6 DECEMBER 1985 · VOL. 230 · NO. 4730

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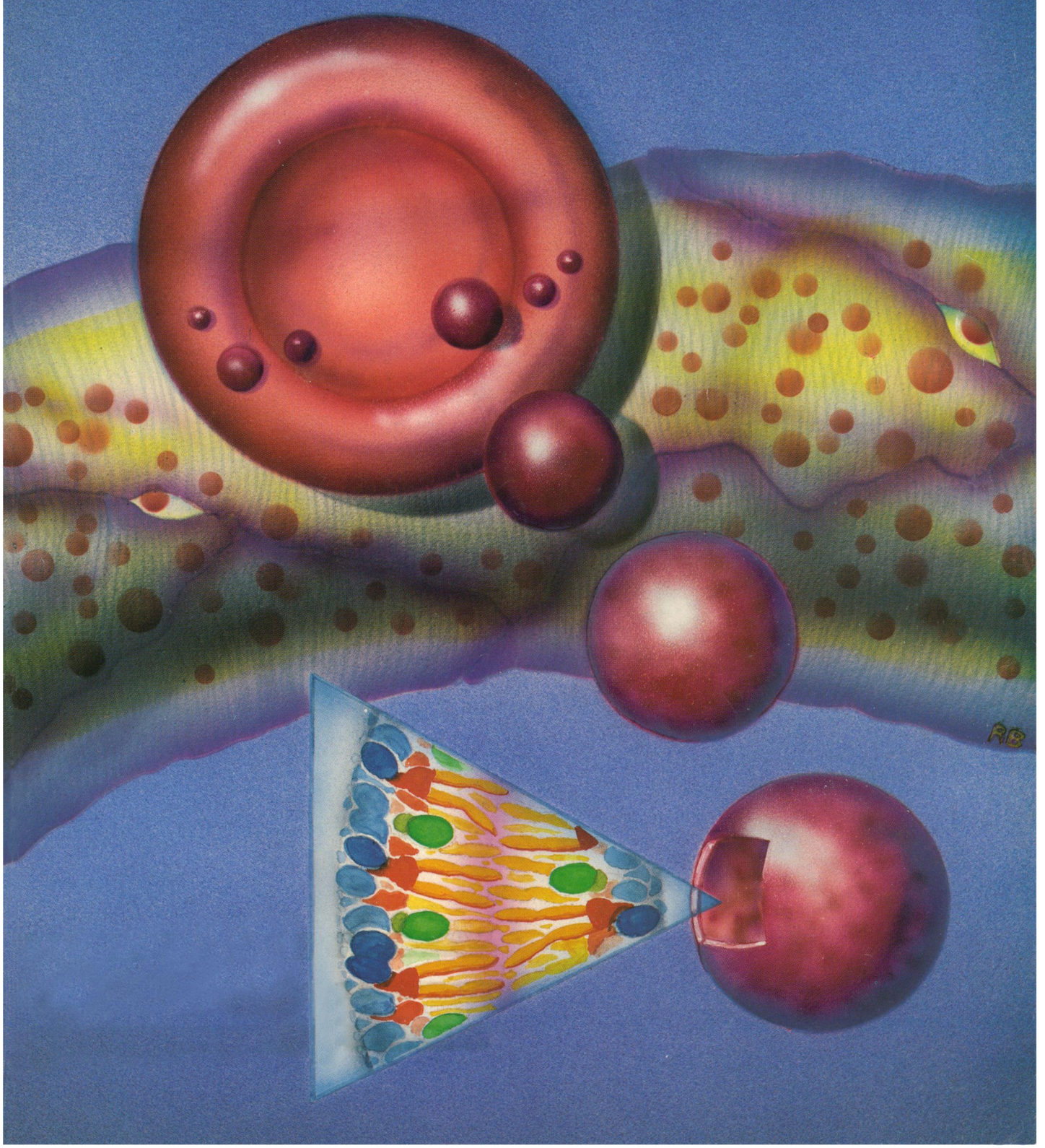

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6 December 1985

Volume 230, No. 4730

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SCIENCE is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1333 H Street, NW, Washington, D.C. 20005. Second-class postage (publication No. 484460) paid at Washington, D.C., and at an additional entry. Now combined with **The Scientific Monthly®** Domestic individual membership and subscription (51 issues): $60. Domestic institutional subscription (51 issues): $98. Foreign postage extra: Canada $24, other (surface mail) $27, air-surface via Amsterdam $65. First class, airmail, school-year, and student rates on request. Single copies $2.50 ($3 by mail); back issues $3 ($3.50 by mail); Biotechnology issue, $5 ($5.50 by mail); classroom rates on request. **Change of address:** allow 6 weeks, giving old and new addresses and seven-digit account number. Authorization to photocopy material for internal or personal use under circumstances not falling within the fair use provisions of the Copyright Act is granted by AAAS to libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $1 per copy plus $0.10 per page is paid directly to CCC, 21 Congress Street, Salem, Massachusetts 01970. The identification code for *Science* is 0036-8075/83 $1 + .10. **Postmaster:** Send Form 3579 to *Science*, 1333 H Street, NW, Washington, D.C. 20005. *Science* is indexed in the *Reader's Guide to Periodical Literature* and in several specialized indexes.

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COVER

Normal red blood cell and smaller hemoglobin-carrying artificial red cells (neohemocytes) set against an isolated capillary. In the capillary, a 25 percent suspension of neohemocytes has replaced the blood. The outer membrane of the neohemocytes, shown enlarged and cutaway, is a bilayer composed of a mixture of four lipids. See page 1165. [Drawing of Robert Burnett, Chartmasters, Inc., San Francisco, California 94133]

THE FIFTH ANNUAL CONGRESS FOR
HYBRIDOMA RESEARCH
JANUARY 26 - 29, 1986
BALTIMORE CONVENTION CENTER, BALTIMORE, MARYLAND

Co-Chairmen:

Zenon Steplewski, The Wistar Institute, Philadelphia, PA • Hilary Koprowski, The Wistar Institute, Philadelphia, PA • Joseph Davie, Washington University, St. Louis, MO

Keynote Speaker: Mark Davis, Stanford University, Stanford, CA **Title:** T-cell Receptor Gene Structure and Function.

We are planning six Working Group Meetings on "Murine Monoclonal Antibodies Available for Clinical Application". These Group Meetings will be restricted to 20 participants each in the following fields:

Group A: Immunohistological Diagnosis
Leader: J. Schlom, NCI, Bethesda, MD
Repporteur: M. Nuti, Laboratorio Di Immunologia, Rome, Italy

Group B: Radioimmunoscintigraphy
Leader: J.-F. Chatal, Center Rene Gauducheau, Nantes, France
Repporteur: J. Powe, Victoria Hospital, Ontario, Canada

Group C: Antigens Shed by Tumor Cells
Leader: R. Bast, Duke University, Durham, NC
Repporteur: J.-Y. Douillard, Center Rene Gauducheau, Nantes, France

Group D: Immunotherapy of Solid Tumors
Leader: A. Houghton, Sloan Kettering Cancer Center, New York, NY
Repporteur: S. Ferrone, New York Medical College, Valhalla, NY

Group E: Immunotherapy of Leukemia and Lymphoma
Leader: J. Ritz, Dana Farber Cancer Institute, Boston, MA
Repporteur: K. Foon, University of Michigan, Ann Arbor, MI

Group F: Immunoconjugates
Leader: K. Krolick, University of Texas, San Antonio, TX
Repporteur: J. Fulton, Southwestern Medical School, Dallas, TX

It is our intent to select participants *actively* involved in the above listed research for in-depth discussion of progress made recently.
The entire day of Monday, January 27, 1986 will be available for these group discussions. The consensus reached by the groups will be presented by the Repporteurs to the whole Congress and results of these discussions will be published in Hybridoma.
Investigators interested in participating in Group Meetings should send a short summary to Dr. Ralph Reisfeld, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, California 92037 by November 30, 1985.

Workshop Topics & Chairmen:

HUMAN REPERTOIRE and AUTOIMMUNE DISEASE
A. Notkins, NIH, Bethesda, MD.

GENETIC PROBES IN IMMUNOLOGY
J.D. Capra, University of Texas, Dallas, TX.

MONOCLONAL ANTIBODIES in DISSECTING NORMAL and MALIGNANT STEM CELLS
I. Bernstein, Fred Hutchinson Cancer Center, Seattle, WA.

ISOTYPE SWITCH VARIANTS IN ANALYSIS of ANTIBODY FUNCTION
M. Scharff, Albert Einstein College of Medicine, New York, NY.

Poster Sessions: TECHNOLOGICAL ADVANCES IN HYBRIDOMA RESEARCH

Participants are invited to submit abstracts for the poster sessions. These abstracts will be reviewed up until the time of the meeting; however, only those accepted by Nov. 15 will be published in the journal, Hybridoma. Contact Dr. Zenon Steplewski (215) 898-3924.

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REGISTRATION FEES:

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Animal models of chronic hepatitis

Because more than 200 million people throughout the world are carriers of hepatitis B virus (HBV), an animal model system in which the carrier state could be analyzed has been widely sought (pages 1157 and 1160). Carriers pose a hazard to others because they may shed infectious virus. In addition, after several decades, carriers have a tendency to develop carcinomas of the liver. Reports by Chisari *et al.* and Babinet *et al.* describe two mouse model systems in which genes of HBV have been injected into fertilized mouse eggs. The eggs are implanted into pseudopregnant mice and the hepatitis genes become integrated into the chromosomes of the next generation of mice. To prevent production of intact viruses, not all the hepatitis virus genes were included in the inserts. Hepatitis antigens were produced by many of the "transgenic" mice: in one study, the antigens were expressed largely by liver cells but, in the other, many tissues expressed them. The genes were further inherited by another generation of mice, which also produced viral markers. In one group of mice, it was demonstrated that immunologic tolerance to hepatitis antigen developed, probably because the gene coding for this antigen was carried in the mouse chromosome. These models may be helpful in explaining how HBV integrates into the host chromosome and in clarifying what cellular and hormonal factors affect gene expression. Modifications of the models to circumvent tolerance may be needed to mimic the conditions that in chronic HBV carriers lead to tissue injury; the injury seems to result not from the production of viral antigens, such as those studied in these models, but from immune responses of the host to the infecting organism.

Fractal surfaces

A mathematical description of the roughness or smoothness of surface regions of a protein can be used to relate protein structure and texture to protein function (page 1163). The fractal dimension of a surface gives a measure of the surface topology of a crystalline molecule; low values describe smooth surfaces, and high values describe surfaces with increasingly more textural irregularities. Lewis and Rees found that the smoothest surface areas of a number of enzymes are those at the active site where the enzyme and its substrate briefly interact. Among the roughest surfaces are those at which two subunits of a single molecule (such as an enzyme or a mitogen) are joined for extended periods or others at which discrete proteins (such as an antigen and an antibody) interact to form tight, stable complexes. As patches of smoothness and roughness on protein surfaces are defined, the dynamics of macromolecular interactions can be understood as consequences of surface textural features.

Artificial red blood cells

Artificial red blood cells (cover) can be used to expand blood volume after tissue injury or trauma and to substitute temporarily for natural red blood cells until appropriate cells are available for transfusion (page 1165). Hunt *et al.* designed red cell surrogates, called neohemocytes, that contain human hemoglobin and phospholipids. The neohemocytes were able to bind oxygen with an affinity near normal. They remained in the bloodstream of test rats for several hours without producing toxic effects and later were cleared from the circulation. Their small size, compared to normal red blood cells, makes them especially valuable for transporting oxygen to those oxygen-deficient tissues which are served by blood vessels that have been partially blocked or constricted by disease or injury.

Natriuretic factor

In response to increases in blood volume, the atria of the heart release atrial natriuretic factor (ANF), a peptide hormone that participates in the control of blood pressure and in the balance of water and salt in the body (page 1168). Bloch *et al.* found that rat heart cells in culture synthesized and secreted ANF in a precursor form; later, when the culture fluid was incubated with serum, the large secreted molecule was cleaved to a smaller form. In the rat, ANF is synthesized as a polypeptide of 152 amino acids, is stored within atrial cells as a smaller (126 amino acid) molecule (proANF), and is active in serum as a molecule of about 25 amino acids. Since the process of conversion of proANF to ANF can occur in serum, proteolytic enzymes in serum responsible for the cleavage can now be sought.

RNA in scrapie and Alzheimer's disease

Brain lesions in victims of Alzheimer's disease and in scrapie-infected mice and hamsters have in common a distinctive messenger RNA molecule (page 1177). Wietgrefe *et al.* used a scrapie-related DNA probe to study the distribution of the unusual marker RNA molecules in brain tissue. In lesions in the brains of affected humans and animals, the RNA molecules were distributed in patches. Similar patches are also characteristic of other gene products in cells that contain various infectious organisms like the scrapie agent. In the human tissues, the marker molecules were associated with the processes that extend out from nerve cells, whereas in the animal samples, the molecules were associated with the bodies of nerve cells. These RNA molecules in brain lesions may be useful markers of pathology in Alzheimer's disease and scrapie. They may provide clues to how the degenerative changes in the brain develop, perhaps contributing also to an understanding of how these and other brain disorders are initiated.

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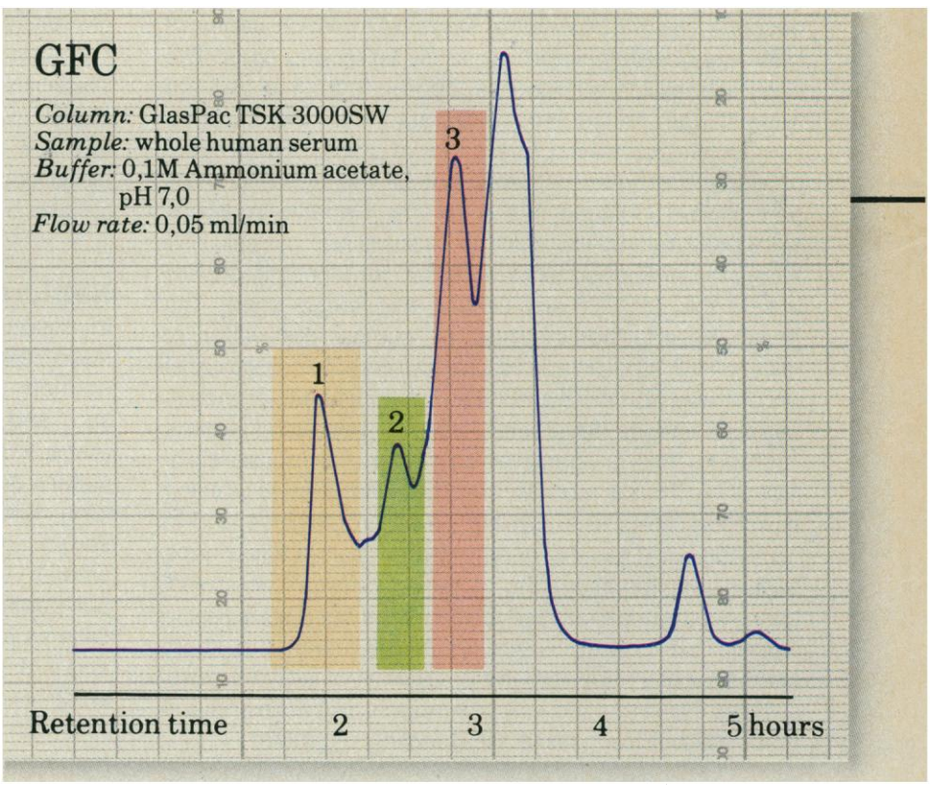

Using GFC as the first step permits the use of a wide range of conditions without interfering with the separation. It is therefore possible to find conditions that promote the dissociation of aggregates as well as minimize proteolysis.

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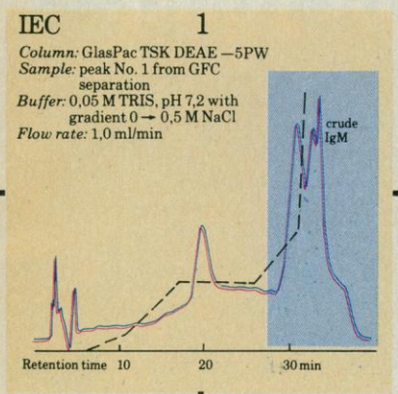

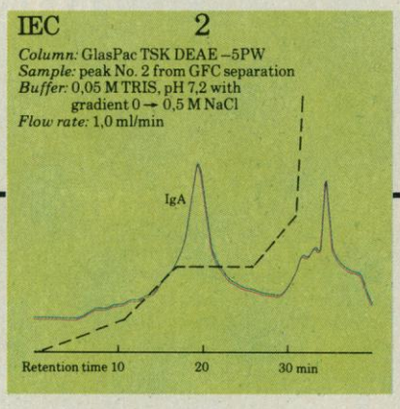

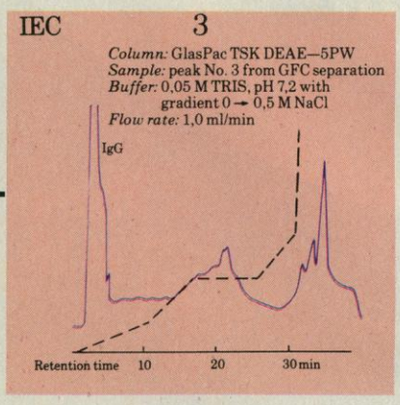

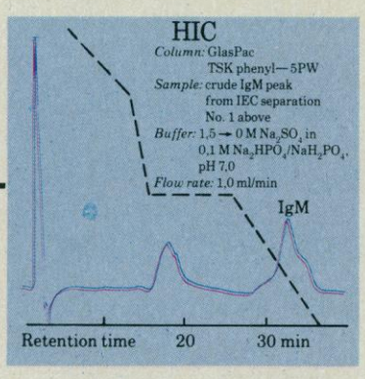

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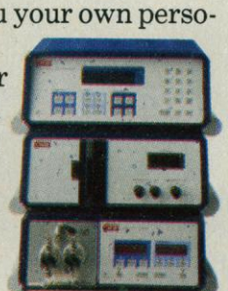

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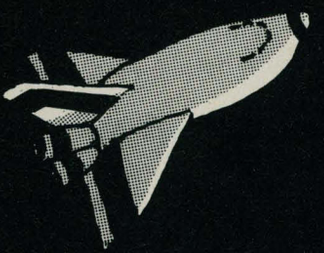

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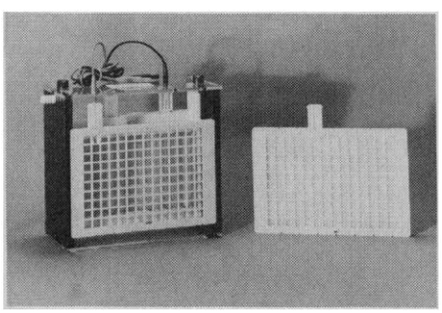

firmly without squeezing. 75% open grid pattern offers maximum transfer. Electrodes *fixed at 10 cm apart* assures a uniform electrical field. *Moving them closer together results in an inhomogeneous electrical field, which in turn causes uneven transfers.* The two electrode panels have platinum wire (more than 120" of it) strung in a closely spaced parallel pattern to assure equal removal of samples. The electrode assemblies lock automatically into place and can be removed instantly. Two important options: The Power Lid, a low cost power source which sits directly on top; and a highly efficient Heat Exchange Manifold which enables you to use higher field strength for more rapid transfer.
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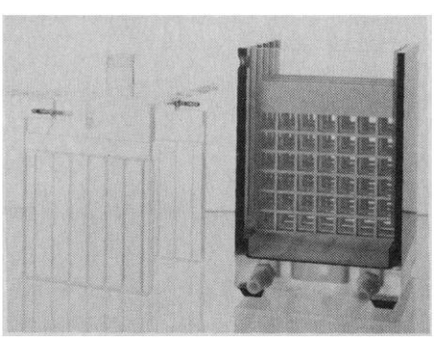

a magnetic stirrer and cooling, the unit will show no more than a 5°C heat rise over the length of the run.
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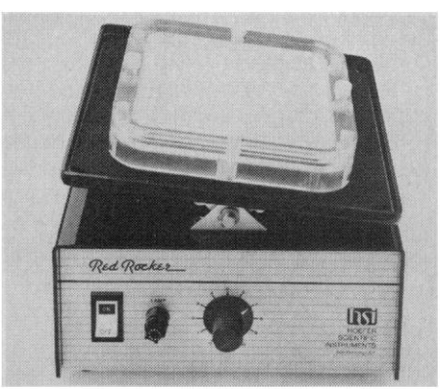
• **Deca-Probe** is a 10-chamber microincubator manifold designed to stain 10 *separate immunotransfers on a single transfer membrane.* It is a sturdy, precisely-engineered unit. Two 19 x 19 cm acrylic plates, each 1.7 cm thick, fit together with a membrane held in place between them. One of the plates has parallel troughs milled into it. These troughs become individual incubation chambers when the plates are clamped together and sealed. An O-ring gasket surrounding each chamber prevents leakage from one to another, which means



you can use up to 10 separate detection methods simultaneously. Reagent volume is low, normally just enough in each chamber to wet the membrane and allow for mixing when the unit is rocked. When screening is finished, you remove the membrane, *intact,* for side-by-side comparison of lanes. No danger of exposure to toxic reagents and radioactivity.

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What are the benefits to the animals?

There are many. Cross-contamination is substantially decreased because air from an infected animal goes to the exhaust system with an absolute minimal exposure of the other animals. Animal stress is also significantly reduced: the enclosed environment is quiet; drafts and thermal and humidity fluctuations are greatly minimized; and animals can be easily observed without inducing stress. The success of this environment is attested to by the fact that the total number of animals born to a species that breeds poorly (DBA/2J mice) is increased and the percent survival is also appreciably higher. Additional evidence: judging by acceleration of weight gain, newly arrived animals housed in this system become acclimated more rapidly. Further evidence? Even multiple species can be successfully housed in the same rack.

What are the benefits to the research workers?

Since the air in the rack is exhausted into the main exhaust system and does *not* re-enter the animal room itself, research workers are effectively isolated from animal dander or other allergens, odor, pheromones, microorganisms, and food and bedding dust. Even with the doors of the unit open, the direction of air flow tends to be *from* the room and *into* the unit which helps to contain contaminated air *within* the unit. Result: virtual elimination of allergic reactions and generally, a cleaner, safer, odor-free work environment for the research people.

What are the benefits to research programs?

Because this system greatly reduces the chance of cross-contamination, and because it provides a much less stressful environment generally (e.g., it tends to reduce the amount of animal handling required), the chances of jeopardizing expensive research programs are substantially minimized.

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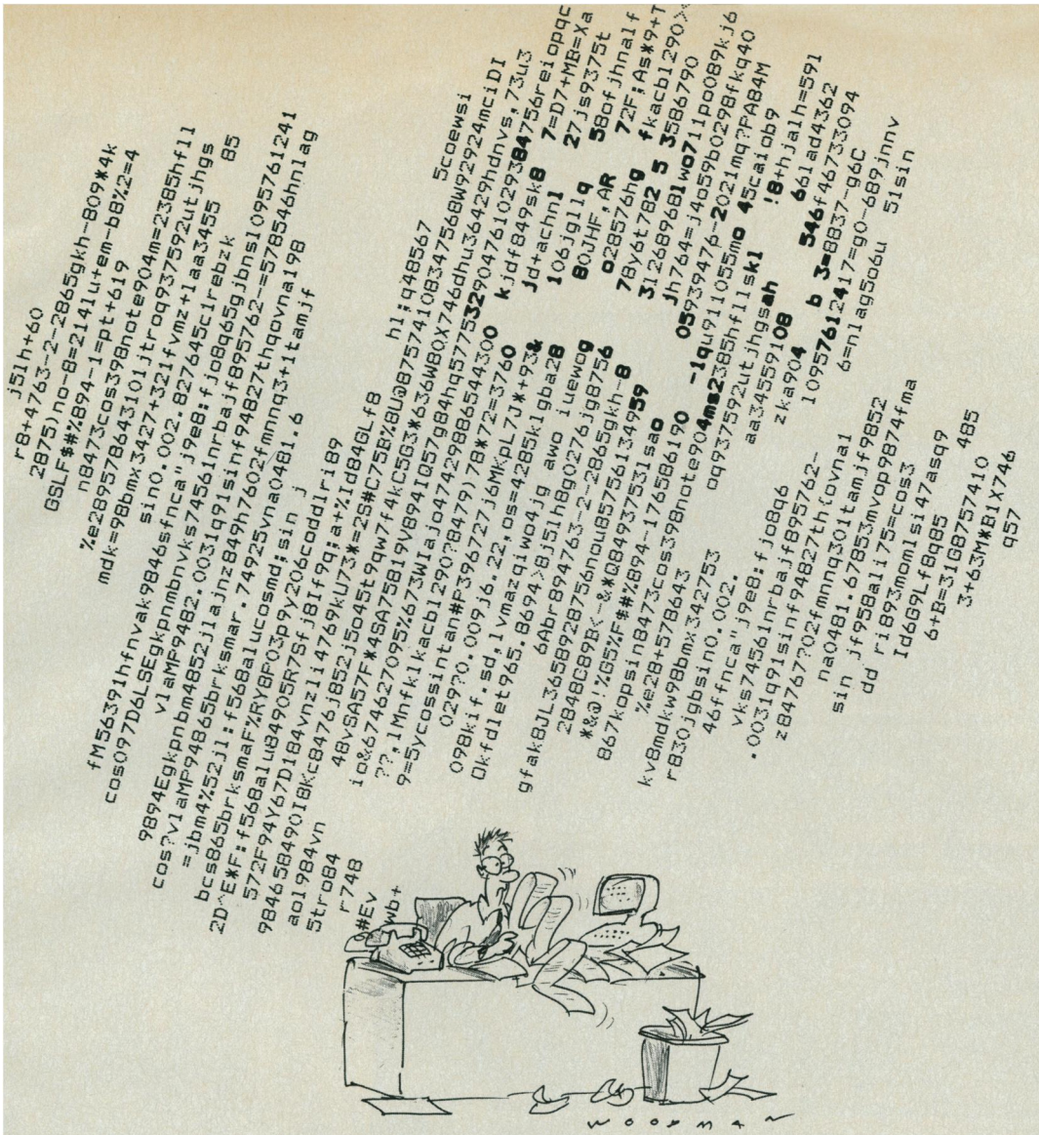

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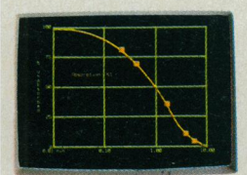

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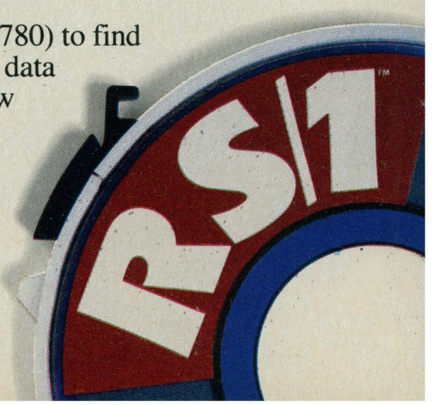

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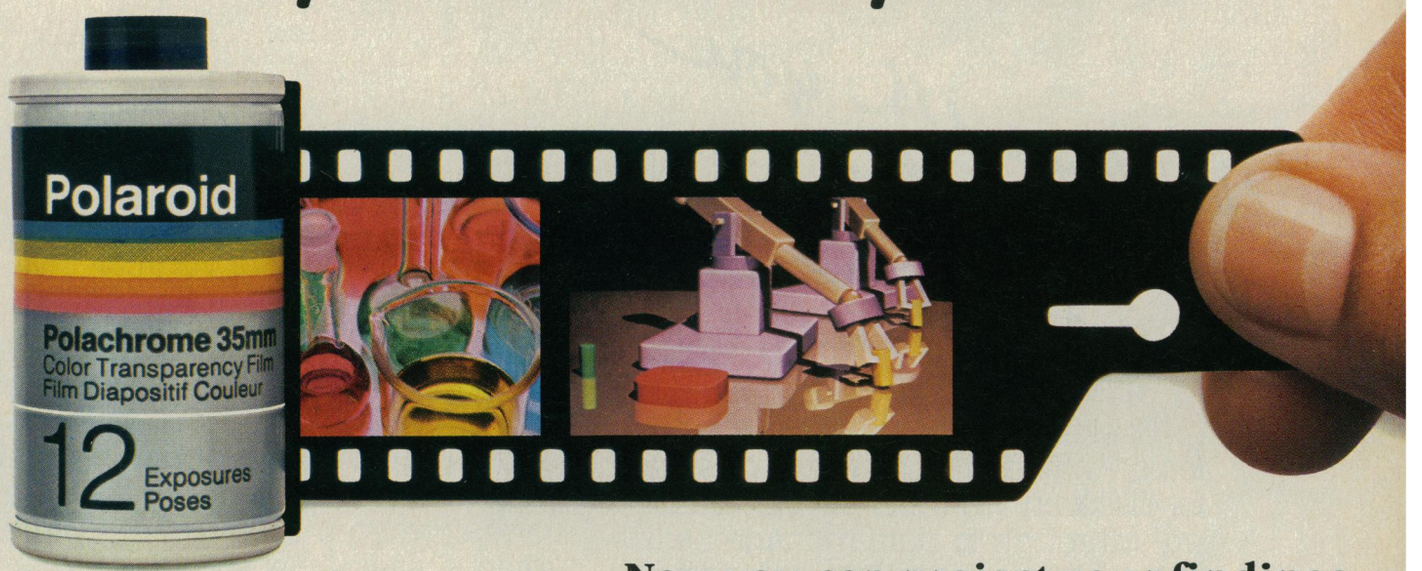

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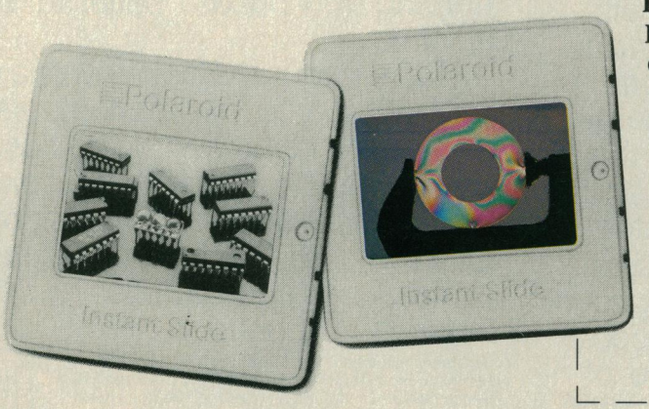

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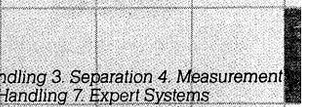

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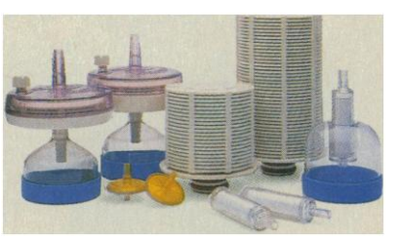

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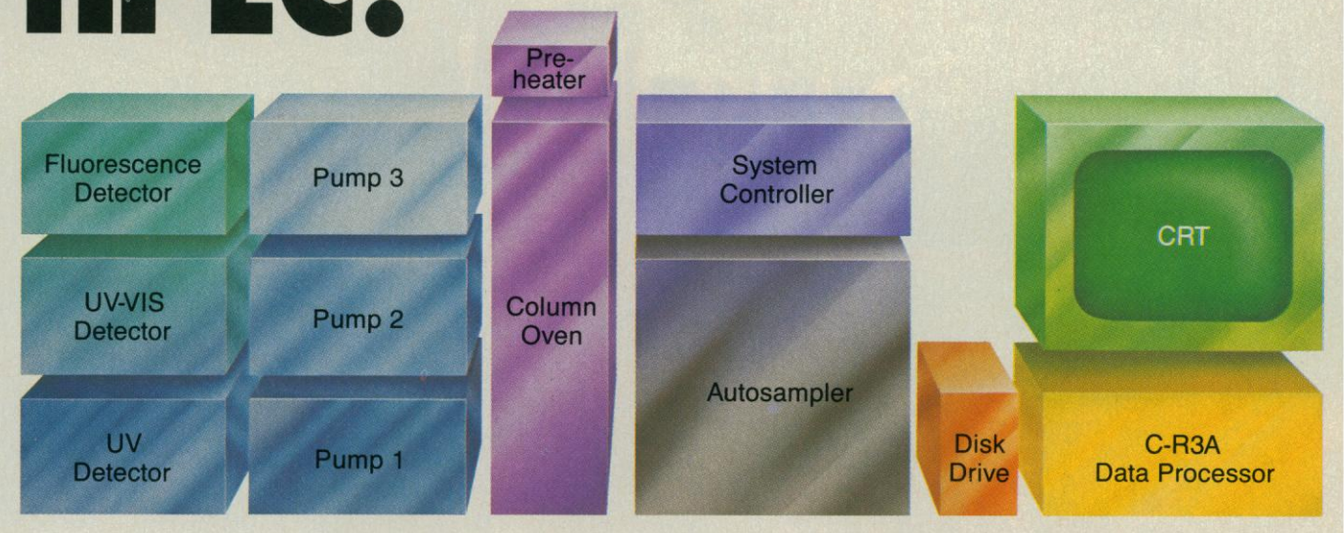

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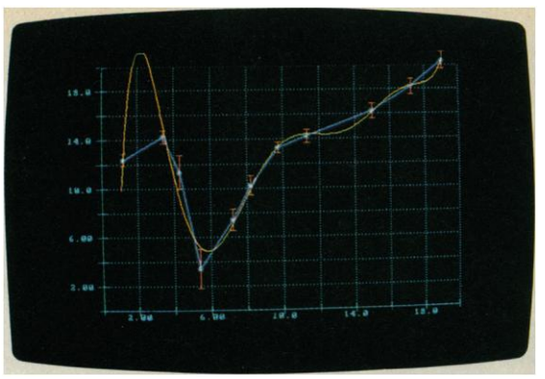

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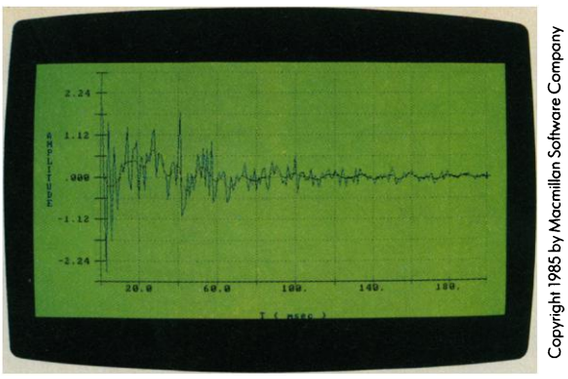

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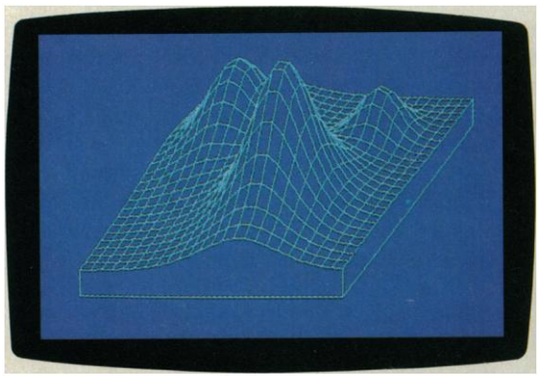

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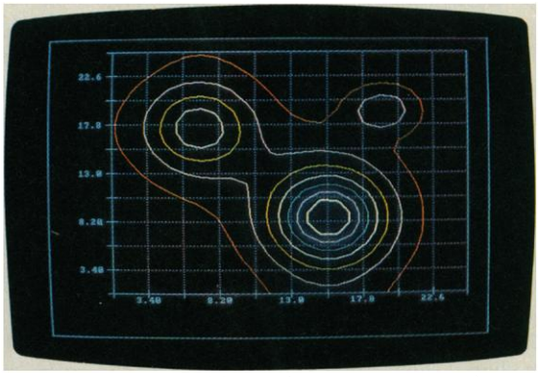

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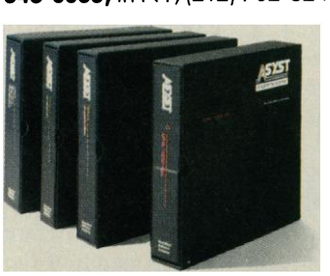

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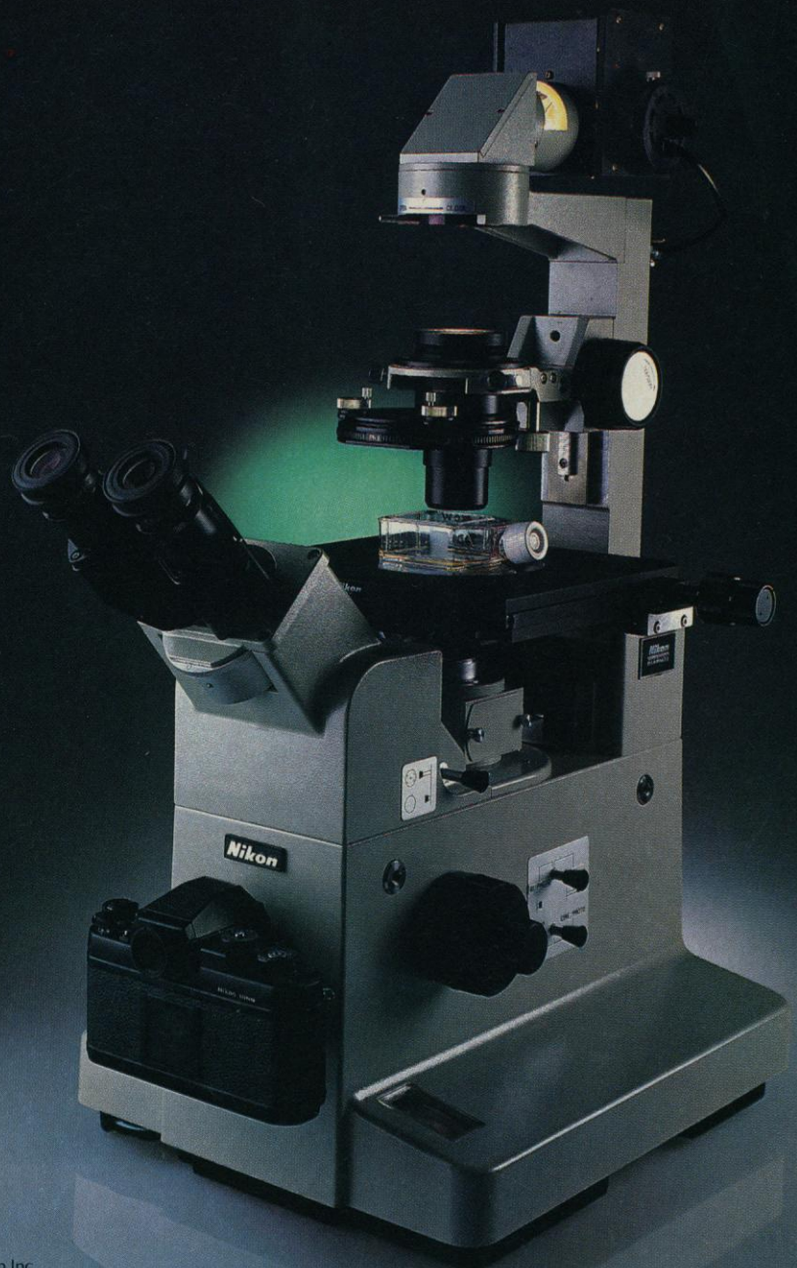

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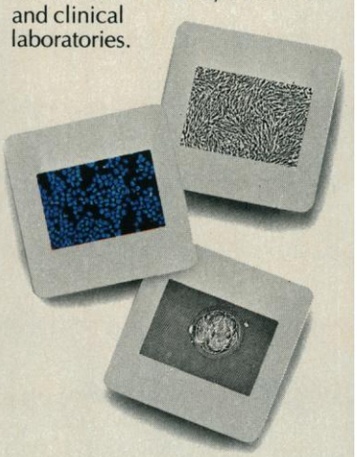

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6 December 1985, Volume 230, Number 4730 **SCIENCE**

Alzheimer's Disease: A Biologist's Perspectives

Public concerns about Alzheimer's disease are rising. With the increasing survival to advanced ages, it is predicted that Alzheimer's disease will afflict about 2 million people in the United States by the year 2000. Funding for basic and clinical studies on this disease has been increased and now includes $9 million a year that Congress added to the budget of the National Institute on Aging for ten Alzheimer's disease research centers, about $40 million from other National Institutes of Health programs, and $2 million from private foundations. Biologists may ask how the emphasis on Alzheimer's disease could influence support and opportunities for basic research.

My view is that little recognized but implicit aspects of these programs will greatly benefit the neurosciences and biogerontology. An important resource will be the greater availability of brain tissues from normal subjects. To delineate Alzheimer's disease from other common age-related changes requires at least as many (probably several times more) normal controls as individuals with Alzheimer's and other age-related dementias. Postmortem specimens from normal individuals with detailed personal and medical histories are usually scarce. However, healthier relatives and friends of victims of Alzheimer's disease are often willing to donate their own tissues. The Alzheimer's disease research centers could provide the complex logistical support for the short postmortem intervals (4 hours or less) needed to preserve many macromolecules and microscopic structures.

The tissue resources will permit new approaches concerning the impact of heredity and environment on the cellular structure and chemistry of the healthy human brain. The correlation of detailed pre- and postmortem data promises to support major growth of research on human neurobiology and could reveal long-lasting effects of drugs, diet, stress, or even subtler experiences. Pursuit of these far-reaching and difficult questions will also build on the spectacular advances from brain imaging in vivo. Other topics so far studied much less in humans than in animals include mechanisms of nonischemic neuronal death; cytoskeletal organization; sex differences; receptors; membrane transport; tissue factors that influence neurite outgrowth; and messenger RNA. The brain messenger RNA's examined at my laboratory and that of M. Morrison have a remarkable postmortem stability; this invites aggressive use of molecular genetic technology.

Screening for hereditary influences on Alzheimer's disease could also reveal genetic markers linked to depression and other common late-onset neurological disorders. Moreover, even without knowing the base sequence of an Alzheimer's locus, linked genetic markers could reveal environmental factors as well as other genes that influence the age of onset and progress of neurological diseases in high-risk individuals.

Studies on Alzheimer's disease also probe basic mechanisms of synaptogenesis. Recently, evidence of neuronal plasticity and sprouting in the human brain was found in the hippocampus of victims of Alzheimer's; these synaptic reorganizations are similar to the changes induced in the rat hippocampus by lesions of the entorhinal cortex.* Intriguing results are being obtained by C. Cotman, F. Gage, D. Gash, and others in the use of embryonic cell transplants to correct experimental or congenital brain lesions that may yield therapies for victims of Alzheimer's. Moreover, research leading to the prevention or effective treatment of Alzheimer's disease seems likely to illuminate one of the great mysteries in biology—the nature of memory and cognition. I would be surprised if the major new resources required for a serious attack on Alzheimer's do not also benefit the basic neurosciences on the same scale as funding for cancer research has done for many areas of molecular, cell, and developmental biology.—

CALEB E. FINCH, *Andrus Gerontology Center, Department of Biological Sciences, and Alzheimer Disease Research Center Consortium of Southern California, University of Southern California, Los Angeles 90089*

*J. W. Geddes, D. T. Monaghan, C. W. Cotman, I. T. Lott, R. C. Kim, H. C. Chui, *Science*, this issue, page 1179.

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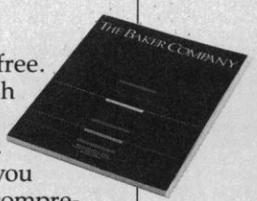

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