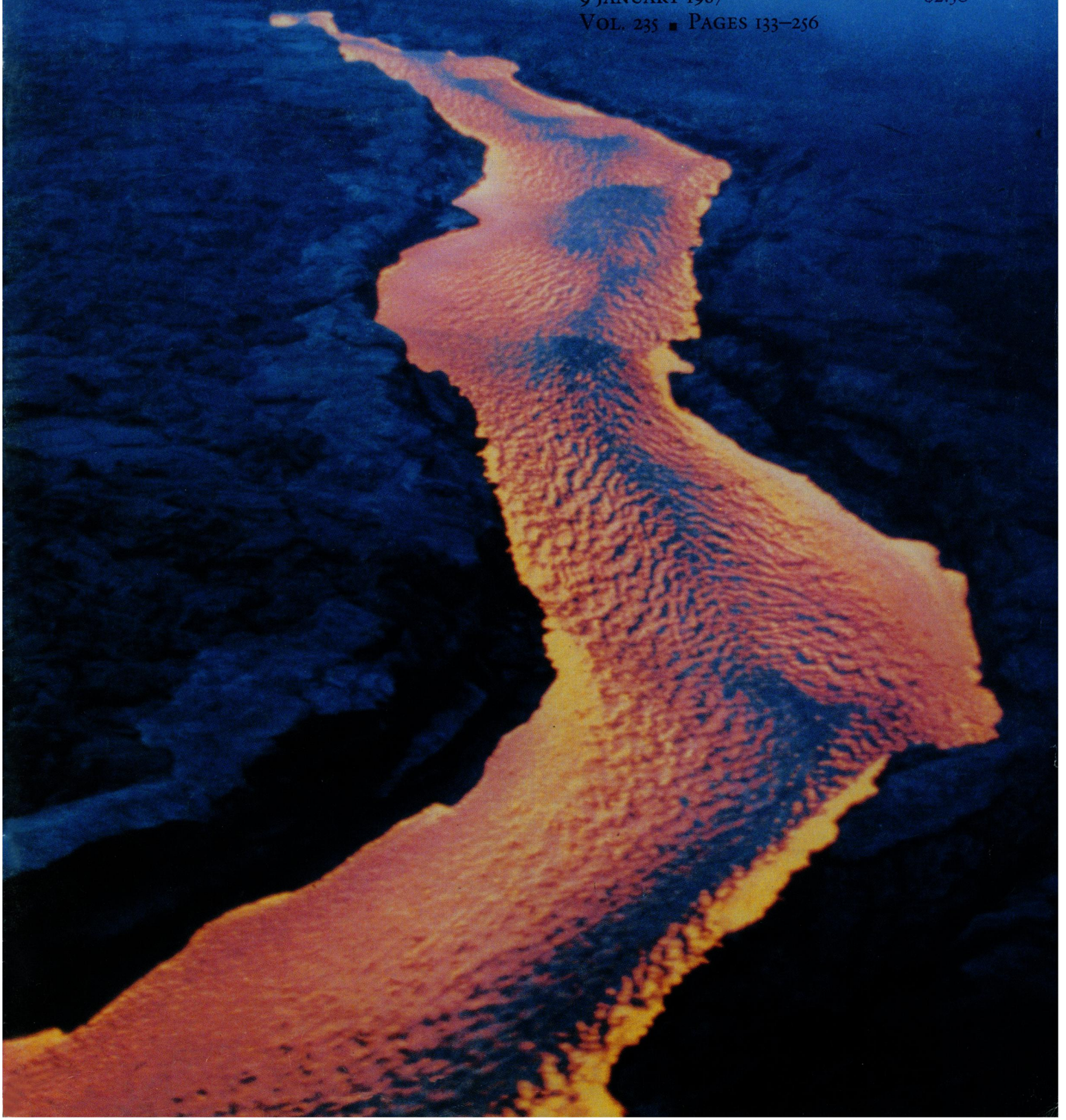
American Association for the Advancement of Science

SCIENCE

9 JANUARY 1987 $2.50
VOL. 235 ■ PAGES 133–256



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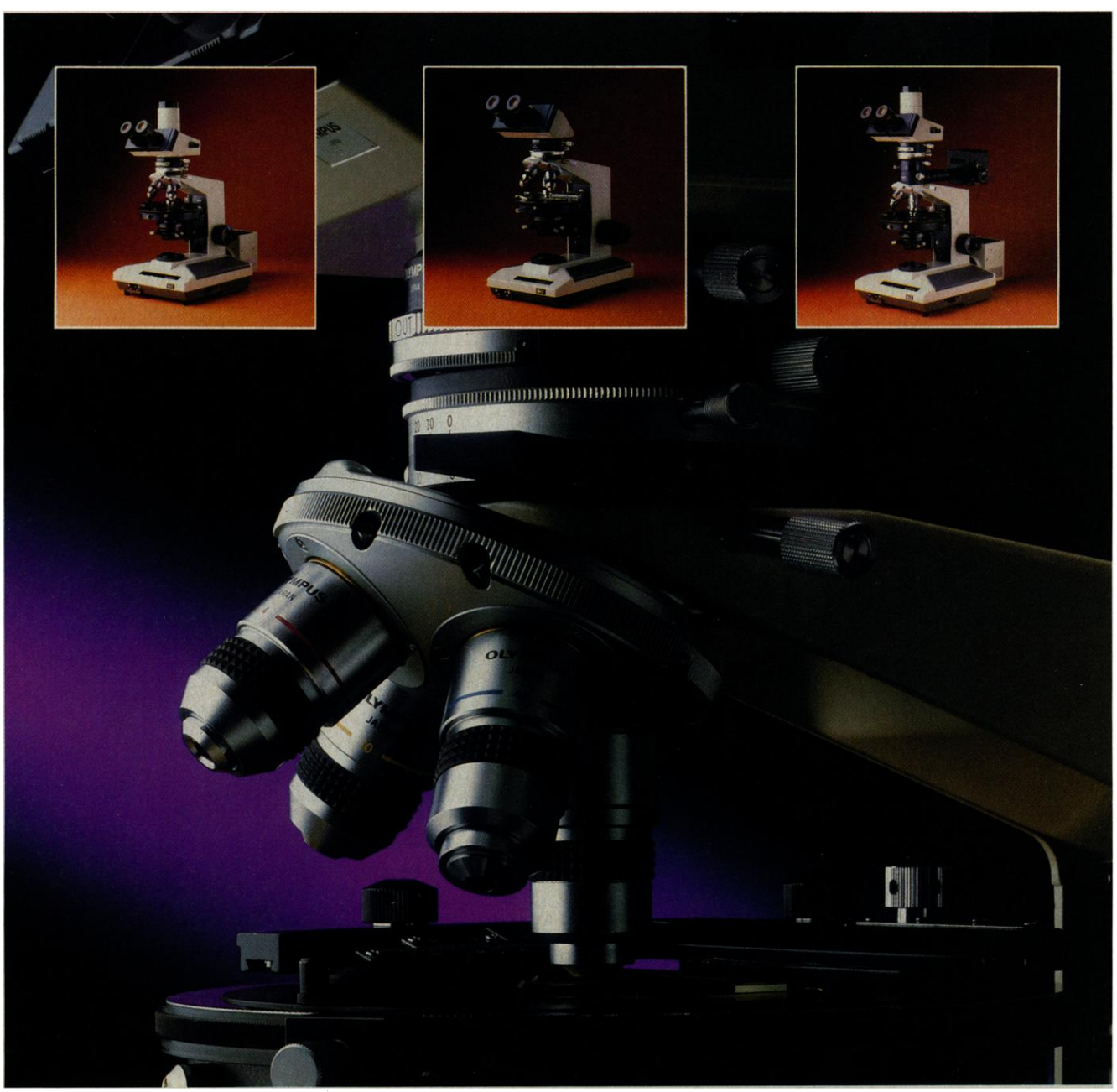

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

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NUMBER 4785

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COVER Lava flow after eruption of Mauna Loa Volcano, March 1984. Lava flows advanced nearly 20 kilometers in about 5 days toward the city of Hilo, largest city on the island of Hawaii. The flow slowed and stopped about 8 kilometers from nearest buildings on city's outskirts. All eruptive activity ceased by early April 1984. See page 196. [Scott Lopez, National Park Service]

Reports

Book Reviews

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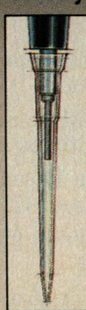

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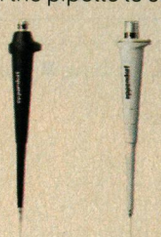

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Oncogene amplification and cancer prognosis

In cells of primary human breast cancers, the oncogene HER-2/*neu* may be amplified; Slamon *et al.* have found that when it is, relapse occurs more rapidly and patients have shorter overall survivals (page 177). HER-2/*neu* thus may be a significant factor in breast cancer pathogenesis. Patients who had five or more copies of the gene had the poorest prognoses. The oncogene, situated on human chromosome 17, codes for a protein of 185,000 daltons that is thought to be a cellular receptor because of its similarity to the epidermal growth factor receptor; what it "receives" or binds is currently unknown. A correlation was found between gene amplification and the presence of more than three cancer-positive axillary lymph nodes in patients. Multiple copies of HER-2/*neu* were present in 15% of human primary breast cancer cells and in 40% of cells from patients known to have positive nodes. This marker and the number of positive nodes are the two most accurate indicators known for predicting whether patients with primary breast cancers will have rapid relapses or a disease-free future. Kolata discusses use of oncogenes in cancer diagnosis and prognosis (page 160).

Mengo virus structure

The three-dimensional structure of the Mengo virus has been determined from crystallographic studies that include use of a similar virus as a model, protein sequence data, and molecular replacement techniques (page 182). Luo *et al.* describe the structure of the Mengo virus and relate structure to properties of the virus. The Mengo virus, like the rhinoviruses and the poliovirus, is a picornavirus; its genetic material, single-stranded RNA, is enclosed in a spherical shell. In mice, Mengo viruses can cause fatal encephalitis. Four proteins (VP1, VP2, VP3, and VP4) make up the coat of the Mengo virus; compared with VP proteins of other picornaviruses, those of the Mengo virus differ in the positioning of VP4 (it is more internal and more extensively exposed to RNA) and in a number of insertions and deletions. Picornaviruses invade host cells by binding to host surface receptors; binding sites on the Mengo virus may be in deep surface pits, which may be shielded from host antibodies that could otherwise block the binding process. Differences in surface features of Mengo viruses and rhinoviruses appear to account for the ability of new antiviral compounds, called WIN compounds, to be effective against rhinoviruses but not against the Mengo viruses. On the basis of their similar three-dimensional structures, the various picornaviruses and some plant viruses may have evolved from common ancestral viruses.

Fish get good vibes from prey

A number of fish and amphibians have lateral line sensory systems—consisting of end organs and nerves running down the side of the body—that are activated by water movements (page 195). Such systems help in the detection of prey and stationary objects and in the coordination of travel in schools. Montgomery and Macdonald show that the lateral line system of the Antarctic fish *Pagothenia borchgrevinki* is responsive to vibrations at the same high frequency as vibrations produced by some prey at close range: three crustacean species that this fish regularly eats produced their strongest vibrations at frequencies between 30 and 40 hertz; vibrations at 40 hertz generated by a vibrating sphere that was suspended near test fish in a tank most strongly stimulated individual neurons in the lateral line. When fish and crustaceans were put in the aquarium together, the prey's vibrations directly induced responses in the fishes' lateral line systems. For fish that spend long periods in the darkness of the polar winter and cannot, therefore, rely on vision for finding food even at close range, the lateral line may be a crucial system for ensuring survival.

G protein and K^+ channels

A purified G protein, named G_k, isolated from human red blood cells, interacts directly and not through intermediaries with potassium (K^+) channel proteins in heart cells; as a result of such interaction, K^+ channels are activated (page 207). Yatani *et al.* measured currents generated in single K^+ channels in dispersed atrial cells from guinea pig hearts. The channels control heart rate; the vagus nerve releases acetylcholine, which stimulates muscarinic acetylcholine-sensitive receptors on atrial cells, G proteins carry the signal to the channel protein to activate it, and heart rate is thereby regulated. G proteins that regulate channel proteins are likely to be found in other cell types besides heart cells.

Lung cancer from "smoky" coal in China

Women in China's Xuan Wei County who heat their homes and cook their meals with "smoky" coal have an unusually high incidence of lung cancer (page 217). Less than 0.1% of these women smoke cigarettes. Collaborative studies by Chinese and United States researchers, reported by Mumford *et al.*, show that the air in homes in which "smoky" coal is burned contains enormous numbers of tiny organic carcinogenic particles that remain airborne for a long time and can eventually lodge in the residents' lungs; concentrations of one known carcinogen—benzo[*a*]pyrene—were comparable to those found in coke oven plants. Wood, a fuel burned in some homes, also generates large numbers of particulates, but in biological tests they have lower mutagenicity and the particles are larger (and settle out of the air faster) than those generated by "smoky" coal. The third fuel, "smokeless" coal, generates the lowest concentration of pollutants. Lung cancer incidence is higher among the women who spend their time indoors than among the men, most of whom are farmers and spend the day outside.

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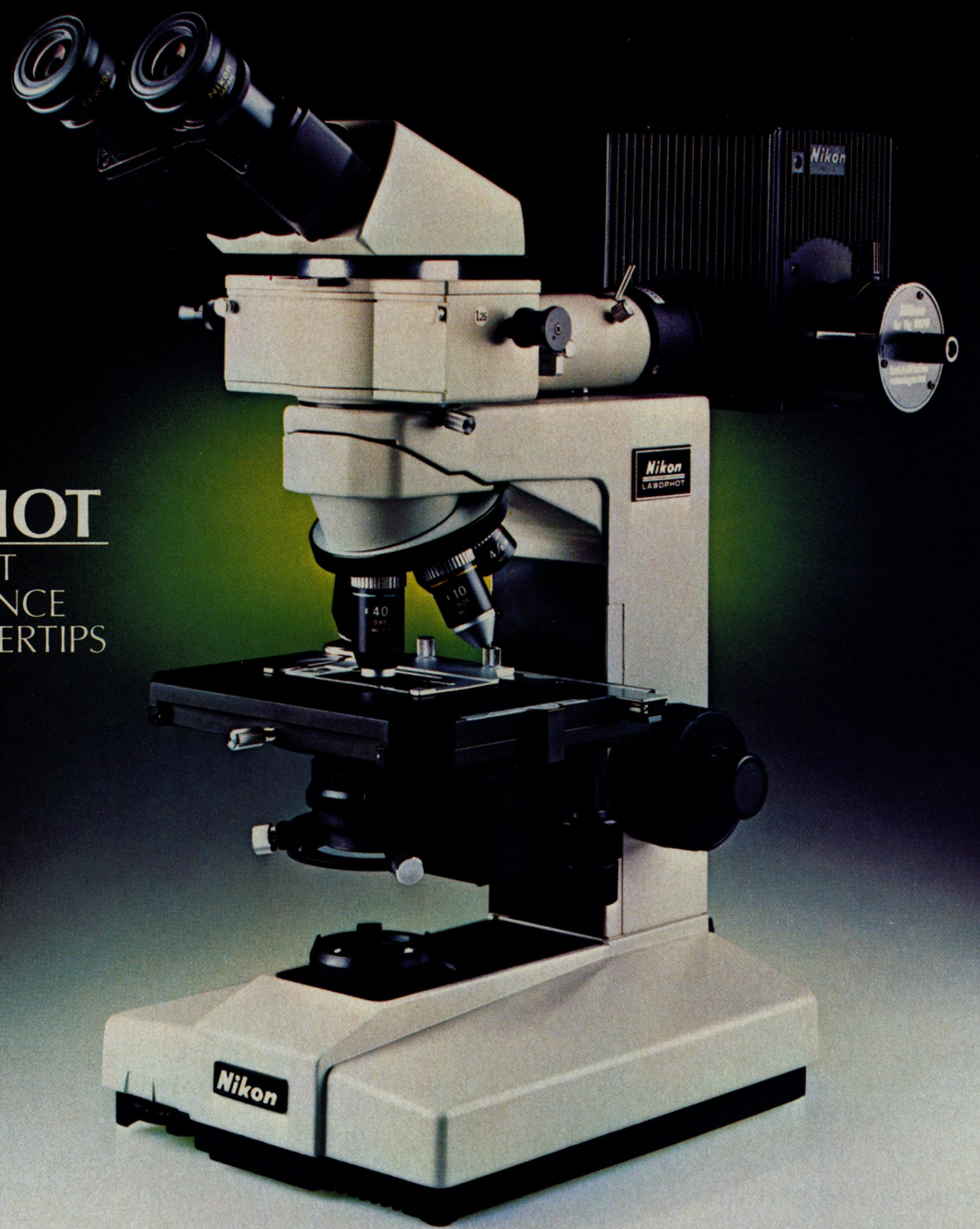

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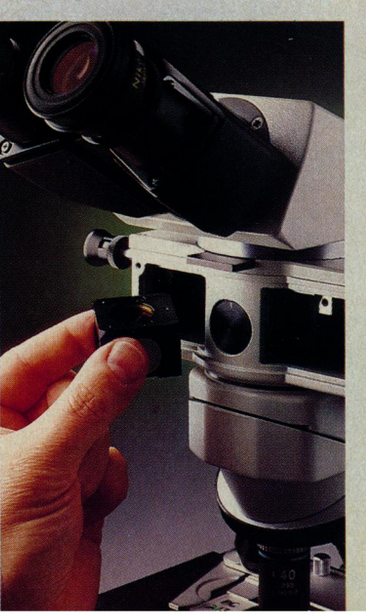

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SCIENCE

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NUMBER 4785

Fraud in Science

Fraud in scientific research is unacceptable and inevitable. It is unacceptable because the entire procedure of publishing and advancing knowledge is based on trust—that the literature reports accurate measurements of actual experiments. If each researcher had to go back and repeat the literature, the enormously productive rush of modern science would slow to a snail's pace. Even good intentions are not enough. Sloppy experimentation and poor scholarship are condemned. Outright fraud is intolerable.

Nevertheless, some fraud will exist as long as human beings are doing the experiments. Any system in which advancement, fame, and fortune await a successful practitioner will tempt a certain number of individuals to cut corners. That number may well be smaller in science than in other fields, not because scientists are more moral than others, but because the cumulative nature of science means inevitable exposure, usually in a rather short time.

An oversimplified admonition might be, "You may escape detection by falsifying an insignificant finding, but there will be no reward. You may falsify an important finding, but then it will surely form the basis for subsequent experiments and become exposed." Therefore, there is little percentage in falsifying science, and the speed with which recent examples of this unfortunate human frailty have been revealed is an indication of the pace of modern science. Some newspaper reporters have used recent fraud cases to imply that the structure of science is crumbling or that there is a cover-up, forgetting that the extent of the scientific enterprise has grown a thousandfold since the 1800s. We would expect a greater number of cases of fraud today, but there is no evidence of an increased percentage. And there is no modern equivalent of Piltdown man, a fraud that took years to uncover. Still, it is important that scientists be ever vigilant, and the rash of recent frauds does suggest some dangers in modern science.

One danger arises from the nature of interdisciplinary research. Many papers have numerous authors: investigators in a laboratory that has cloning expertise collaborate with others in a laboratory that has expertise in physical instrumentation and another laboratory that does animal tests to publish a joint paper. The results of this kind of collaboration have had spectacular success, in the main, and no one would wish to limit such joint efforts. Yet when no one person has expertise in all aspects of the research, there can be dangers. A second problem arises when busy scientists, who have too many projects and too little time, supervise projects in which they have infrequent contact with those doing the experiments. Finally, the competitive world of modern science fosters some entrepreneurs who are so intent on the next grant or the big success that they forget that every good experimenter must be his own devil's advocate. A principal investigator must not only devise critical tests for his findings, but must also generate an atmosphere that encourages co-workers to report the bad news as well as the good news.

The procedures recently established by the National Institutes of Health and various universities to deal with fraud seem admirable and appropriate. The punishments for offenders are severe: usually, total derailment of a career. Because the repercussions associated with fraud are so serious, some investigations of such charges take long periods of time, but fairness to the accused is essential. Once guilt is ascertained, the loss of a career in science seems appropriate in many cases. Restitution in some form for the wasted time of those who based further experiments on the false report might be considered appropriate as well. The larger the group, the more interdisciplinary the research, the more competitive the area, the more is the need for watchful skepticism.

Having acknowledged that, we must recognize that 99.9999 percent of reports are accurate and truthful, often in rapidly advancing frontiers where data are hard to collect. There is no evidence that the small number of cases that have surfaced require a fundamental change in procedures that have produced so much good science. To continue the great advances that are being made, we must accept that perfect behavior is a desirable but unattainable goal. Vigilance? Yes. Timidity? No.—DANIEL E. KOSHLAND, JR.

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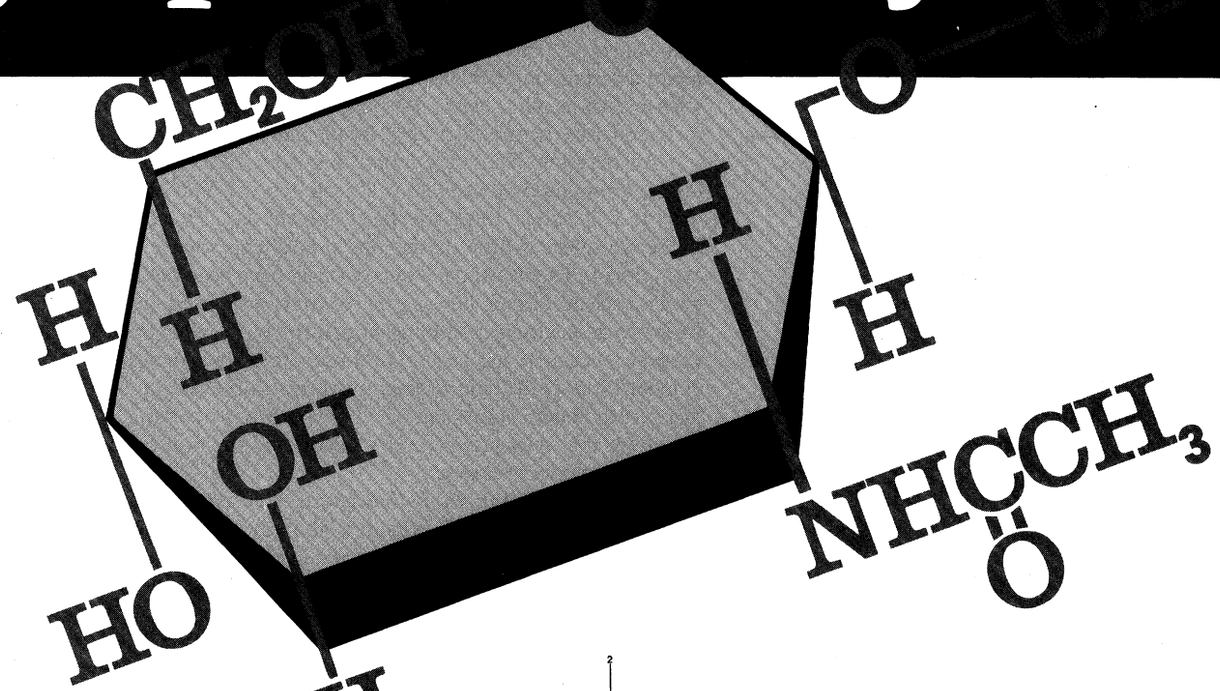
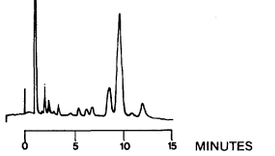


MANNOSIDE HEXAMERS FROM PATHOLOGIOCAL URINE

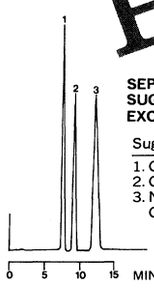
Sample: (Mannose)$_5$-N-acetyl-Glucosamine



SEPARATION OF AMINO SUGARS BY ANION EXCHANGE

Sugar

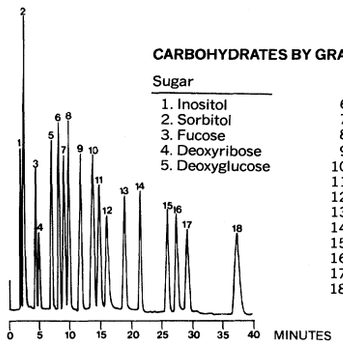
1. Galactosamine
2. Glucosamine
3. N-Acetyl Galactosamine



CARBOHYDRATES BY GRADIENT ELUTION

Sugar

1. Inositol
2. Sorbitol
3. Fucose
4. Deoxyribose
5. Deoxyglucose
6. Arabinose
7. Rhamnose
8. Galactose
9. Glucose
10. Xylose
11. Mannose
12. Fructose
13. Melibiose
14. Isomaltose
15. Gentiobiose
16. Cellobiose
17. Turanose
18. Maltose



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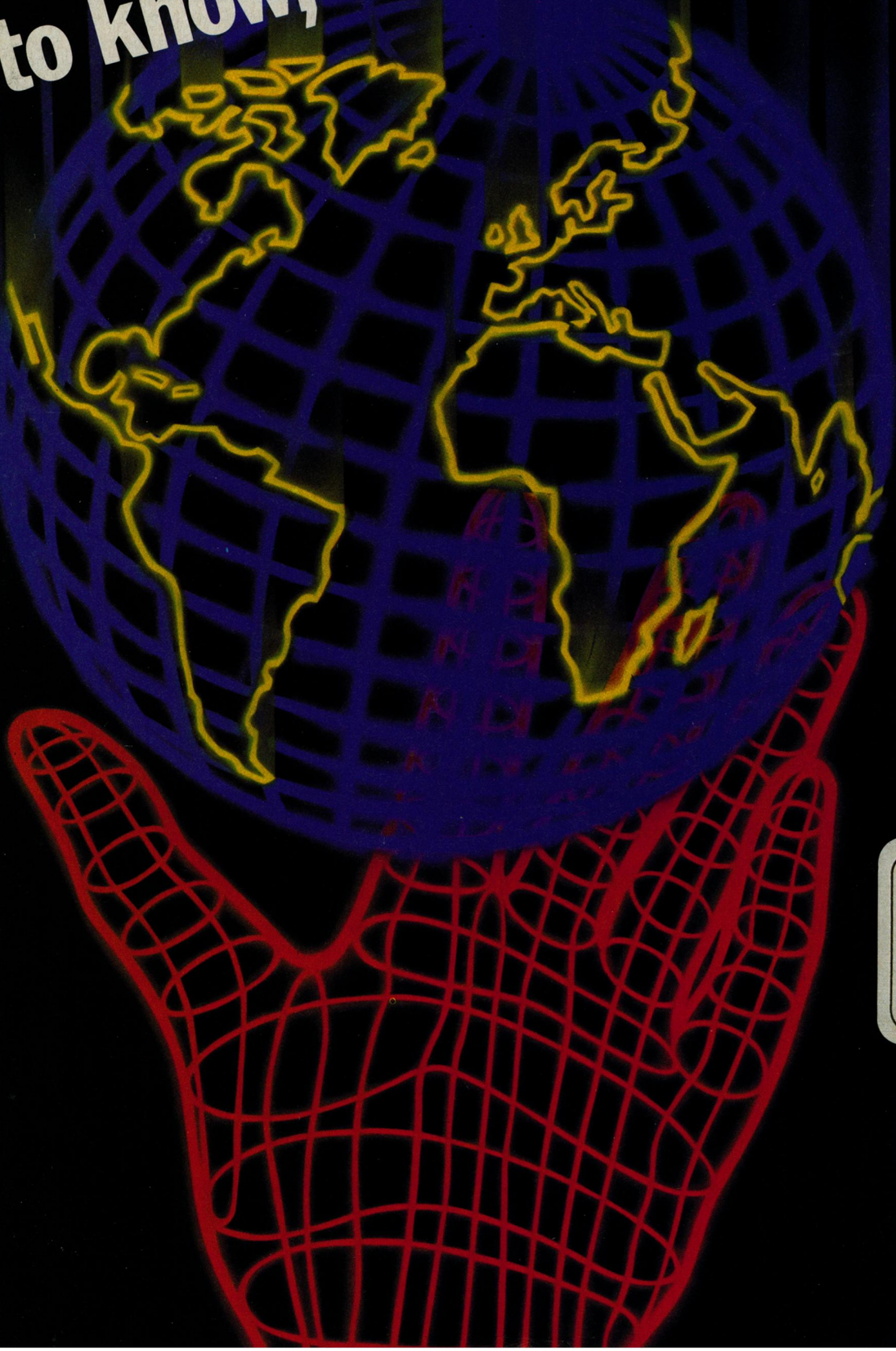

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Scientific Organization: F. De Palo (I), F. Rilke (I) and H. Zur Hausen (D)

IV Pan American Congress of Andrology
São Paulo, Brazil / May 4-6
Scientific Organization: A. Negro-Vilar (USA) and M. P. De Castro (BZ)

Inhibin - Non-Steroidal Regulation of Follicle Stimulating Hormone Secretion
Tokyo, Japan / May 21-22
Scientific Organization: H. Burger (Aus) and M. Igarashi (J)

Development and Function of the Reproductive Organs
Turku, Finland / June 10-12
Scientific Organization: M. Parvinen (SF)

IV Colloquium of the European Pineal Study Group
Modena, Italy / August 31 - September 4
Scientific Organization: G.P. Trentini (I), A. Oksche (D) and P. Pèvet (F)

Cell-to-Cell Communication in Endocrinology
Florence, Italy / October 8-9
Scientific Organization: L. Martini (I), M. Serio (I) and C.W. Bardin (USA)

Differentiation Therapy for Cancer
Tucker's Town, Bermuda / October 23-25
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Research Practices

Our study "Professional practices among biomedical scientists: A study of a sample generated by an unusual event" was mentioned in a recent News & Comment article by Eliot Marshall (31 Oct., p. 535). Marshall indicates that we studied the Darsee affair, but our focus was actually different: we examined the research practices of his 47 coauthors. Because our report is unpublished, many readers may not realize that its subject is not research fraud by an individual. Instead, we looked for evidence of questionable practices that are less extreme, perhaps more common, and may in aggregate have more effect on the integrity of the scientific literature than outright research fraud. Another point: the term we use for describing unearned authorship is "honorary." It is referred to erroneously in Marshall's article as "honorific."

WALTER W. STEWART
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Erratum: In the report "The color of the surface of Venus" by C. M. Pieters *et al.* (12 Dec., p. 1379), figure 2 on page 1382 was incorrectly printed upside down. The correct figure and caption appear below. Reference 11 in the caption is to A. S. Selivanov *et al.*, *Kosm. Issled.* **21**, 176 (1983) and A. S. Selivanov *et al.*, *ibid.*, p. 183.

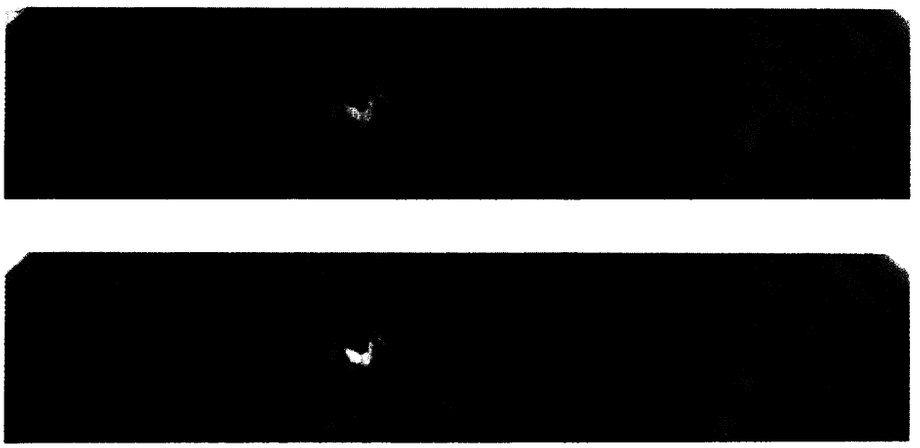
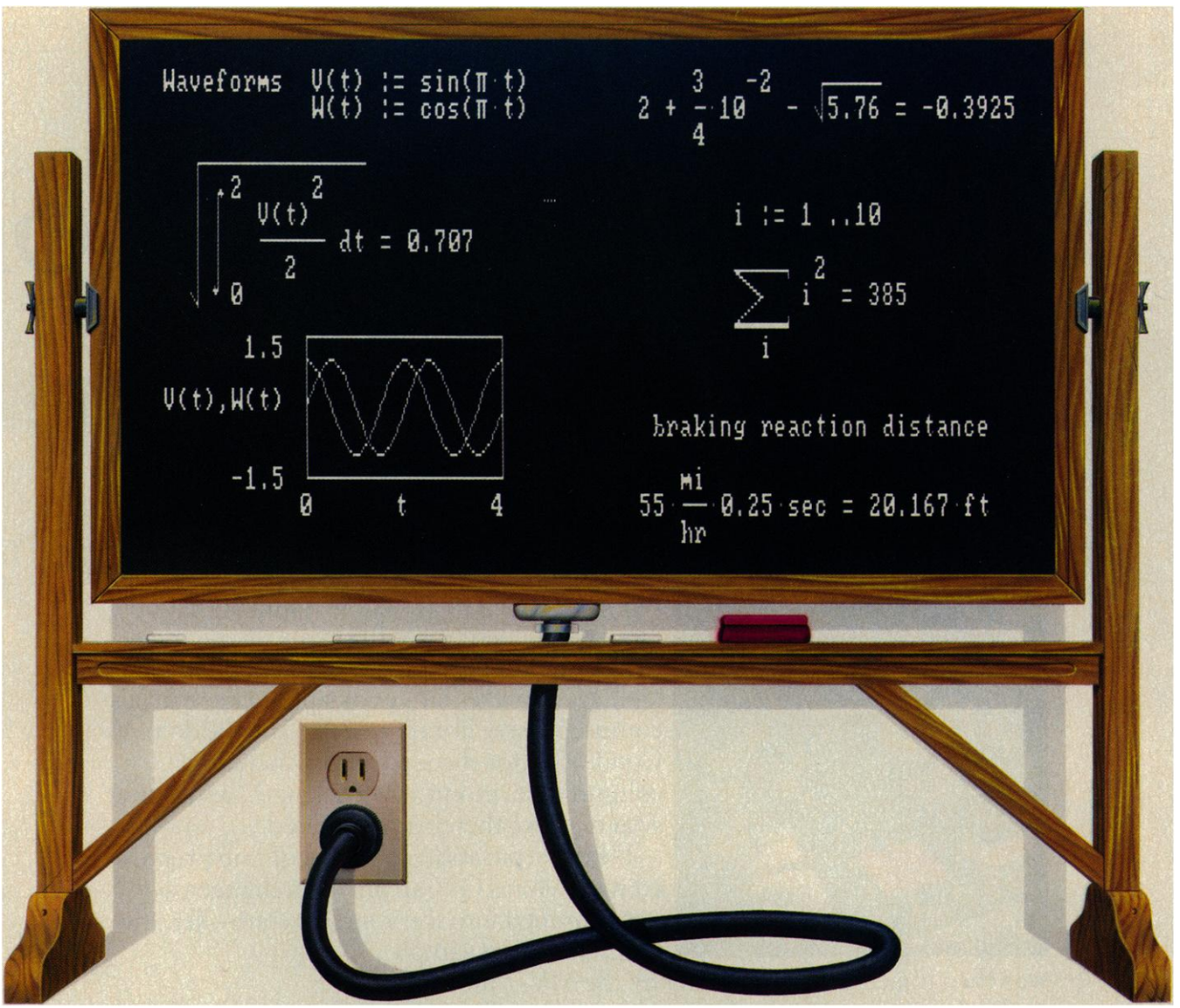


Fig. 2. Venera 13 color panorama for the surface of Venus. (Upper panel) This reproduction is similar to that originally published (*11*) and is comparable to the actual appearance of the scene at visible wavelengths. The orange hue is due to the diffuse incident radiation from which blue radiation has been efficiently removed by the thick Venus atmosphere. (Lower panel) The same color panorama data reprocessed to remove the effects of the strongly colored incident radiation. This image represents the surface of Venus as it would appear in "white light" illumination, that is, without the interference of an atmosphere.



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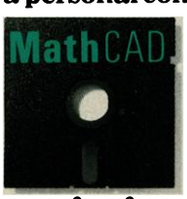

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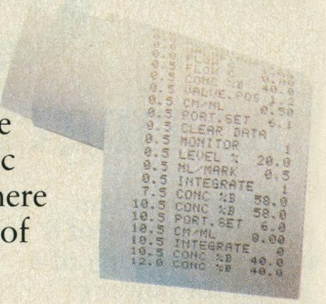
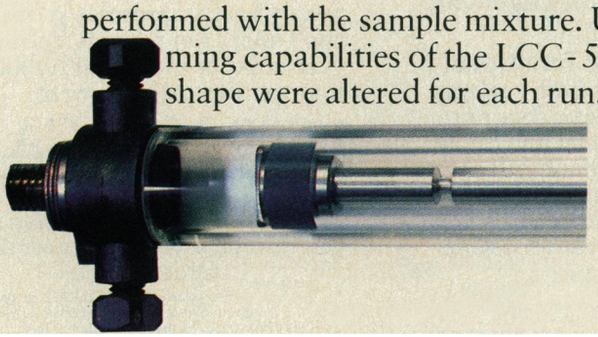
SEVEN PEAKS INSTEAD OF TWO. During the early stages of the project, the group invited a Pharmacia representative to come and demonstrate the

FPLC System. The system was quickly assembled. Knowing the approximate characteristics of the sample's proteins (pI, stability and size), the representative consulted Pharmacia's comprehensive library of FPLC methodology. Conditions for the separation, including column type, monitor wave length, and buffer system, were thereby determined.

Next a separation run on a column prepacked with Mono Q™, an anion exchanger, was programmed into the system's controller, the LCC-500. The sample was then injected automatically by the MV-7 motorized valve. In the course of ten minutes, a totally unexpected chromatographic pattern had appeared on the controller's printout. The sample contained two specific proteins that should have given rise to two peaks. But here were seven peaks – casting some doubt upon the merit of this high performance liquid chromatography system.



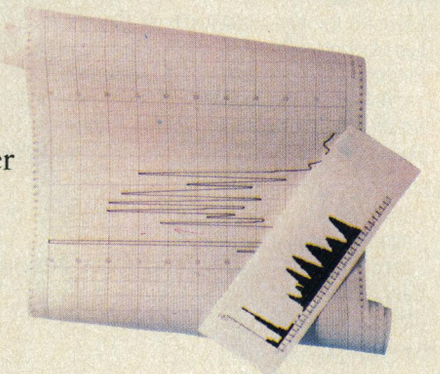
SAME UNEXPLAINED RESULTS. That same day, several separations were performed with the sample mixture. Using the simple, automatic programming capabilities of the LCC-500, other conditions such as gradient shape were altered for each run. Because of the great speed of the system – 10 minutes per run in this case – many runs could be completed. Yet the same results appeared every time.



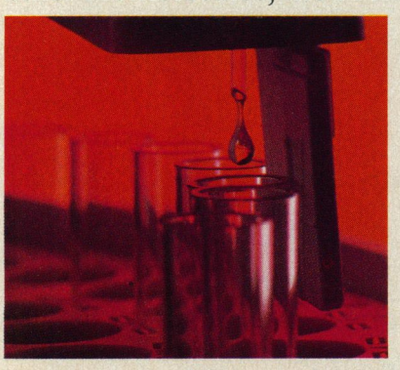
THE FIVE EXTRA PEAKS

THE BREAKTHROUGH. The reproducible results from the FPLC System convinced the researchers to take a second look at the seven peaks. After several days of further investigation they again contacted Pharmacia – the peaks were revealed to be iso-forms. No other high performance liquid chromatography system had been able to isolate these particular iso-forms, let alone in just ten minutes.

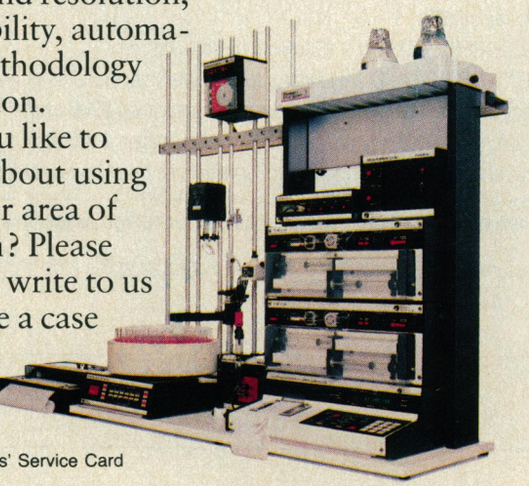
Central to the breakthrough was the system's biocompatibility, which enabled the researchers to maintain the biological activity of the collected fractions. This activity also permitted the study of the immunoregulatory activity of the fractions. The peaks were found to represent different immunostimulants and immunosuppressants, which had never before been so well separated and characterized. The FPLC System has enabled the group to extend their investigations into unexplored areas of biomedical research.



DISCOVER MORE. You can extend your own investigations, too. If your work involves the separation and purification of proteins, peptides, and other biomolecules, the FPLC System can provide you with advantages that turn problems into discoveries. Like the advantages that created success in this case history: high speed and resolution, biocompatibility, automation, and methodology documentation.



Would you like to learn more about using FPLC in your area of investigation? Please contact your Pharmacia representative or write to us at the address below. Maybe we can make a case for having an FPLC in your laboratory.



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THE SEVENTH ANNUAL CONGRESS FOR

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MARCH 1 – 4, 1987
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Peter Gruss, Max Planck Institute, Göttingen, West Germany

DNA SESSIONS

KEYNOTE ADDRESS (Sunday P.M.)
Genetics and Biochemistry of Retroviral Replication
Stephen Goff, Columbia University, College of Physicians and Surgeons
Left-Handed and Right-Handed DNA in Genetic Recombination
Alexander Rich, Massachusetts Institute of Technology

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)
(Monday A.M. - P.M.)
Chairman: Erling Norrby, Karolinska Institutet, Stockholm, Sweden
Speakers: Luc Montagnier, Paris
Robert C. Gallo, Bethesda
Jay A. Levy, San Francisco
Simon Wain-Hobson, Paris
Flossie Wong-Staal, Bethesda
William Haseltine, Boston
Myron Essex, Boston
Robin Weiss, London
Dani P. Bolognesi, Durham
Bernard Moss, Bethesda

CHROMATIN (Monday P.M.)
Chairman: Gary Felsenfeld, N.I.H.
Speakers: Robert Simpson, N.I.H.
Harold Weintraub, Fred Hutchinson Cancer Research Center
Gary Felsenfeld, N.I.H.
John Sedat, U.C.S.F.

TRANSCRIPTION (Tuesday A.M.)
Chairman: George Khoury, N.I.H.
Speakers: Robert Tjian, U.C. Berkeley
Carl Wu, N.I.H.
Keith Yamamoto, U.C.S.F.
George Khoury, N.I.H.

INTRACELLUAR PROTEIN TARGETING (Tuesday P.M.)
Chairman: Harvey Lodish, Whitehead Institute, M.I.T.
Speakers: Keith Mostov, Whitehead Institute, M.I.T.
James Rothman, Stanford
Peter Walter, U.C.S.F.
Harvey Lodish, Whitehead Institute, M.I.T.

NEUROBIOLOGY (Wednesday A.M.)
Chairman: James L. Roberts, Mt. Sinai Medical Center
Speakers: Louis Reichard, U.C.S.F.
Mark Darlison, Cambridge University (UK)
Alex Ullrich, Genentech
Peter Seeburg, Univ. of Heidelberg, West Germany

DEVELOPMENTAL BIOLOGY (Wednesday P.M.)
Chairman: Peter Gruss, Max Planck Institute, Göttingen, West Germany
Speakers: Patrick O'Farrell, U.C.S.F.
Gerald M. Rubin, U.C. Berkeley
Igor Dawid, N.I.H.
Erwin Wagner, E.M.B.O. Labs
Peter Gruss, Max Planck Institute, Göttingen, West Germany

POSTER SESSIONS AND EXHIBITS

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4-7 registrations received together from same organization $300 each.
8-10 registrations received together from same organization $200 each.
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