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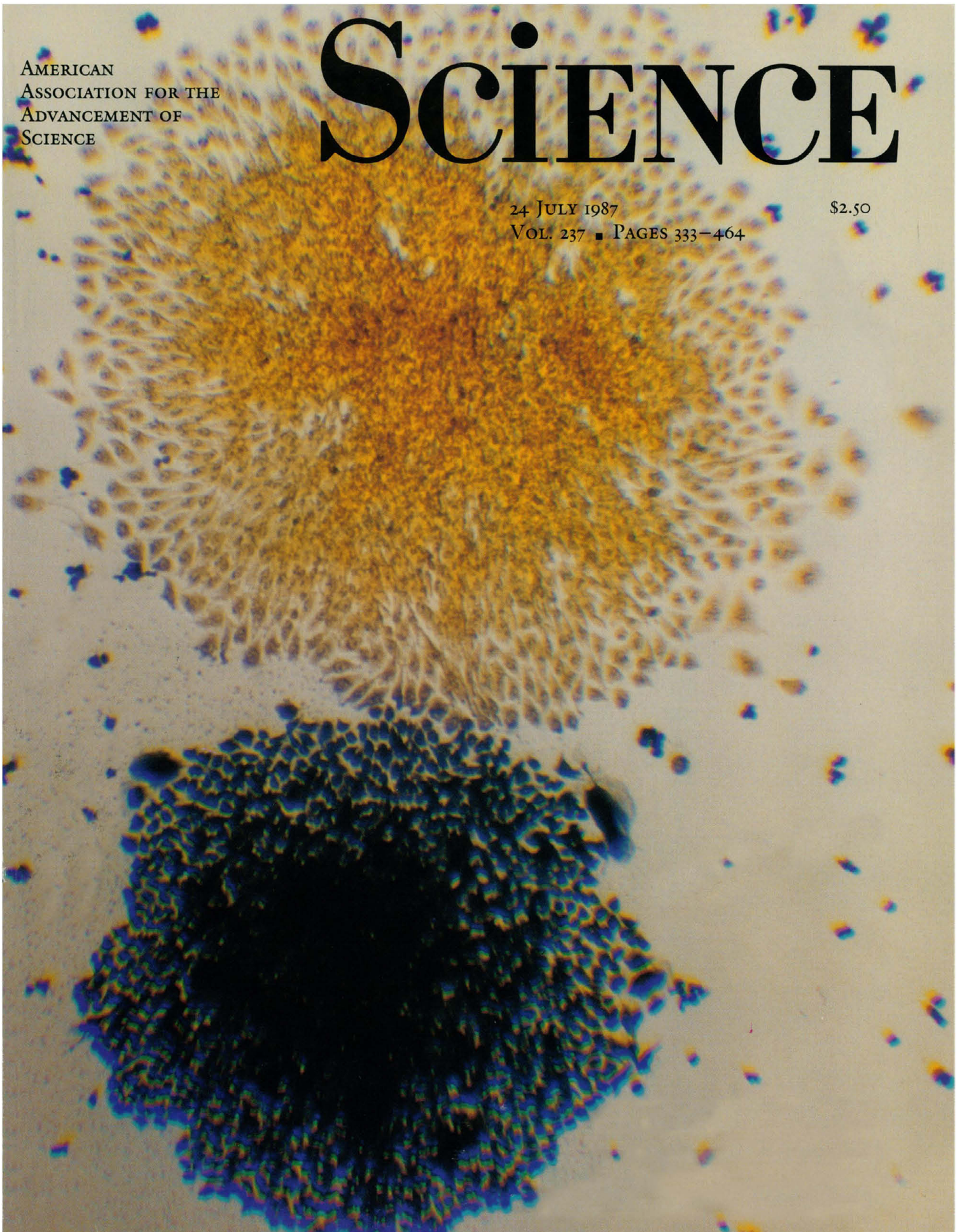

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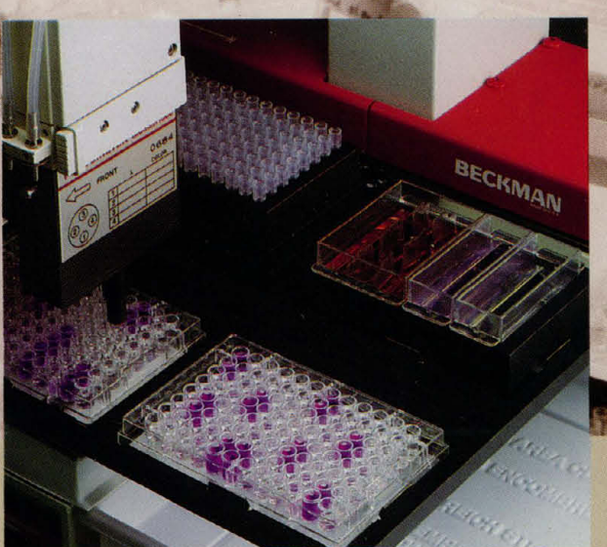

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SCIENCE

ISSN 0036-8075
24 JULY 1987
VOLUME 237
NUMBER 4813

339 This Week in *Science*

Editorial

341 TPA and PDQ

Letters

349 Uranium Enrichment: B. J. HULL ■ Indictment of Soviet Physicist: G. C. VEZZOLI ■ Is Female Math Anxiety Real?: S. L. SEGAL

News & Comment

351 Congress Considers Upgrading Labs
352 Pork Barrel Unbound?
353 Corporations on Campus
354 Foreign Investors Outstrip U.S.
355 AIDS and Insects
356 Some Refuseniks See No *Glasnost*
357 *Briefing*: SSC Deadline Extended ■ "Greens" Challenge French Gene Research ■ France to Boost Research Spending

Research News

358 Who Owns the Human Genome?
361 A Younger Universe Is Seen in the Stars
363 New Tumor Factor May Disrupt Calcium Levels

Articles

379 Off-Design Performance of Power Plants: An Integrated Gasification Combined-Cycle Example: M. R. ERBES, J. N. PHILLIPS, M. S. JOHNSON, J. PAFFENBARGER, M. GLUCKMAN, R. H. EUSTIS
384 The Shapes of Random Walks: J. RUDNICK AND G. GASPARI

Research Articles

389 The 30-Kilodalton Gene Product of Tobacco Mosaic Virus Potentiates Virus Movement: C. M. DEOM, M. J. OLIVER, R. N. BEACHY
394 Engineering Enzyme Specificity by "Substrate-Assisted Catalysis": P. CARTER AND J. A. WELLS

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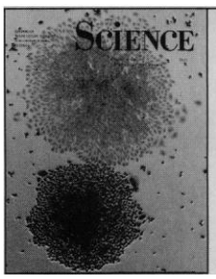

COVER Fragile X–bearing somatic cell hybrids cultured under positive selection for hypoxanthine guanine phosphoribosyl transferase (HGPRT) followed by in situ histochemical staining for glucose-6-phosphate dehydrogenase (G6PD) activity. The $G6PD^+$ (blue) and $G6PD^-$ (yellow) colonies indicate segregation of the HGPRT and G6PD genes, suggesting chromosome breakage at the fragile X site. See page 420. [Photo by S. T. Warren, Emory University School of Medicine, Atlanta, GA 30322]

Reports

400 Parallel and Serial Processes in Motion Detection: M. DICK, S. ULLMAN, D. SAGI

402 Adipsin: A Circulating Serine Protease Homolog Secreted by Adipose Tissue and Sciatic Nerve: K. S. COOK, H. Y. MIN, D. JOHNSON, R. J. CHAPLINSKY, J. S. FLIER, C. R. HUNT, B. M. SPIELGELMAN

405 Severely Impaired Adipsin Expression in Genetic and Acquired Obesity: J. S. FLIER, K. S. COOK, P. USHER, B. M. SPIEGELMAN

409 Linear Plasmids of the Bacterium *Borrelia burgdorferi* Have Covalently Closed Ends: A. G. BARBOUR AND C. F. GARON

411 Neuronal $pp60^{c\text{-}src}$ Contains a Six–Amino Acid Insertion Relative to Its Non-Neuronal Counterpart: R. MARTINEZ, B. MATHEY-PREVOT, A. BERNARDS, D. BALTIMORE

415 The Molecular Basis of the Sparse Fur Mouse Mutation: G. VERES, R. A. GIBBS, S. E. SCHERER, C. T. CASKEY

417 Physiological Evidence for Serial Processing in Somatosensory Cortex: T. P. PONS, P. E. GARRAGHTY, D. P. FRIEDMAN, M. MISHKIN

420 The Fragile X Site in Somatic Cell Hybrids: An Approach for Molecular Cloning of Fragile Sites: S. T. WARREN, F. ZHANG, G. R. LICAMELI, J. F. PETERS

423 Smooth Muscle–Mediated Connective Tissue Remodeling in Pulmonary Hypertension: R. P. MECHAM, L. A. WHITEHOUSE, D. S. WRENN, W. C. PARKS, G. L. GRIFFIN, R. M. SENIOR, E. C. CROUCH, K. R. STENMARK, N. F. VOELKEL

Book Reviews

441 Coevolution and Systematics, D. J. FUTUYMA AND J. KIM ■ Gamma-Ray Astronomy, F. W. STECKER ■ Paleosols, R. D. STIEGLITZ ■ Proteins of Excitable Membranes, C. MILLER ■ Books Received

Products & Materials

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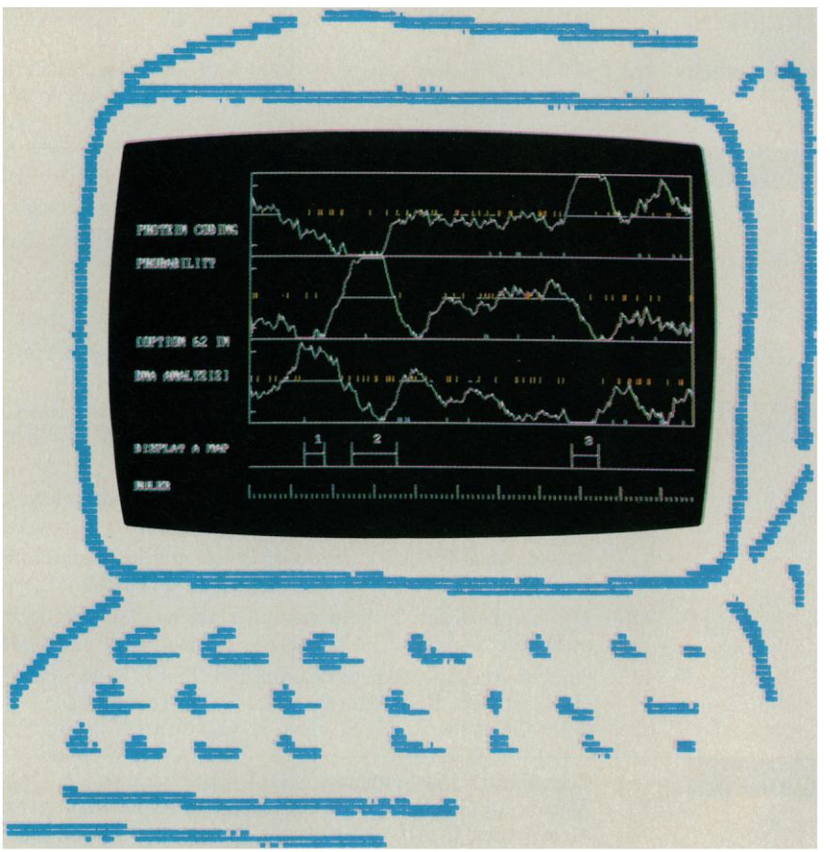

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Virus movement through plant cells

ENCODED in the genetic material of the tobacco mosaic virus is information for synthesis of a 30-kilodalton protein that makes the movement of this virus through the cells of tobacco plants possible (page 389). The same protein is crucial to the virulence of the virus, because infection of a plant requires that the virus spread through plant tissues. The facilitating role of the 30-kD protein in movement and infection by the tobacco mosaic virus is described by Deom *et al.*, who inserted a gene that included the nucleotide sequence coding for the protein into cells of a tobacco plant. A defective virus (a temperature-sensitive mutant) that lacked the ability to spread in normal tobacco plants at certain temperatures spread in the transgenic plants (those containing the viral gene) both locally (as seen by the growth of lesions on individual leaves) and systemically (as evidenced by the systemic spread of disease symptoms). These studies employ new genetic engineering methods that may be useful in studying functions of viral genes that influence the interactions of viruses and plants.

Substrate-assisted catalysis

A substrate can assist its enzyme in catalysis (page 394). Carter and Wells removed the catalytic histidyl side chain of the enzyme subtilisin and then made a series of substrates, some of which contained histidine residues. Mutant enzymes had exquisite specificity for the substrates in which histidyl residues were located such that, when substrate and enzyme were bound, the histidine was properly positioned for catalytic functioning. Although catalytic activity was not fully restored with any of the histidine-containing substrates, partial restoration was achieved with some. The technology developed in these studies will be useful in the design of new highly specific enzymes and substrates for experimental and industrial purposes. These experiments shed light on how increasingly self-reliant enzymes might evolve: if an enzyme can acquire a functional group, then it can dispense with the requirement that its substrate carry that group.

Seeing motion

THE detection of short-range motion involves a different form of visual processing from that required for the detection of long-range motion (page 400). Over the short range, the start and end positions of a moving object can be detected together—in parallel—using only preattentive vision. In contrast, long-range motion requires attentive vision in which a series of clues—for example, the appearance, disappearance, and reappearance of the object—are sought. These differences are described by Dick *et al.* who studied how human subjects detected the apparent movement of dots in a grid (25 to 100 dots), the direction of the movement, and the appearance or disappearance of a dot from the grid. The "motion" of the dots was simulated by flashing two different patterns on a computer screen, one at a time and each for 48 milliseconds. Response times required for detecting the changes in the grid were indicators of which type of visual processing, preattentive or attentive, was operating.

Fragile sites

THE most common form of inherited mental retardation, which occurs in more than 1 out of 2000 newborn males, is fragile X syndrome (page 420). The syndrome is so named because there is a vulnerable region on the X chromosome that can be induced to break under certain experimental conditions. Other human chromosomes have fragile sites, but the one on X is the only one so far that has firmly been associated with a specific pathology. Warren *et al.* examined features of the human fragile X site in a hybrid cell line (cover) and found that, within dividing hybrid cells (and not just as a result of experimental induction), chromosome breakage occurs at the fragile site. The subsequent rearrangement of broken chromosomes occurs nonrandomly and can be followed with markers that originally flanked the fragile site. In rearranged chromosomes, fragile sites were less fragile than those of the original chromosome, supporting the theory that the fragile site is a reiterated DNA sequence: the smaller the sequence (some DNA is lost in the rearrangement) the more stable the site. The regular juxtaposition of the human fragile site to a rodent chromosomal sequence should simplify the task of isolating the fragile site for cloning and further analysis. That breaks at fragile sites are followed by nonrandom rearrangements of chromosomal pieces lends support to the assumption that certain leukemias and lymphomas develop as a result of breakages and rearrangements involving specific fragile sites.

Smooth muscle cells and pulmonary hypertension

SMOOTH muscle cells probably play a key role in the development of pulmonary hypertension of premature infants (page 423). In this and other vascular diseases, such as atherosclerosis, connective tissue is deposited inappropriately in blood vessels, and the blood vessel walls grow increasingly stiff. Using tissues from newborn calves that were suffering from pulmonary hypertension, Mecham *et al.* show that smooth muscle cells from damaged pulmonary arteries secrete factors or process factors in the serum or plasma that, in turn, cause surrounding cells to produce or increase their production of elastin, the constituent of connective tissue that is responsible for the elastic recoil of vessels. The changes that these "elastogenic" factors, elastin, and elastin-derived peptides induce in cellular differentiation and functioning can lead to a number of major physiologic consequences (for example, altered cellular movement and altered responsiveness to stimuli); such effects contribute to the further deterioration of the blood vessels.

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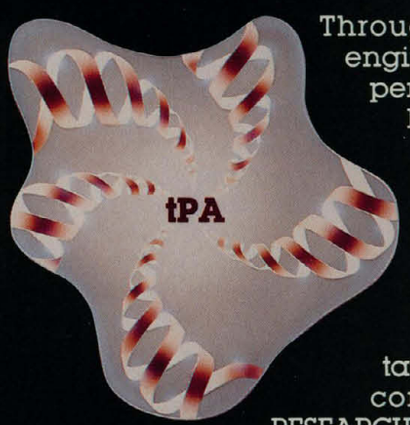

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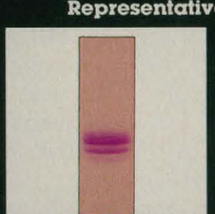

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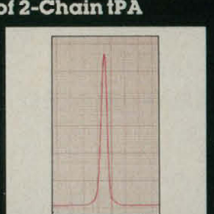

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TPA and PDQ

When a circus clown steps on his toes and falls on his face, it is a cause for laughter. When a regulatory agency that licenses drugs for heart attacks stumbles, it may have not only egg on its face but blood on its hands. Complex questions seen in an oversimplified way, however, can make good intentions look like bureaucratic bungling. The recent decision by the Food and Drug Administration (FDA), or lack thereof, in the tissue plasminogen activator (TPA) controversy is an interesting case in point.

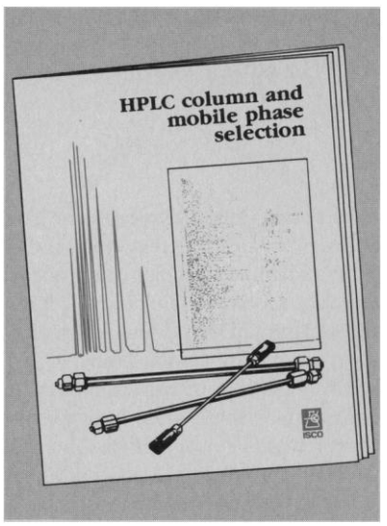
The questions surrounding the controversy involve science, turf battles, money, ethics, public health, and historical complexities. The science starts with the attempt by Genentech, Inc., to get approval for what many consider a major wonder drug for dissolving blood clots. The company approached the FDA, was told what it needed to do, and proceeded to do so. The apparent turf battle arose when at the last moment a second committee of the FDA requested that Genentech satisfy a new set of criteria that would delay approval by months. The FDA's advisory committee was quoted as saying that Genentech had failed so far to demonstrate that dissolving a clot would prolong the life of the patient, a seemingly absurd charge. A closer look, however, indicated that the committee was pointing out that tests on dose levels of the drug were incomplete. The money issue was highlighted by the fact that other companies were pushing their own versions of TPA, and any delay to the front-runner had enormous financial implications. The ethical issue arose when a committee of cardiologists judged TPA to be so effective that the ethics of continuing to give placebos to a control group came into question. The historical complexity was caused by recent approval of a similar but probably less effective drug for clot removal, streptokinase. Should discoverers of new drugs be required to repeat all the trials of previously approved drugs, or may they use earlier results to buttress approval?

Aside from matters of procedure, there are interesting scientific and intellectual questions illustrated by this case. When a new drug appears on the market in 1987, it inevitably incorporates proven information accumulated over the years. A drug that dissolves blood clots should no longer have to answer whether such an action prolongs life. The new drug must not have unforeseen side effects, and its balance between dissolving clots and preventing bleeding must be shown. Since there are 750,000 heart attack victims per year in the United States alone, any appreciable delay in approving a drug widely considered to be a drug of choice is not simply a bureaucratic minuet—it is a matter of life or death to many patients. It is therefore incumbent on an agency to ask truly scientific questions and not simply go through pro forma experiments that were appropriate in 1967 but not in 1987.

There is an apparent irony in the delay on the TPA drug, since the same agency was recently criticized for failing to put azidothymidine (AZT), a drug for AIDS, on the market more rapidly. Like AIDS, the drug AZT itself is not well understood, far less than is blood clotting. Therefore, it could be argued that approving AZT and denying license to TPA is inconsistent. Yet the agency is legitimately more cautious in the TPA case because an alternative, streptokinase, does exist. In the case of AZT there is no comparable drug, and the disease is also fatal.

The question of money also inevitably enters but cannot and should not be determining in such decisions. If an agency delays a front-runner, it unavoidably helps the followers. A pattern of bureaucratic timidity would surely deter companies from investing in basic research, since it is far cheaper to be a follower. Front-runners always will want decisions PDQ (pretty damn quick), whereas followers will delight in a glacial approach to certainty. Haste has dangers of commission; excessive caution, dangers of omission.

In the TPA case, a final decision had not been made by the FDA commissioners as of this writing. And they are allowed to consider additional evidence accumulated since the time of the advisory committee recommendation. Turf battles, money, and excessive publicity will hopefully be eliminated at this Olympian level. To the second-guessers of the world, accreditation of new drugs will continue to offer fertile ground for controversy. The controversy in this case has served a useful purpose, for it highlights the fact that delay is a decision in itself that can be as damaging as excessive speed. Scientists should continue to exert pressure for maximum efficiency and maximum fairness in the licensing of new drugs. TPA is only one case, but PDQ will arise in every case.—DANIEL E. KOSHLAND, JR.



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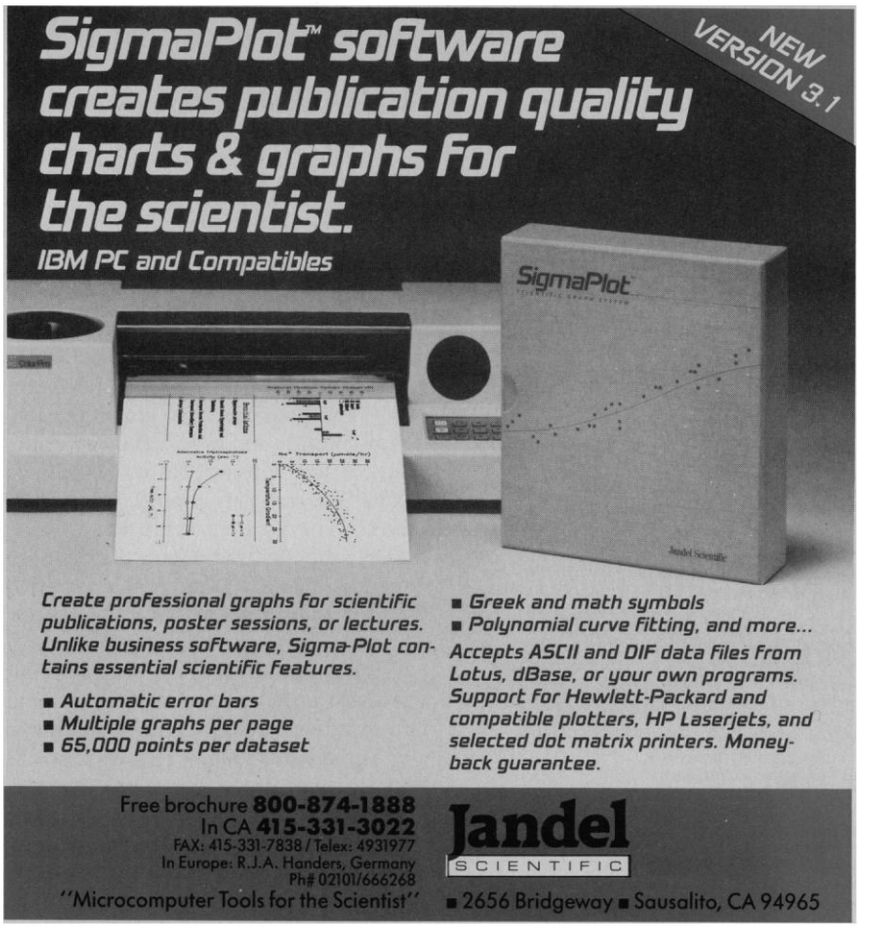

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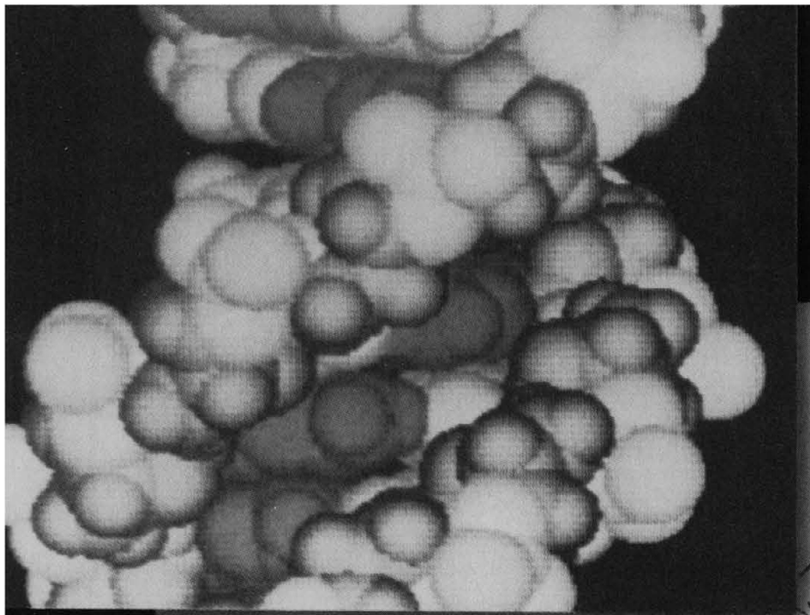

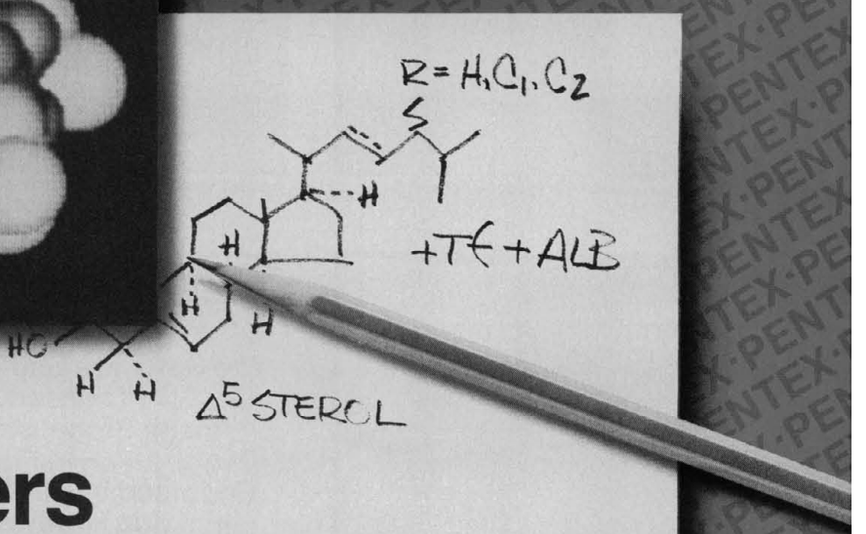

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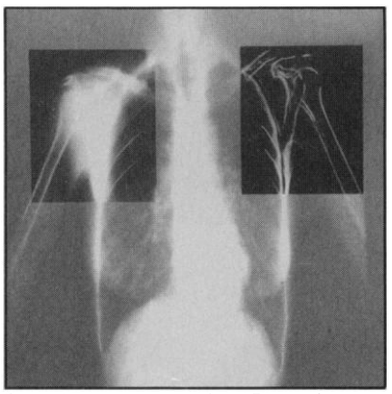

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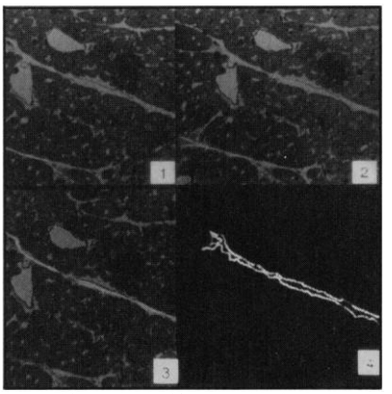

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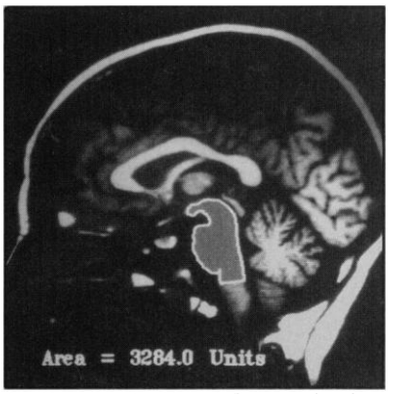

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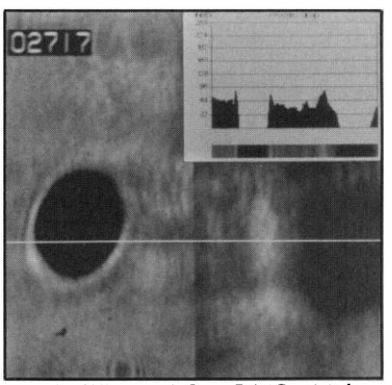

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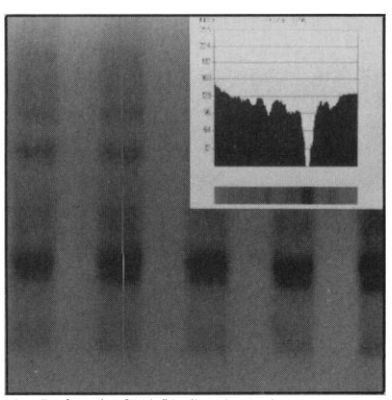

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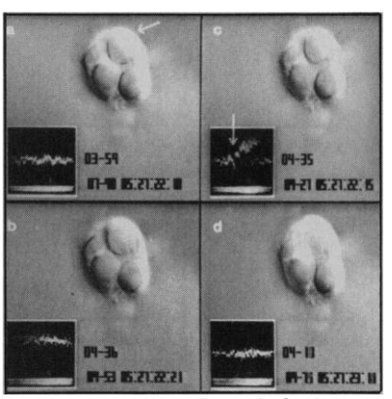

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Figure 1. Separation of crude brain extract using selectivity control on a BAKERBOND WP PEI (weak anion exchange) SCOUT column

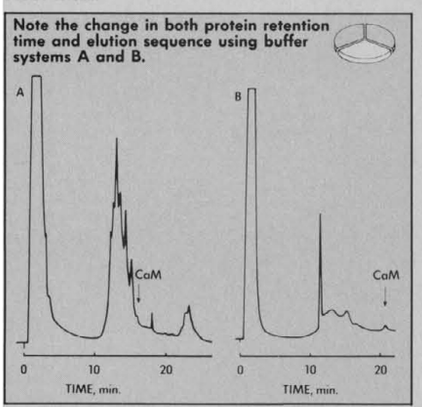


Figure 2. Chromatography of crude brain extract using a BAKERBOND WP PEI SEMI-PREP Column with Buffer System B

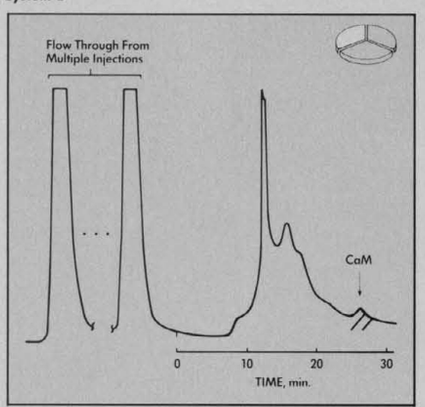
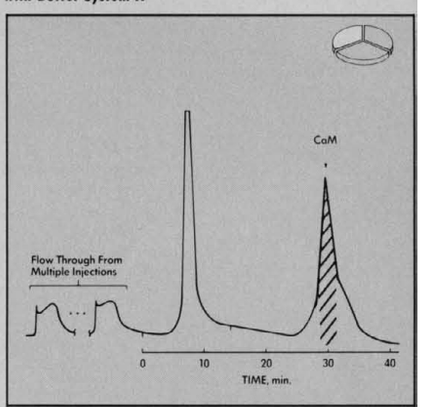


Figure 3. Rechromatography of calmodulin active fractions from Figure 2 using a BAKERBOND WP PEI SCOUT Column with Buffer System A



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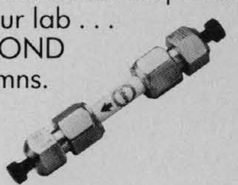

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[1]S. Berkowitz, *J. Chromatography* 398 (1987) pp. 288–293.

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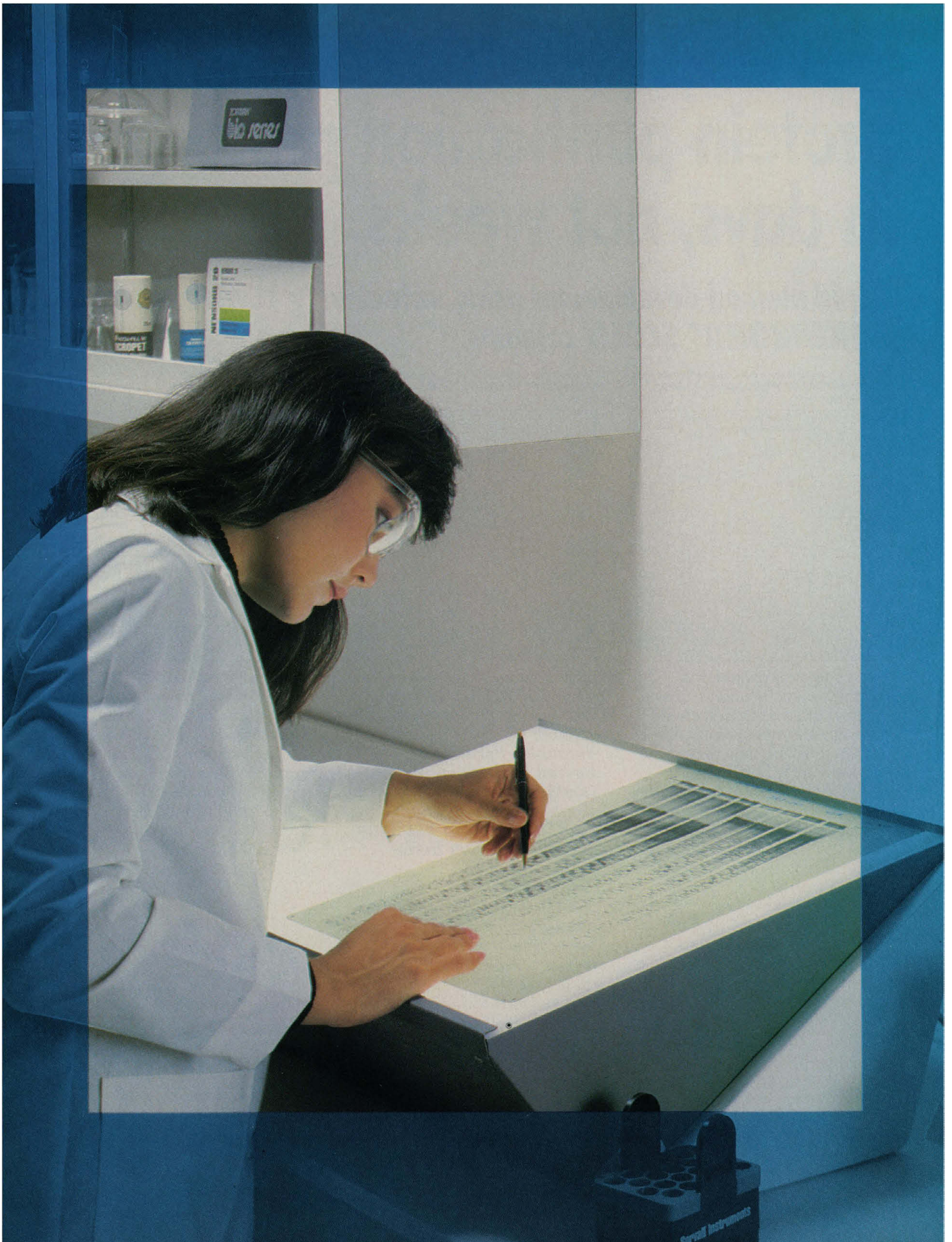
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Letters

Uranium Enrichment

Colin Norman's article "Uranium enrichment: Heading for a cliff?" (22 May, p. 906) states that "[t]he Department of Energy . . . has managed to pull the [uranium enrichment] business back from the brink with some severe and painful cost cutting" but that Congress must resolve the dispute over some $8.8 billion in debt that the program has accumulated. Unfortunately, the Enrichment Program is far from stabilized, and the simplest "resolution" of the debt—which is acknowledged by all relevant government agencies—is repayment.

As Norman notes, Senators Ford and Johnston have introduced a bill to "forgive" approximately 95%, or all but $360 million, of the debt owed to the taxpayers. One of the reasons for this enormous subsidy is ostensibly to prevent U.S. utilities from going abroad for cheaper enrichment services furnished by foreign government-owned suppliers. There are ways to accomplish the same goal without costing the taxpayers more than $8 billion. For example, DOE's domestic market (about two-thirds of DOE's business) can be maintained through use of existing authority in the Atomic Energy Act to require domestic utilities to purchase enrichment services from DOE.

Another objective of the $8.4-billion "write-off" is to hold on to foreign sales of approximately $400 million per year. But many of these sales would remain with DOE regardless of price because of political considerations in the foreign trade area. The $400 million is not all, and may not represent any, profit. Therefore, the cost of the subsidy grossly overshadows the value of retaining a market that costs more to serve than can be recovered.

Furthermore, most of DOE's foreign sales are lost, not to higher prices, but to foreign utilities (which are generally government-owned) patronizing their home countries' new enrichment services.

Booz-Allen & Hamilton, the consulting firm that reviewed the situation for Martin Marietta (DOE's enrichment plant operator), recently testified before Congress that DOE's foreign competitors lack the capacity to service defecting DOE customers until the mid-1990s. Therefore, DOE could maximize the value of the enterprise and in the process recover most if not all of the debt by simply raising its prices with no fear of lost sales. While we do not agree with all of the policy recommendations made by Booz-Allen, we do agree with their conclusion that DOE's current strategy of cutting prices without much attention to the future is "not viable."

There are two additional matters that Norman does not mention in his article. First, DOE has a legal obligation to recover all the costs of its civilian enrichment program under section 161v. of the Atomic Energy Act. This requirement, which has been in the law since the federal government began providing enrichment services to civilian customers in 1969, is designed to prevent exactly the type of taxpayer subsidy now advocated by Senators Ford and Johnston, DOE, and the nuclear utility industry.

Second, DOE ran up the $8.8-billion debt in question by investing in unnecessary capacity (diffusion plant upgrades and the gas centrifuge) rather than repaying the Treasury. DOE took these actions at the insistence of the nuclear utility industry, as evidenced by congressional testimony of the Edison Electric Institute and others. The utilities testified that they would pay for the capacity and that the risks of not having it available outweighed the risks of having too much. They are now reneging on their own commitment by threatening to turn to other suppliers unless DOE or Congress "forgives" their $8-billion debt.

Contrary to Norman's assumptions, the Ford-Johnston approach would not result in a more "businesslike" enrichment program, would write-off a debt that *can* be recovered and would not protect against the accumulation of additional debt to taxpayers requiring additional write-offs in the future. Also, payback to the Treasury can be made without harm to DOE or to the nuclear industry or its ratepayers. Full recovery of the debt would add less than one-tenth of a cent to the cost of each nuclear-generated kilowatt-hour. Such a payback would be in accordance with existing law and more than 20 years worth of commitments by the federal government and the nuclear utility industry.

John Longnecker, the DOE official in charge of the enrichment program, is quoted as proposing that the enrichment business "is a profitable niche of the nuclear business internationally" and that "[t]he only way we can be beaten is for the United States to choose not to compete." He has proved that the only way the program is "profitable" is by gargantuan taxpayer support. The cost to the United States for increasing DOE's market share as suggested by Longnecker and as proposed by Senators Ford and Johnston is $8 billion now and more later out of the pockets of U.S. taxpayers. Even this negative "profit" would result in only marginal expansion of DOE's mar-

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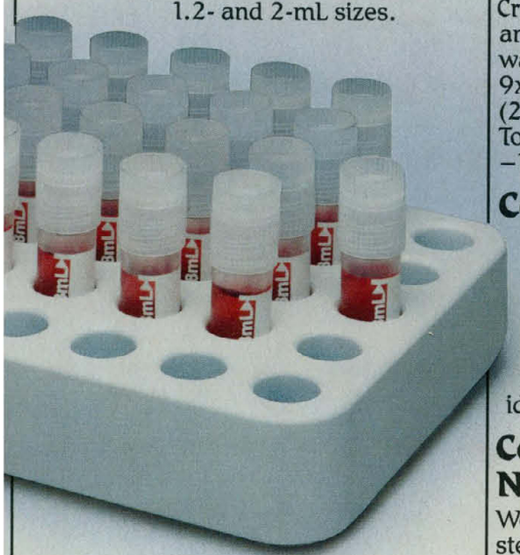

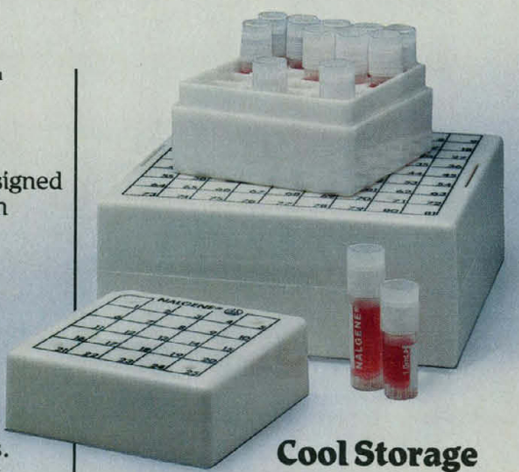

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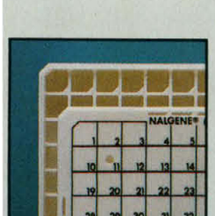

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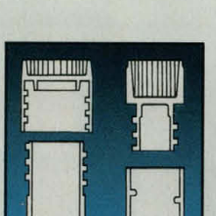

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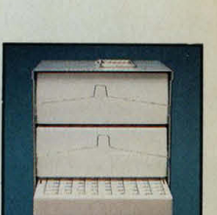

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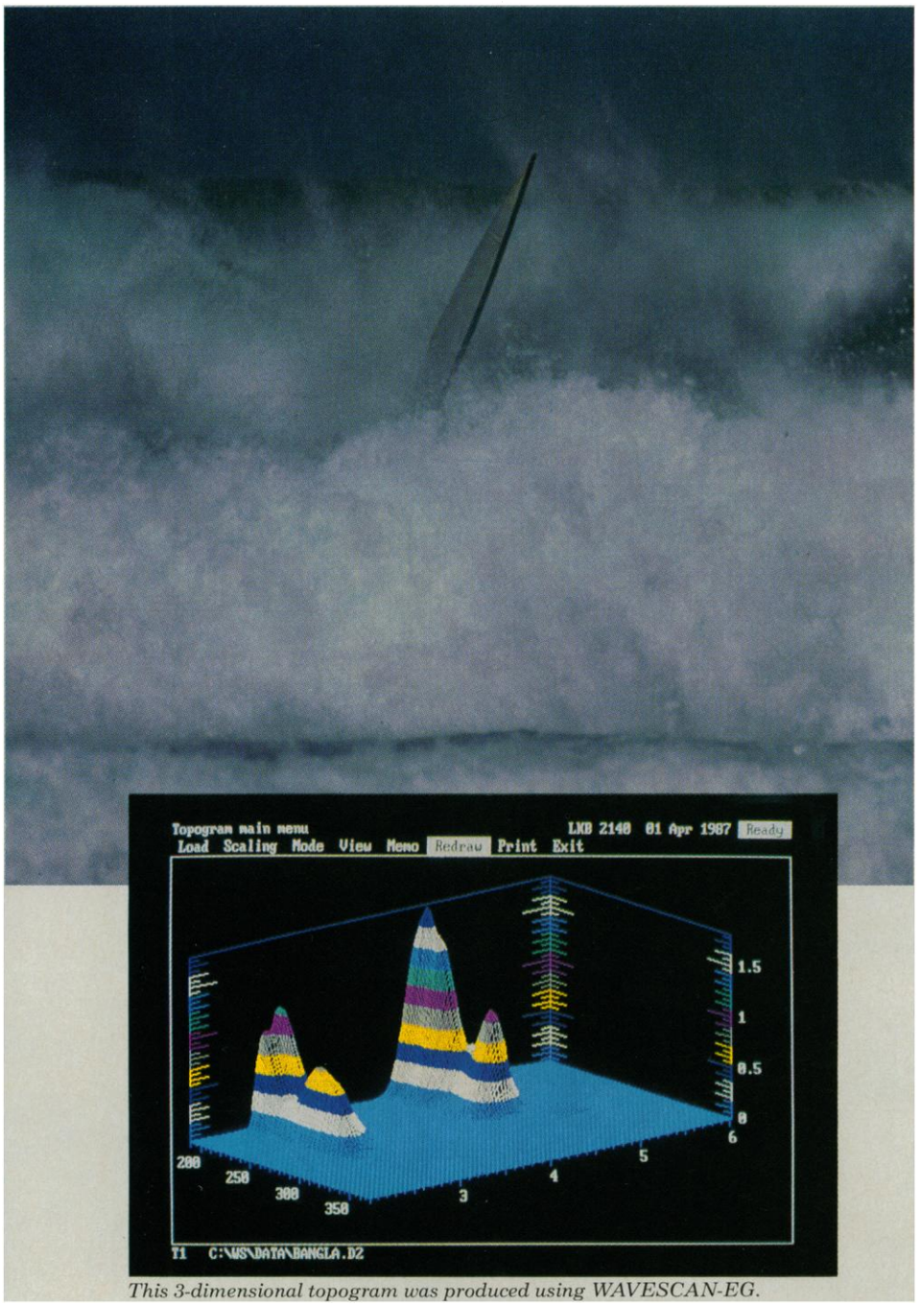

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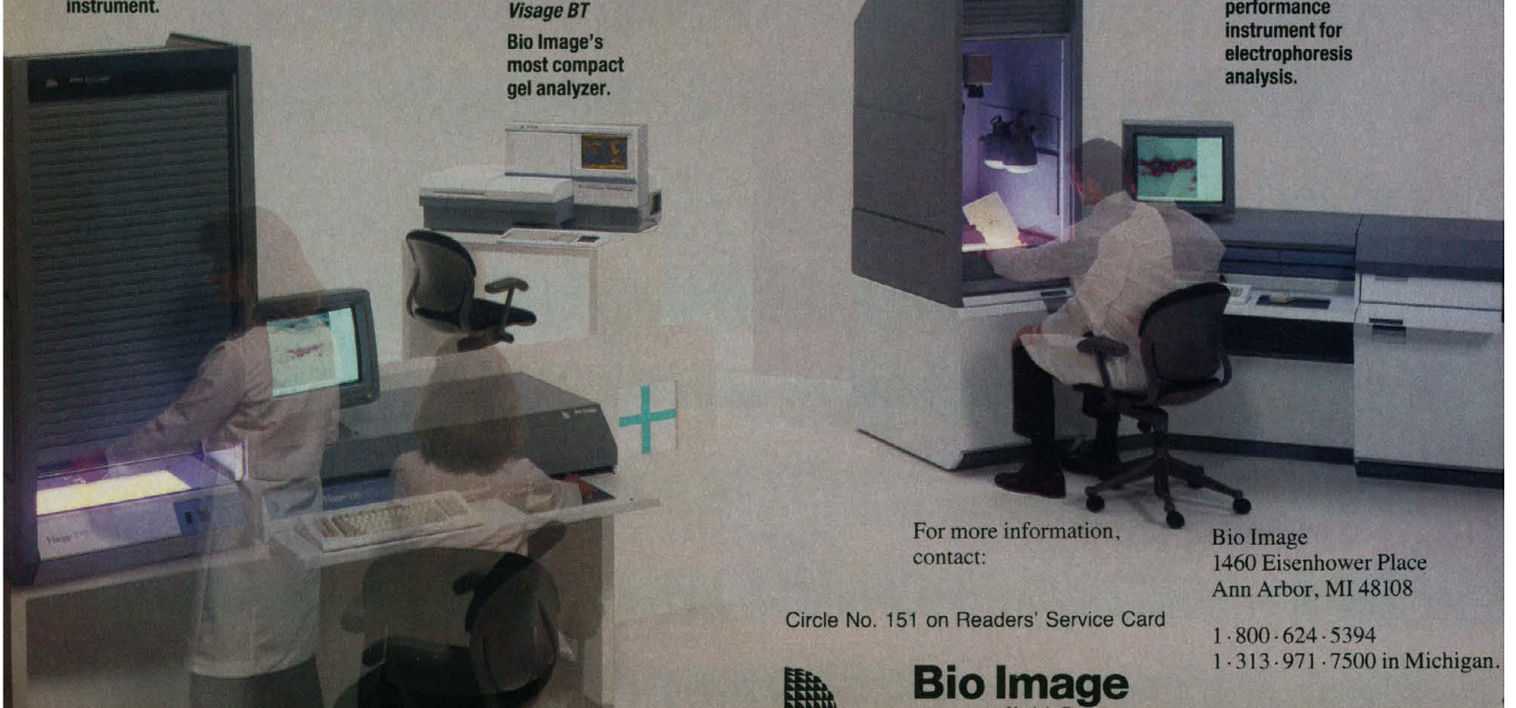

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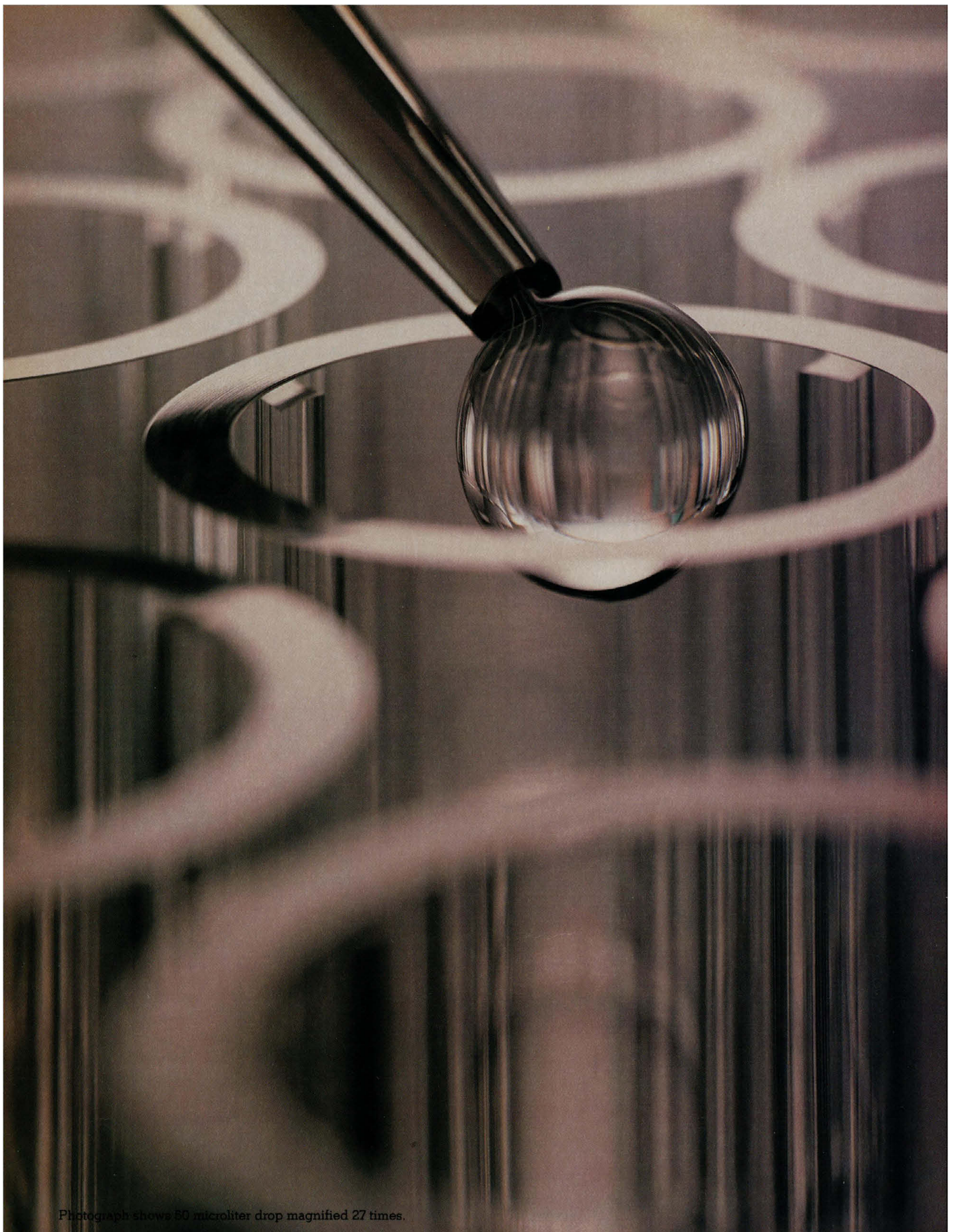

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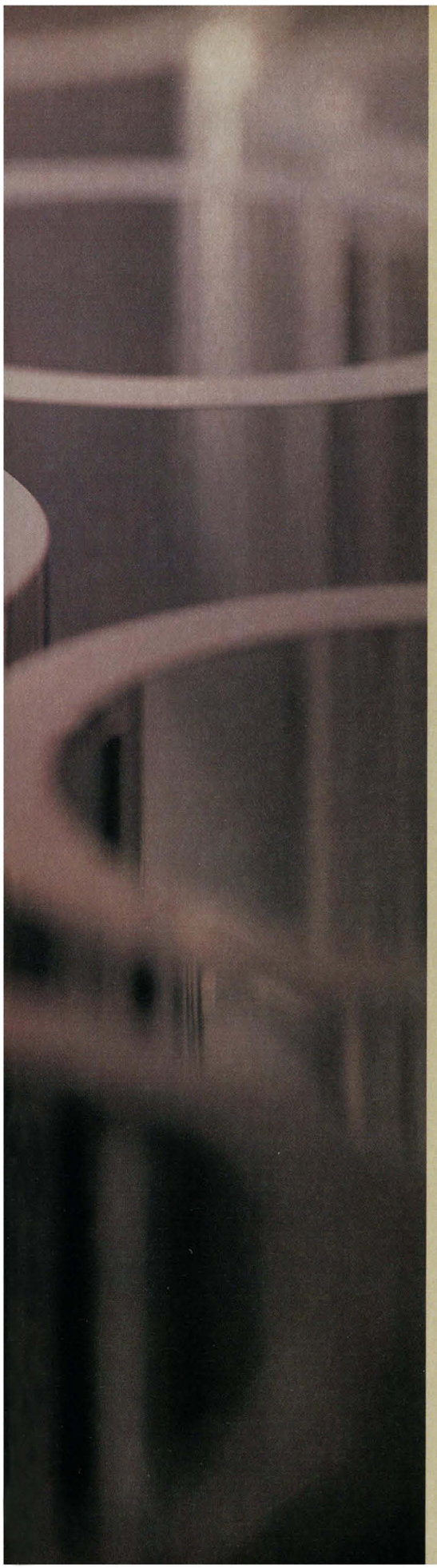

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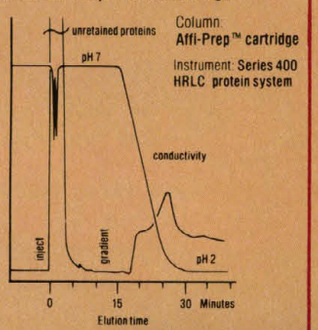

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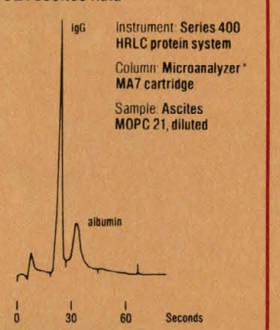

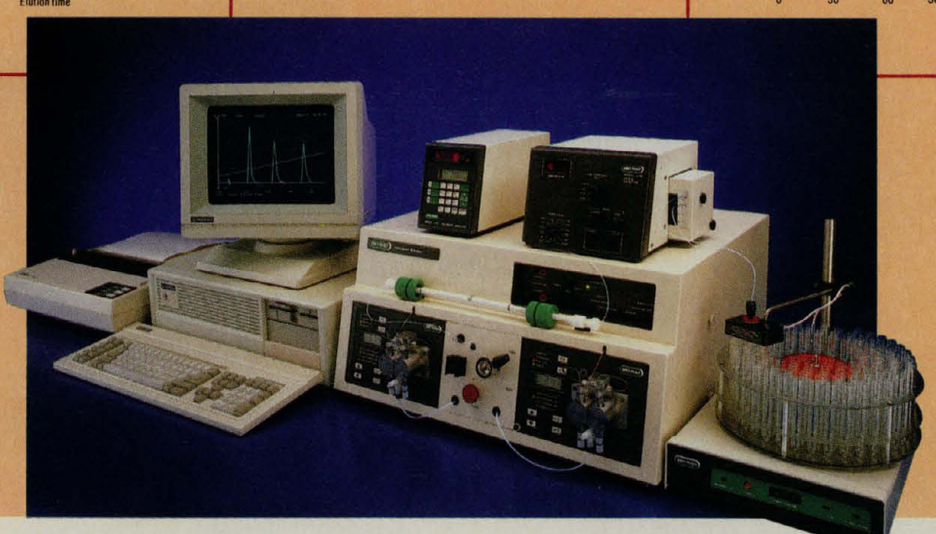

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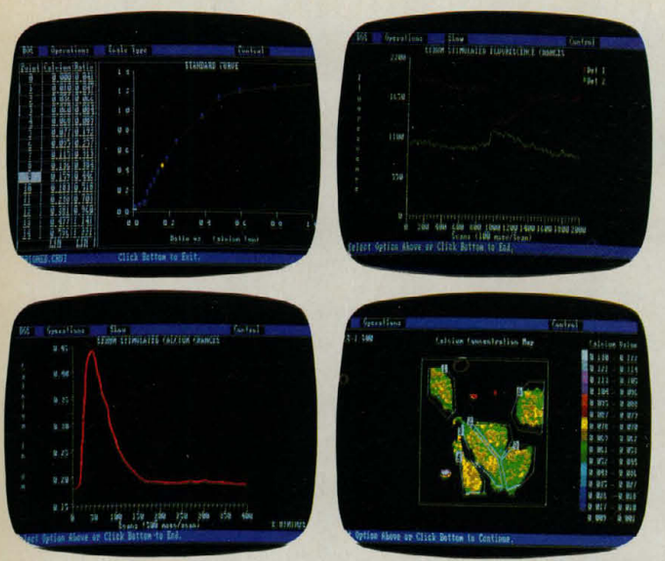

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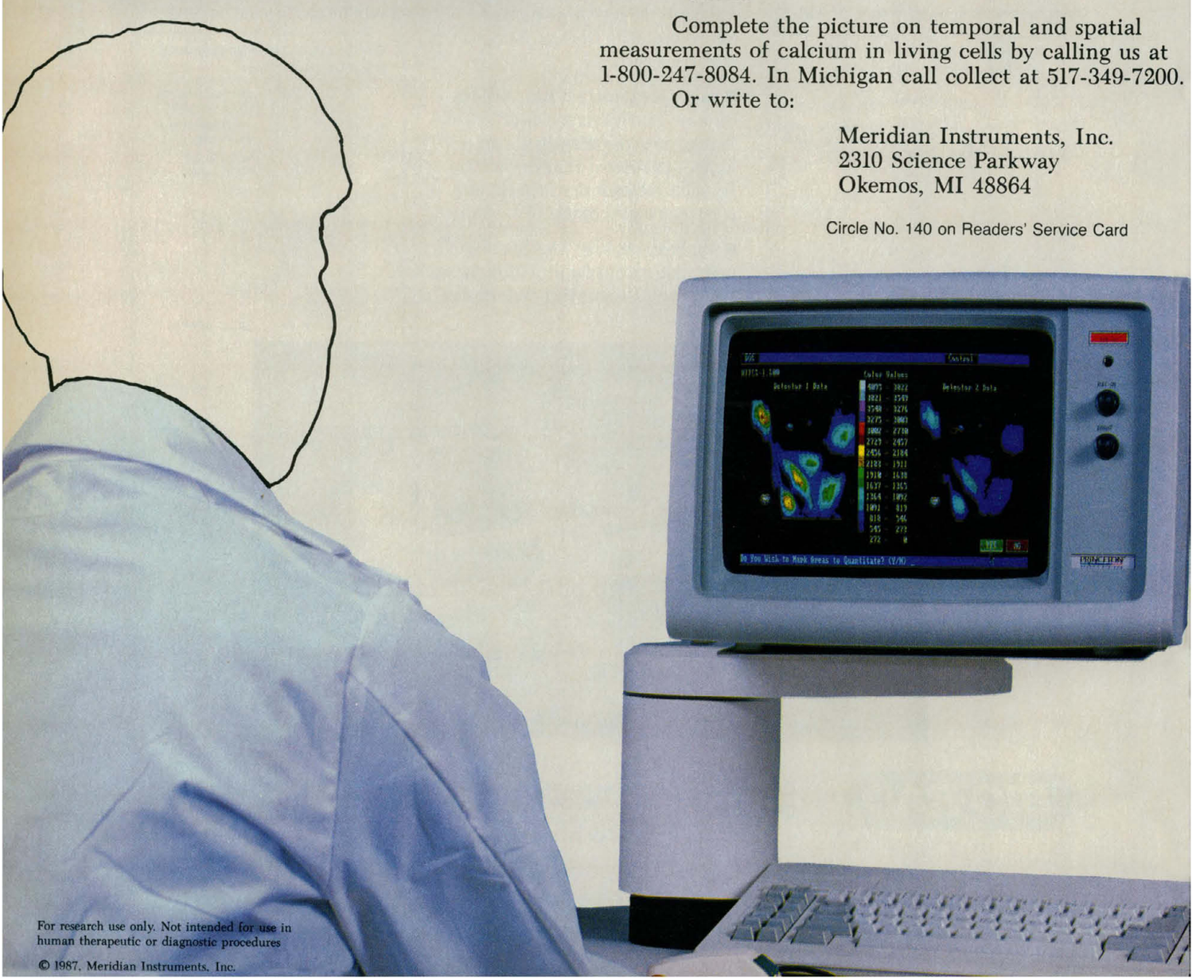

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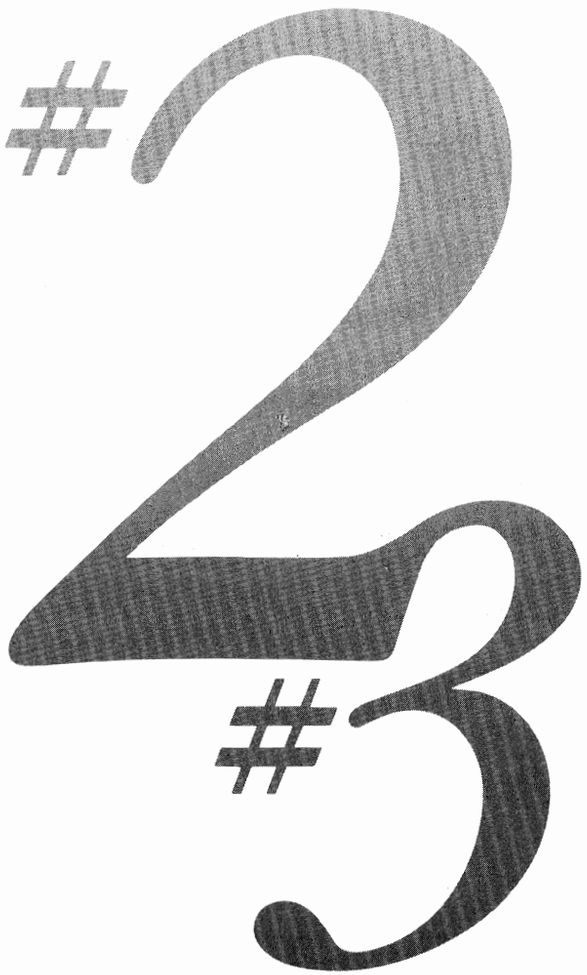

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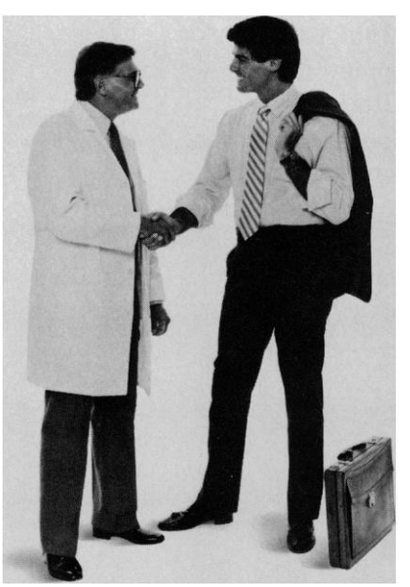

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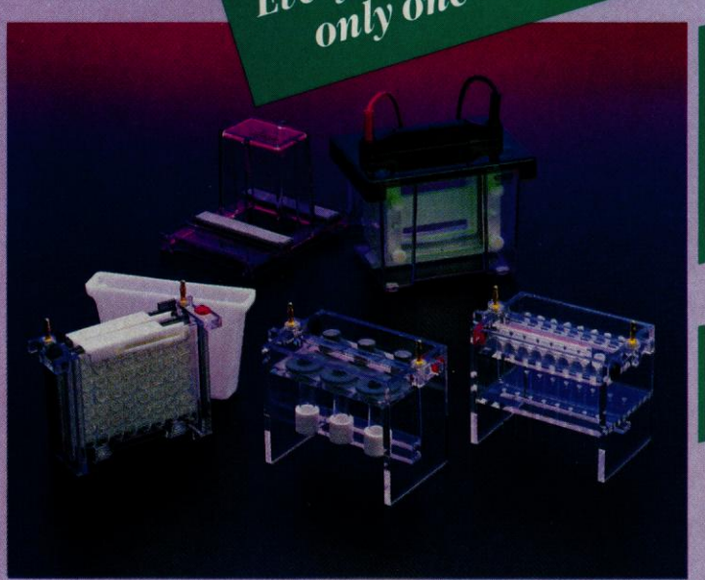

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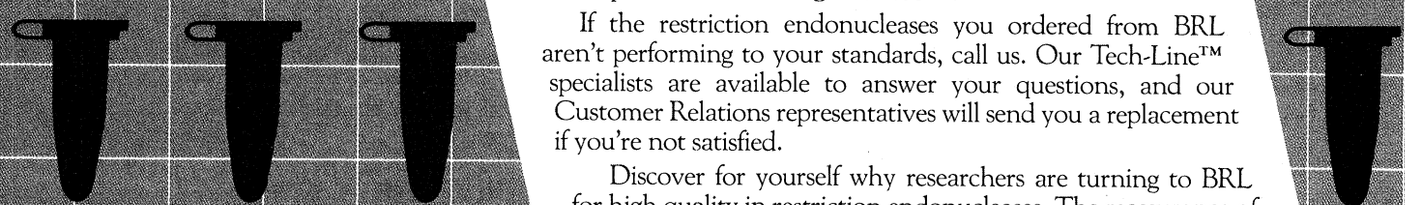

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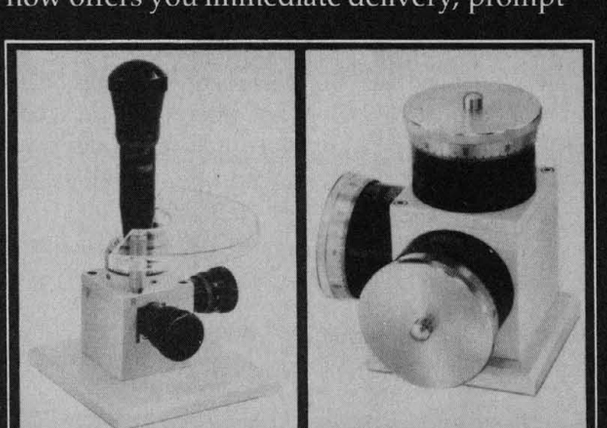

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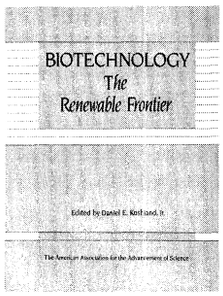

Biotechnology: The Renewable Frontier, *D.E. Koshland, Jr., ed.* Like its predecessor, this volume covers the latest and most important topics in biological R&D. It illustrates the extraordinary cross-disciplinary aspects of modern biology and its tremendous impact on the future with sections ranging from new techniques, immunology, developmental biology, cancer, hormones, sensory phenomena, and more.

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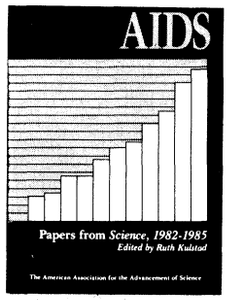

AIDS, *R. Kulstad, ed.* Research papers and reports on acquired immune deficiency syndrome (AIDS) published between August 1982 and September 1985 show how far AIDS research has come and provide an indication of the direction in which it might go. An overview of research in AIDS is provided by Myron Essex, chairman of the Department of Cancer Biology, Harvard University School of Public Health.

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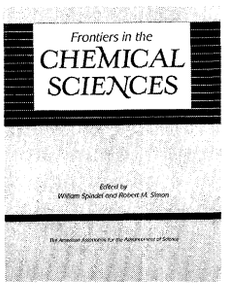

Frontiers in the Chemical Sciences, *W. Spindel, R.M. Simon, eds.* Focuses on the themes of fundamental chemical change and extreme molecular complexity. Details progress in all areas of chemistry, including new work in ultrafast reactions, catalysis, conduction organics, enzyme mechanisms, and materials and analysis.

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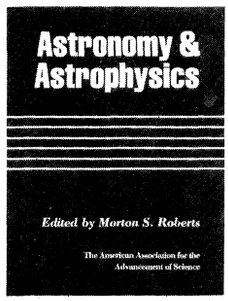

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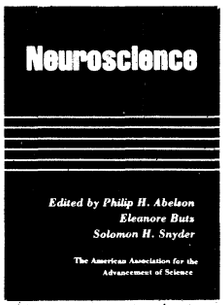

Neuroscience, *P.H. Abelson, E. Butz, S.H. Snyder, eds.* Neuroscience research ranging from genetic engineering to clinical therapy is presented. Provides an integrative treatment of brain anatomy, physiology, and chemistry and addresses fundamental questions concerning nervous system functioning.

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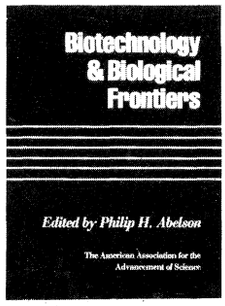

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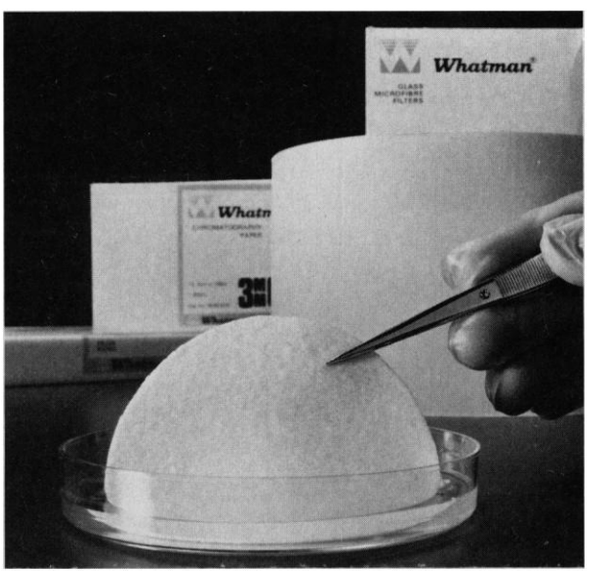

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[1]Aebersold, R.H., Teplow, D.B., Hood, L.E., and Kent, S.B.H. (1986) *J. Biol. Chem.* **261**, 4229-4238.

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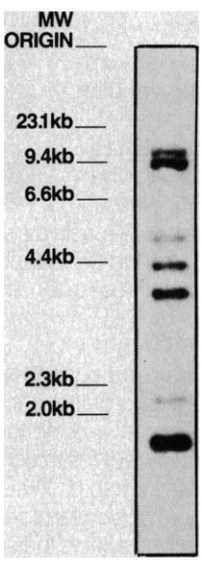

DNA was prepared from normal peripheral blood leukocytes, digested to completion with *Pvu* II (Genomic Grade) and transferred from a 1.5% agarose gel to a nylon filter membrane. A 1.2 Kb DRβ cDNA clone contained in the *Pst* I site of pBR322 was used as the probe. Densitometry values are presented as ratios in the following format: filter background/lane background/band signal or, in this example, an average signal-to-noise ratio of 30:1.

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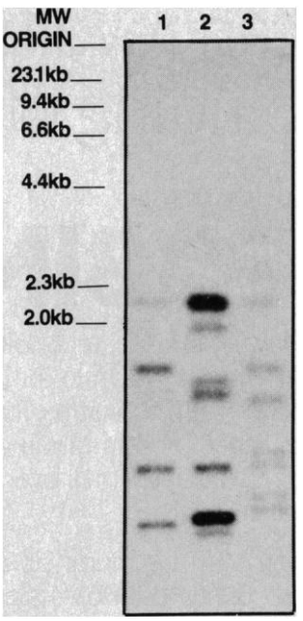

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Illustration at right shows how CO-BIND™ surface (top) binds a higher concentration of protein more uniformly than other protein binding methods (bottom).

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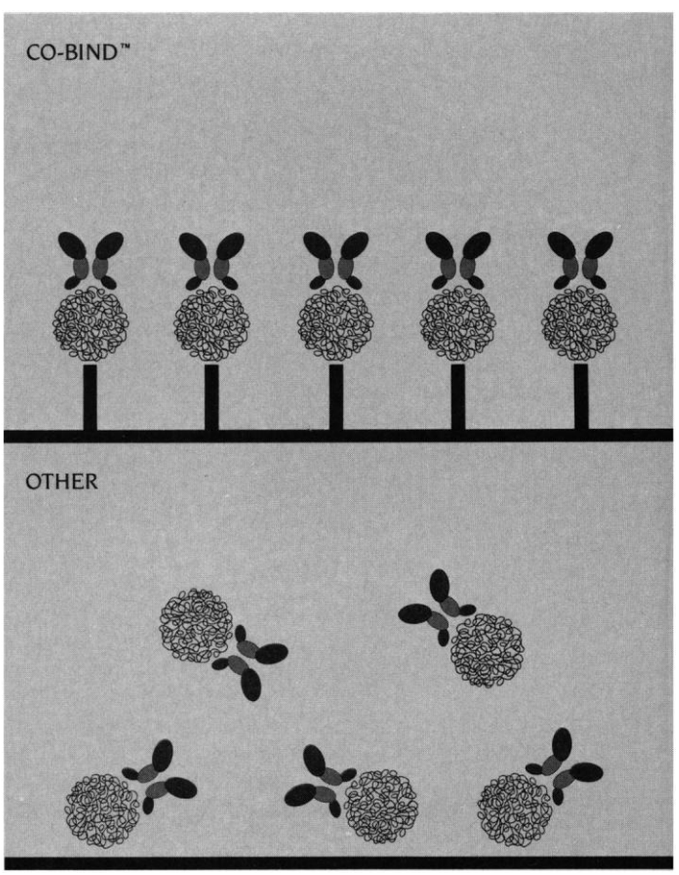

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Phylogeny and Coevolution

Coevolution and Systematics. A. R. STONE and D. L. HAWKSWORTH, Eds. Clarendon (Oxford University Press), New York, 1986. xii, 147 pp., illus. $39.95. Systematics Association Special Volume no. 32. From a symposium, Brighton, U.K., July 1985.

With the development of increasingly rigorous methods and new kinds of data for inferring genealogical relationships among species, systematics is emerging from a period of eclipse to take its rightful place as an essential, integral party to evolutionary studies. There is increasing recognition that the study of both adaptive and nonadaptive traits cannot be divorced from the historical analysis that systematics includes among its subjects. Among the topics on which systematic analyses should make especially critical contributions is the coevolution of ecologically interacting species. As J. N. Thompson points out in this volume, coevolution includes two phenomena: coadaptation, the reciprocal adaptation of taxa to each other, and cospeciation, the joint speciation of associated taxa such as hosts and their parasites.

In principle, systematics should contribute to answering several kinds of questions about coevolution. For example, Ehrlich and Raven postulated in 1964 that adaptive radiation (hence, species diversity) of hosts may be stimulated by escape from parasitism via the evolution of novel defenses and that parasites (or herbivorous insects) may diversify when a lineage becomes adapted to a host group that had escaped exploitation. As Thompson shows by an analysis of a controversial case in plants and insects, this hypothesis can be tested only by an adequate diagnosis of species and monophyletic groups.

If cospeciation is general, the phylogenies of hosts and their parasites should be topologically congruent, in the absence of extinction of parasite lineages and of lateral transfer of parasites between host lineages. The supposition that parasite phylogenies mirror host phylogenies has been christened "Fahrenholz's rule" by parasitologists and has long been used as a guide to classification in parasitology. This rule is examined in this volume both by workers who do not use explicitly cladistic methods to infer phylogeny (V. F. Eastop on aphid-plant associations and I. Beveridge on the helminths of Australian marsupials) and by several workers who do (C. J. Humphries *et al.* on associations of moths, scale insects, and fungi with southern beeches, *Nothofagus*, and C. H. C. Lyal on trichodectid lice of mammals). It will be necessary to read these authors' primary publications to evaluate their methods, which in some cases are not specified and in others may evoke skepticism. Lyal, for example, uses manual methods, which are notoriously inexact, to determine relationships among 351 taxa of lice on the basis of only 187 characters. Humphries *et al.* report 190 equally parsimonious trees for 17 species of *Nothofagus*, which leads one to wonder if the shortest trees were indeed found. (Incidentally, their important figure 4.6, on the *Nothofagus* relationships implied by the moth phylogeny, is in error.) These essays also illustrate the need for explicit methods of finding, and testing the significance of, points of incongruence between phylogenies.

With these caveats, the message nonetheless emerges that the phylogenies of hosts and parasites show little congruence at any taxonomic level. Cospeciation is far from universal, and host lineages seem often to have lost their parasites. In every case, sister groups of parasites often occupy unrelated hosts (for example, rodents and marsupials), so lateral transfer has been a major feature of parasite evolution. As the population biologists (J. A. Barrett, J. E. Parlevliet, J. N. Thompson) note, genetic variation in many groups of parasites enables ready transfer to new hosts; moreover, strict cospeciation would be expected only if evolution in one partner caused reproductive isolation in the other or if populations of both hosts and parasites acquired reproductive isolation at similar rates.

Perhaps because long-term associations are so frequently confounded by transfers to unrelated hosts, it is hard to demonstrate progressive coadaptation between associated lineages—which systematics should in principle be able to document from character analysis. This topic is not treated explicitly in the volume; still, as Eastop says, it is hard to show that the macroevolution of either hosts or associates has been affected by their interaction, even though adaptation of individual species to their hosts is clear.

This volume, informative as it is, only sketches what has been done and what we may hope for. That Fahrenholz's rule is more evident in the breach than the observance points to the role that systematics may play in documenting the history of host