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Science

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Frontiers in Biology
The Cell Cycle


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COVER SYNGAMY II is one of a series of paintings by the Pennsylvania artist Peter Cohen on the first mitosis within the fertilized egg. The mitochondria, which have assumed the round shape seen in the painting, leave a clear space within the cytoplasm for the dance of the chromosomes on the luminous spindle. The paintings of Peter Cohen are currently on exhibit at AAAS in Washington as part of the AAAS Art of Science and Technology Program, which displays work reflecting the interaction of art and science. See the articles on the cell cycle that begin on page 603.

Reports

Book Reviews

Products & Materials

This Week in SCIENCE

The RNA world

THE first organisms on the earth are thought to have relied entirely on RNA for storing genetic information and for carrying out functions that now are parceled out between RNA, DNA, and proteins. The so-called riboorganisms lived in an RNA world. A number of researchers have been working backwards from existing organisms—studying and comparing the structures and metabolic activities of organisms in different kingdoms—in order to develop a picture of the "breakthrough organism," the first organism to contain, though probably not use, DNA and protein. Waldrop describes the methods that have been developed and used for characterizing the inhabitants of the RNA world and for defining the breakthrough organism, the new models that have been proposed, and the controversies that surround this approach to understanding how an RNA-exclusive system was transformed to one consisting not only of RNA but DNA and proteins as well (page 578).

Cell cycle controls

ALL dividing cells experience relatively quiescent phases, engage in active DNA replication, and then undergo cell division; what controls the orderly progression from stage to stage in the cell cycle has been the topic of intense biochemical and genetic research for many years. A number of highly conserved proteins and specific "checkpoints" that exert control over the cell cycle have been identified. The best studied proteins are the maturation promoting factor and cyclin (which may actually be a component of the maturation promoting factor). The checkpoints represent control mechanisms that ensure that later events will not begin until earlier events have been completed properly. All eukaryotic cells that have been studied appear to use remarkably similar proteins for controlling transitions in the cell cycle; checkpoints seem more important in the cell cycles of somatic cells than of embryonic cells in which sequential events can often be independent. Murray and Kirschner (page 614) and Hartwell and Weinert (page 629) describe experimental work that has provided evidence for and led to the characterization of these controls. Other aspects of the cell cycle are discussed on pages 545, 603, 609, 614, and 635.

Cesium iodide under pressure

CESIUM iodide (CsI) has been used in a variety of studies of the physics of condensed matter, serving as a prototype for investigations of crystal structures, equations of state, and transitions to metallic phases. X-ray diffraction measurements of CsI, previously carried out under pressures up to 95 gigapascals, now have been extended to pressures between 150 and 302 gigapascals by Mao *et al.* (page 649). The ultrahigh pressures were exerted on samples in diamond-anvil cells: the diamond acts both as an anvil and as a window through which diffraction measurements are made. Above 200 gigapascals, the shape of CsI is like that of hexagonal close-packed structures. This new crystal structure and the pressure-volume relations of the crystal are almost exactly like those of solid xenon, confirming predictions based on theoretical analyses that the crystal structures of the rare-gas solid xenon and CsI (which have the same number of valence electrons) would converge at high pressures.

Crystals from space

PROTEIN crystallographic analyses have often been stymied by inadequate procedures for the preparation of high-quality crystals; the opportunity to prepare crystals in space may circumvent this problem. Protein crystals have been grown in space that are larger and more uniform in structure and have better internal order than similar crystals grown on the earth; therefore they diffract to much higher resolution (page 651). During the shuttle flight of September 1988, attempts were made to crystallize 11 proteins; the successful preparations of crystals of γ-interferon D^1, elastase, and isocitrate lyase are described by DeLucas *et al.* The crystallizations were activated after the shuttle was in orbit; samples were evaluated with x-ray diffraction procedures when the shuttle returned to the earth. When crystals grow on the earth, the earth's gravitational field causes density-driven convective flow and sedimentation; in the microgravity conditions prevailing in space, these two effects, which interfere with the growth of single crystals and with the orderly packing of molecules, are largely eliminated. Pool elaborates on the methods used and potential value of space crystals on page 580.

Peptide vaccine for autoimmunity

AN effective vaccine has been developed for experimental allergic encephalomyelitis (EAE); this is an animal model of multiple sclerosis, which is an autoimmune disease of the central nervous system (page 668). Pathology in EAE is induced by the affected animal's own T cells. The cells react with and destroy the myelin basic protein that surrounds and shields the nerves; the stripping away of this protective layer causes wasting and severe paralysis. Synthetic peptides patterned on portions of receptor molecules that are present on the surfaces of involved T cells were prepared by Howell *et al.*; the receptors on such "encephalitogenic" cells have only limited variability and appear to be shared among and conserved in the T cells that participate in autoimmune disease in a number of different animal models. Immunization with the peptide vaccines prevented subsequent development of EAE. Because this approach targets T cells that contribute to pathology, it may also prove beneficial in providing protection against other diseases in which a restricted set of T cell clones induces pathogenesis. ■ RUTH LEVY GUYER

SCIENCE

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VOLUME 246
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The Cell Cycle

In each of our bodies there are molecular choreographers programming a minuet in which chromosomes appear from obscurity, line up with their partners, separate, rejoin, and then disperse. That minuet is called the cell cycle, and it must proceed according to certain rules and cadences if we are to lead normal lives. In embryonic cells, the cycle must frequently proceed very rapidly, in some adult cells more slowly, and in some neural tissue not at all. If the cycle fails in growing cells, death results. If it goes incorrectly in mature cells, cancer is caused.

The advent of the microscope made it possible to distinguish phases of this cycle such as anaphase, metaphase, and interphase on the basis of morphological changes. Inevitably in modern times the morphological studies have been followed by biochemistry and cell biology to find the molecules that direct and control this vital process. Further categorization followed, based on the time of DNA synthesis, which resulted in the addition of the following phases: G_1 (before DNA synthesis), S (DNA synthesis), G_2 (after DNA synthesis), and M (cell division). The combination of approaches has added greater understanding and complexity to this area of research. This issue of *Science*, assembled under the guidance of Barbara Jasny, describes the state of the art as seen by six leaders in the field.

As explained by Hartwell and Weinert, genetic and biochemical studies indicate two types of control. There is direct control, in which the completion of previous steps is essential to produce the substrate for the subsequent step. The other is indirect in that early steps release inhibitors of late steps and late steps feed back to control early steps. Pardee discusses G_1 in which nucleotide, histone, and enzyme synthesis occur to build up supplies for the S phase. Regulatory molecules can divert G_1 into a quiescent phase (G_0) or stimulate quiescent cells to active cycling. Quiescence can be deleterious if it lasts too long and uncontrolled proliferation can lead to cancer. A critical regulatory event occurs at a restriction or start point in the G_1 phase. If nutrients and control signals are appropriate, the cell passes through this start point and an inexorable chain of events is initiated.

Laskey *et al.* describe the S phase, which can take 10 hours in mature *Drosophila* or less than 4 minutes in the embryonic cells of the same species. Since a single replication fork moving at an observed rate of 3 kilobases per minute would require a month to replicate a human chromosome, synthesis must occur at many foci. This process, which is highly accurate, must therefore involve complex coordination. Not only the linear sequence but also the entire chromatin package must be reproduced with high fidelity.

Contrary to early guesses that major control points for embryonic cell cycles would occur in G_1, a great deal of regulation occurs in G_2 as discussed by O'Farrell *et al.* They have focused on the *string* gene, which appears to act as a mitotic trigger in early *Drosophila* embryogenesis. Murray and Kirschner describe the intricate relations of maturation promoting factor (MPF) and cyclin in the frog embryo. These two molecules seem to have a love-hate relationship in that changes in one can lead to activation or destruction of the other. Both increase and decrease at various stages, appearing as dei ex machina to control progress—but these powerful proteins use such common mechanisms as phosphorylation to accomplish their tasks. The finding that yeast proteins can replace frog proteins indicates high conservation of proteins and great similarity in mechanisms in different organisms.

McIntosh and Koonce describe the M phase in which mitosis occurs. This was the most mysterious part in the premolecular days because chromosomes were lined up and pulled apart by invisible and highly specific forces. This is now becoming explainable in terms of microtubules, spindles, and kinetochores. Both repulsive and attractive forces are needed to develop the reproducibility and specificity required.

The early microscope studies revealed an almost unbelievable event in which chromosomes were held in a meticulous alignment by unseen forces that appeared to arise spontaneously. Today we are a long way along the path of explaining those pictures in molecular terms. The molecules seem to be ordinary garden variety enzymes and receptors, but the cleverness of their feedback and feedforward relationships is as intellectually pleasing as the early microscopic pictures. Thus the molecular discoveries explain, but in no way diminish, the awe of the reader at the sophistication of the processes leading to the cell cycle.—DANIEL E. KOSHLAND, JR.

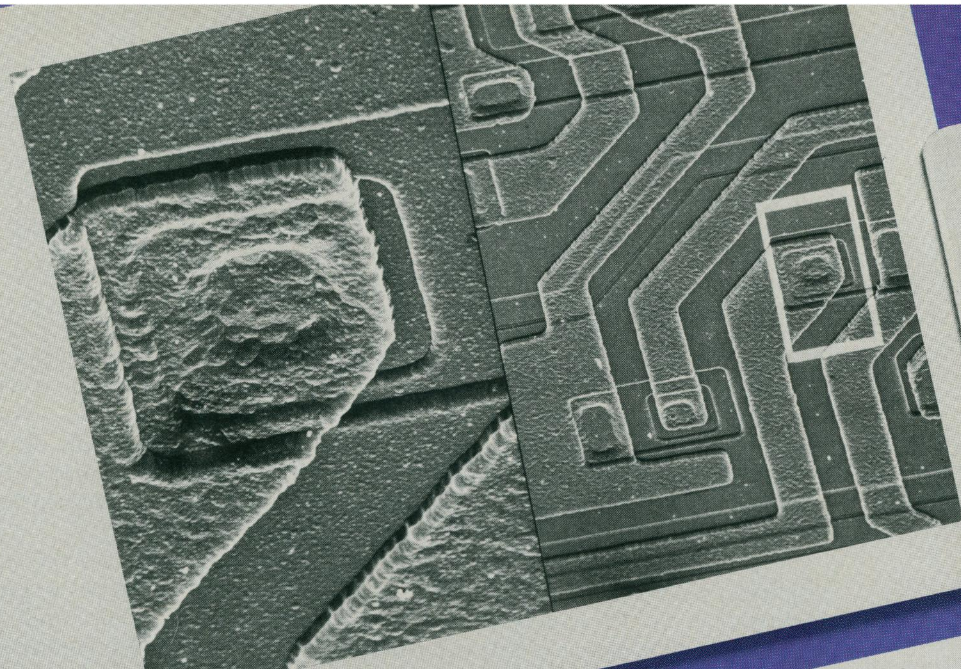


Fig. 1

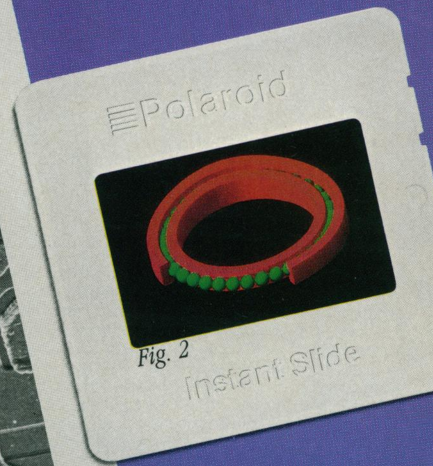


Fig. 2

Alex Zinkosky

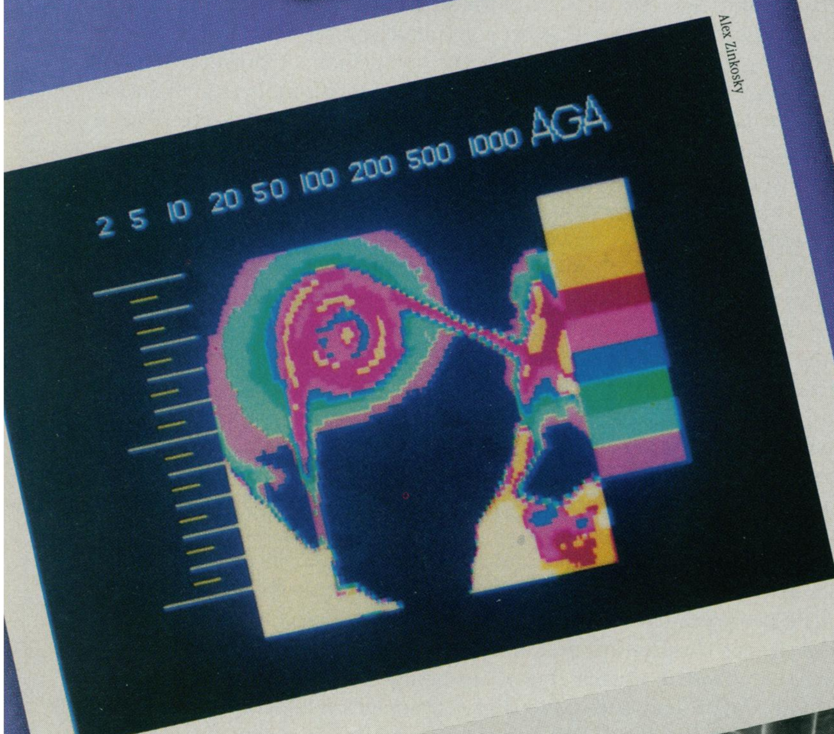


Fig. 3

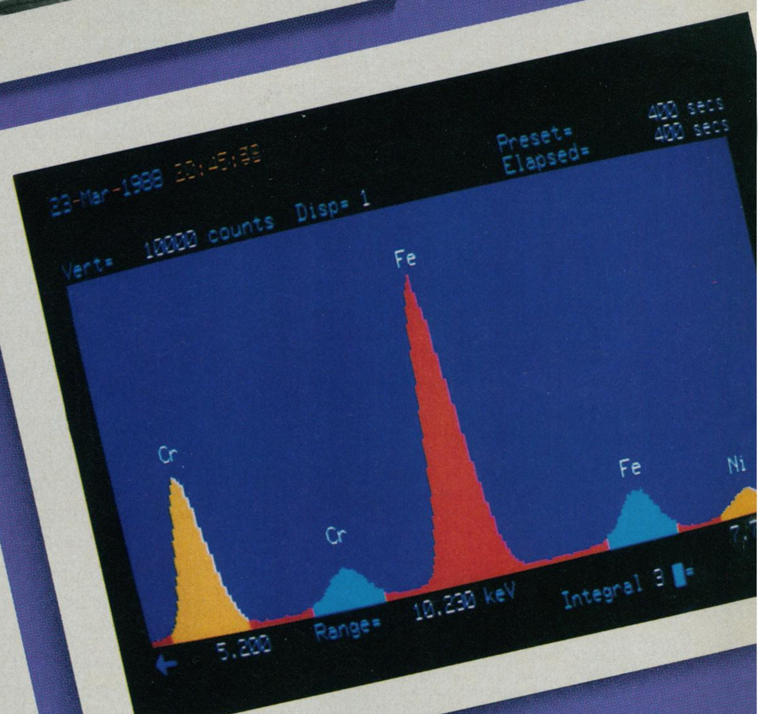
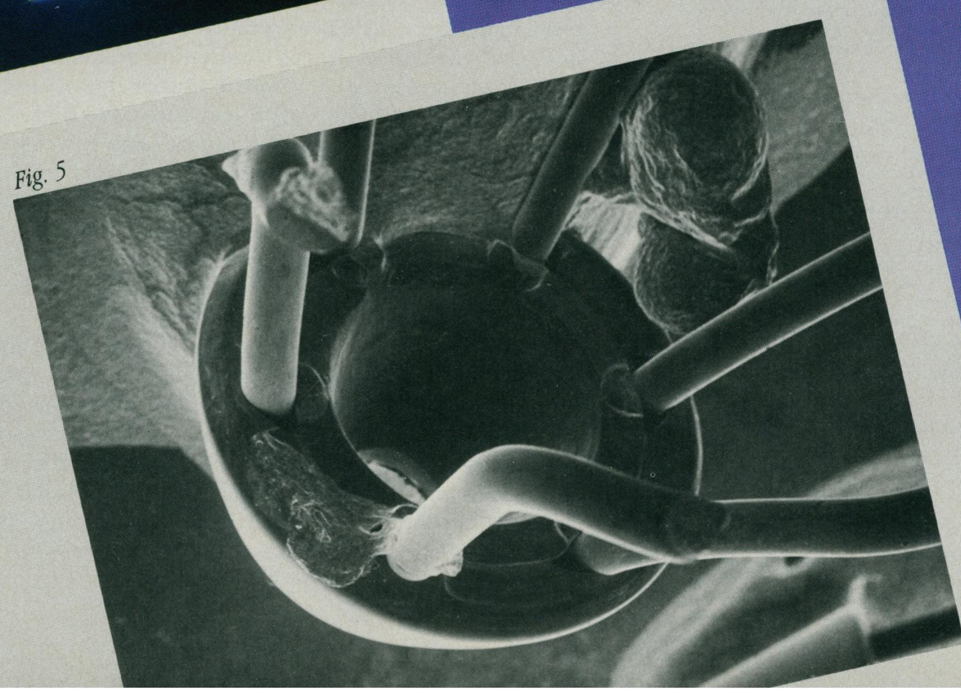


Fig. 4

Fig. 5



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Announcement and official presentation of the award will take place at the 1990 annual meeting of the SOT in Miami, Florida. Funding may commence at that time, or no later than September 1, 1990.

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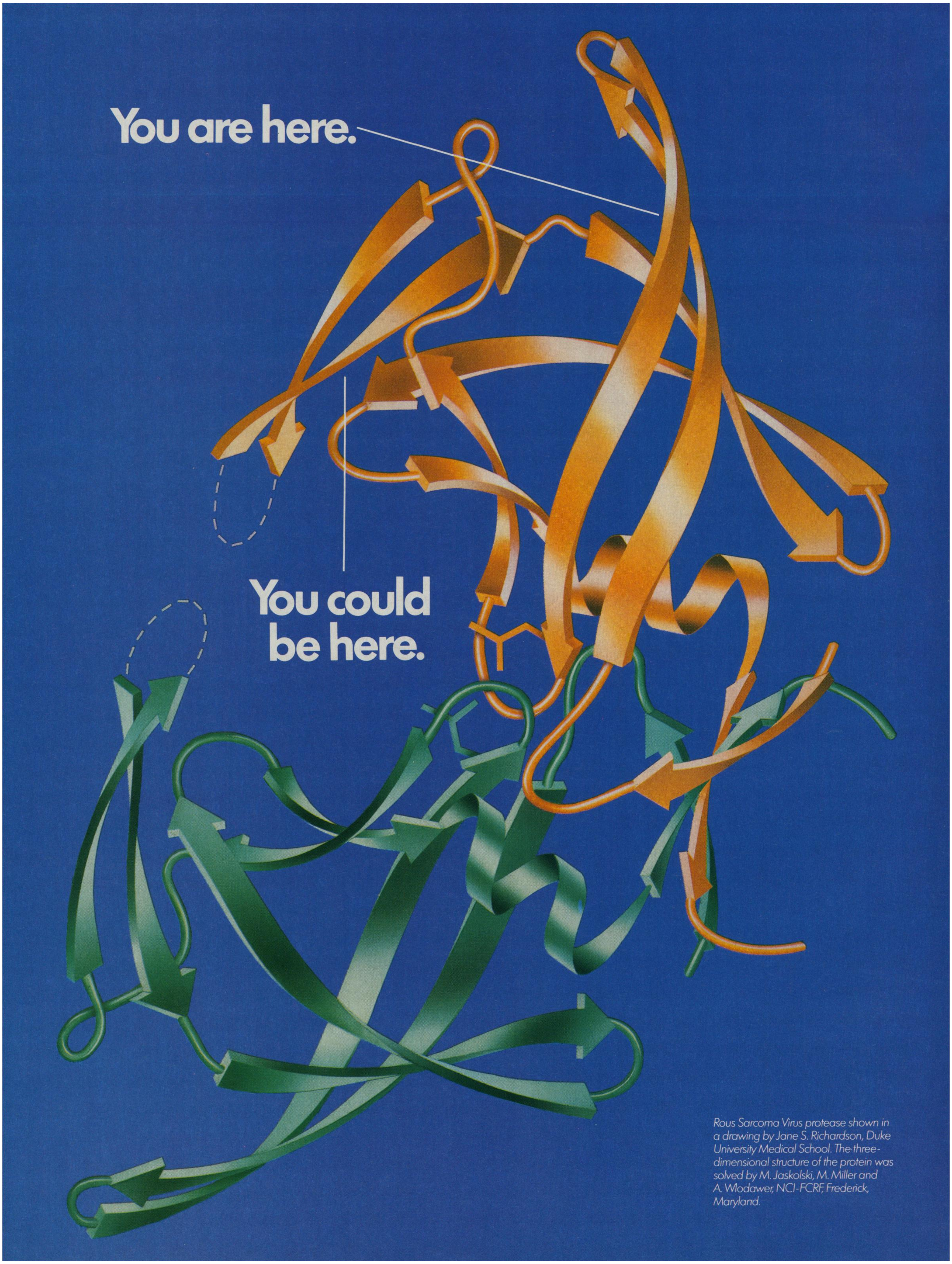

Rous Sarcoma Virus protease shown in a drawing by Jane S. Richardson, Duke University Medical School. The three-dimensional structure of the protein was solved by M. Jaskolski, M. Miller and A. Wlodawer, NCI-FCRF, Frederick, Maryland.

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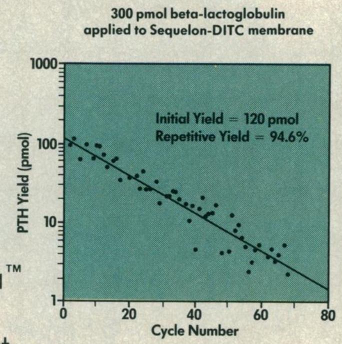

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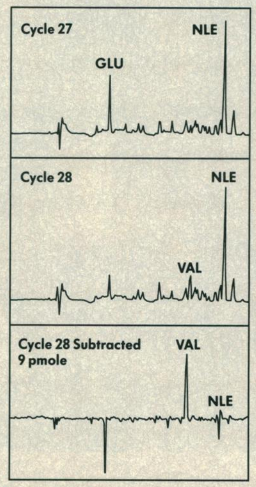

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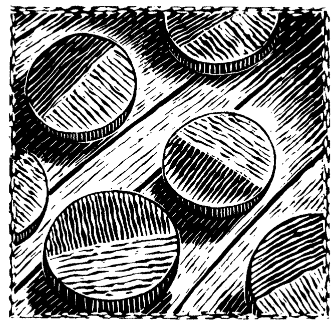

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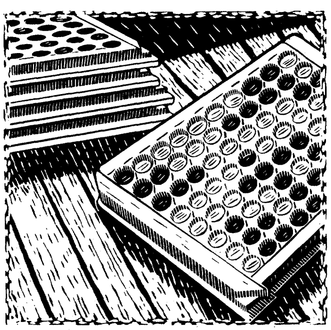

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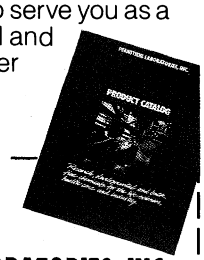

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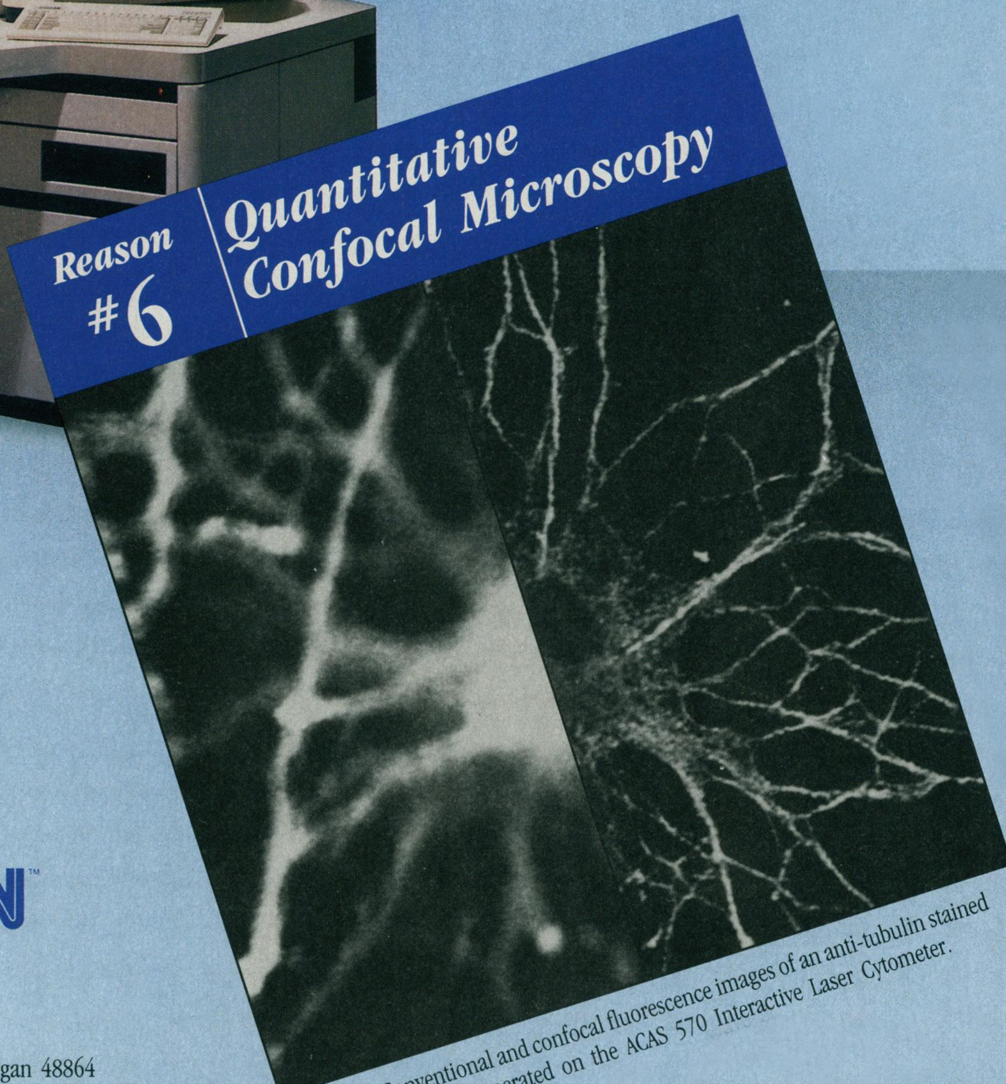

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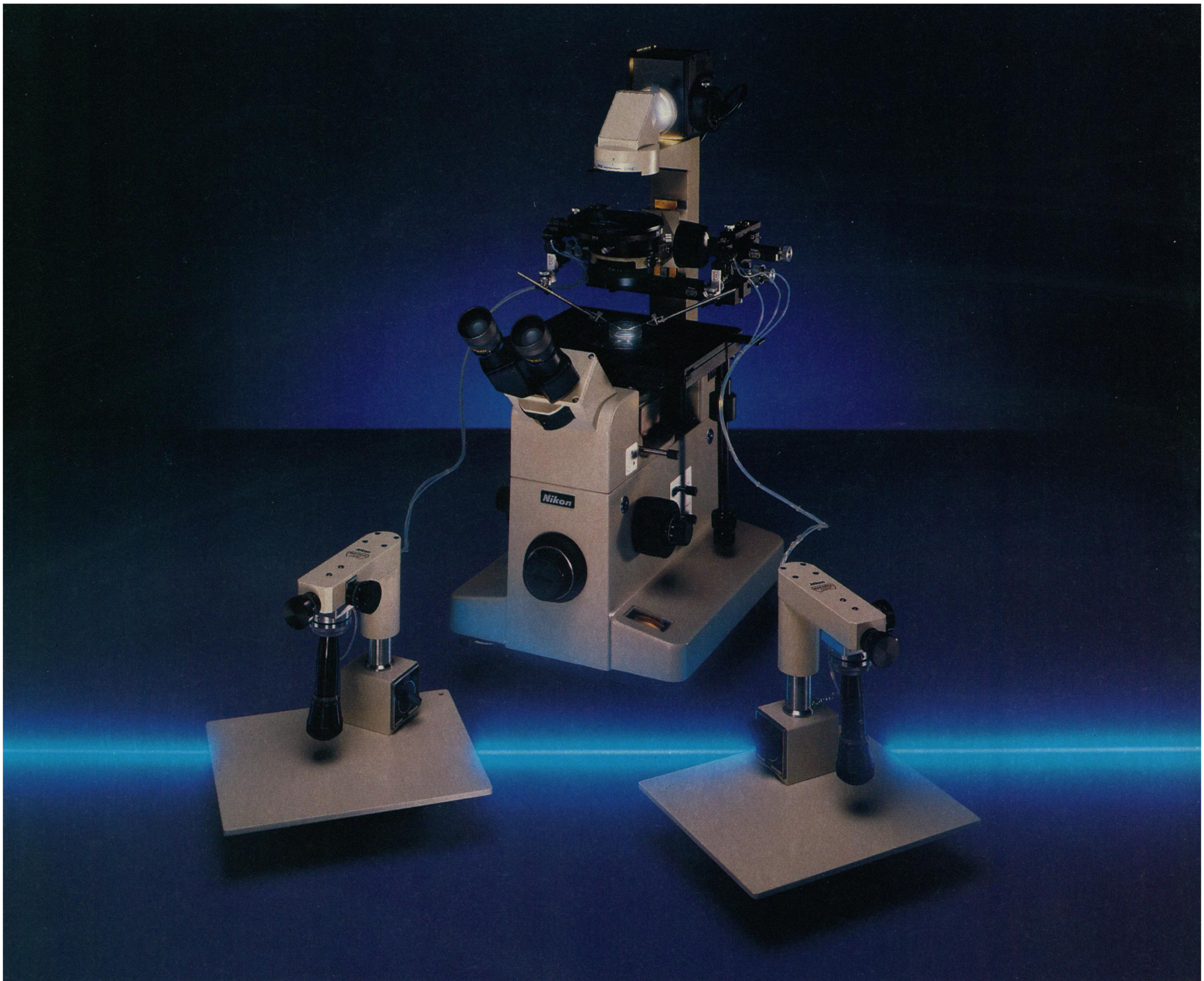

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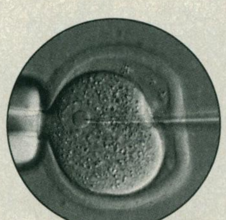

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at the congressional hearing (2) that the MIT "inquiry went forward in conformance with our policy of investigating suspicion of fraud, even though Dr. O'Toole chose not to characterize her concerns as [fraud]." The statements of Eisen and of Deutch cannot both be true.

MARGOT O'TOOLE
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2. J. Deutch, statement before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce, U.S. House of Representatives, 9 May 1989.

Oil Spill Health Effects

Marcia Barinaga's article "Alaskan oil spill: Health risks uncovered" (News & Comment, 4 Aug., p. 463) captured the flavor of the Conference on the Alaskan Crude Oil Spill and Human Health very well.

A matter that could cause some misunderstanding, however, is the misstatement in the middle of the article labeled "the good news," that the highly toxic polycyclic aromatic compounds "evaporated from the spilled oil within several days." The lightest fractions of the oil, the single ring compounds that are of most concern for inhalation exposures, did evaporate rapidly. The polycyclic aromatic hydrocarbons, on the other hand, tend to concentrate in the weathered oil and may be of significant long-term concern for health, since we know that some of these compounds are hazardous and some are associated with cancer.

DAVID P. RALL
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Management at DOE

Readers of the article by Mark Crawford about Robert O. Hunter (News & Comment, 15 Sept., p. 1182) may obtain the impression that Hunter is a man of vision who is meeting opposition from a stodgy bureaucracy. The article quotes Hunter as saying that his "most ambitious activity" is "to maintain the flow of new ideas and . . . the quality of research." The impression one gains from the article and from the quote, however, is inconsistent with my experience.

Like Hunter, I came to Washington "just over a year ago." Unlike Hunter, I came, not to "head the Department of Energy's [DOE] $1.7-billion" Office of Energy Research, but to work in the "tiny geophysical research program" referred to in the article. The Geosciences Program is part of the Office of Basic Energy Sciences (OBES) within the Office of Energy Research. The program has an annual budget of about $18 million and supports the basic geoscience research of about 90 investigators at eight national labs and 70 investigators at almost 40 universities. Research grants are given on the basis of a peer-review system similar to that used at the National Science Foundation. The Geosciences Program office consists of one DOE employee, a portion of a secretary, a rotator from academia, and a detailee from one of the national labs—the position I have occupied on a half-time basis for the past 15 months. Thanks to Hunter, it has been a most exciting year—exciting, exasperating, but mostly, frustrating.

One particularly frustrating task was to help my colleagues decide how to take back

$3.5 million committed to research tasks already in progress in fiscal year 1989. This was the amount that Hunter required us to commit to his initiative in High Resolution Underground Imaging Using Acoustic Means in fiscal year 1989, and he wanted this initiative to grow to $10 million in fiscal year 1990, with no additional funding available. The Geosciences Program staff responded by pointing out that (i) it was already supporting underground imaging with approximately 20% of its total budget; (ii) the projects supported had been judged most competitive by scientific peer review; and (iii) his last-minute requirement would have an adverse impact on important research already committed to. Hunter's reply, impersonally transmitted down the DOE chain of command, ignored the points above and made the general statement that "orders of magnitude improvement in resolution" could be achieved by adopting advances developed by the antisubmarine warfare (ASW) community. This statement was thoroughly investigated by the Geosciences Program staff in a series of consultations with representatives of the ASW, seismology, and electromagnetic sounding communities and found to have no basis. Hunter would not meet with us or them to discuss the technical merits of his proposed initiative and simply insisted that we do as he asked. That may be "high energy management," but it is not the scientific leadership that the nation and DOE need, in my opinion.

As a result of the Hunter-imposed initiative, we have funded additional imaging work, most of it along lines already supported and none of it claiming to achieve "orders of magnitude improvement in resolution." Underground imaging–related research now makes up about 40% of our total budget and will be much larger in fiscal year 1990 if Hunter's recommendations are followed. The underground imaging program that "received positive review" by the JASONs was already in place before the Hunter-imposed initiative. I do not know whence Hunter's vision of dramatic improvements in resolution in underground imaging. I do know that it is not consistent with the best advice available from experts in the field.

In summary, I feel that Hunter's directive significantly underestimated the contrasting nature of energy transmission in the earth and oceans and, perhaps more important, underestimated the ability of solid-earth scientists to effectively cross discipline boundaries and bring new and relevant technologies to bear on their research. The situation was further confounded by Hunter's treating genuine technical misgivings about the initiative, relayed by his subordinates, as the stalling tactics of a stodgy bureaucracy. In the final analysis, I believe the productive research programs of scores of scientists have been threatened by a technically flawed, poorly defined initiative.

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Erratum: In the article by B. F. Chmelka and A. Pines, "Some developments in nuclear magnetic resonance in solids" (6 Oct., p. 71), several references were transposed. Figure 1 was adapted from (*6*) [C. A. Fyfe *et al.*, *J. Am. Chem. Soc.* **110**, 3373 (1988)], not (*10*) and (*14*), as printed. Figure 2 was adapted from (7) [H. B. Cole, S. W. Sparks, D. A. Torchia, in preparation], not (*11*), as printed. The reference, to rotational resonance (p. 74, col. 2, line 22) should have been (*10*) [D. P. Raleigh *et al.*, *J. Am. Chem. Soc.*, in press], not (7), as printed. The authors in reference (*55*) should have been D. R. Nelson and F. Spaepen.

Erratum: In the Briefings section of 22 September (p. 1332), the credit for the x-ray image of the sun should have included Eberhard Spiller of IBM's Watson Research Center.

Erratum: In Eliot Marshall's News & Comment article "Old bones solve new problems" (15 Sept., p. 1185), the term "pubic symphysis" was misspelled in the third sentence of the sixth paragraph.

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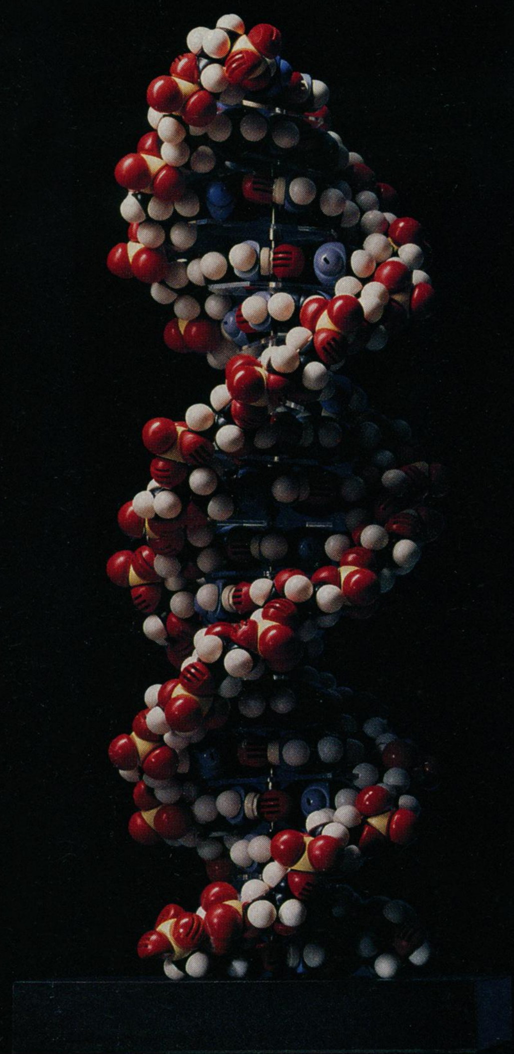

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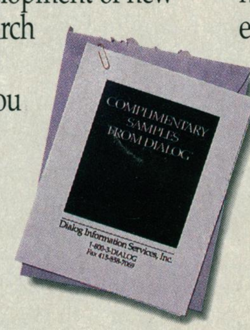

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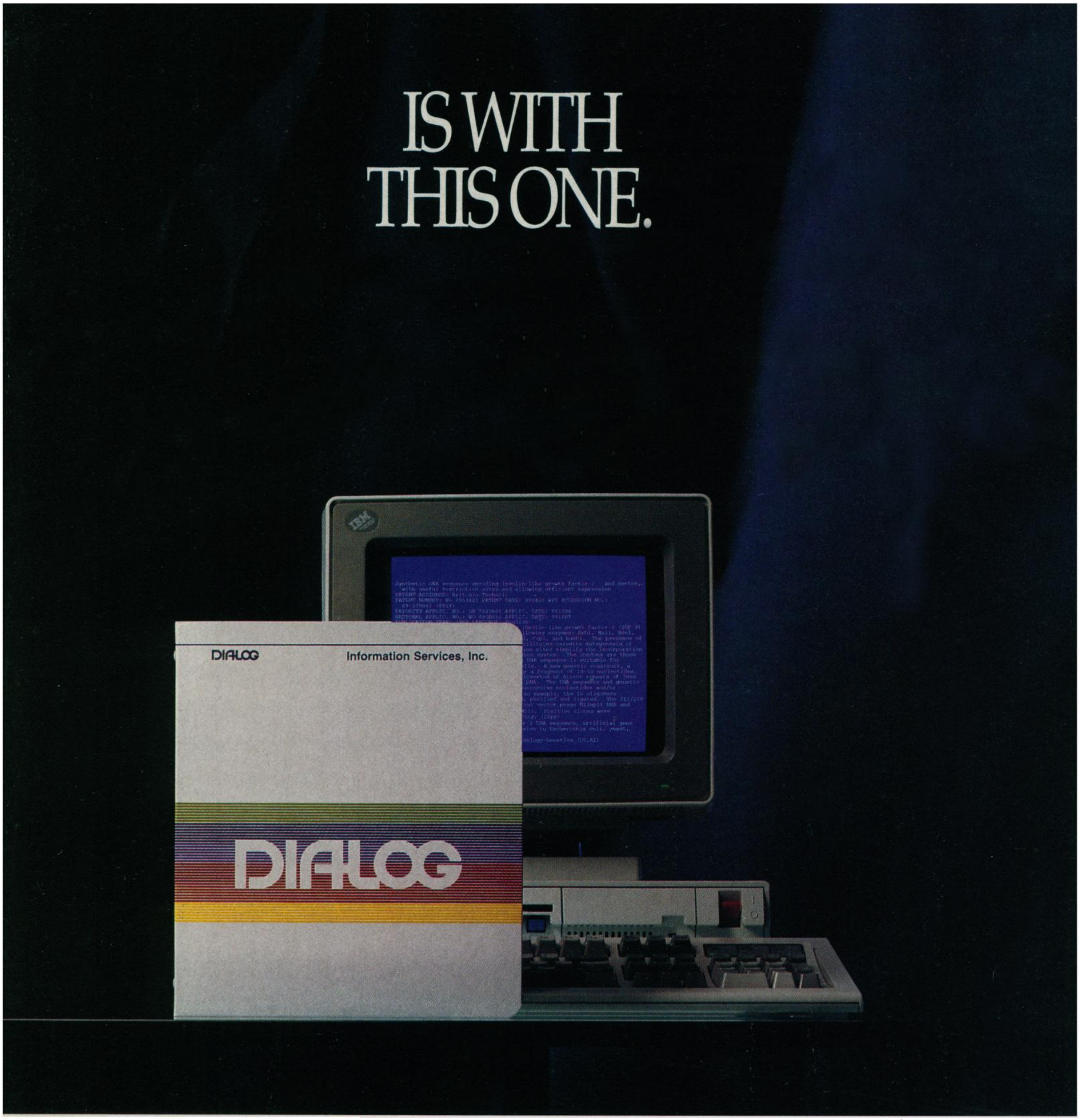

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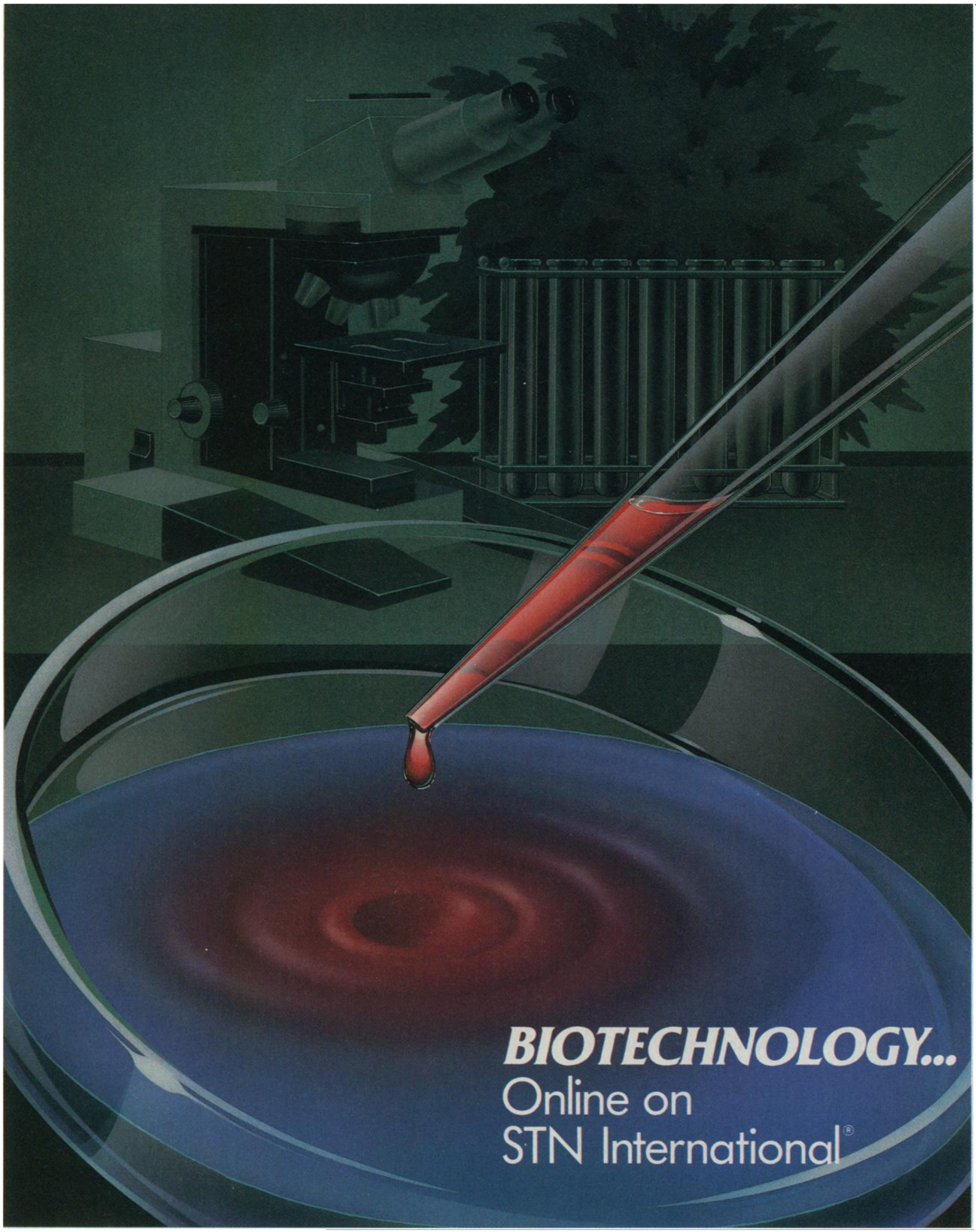
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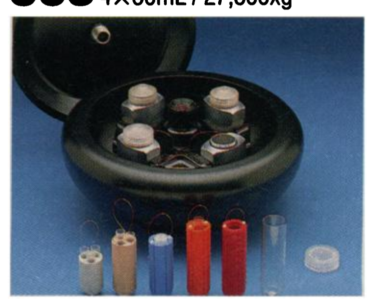

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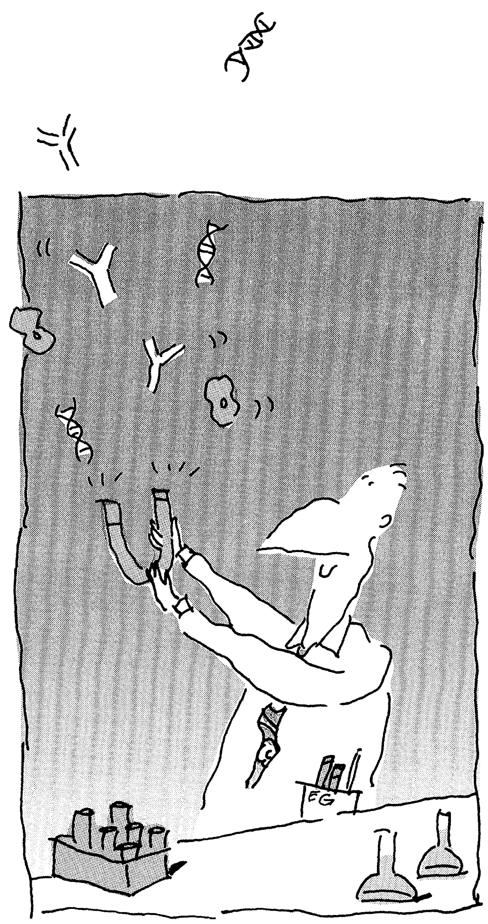

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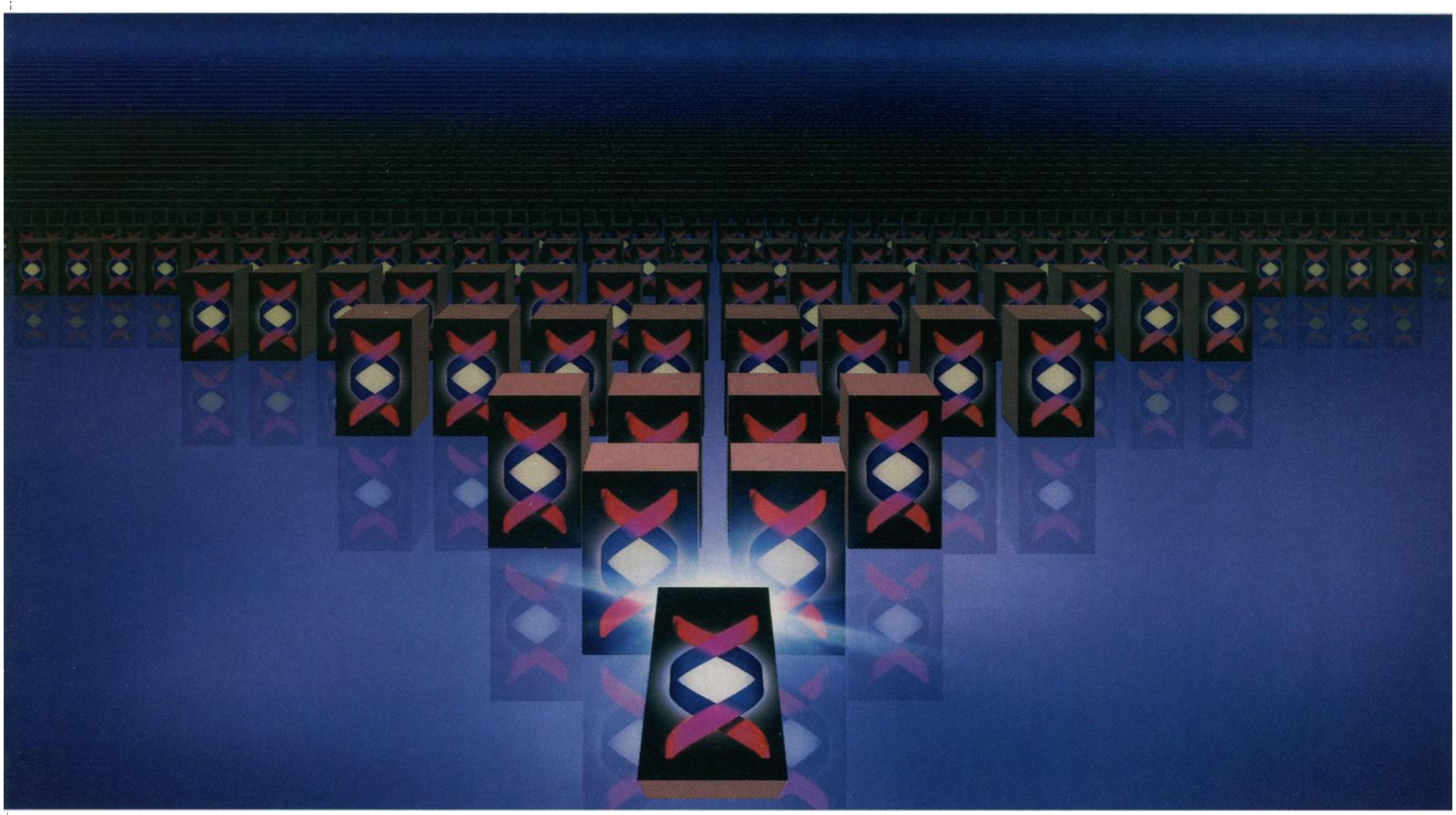

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The final section of the book contains Fuster's arguments that the prefrontal cortex has "a cardinal function . . . in the temporal order of behavior, consisting of and supported by three subordinate functions: provisional memory, anticipatory set, and control of interference." This idea arises from many experiments, starting with those of Jacobson in the 1930s demonstrating that the prefrontal cortex is necessary for the performance of delayed response tasks by nonhuman primates. Physiological experiments, especially those of Fuster and his group, have established that neurons in the prefrontal cortex have properties consistent with the necessary components for performing these tasks. The theory is not unreasonable, but Fuster does little to flesh it out, instead resorting to generalizations such as "the activated neural ensemble constitutes a giant associative network representing the stimulus in all its cognitive aspects and relationships."

Nonetheless, the book is valuable, precisely because it collects in one place the literature about the prefrontal cortex and illustrates by its very failures the sort of problems awaiting one who would tackle the topic. It may be unsatisfying, but, because of the diffuse and difficult nature of the field today, it is the best book we have.

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Some Other Books of Interest

Biology and Conservation of the River Dolphins. W. F. PERRIN, R. L. BROWNELL, JR., ZHOU KAIYA, AND LIU JIANKANG, Eds. International Union for the Conservation of Nature, Cambridge, U.K., 1989. vii, 173 pp., illus. Paper, $25. IUCN Species Survival Commission Occasional Paper no. 3. From a workshop, Wuhan, China, Oct. 1986.

Handbook of Marine Mammals. Vol. 4, River Dolphins and Larger Toothed Whales. SAM H. RIDGWAY AND RICHARD HARRISON, Eds. Academic Press, San Diego, CA, 1989. xx, 442 pp., illus. $99.50.

The river dolphins, Platanistidae, are "in trouble around the world" and "are the most endangered of all cetaceans," according to the editors of these two volumes. In 1986 the International Union for the Conservation of Nature sponsored a workshop in Wuhan, China, to inaugurate a campaign for their preservation, an event to which these books owe their content in whole or in part.

The proceedings volume consists of a general Report of the Workshop and revised versions of 24 of the 38 "working papers"