American Association for the Advancement of Science

SCIENCE

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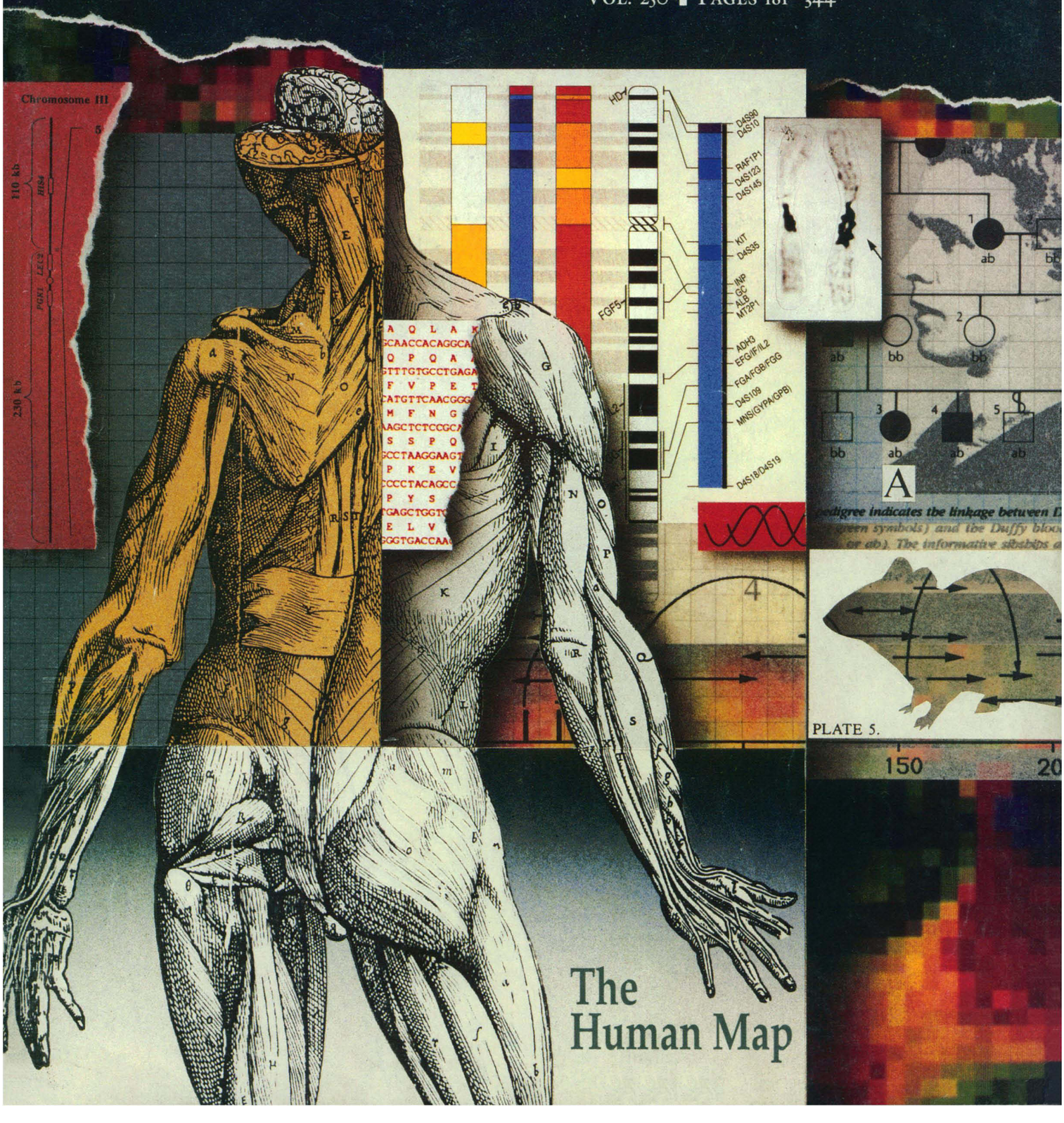

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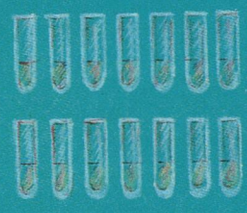

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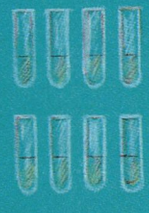

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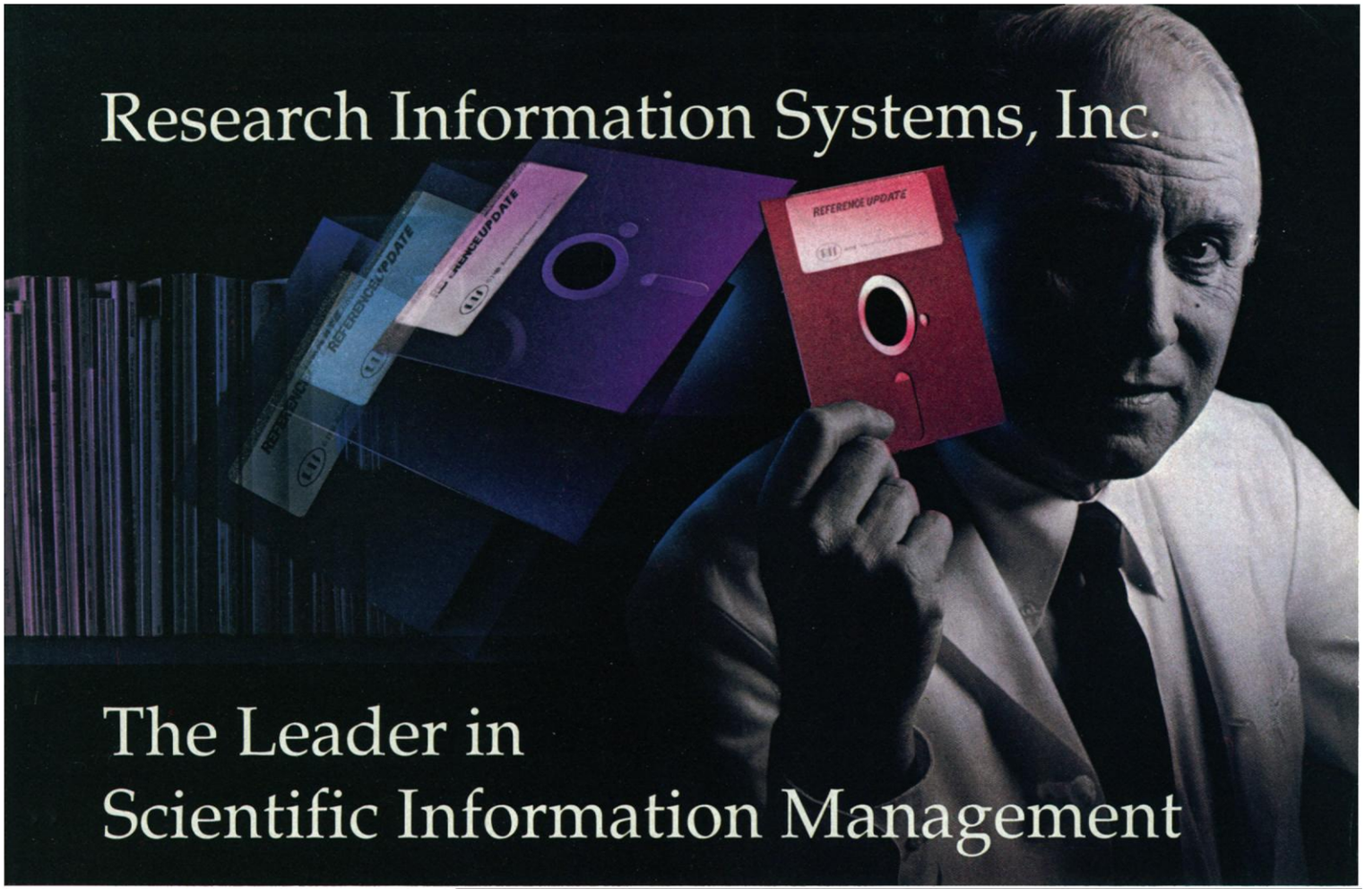

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AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

SCIENCE

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THE HUMAN GENOME MAP 1990

Pullout chart appearing on pages 262 a–p

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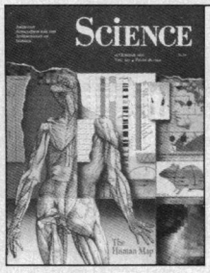
■ The American Association for the Advancement of Science was founded in 1848 and incorporated in 1874. Its objectives are to further the work of scientists, to facilitate cooperation among them, to foster scientific freedom and responsibility, to improve the effectiveness of science in the promotion of human welfare, to advance education in science, and to increase public understanding and appreciation of the importance and promise of the methods of science in human progress.



COVER Just as the ancient navigators depended on maps and charts to explore the unknown, investigators today are building maps and charts with which to explore new scientific frontiers. This issue contains a special feature, The Human Genome Map 1990 (pages 262*a*–262*p*), and special articles and reports relating to genome mapping and the neurosciences. [Cover illustration by Scott Roberts, Baltimore, MD]

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The human genome

INSERTED in this issue is a wall chart of the human genome; it illustrates what is currently known about the distribution of genes, genetic markers, and other landmarks on the 23 pairs of human chromosomes. The chart is a compilation of data from diverse sources and should serve as a jumping-off place for future gene mapping efforts. How the chart was prepared and some of the limitations and goals of current mapping strategies are summarized by Stephens *et al.* (page 237). A historic perspective on gene mapping is provided by Culliton (page 210). One of the newer techniques that promises to facilitate genome mapping—radiation hybrid mapping—is described by Cox *et al.* (page 245). Chromosomes are exposed to a high dose of radiation; this breaks them into a number of fragments; the fragments are then rescued in cells where genetic markers present on the fragments can be identified. With statistical methods, the distance between markers can be determined and a likely order for the markers on the chromosomes can be assigned. Koob and Szybalski take a different strategic tack for mapping: their Achilles' heel cleavage method cuts a large chromosome at only a single precisely defined site that was made vulnerable by bioengineering techniques (page 271). Just how important is a human genome for individual development? Bouchard *et al.* summarize the results of a continuing study of identical human twins who have been reared apart; this study shows the strong role played by the genome in IQ development (page 223). Koshland's editorial also addresses this issue (page 189).

Neuroscience research

RESEARCH on channels, receptors, proteins, cellular networks, and cognition is contributing to the development of increasingly plausible and well-defined models for how the whole nervous system operates. These studies have been carried out in experimental systems that range from simple cultures to complex primates. Seven reports this week illustrate both the range of topics covered by neuroscience research and the levels of complexity possible. At the "simple" end of the spectrum are studies of membrane channels through which ions enter cells; at the complex end is an investigation of where memories reside in the brain. *Channels*: A magnesium-dependent inward current has been identified in *Paramecia*, likely presaging the discovery of similar channels in other organisms. Changes in magnesium concentrations inside the cell are viewed as important physiologic regulators of cell activity (Preston, page 285). Two "contact" amino acids have been identified in the outer mouth of a potassium ion channel; these amino acids may be central to ion conductance not only in potassium channels but also in other cation channels (MacKinnon and Yellen, page 276). *Receptors*: Motor and sensory stimulation have an impact on the development of the mammalian nervous system and one mediator of this effect may be NMDA receptors: NMDA receptor activation was shown to directly affect expression of a surface glycoprotein of motor neurons in the developing spinal cord of the hamster; the affected protein is one thought to have a role in synapse formation (Kalb and Hockfield, page 294). *Proteins*: Development and functioning of the nervous system are also influenced by secreted neurotrophic factors. The patterns of expression of two factors, BDNF and NT3, were mapped in normal rodent brains and found to be distinctive. BDNF (like classic nerve growth factor) was expressed in just those areas of the brain where damage in Alzheimer's disease is most severe; BDNF supplementation (or supplementation with nerve growth factor) might therefore prove ameliorative in patients with this disease (Phillips *et al.*, page 290). Another protein, amyloid β, can be neurotrophic to certain types of cells in culture and neurotoxic to others. If it has similar effects in vivo, low concentrations of amyloid β might serve to stimulate development of young differentiating neurons; accumulation of amyloid β in aging or diseased brains might promote the degeneration of older cells. Tachykinin neuropeptides reversed the effects of amyloid β, raising the possibility that tachykinins might be effective in reversing neurodegeneration in Alzheimer's disease and Down syndrome, two clinical situations in which amyloid β plaques accumulate (Yankner *et al.*, page 279). *Cellular networks*: For the first time a simple neural network—the three-cell "central pattern generator" that underlies respiration in air-breathing pond snails—has been made operational in vitro (Syed *et al.*, page 282). The significance of this accomplishment is discussed in a story on networks (Barinaga, page 206). *Cognition*: Memories for learned tasks have been shown to reside temporarily in the hippocampal formation of the brain and to be transferred elsewhere (probably to the neocortex) after a period of time: normal monkeys remember best recently learned task; monkeys whose hippocampal formation is removed after training remember best tasks that were learned in the more distant past (Zola-Morgan and Squire, page 288).

Accelerated particles from the sun

HIGH-ENERGY electrons and ions are produced in association with solar flares. Acceleration of these charged particles to energies as high as 20 gigaelectron volts has been observed. What mechanism or mechanisms can account for particle acceleration and do similar processes operate elsewhere in the universe where transient x-ray and γ-ray bursts occur? Data on emissions from solar flares and other sources have been collected by many different types of ground-based and space-based instruments during the past few decades. In a review, Chupp presents the spectral signatures that have been inferred and plausible models for explaining what might drive acceleration; he points out that space missions concentrating on the high-energy physics of the sun are essential for obtaining the higher resolution data needed to understand what really drives these acceleration phenomena (page 229).

■ RUTH LEVY GUYER

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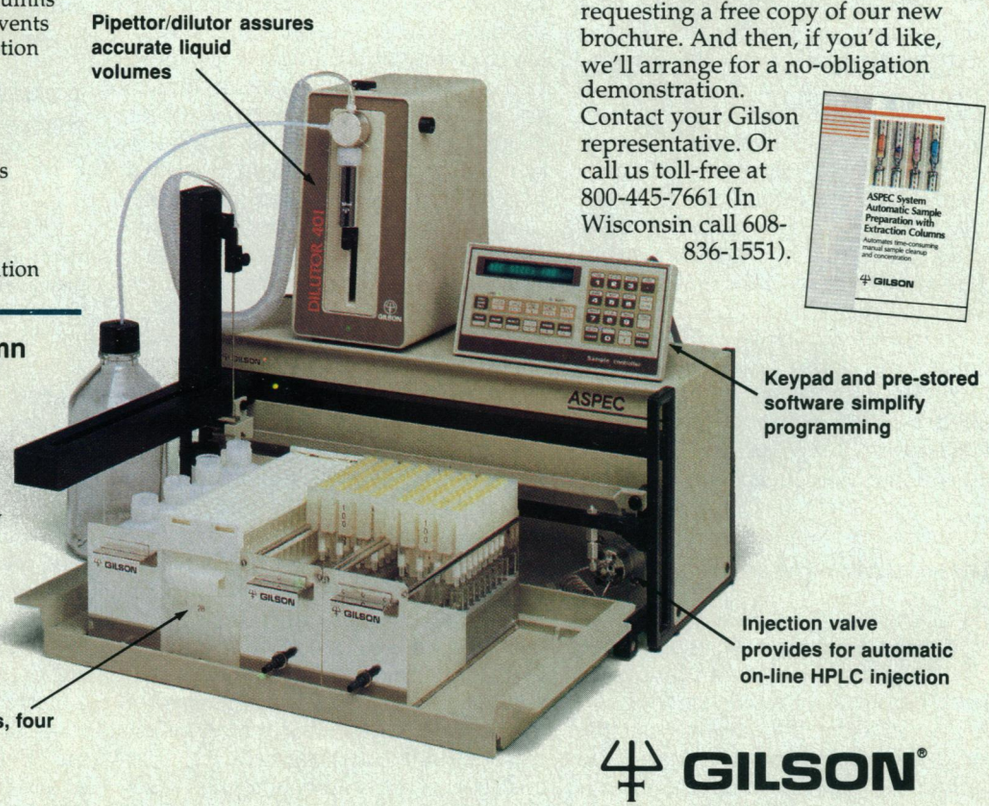

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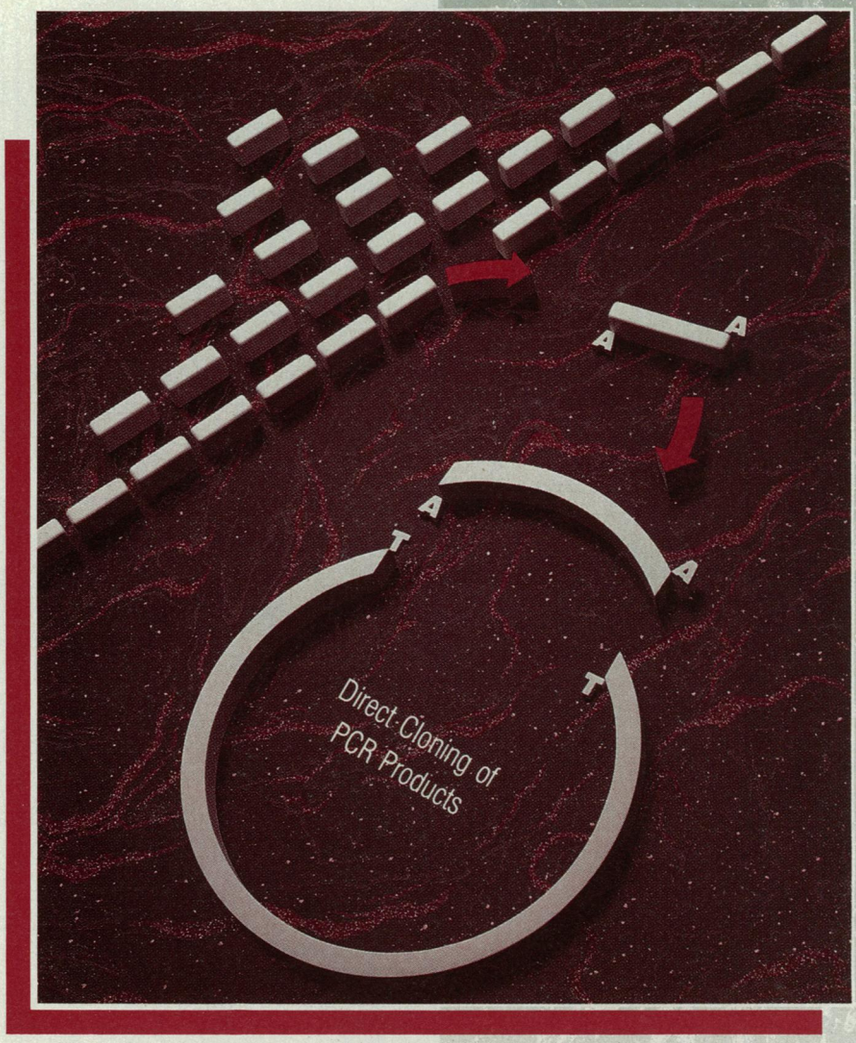

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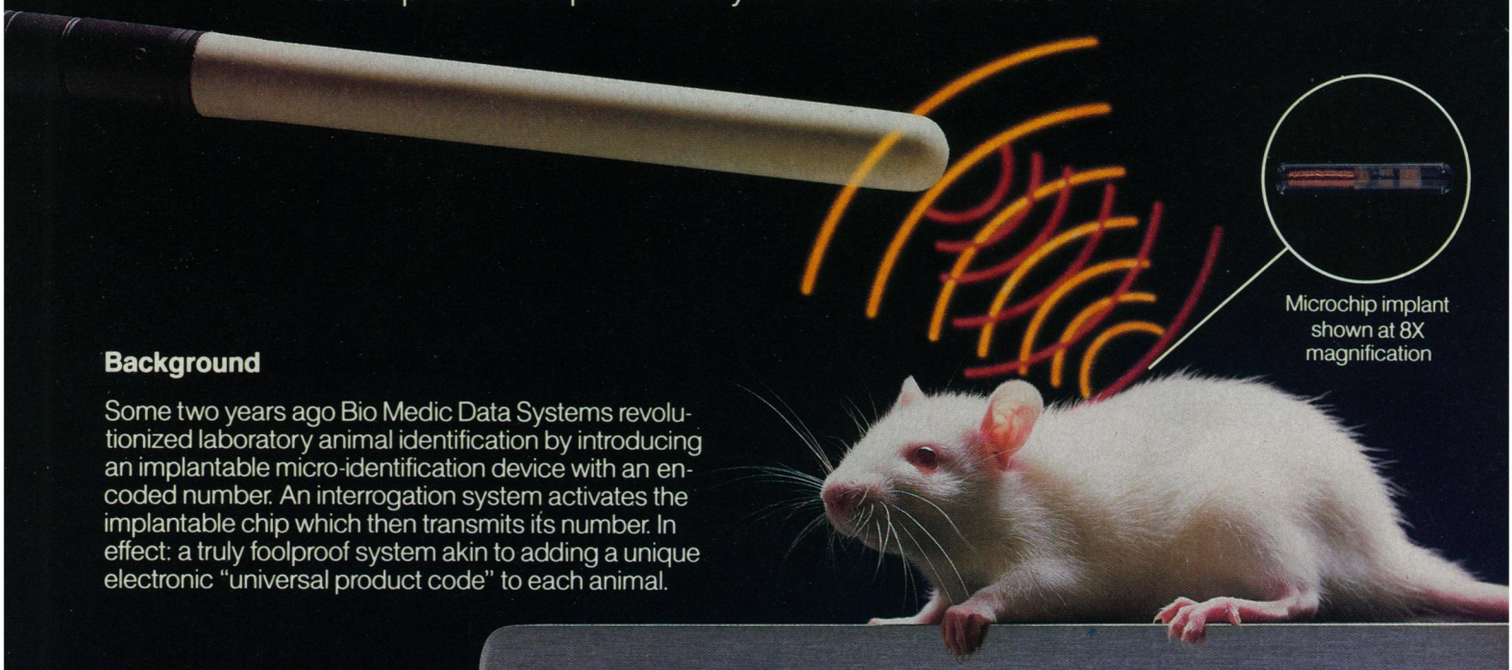
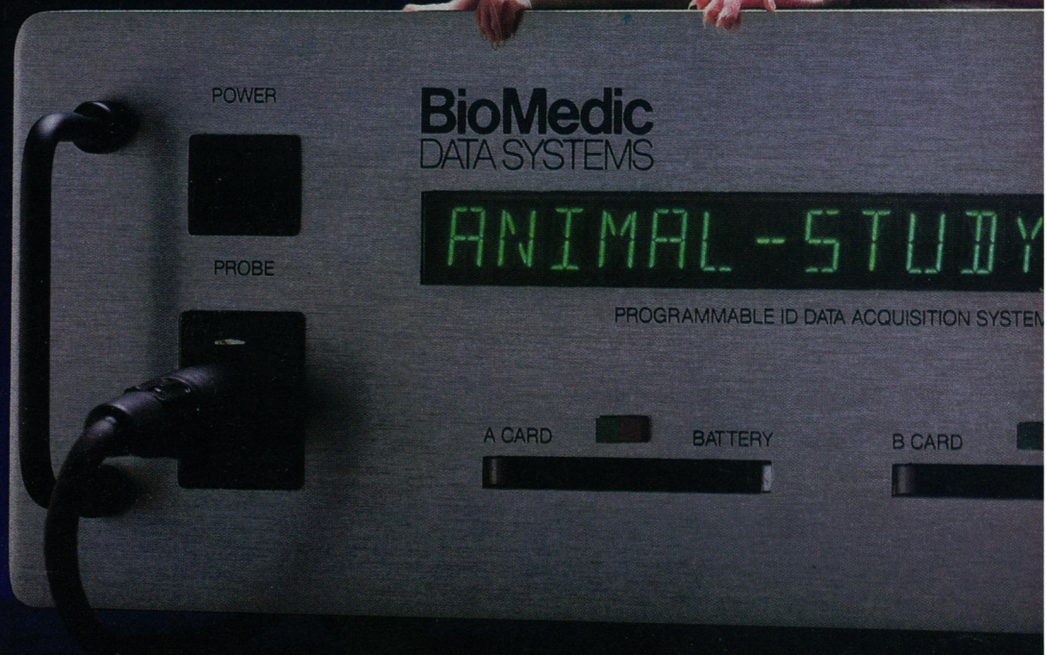


Microchip implant shown at 8X magnification

Background

Some two years ago Bio Medic Data Systems revolutionized laboratory animal identification by introducing an implantable micro-identification device with an encoded number. An interrogation system activates the implantable chip which then transmits its number. In effect: a truly foolproof system akin to adding a unique electronic "universal product code" to each animal.



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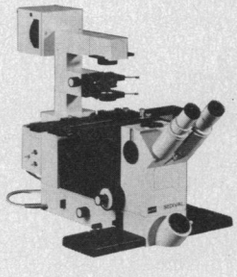

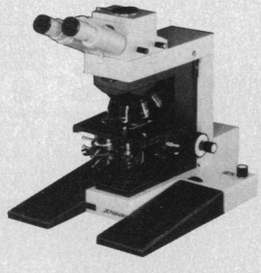

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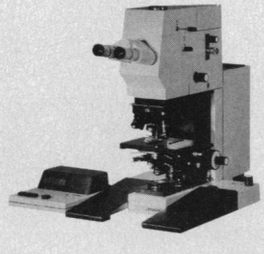

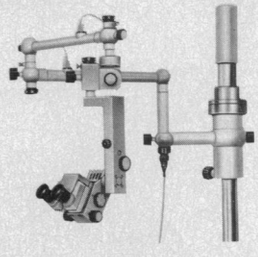

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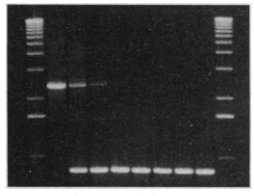

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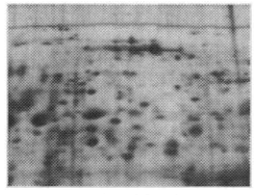

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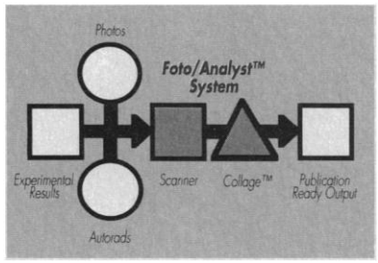

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The Division of Cancer Etiology

National Cancer Institute

Announces To the Scientific Community The Availability of the Following Resources/Services For Cancer Related Research As Noted Below:

Biological Resources

■ Cell Culture Identification Service. Using Isozyme Analysis, Immunofluorescence and Karyotypic Analysis (Chromosome Banding).

Contact: Dr. Ward Peterson
Children's Hospital of Michigan
3901 Beaubien Boulevard
Detroit, MI 48201
(313) 745-5570

Citing Contract #N01—CP—85645

Cost: $375/Analysis

■ Goat Antisera Against: Avian, Bovine, Feline, Murine, and Primate Intact Viruses and Viral Proteins; Antibodies to Immunoglobulins for a number of species. Preimmune Sera available for some Virus Antisera.

Contact: Ms. Elizabeth Donley
BCB Repository
Microbiological Associates, Inc.
5221 River Road
Bethesda, MD 20816
(301) 657-8169

Citing Contract #N01—CP—61020

Cost: $75.00/5 ml. (Antisera)
25.00/5 ml. (Preimmune Sera)
65.00/100 ml. (Immunoglobulins)
(Frozen Material)

■ Viruses: Avian, Feline, Murine, and Primate Viruses Produced in vivo and in vitro.

Contact: Ms. Elizabeth Donley
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Microbiological Associates, Inc.
5221 River Road
Bethesda, MD 20816
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Citing Contract #N01—CP—61020

Cost: Inquire

■ Monoclonal Antibodies are available with specificities for synthetic peptides representing the amino acid sequences of the left end, right end and active site of the oncogene products of avian and mammalian retroviruses. Blocking peptides are also available, as are a limited number of cell lines producing the monoclonal antibodies.

Contact: Ms. Elizabeth Donley
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Microbiological Associates, Inc.
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(301) 657-8169

Citing Contract #N01—CP—61020

Cost: Peptides —$25.00/mg.
Ascites Fluid — 45.00/ml.
Cell Culture —100.00/culture.

(Plus Shipping and Handling)

■ Human sera from donors with: Malignancies (including nasopharyngeal carcinoma), Non-Malignant Disorders, and Normal Individuals

Contact: Coordinator for Research Resources
Biological Carcinogenesis Branch,
DCE, NCI, NIH
Executive Plaza North, Room 540
Bethesda, MD 20892

Cost: Shipping and handling charges only.

■ The Division of Cancer Etiology's Registry of Experimental Cancers announces the availability of 16 different study sets containing histologic slides of rodent tumors. The study sets, with accompanying syllabi, illustrate a variety of spontaneous and induced tumors, chiefly of rats, mice, and mastomys. Each set is available to cancer investigators worldwide, without charge, for up to two months. Requests or inquiries should be addressed to:

Contact: Registry of Experimental Cancers
National Cancer Institute
Building 41, Room D311
NIH, Bethesda, MD 20892
USA

Chemical Resources

■ Analytical resources for the collection, separation, and elucidation of the components of cigarette smoke and cigarette smoke condensates: A contractor with experience in the development of analytical methods for the determination of constituents of cigarette smoke and of specialty instrumentation for inhalation toxicology is available to assist qualified investigators with particular interest in studies on human and animal model exposure to environmental and sidestream smoke. A large inventory of reference experimental cigarettes, Standard Low Yield Reference Cigarettes, and an extensive chemical data base on smoke and smoke condensate components is available.

Contact: Harold E. Seifried, Ph.D.
Chemical and Physical
Carcinogenesis Branch
DCE, NCI
Executive Plaza North, Room 700
Bethesda, MD 20892
(301) 496-5471

Cost: Inquire

■ Chemical Carcinogen Reference Standard Repository: Reference quantities of over 750 compounds are available. The newest additions are dilute aqueous standards of PAH deoxyguanosine-3'-monophosphates for Randerath ^{32}P post labelling assays. Other classes of available compounds are: fecapentaenes, food mutagens, polynuclear aromatic hydrocarbons (PAH), PAH metabolites, radiolabeled PAH metabolites, nitrogen heterocycles, nitrosamines/nitrosamides, aromatic amines, aromatic amine metabolites, azo/azoxy aromatics, inorganics, nitroaromatics, pesticides, pharmaceuticals, natural products, dyes, dioxins and chlorinated aliphatics. Data sheets provided with the compounds include chemical and physical properties, analytical data, hazards, storage, and handling information. Catalog available upon request.

Contact: Manager, NCI Chemical
Carcinogen Repository
Midwest Research Institute
425 Volker Boulevard
Kansas City, NO 64110
(816) 753-7600, Ext. 332

Cost: Subject to chemical class code and quantity (see catalog) plus handling and shipping charges.

Epidemiology Resources

■ The Tumor Virus Epidemiology Repository (TVER) contains sera and other biological samples from more than 13,000 patients and controls obtained in 12 different countries. The TVER was established primarily to support collaborative research on the role of Epstein-Barr virus (EBV) in Burkitt's lymphoma, nasopharyngeal carcinoma, and related diseases.

The TVER is able to adjust its collection to facilitate the development of new collaborative studies. In addition, some samples are available for reagents and independent research. The most extensive collections are serum samples from patients with Burkitt's lymphoma (sera from more than 1,000 patients).

Contact: Dr. Paul H. Levine
Environmental Epidemiology Branch, DCE, NCI, NIH
Executive Plaza North, Room 434
Bethesda, MD 20892
(301) 496-8115

Cost: Free to Collaborating Investigators; Others: Dependent on Processing Time

---

■ The National Institute of Allergy and Infectious Diseases and the National Cancer Institute have developed a repository of biological specimens from homosexual men. The specimens were collected through contracts with five major U.S. universities for studies of the natural history of acquired immune deficiency syndrome (AIDS).

Information about applying for collaborative use of these specimens is available from the NIAID Project Officer or the NCI Co-Project Officer.

Contact: Chief, Epidemiology Branch, AIDS Program
National Institute of Allergy and Infectious Diseases
CDC Bldg., Room 240
National Institutes of Health
Bethesda, MD 20892

or to Chief
Extramural Programs Branch, EBP,
Division of Cancer Etiology, NCI
Executive Plaza North, Room 535
Bethesda, MD 20892

■ Human fibroblast cultures from individuals at high risk of cancer, members of cancer-prone families, and normal family members are available. Collection is historical with unknown viability. Catalogue unavailable. Information requests should include potential use of cultures.

Contact: Chief, Family Studies Section, EEB, DCE, NCI, NIH
Executive Plaza North, Room 439
Bethesda, MD 20892
(301) 496-4375

Cost: Free to collaborating investigators
Others: $70/cell line.

■ The National Cancer Institute has available the Animal Morbidity/Mortality Survey of Colleges of Veterinary Medicine in North America (also known as the Veterinary Medical Data Program). This unique registry of veterinary medical information represents patient data on animals seen at collaborating veterinary teaching facilities; 3 million hospital episodes have been abstracted and computerized in a standardized record format. Disease information is coded using the scheme of the Standard Nomenclature of Veterinary Disease and Operations. The computer tapes will be made available upon request.

Contact: Dr. Howard M. Hayes
Environmental Epidemiology Branch
Epidemiology and Biostatistics Program
Division of Cancer Etiology
Executive Plaza North, Room 443
Bethesda, MD 20892
(301) 496-1691

Cost: Inquire

■ The Epidemiology and Biostatistics Program of the National Cancer Institute has developed the Observed versus Expected (O/E) software system which calculates: (1) the number of observed events (e.g. cancer cases or deaths) in a study group at risk; (2) the number of expected events in a study group based on the rate of occurrence in some standard or referent population; (3) the ratio of observed to expected events; and (4) the significance of this ratio. The system is user friendly and capable of executing a series of calculations by different variables such as age, time group, date of exposure, age at date of exposure, duration of exposure, year relative to entry and cause of event. The O/E System provides tables by race, sex and user defined variables, allows user defined latency intervals and accepts standard or user prepared rates. O/E is written in COBOL and is exportable to most mainframes.

Contact: Ruth Wolfson
Epidemiology and Biostatistics Program
Division of Cancer Etiology, NCI
Executive Plaza North, Room 531
Bethesda, MD 20892
(301) 496-1606

Cost: Free to investigators interested in epidemiologic research.

Environmental Cancer

■ NCI's Chemical Carcinogensis Research Information System (CCRIS) is available online through the National Library of Medicine's Toxicology Data Network (TOXNET) system. Through an interagency agreement between NCI and NLM, the CCRIS database has been built and will be maintained and updated as one ot TOXNET's sponsored databases in the broad areas of chemistry, toxicology, and hazardous waste information. The CCRIS database contains evaluated data and information on carcinogens, mutagens, tumor promoters, co-carcinogens, metabolites of carcinogens and carcinogen inhibitors derived from published review articles, on-going current awareness survey of primary literature, NCI/NTP's short- and long-term bioassay studies, the IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, and special studies and reports.

Contact: Dr. Thomas P. Cameron
Office of the Director
Division of Cancer Etiology
National Cancer Institute
Executive Plaza North, Room 712
Bethesda, MD 20892
(301) 496-1625

Cost: Inquire

■ The Special Assistant for Environmental Cancer, Office of the Director, announces the availability of a limited number of copies of the following publications, which have been prepared under contract to NCI:

Survey of Compounds Which Have Been Tested for Carcinogen Activity, PHS-149, 1987-1988
And Proceedings of the Fourth NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, 1986

Contact: Ms. I.C. Blackwood
Office of the Director
Division of Cancer Etiology
National Cancer Institute
Executive Plaza North, Room 712
Bethesda, MD 20892
(301) 496-1625

Cost: Free to investigators interested in environmental cancer

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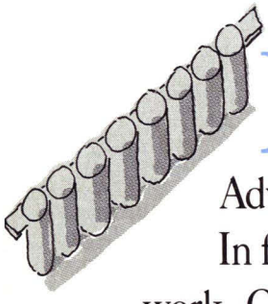

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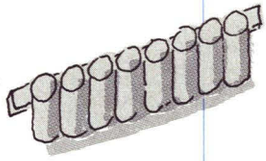

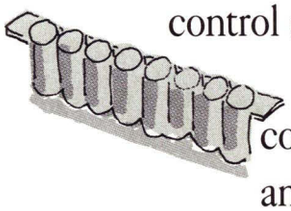

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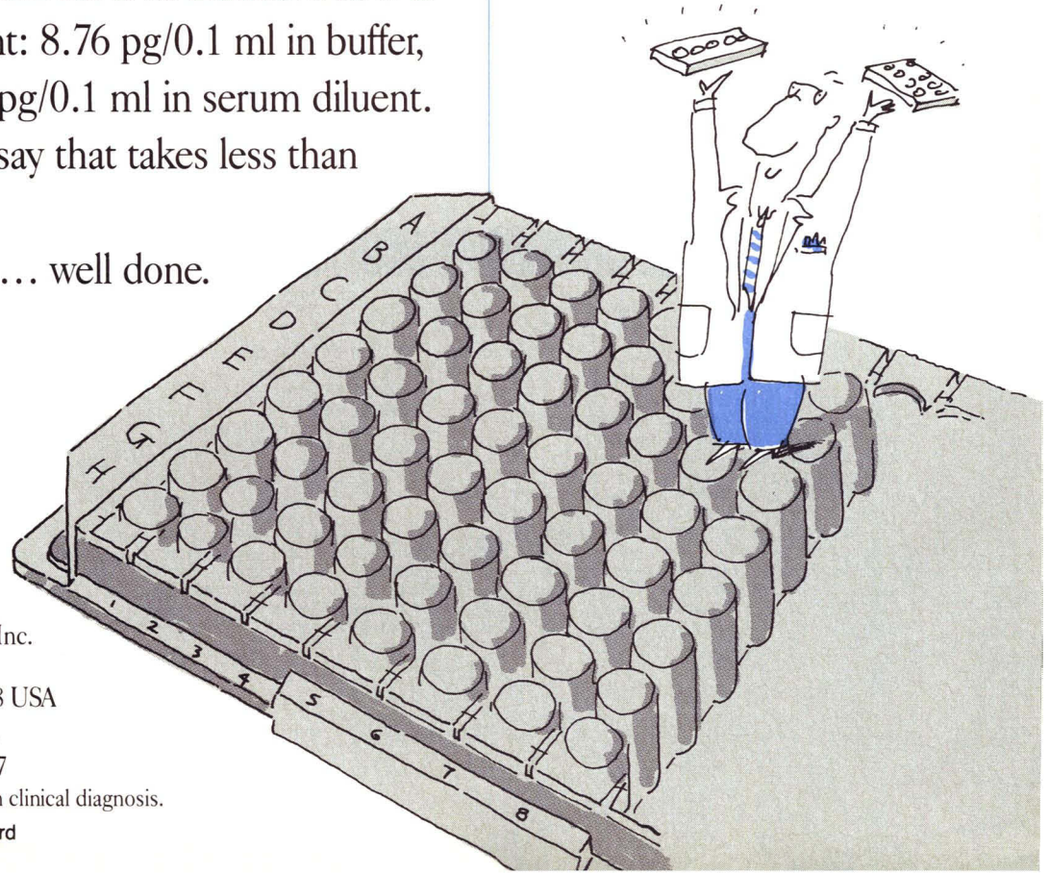

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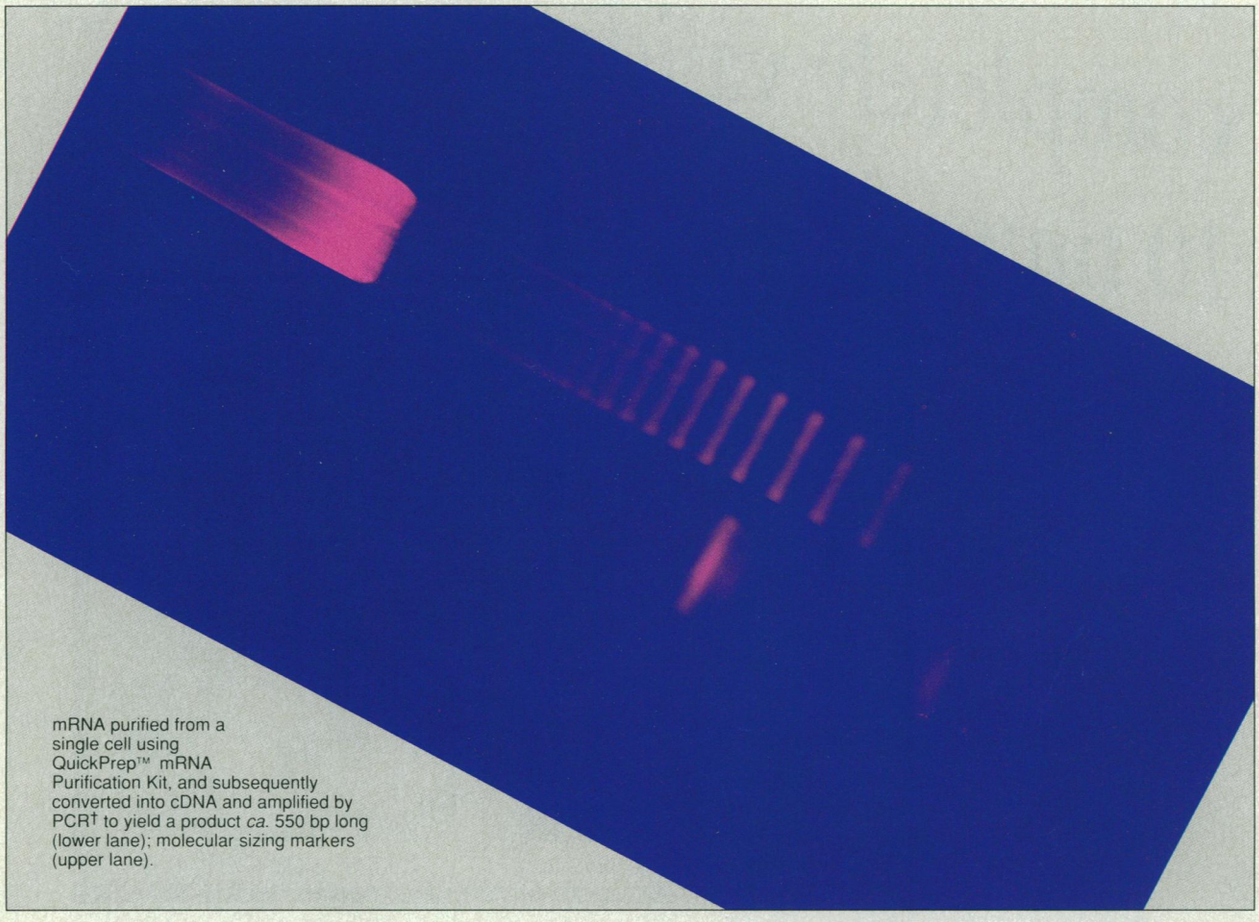

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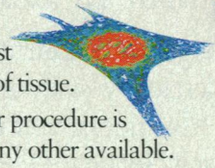

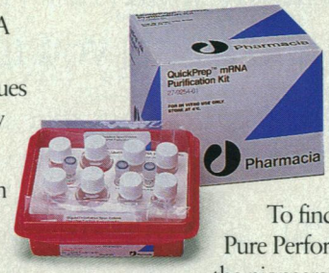

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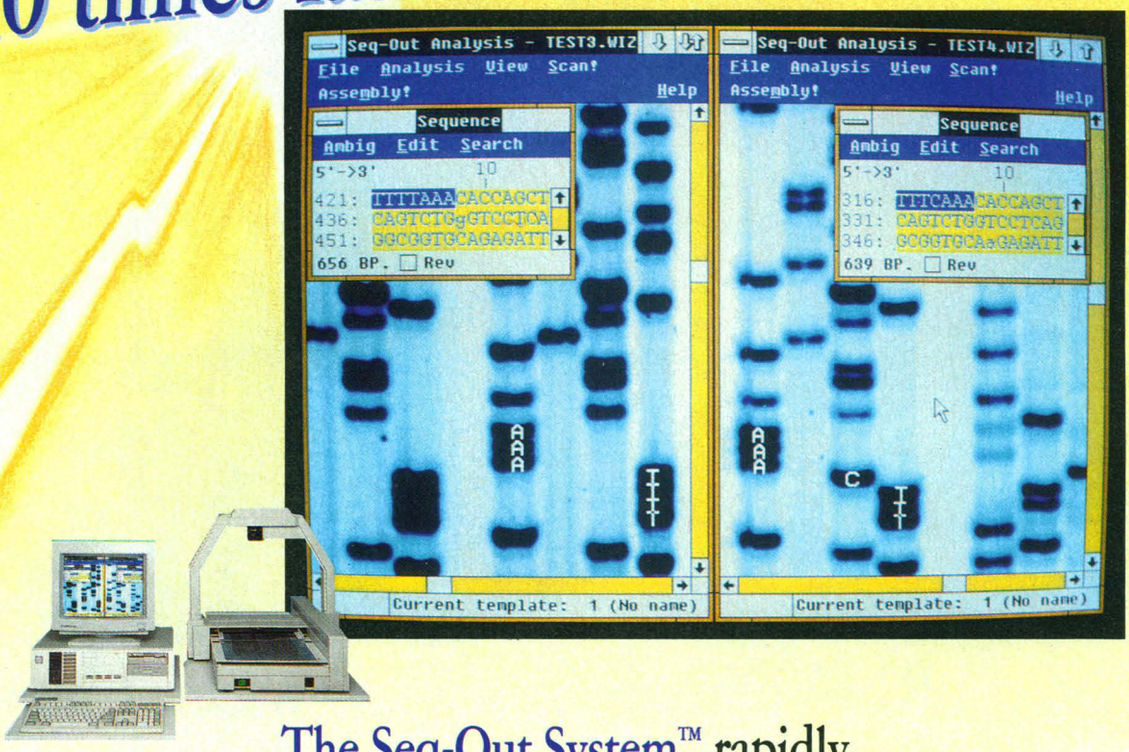

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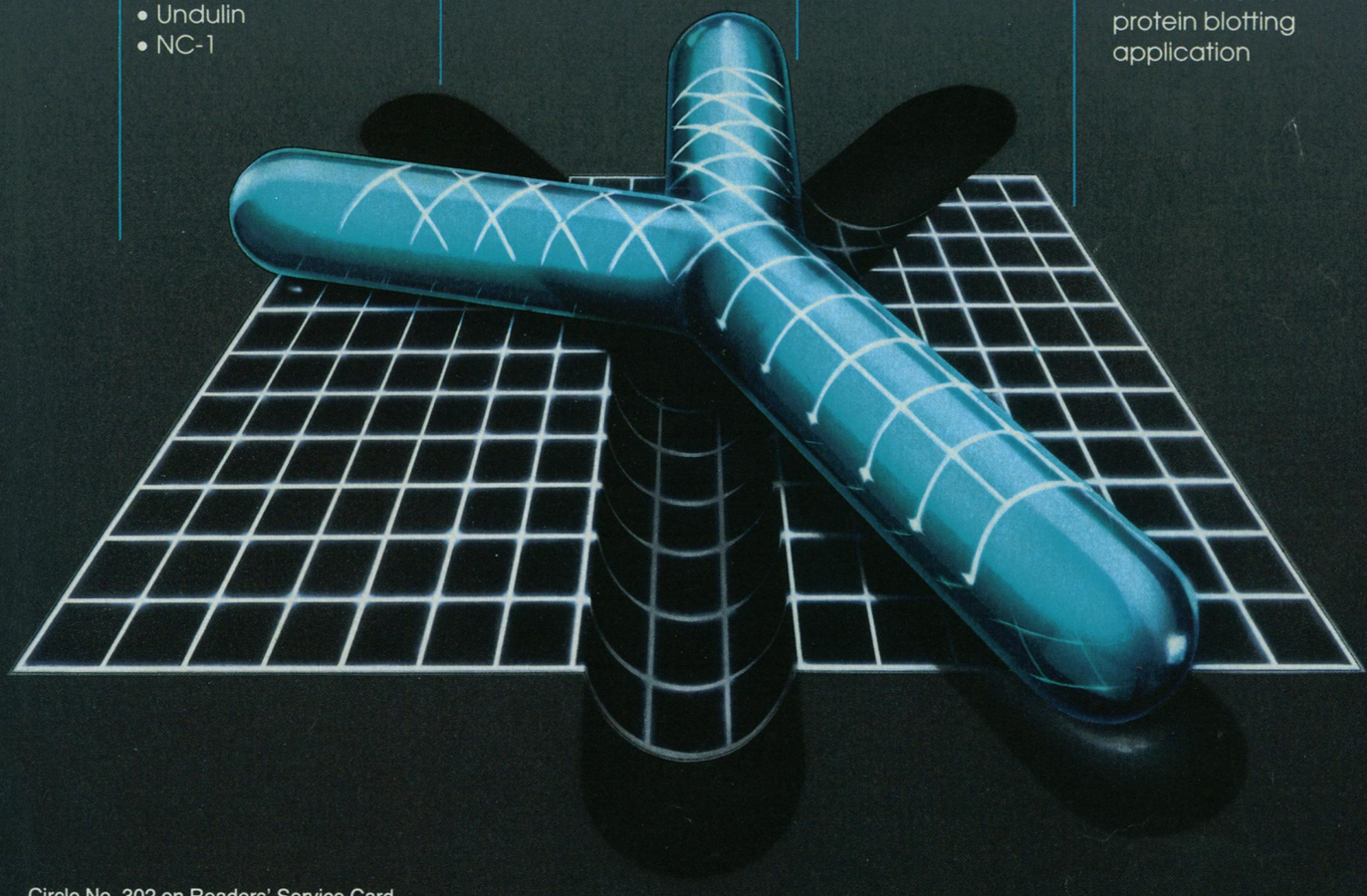

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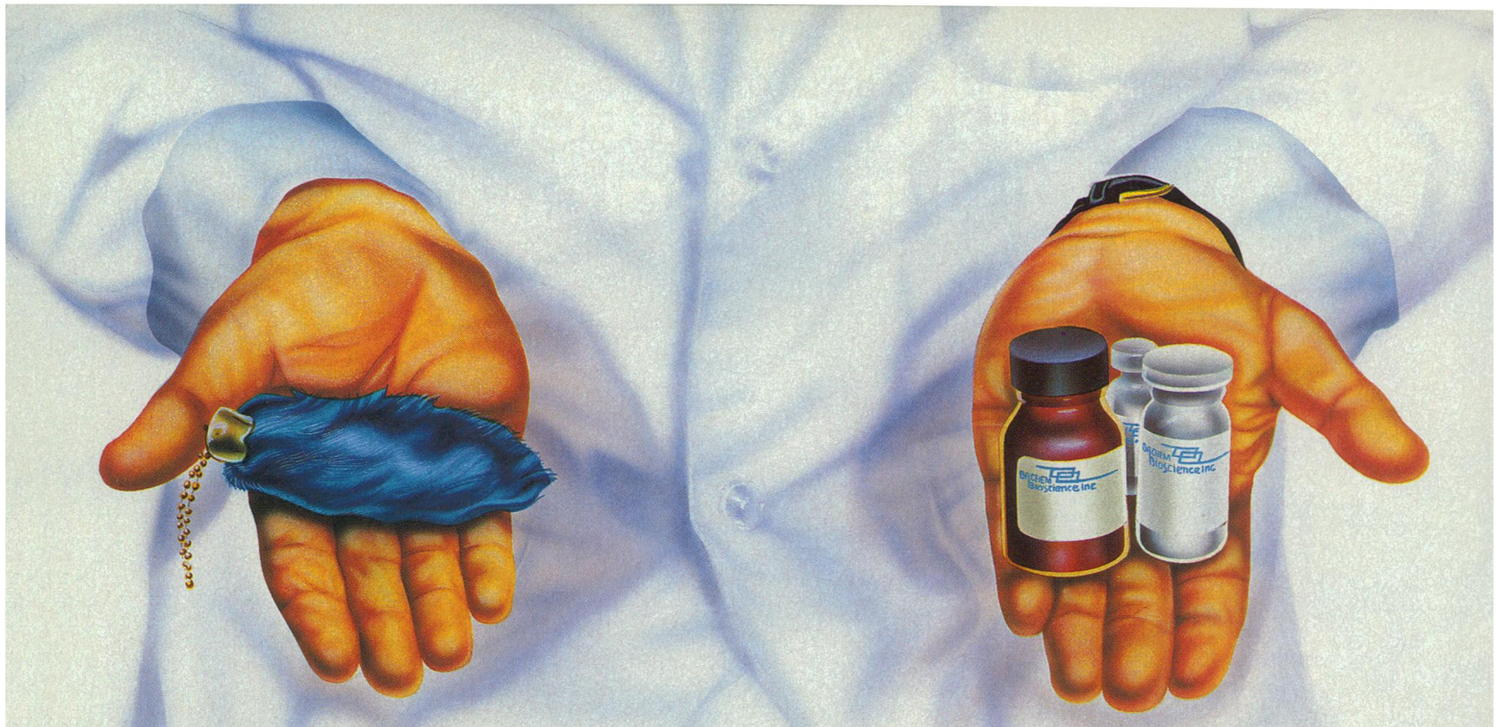

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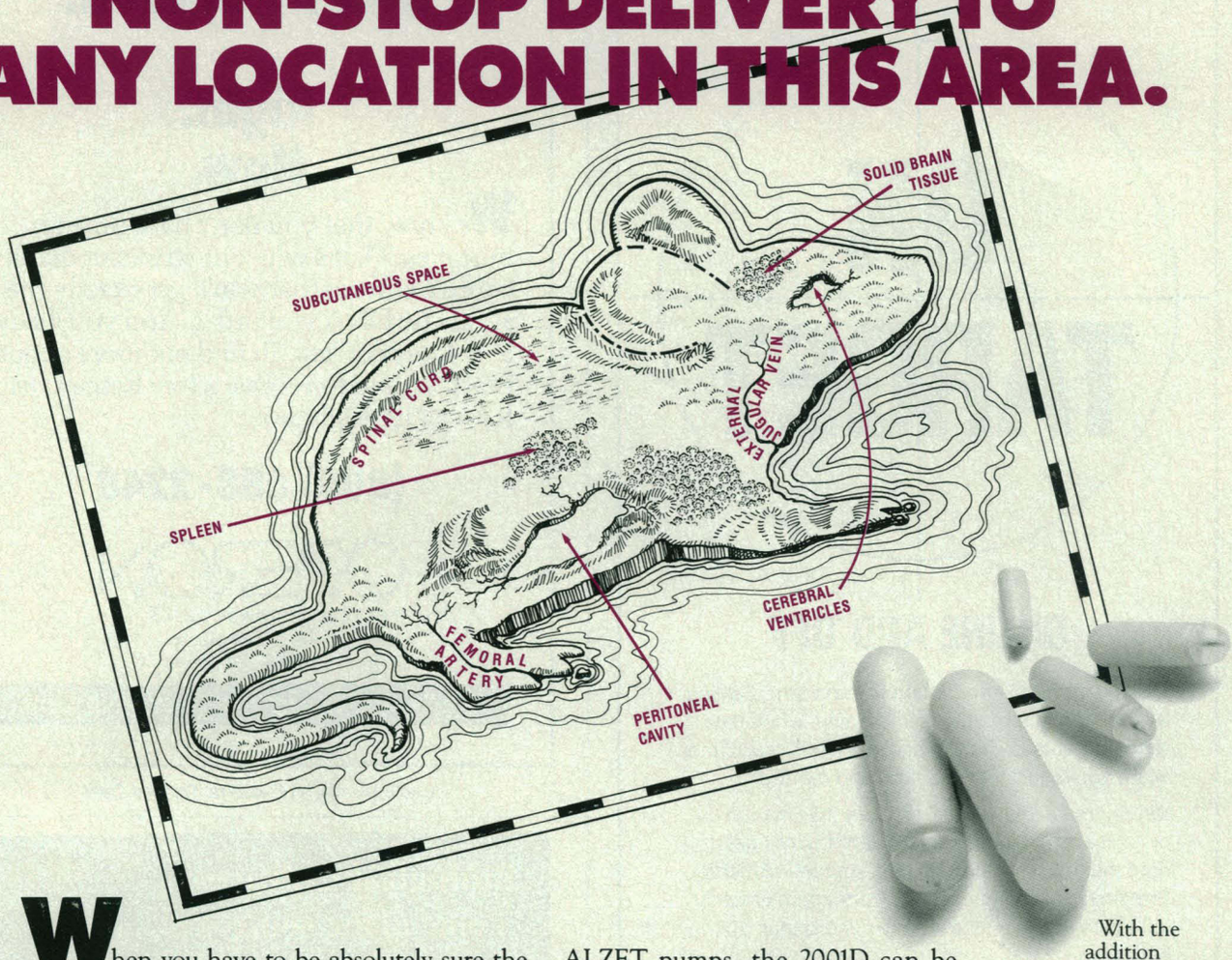

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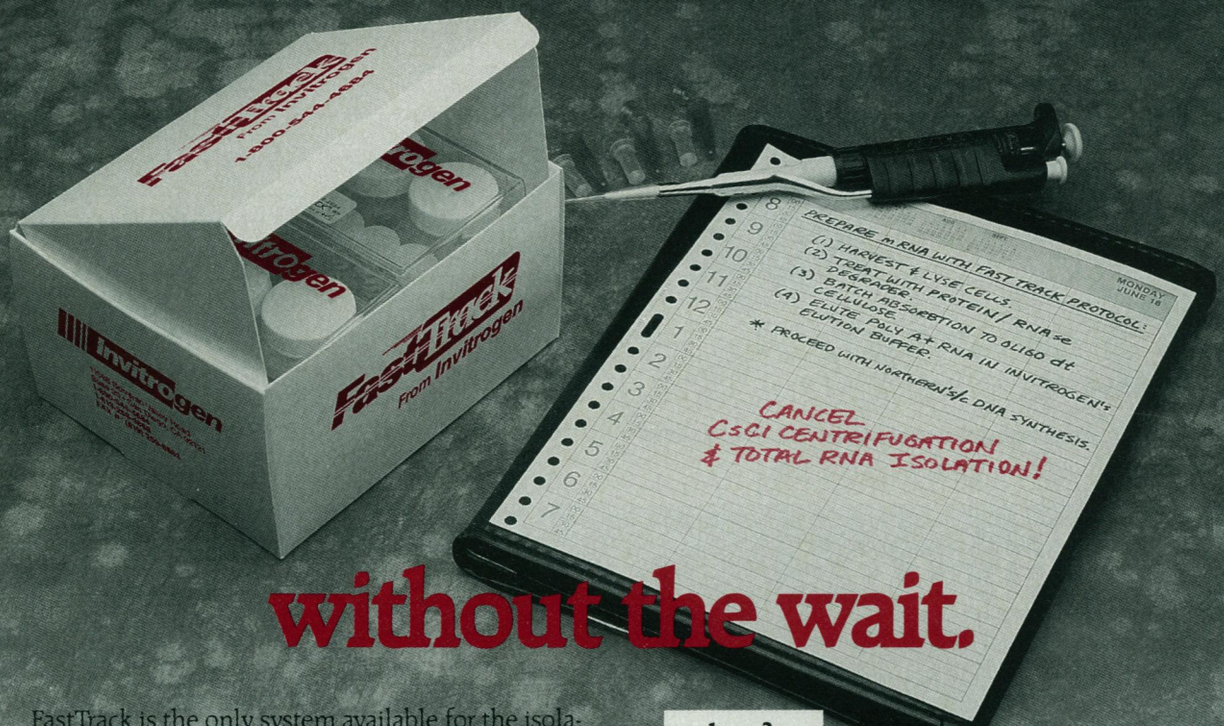

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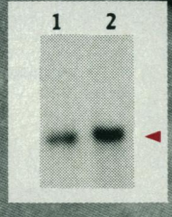

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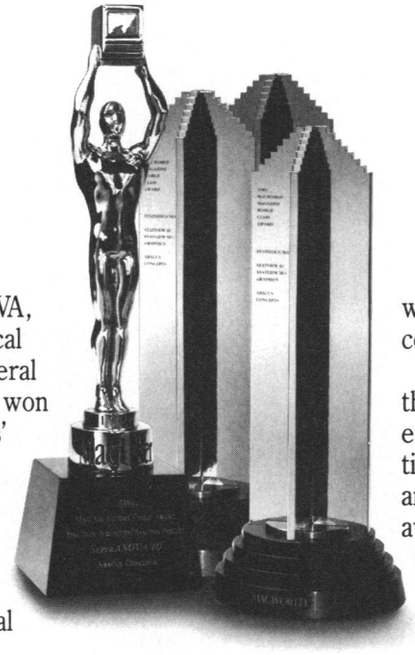

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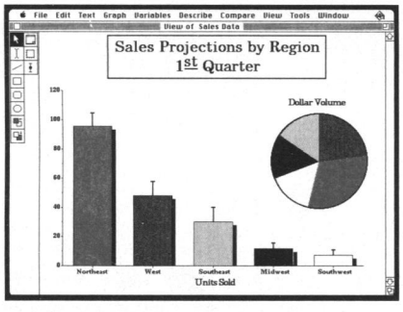

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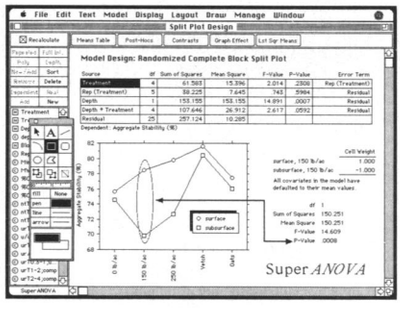

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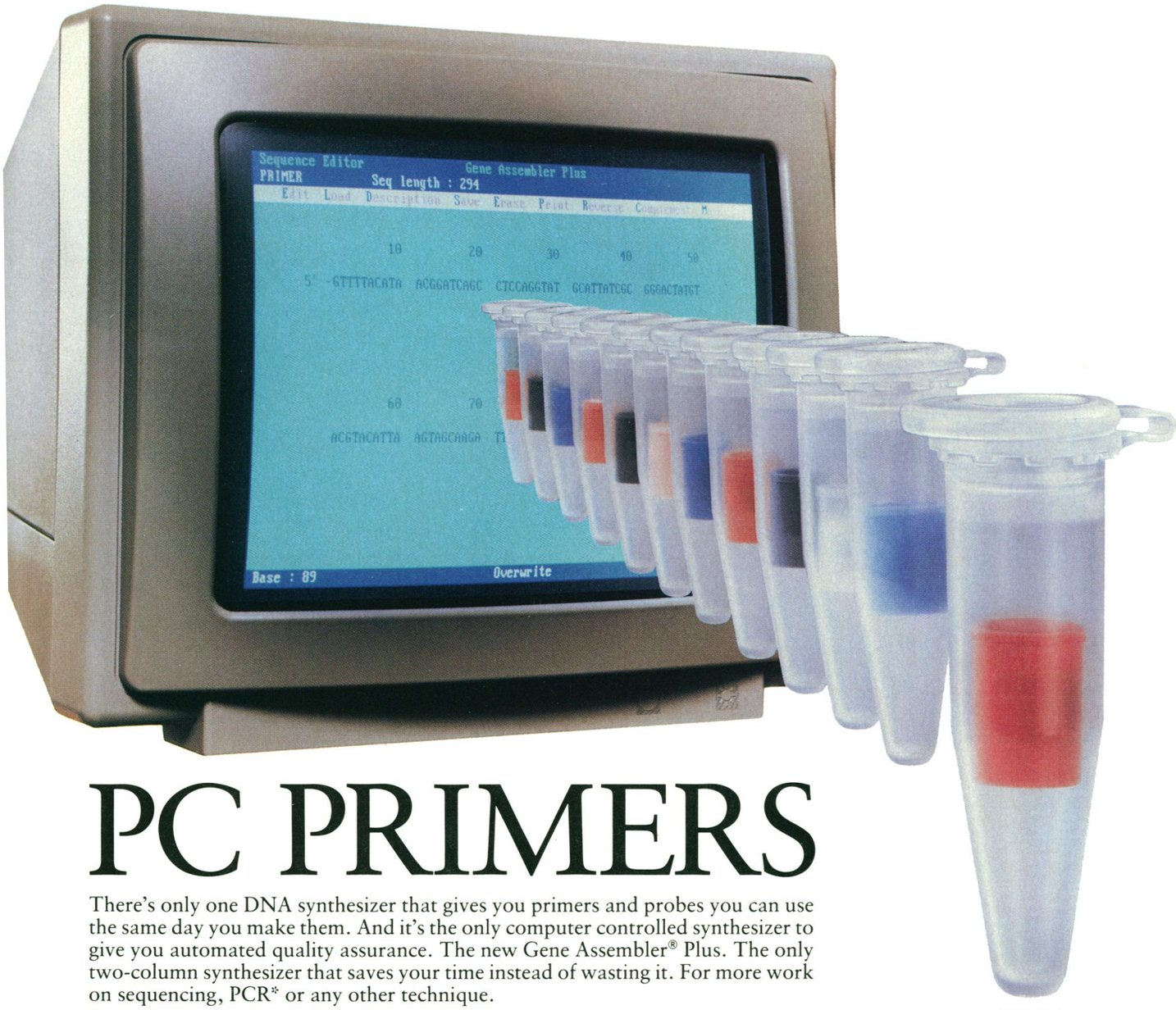

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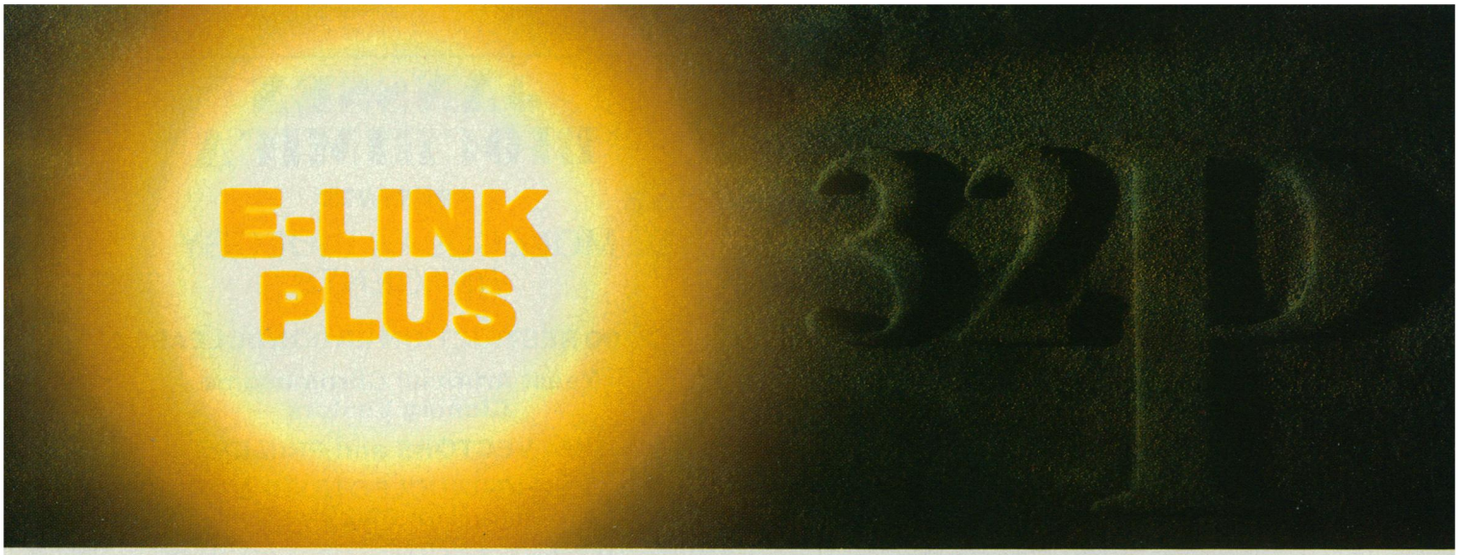

A BRILLIANT NEW STANDARD IN NON-ISOTOPIC DNA DETECTION

CAMBRIDGE RESEARCH BIOCHEMICALS HAS CREATED A NEW NON-ISOTOPIC LABELLING KIT FOR USE WITH OLIGONUCLEOTIDE PROBES. IT'S CALLED E-LINK PLUS™ AND IT USES LUMI-PHOS™ — A STABLE CHEMILUMINESCENCE SUBSTRATE THAT GIVES DETECTION SENSITIVITIES IN EXCESS OF **ONE ATTOMOLE** USING NORMAL X-RAY FILM.

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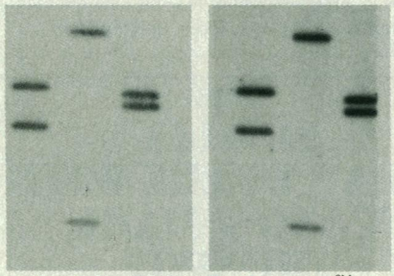

A. Autoradiograph B. Lumigraph℠

DNA fingerprint of 3 genomic samples hybridised with:

A. Minisatellite probe labelled with ^{32}P: Film exposed for 6 hours
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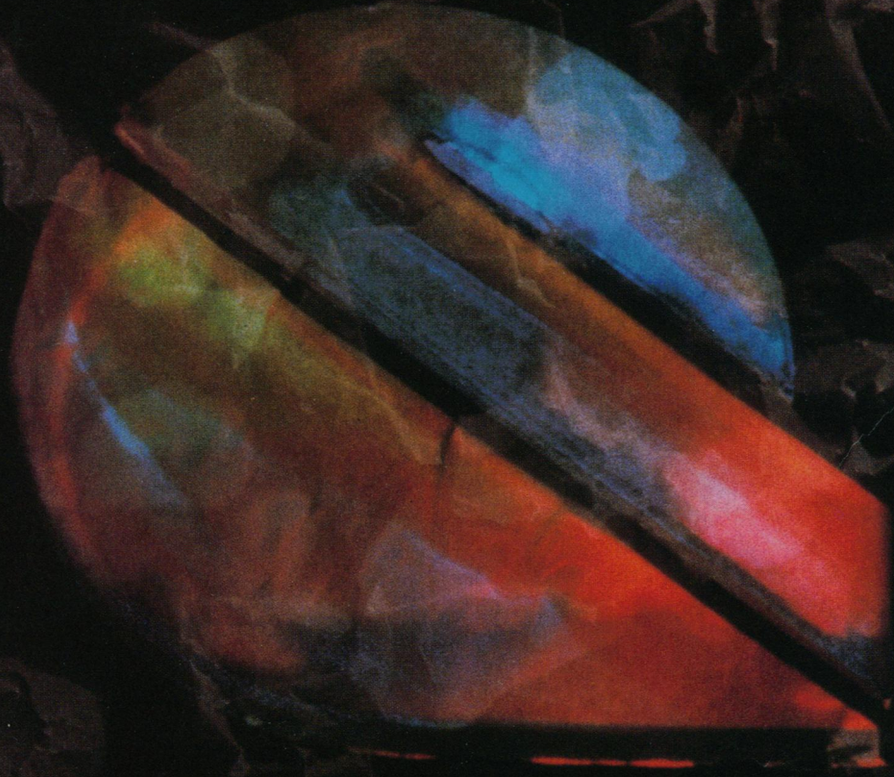

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Scientific Organization:
G.D. Aurbach (USA) and U. Veronesi (I)

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Nutritional Aspects of Osteoporosis
May 16-18 / Lausanne (CH)
Scientific Organization:
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Biotechnology of Cell Regulation
June 20-22 / Siena (I)
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Stress and Reproduction
July 25-27 / Port Douglas (AUS)
Scientific Organization:
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Molecular and Cellular Biology of Reproduction
September 9-10 / Capri (I)
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W. Bardin (USA) and K.J. Catt (USA)

A Molecular View of Steroid Biosynthesis and Metabolism
October 14-16 / Jerusalem (IL)
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The Role of Technology In the "Genome Project"

In the lively debate surrounding the initiative to sequence the human genome, there is one subject on which few disagree: the important role which technology will play in the overall success of the project.

Most discussions of technology tend to focus on new developments, particularly in the areas of automation and data handling. Although developments in these areas will clearly have a major impact, the "genome project" will still depend very heavily on judicious application of well-established (though less glamorous) technologies. In this bulletin, we will examine the likely role of one such well-established technology – separation technology.

According to the most popular scenario for the project, the sequencing of the human genome will be accomplished in two main stages: first, a detailed map will be constructed covering the entire genome; second, sequences will be determined for individual DNA segments corresponding to all of the known map positions (some of which will already have been sequenced in the course of ongoing life science research).

Mapping

For the mapping stage of the project, there is one essential application for separation technology which is immediately apparent: the electrophoretic separation of DNA fragments by size. Two different methods of electrophoresis will be important, depending on the length of the segment being mapped.

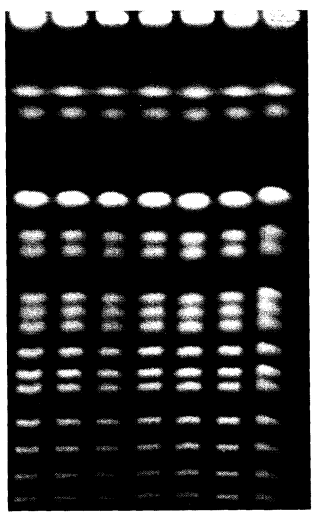
For mapping longer segments of DNA, the method which will be important is pulsed-field gel electrophoresis (PFGE). Depending on the precise conditions chosen by the user, this technique allows the separation of DNA fragments ranging in length from several thousand to several million base-pairs. The technique may be used to map either uncloned genomic DNA (by hybridizing labelled probes to Southern blots of PFGE gels) or large fragments which have been cloned into YAC vectors. In either case, the mapping technique will often involve digestion with a rare-cutting restriction enzyme; Pharmacia LKB Biotechnology offers a number of such enzymes, all prepared to very high standards using our proprietary expertise in purification technology. The long fragments generated by digestion with rare-cutting enzymes can then be separated very conveniently using the Pulsaphor® system from Pharmacia LKB. The original Pulsaphor was the first commercially available equipment for PFGE, and has since been substantially refined with additions such as the Hexagonal Electrode Array and Pulsaphor Plus Controller. These make it simple to obtain "straight-lane" results which are easy to interpret using our "lambda ladder"and yeast chromosome PFGE markers.

For mapping shorter segments of DNA, conventional submarine electrophoresis is the method of choice. This allows the separation of DNA fragments ranging in length from a few base-pairs to tens of thousands of base-pairs. The technique can be applied either to uncloned genomic DNA, or to fragments which have been cloned into lambda, plasmid, or cosmid vectors; it is often used as a prelude to Southern blot hybridization. Again, Pharmacia LKB can supply a wide range of high-quality products for this type

Table of Rare-Cutting Restriction Enzymes from Pharmacia LKB Biotechnology

The following enzymes are all judged to be potential rare-cutters because their recognition sequences include the CG dinucleotide, which is relatively rare in human DNA

Enzyme	Recognition sequence
Aat II	GACGT↓C
Cla I	AT↓CGAT
Mlu I	A↓CGCGT
Nar I	GG↓CGCC
Not I	GC↓GGCCGC
Nru I	TCG↓CGA
Nsp V	TTCGAA
Pvu I	CGAT↓CG
Sac II	CCGC↓GG
Sal I	G↓TCGAC
Sfi I	GGCCN$_4$↓NGGCC
Sma I	CCC↓GGG
Xho I	C↓TCGAG



Yeast DNA PFGE Markers

Separated using the Pulsaphor® system, equipped with the Hexagonal Electrode Array and the Pulsaphor® Plus Controller.

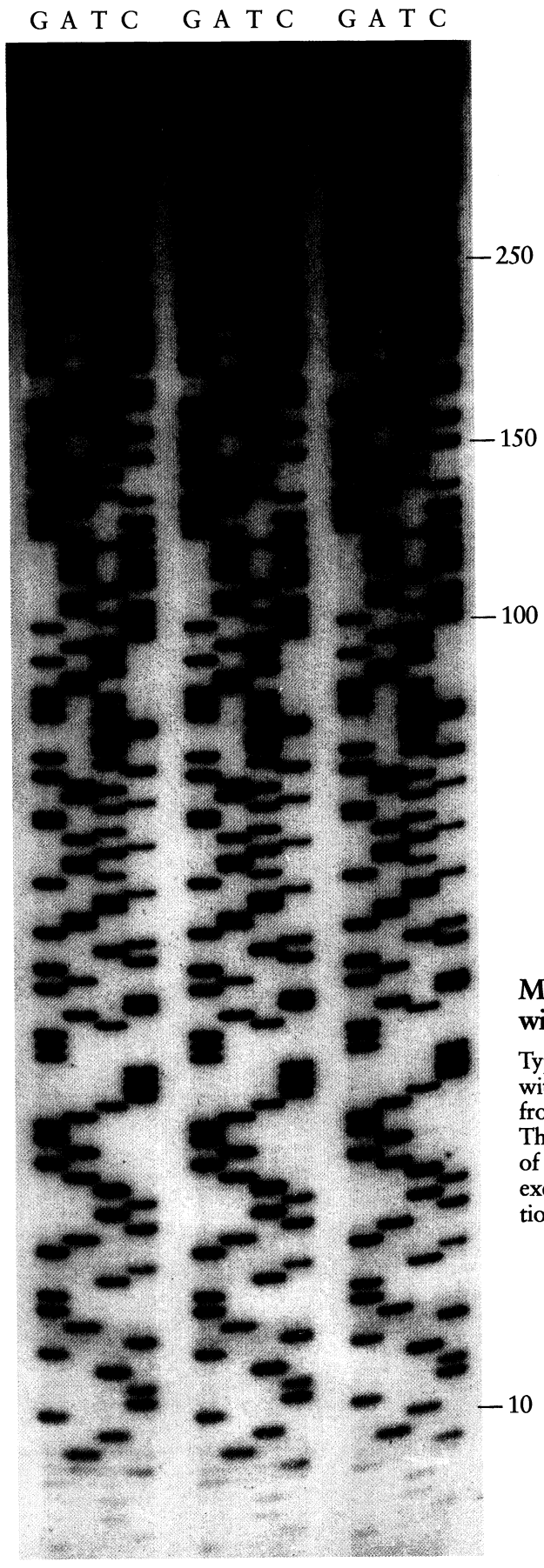
of mapping: restriction enzymes and molecular-weight markers; tried and tested equipment, such as the GNA series of submarine units and a variety of power supplies; and the VacuGene® XL vacuum blotting apparatus, an outstanding alternative to capillary blotting for the very rapid transfer of separated DNA fragments to hybridization membranes.

Sequencing

As the focus of the genome project shifts to sequencing, separation technology will play an important role in at least three areas: template preparation, reagent preparation, and the analysis of sequencing reactions.

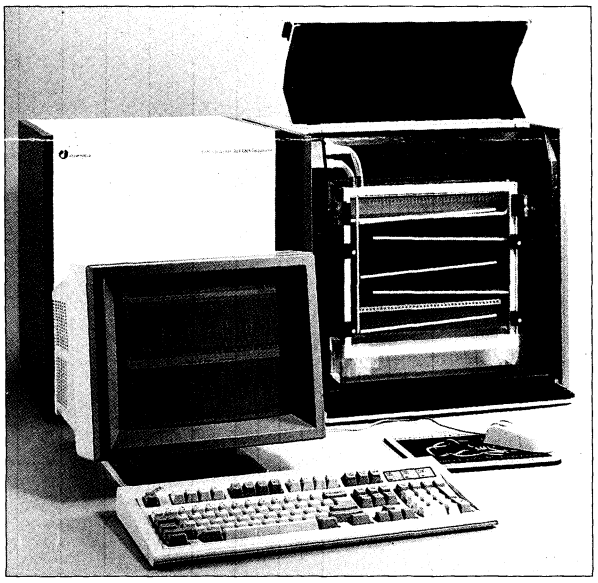
To sequence the entire genome, an enormous number of templates will need to be prepared and sequenced. Suppose, for example, that each individual template preparation yields one kilobase of sequence information, and that two-fold oversequencing will be required to determine the sequence of each strand of each chromosome unambiguously; in this case, approximately 12 million template preparations would be needed to sequence the entire genome. Although advances in technology may bring this number down significantly, the final number of templates required is still likely to be huge. It will therefore be important to develop fast, reliable, and easily automated approaches to template preparation. Recent advances in this area have included the use of PCR to bypass the need for cloning and isolation of templates; and the development of improved methods for rapid template purification, such as those featured in the Miniprep Kit Plus and Sephaglas™ M13 Miniprep Kit from Pharmacia LKB.

Successful sequencing of a vast number of templates will of course depend on a prolific and reliable supply of sequencing reagents. It is easy to overlook the crucial role which separation technology plays in the preparation of these reagents. For example, the outstanding results which can be obtained using the T7Sequencing™ Kit from Pharmacia LKB are due in large measure to the care we exercise in the purification of T7 DNA polymerase, dNTPs and ddNTPs for the kit. The same is true for the AutoRead™ Sequencing Kit, which we



Manual Sequencing with T7Sequencing™ K

Typical results obtained with T7Sequencing Kit from Pharmacia LKB. The excellent performan of this kit reflects the car exercised during purifica tion of its components.



A.L.F. DNA Sequencer™

developed specifically for the automated laser fluorescent A.L.F. DNA Sequencer™. The excellent performance of the sequencer is crucially dependent on the performance of the kit, which in turn depends on the purity of the components it contains. In the future, further advances in sequencing technology are also likely to depend on the availability of highly pure reagents — and thus on the separation technology required to prepare these reagents.

Automated DNA sequencers are of course prime illustrations of the third major application for separation technology in large-scale sequencing: analysis of sequencing reactions in large numbers.

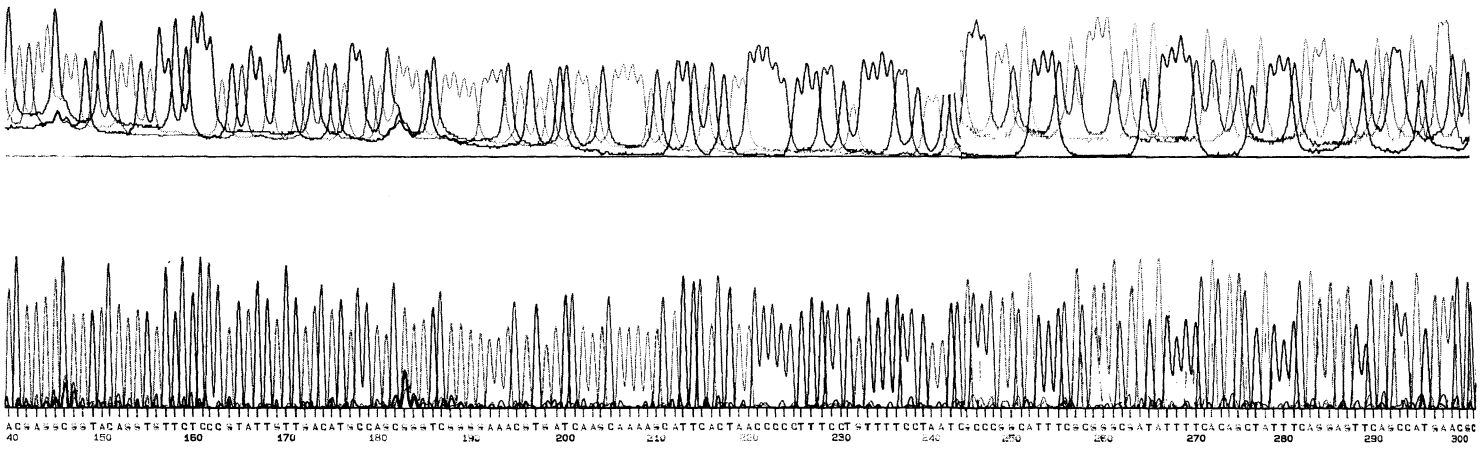
Current methods of DNA sequencing all depend absolutely on the ability of electrophoresis to separate successively larger DNA fragments differing from one another in length by just a single nucleotide. Automated sequencers capitalize on this ability by recording the signals generated in adjacent lanes as fluorescently labelled fragments move past a specified point in a sequencing gel. This approach is best exemplified by the A.L.F. DNA Sequencer from Pharmacia LKB, which uses a single fluorescent label, a fixed laser beam, and fixed detectors spaced across the width of the sequencing gel. This arrangement offers both mechanical simplicity and the ability to generate raw data which can be interpreted very easily. It also permits high throughput, because electrophoresis times do not have to include "scanning time" for a moving laser beam and filters. And finally, it keeps sequencing reactions simple: only one fluorescent primer is required for each set of reactions (suitable primers can be prepared very conveniently using our AutoPrimer™ Synthesis Kit), and the protocol for dideoxy sequencing reactions is pleasingly simple (especially if they are performed using the AutoRead Sequencing Kit).

Currently, A.L.F. DNA Sequencer represents the state of the art in applying separation technology to the automated analysis of DNA sequencing reactions. Of one thing we can be certain, however: by the time the complete sequence of the human genome has been determined, many further advances will have been made in this field of analysis.

Conclusions

Separation technology will play a vital role in the sequencing of the human genome. In many respects, analytical electrophoresis seems likely to be the most important application for separation technology, given its significance for the mapping of both large and small DNA fragments, and for the analysis of DNA sequencing reactions. Nevertheless, preparative separations will also play an essential role, particularly for the purification of DNA templates, and for the provision of high-quality sequencing reagents.

Data from A.L.F. DNA Sequencer



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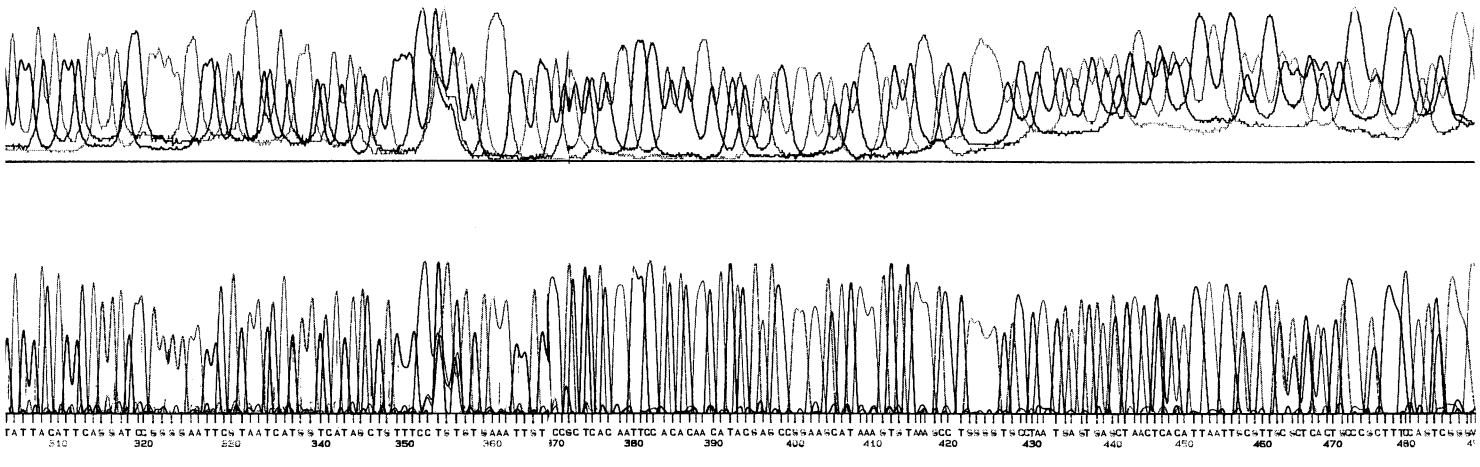
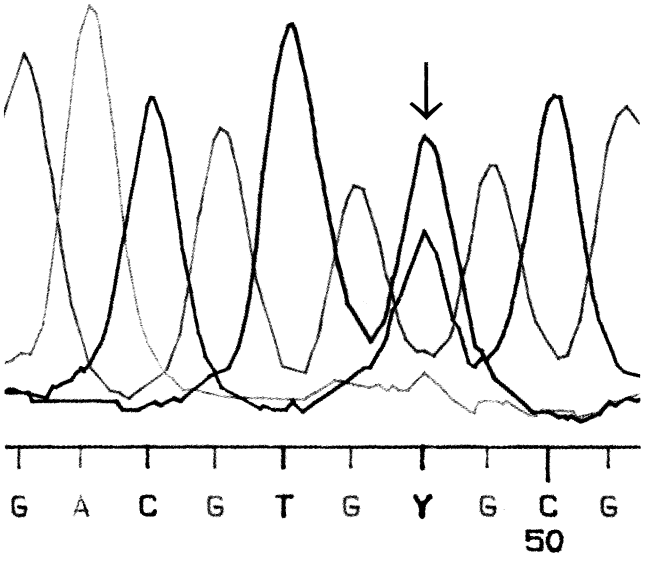
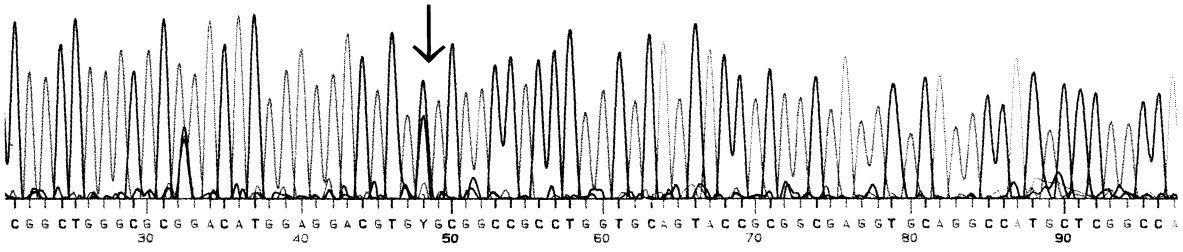




Direct genomic solid phase sequencing of the human apolipoprotein E gene for diagnosis of a heterozygotic point mutation, Hultman and Uhlén (1990) submitted for publication.

Raw DNA sequencing data



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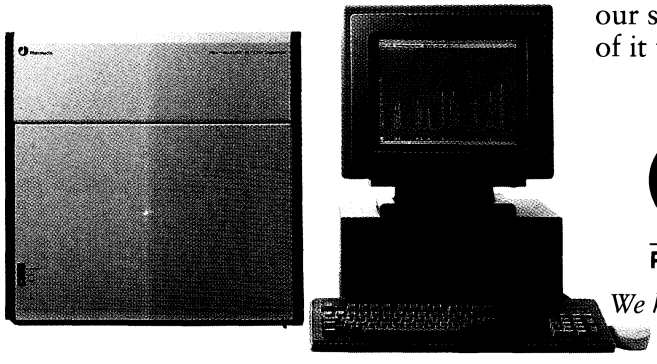

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THE HUMAN GENOME MAP 1990

Barbara R. Jasny, *Science Coordinator*

Authors
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With the assistance of the HGML staff: H. Chan, M. Chipperfield, I. Cohen, A. Ferrara, C. Partridge, F. Ricciuti, and R. Track as well as W. Alles, HGM10 Workshop staff

We also acknowledge the contribution of CEPH to most of the genetic maps through helpful discussions and published linkage maps based on genotypes from the CEPH reference families.

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Chromosomes are drawn to scale from the high resolution ideograms (860 bands total) of the International System for Human Cytogenetic Nomenclature (ISCN). Most bands are light (R-bands or Giemsa negative) or dark (G-bands or Giemsa positive). There are also heterochromatic regions, shown either as diagonal shading or as an interrupted region within a chromosome (secondary constriction; for example, see chromosome 21). The centromere of each chromosome, shown as a constriction surrounded by centric heterochromatin (heavy diagonal shading), separates the short arm above from the long arm below.

Numbers and cytogenetic locations of loci, probes, and polymorphic loci were taken from the Human Gene Mapping Library (HGML) database. All probes derived from another probe or known to detect multiple loci were omitted. A collaborative effort between the HGML and GenBank established links between GenBank sequence entries and over 750 mapped loci. Map locations for these loci were used to allocate base pairs from the sequence entries to each chromosomal band after sequence duplication was eliminated. There are an additional 1.5 million bp of human DNA sequence in GenBank that have yet to be linked to mapped loci and hence could not be included.

Data included on the wall chart represent information in manuscripts published or in press by July 31, 1990. On this date, the HGML database contained relevant information for 6652 loci (genes and anonymous DNA segments), 11,852 probes, 2275 polymorphic loci, and links to GenBank records with 5,066,049 bp of DNA sequence. All gene symbols shown, other than the exceptions noted below, are the official HGM10 Human Gene Mapping Workshop symbols.

Loci in the linkage maps, their order, and their approximate sex-averaged centimorgan distances were taken from published linkage maps, and were often based on CEPH families. Preference was given to inclusion of genes rather than anonymous DNA segments. All linkage maps were drawn to the same scale, which is shown in the legend.

Genetic linkage maps have the same locus order as physical maps, but a very different measure of distance, as genetic maps are derived from the frequency of recombination during meiosis. There is no universal relationship between the two distance measures and they cannot be readily converted because recombination rates per megabase of DNA vary considerably by sex and chromosomal region.

REPRESENTATIVE GENES

ABL Abelson murine leukemia viral oncogene homolog
ABO ABO blood group
ADA adenosine deaminase; severe combined immunodeficiency
ANCR Angelman syndrome chromosome region; happy puppet syndrome
APOB apolipoprotein B; hypo- & abetalipoproteinemia
APOC1 & C2 apolipoproteins C-I and C-II; hyperlipoproteinemia Ib (C2 only)
APOE apolipoprotein E; familial hyperlipoproteinemia III
APP amyloid beta precursor protein; cerebroarterial amyloidosis, Dutch type
BCL2 B cell chronic lymphocytic leukemia/ lymphoma 2
BCR breakpoint cluster region; chronic myeloid leukemia
C2 complement component 2; lupus systemic/ discoid syndrome
CAT catalase; acatalasia
CBS cystathionine-beta-synthase; homocystinuria
CDC2 cell division cycle 2
CF cystic fibrosis
COL1A1 collagen, type I, alpha 1; osteogenesis imperfecta,various forms
COL2A1 collagen, type II, alpha 1; spondylepiphyseal dysplasia congenita
COL3A1 collagen, type III, alpha 1; Ehlers-Danlos IV and familial aneurysms
DM dystrophia myotonia; myotonic dystrophy
DMD muscular dystrophy, Duchenne and Becker types
EGFR epidermal growth factor receptor
F8C coagulation factor VIIIc, procoagulant component; hemophilia A, FVIII deficiency
FGG fibrinogen, gamma polypeptide; afibrinogenemia
FNRB fibronectin receptor, beta polypeptide
FRAXA fragile site, folic acid type, rare; Fragile X mental retardation
FRDA Friedriech ataxia
GBA glucosidase, beta, acid; Gaucher disease
GYPA & B glycophorins A & B (includes MNS blood group)
HBA1 & A2 hemoglobin, alpha 1 & alpha 2; alpha-thalassemia and other hemoglobin diorders
HBB@* hemoglobin, beta, cluster; beta-thalassemia, sickle cell anemia, and other hemoglobin disorders
HD Huntington disease
HEXA hexosaminidase A; GM2-gangliosidosis I (Tay-Sachs disease, juvenile & adult types)
HEXB hexosaminidase B; GM2-gangliosidosis II (Sandhoff disease)
HLA@* major histocompatibility complex (multiple genes, multiple diseases)
HOX2@* homeo box region 2 cluster
HP haptoglobin
HPRT hypoxanthine phosphoribosyltransferase; Lesch Nyhan, severe juvenile gout
HRAS Harvey RAS viral oncogene homolog
IGH@* immunoglobulin heavy chain gene cluster (V, D, J, C)
IL2 interleukin 2
INS insulin; hyperproinsulinemia, diabetes (rare)
INSR insulin receptor; acanthosis nigricans, insulin resistant diabetes, leprechaunism
KRAS2 Kirsten RAS 2 viral oncogene homolog
LDLR low density lipoprotein receptor; familial hypercholesterolemia, hyperlipoproteinemia II
LPL lipoprotein lipase; hyperlipoproteinemia I, hyperchylomicronemia
MBP myelin basic protein
MEN1 multiple endocrine neoplasia type I
MYC avian myelocytomatosis viral oncogene homolog
NF1 neurofibromatosis 1; von Recklinghausen disease
NRAS neuroblastoma RAS viral oncogene homolog
OAT ornithine aminotransferase; hyperornithinemia with gyrate atrophy of choroid and retina
PABY pseudoautosomal boundary region, Y-linked
PAH phenylalanine hydroxylase; phenylketonuria, hyperphenylalaninemia
PALB prealbumin; familial amyloid neuropathy
PDGFB platelet-derived growth factor beta polypeptide 1
PFKL phosphofructokinase, liver type; hemolytic anemia
PI alpha-1-antitrypsin; emphysema with cirrhosis
PRB@* proline-rich protein BstNI subfamilies 1 to 4
PRIP prion protein; Gerstmann-Straussler disease, Creutzfeldt-Jakob disease
PWCR Prader-Willi syndrome chromosome region
RB1 retinoblastoma 1
RHO rhodopsin
SST somatostatin
STS steroid sulfatase; ichthyosis (X-linked)
TAT tyrosine aminotransferase; tyrosinemia, type II, oculocutaneous
TCRA & D T cell receptor, alpha (V, D, J, C) and delta (V, D, J, C)
TCRB T cell receptor, beta cluster
TCRG T cell receptor, gamma cluster
TF transferrin; atransferrinemia
TP53 tumor protein p53
WAGR Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation triad

* Unofficial symbols (as of HGM10) used for gene clusters.

Loci (both genes and anonymous DNA segments) have been mapped to the chromosomes with different degrees of precision; resolution ranges from an entire chromosome to a single band. To estimate the number of loci currently mapped to each chromosomal band, a band was assumed to occupy the proportion of the human genome equal to the band's relative length as shown in the ISCN. Thus, genes, probes, or sequenced DNA mapped to a single band contributed only to that band; those less precisely mapped contributed proportionately to multiple bands. The proportional contribution to each band was calculated as the length of that band relative to the length of all bands spanned. For each band, the final estimate is simply the sum of all contributions.

Estimates of the expected numbers of genes and base pairs of DNA in each band followed the same rationale — a band that was 0.1% of the genome length in the ISCN depiction was estimated to contain 0.1% of the genes and 0.1% of the base pairs in the genome. The prevailing, albeit crude, estimates of 1 x 10^5 genes and 3 x 10^9 bp were used as the size of the human genome. These calculations make the simplfying assumption that the densities of DNA and genes are uniform across bands. It is probable that the density of each differs systematically among band types, but no numerical corrections exist as yet.

A logarithmic scale was chosen to depict progress towards completion for sequence and gene densities. An open-ended linear scale was chosen for polymorphism and probe counts since there is no easily definable limit to the numbers that will be identified.

GLOSSARY

Anonymous DNA segment: A piece of DNA of unknown gene content that has been localized to a chromosome. Referred to by unique "D number" symbols assigned by the Human Gene Mapping Workshop's DNA Committee .

Centimorgan (cM): The unit of genetic distance derived from the frequency of recombination between genetic markers. When the markers are physically close together, a distance of 1 cM corresponds to a 1% chance of recombination occurring between them. However, because multiple recombination events can occur between two loci far apart, recombination frequencies are not themselves additive over large distances. The centimorgan scale is additive.

CEPH families: A reference panel of 40 Caucasian families from whom cell lines have been collected and distributed to researchers collaborating with the Centre d'Étude du Polymorphisme Humain (CEPH, Paris). The CEPH collaboration provides genotypes for a large number of DNA polymorphisms on this common set of families.

Chromosome band: A subdivision of a chromosome that can be observed by light microscopy after any of several staining procedures. Each chromosome displays a characteristic banding pattern typically represented as an ideogram.

Contig: A set of partially overlapping cloned DNA fragments that together cover an uninterrupted stretch of the genome.

DNA polymorphism: Normal, common variation in DNA sequence at a locus in the population. Multiple molecular methods can be used to detect these polymorphisms. Currently, most are detected with restriction endonucleases, which are enzymes that cleave DNA at specific nucleotide sequences. Loci with variation in the length of fragments of DNA generated by digestion with these enzymes are called restriction fragment length polymorphisms (RFLPs).

Genetic linkage map: A map of polymorphic loci indicating order and relative genetic distances measured in centimorgans.

Genome: The genetic constitution of an organism. One full set of the 24 distinct human chromosomes is estimated to contain ~3 x 10^9 base pairs of DNA, throughout which are distributed ~1 x 10^5 genes.

Physical map: A map in which distances are expressed in numbers of nucleotide base pairs between identifiable landmarks (contigs, restriction sites, or STSs). A cytogenetic map is a low resolution physical map.

Recombination: The normal process by which tracts of DNA are exchanged between the homologous chromosomes during gametogenesis. The resulting gametes contain chromosomes that are derivatives of both homologs. Generally, the farther apart two loci are, the higher the frequency of recombination (up to a maximum of 50%, as for two loci on separate chromosomes).

Polymerase chain reaction (PCR): A method to rapidly amplify a given DNA sequence for subsequent analysis. Very short DNA sequences (primers) flanking the targeted DNA sequence are required to initiate and sustain the reaction.

Sequence tagged site (STS): A short DNA sequence, readily located and amplified by PCR techniques, that uniquely identifies a physical genomic location.

Yeast artificial chromosome (YAC): A type of clone formed from foreign DNA joined to the replicating parts of a yeast chromosome. With YACs, it has been possible to propagate large (>100 kb), contiguous tracts of human DNA in yeast cells.

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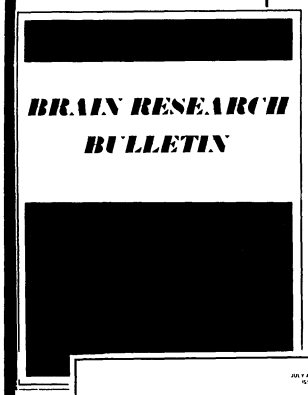

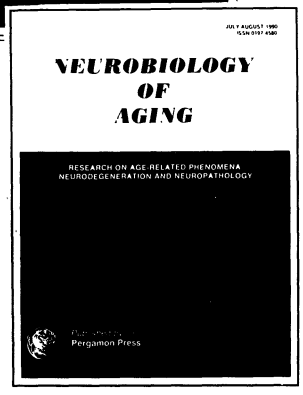

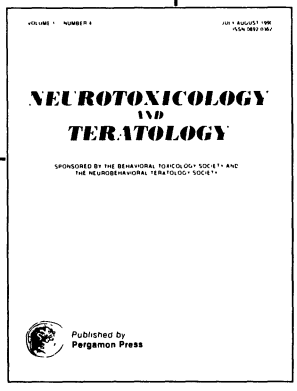

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