differentiation. Wallin *et al.* (p. 1961) have shown that the concentration of the transcription factor BSAP (regulated by cytokines) correlates with whether it acts as a repressor or activator of transcription. Although the genes positively

*(Continued on page 1827)*

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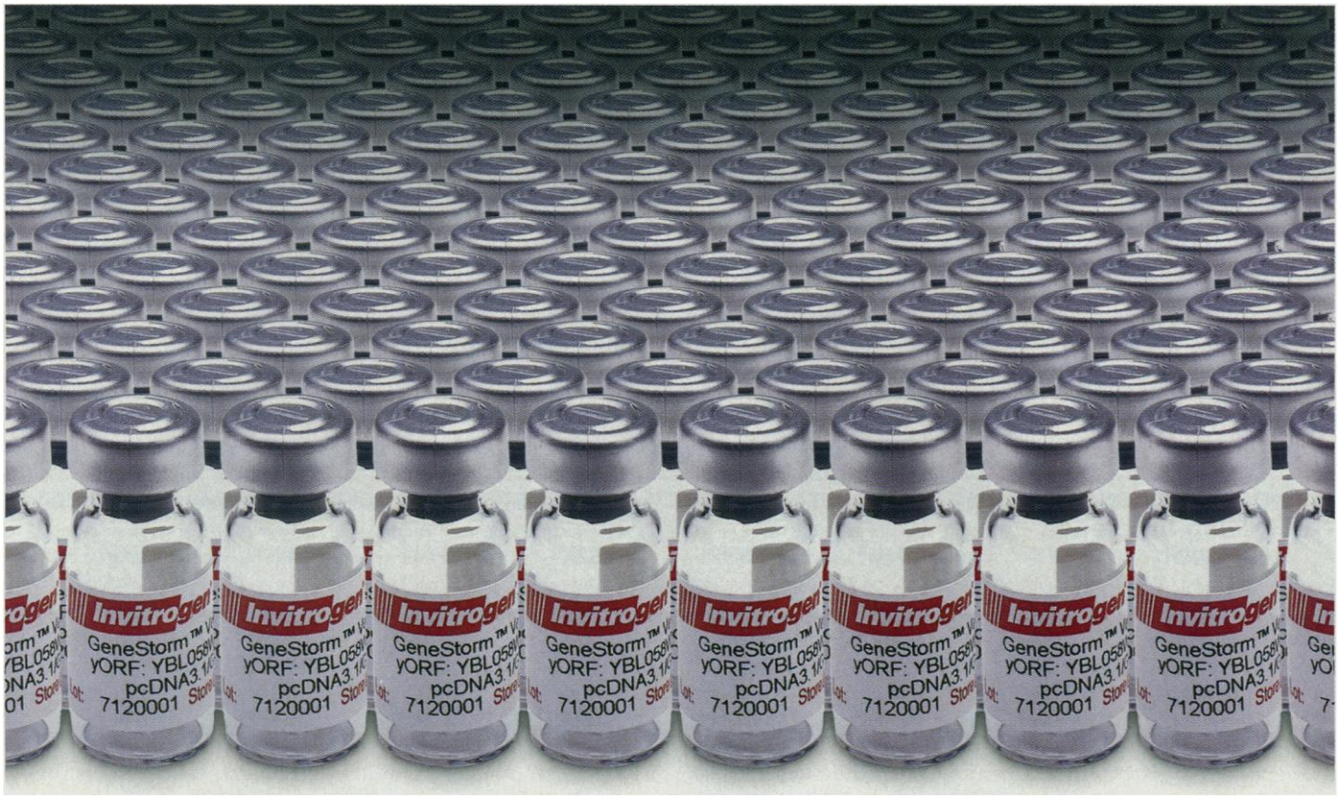


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(Continued from page 1825)

regulated by BSAP had high affinity binding sites and the genes negatively regulated had low affinity sites, this correlation did not explain the concentration dependence. When a high affinity motif was inserted into a repressing promoter that normally has a low affinity site, the gene still acted as if it had a repressor binding site in it, yet retained its high affinity. Thus, this illustration of concentration-dependent gene regulation in mammals is not explained by the affinity of the binding site, but by the context of the promoter.

■

## Transcription factors and hearing loss

Studies of rare, family-associated hearing disorders may provide molecular insights into the basis for the hearing loss that affects many members of the general population, especially after age 65. The identification of a region on chromosome 5 that was associated with deafness in one family allowed Vahava *et al.* (p. 1950; see the commentary by Steel, p. 1870) to make a prediction about the associated gene, as the homologous region in the mouse contains a gene, *Pou4f3*, that is known to cause complete deafness. The authors showed that the human form of this transcription factor had an 8–base pair deletion and was normally expressed in fetal cochlea.

■

## Cutting enzymes down to size

Many enzymes function as dimers in which each monomer contributes structural elements to the two active sites. MacBeath *et al.* (p. 1958; see the news story by Stokstad, p. 1852) used a combination of structure-based design and directed evolution to convert a dimeric chorismate mutase (CM), which converts chorismate to prephenate in the tyrosine and phenylalanine pathways, to a monomer that is nearly as active. A more stable CM from a thermophile had certain residues mutated to decrease its dimerization tendency, but residues needed to introduce a critical turn were identified by library screening. Only a small fraction (less than 0.05 percent) of the turn sequences led to an active monomeric enzyme.

■

## A glimpse into the photocycle

Recent developments in time-resolved x-ray crystallography allow the real-time characterization of transient states of biomolecules. This approach is of particular interest in the study of proteins involved in the conversion of light energy into a chemical signal, such as photoisomerization. Perman *et al.* (p. 1946) have investigated an intermediate in the photocycle of xanthopsin, a eubacterial photoreceptor. They demonstrate that photoisomerization is completed in this state, which forms within 1 nanosecond of irradiation, and provides a structural model for this intermediate state.

■

## Death receptor with a heart

Some "death receptors," which transmit an external death signal from ligands such as FasL or tumor necrosis factor (TNF), engage a molecule called FADD to initiate the death signaling pathway. Yeh *et al.* (p. 1954) generated mice that were genetically deficient in FADD and confirmed the necessity for FADD in Fas and TNF receptor signaling, but not for signaling by the DR4 death receptor or for apoptosis induced by c-myc. Surprisingly, FADD deficiency was lethal, unlike deficiencies in Fas or the TNF receptor. FADD was necessary for normal heart development, implying that cell death is a prerequisite for, or FADD is used in pathways that promote, cardiogenesis.


■

## Antibodies catalysis of Diels-Alder reactions

Organic chemists make extensive use of the Diels-Alder reaction, which couples a diene (a molecule with two adjacent double bonds) to the double bond of a dienophile to form a ring. Although few enzymes appear to catalyze this reaction, antibodies have been made that do. Two reports describe crystallographic studies of such antibodies that have revealed insights into their formation and mechanism. Romesberg *et al.* (p. 1929) compare a Diels-Alder catalytic antibody to its germline precursor and show that a single somatic mutation increases the catalyst's affinity and activity. Heine *et al.* (p. 1934) describe an antibody that performs a highly specific transformation to produce the normally disfavored *exo* conformation of the product molecule. Studies of an inhibitor complex show how particular residues activate the dienophile and how hydrogen-bond networks influence stereospecificity.

## Technical Comment Summaries

### Patterns of Genome Organization in Bacteria

F. R. Blattner *et al.* (Articles, 5 Sept. 1997, p. 1453) showed that, in *Escherichia coli*, the distribution of a global statistical property of the genome "GC skew" correlated with the direction of DNA replication. J. R. Lobry (Technical Comments, 3 May 1996, p. 745) showed that GC skew changes sign at the origin of replication in *E. coli*, *Haemophilus influenzae*, *Bacillus subtilis*, and *Mycoplasma genitalium*, as well as in the terminus of *H. influenzae*.

J. M. Freeman *et al.* present data showing that integral functions of the base composition and coding sequence (CDS) directionality capture these same features and others. The functions provide "a powerful method of prokaryote whole-genome analysis."

"Purine excess," the cumulative sum of purines minus that of pyrimidines along the DNA sequence, displays minima at the six known whole-genome replication origins and maxima at the three known termini. The GT ("keto") excess tracks the same features in four out of nine genomes. The strong correlation between CDS directional excess and purine excess (in particularly fine detail in the case of archaebacteria) is likely a result of (i) the avoidance of "head-on collisions" between DNA and RNA polymerases and (ii) transcription-coupled repair. Graphs of the different prokaryotes reveal characteristic features such as the extreme discontinuity of the purine excess in *Synechocystis* (known for its uptake of foreign DNA) and the prominence of the phage μ insertion site in *H. influenzae*. The degree of correlation between CDS directional excess and purine excess, or keto excess, or both, reflects chromosome regional codon usage and gene density.

The full text and figures of this comment can be seen at www.sciencemag.org/cgi/content/full/279/5358/1827a

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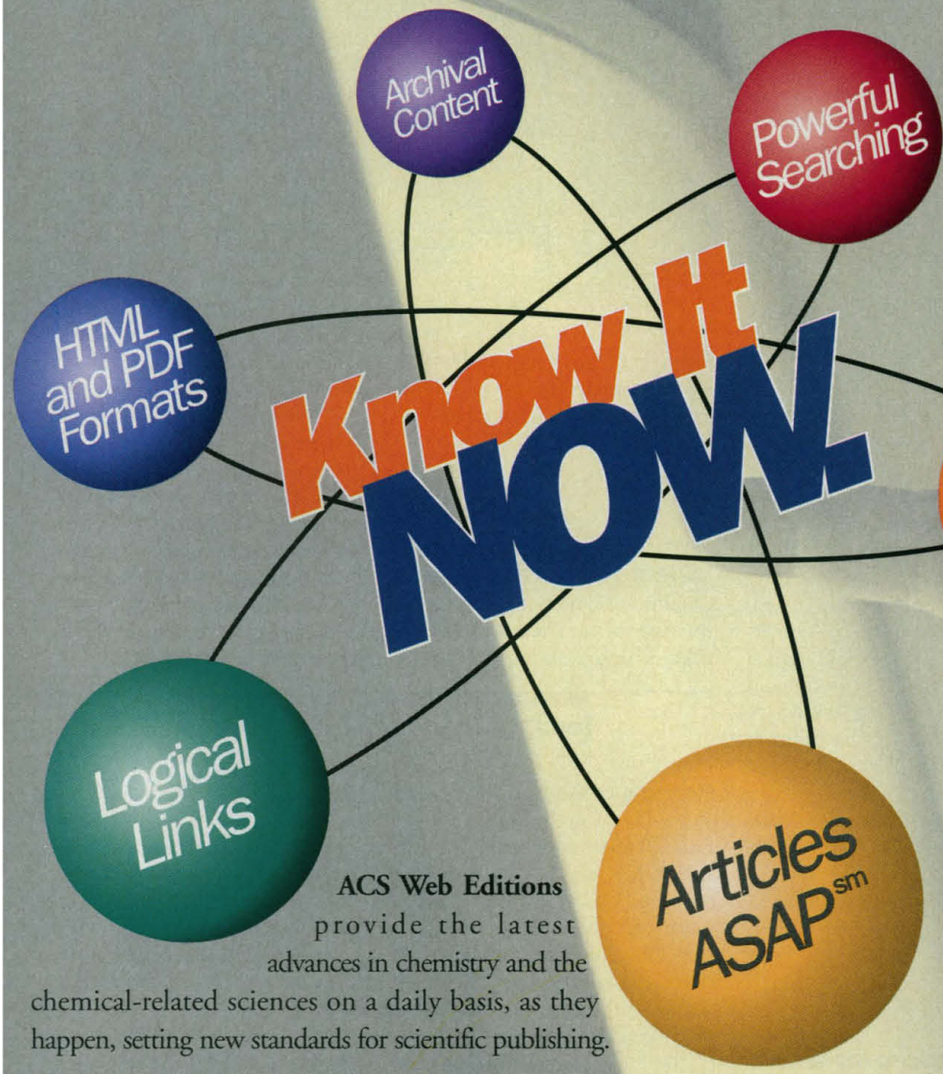


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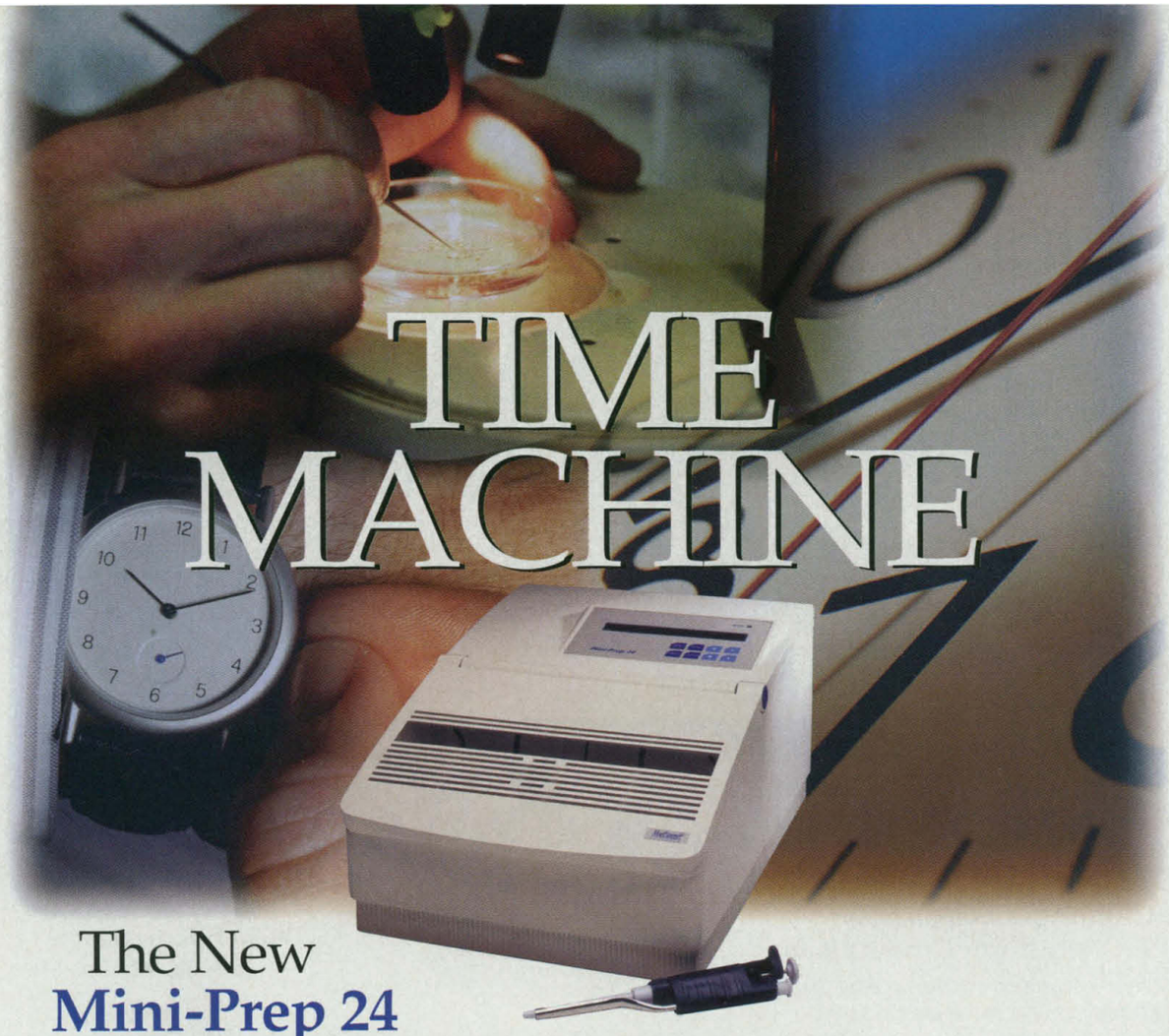


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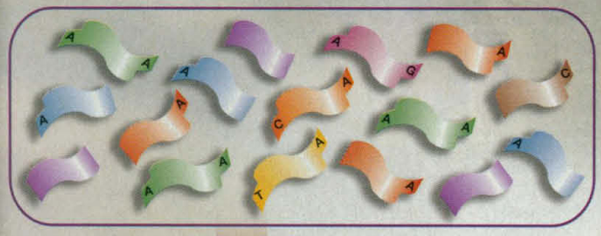
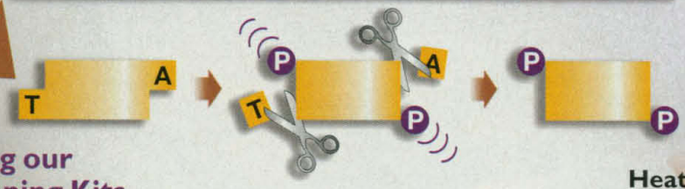
**"Soup" of PCR Products with Heterogeneous Termini**



Typical PCR conditions† generate a mixture of products with heterogeneous termini.[1,2] This heterogeneity results in difficulty ligating PCR products to either blunt or dT-tailed vectors[3] for cloning purposes. Novagen's *new* **Perfectly Blunt™ Cloning Kits** simplify cloning of any DNA fragment regardless of composition or condition of 3' termini; blunt ends, 3' overhangs, or ragged ends ligate with equal ease and greater cloning efficiency (3-fold to 24-fold higher). The kits contain everything needed for end conversion, ligation, and transformation.

**End Conversion Reaction**




**Heat Inactivation (5 minutes)**

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**Ligation Reaction**


**Perfectly Blunt Vector**

Insert is combined with ready-to-use vector and ligated (15 minutes). Subsequent transformation into NovaBlue Competent Cells generates recombinant colonies that are visualized easily by blue/white screening.


**References**

1. Brownstein, J.M., *et al.* (1996) *BioTechniques* **20**, 1004–1010.
2. Magnuson, V.L., *et al.* (1996) *BioTechniques* **21**, 700–709.
3. Novy, R.E., Yaeger, K.W., and Kolb, K.M. (1996) *In**Nova**tions* **6**, 7–11.


*The Polymerase Chain Reaction (PCR) process is covered by patents owned by Hoffmann-La Roche.
†Conditions that use DNA polymerases lacking 3'→5' exo-activity (*e.g., Taq, Tth*)

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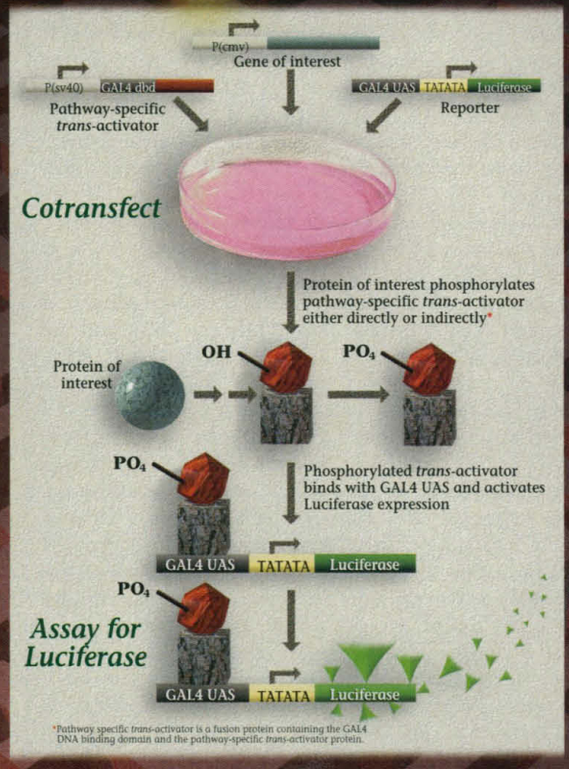


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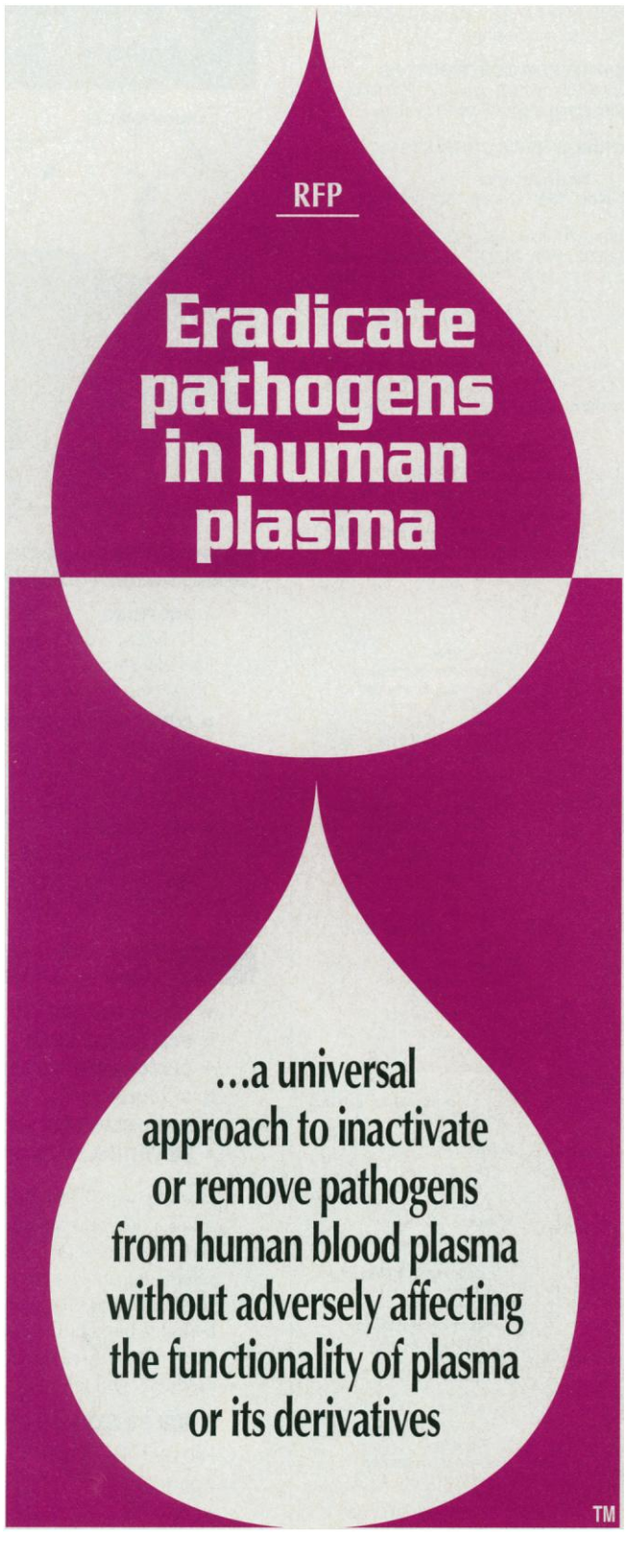


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- continuation of funding possible upon favorable evaluation of progress and potential.

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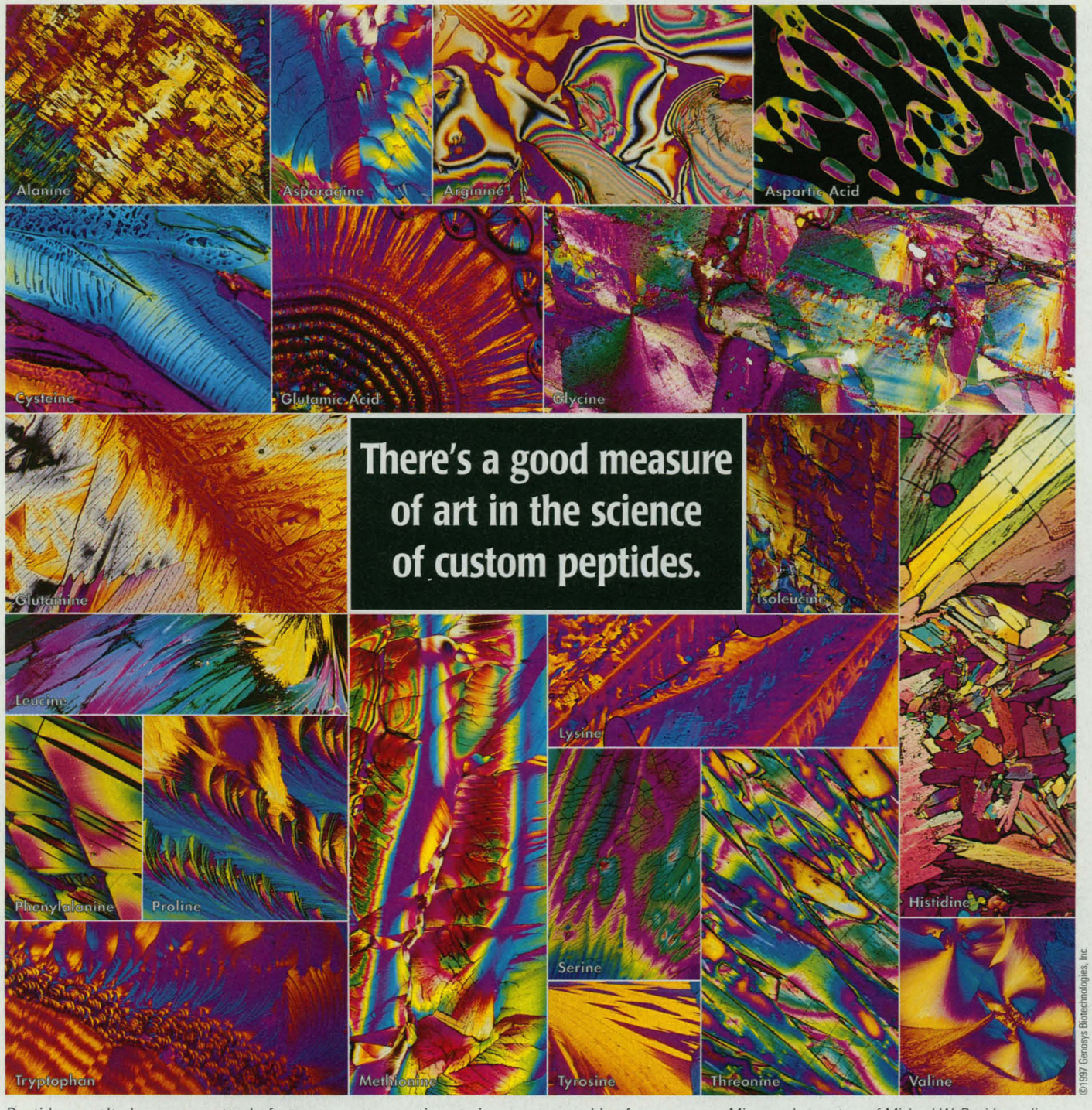




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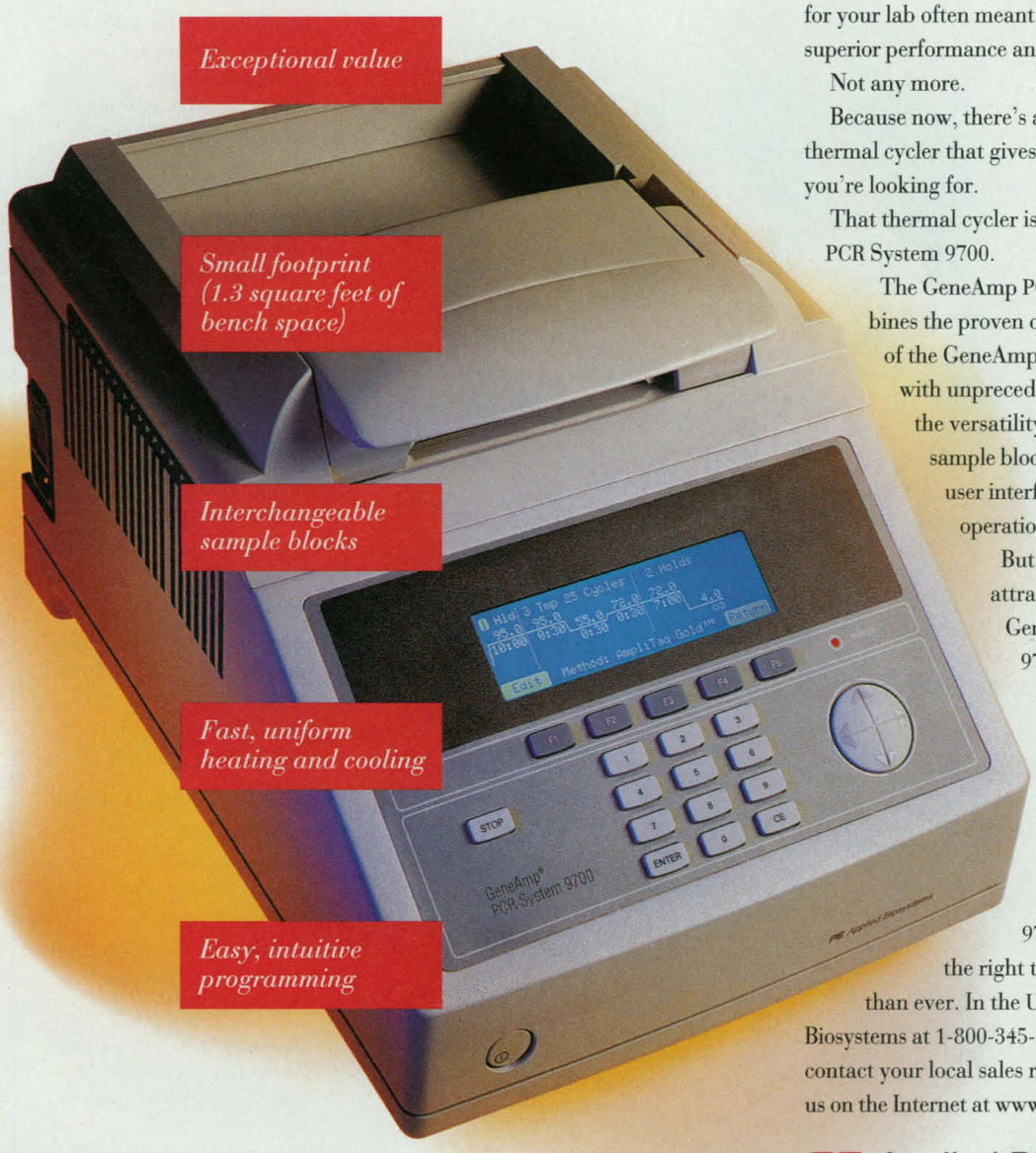


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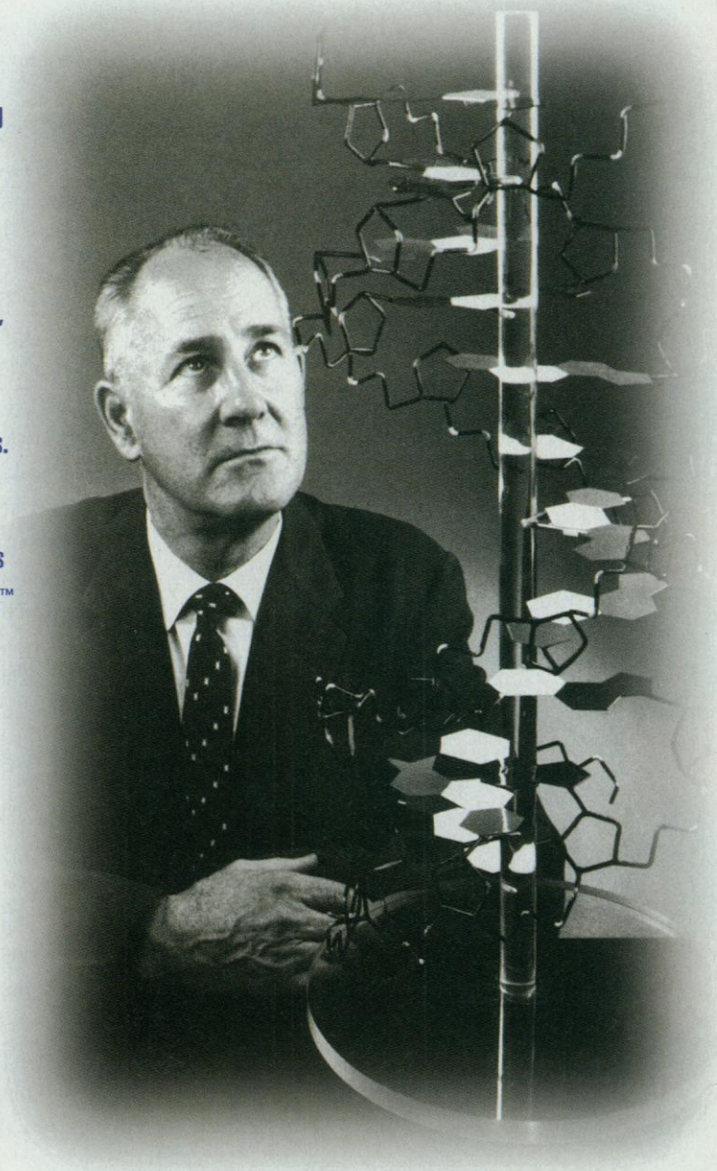

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# Exact Graphs for Exact Science

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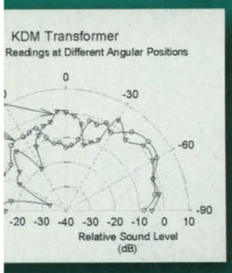


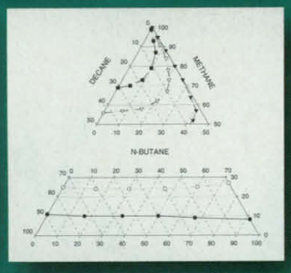


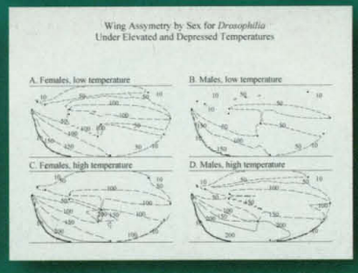


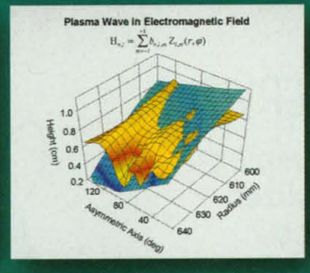


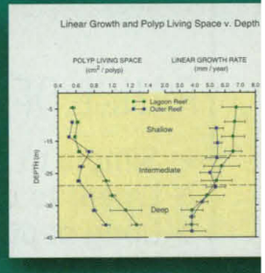


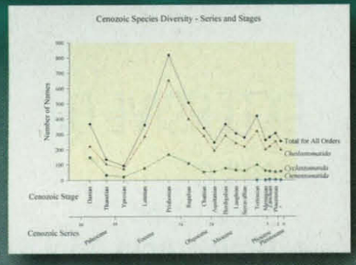


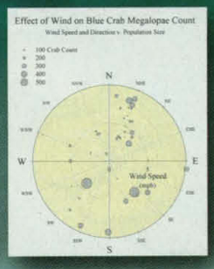


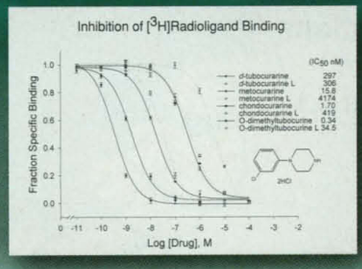


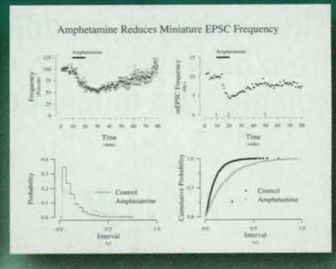


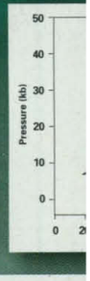



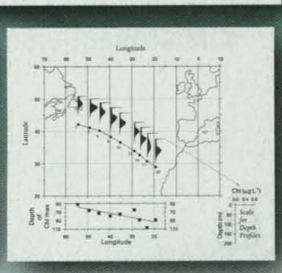


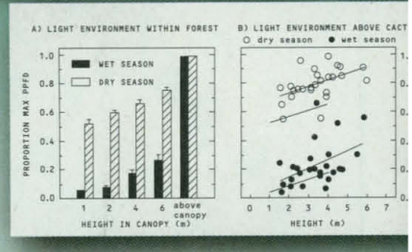


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Dr. Barry Simon, Ph.D.
Review of eleven competitive products
*Desktop Engineering* Magazine,
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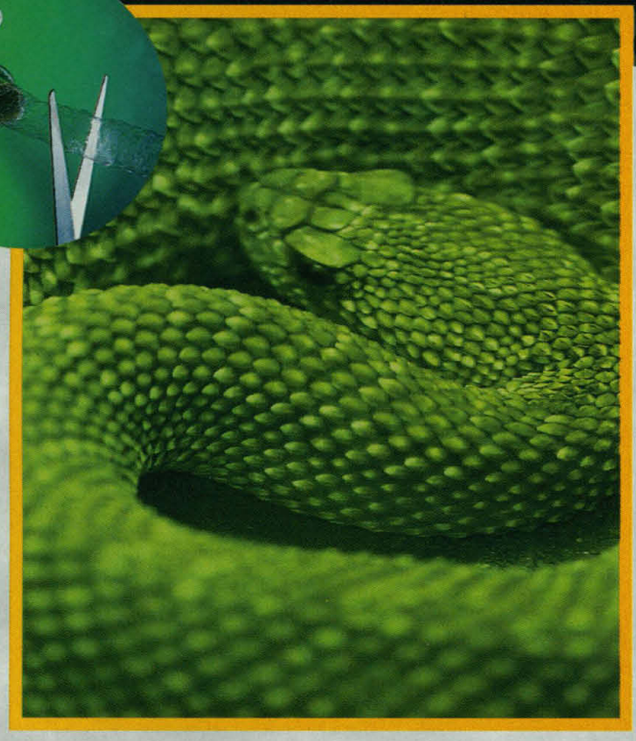
Dialysis



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