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SCIENCE

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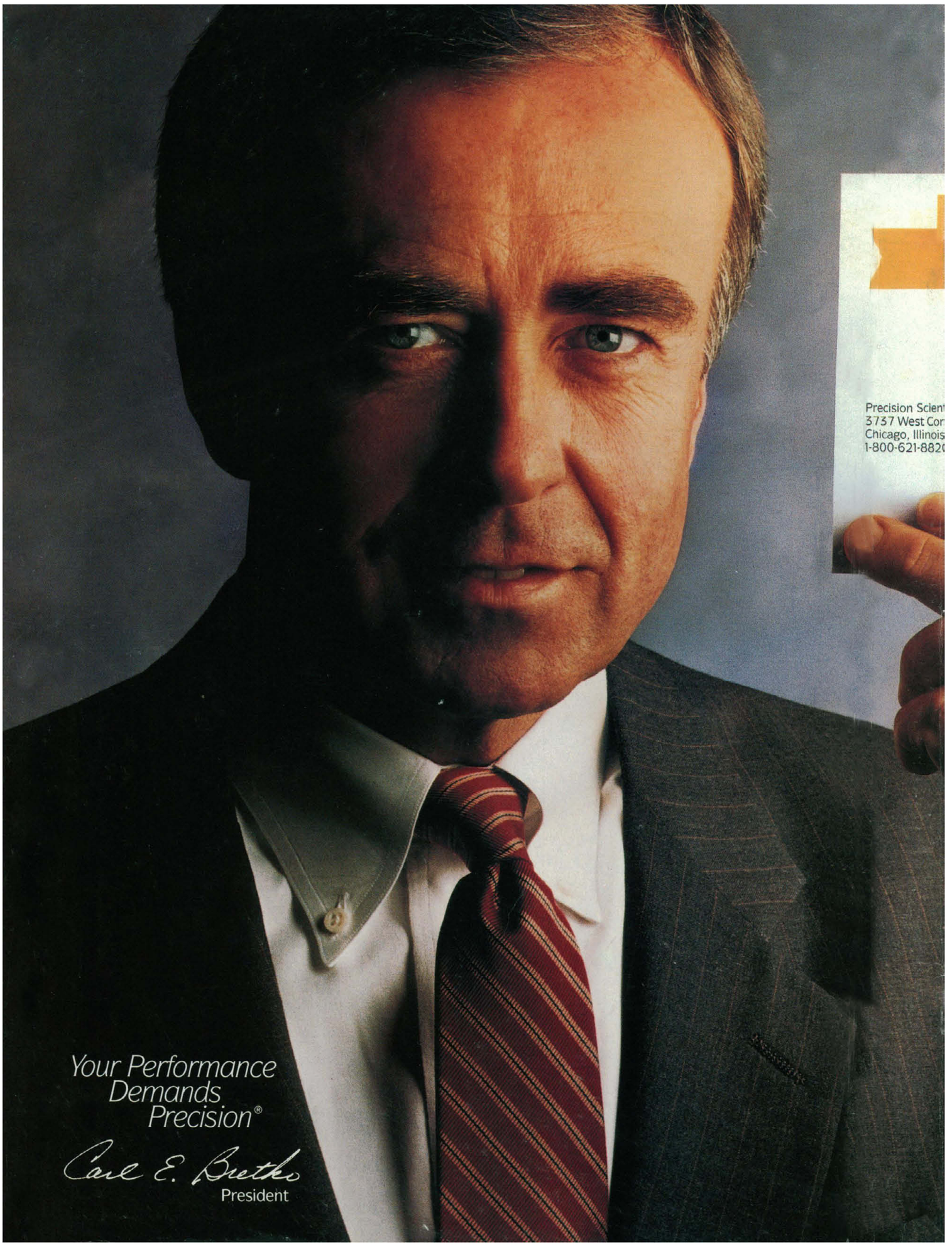
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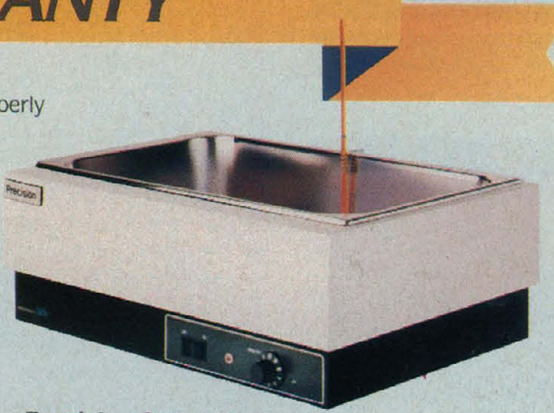

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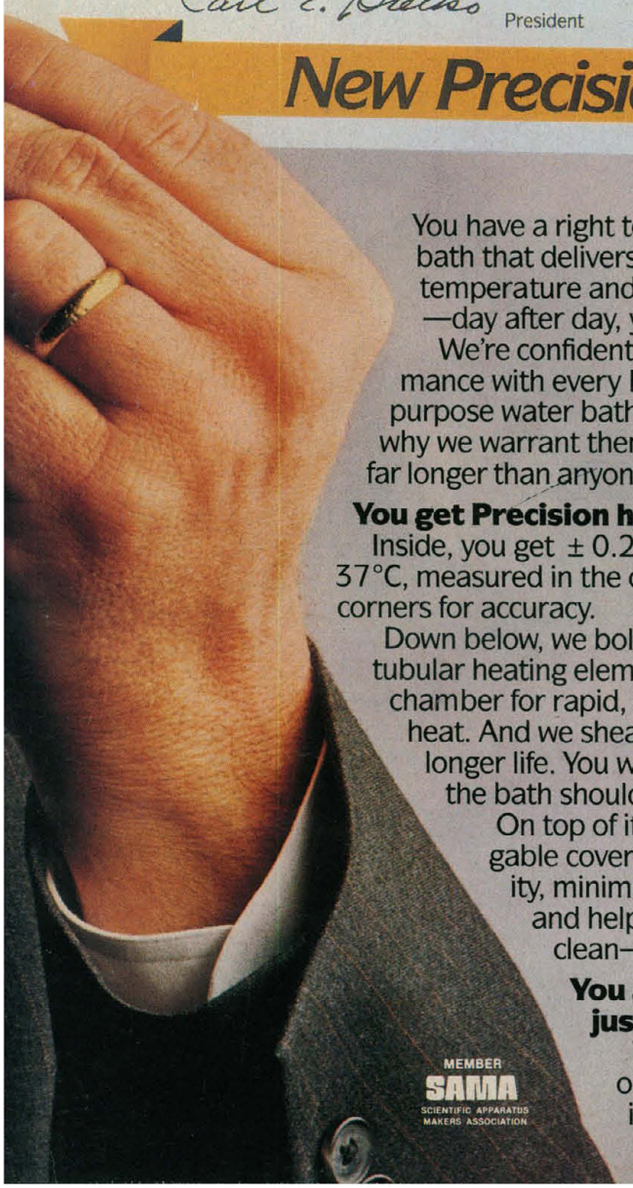

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■ The American Association for the Advancement of Science was founded in 1848 and incorporated in 1874. Its objects are to further the work of scientists, to facilitate cooperation among them, to foster scientific freedom and responsibility, to improve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

COVER Bioengineer seated at apparatus for making microelectrodes. This year marks the 100th anniversary of the founding of the National Institutes of Health (NIH). Since its inception, NIH's mission has been to improve the health of the American people. To attain this goal, NIH conducts and supports biomedical research into the causes, prevention, and cure of diseases; supports research training and the development of research resources; and makes use of modern methods to communicate biomedical information. This issue contains articles on NIH's approach to that goal: research, training, and communication. See page 861. [Photo courtesy of National Institutes of Health, Bethesda, MD 20205]

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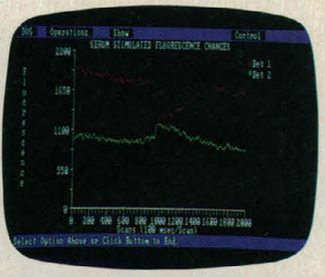

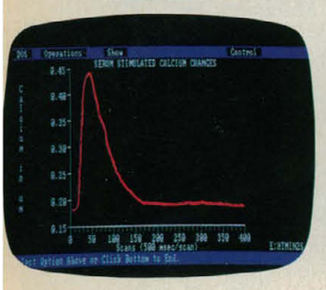

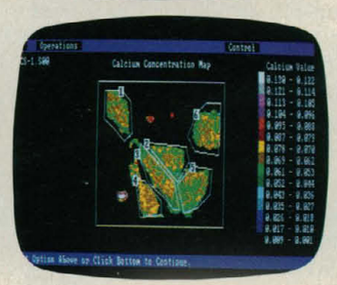

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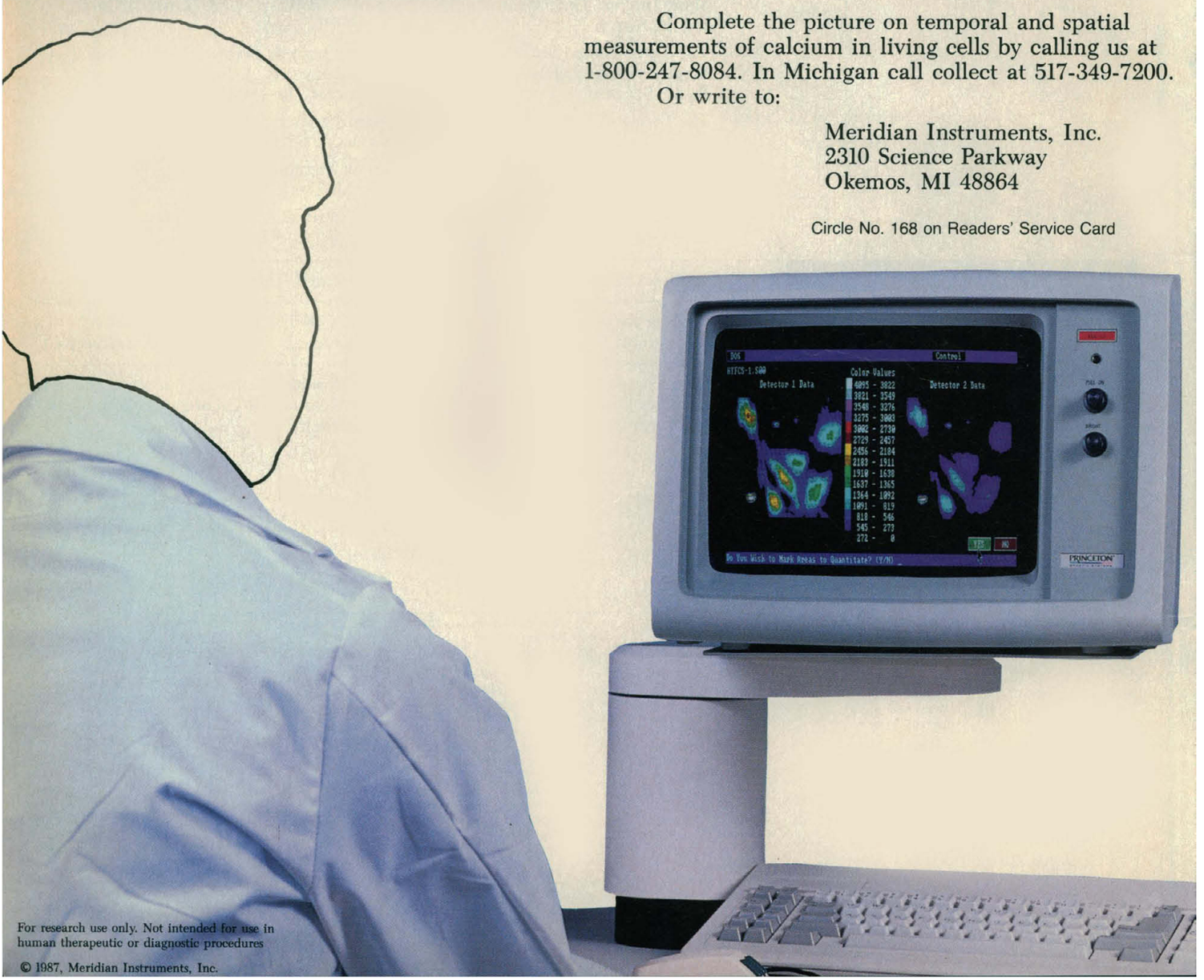

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This Week in
SCIENCE

Yeast genes rise to the occasion

A small number of regulator genes, working in different combinations, appear to control the expression of other genes in diverse metabolic pathways in yeast cells (page 874). Such "global" regulation also operates in mammalian cells but not in bacteria. Using the yeast *Saccharomyces cerevisiae*, Arndt *et al.* show that expression of *HIS4* (which affects synthesis of the amino acid histidine when histidine is present in excess in the medium) is regulated by two genes, *BAS1* and *BAS2*, that function synergistically and in conjunction with the *HIS4* promoter region. *BAS1* and *BAS2* were isolated and cloned, their respective locations on chromosomes XI and IV were identified, and their activities were studied. The two genes were involved in both overlapping and distinct regulatory effects. Detailed studies of *BAS2* indicated that it codes for a DNA binding protein, is required for expression of *HIS4*, and regulates a gene required for phosphate utilization and a gene affecting synthesis of the purine adenine. Strong sequence homologies exist between the promoter binding sites for the *BAS2*-encoded protein on the different genes that it regulates.

Inconstant gravitational constant

THE value of the constant G in Newton's law of gravitation differs depending on how it is measured; it is 1 to 1.5 percent greater when calculated from measurements made over large distances in the field than when calculated from those made over small distances in the laboratory (page 881). Hsui has calculated the value of G over intermediate distances from gravity measurements (which increased almost linearly with depth) made in a borehole in Michigan that was 2 kilometers deep. G values were computed from gravity measurements at numerous stations along the hole and from measurements of the total mass between pairs of stations 250 meters to 1.2 kilometers apart. The G values confirm an earlier calculation made from measurements in an Australian mineshaft. The disparity between geophysically determined values for G and laboratory values is compatible with the possibility that a fifth force—not gravity, electromagnetism, the strong nuclear force, or the weak nuclear force—interferes with the force of gravity over kilometer-range distances.

Fats and diabetes

ESKIMOS, who eat a lot of fish, have a strikingly low incidence of non–insulin-dependent diabetes mellitus (NIDDM); this and other observations hint at a possible role of fish oil in preventing this disease (page 885). NIDDM is a metabolic disease; the major pathologic effect is impaired functioning of insulin, called insulin resistance. Storlien *et al.* show that substitution of fish oil (rich in long-chain polyunsaturated ω-3 fatty acids) for only 6 percent of the total oil in a high-fat diet prevents development of insulin resistance in rats. The effects of the fish-oil substitution on glucose metabolism were especially marked in the liver (where most of the body's glucose is produced) and skeletal muscle (the major site for glucose disposal). Roles for polyunsaturated fatty acids in development and perhaps treatment of human disease need further investigation.

Humoral hypercalcemia of malignancy

PATIENTS with lung cancer or with certain other malignancies often have high concentrations of calcium in their blood even though their malignancies are not directly associated with the skeleton (page 893). This humoral hypercalcemia of malignancy (HHM) is thought to be a result of tumor products that promote bone loss or restrict the extent to which the kidneys can excrete calcium. Suva *et al.* studied human lung cancer cells from a patient with HHM; cells maintained in culture secreted a protein for which the complementary DNA was cloned and expressed. The HHM protein had parathyroid hormone–like activity as well as partial sequence homology with parathyroid hormone. This homology, which was especially pronounced at the amino terminus of the chain of 141 amino acids, was not unexpected; HHM and primary hyperparathyroidism share a number of biochemical features. Although the HHM protein has been identified through its association with a pathologic process, it could, like parathyroid hormone, also be involved in the normal metabolism of calcium. Depending upon the extent to which it is uniquely associated with HHM, it may serve as a marker for early diagnosis of HHM or for following disease development and treatment.

Insects bite in vein but not in vain

LATEX in the veins of certain plants serves as a defensive substance against herbivorous insects (page 898). A number of insects have a way of circumventing this defense: they bite a vein and, after the latex drains out, eat distal portions of the leaf into which latex can no longer flow. Dussourd and Eisner studied the aversive action that latex has for a number of insects that attack milkweed leaves. A drop of latex placed next to a feeding insect caused it to "clean up" and move away. Experimentally drained leaves were eaten not only by vein-cutting insects but also by insects that, in nature, generally stay away from milkweed plants altogether or eat the remains of leaves that vein-cutters have abandoned. The way in which latex works may include both chemical effects (it contains some toxins and other noxious substances) and mechanical aversive effects (it hardens in air and may "muzzle" insects). Plants that do not contain latex may contain other defensive substances that work in similar fashion, since some insects that eat these plants have been observed to cut veins before they begin eating.

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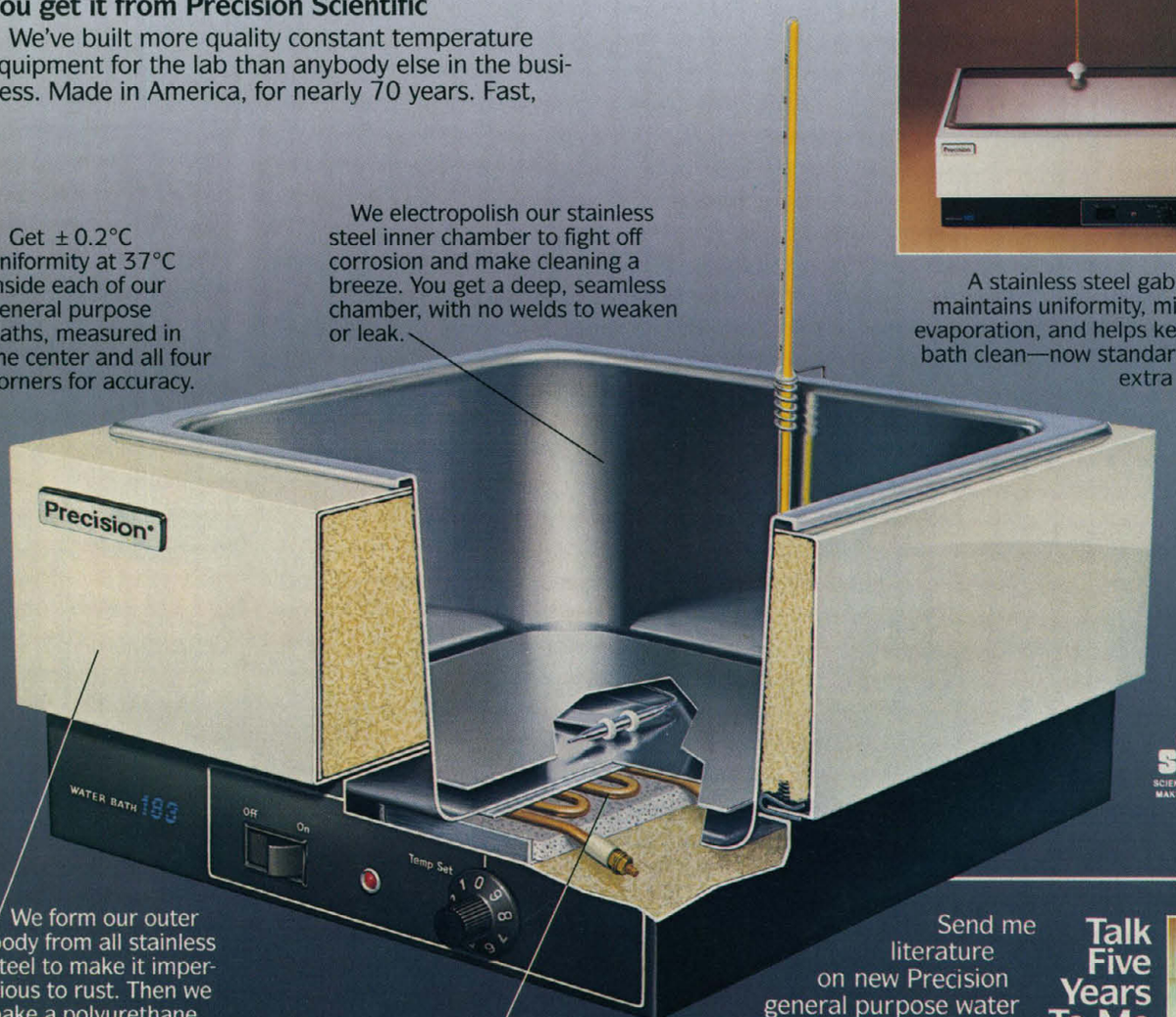

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21 AUGUST 1987
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National Institutes of Health: The Centennial Year

The National Institutes of Health (NIH) today is such a highly differentiated mature organism that it is difficult to visualize its origin as a single cell: a small room in the attic of a building on Staten Island. The Hygienic Laboratory, created from a desire to provide relief for sick and disabled seamen, soon proved its worth after cases of cholera were diagnosed among immigrant passengers on the steamship *Alesia* in the 1880s; shortly thereafter, Joseph Goldberger conducted his landmark study on the prevention and cure of pellagra. Those early events established two of the hallmarks of basic research: surprise (pellagra was thought to be a contagious disease and turned out to be a nutritional problem) and delight (the revelation that very practical things result from basic research). The laboratory was later moved to a building in Washington built for the stupendous sum of $35,000, and eventually became the National Institutes of Health.

In the 1950s Director James Shannon formed an alliance with Congress that vastly increased support for this mission-oriented sponsor of basic research. That special relation between Congress and NIH has been maintained by subsequent directors, including NIH's present leader, James Wyngaarden. In fact, its relation with Congress is so good that each year we watch a soap opera in which the foul fiend (the Office of Management and Budget) threatens the beautiful damsel (NIH) with a fate worse than death (a budget cut) only to be foiled by her rescue by the heroic knight (Congress).

In this issue of *Science*, NIH directors Shannon and Wyngaarden and several staff reporters look at NIH in its centennial year. In discussion of the many facets of NIH, two major reasons for its success stand out. The first is the sophisticated democracy of its research granting procedures. Like democracy, peer review has plenty of critics, some knowledgeable and some not, who point out its flaws with gusto; like democracy, peer review has emerged triumphant because it is so much better than any of the alternatives. It is a process inevitably identified with the vagaries of human judgment, but nevertheless one that is based on expertise, hard work, and a fundamental integrity. Only loyalty to a higher ideal would drive a competent scientist who supposedly values his or her own time to participate three times a year in reading 106 grant proposals and attending a 3-day meeting for an honorarium of $300.

The second major reason for the success of NIH is that it has always had a broad vision of its mission. Many forget that NIH has always been a mission-oriented agency, beginning with tending to sick sailors and progressing to advocating the health needs of the general public. An early decision of NIH was to interpret Congress' call for cancer research to be best implemented by a general understanding of growth. If cancer research had been narrowly focused on the direct approach of chemotherapy, we would be far behind our current understanding not only of cancer but also of many other diseases. The study of the basic biology of viruses (because they were hypothesized to be a cause of cancer) led to the serendipitous cure for poliomyelitis. The success of the Salk and Sabin vaccines and the increased study of DNA then led through the genetic code back to oncogenes. The decision to emphasize basic research as the route to a practical goal has vastly improved our understanding of cancer as well as viruses, the genetic diseases, hormonal disorders, and mental illness.

NIH sponsors many programs but its leadership in research and its symbiotic relation with universities to expand the frontiers of knowledge in a sophisticated, fair-minded, and cost-effective way provide the soul to an operation in which all those who participate can be justly proud. Idealism is not enough. If altruistic concepts benevolently administered had produced repeated failures, NIH would have a tiny budget today. Its role in the cure and prevention of disease and its contribution to the expansion of basic scientific knowledge have made NIH one of the most successful enterprises of our government. Because the little laboratory in the attic on Staten Island had a combination of vision and altruism, the present organization cannot claim to have invented those values. What NIH has done, and why it deserves a place in history, is to preserve both creativity and integrity in a vast and expensive bureaucracy, an accomplishment which our daily headlines tell us is not easy to achieve.

—DANIEL E. KOSHLAND, JR.

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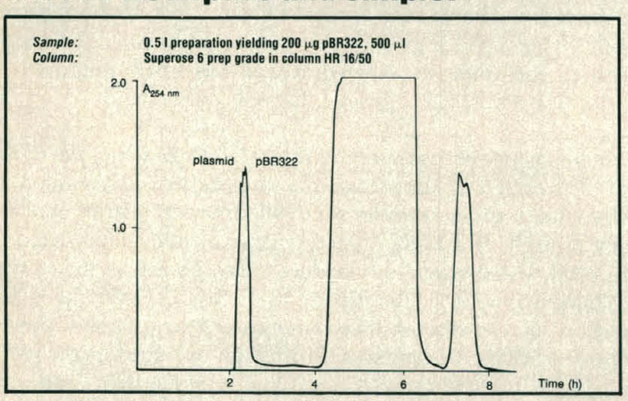
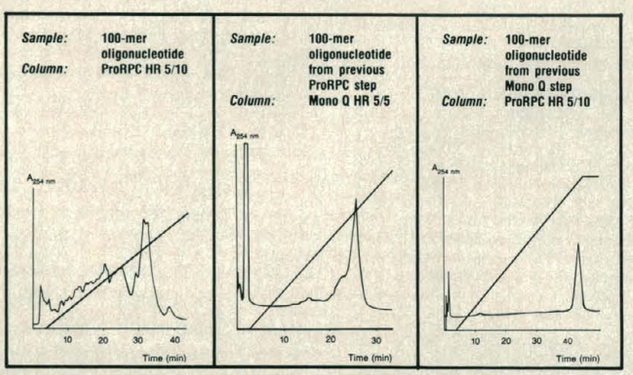


Preparative purification of the plasmid pBR322.



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stars, some of these should be red supergiants. These would have an apparent p-magnitude of 18 to 20 if Mkn 348 is associated with the M31 group as Arp suggests. Our 0.9-meter charge-coupled detector-(CCD) calibration frames of this object can detect individual stars fainter than magnitude 21 (*2*); however, we see no such individual stars in our measurements, which suggests that it is more distant than the M31 group. If the telescope time can be found for such a project, a definitive confirmation of this could be obtained with one or two 20-minute R-bandpass CCD exposures with a 4-meter or 5-meter telescope.

If, on the other hand, Mkn 348 is at the distance derived from its red shift and the Hubble law, there is no reason to expect that it would have a supernova rate any greater than that of M51. Supernovae, after all, are associated with stars, and the low optical surface brightness in the outer regions of Mkn 348 implies a small number of stars in the extended outer regions of this galaxy.

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2. S. Simkin, *Astrophys. J.* **309**, 100 (1986).

Reference Manager

Ruth E. Wachtel's review (27 Feb., p. 1093) of bibliographic software designed for the scientific community served a useful purpose in bringing the features of such programs to the attention of investigators. Although I was naturally pleased with her favorable evaluation of Reference Manager, I would like to correct several inaccuracies. Reference Manager *does* perform searches using the Boolean operator OR (as well as AND and NOT). Although this is not indicated in the main menu, it is clearly explained both in the help messages that can be brought up on the screen and in the documentation that comes with the program. The results of a search *can* easily be alphabetized not only by author but even by year of publication or journal name.

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

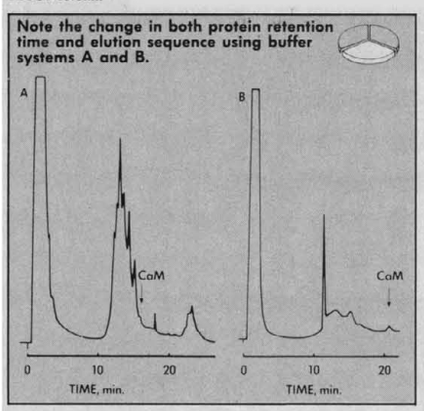


***Figure 2.** Chromatography of crude brain extract using a BAKERBOND WP PEI SEMI-PREP Column with Buffer System B*

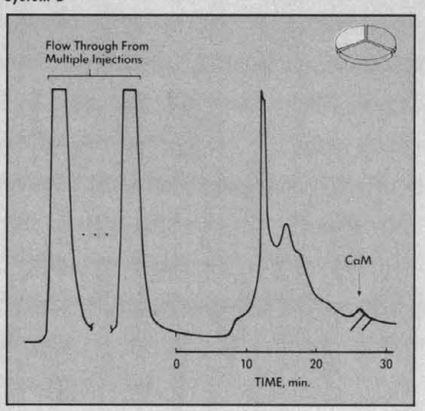
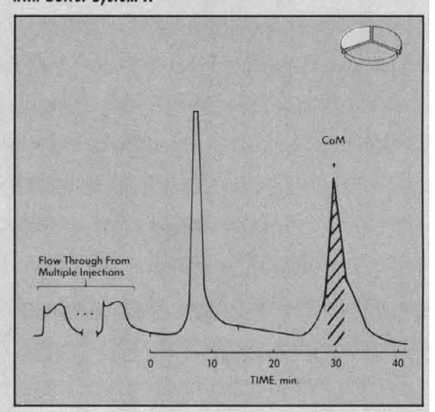


***Figure 3.** Rechromatography of calmodulin active fractions from Figure 2 using a BAKERBOND WP PEI SCOUT Column with Buffer System A*



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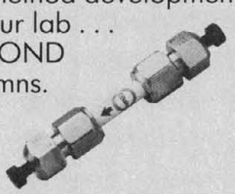

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[1]S. Berkowitz, *J. Chromatography* 398 (1987) pp. 288–293.

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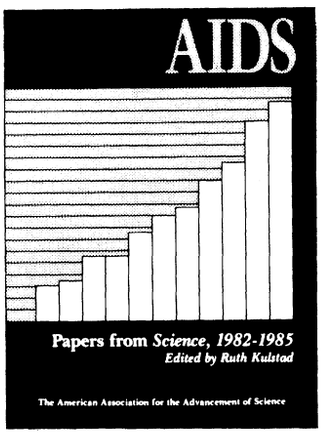

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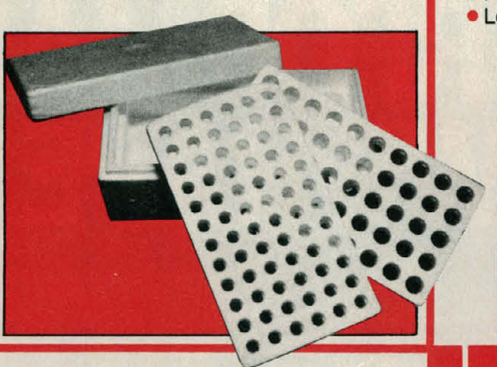

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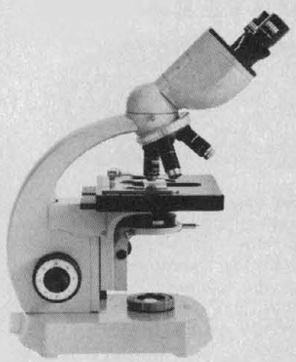

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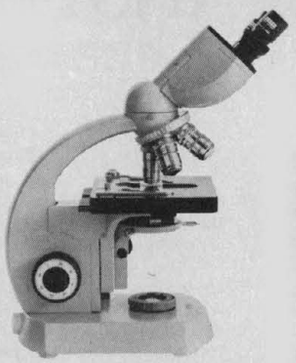

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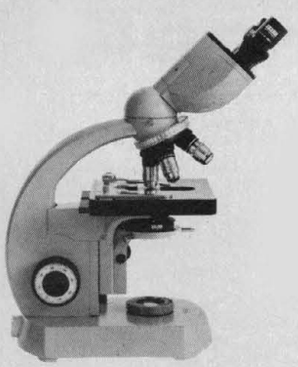

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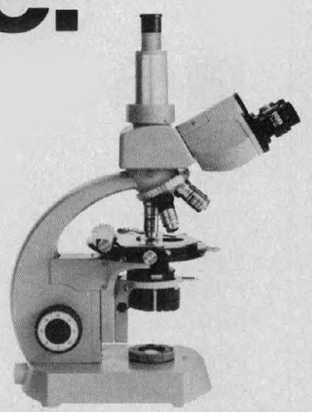

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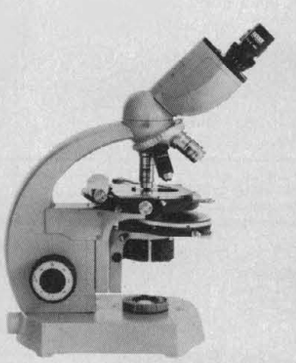

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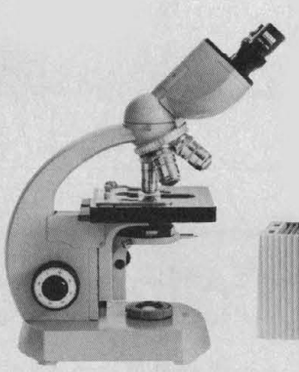

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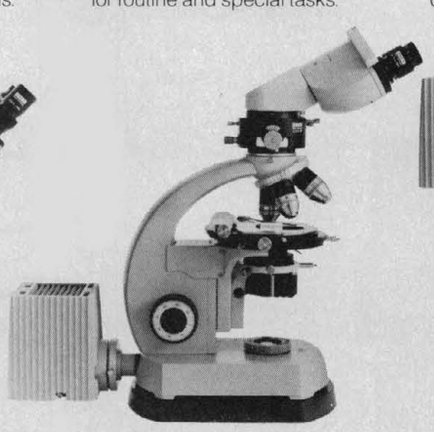

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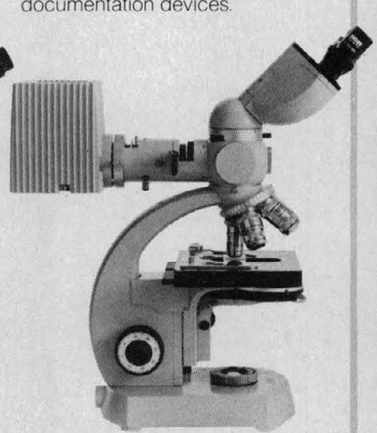

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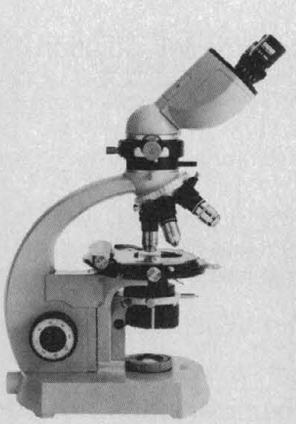

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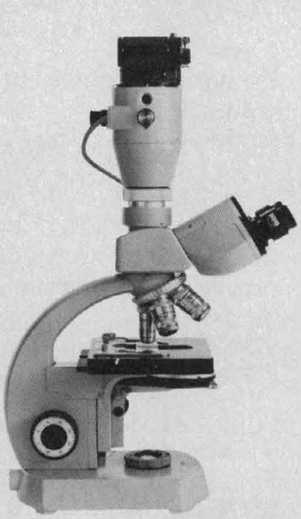

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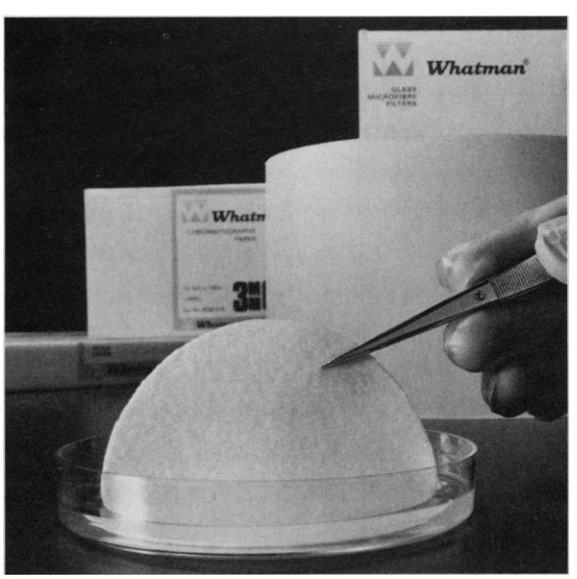

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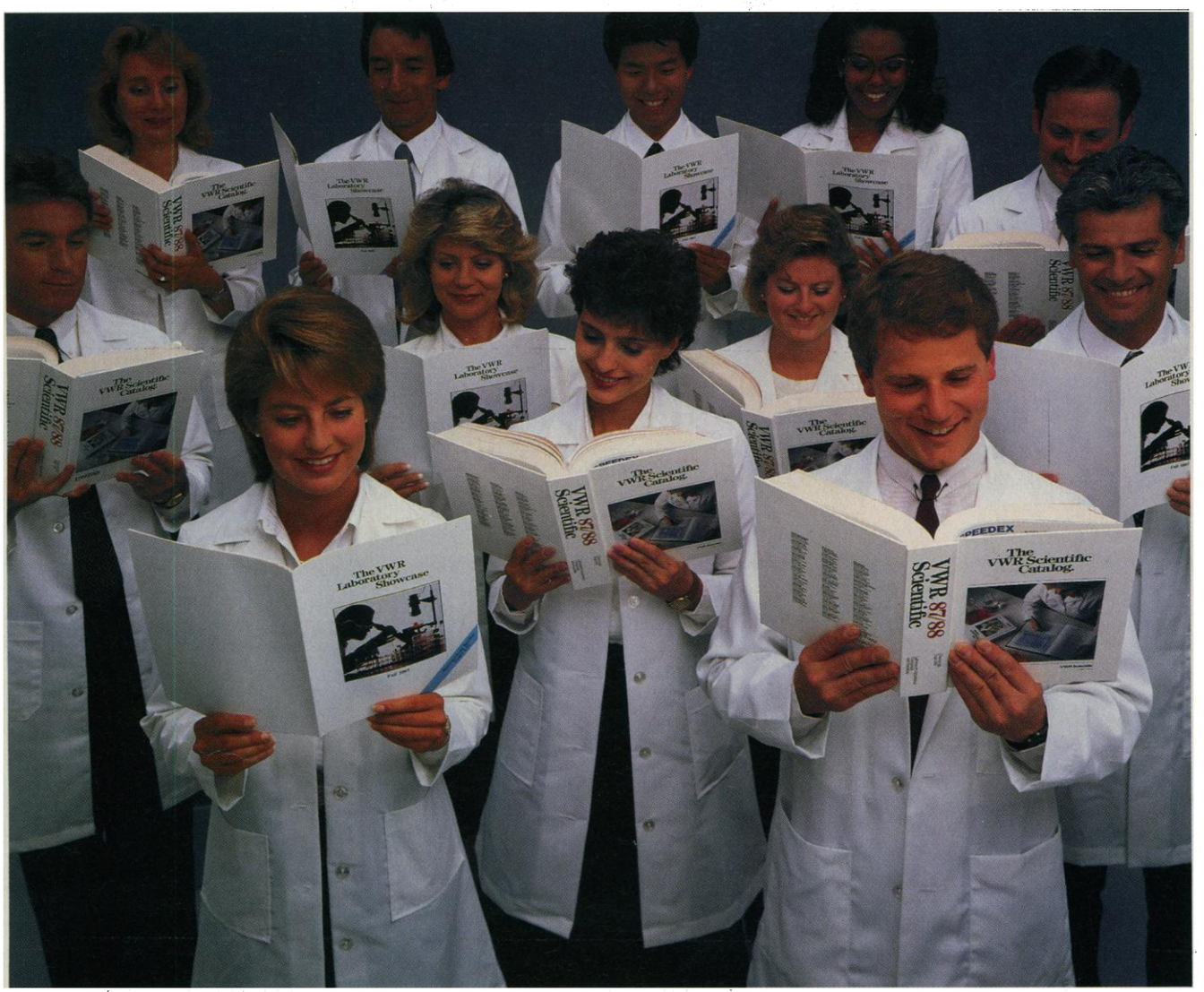

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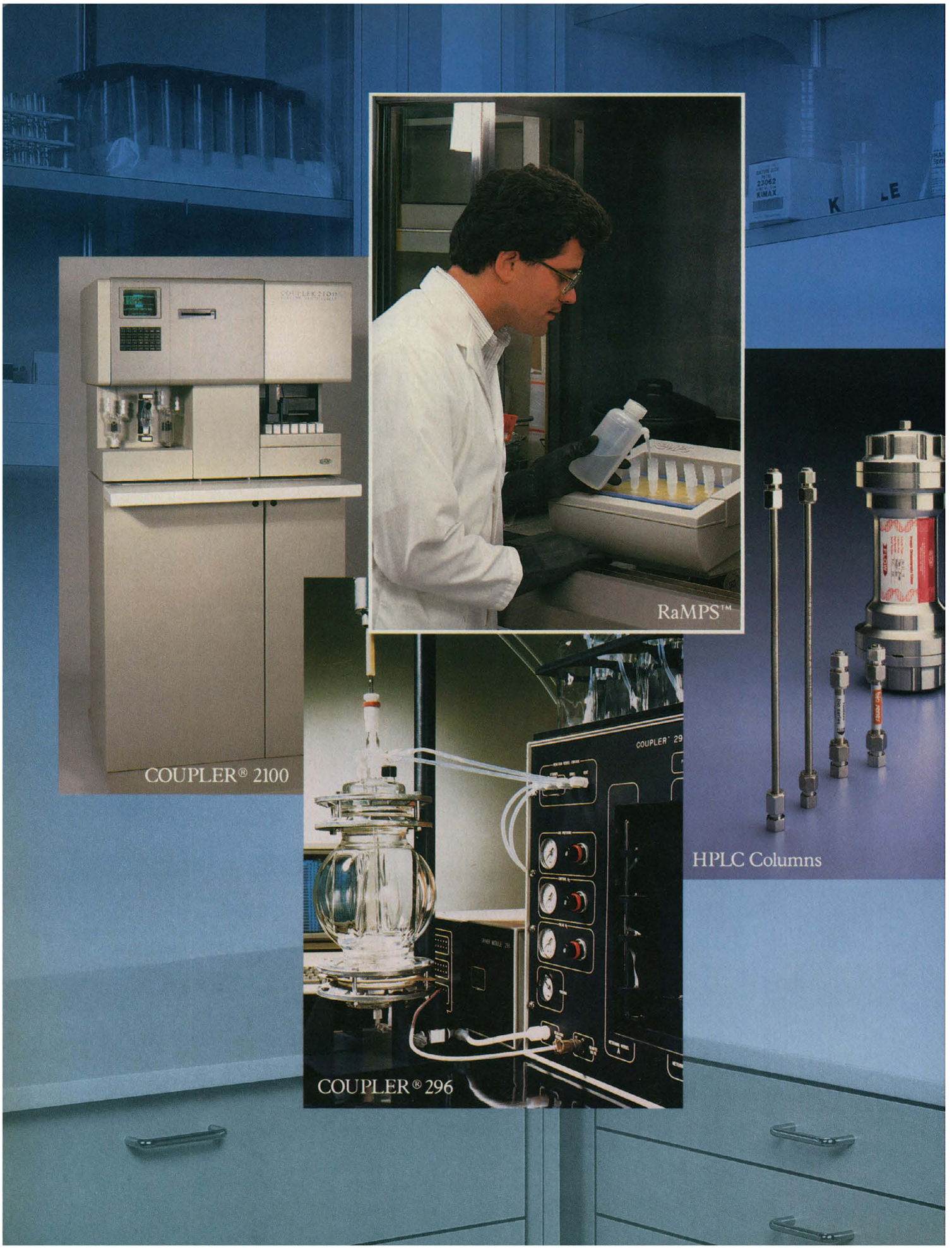
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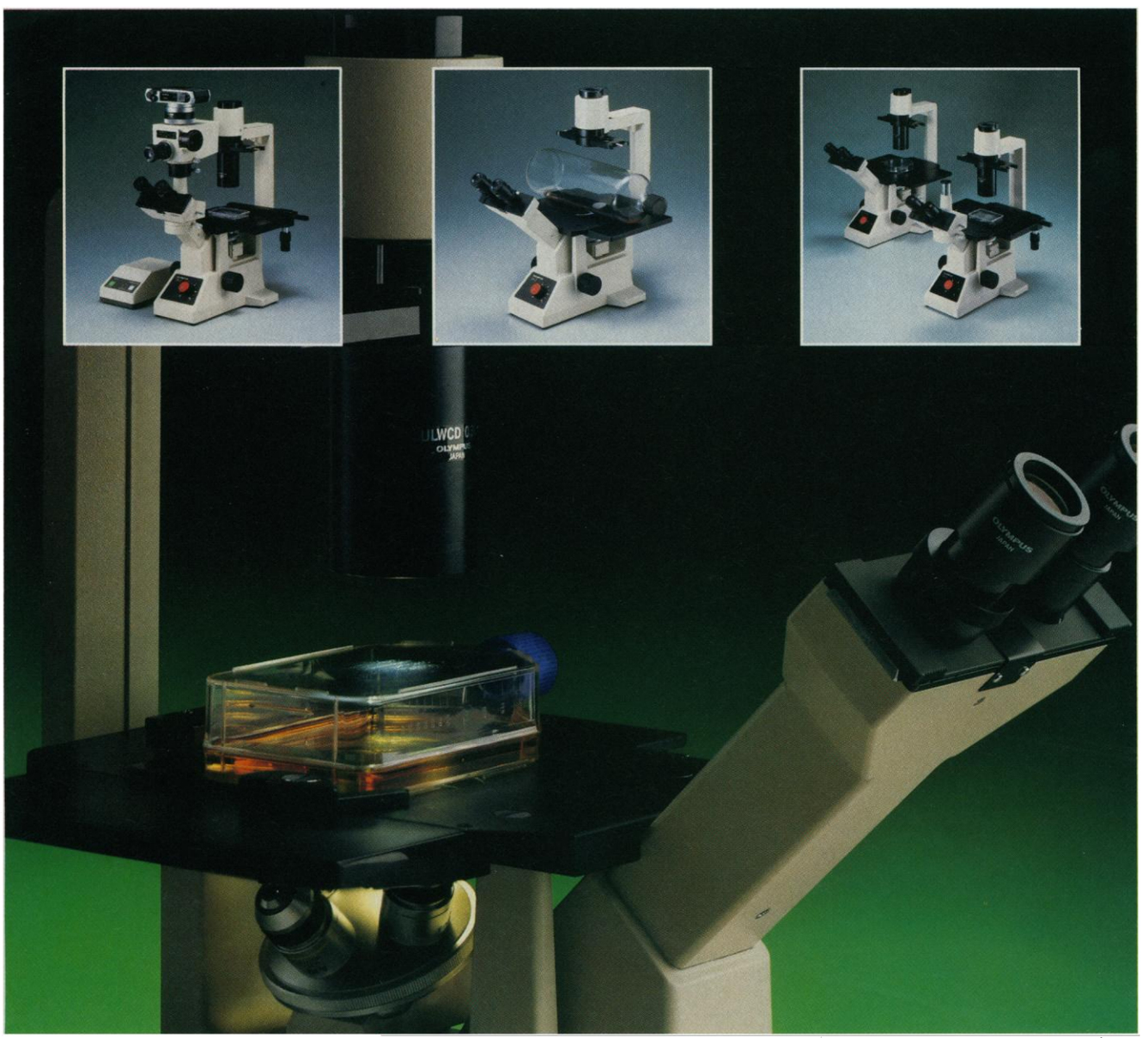

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$$\Gamma^{\mu}_{\lambda\nu} = \frac{1}{2} g^{\mu\sigma}\left(\frac{\partial g_{\sigma\lambda}}{\partial x^{\nu}} + \frac{\partial g_{\sigma\nu}}{\partial x^{\lambda}} - \frac{\partial g_{\lambda\nu}}{\partial x^{\sigma}} \right)$$

$$R_{\mu\nu} = \frac{\partial \Gamma^{\lambda}_{\mu\lambda}}{\partial x^{\nu}} - \frac{\partial \Gamma^{\lambda}_{\mu\nu}}{\partial x^{\lambda}} + \Gamma^{\sigma}_{\mu\lambda}\Gamma^{\lambda}_{\nu\sigma} - \Gamma^{\sigma}_{\mu\nu}\Gamma^{\lambda}_{\lambda\sigma}$$

as indicated in this example.

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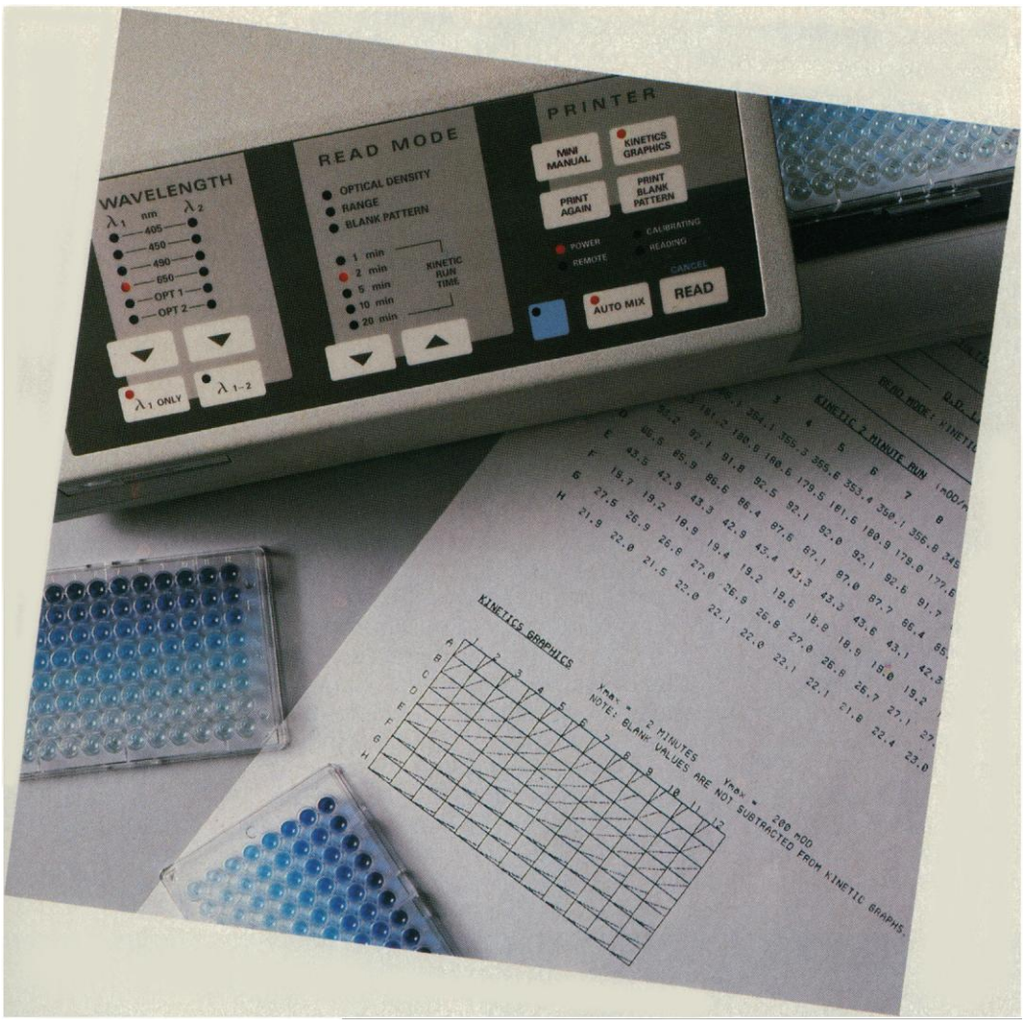

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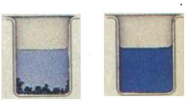

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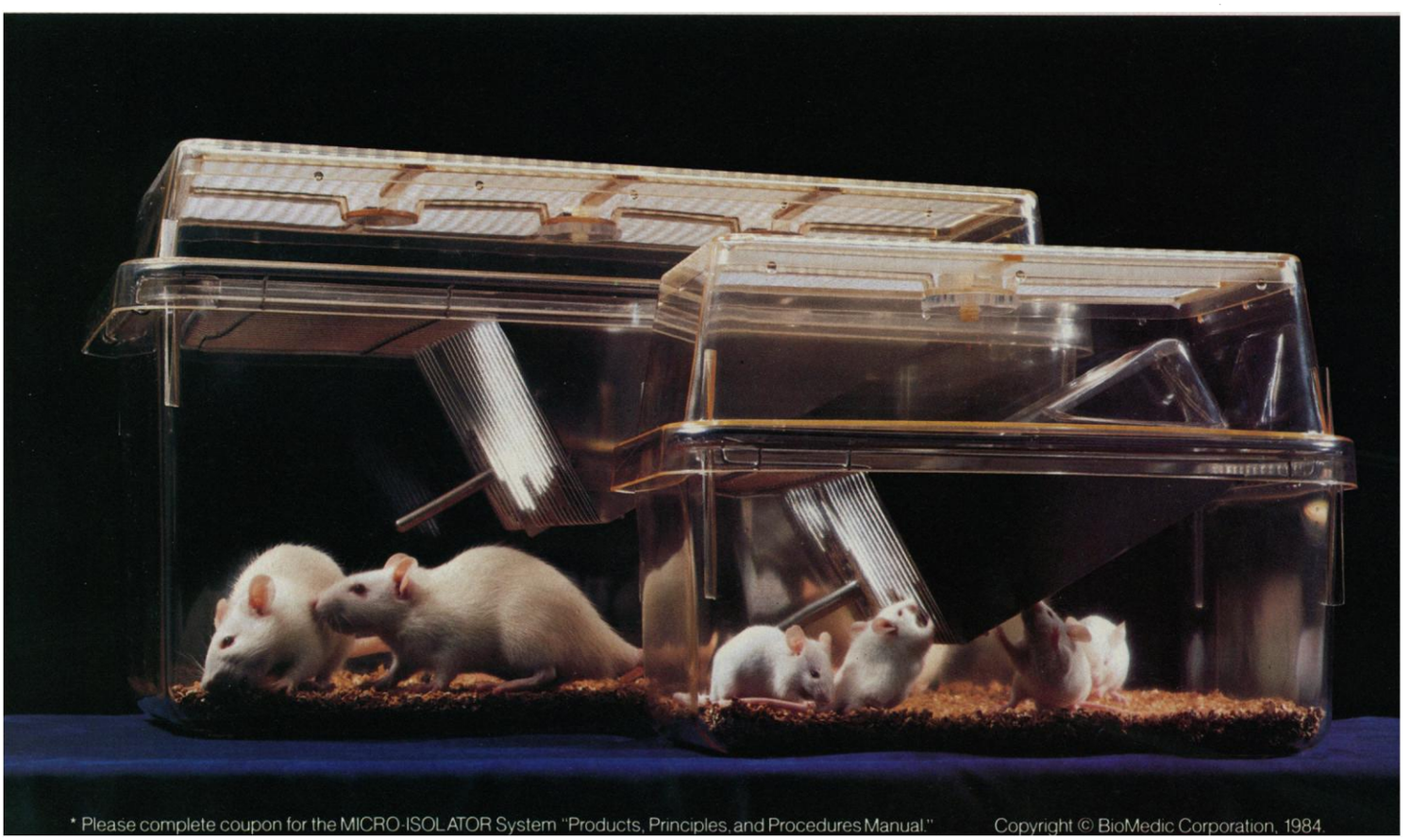
MICRO-ISOLATOR units, fabricated of autoclavable plastic material, are now available for mice, rats, hamsters, and guinea pigs.



* Please complete coupon for the MICRO-ISOLATOR System "Products, Principles, and Procedures Manual."

The Service Cart

The service cart completes the MICRO-ISOLATOR System by simplifying the movement of all necessary supplies to the laminar flow workbench for servicing the MICRO-ISOLATOR units.

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

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