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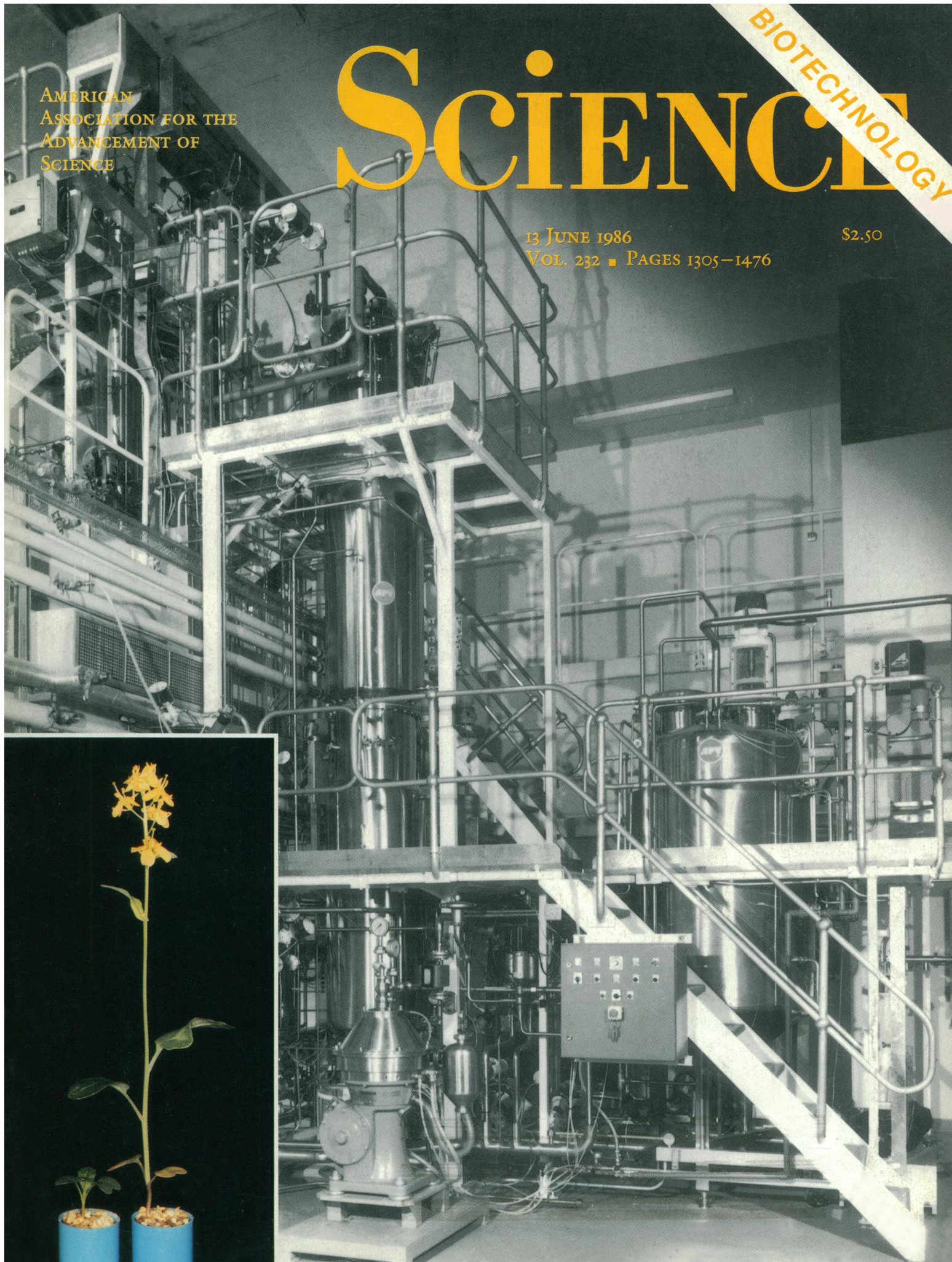
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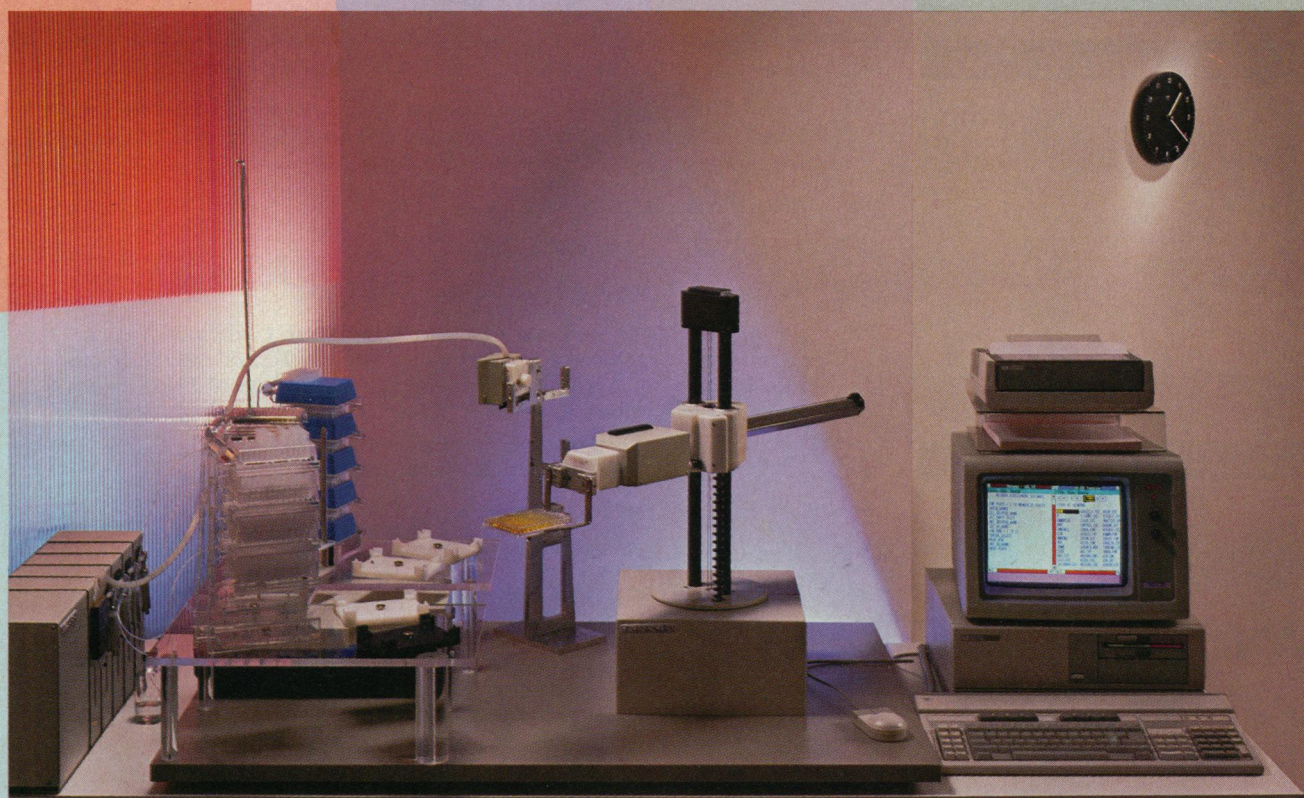
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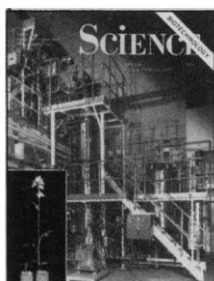
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COVER Two sides of biotechnology. (Background) Large-scale cell culture has become a multimillion dollar industry, vital to the manufacture of vaccines, monoclonal antibodies, and other pharmaceutical products [1000-liter fermenter, courtesy of Celltech Ltd., Slough SL1 4DX, United Kingdom]. (Foreground) By selective breeding in the laboratory, rapid-cycling *Brassica campestris* plants have been developed that will be useful in basic research, in improving crop production, and as educational tools. See page 1385. [Paul H. Williams, University of Wisconsin, Madison, WI 53706]

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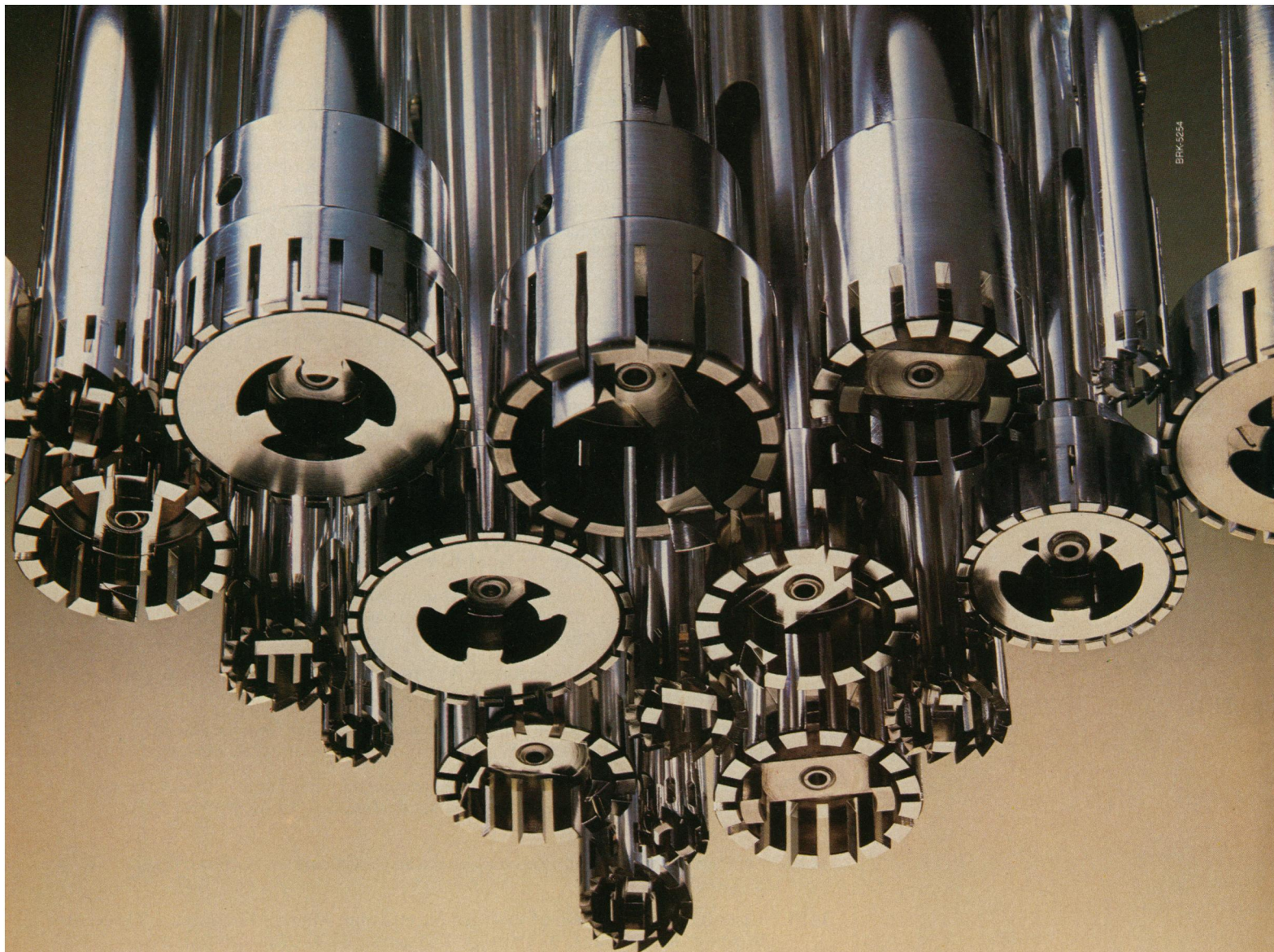
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This Week in **SCIENCE**

Regulation of food ingestion

CENTRAL secretion of the hormone oxytocin accompanies states of satiety produced by eating and of nausea produced by toxins such as lithium chloride (page 1417). Normal animals and humans stop eating when they are full, and both also avoid eating if they have developed an aversion to a particular food. Coyotes, if fed on baited sheep laced with the emetic agent lithium chloride, will subsequently avoid attacking live sheep. Cholecystokinin, a gut hormone, may be active during normal feeding behavior to produce satiety; when large doses of this hormone are injected into rats, it mimics the nausea-producing activity of lithium chloride. Verbalis *et al.* show that these various manifestations of the regulation of food intake have in common a concomitant increase in the plasma levels of the neural peptide oxytocin. Plasma oxytocin rises in a dose-dependent manner when cholecystokinin is administered to rats. Other experiments indicate that oxytocin secretion without nausea can occur as a response to normal eating. These findings provide clues to a neural-hormonal circuit that controls one of the basic animal behaviors, food ingestion.

High-pressure laboratories

STATIC pressure at the center of the earth is about 3.5 megabars (0.35 terapascal); Xu *et al.* have successfully generated pressures of this magnitude in the laboratory with a diamond anvil apparatus and have calibrated the pressure with an internal ruby fluorescence standard (page 1404). Previous experiments at these extremely high pressures had been hampered by interfering fluorescence from the diamond anvils. At pressures above 0.28 terapascal the diamond fluorescence diminishes, and the ruby fluorescence can again be measured by extrapolation of an already established ruby scale. The highest pressure obtained, 0.55 terapascal, is about three times as high as the previous record. Application of this

high-pressure apparatus should yield insights into the structure of matter in the interior of the earth and of other planets. Synthetic carat-sized diamonds have recently become available, and anvils have now been made of this material (page 1419). Onodera *et al.* show that synthetic diamonds have advantages over natural gem-quality diamonds used in laboratory high-pressure research in that they have fewer imperfections, greater strength, more isotropic pressure transmission, and less variation in quality among individual anvils.

Beetles protect their turf

BEETLES that feed on leaves typically secrete an array of chemicals that mitigate attack by a variety of predators, both vertebrates and invertebrates. The larvae of a willow leaf beetle, *Plagiodera versicolora*, secrete a mixture of monoterpenes that deter other insects, including adults of their own species, from feeding on the leaves occupied by the larvae (page 1408). Raupp *et al.* found that placing live or dead larvae on a leaf or coating the leaf with the natural excretion of the larvae protected the leaf from being eaten by adult *Plagiodera*. Similar experiments showed that the larvae were able to diminish the eating of leaves by larvae of another willow-leaf eater, *Nymphalis*, presumably by the action of the monoterpene secretions. The demonstration that secretions by one species of insects influence the feeding behavior of other insects adds one more use to the vast assemblage of chemical substances produced by insect herbivores.

University-industry research relationships

BIOTECHNOLOGY faculty members who receive support from industry publish more, are more involved with professional and university activities, apply for more patents, and earn more than their colleagues without such support (page 1361). Blumenthal *et al.* surveyed more than 1200 faculty members at 40 large universities in an

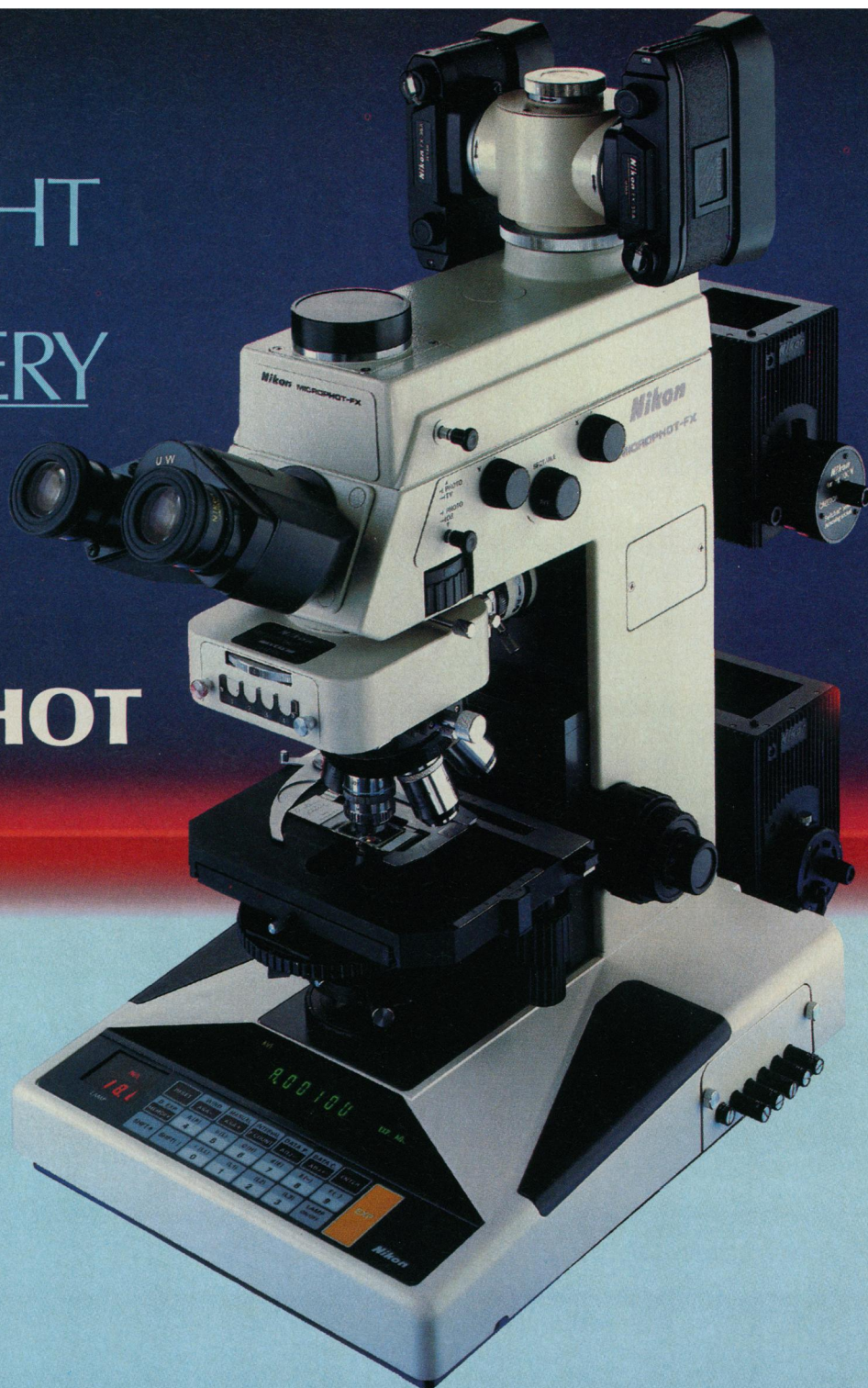
attempt to measure the benefits and risks of university-industry research relationships (UIRR's). The survey respondents were members of the departments judged to be most likely to contain faculty conducting research involving the new biotechnologies: biochemistry, molecular biology, genetics, microbiology, biology, cellular biology, and botany. The findings from this survey should be reassuring to the university community. Faculty with industrial support showed higher productivity than other faculty as measured by the number of publications and involvement in professional activities, with no reduction in time devoted to teaching. Possible risks to the university were identified in the areas of secrecy, a tendency to perform applied research or research of a commercially oriented nature as opposed to basic research, and potential conflicts of interest. Universities should structure their UIRR's so that the benefits of such arrangements can be preserved and the adverse effects minimized.

Overlooked plant resources

THROUGHOUT history people have used perhaps 3000 plant species for food. Today, most of the world's food supply comes from only about 20 species (page 1379). Vietmeyer calls attention to many forgotten and underexploited plants that could be developed for use as food, fuel, fiber, building materials, and industrial raw materials. Some of these plants already feed large numbers of people, especially in the Third World, but have received little attention from agricultural researchers. Some are good sources of protein, and others have remarkable resistance to drought, tolerance to saline soils, or abilities to fix nitrogen or grow in marginal or worn-out agricultural lands. Some of these plants are threatened with extinction. Conservation and improvement of these valuable plant resources should go hand in hand with biotechnology in enhancing the expansion of our agricultural resource base.

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The Biotechnology Issue

President Kennedy once invited a large group of distinguished scientists to the White House for dinner and there remarked, "I think this is the most extraordinary collection of talent, of human knowledge, that has ever been gathered together at the White House, with the possible exception of when Thomas Jefferson dined alone."

Adapting this observation to the new biotechnology industry, we might say that we are today mobilizing the most amazing collection of brains for a new technology since Louis Pasteur worked alone. The biotechnology industry has been around for a long time, starting with the herb doctors and wine-makers of ancient civilizations. For deliberate application of the problems of science to the needs of health and the economy, however, Louis Pasteur is unique. He represents in one person the combination of pure research and practical application that is the hallmark of the current biotechnology industry.

In Pasteur's early studies he pursued the academic problem of optical antipodes, performing his classic work on the separation of dextro and levo tartaric acids. He also performed his seminal studies on the spontaneous generation of life, demonstrating that fermentation was the product of living cells and that life was necessary to create new life. His understanding of microbes and their behavior was the handle in his generation that recombinant DNA is in ours. Pasteur's genius and the smaller size of his scientific world produced a different relationship, however. Pasteur personally was involved in one major industrial application after another. He discovered the cause of the souring of wine and beer, thereby providing enormous economic savings for his own country as well as England and Germany. He corrected the devastation of the silk industry by identifying the parasite preying on the silkworm. He developed the technique for attenuating viruses and protected chickens from cholera. He then studied the disease of anthrax and demonstrated the protection of sheep in one of the great experiments illustrating the scientific method. In the culminating act of his incredible career, Pasteur saved the life of a young boy who had rabies by giving him ground-up tissues from organs of infected animals.

The modern technology industry parallels in uncanny ways the approach of Louis Pasteur. Its hallmark is the continuously changing line between basic academic research and practical industrial applications. Basic research in academia leads to applications in industry. Questions posed by industrial problems generate new academic initiatives. To the credit of many modern biotechnology companies, they have become more permissive in allowing their scientists to publish and less secretive in regard to their procedures than the pharmaceutical industries in the past. It is a farsighted approach, since secrets are difficult to secure and the industry itself thrives on the constant interaction with academia.

This issue of *Science* deals with new advances from which new medicines and industrial products may be produced. Even those who do not like broccoli will have to concede that a member of the broccoli family that goes through its life cycle in 6 weeks can provide a powerful research tool for plants (Williams and Hill). Vietmeyer describes some "poor people's plants" that may provide more new bases for industrial crops than the 20 species on which most modern agriculture now focuses. Parkman discusses those diseases for which bone marrow transplantation is most appropriate, a technology whose importance is accentuated vividly by the Chernobyl disaster.

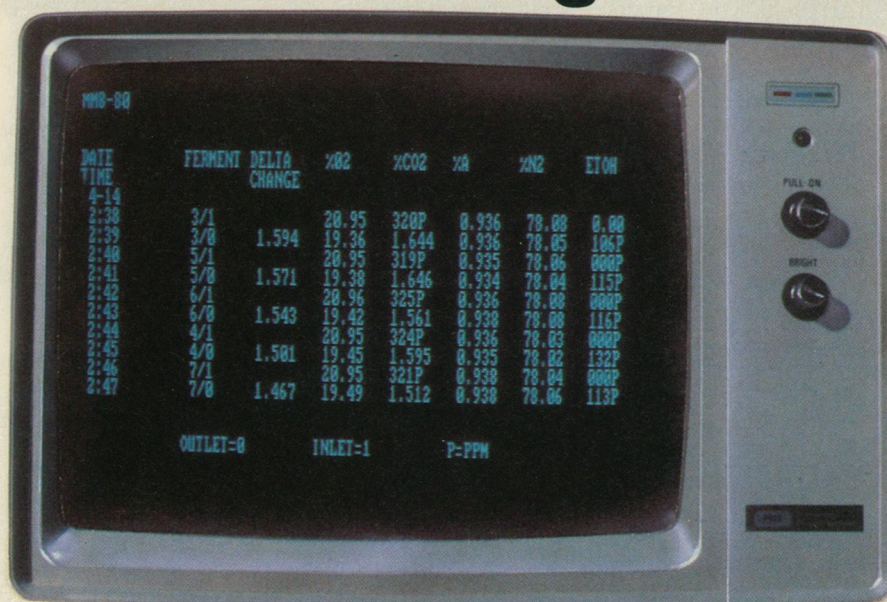
Arathoon and his colleagues describe the improving expertise in growing large amounts of mammalian cells, a critical requirement for such products as vaccines, interferons, and monoclonal antibodies. Blumenthal provides insight into the opportunities and hazards of university-industry relations, and Dibner discusses the growth of biotechnology in Europe. Weetall and Pitcher describe factors involved in scaling up an immobilized enzyme system.

It is worth noting that Pasteur operated with an incredible freedom not given to modern researchers. His treatment of the boy bitten by a rabid dog was done without extensive field trials, which would have delayed its application for years. His studies on soured wines and diseased silkworms were not greeted with cries that he was introducing organisms into the environment. Allowing one genius unparalleled freedom is easier than attempting to control a boisterous and explosively growing technology. Pasteur's willingness to take risks for good cause and to tackle academic and practical problems with equal enthusiasm are standards of conduct that have aged as well as the wines he preserved.

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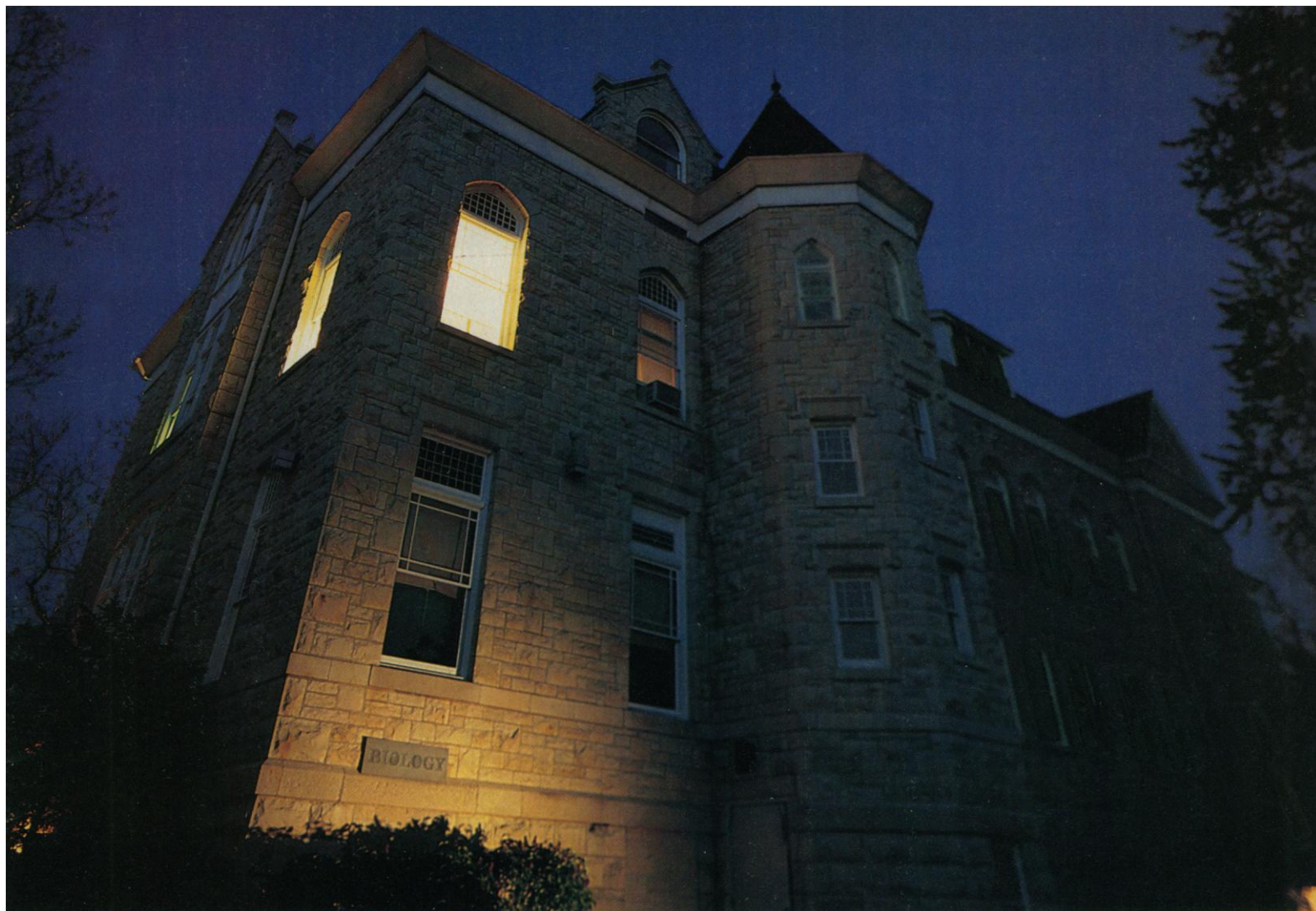


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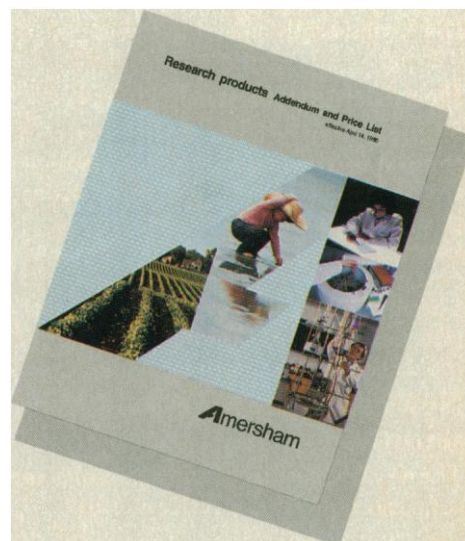
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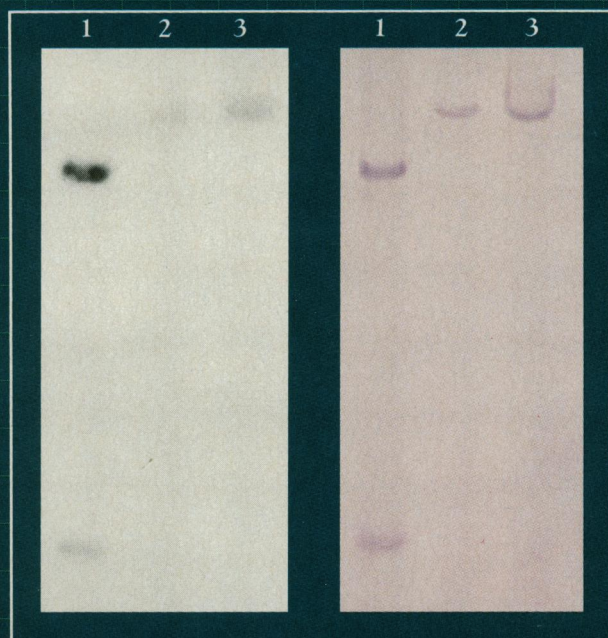
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After 3 hours a single-copy human β -globin gene was detected using autoradiography with an intensifying screen (left) and BluGENE™ (right).

Samples of a plasmid containing the 1.1-Kb Mst II fragment of the human β -globin gene in the EcoR I site of pBR322 (Chang, J. C. and Kan, Y. W. (1982) N. Engl. J. Med., 307, 30) were labeled by nick translation with [α - 32 P]dATP (1.5×10^8 dpm/ μ g DNA) (left) or biotin-11-dUTP (right) and hybridized to Southern blots for 18 hours under identical conditions. Lane 1 contains sheared herring sperm DNA (1 μ g) and EcoR I-digested plasmid (5 pg DNA: 4 pg vector in the upper band and 1 pg insert in the lower band). Lanes 2 and 3 contain 2 μ g and 10 μ g, respectively, of EcoR I-digested human genomic DNA.

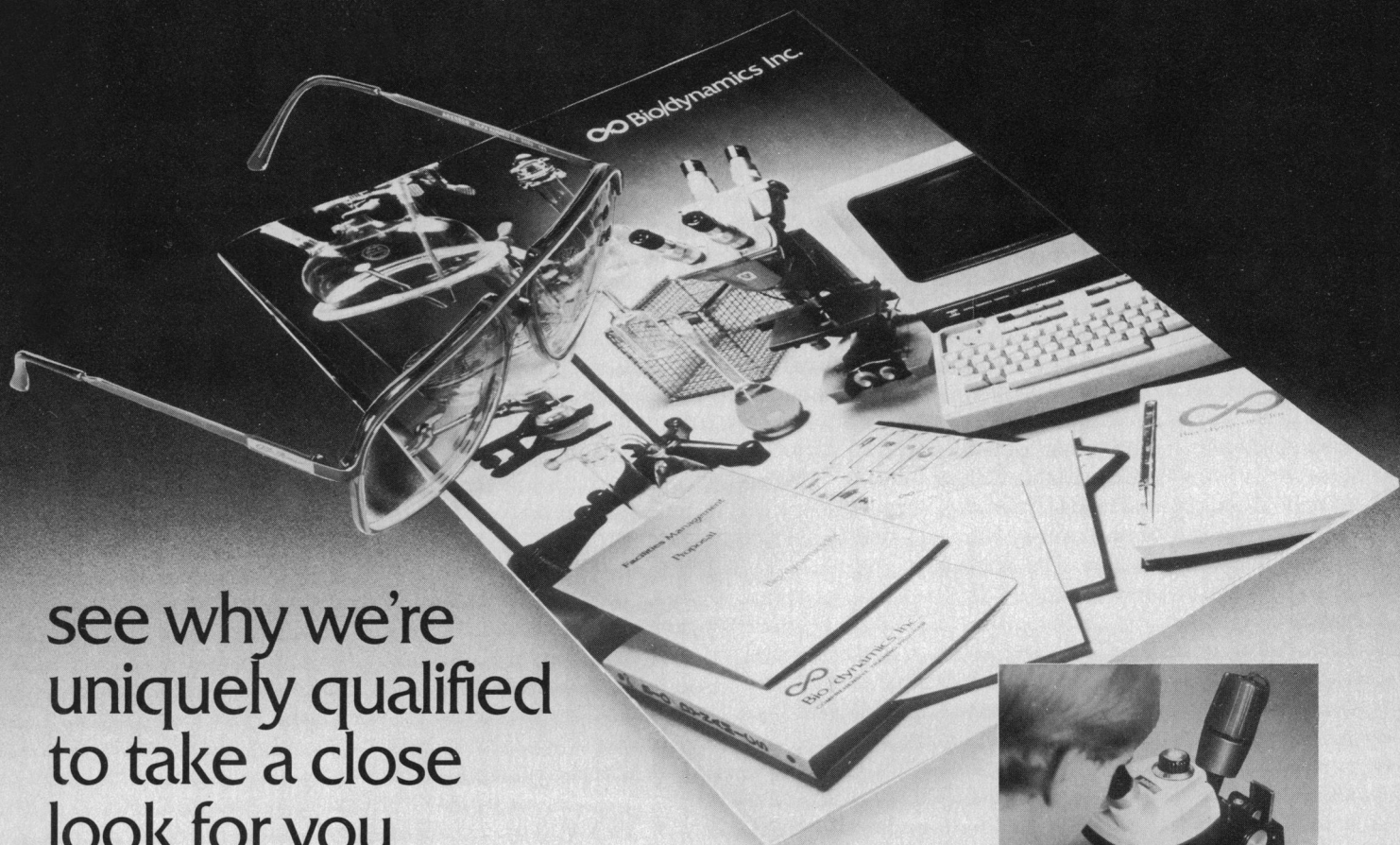
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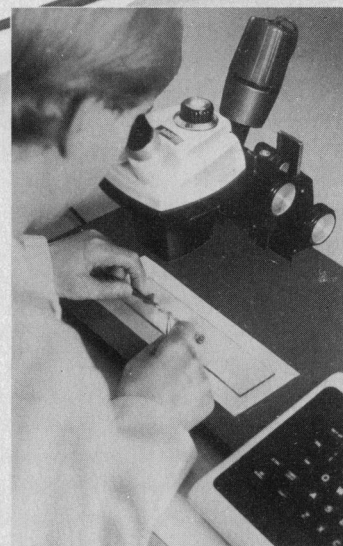
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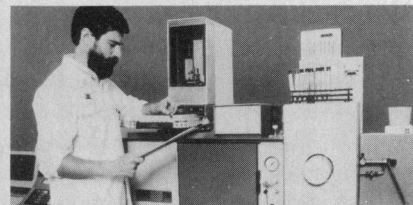
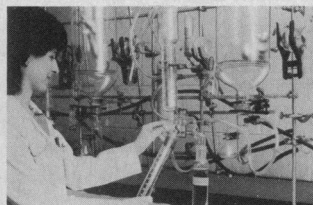
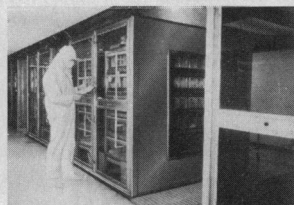
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Greenwich Observatory (RGO) from its home at Herstmonceux Castle in Sussex. Sadly the situation seems to be that the British Science and Engineering Research Council (SERC) has decided to decrease support for optical astronomy, but rather than say so, has tried to persuade British astronomers that such a move of the RGO would somehow be "a good thing." Last year SERC set up a panel to review the future of the two royal observatories (at Herstmonceux and at Edinburgh). After 8 months of deliberating, the panel found no good reason, either scientific or financial, to change the status quo. It is ominous that SERC has not published the report of this panel, although its findings are well known in the astronomical community.

SERC's stated preference is to move England's national observatory of more than 300 years' standing to the capital of Scotland, to merge with the Royal Observatory Edinburgh (without apparently considering the more logical move in the opposite direction). Dickson quotes SERC as stating that "the benefits to RGO of a campus associa-

tion are considerable." It is hard to imagine what SERC has in mind. For the past 20 years we have collaborated very successfully in both teaching and research with Sussex University, just 20 miles away. In this time some 60 students have received doctorates in astronomy, of whom nearly half were supervised by RGO staff. In addition, RGO staff are collaborating with 12 groups on instrumental projects and in the past year alone have published research papers with astronomers from more than 50 British and foreign research centers.

While the operation of the La Palma Observatory is our major project, the activities at the RGO are considerably more extensive than Dickson's briefing suggests. We, the staff of the RGO, believe that the RGO is not only an important modern observatory but also part of our British national heritage which must be saved. We are not against the idea of change if some real benefit to astronomy is likely to come from it. However, we believe the opposite to be the more likely outcome and do not think there is any justification for the up-

heaval which will be caused to some 150 families in addition to the destruction of the oldest nationally funded scientific institution in Britain and considerable disruption to the national astronomy program.

MARGARET PENSTON
Royal Greenwich Observatory,
Herstmonceux Castle,
Hailsham BN27 1RP, England

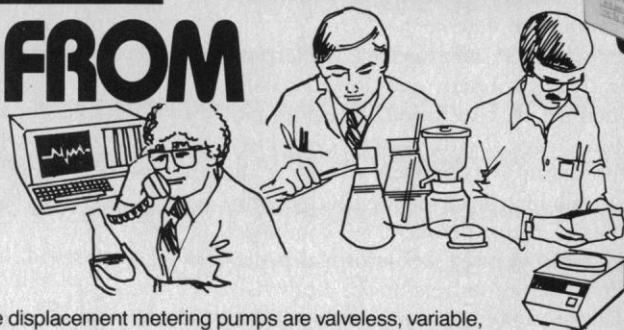
Erratum: In the Technical Comment "Measurement of brain deoxyglucose metabolism by NMR" (9 May, p. 776), the first sentence of the second paragraph should have read, "The agreement between the NMR curve and the data of Sokoloff is remarkably close between 40 and 120 minutes after administration of deoxyglucose."

Erratum: The author note for the article "Safeguarding our military space systems" by Michael M. May (18 Apr., p. 336) should have stated that the article will appear in the Aspen Strategy Group's forthcoming volume *Seeking Stability in Space*, to be published by the University Press of America in 1986.

Erratum: The fifth sentence in M. Granger Morgan's editorial "Risk research: When should we say 'enough'?" (23 May, p. 917) should have read, "But suppose that after significant effort a risk is not demonstrated."

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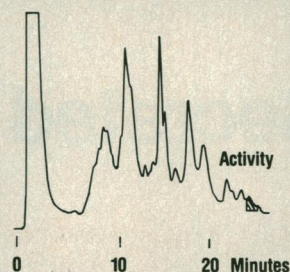
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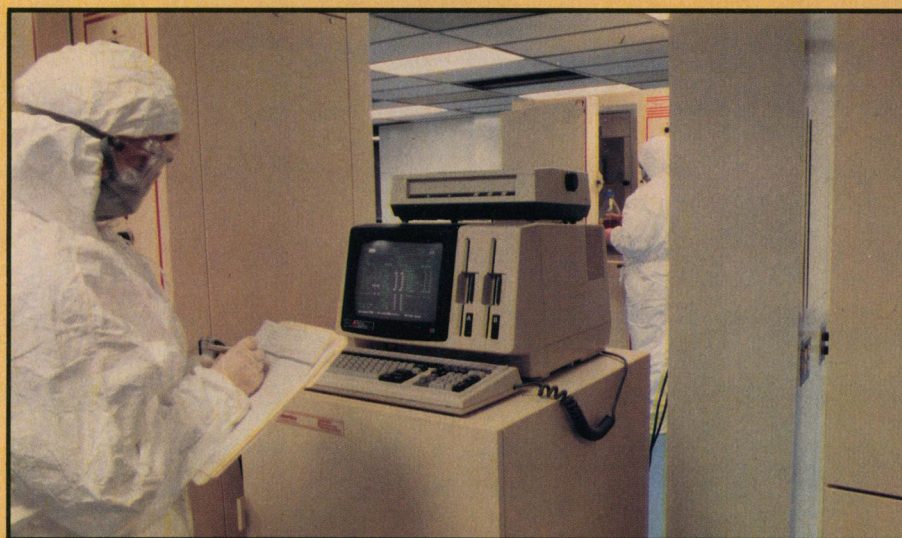
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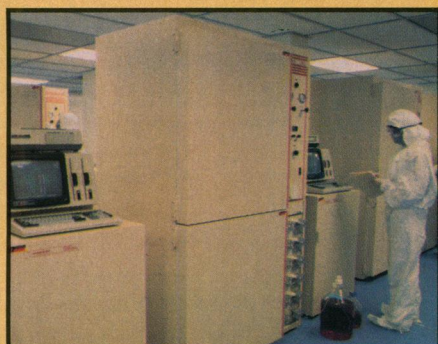


Supernatant through clinical grade material can be delivered to your specifications. The purification schemes are discussed between our respective research staffs to incorporate your input with our expertise.

The correct choice of a mass cell culture technology during the early stages in the development of biotechnology-derived product is critical to successful commercialization in the future. The culture technology chosen today must be capable of producing the product economically so it can effectively compete in the marketplace.

There are a variety of technologies currently available for mammalian cell culture including roller bottles, continuous stirred tank reactors, airlift fermentors, hollow fibers (ultrafiltrative and microporous), encapsulation and ceramic

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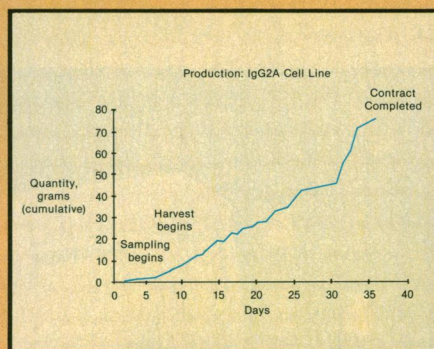
matrix technologies. Economics, feasibility, and ability to deliver product consistently are the key factors in choosing a cell culture technology.

The ACUSYST-P technology is the most economical cell culture production technology available today. It incorporates a patent-pending hollow-fiber technology that, for the first time, allows the use of hollow fibers from research to production scale. The benefits of hollow-fiber technology for mammalian cell culture have been known for over 10 years. Not until the development of the ACUSYST-P system has this technology been useful on a commercial scale.

Production Data

Production data will vary depending upon the cell line used in manufacturing. The stability of a cell line, nature of protein being produced, and process control parameters will determine the efficiency of a cell line in production for long periods.

In the example shown below, the cell line was an average producer in stationary culture (concentration of 40 ug/ml after 4 days). This hybridoma cell line produced over 70 grams during the 3-month production run.



A 70 gram production run, completed in 3 months from cell line inoculation. Delivery schedules, final product purity, and quantity requirements are discussed with each client to arrive at the lowest cost possible, in the shortest period of time.

The Need for Process Control

Successful large scale culture of mammalian cells is an operation requiring good timing and strict control. Detailed knowledge of the cell line's metabolic characteristics is the first requirement. This data is often derived during the research phase of a cell line's development and is used to define the parameters used by the ACUSYST-P system to control the bioreactor environment.

Purification system is flexible

Milligrams, grams, kilograms — depending on client needs. The path leading to product acceptance and marketing requires each scale at some point along the way. Flexibility of scale is a basic necessity for a full service contract manufacturer.

Purification system is designed specifically to be in full regulatory compliance. Total system configuration — hardware, media, procedures — are under GMP for human-injectable biological products. Product analyses meet or exceed guidelines by Bureau of Biologics.



Our facility meets or exceeds all GMP facility guidelines. We apply appropriate procedures to comply with production of biological standards as set by the regulatory authorities. Our Drug Master File is available for referencing also.

Facilities for Commercial Volumes ...

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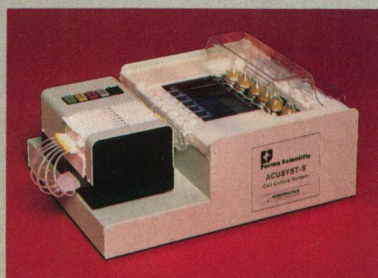
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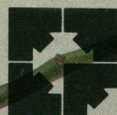
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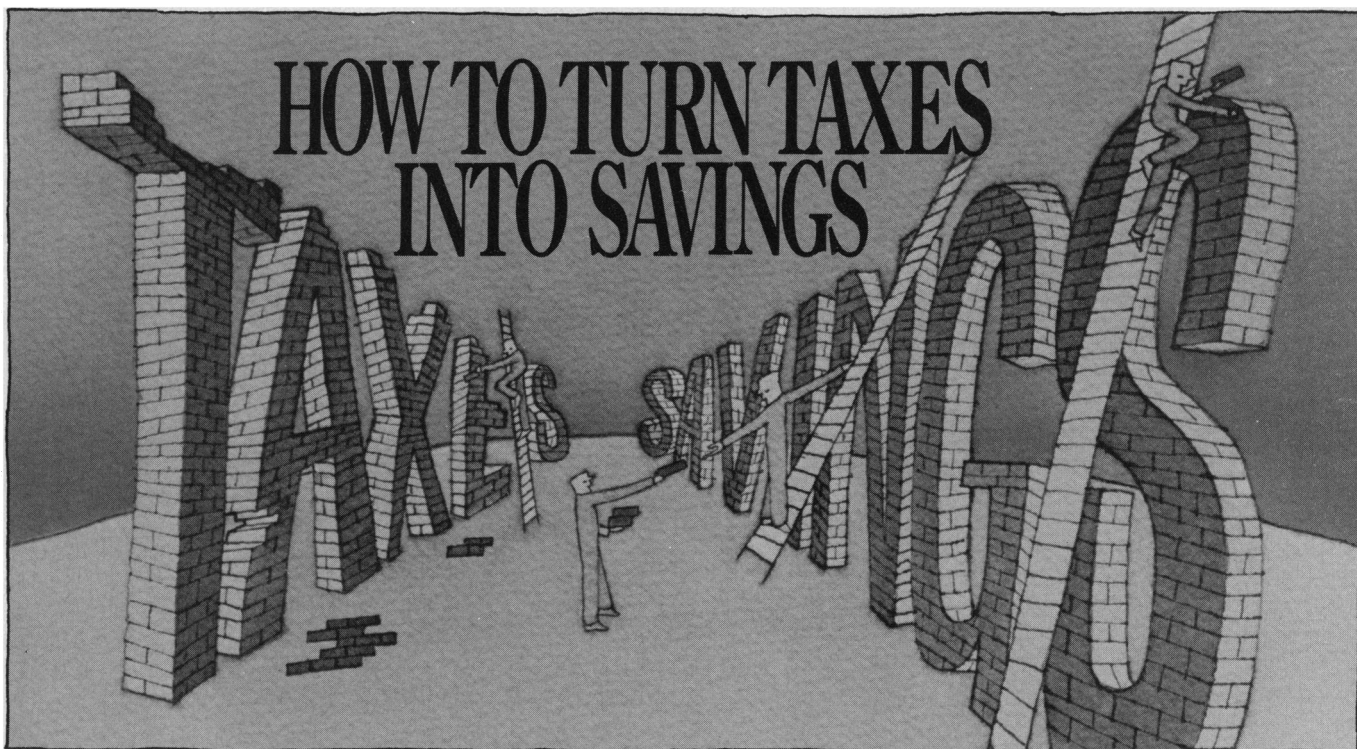
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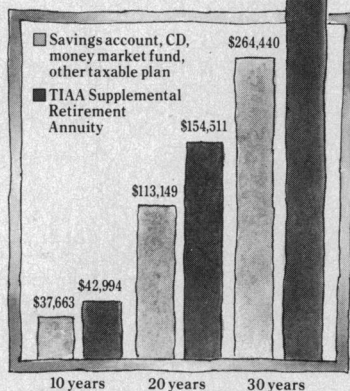
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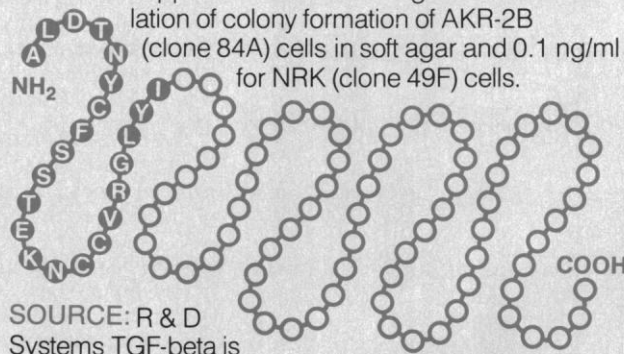
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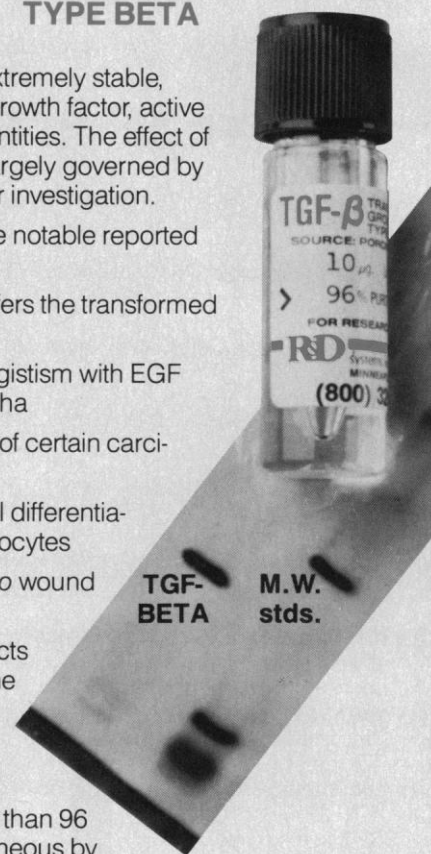
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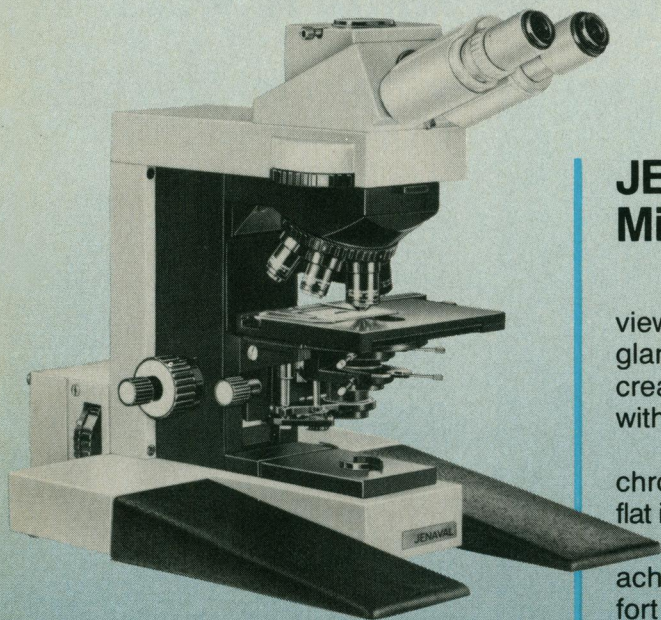
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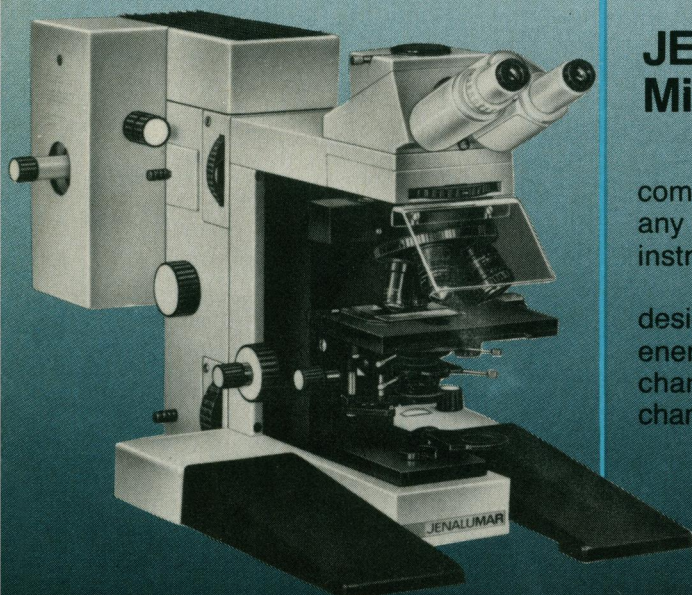
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Fig. 1 and 2
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Fig. 1, Normal Sample

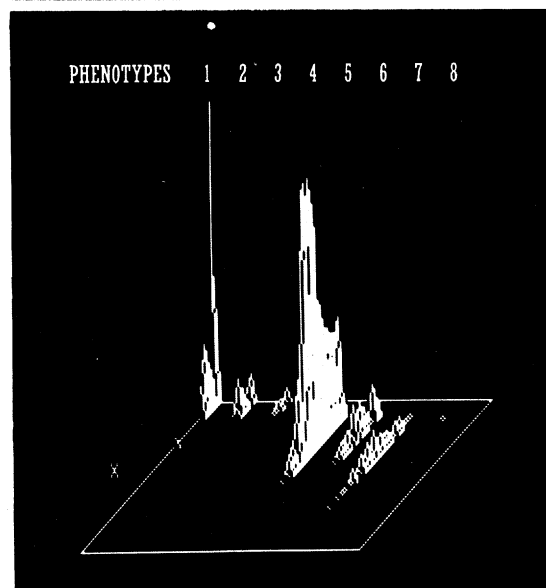
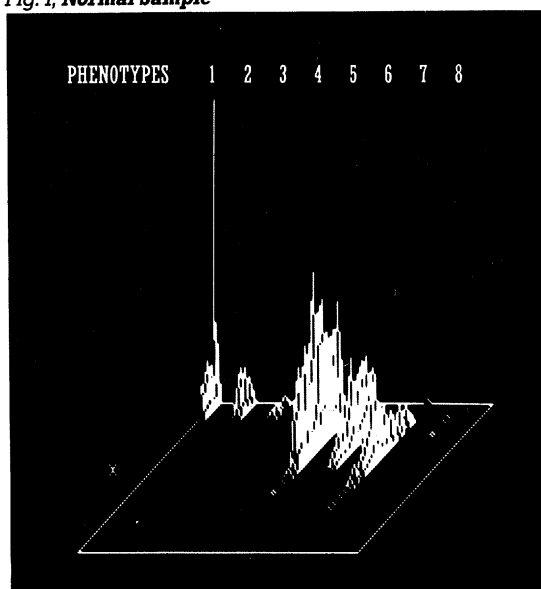


Fig. 2, AIDS Sample

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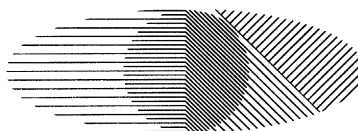
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1. Morimoto, Chikao, et al.: The isolation and characterization of the human helper inducer T cell subset. *J Immunol*, 134(6):3762-3769, 1985.
2. Morimoto, Chikao, et al.: The isolation and characterization of the human suppressor inducer T cell subset. *J Immunol*, 134(3):1508-1515, 1985.

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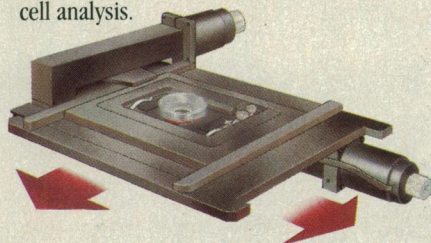
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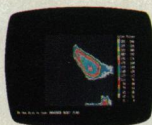


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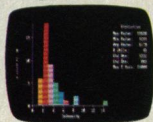
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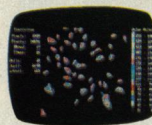
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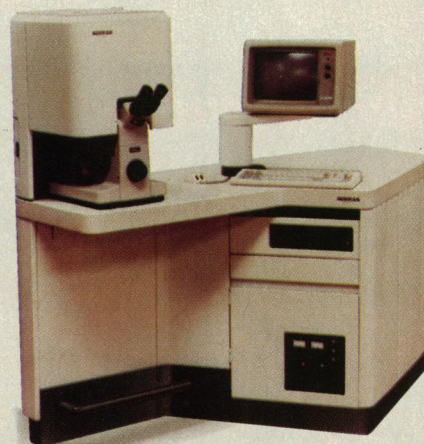
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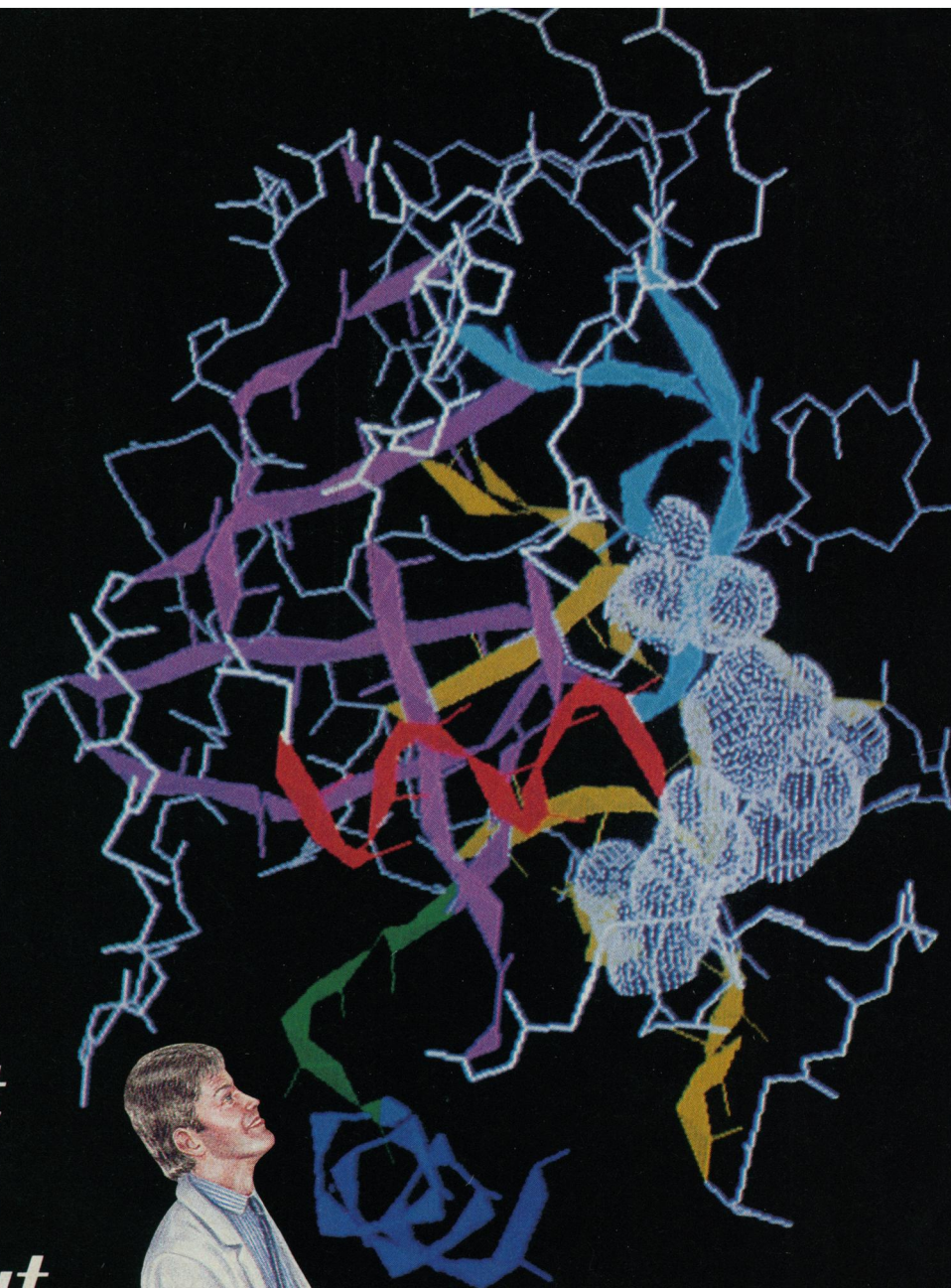
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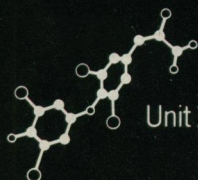
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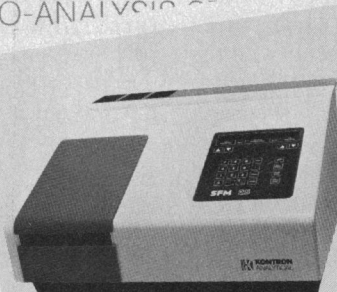
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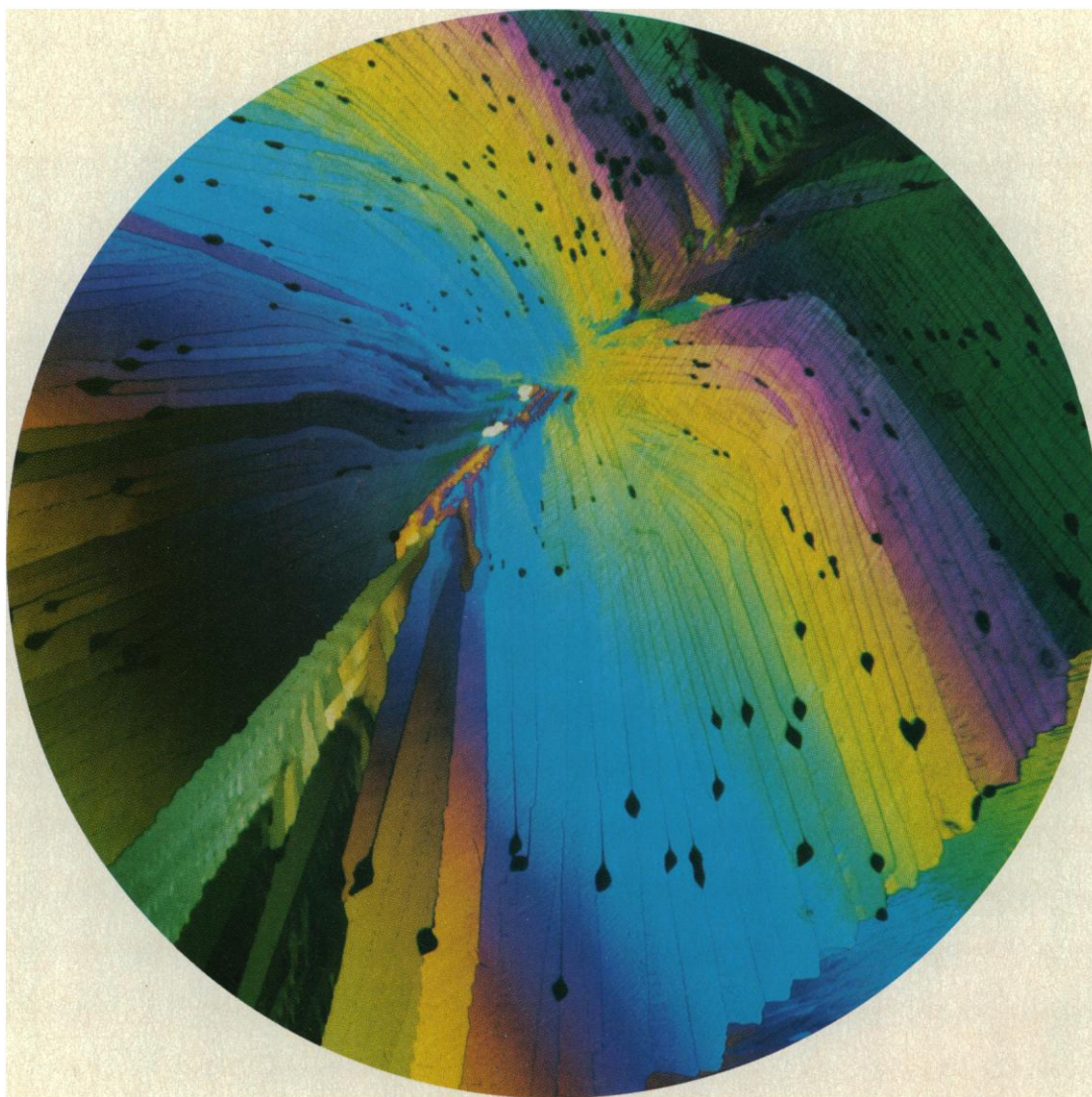
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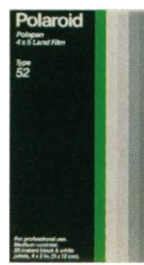
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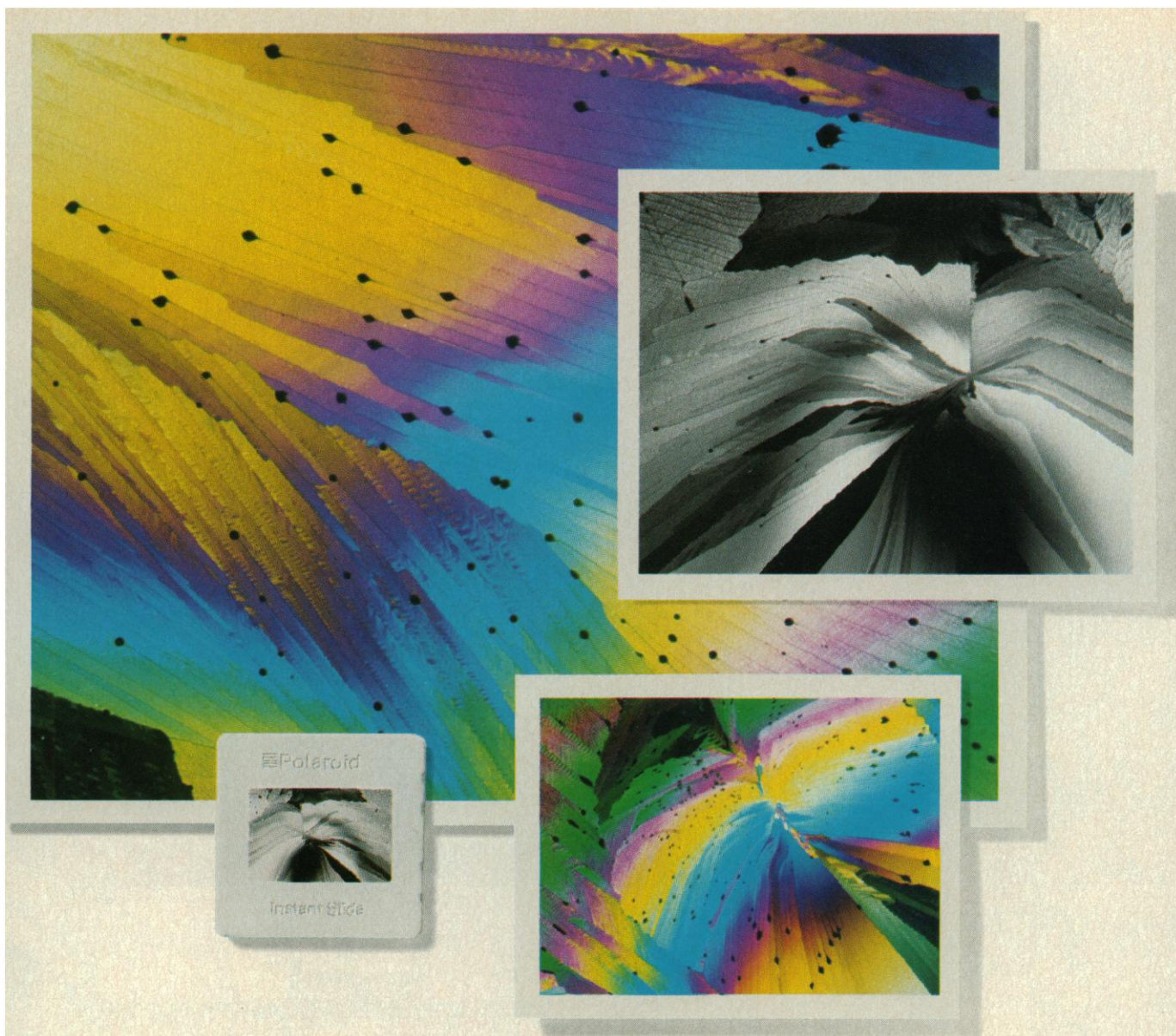
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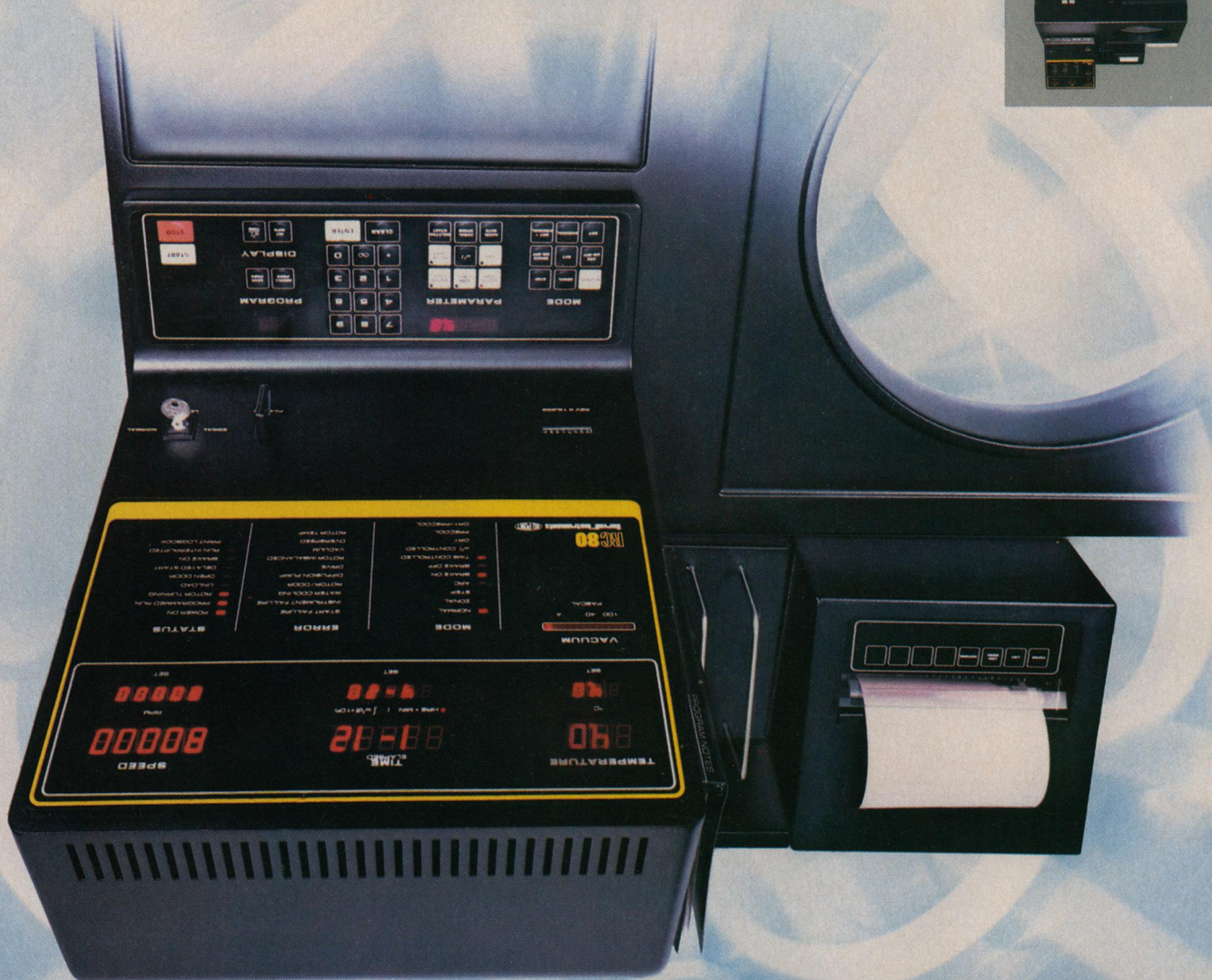
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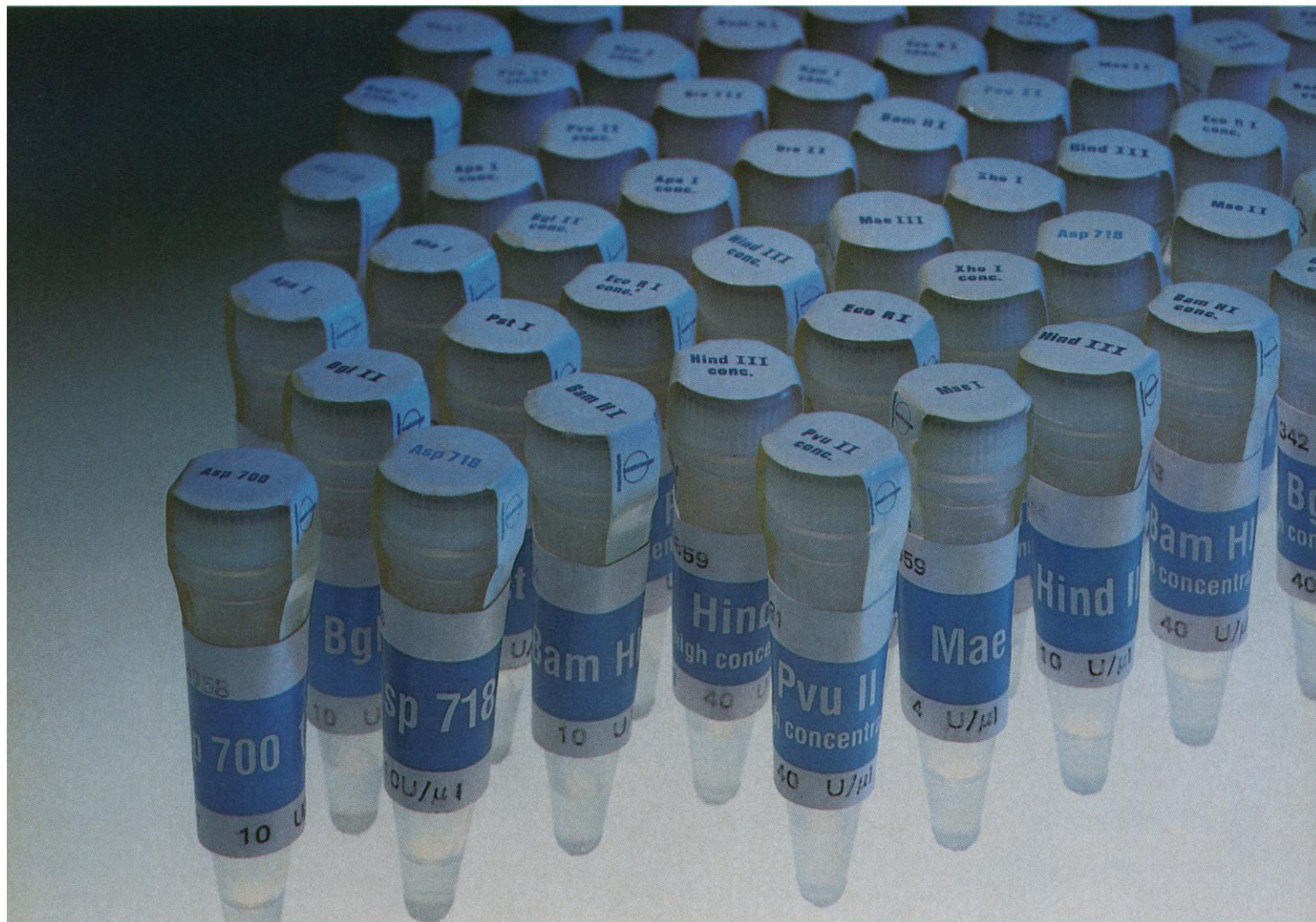
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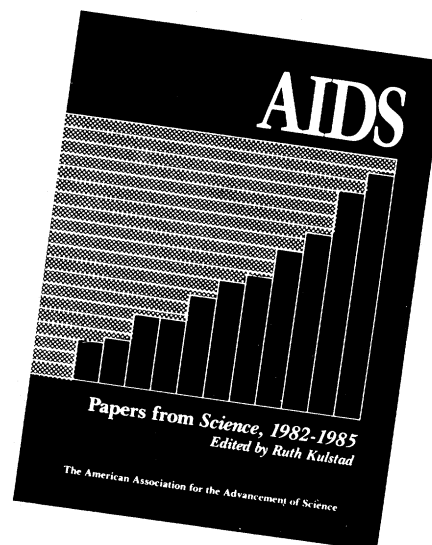


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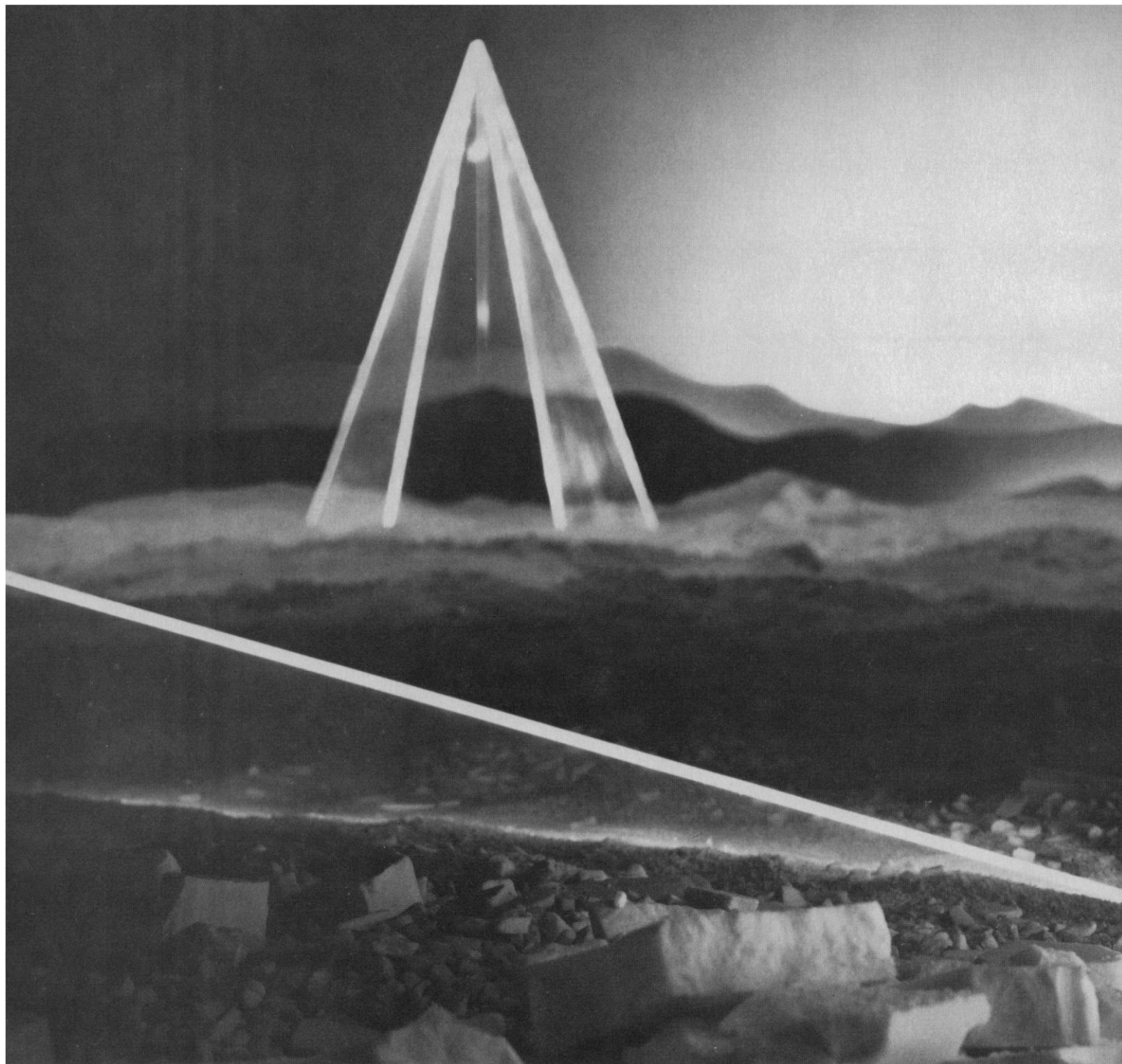
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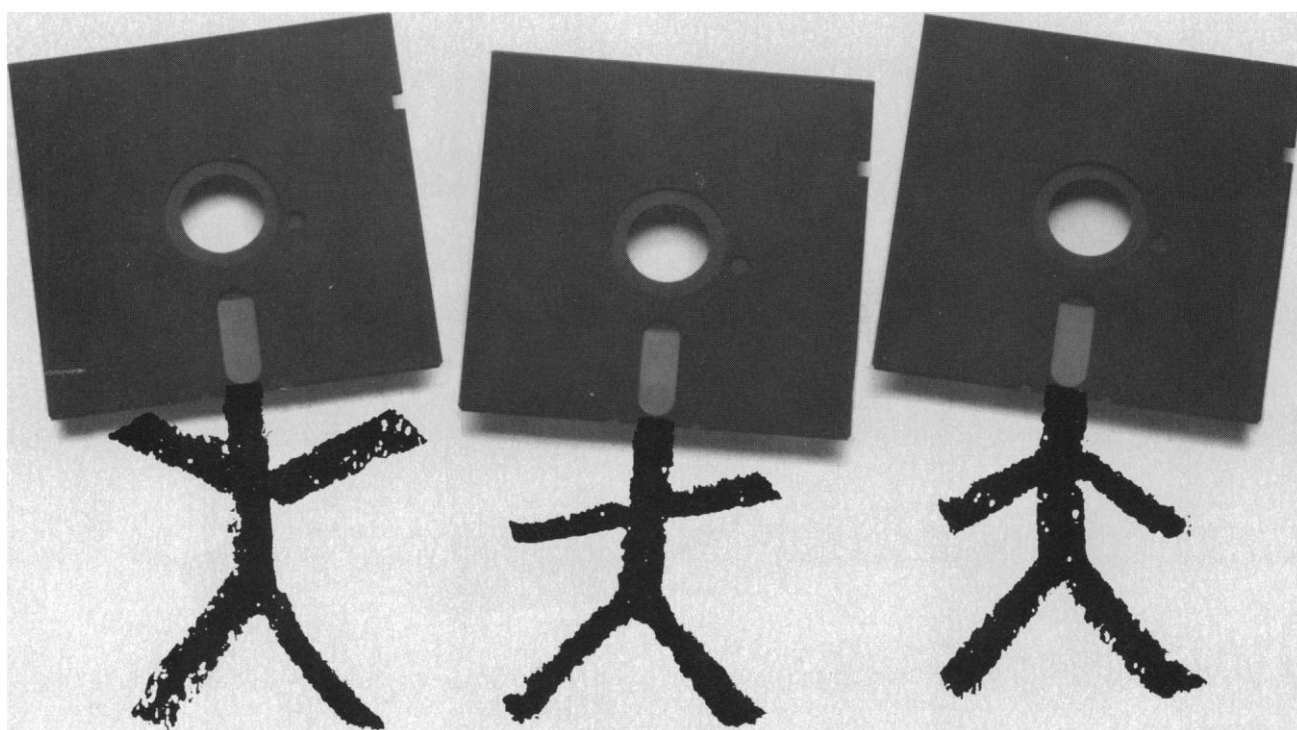
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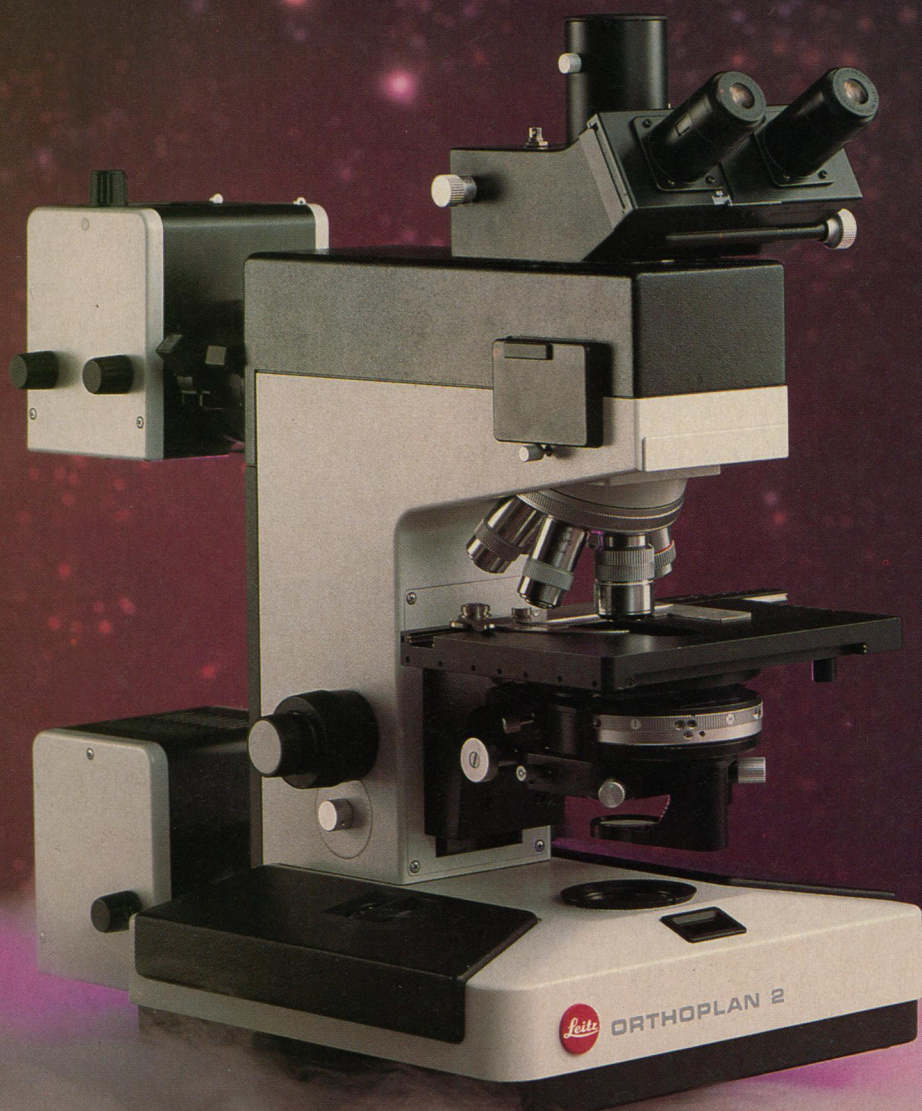
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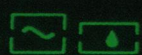
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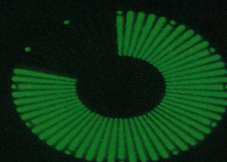
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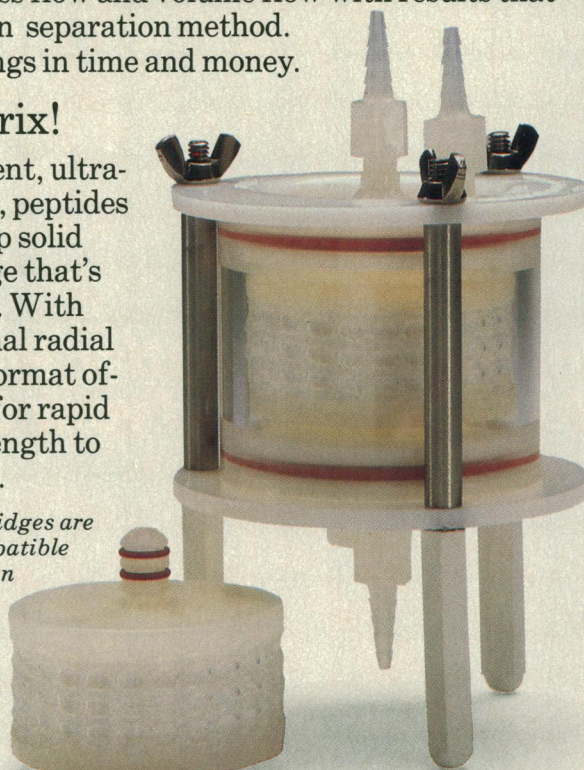
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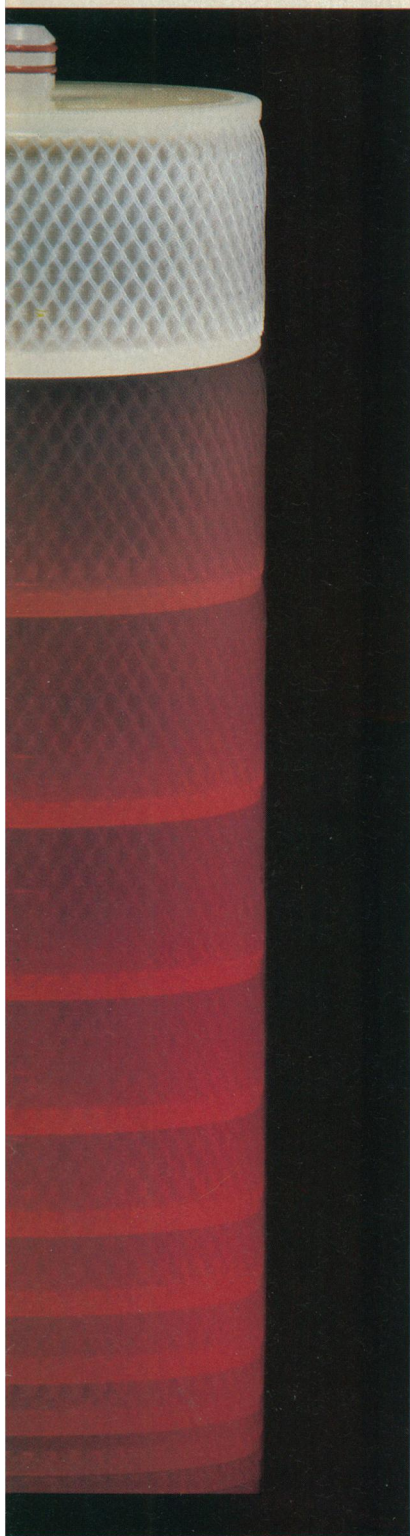
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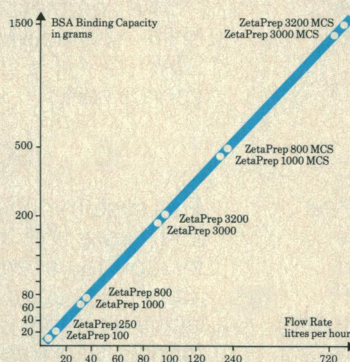
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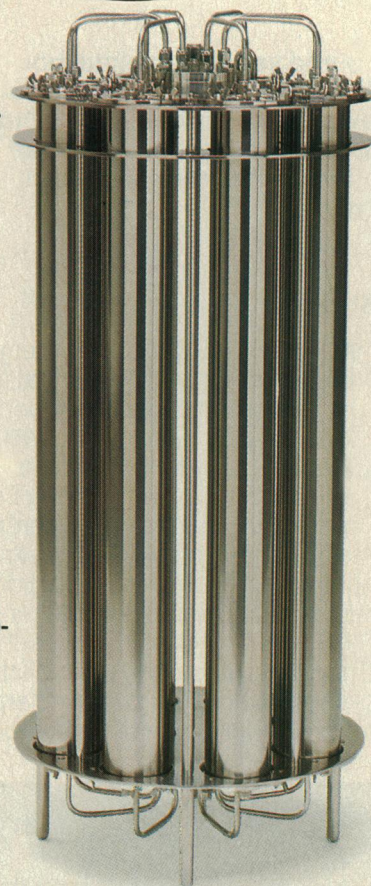


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Patents applied for on the MICRO-ISOLATOR units and other elements of the complete system.

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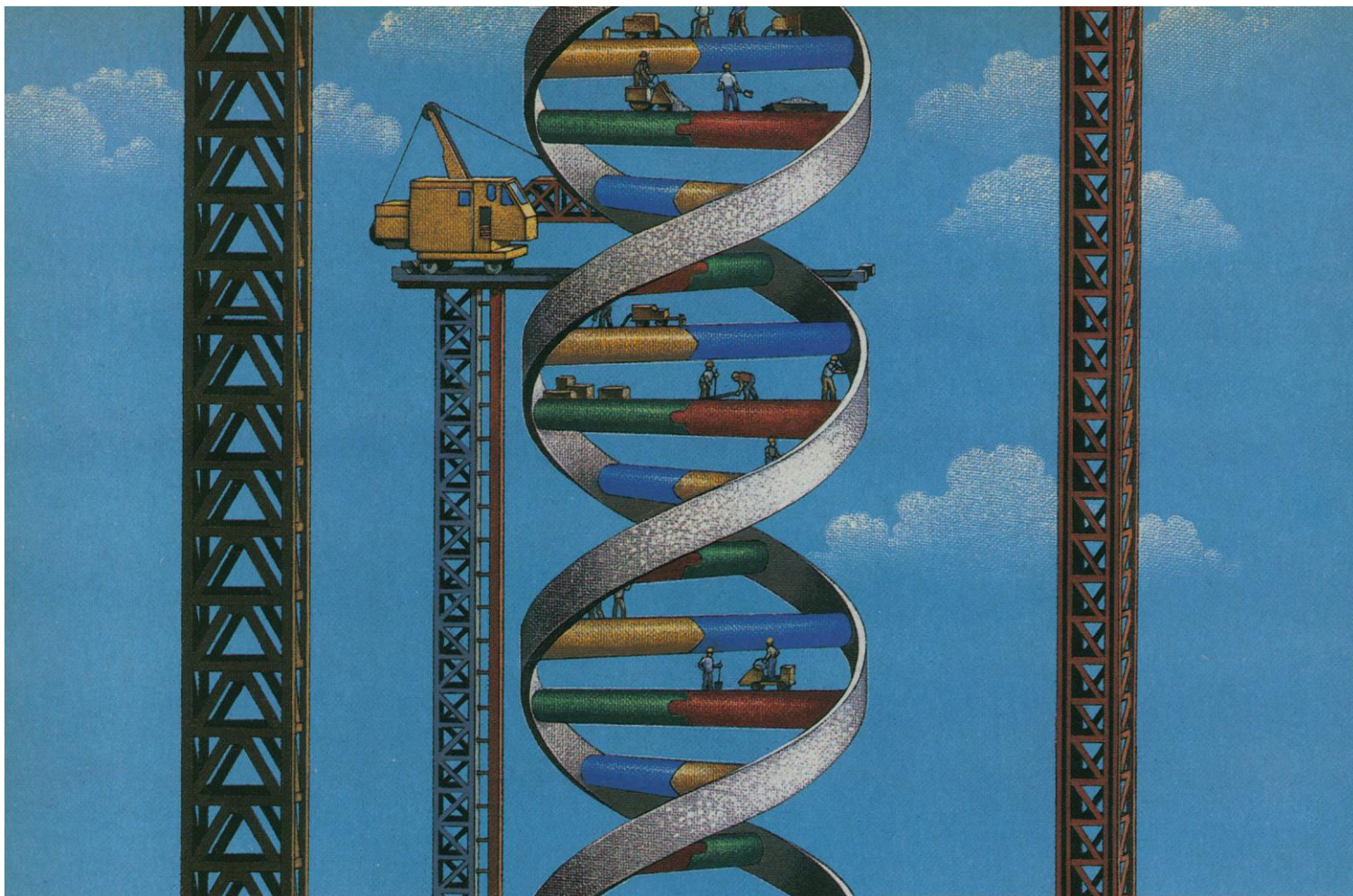
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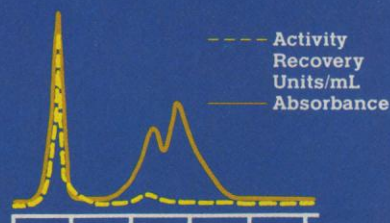
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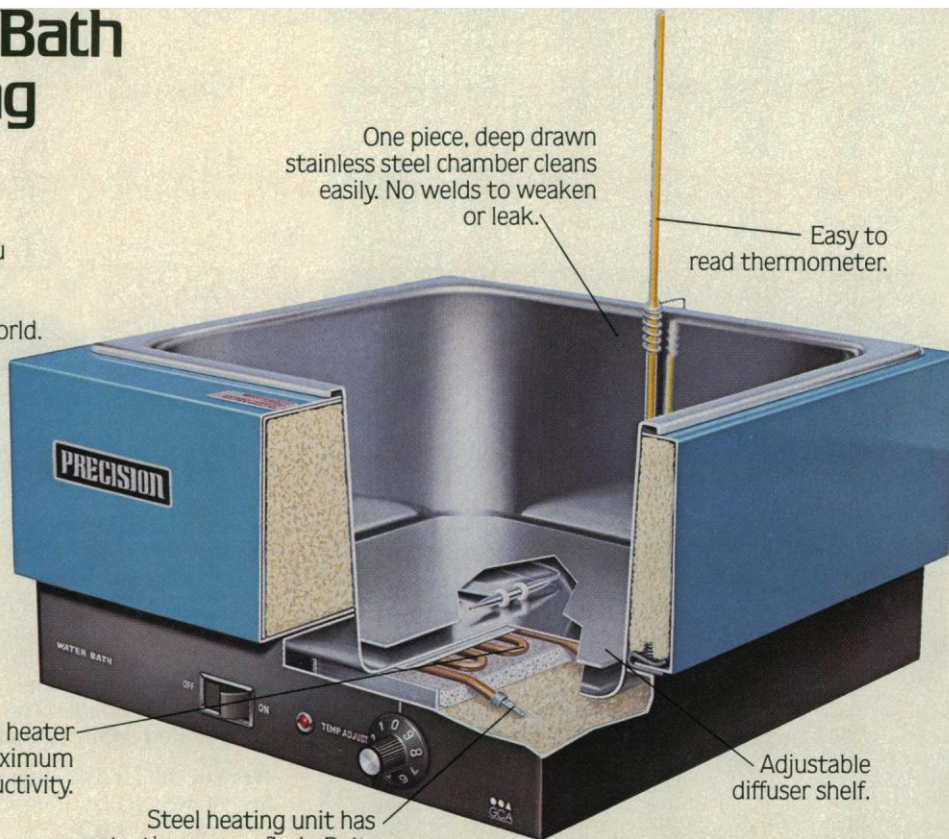
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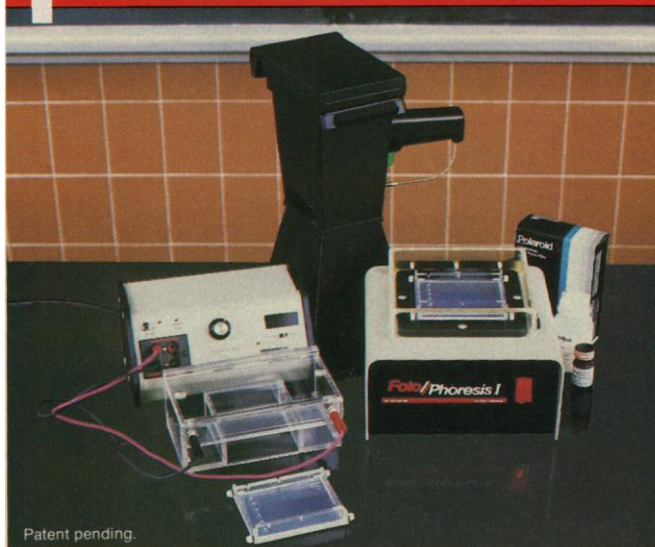


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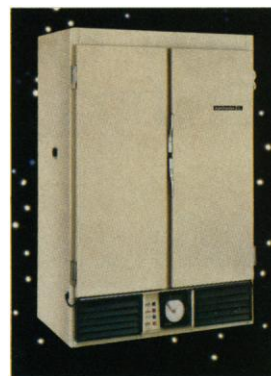
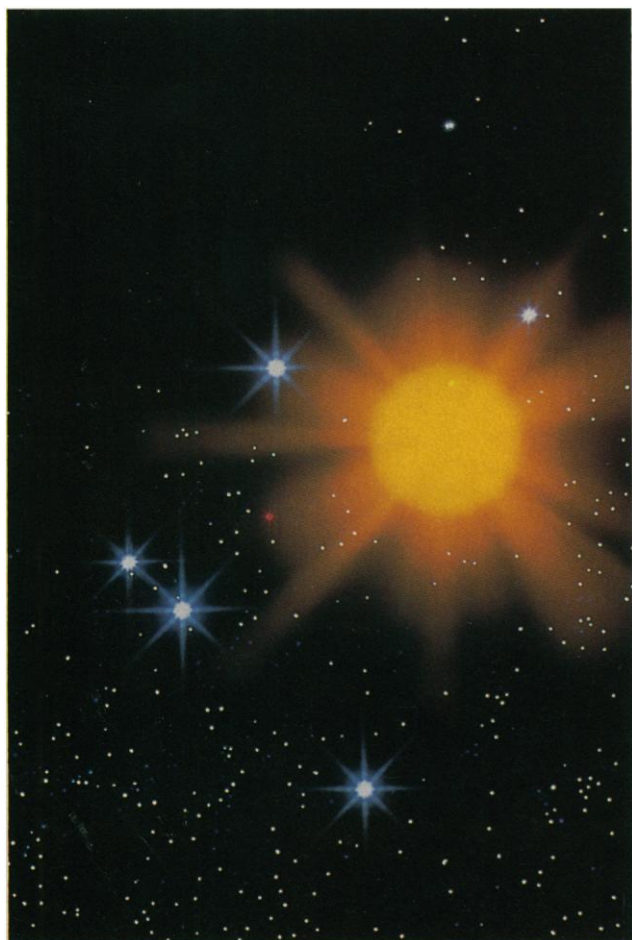
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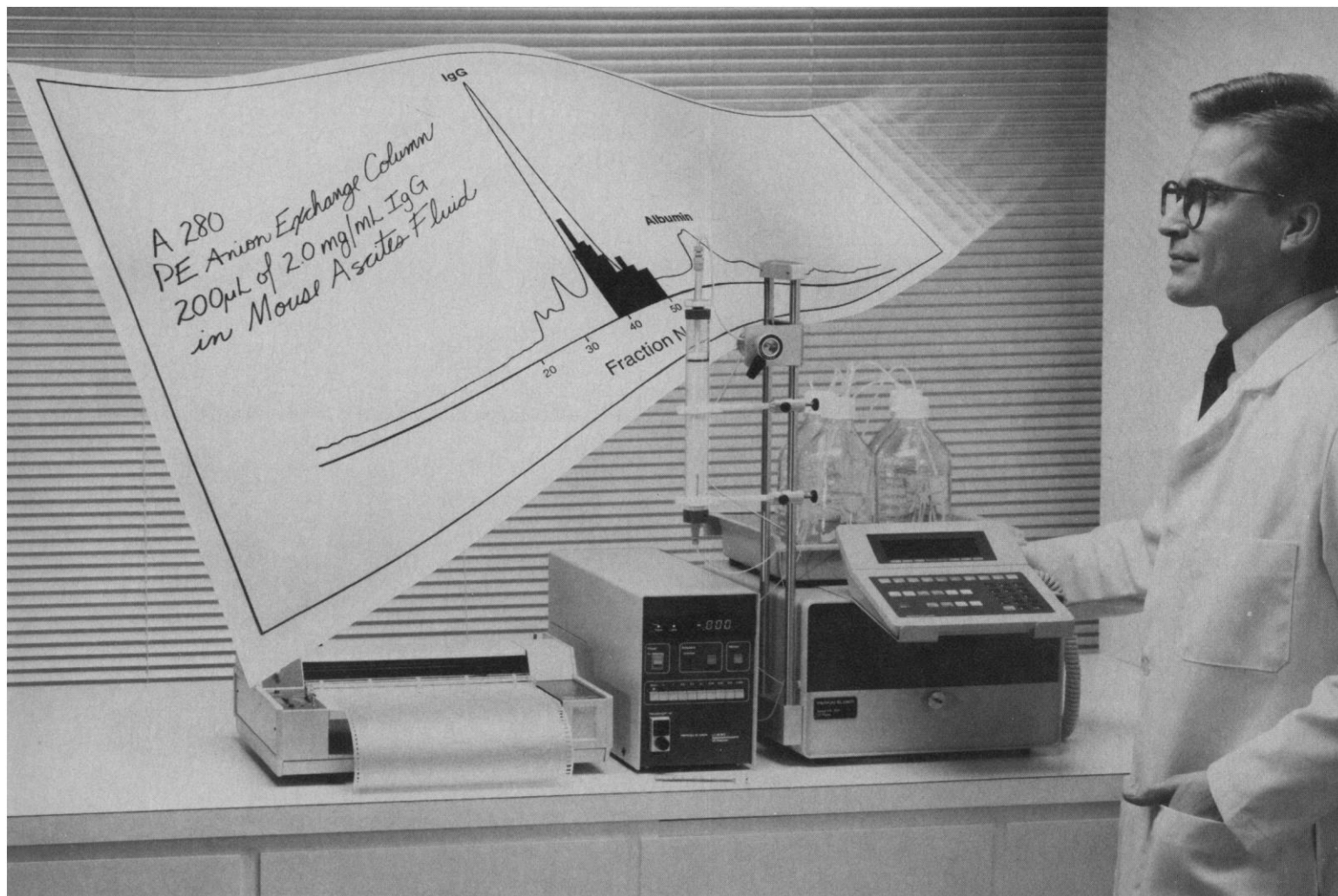
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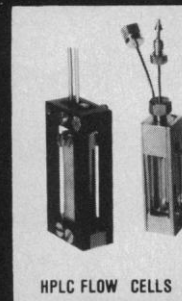
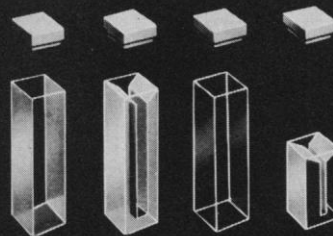
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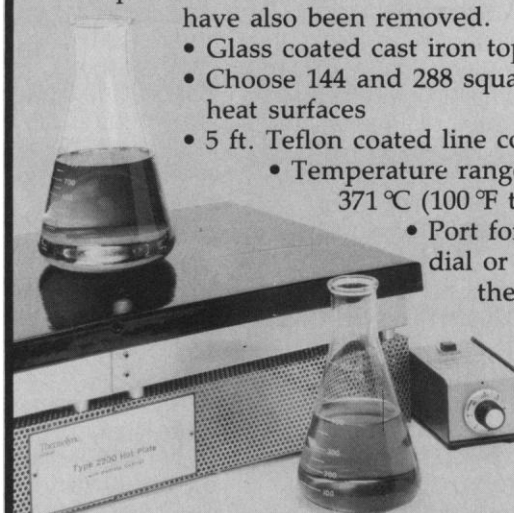
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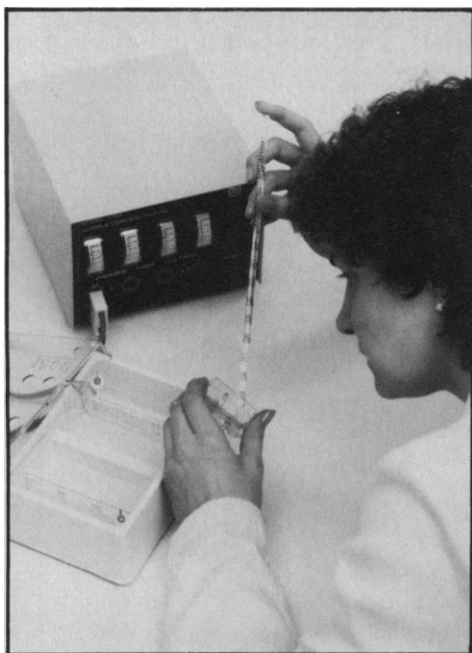


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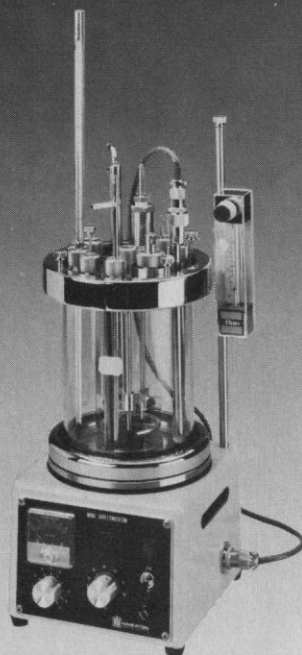
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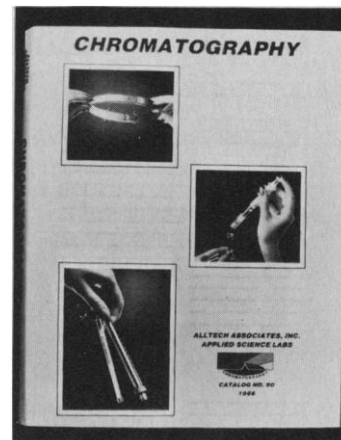
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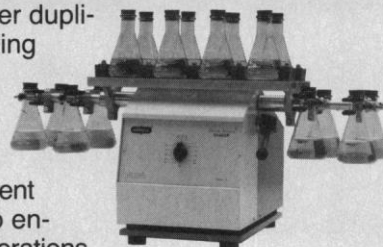
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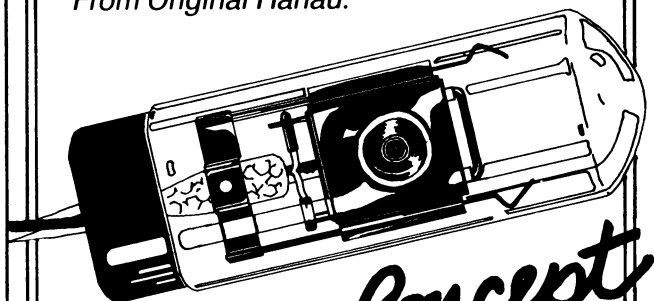
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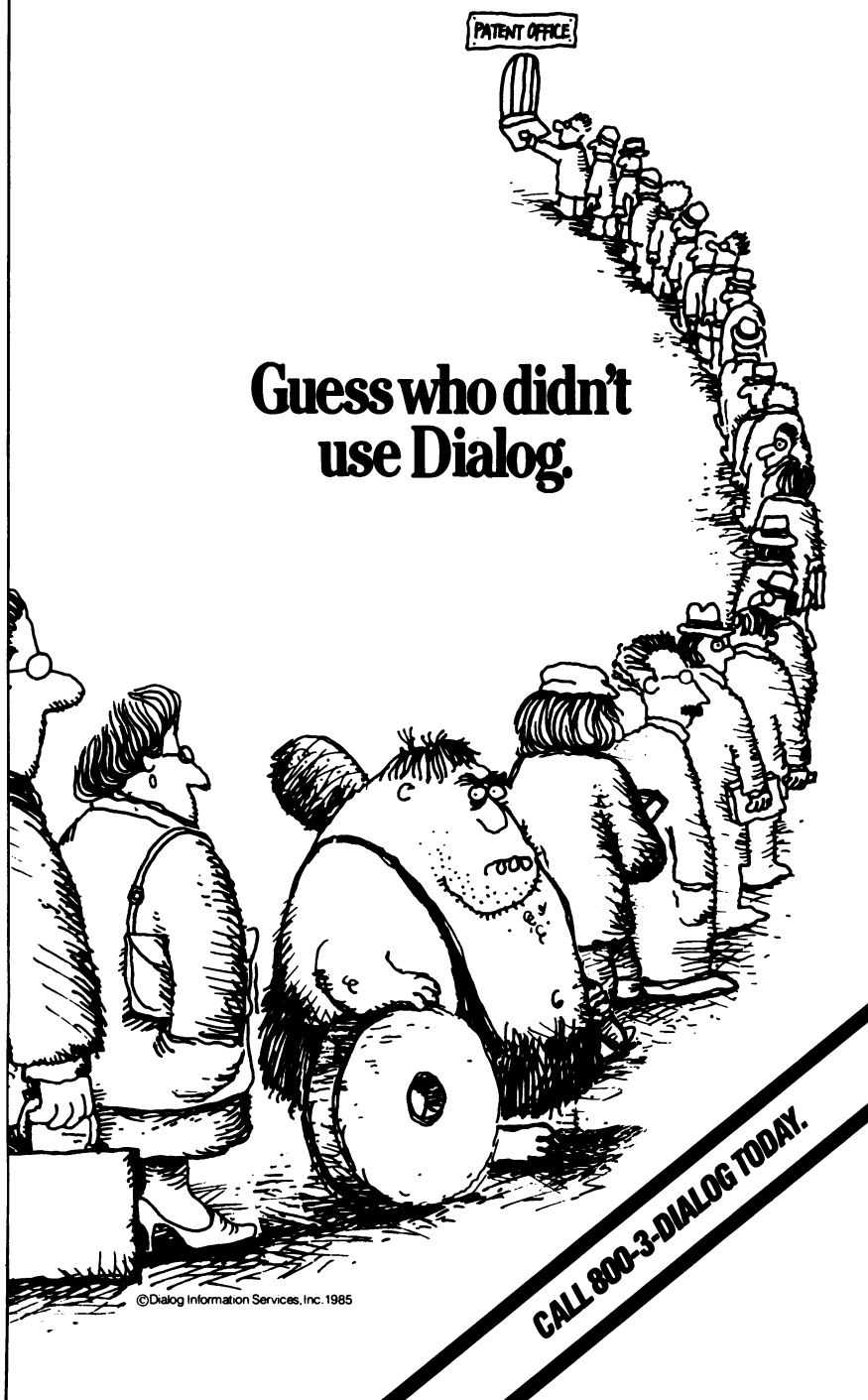
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