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GENOME ISSUE

Imagine Having The Tools To

Remember the milestones in your life. The ones that revealed your talent to create, solve, explore, and discover.

Maybe it was a special science fair project. Or a certain insight you had in a college lab. Or maybe it was a tool, like an EM, that let you really delve into what makes things tick. Somehow it all came together into a career in the sciences.

Biosearch specializes in creating tools that fuel your inner drive to discover. Tools that allow your imagination to take on today's frontiers.

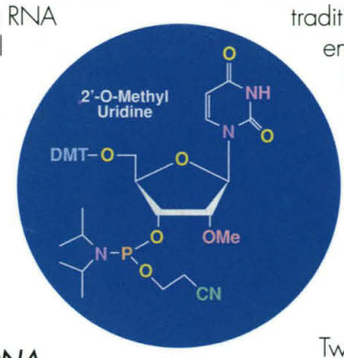
RNA

RNA oligomers have shown promise in therapeutic and diagnostic applications, including inhibition of viral replication, cancer etiology, and gene regulation and expression.

To bring these applications within easy reach, Biosearch was the first to introduce a complete, automated RNA synthesis system with nucleotide monomers, reaction columns, pre-packaged reagents, and optimized synthesis protocols.

Our new Expedite™ RNA chemistry makes your work-up procedures faster, easier, and more efficient. The milder cleavage and deprotection conditions reduce chain degradation and increase yield. The Expedite RNA reagents employ our patented betacyanoethyl phosphoramidite chemistry that's become the method of choice in DNA and RNA synthesis.

Our researchers are currently developing protocols for large-scale synthesis of RNA oligomers. (Photo of RNA crystal, courtesy of Dr. Alex Rich, MIT, was synthesized at a scale of 70 μ mole on Biosearch's 8800 Synthesis System.)



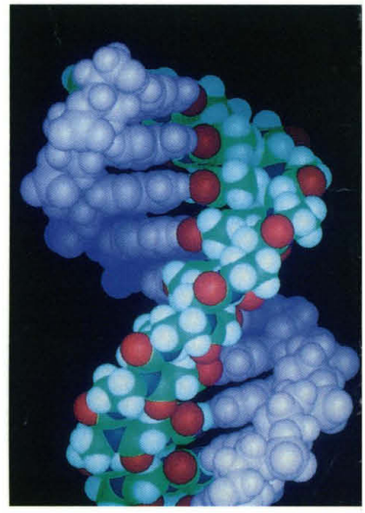
Therapeutic and diagnostic grade DNA

Researchers in the clinical and diagnostic use of DNA are on the verge of creating a new class of pharmaceuticals. Biosearch is proud to pioneer new tools for their work.

Biosearch is the world's leading supplier of systems, chemicals, and reagents for the synthesis, purification, and analysis of therapeutic and diagnostic DNA. We've tightened the specifications on our products to ensure that they can be used for the most demanding applications. A Certificate of Analysis is automatically supplied with all of our DNA synthesis reagents.

We've also substantially expanded our manufacturing capacity to meet the needs for large single-batch production of material, minimizing your need for internal quality control.

In addition to standard reagents, Biosearch can also supply phosphoramidites and bulk quantities of synthesized oligomers on a custom-synthesis basis.



PNA

Peptide Nucleic Acids–PNA oligomers. These molecules are so novel that they're rewriting the very nature of nature. Biosearch is the world leader in the development and synthesis of these exciting new molecules.

Similar to DNA and RNA, PNA carries information in sequences of the four bases: adenine, guanine, cytosine, and thymine. In PNA, however, these code carriers are connected to a completely different backbone–a polyamide backbone similar to that found in peptides. PNA oligomers are more stable than their natural counterparts yet bind more specifically and with higher affinity to natural DNA and RNA.

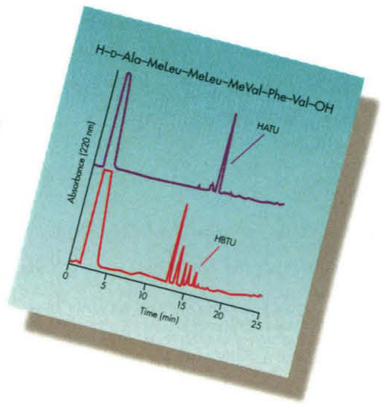
PNAs can be used in many of the same applications as traditional DNA. Their greatest contribution, however, may come from applications that can't be performed using traditional DNA oligonucleotides, such as restriction enzyme blocking, PCR clamping, and DNA mapping.

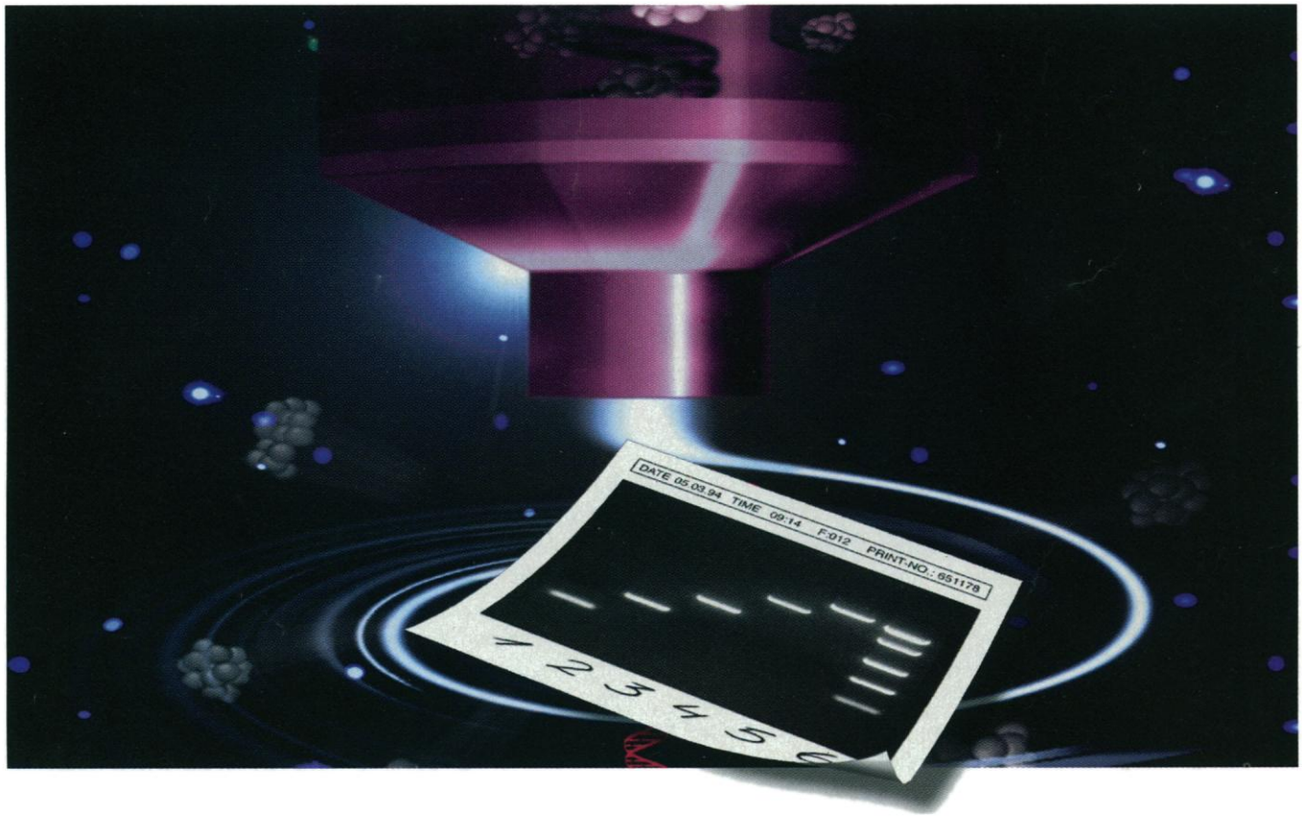
Biosearch can provide you with custom PNA oligomers, or the monomers, supports, and reagents to synthesize your own oligomers.

HOAt and HATU peptide coupling reagents

Two new coupling reagents, HOAt and HATU, simplify your peptide synthesis. These new reagents enhance coupling yields and reduce racemization and coupling times. They are particularly effective with difficult couplings and in the synthesis of peptides containing hindered amino acids.

HOAt and HATU have structures similar to the commonly used reagents HOBt and HBTU, and are compatible with all standard activation strategies.



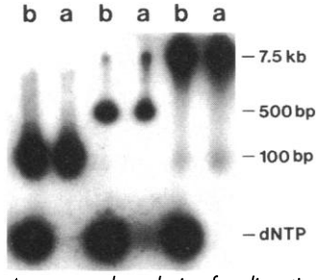


Spin your way to clean DNA with QIAquick

Take QIAquick Kits for a spin and see how easy it is to clean up DNA fragments. QIAquick microspin membrane technology means:

- 99% contaminant removal
- up to 90% recovery of DNA
- fast 5 – 15 minute procedures
- optimized buffers for each application

Say good-bye to time-consuming phenol extraction, gel filtration, ethanol precipitation and electroelution — with QIAquick microspin technology you simply load the sample, wash, and elute. The whole procedure takes 5 to 15 minutes from start to finish. Purified DNA is recovered with up to 90% efficiency, ready for use in all standard applications, such as restriction, ligation, transformation, hybridization, PCR, and sequencing.



Agarose gel analysis of radioactive labeling reactions before (b) and after (a) purification using QIAquick Nucleotide Removal Kit.

QIAquick is available in 3 specialized kits. Each kit has different buffers, designed to provide optimum purification in each specific application:

QIAquick Gel Extraction Kits extract DNA fragments between 100 bp and 10 kb from TAE and TBE agarose gels.

QIAquick PCR Purification Kits separate primers (up to 40 bases), nucleotides, mineral oil, and other reagents from ds and ss PCR products as small as 100 bp.

QIAquick Nucleotide Removal Kits clean up DNA fragments and oligos as small as 20 bases after labeling, sequencing and other enzymatic reactions.

To find out more about the range of QIAquick Kits, contact QIAGEN or your local distributor — and spin your way to clean DNA.

QIAGEN GmbH: Max-Volmer-Straße 4, 40724 Hilden, Germany, Orders (0)2103-892-230, Fax (0)2103-892-222, Technical Service (0)2103-892-240
QIAGEN Inc.: 9600 De Soto Avenue, Chatsworth, CA 91311, USA, Orders 800-426-8157, Fax 800-718-2056, Technical Service 800-DNA-PREP (800-362-7737)
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QIAGEN

Keep Up With Your Imagination.

PEG-PS™ peptide synthesis supports

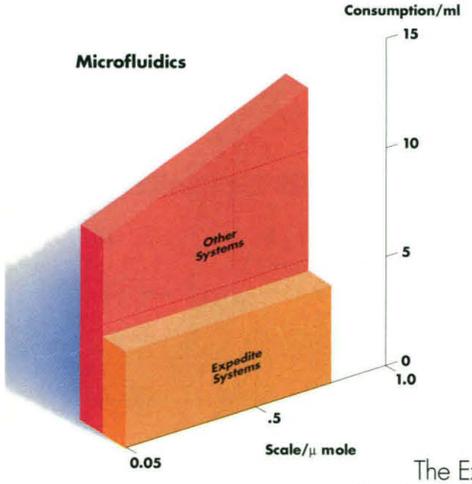
PEG-PS (polyethylene glycol-polystyrene) peptide synthesis supports from Biosearch help you achieve improved peptide purity with shorter cycle times.

Unlike traditional supports, PEG-PS beads more closely resemble the nature of the growing peptide chains. Solvation of the peptide resin is higher, resulting in a higher peptide purity. Synthesis is fast and effective due to high coupling efficiency and minimal side reactions.

PEG-PS supports are easy to handle, compatible with a wide range of solvents, and are especially well suited for the synthesis of long or difficult peptides.

Microfluidics

In the real world, achieving "end product" is not the only concern. There are dozens of production costs as well as the escalating costs of hazardous waste disposal.



Biosearch's Expedite Nucleic Acid Synthesis System, with its patented microfluidics technology, not only enables fast cycle times but also provides the bonus of reduced reagent consumption. The distance between the reagent reservoir and the column is minimized so that a single coupling cycle requires less than 4.5ml of reagents. The Expedite system (with optional trityl monitor) can also separate the chlorinated waste–simplifying disposal tasks and reducing associated costs.

Membrane synthesis

Perform nucleic acid synthesis on a membrane? It's now possible–and practical–thanks to Biosearch Nucleic Acid Membrane Supports, a breakthrough synthesis technology developed by Biosearch.

Biosearch membrane supports use a proven PTFE membrane system that directly replaces traditional controlled pore glass (CPG) supports. Membrane devices have standard luer fittings, so they can be plugged into any brand of synthesizer.

Biosearch membrane supports allow you to synthesize both long and short oligomers on the same type of membrane; no longer do you need to select the size of the CPG according to the length of the oligomer.

With Biosearch membrane supports, not only do you eliminate beads, but there's no centrifuging and no washing. Just remove the membrane from its holder, cleave, and deprotect.

Allyl-based protection for complex peptides

The synthesis of cyclic, branched chain, sulfonated, glycosylated, and phosphorylated peptides have traditionally been time consuming and problematic.

To synthesize these complex peptides quickly and efficiently, Biosearch scientists have perfected convenient techniques using allyl-based protecting groups. Allyl amino acids can be selectively deprotected in a manner which is compatible with other classical protecting groups (such as Fmoc, Boc, *t*Bu), sensitive amino acids (Met, Trp), and side chain modifications (Tyr(SO_3H)). Biosearch has also developed protocols for the fully automated synthesis of cyclic peptides, branched peptides, and MAPs on our 9050 Plus PepSynthesizer.™

If we've intrigued you with some of these innovative tools, it's easy to find out more. For our "Directory of Chemical Products"–one of the most comprehensive synthesis tool kits in the world–call the Biosearch Group in the US and Canada at 1-800-872-0071, in Germany at (49) 040-853267-36, in Japan at (03) 3471-8191, in France at (33) 1 30127002, and in the UK and the rest of Europe at (44) 0923 211107.

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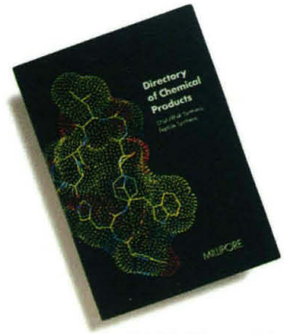

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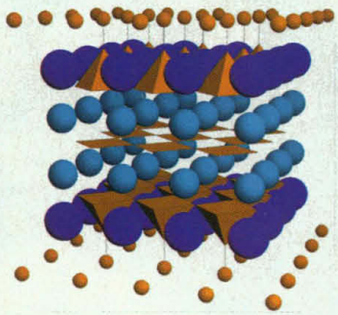
2005
A timely forecast



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COVER

We are entering a new age in which the results of the Human Genome Project will be increasingly applied to fundamental questions in molecular biology and medicine. This special issue contains a chart (page 2055) representing progress in the development of a complete human genetic map; in addition, a guest Editorial, a Research News report, Articles, Perspectives, a Policy Forum, and Reports highlight features of current research and future challenges. [Illustration: Creative Services, EPI Communications, Rockville, MD]

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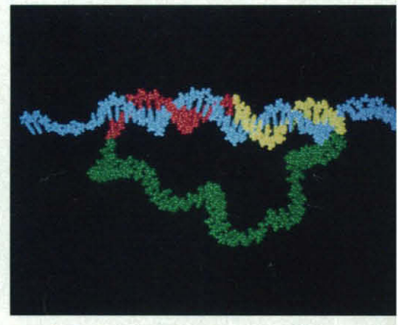

2085
Padlocking DNA for detection

◩ Indicates accompanying feature

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Luciferase: the next generation.

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Promega Corporation, the leader in luciferase technologies, is pleased to introduce an exciting advance to the firefly luciferase gene in the new pGL3 family of luciferase reporter vectors. Highlights include:

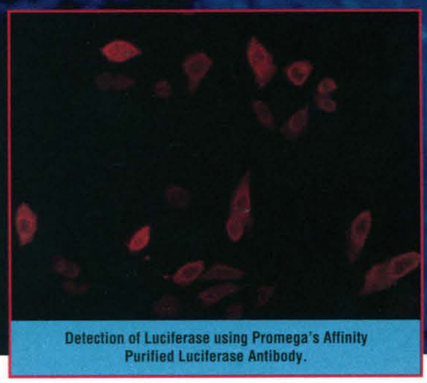
- Cytoplasmic localization of expressed luciferase, providing greater sensitivity through increased *in vitro* and *in vivo* luciferase activity
- Removal of intragenic consensus regulatory elements to minimize potential interferences
- Sequence modifications to enhance translational efficiency
- Increased RNA processing fidelity

Other new additions to our product line include:

- Anti-Luciferase, Affinity Purified for increased specificity and minimal cross reactivity. Performance tested in Immunochemistry applications.
- Luciferase Assay System with Reporter Lysis Buffer allows luciferase, CAT, and β-galactosidase assays to be performed on the same cell extract. The system features increased luminescence over conventional methods and a simpler assay procedure.
- New pGL3 Sequencing Primers

For larger volume users, we offer a variety of money-saving bulk systems. We also offer the Turner Designs Model 20 Luminometer.

Promega–the gold standard in bioluminescence!



Detection of Luciferase using Promega's Affinity Purified Luciferase Antibody.

Bioluminescence from an adult *Drosophila* expressing luciferase fused to an *hsp70* promoter, imaged using an intensified CCD camera. Photo courtesy of Dr. Steve Kay, NSF Center for Biological Timing.

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edited by PHIL SZUROMI

Sensitive tips

Atomic force microscopy can be used to determine frictional and adhesive forces at surfaces. Frisbie *et al.* (p. 2071; see news story by Kaiser, p. 2010) have determined chemical properties of surfaces by performing force measurements with derivatized tips (either CH_3 groups, which are hydrophobic, or COOH groups, which are hydrophilic). On surfaces that were lithographically patterned with CH_3 and COOH groups, the adhesive interactions were much stronger when the tip and surface had similar functional groups. These friction images correspond to chemical maps.

■

Layer by layer

One route to new superconducting thin films is to grow new combinations of layers artificially. Norton *et al.* (p. 2074) grew two new families of high-temperature superconductors by using pulsed laser deposition, in which either $BaCuO_2$ or $SrCuO_2$ was ablated from a target and deposited onto the growing surface. These materials have an "infinite layer" structure and superconduct at temperatures as high as 70 kelvin.

■

Specific cuts

Genetic data have indicated that the *RAD1* and *RAD10* genes of *Saccharomyces cerevisiae* are required for both recombination and nucleotide excision repair. Bardwell *et al.* (p. 2082) define the substrate specificity of a Rad1-Rad10 complex. They find that the Rad1-Rad10 endonuclease cleaves within duplex DNA adjacent to duplex–single-strand junctions on only the strand with the 3' single-stranded tail. Such a substrate is predicted to be an intermediate in both the recombination and nucleotide excision repair processes, thus explaining the role of Rad1-Rad10.

■

Mapping a second breast cancer gene

About 45 percent of families with inherited breast cancer show genetic linkage to a locus on chromosome 17q21, called *BRCA1*. Analysis of the subset of families that are not linked to *BRCA1* enabled Wooster *et al.* (p. 2088; see News stories in 23 September by Nowak, p. 1796, and O'Brien, p. 1798) to localize a second breast cancer susceptibility locus, *BRCA2*, to chromosome 13q12-13. *BRCA2* appears to account for the same proportion of inherited breast cancers as *BRCA1* but, unlike *BRCA1*, does not seem to elevate the risk for ovarian cancer.

Yeast chromosome VIII

An international effort is underway to identify all of the genes in the yeast *Saccharomyces cerevisiae*. Johnston *et al.* (p. 2077) have completed one part of this project, the nucleotide sequence of chromosome VIII. Almost one half of the open reading frames identified that are likely to encode proteins are not significantly similar to previously identified sequences.

■

Focusing on DNA

Particular gene sequences can be targeted for mapping studies with oligonucleotide probes, but nonspecific binding often limits this approach. Nilsson *et al.* (p. 2085) have developed a padlock probe in which two target complementary sequences are split between the two ends of the probe and held together by a long linker sequence, such as poly(T). After specific binding, the probe ends can be ligated, which links the probe around the target DNA. Such tight tethering allows stronger washing conditions to be used, thus minimizing the background signal from nonspecific binding. High-resolution DNA mapping benefits from stretching the DNA as much as possible so that marker positions can be determined more accurately. Bensimon *et al.* (p. 2096) show that large DNA fragments (10^6 base pairs) can be extended and aligned on a glass surface covered with a silane monolayer. As water evaporated from a drop of a solution of DNA, the receding air-water interface left DNA molecules that were bound to the surface in a fully extended state.

■

Deadly collaborators

The proto-oncogene c-*Myc* and the tumor suppressor gene *p53* have been independently linked to the control of programmed cell death (apoptosis). In experiments with cultured mouse fibroblasts, Hermeking and Eick (p. 2091) show that induction of apoptosis by c-Myc activation requires the presence of functional p53 protein. Thus, p53 may mediate apoptosis as a safeguard mechanism to prevent cell proliferation induced by oncogene activation.

■

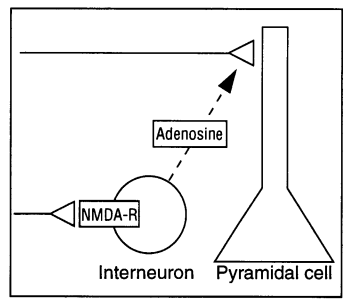
Off axis

The establishment of the embryonic axes in *Drosophila* requires the asymmetric localization of morphogenetic molecules within the ooctye, a process that depends on the microtubule cytoskeleton. Theurkauf (p. 2093) examined the effects of two mutations, *cappuccino* and *spire*, on the cytoskeleton, that affect the specification of both the dorsoventral and posterior axes. Microtubules are prematurely reorganized within *cappuccino* and *spire* oocytes, and cytoplasmic streaming begins prematurely. This early streaming is proposed to be incompatible with the proper localization of morphogenetic determinants and leads to the disruption of axis determination in the mutants.

■

Adenosine effects in the brain

Large amounts of adenosine, a potent modulator of synaptic transmission, are present in the mammalian brain. Manzoni *et al.* (p. 2098) have studied synaptic activity in guinea pig hippocampal slices and worked out a pathway for the effects of adenosine release. Activation of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor by released



or applied glutamate increased the extracellular concentration of adenosine, at least some of which was released from interneurons. Adenosine in turn spreads to nearby synapses and presynaptically inhibited excitatory neurotransmission.

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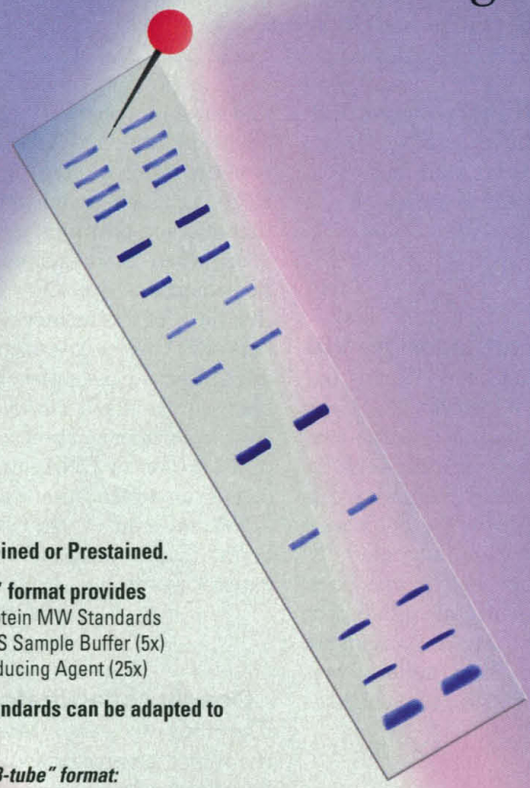

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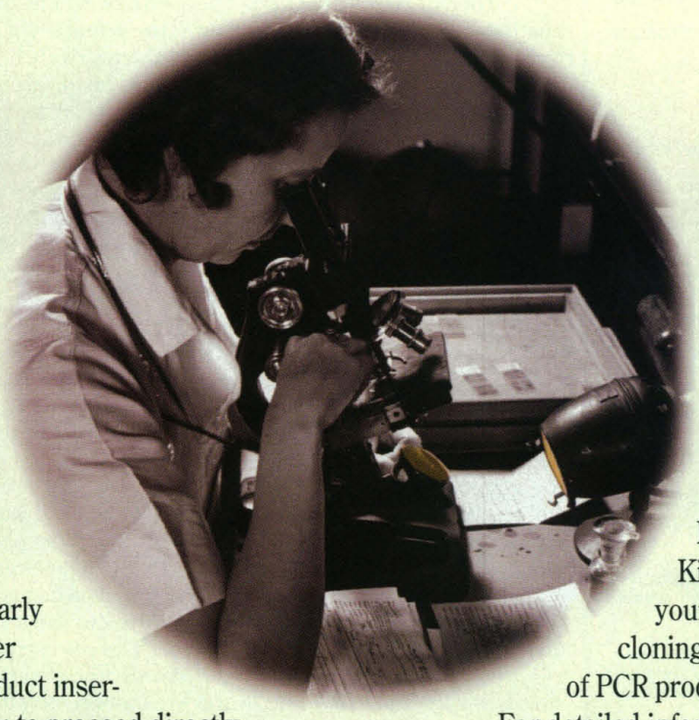

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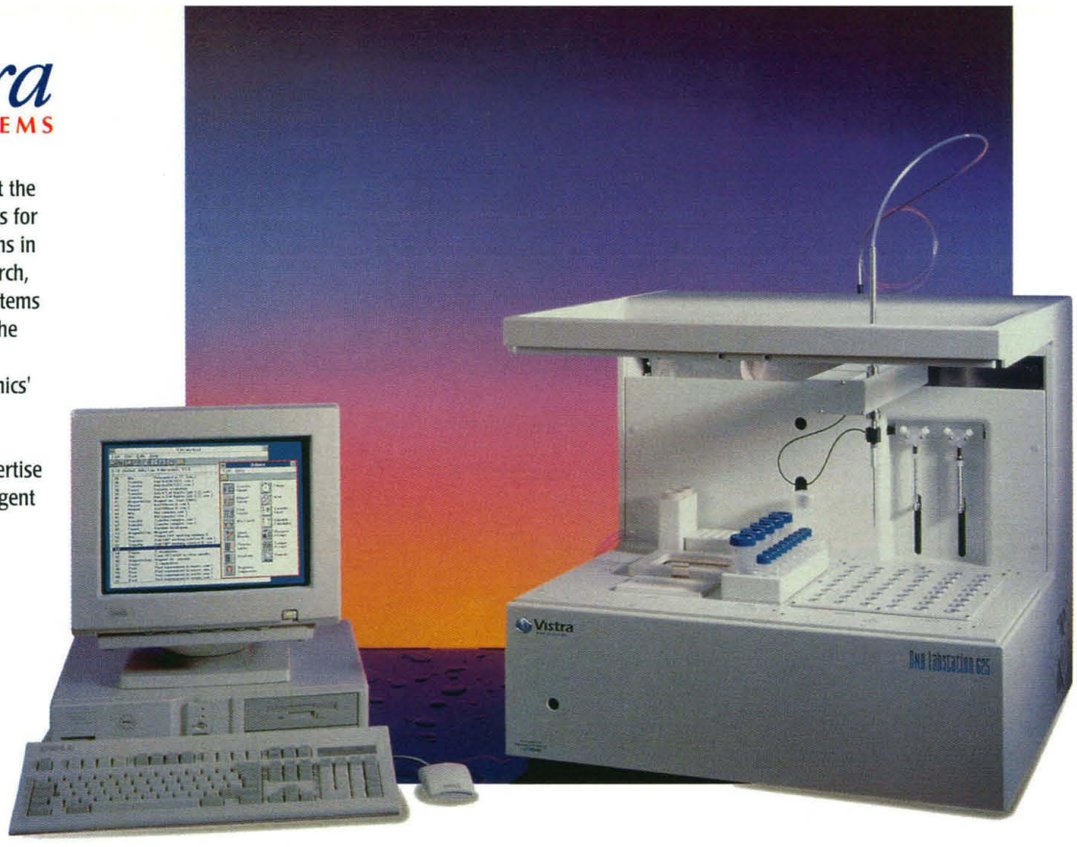

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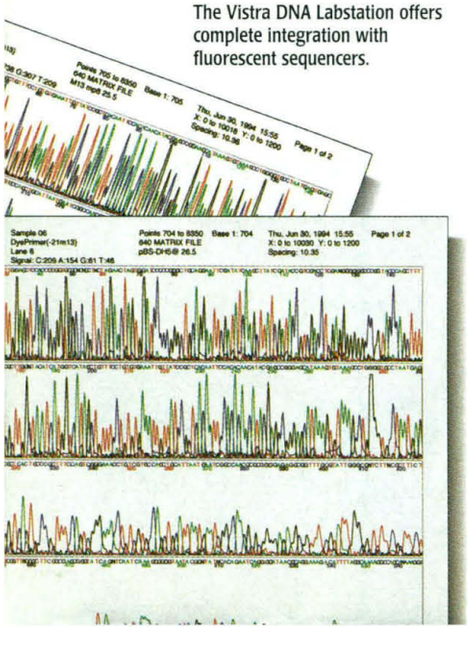

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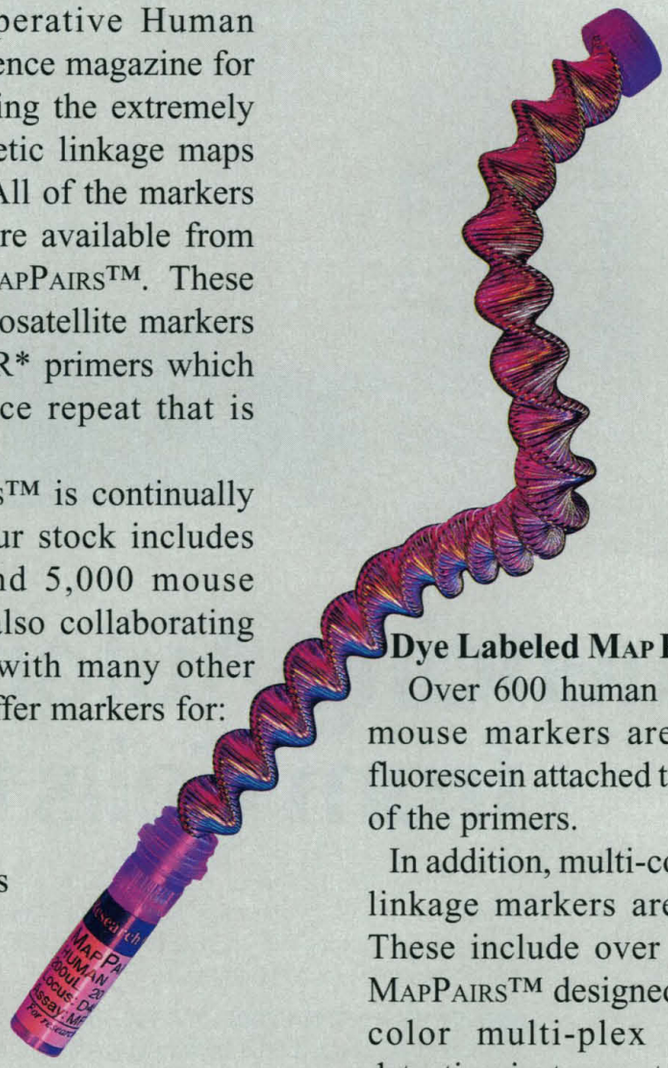

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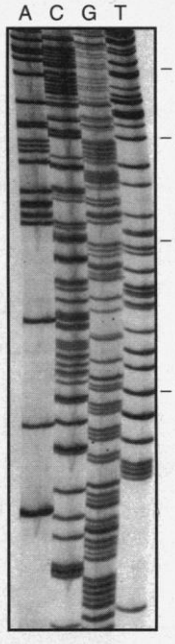

500 fmoles of a single-stranded DNA template with approximately 70% G+C content was sequenced with the IsoTherm DNA Sequencing Kit using internal labeling with [α-^{35}S]-dATP. As shown in this autoradiogram, over 300 bases of sequence are clearly readable on a standard 8% polyacrylamide gel.

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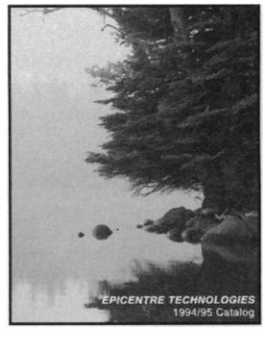

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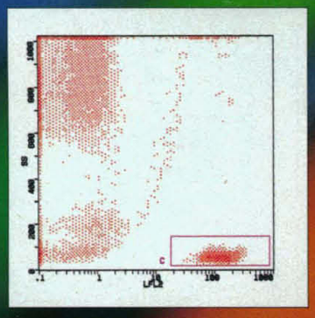

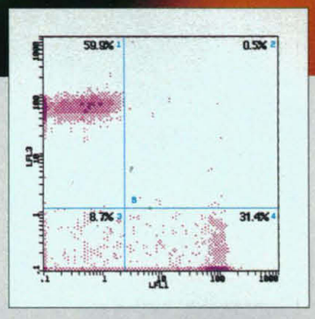

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And we're even prouder to know that, thanks to Graduate Fellows like Sally Ann Cooper, more students are gaining insight into how math and science will enhance their careers after graduation.

Every breakthrough in science starts with a discovery. Sally Ann Cooper's students enjoyed finding that out.

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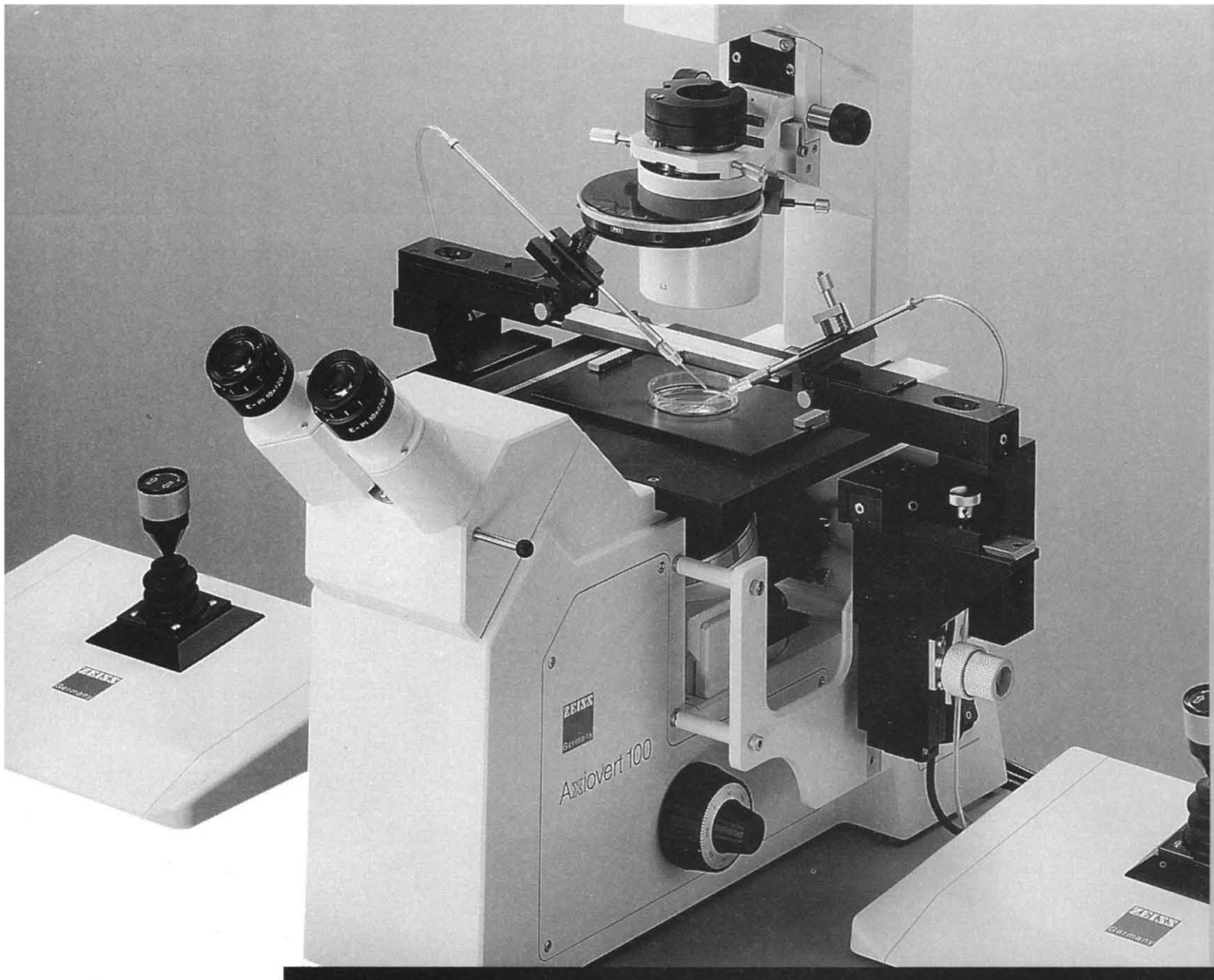

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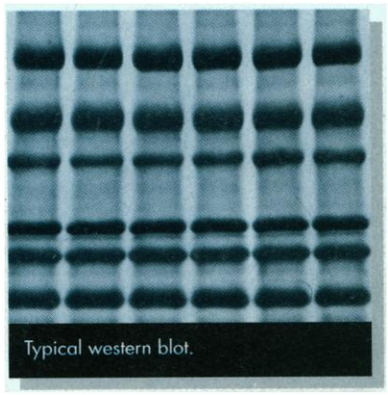

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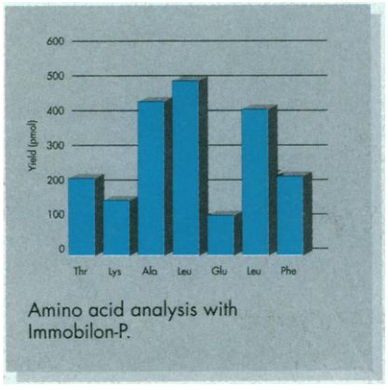

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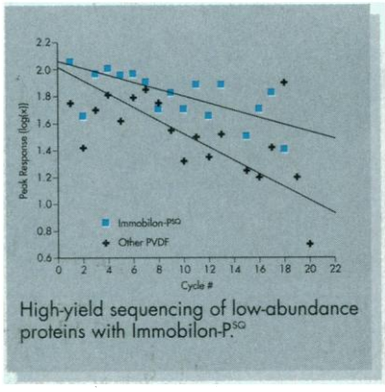

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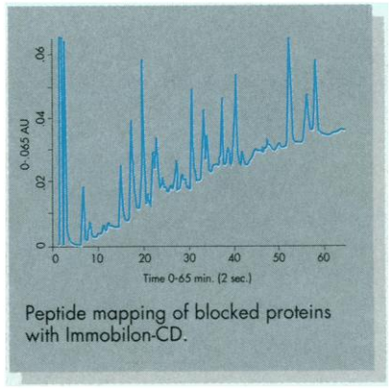

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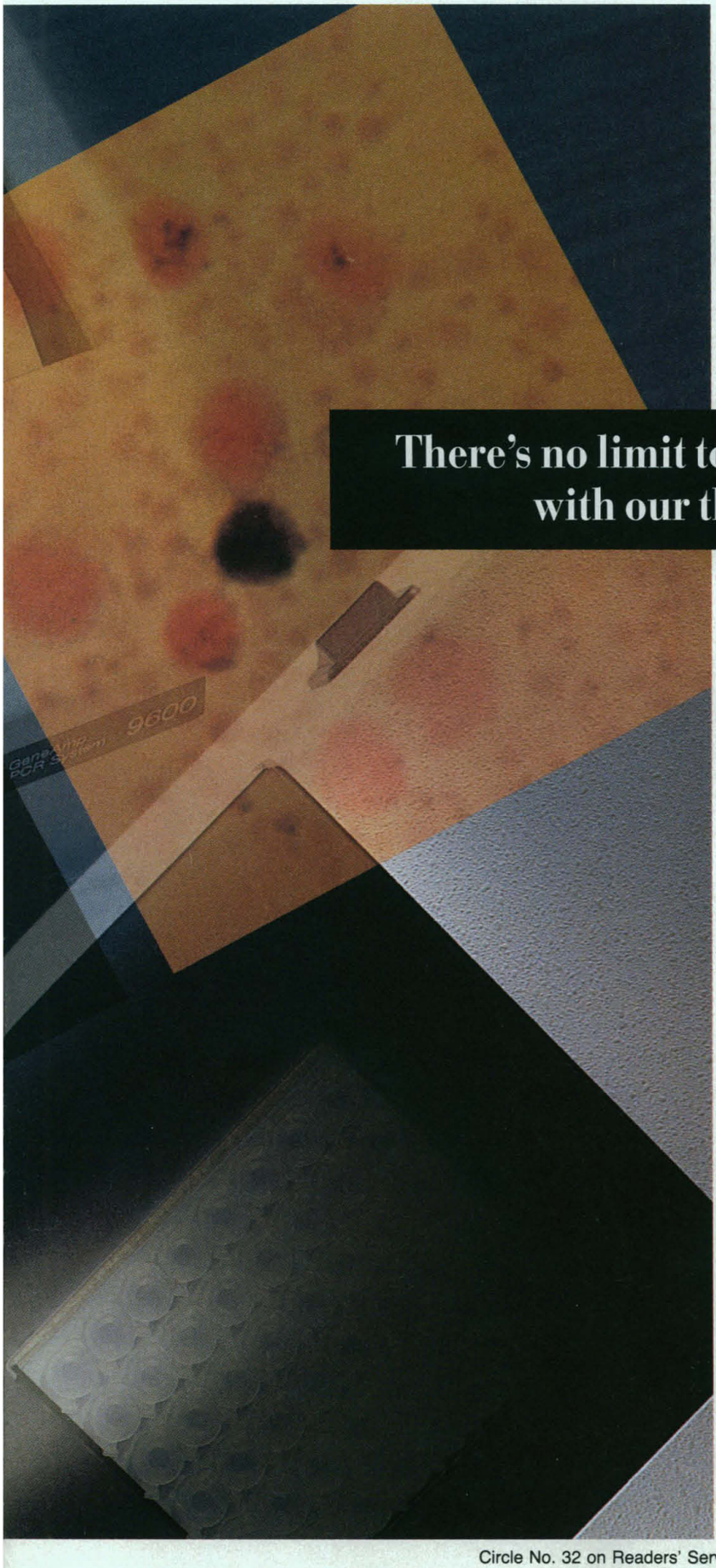

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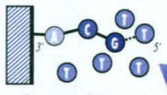

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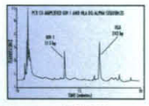

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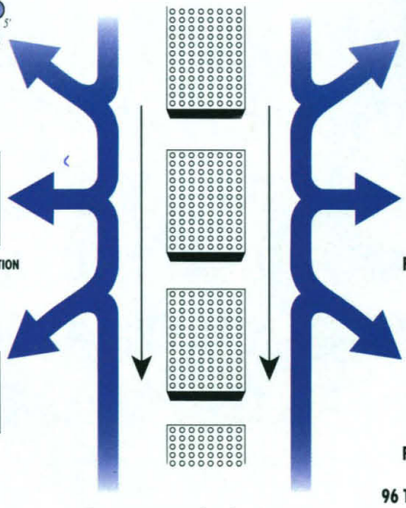

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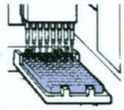

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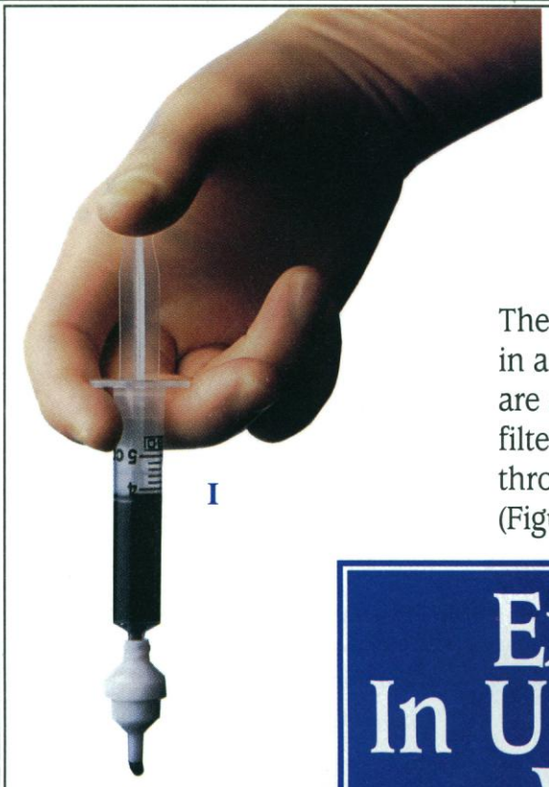

I

Extract DNA In Under An Hour Without A Centrifuge.

II

The blood sample is placed in a syringe. The white cells are adsorbed by the Leukosorb filter as the blood passes through the fibrous matrix (Figure I).

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After adsorption of the white cells, the filter medium is washed in a hypotonic saline solution. After the wash, no red cells remain on the Leukosorb medium.

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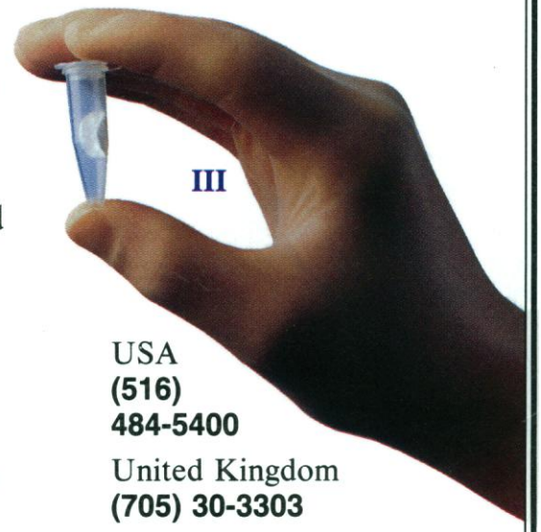

III

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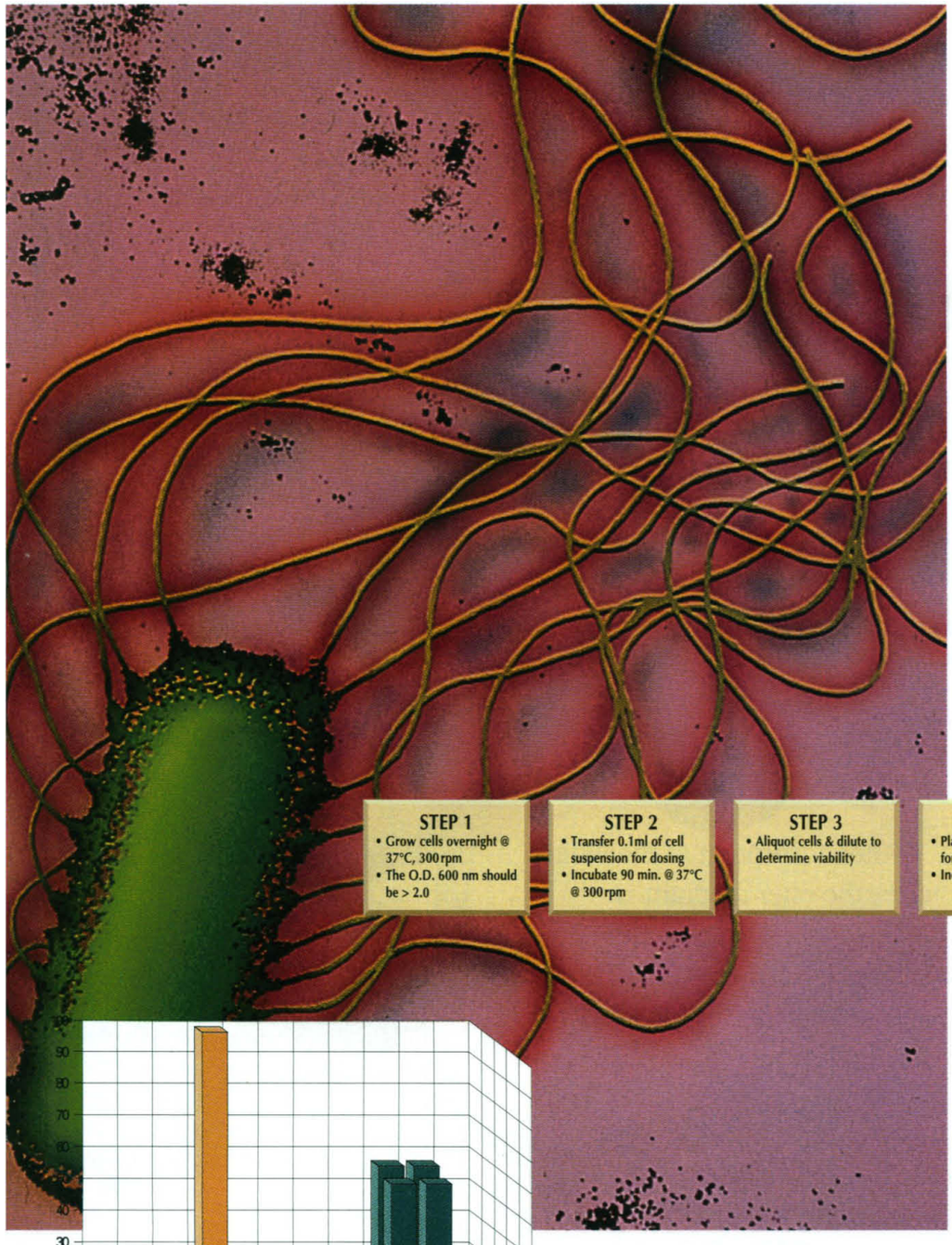

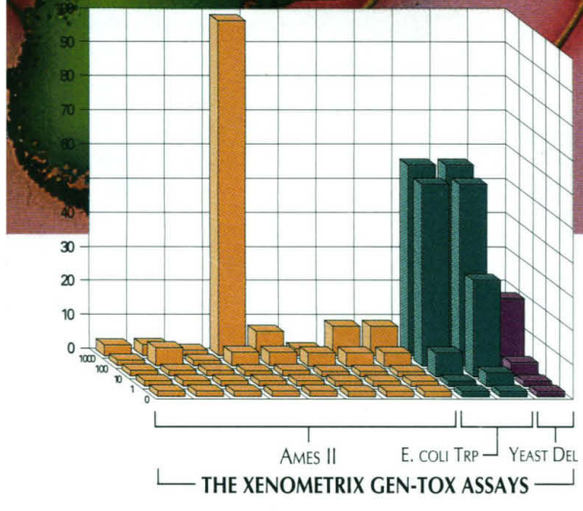

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** Developed by P. Gee, D.M. Maron and B.N. Ames, Proc Nat Acad Sci*

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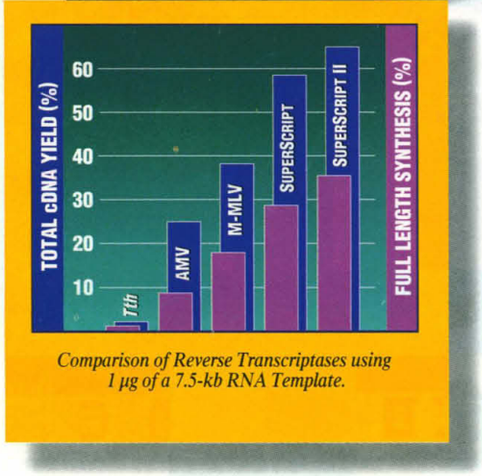

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Science

HUMAN GENETIC MAP

GENOME MAPS V

***SCIENCE* COORDINATOR**

Barbara R. Jasny

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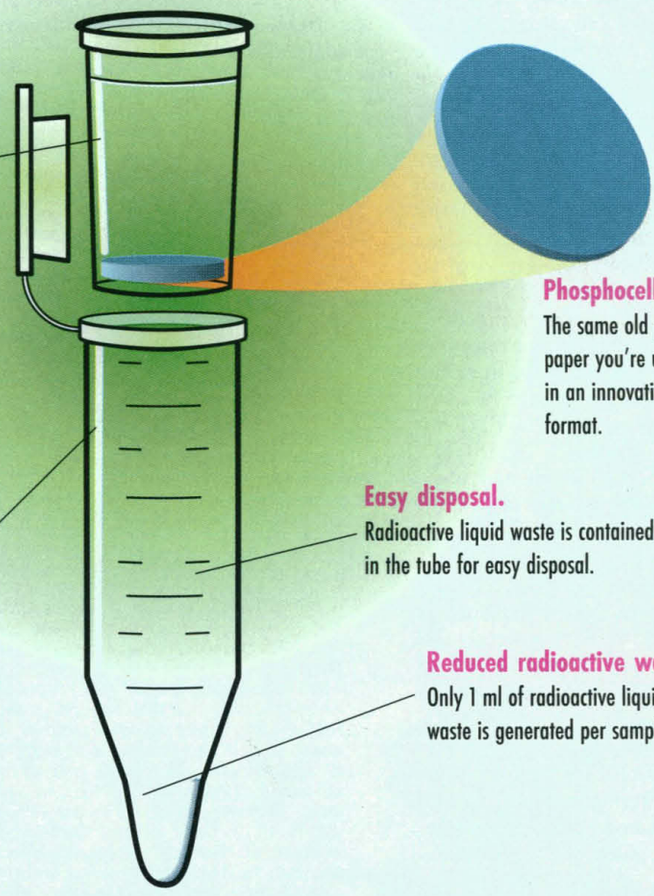

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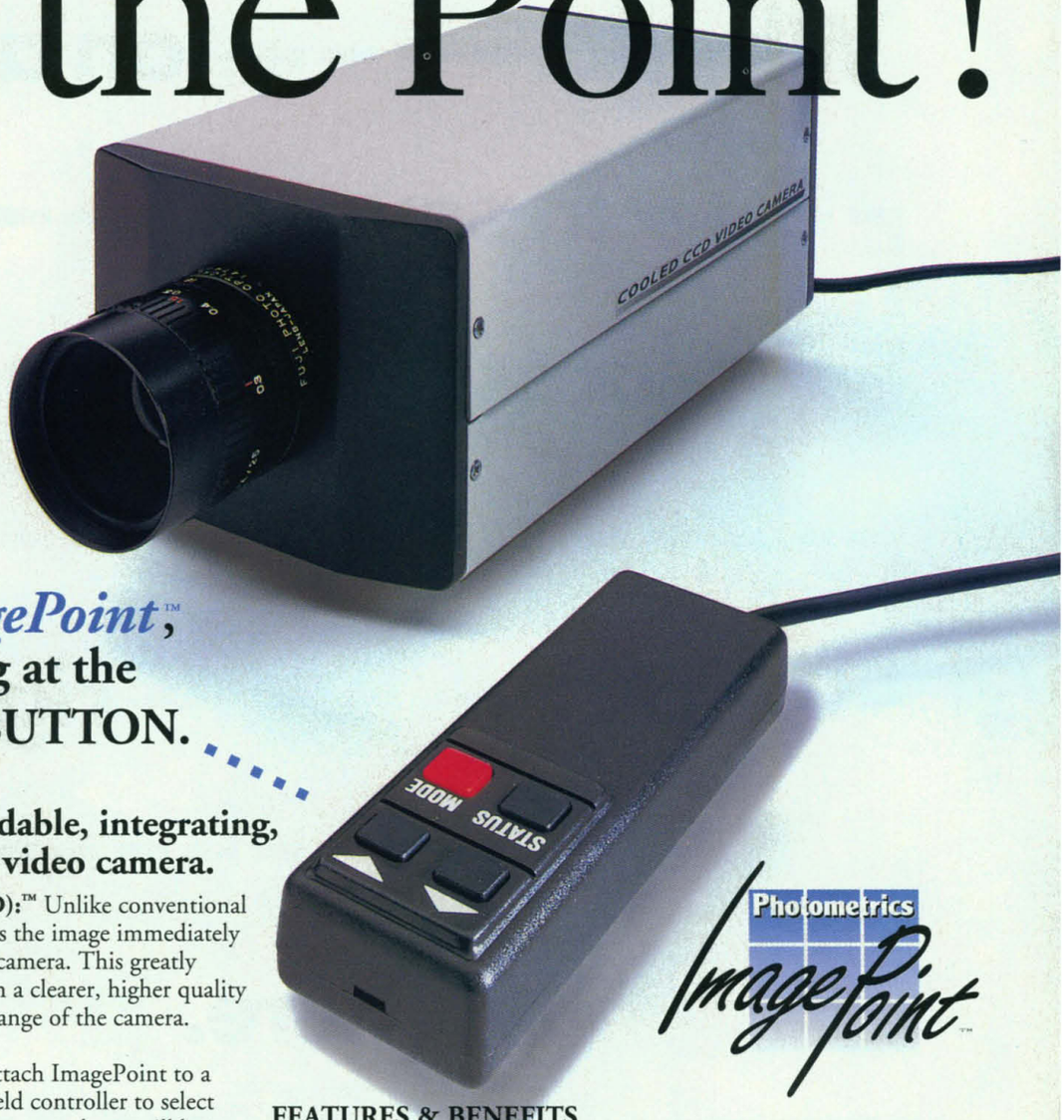

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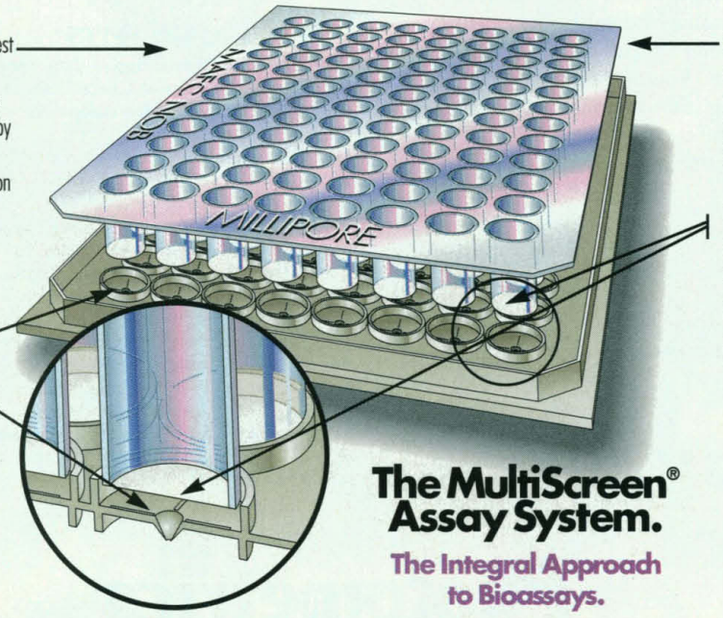

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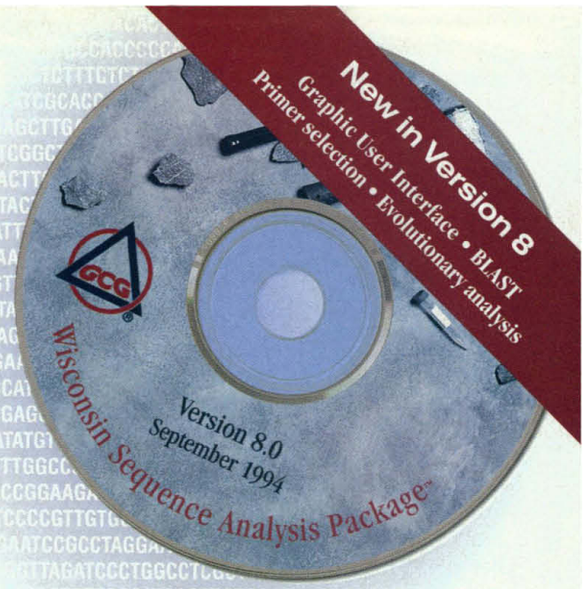
And now, the development of gene sequencing has made it possible to make the first accurate maps of the world of inheritance.



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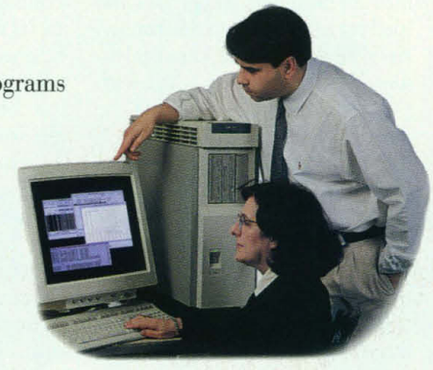

Dr. J.C. King and V.J. LaRosa of Tufts University.
Project: *Guinea pig LHRH gene in collaboration with Dr. S. Radovick of The Children's Hospital, Boston.*
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