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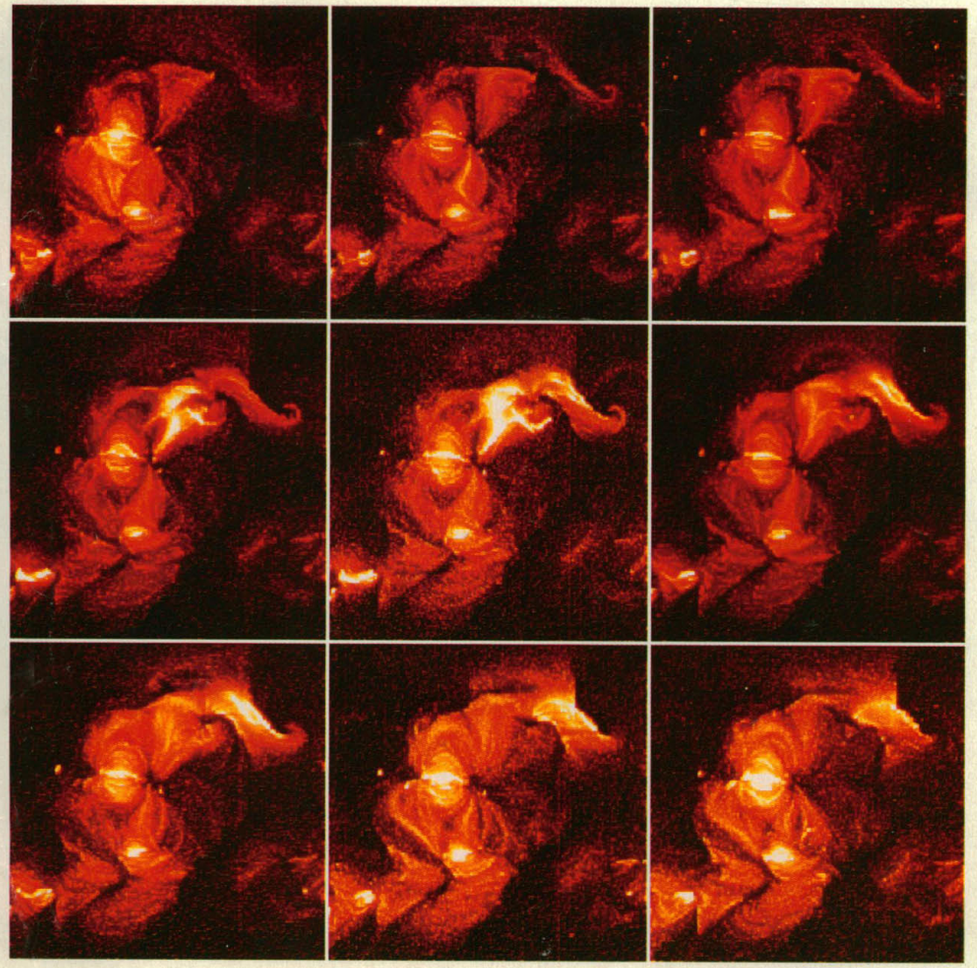
SCIENCE

23 OCTOBER 1992 $6.00
VOL. 258 • PAGES 517–712



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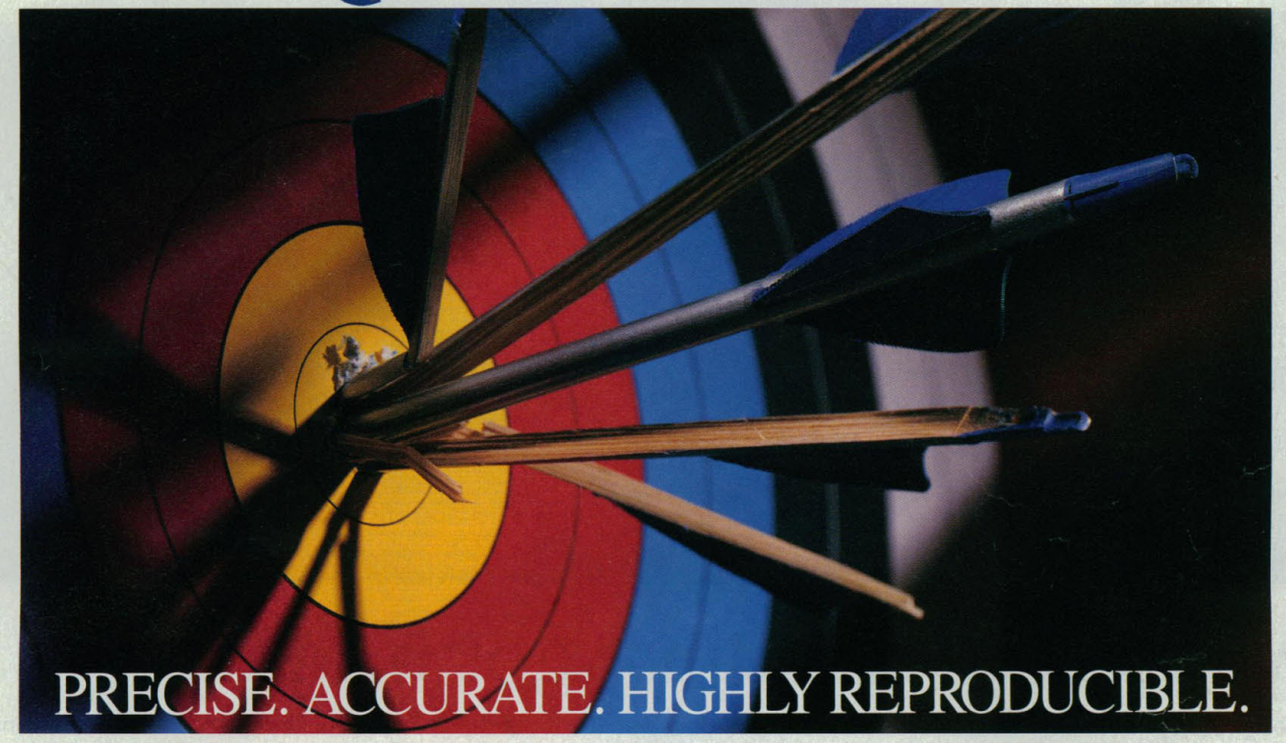

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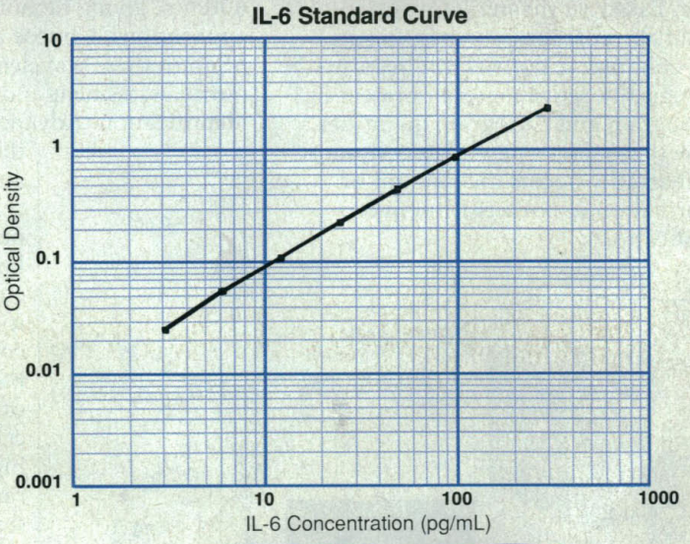

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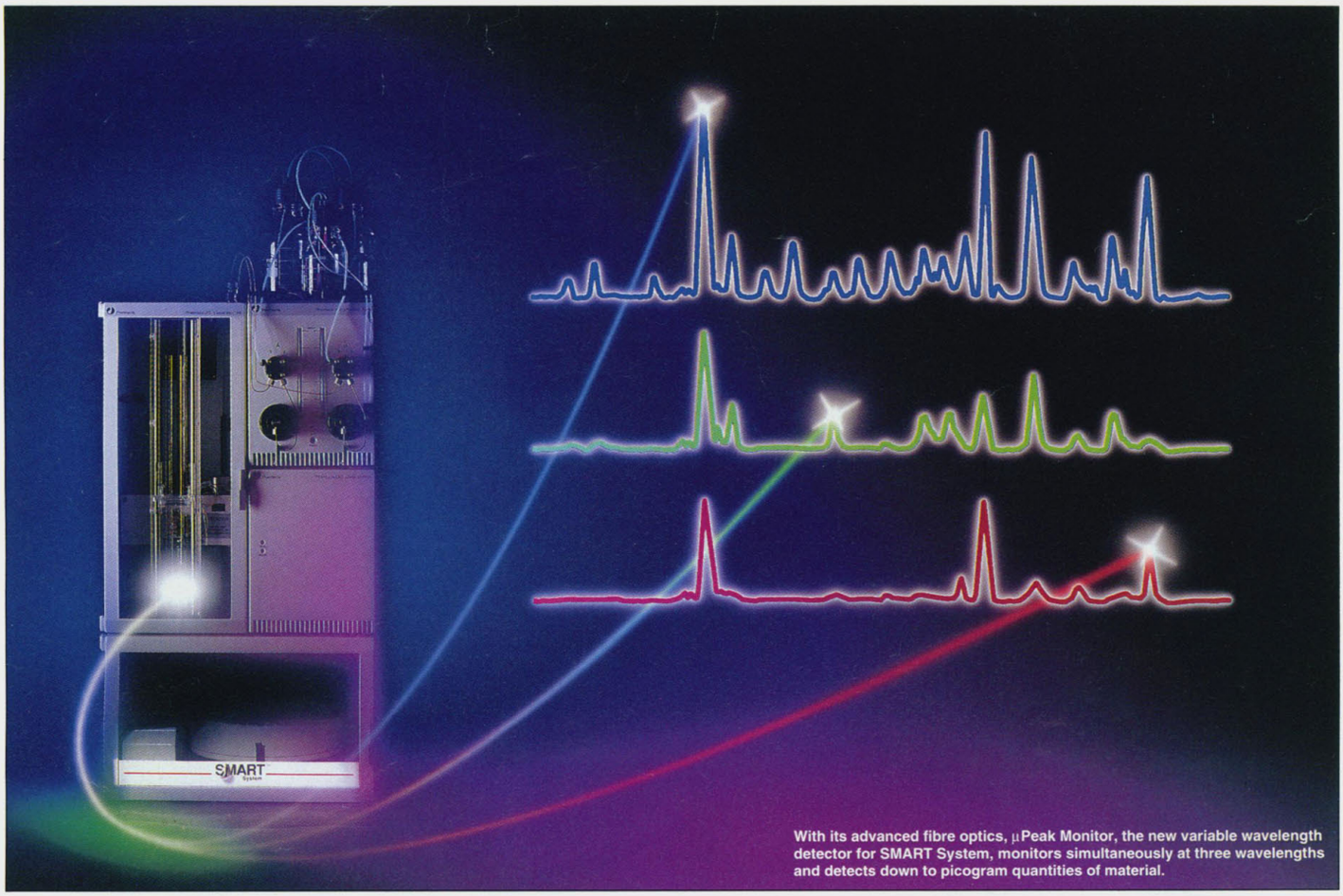

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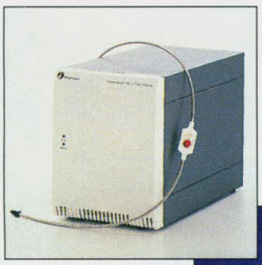

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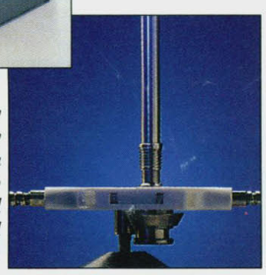

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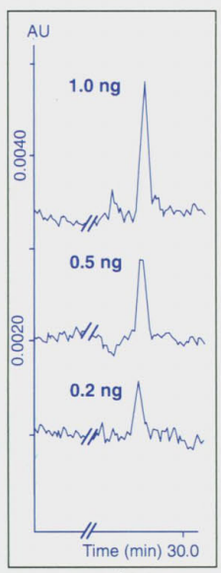

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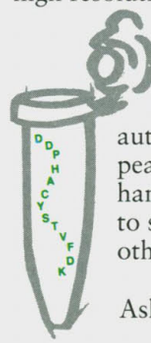

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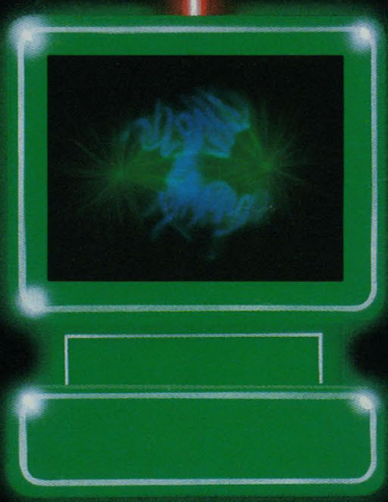

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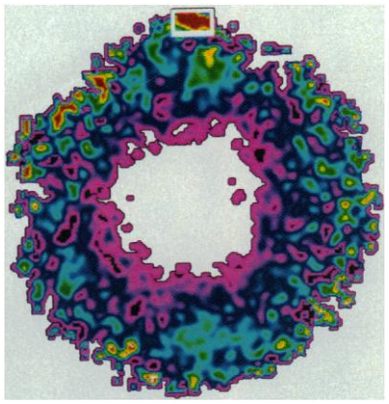

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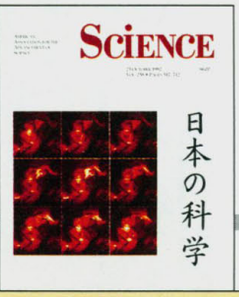
COVER

Images of an x-ray flare in the sun's corona taken by the Yohkoh satellite, a collaborative effort of scientists in Japan, the United States, and the United Kingdom, alongside the Japanese for "Science in Japan." Each image in the series shows a region 10 arc minutes on a side; the interval between them is about 1.3 hours. See page 618. This special issue features News reports, Perspectives, and Articles on science in Japan. [Images: SXT Science Team]



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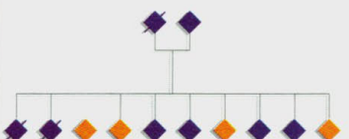

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Early-onset familial Alzheimer's disease linked to chromosome 14

◩ Indicates accompanying feature

■ **SCIENCE (ISSN 0036-8075) 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, DC 20005.** Second-class postage (publication No. 484460) paid at Washington, DC, and additional mailing offices.

Domestic individual membership and subscription (51 issues): $87 ($47 allocated to subscription). Domestic institutional subscription (51 issues): $195. Foreign postage extra: Mexico, Caribbean (surface mail) $50; other countries (air assist delivery) $95. First class, airmail, student and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. **Change of address:** allow 6 weeks, giving old and new addresses and 11-digit account number. **Postmaster:** Send change of address to *Science*, P.O. Box 2033, Marion, OH 43305-2033. **Single copy sales:** $6.00 per issue prepaid includes surface postage; Guide to Biotechnology Products and Instruments, $20. Bulk rates on request.

Science is indexed in the *Reader's Guide to Periodical Literature* and in several specialized indexes.

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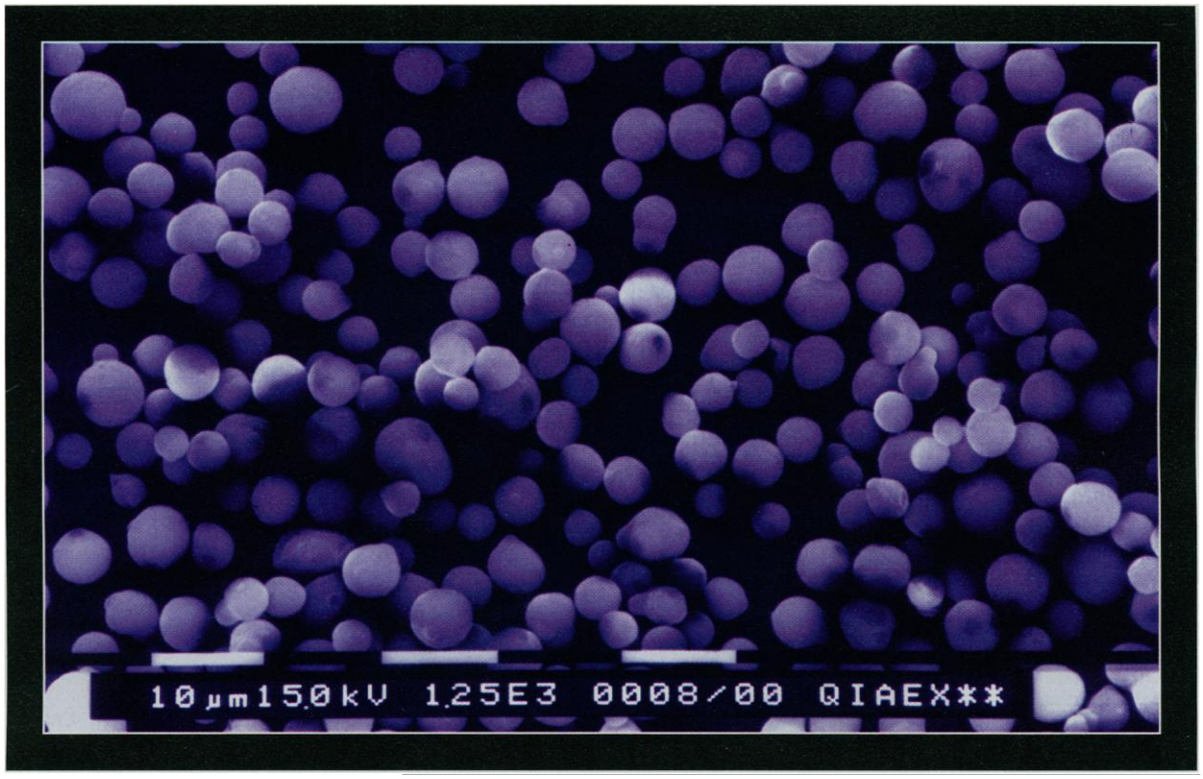

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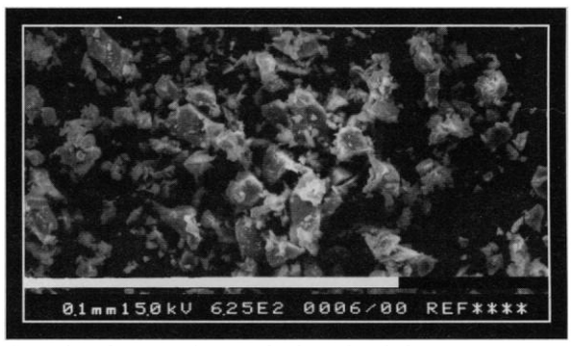

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Simulating water

Despite its apparent simplicity, water is a challenging molecule for theoretical chemists, especially those trying to understand polarization effects when a solute is dissolved in water. Gao and Xia (p. 631) present results for Monte Carlo simulations of aqueous solvation that combine quantum mechanical and molecular mechanical methods. The interaction of the solute with nearby water molecules is treated quantum mechanically, thus improving on averaged potentials. The remaining solvent molecules are described by molecular mechanics, thus making the overall calculation tractable. Good agreement for dipole moments was obtained with experimental results and with ab initio calculations.

■

Mercury mapping

Ice forms on Earth, Mars, and the cold outer planets, but is absent from Venus, and would appear to be unlikely to form on Mercury, where temperatures are as high as 700 K at the equator. In two complementary radar studies, however, Slade *et al.* (p. 635) and Harmon and Slade (p. 640) present evidence for highly reflective regions on the north and south poles of Mercury that appear to indicate the presence of water ice. Paige *et al.* (p. 643) present a model of Mercury's temperatures that suggests that the poles could be cool enough for ice to be stable. The polar ice appears to be located in large ancient impact craters; temperatures calculated for shaded parts of high-latitude craters are as low as 60 K, sufficient to have preserved ice against evaporation for billions of years.

Touring Japanese research

Research in Japan is the focus of this special issue of *Science* (see Editorial by Koshland, p. 527). Several news stories (pp. 561 to 577) examine the state of academic and industrial research labs, including how quickly they are changing and how they are being funded. A historical overview of Japanese science before the opening of Japan to Western learning is provided by Emperor Akihito (p. 578). Yonezawa (p. 581) outlines the goals for the next computing initiative, which include developing the theoretical foundations for flexible information processing and massively parallel computers. Hirano (p. 582) and Arima (p. 590) discuss basic research funding, and Koizumi (p. 589) discusses how well industry, government, and academia manage to collaborate. Noyori (p. 584) summarizes chemical research initiatives, and Aono (p. 586) looks at the future of materials processing on the atomic scale with devices such as the scanning tunneling microscope. In astronomy, Tanaka (p. 587) discusses the growth of radio and x-ray astronomy in Japan and Acton *et al.* (p. 618; cover) summarize the Yohkoh solar physics mission. Honjo (p. 591) discusses the use of a transgenic mouse to understand aspects of autoimmunity, and Kishimoto *et al.* (p. 593) reviews the signal transduction mechanism of interleukin-6 and its receptor as a model for cytokine action. The diversity of glutamate receptors and their role in mediating excitatory neurotransmission is reviewed by Nakanishi (p. 597). The role of diet in cancer, the leading cause of death in Japan, is one focus of a review by Sugimura on multistep carcinogenesis (p. 603). Nishizuka (p. 607) discusses the role of phospholipids in activating protein kinase C. Ikegami (p. 614) looks at the success of the Japanese health care system in areas of cost, access, and quality and outlines the challenges that an aging population presents to it. Fukao (p. 625) reviews how seismic tomography helps earth scientists map the movement of the mantle, especially the downwelling that occurs in the west Pacific.

Negative selection early in development

As T cells develop in the thymus, those that express T cell receptors (TCRs) for self antigens are destroyed. This process of negative selection has been thought to begin at the stage where developing T cells are "double positive," expressing both the CD4 and CD8 surface receptors. Takahama *et al.* (p. 653) performed studies in normal mice and in mice that expressed transgenic TCR αβ chain molecules for self molecules, in this case male antigen. Precursor thymocytes that expressed no CD4 and little CD8 that also expressed male antigen TCR did not develop into $CD4^+CD8^+$ cells. Thus, the low number of $CD4^+CD8^+$ cells in the thymus may be due in part to earlier selection events.

■

Face to face

Many functional membrane receptors require the formation of complexes of transmembrane molecules; the assembly process is often associated with interactions between cytoplasmic or periplasmic domains. Cosson and Bonifacino (p. 659) show that for class II major histocompatibility complex (MHC) molecules, mutations within the transmembrane helices themselves can inhibit the correct assembly of functional MHC molecules. Chimeric proteins were produced by substituting the α or β chains into other transmembrane proteins. A direct interaction may occur between glycine-rich faces of the transmembrane α and β chains.

■

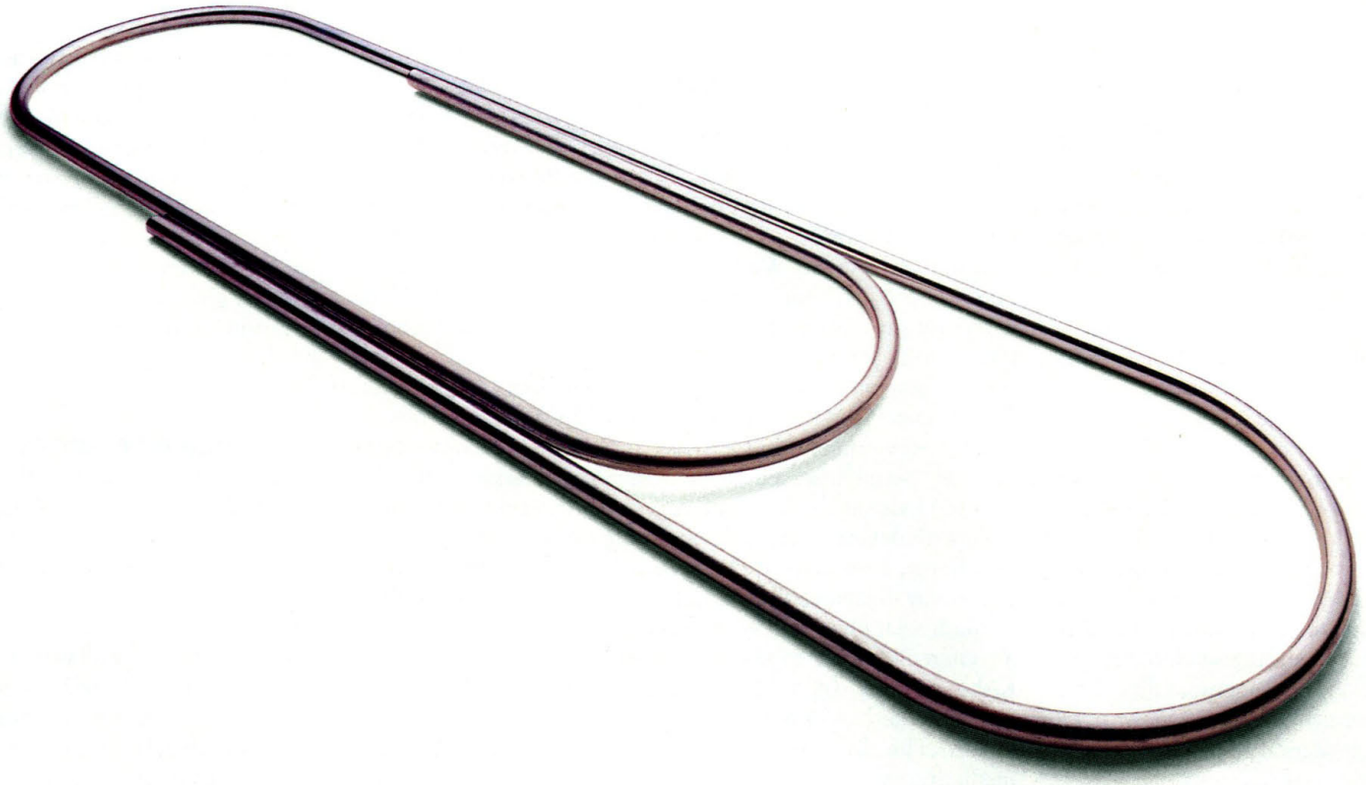
Coupled neurons

Neural systems can activate rhythmic patterns of motion, as occurs in fish when they swim. In the lamprey, the delay of the signal along the spinal cord neurons is about 1 percent of the total cycle time for all swimming speeds. Williams (p. 662) has performed a computer simulation showing that fairly simple neuronal circuitry can reproduce this phase coupling between neurons along a chain. Connections are stronger for signals traveling toward the head than toward the tail. For the case of the lamprey, the phase delay produced in this manner appears to be independent of the frequency of the swimming motion.

■

Alzheimer's disease and chromosome 14

Genes or loci linked to early-onset familial Alzheimer's disease (FAD) in some kindreds have been localized to chromosomes 19 and 21 and can involve mutations in the Alzheimer's amyloid precursor protein (APP). However, the majority of early-onset FAD families studied do not show linkages for these chromosomes or for APP mutations. Schellenberg *et al.* (p. 668) present a linkage analysis supporting the existence of another FAD locus on chromosome 14 (see news story by Marx, p. 550).



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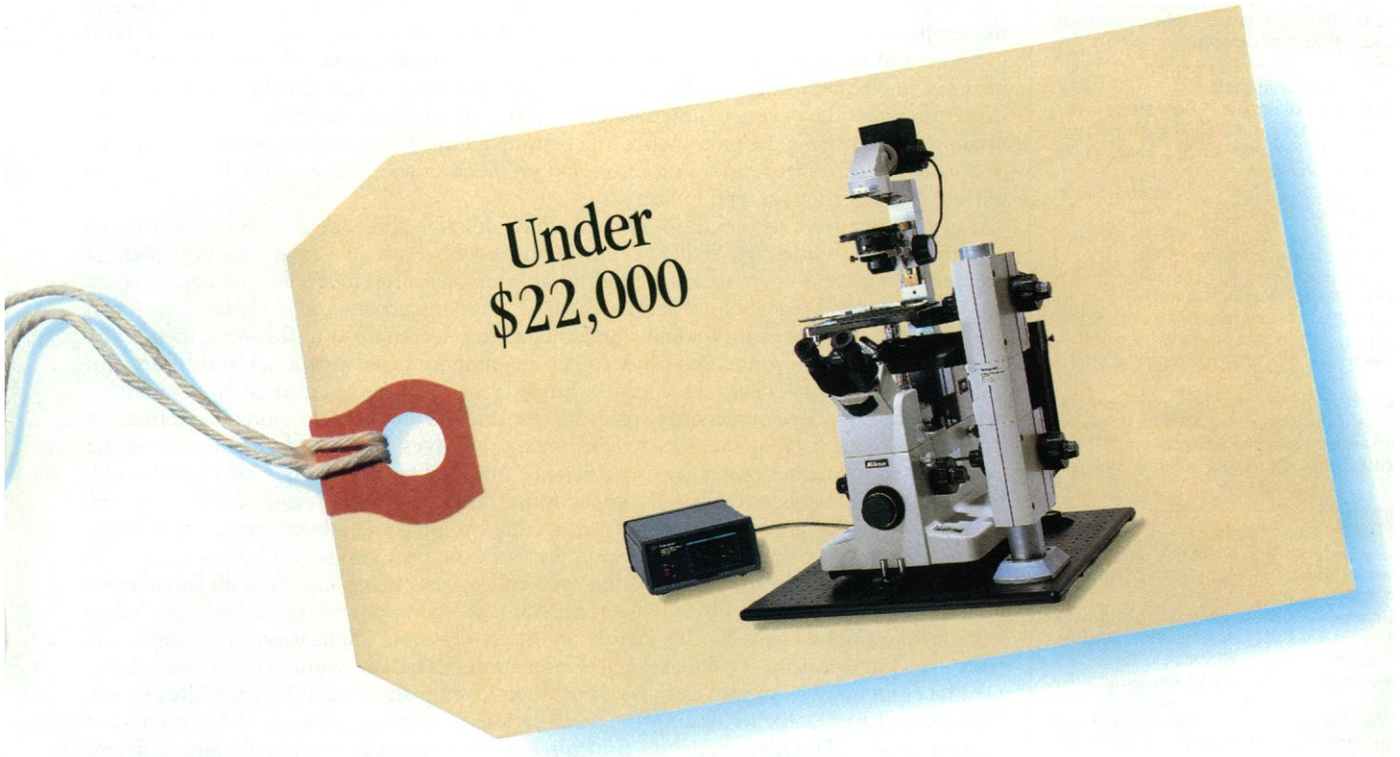

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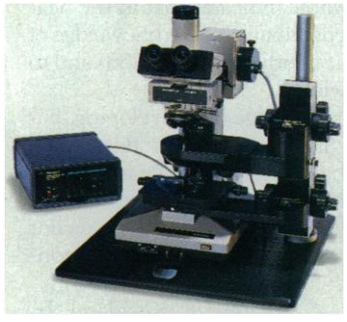

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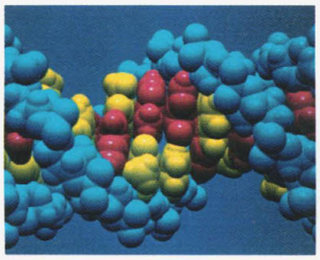
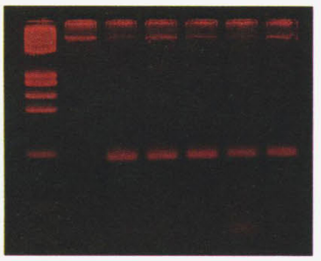
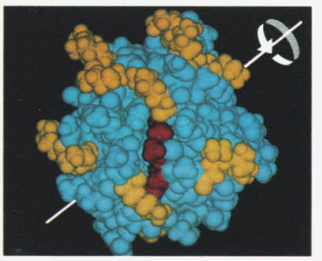


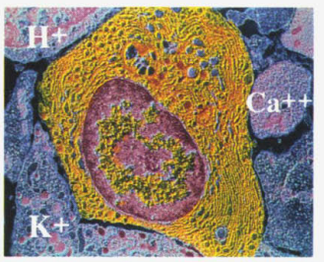
DNA Quantitation



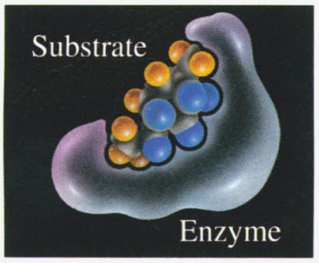
Gel Scanning



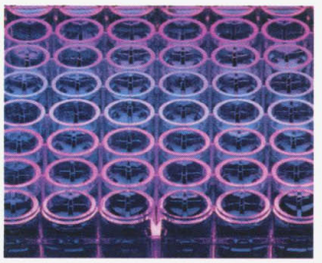
Macromolecular Anisotropy Measurements



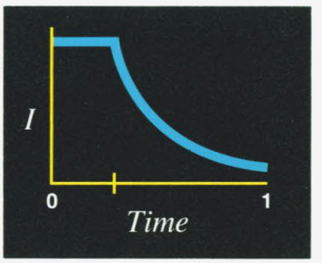
Intracellular Ion Determinations



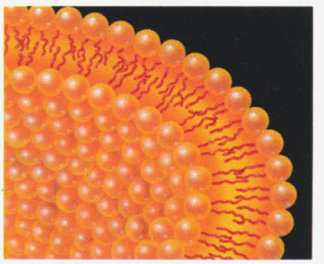
Enzyme Kinetic Analysis



Microplate Assays



Stopped-Flow Kinetic Analysis



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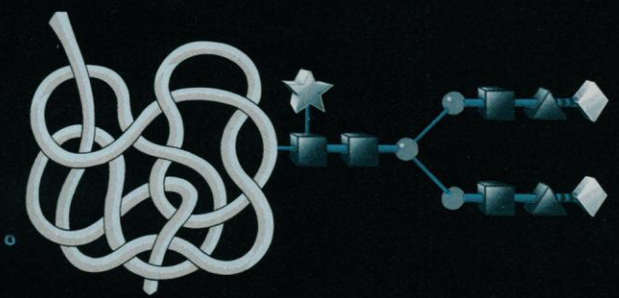

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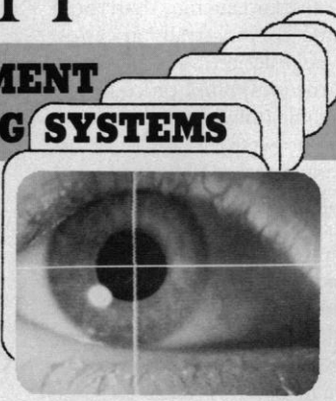

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Bio-Rad: The Evolution of Gene Transfer

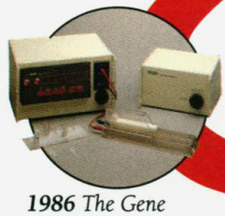
Earlier methods of Gene Transfer

Particle Delivery

1991 *Bio-Rad introduces DuPont's Biolistic® PDS-1000/He particle delivery system to the world market for plant and animal applications.*

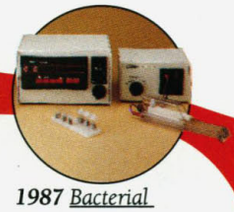
1993 *Particle delivery system expands to accommodate live animal work including gene therapy and genetic immunization.**

Electroporation

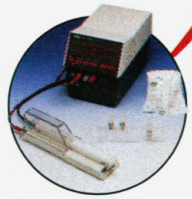


1986 *The Gene Pulser® system brings affordable electroporation to biochemists and molecular biologists.*

1989 *Bio-Rad guarantees high efficiencies with the introduction of convenient Electro-Competent® cells.*



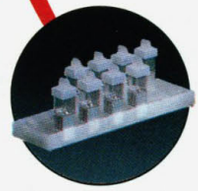
1987 *Bacterial electroporation efficiencies increased dramatically with the introduction of the Pulse Controller and 0.2 cm cuvettes.*



1991 *Bio-Rad introduces the E. coli Pulser™ unit —the first dedicated pulser for efficient, economical library construction.*

Support Data

1988 *Bio-Rad pioneers 10^{10} transformants/μg: E. coli protocol optimized.*



1990 *Prokaryotic applications and efficiencies boosted by new 0.1 cm cuvettes.*

1986-2010 *The users club binder —yours free— continually keeps you up to date on the latest gene transfer protocols for plant and mammalian cells, bacteria, yeast and other fungi, etc.*

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* Tang, D., DeVit, M., and Johnston, S.A., *Nature*, **356**, 152-154 (1992). Biolistic is a registered trademark of the DuPont Company.

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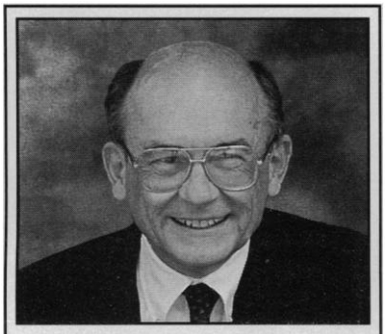
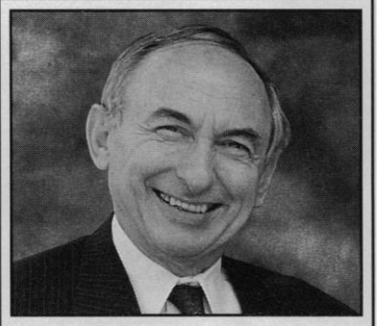
THE 1992 DISCOVERERS AWARD

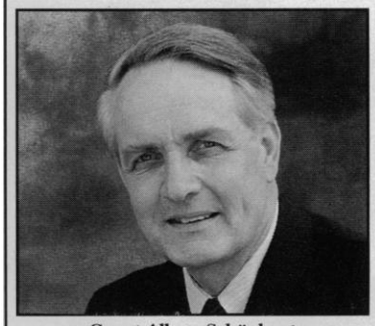
Before Americans ever heard of high cholesterol, this team discovered a way to lower it.



Arthur A. Patchett
V.P., Exploratory Chemistry
Merck & Co., Inc.



Alfred W. Alberts
Distinguished Senior Scientist
Merck & Co., Inc.



Georg Albers-Schönberg
Ex. Dir., Natural
Products Chemistry
Merck & Co., Inc.

Three Merck scientists, whose work led to the development of the cholesterol-lowering drug lovastatin (MEVACOR), have been selected to receive the 1992 Discoverers Award. The annual award honors the outstanding contributions of scientists from America's research-based pharmaceutical companies.

The Story of Mevacor

Scientists at Merck had been researching the biosynthesis of cholesterol since the early 1950's. But it wasn't until 20 years later, when Arthur Patchett developed a unique approach for discovering promising compounds, that the first important step in the discovery and development of lovastatin occurred. After testing over 4,000 extracts for a variety of uses, in 1978, one of them was passed from Dr. Patchett's lab to Alfred Alberts' biochemists for further study.

On November 16, 1978, Alberts' group discovered that the extract inhibited the formation of mevalonic acid — an essential building block in the body's synthesis of cholesterol.

Within days, Georg Albers-Schönberg's chemists were able to determine the molecular structure of the pure inhibitor of cholesterol, lovastatin.

Approved for patients in 1987, Merck's lovastatin was on its way to becoming the most widely prescribed cholesterol-lowering drug in the world, helping millions lead healthier, happier lives.

While these men are being recognized in a special way, their contributions are typical of the efforts of thousands of scientists who continue the search for new medicines that can bring us longer, better lives.

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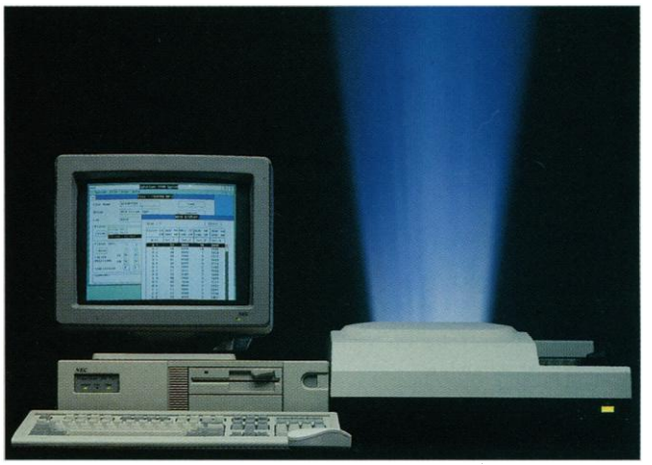

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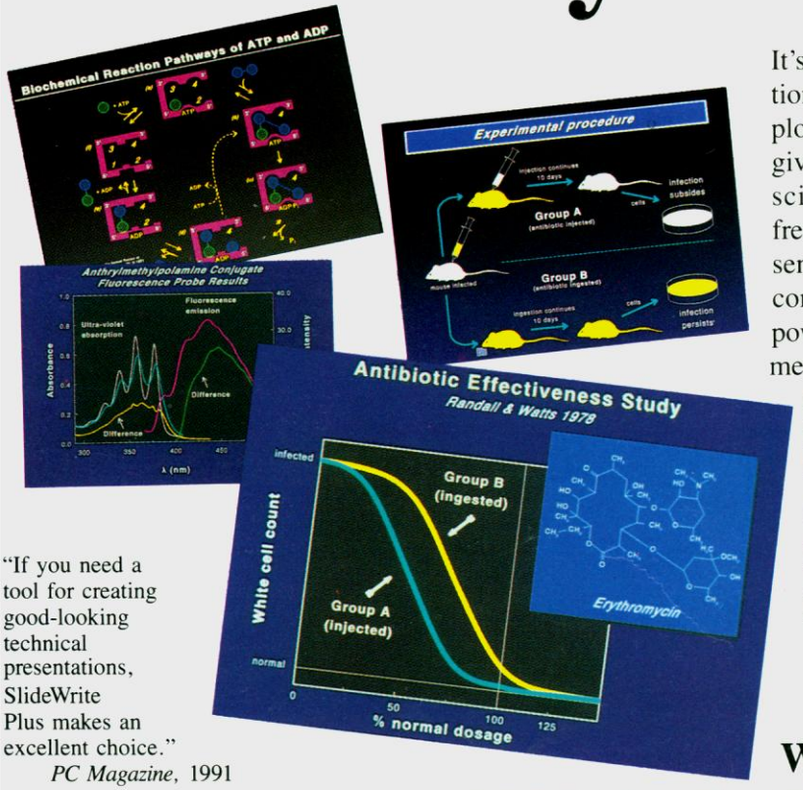

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Protein Kinases and Phosphatases

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Seminar Organizers:
Shirish Shenolikar, *Duke Univ,* and
Anthony R. Means, *Duke Univ*

Protein Phosphorylation and Signal Transduction

Wednesday, 10 February, 8:30 am–11:30 am

Session Chair: **Tony Hunter,** *Salk Inst*

Roger Davis, *Univ of Massachusetts-Worcester*
Signal transduction by the epidermal growth factor receptor

Ann-Marie Pendergast, *Duke Univ*
Oncogenic activation of the ABL protein tyrosine kinases in human leukemias

Patricia Donahoe, *Harvard Univ*
Topic to be announced

Larry Samelson, *NICHD*
The T cell antigen receptor: Phosphorylation events accompanying activation

Topical Lecture

Wednesday, 10 February, 1:15 pm–2:15 pm

Bruce Kemp, *Univ of Melbourne*
Regulation of protein kinases by pseudosubstrates: Intrasteric control

Growth-Regulated Protein Kinases

Wednesday, 10 February, 2:30 pm–5:30 pm

Session Chair: **Anthony R. Means,** *Duke Univ*

Kathy Gould, *Vanderbilt Univ*
Topic to be announced

Thomas W. Sturgill, *Univ of Virginia*
Characterization of activation pathways for 42kDa mitogen-activated protein kinase ($p42^{mapk}$)

Steven Osmani, *Geisinger Clinic*
Protein phosphorylation and regulation of mitosis

George Vande Woude, *NCI, Frederick*
Topic to be announced

Protein Phosphorylation and Gene Transcription

Thursday, 11 February, 8:30 am–11:30 am

Session Chair: **Michael G. Rosenfeld,** *Univ of Calif-San Diego*

Michael Greenberg, *Harvard Univ*
Growth regulation of immediate early gene transcription

Michael G. Rosenfeld, *Univ of Calif-San Diego*
Positive and negative transcriptional control mechanisms

Sandra Peligrini, *Institut Pasteur, Paris*
Topic to be announced

Eric Olson, *Univ of Texas*
Regulation of muscle-specific transcription by protein kinase cascades

Topical Lecture

Thursday, 11 February, 1:15 pm–2:15 pm

Tony Hunter, *Salk Institute*
Topic to be announced

Structure and Function of Protein Kinases

Thursday, 11 February, 2:30 pm–5:30 pm

Session Chair: **Bruce E. Kemp,** *Univ of Melbourne*

Anthony R. Means, *Duke Univ*
Calmodulin-regulated protein kinases as transducers of the Ca^{++} signal

Susan Taylor, *Univ of Calif-San Diego*
Insights gleaned from the structure of the catalytic subunit of cAMP-dependent protein kinase

Peter Parker, *ICRF, London*
Control of protein kinase C in vitro and in vivo

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Marc Caron, *Duke Univ*
Topic to be announced

Protein (Serine/Threonine) Phosphatases

Friday, 12 February, 8:30 am–11:30 am

Session Chair: **Patricia W. Cohen,** *Univ of Dundee*

Shirish Shenolikar, *Duke Univ*
Understanding cell regulation by protein (serine/threonine) phosphatases

Patricia W. Cohen, *Univ of Dundee*
Protein serine/threonine phosphatases regulating cell division

Stuart L. Schreiber, *Harvard Univ*
Molecular investigations of immunophilins

David L. Brautigan, *Brown Univ*
Crosstalk — Regulation of phosphatases by phosphorylation

Topical Lecture

Friday, 12 February, 1:15 pm–2:15 pm

Jack E. Dixon, *Univ of Michigan*
Protein tyrosine phosphatases: Their role in cell regulation and disease

Protein (Tyrosine) Phosphatases

Friday, 12 February, 2:30 pm–5:30 pm

Session Chair: **Jack E. Dixon,** *Univ of Michigan*

Haruo Saito, *Dana Farber Cancer Inst*
Genetic analyses of protein tyrosine phosphatases in signal transduction

Helen Piwnica-Worms, *Harvard Univ*
Regulation of eukaryotic cell cycle

Debby Cool, *Univ of Washington*
Effects of tyrosine phosphatases on cell transformation

Kathleen Kelly, *NCI*
PAC-1: A member of a new family of cell cycle-regulated protein tyrosine phosphatases

American Association for the Advancement of Science

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Protein Kinases and Phosphatases ✧ 10–12 February ✧ Boston

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Why the ACAS 570*C* is The Leader in UV-Visible Confocal Microscopy

From time to time, Meridian Instruments is asked a relatively simple question — "What makes your stage-scanning ACAS 570*C* UV-visible confocal system superior to laser-scanning confocal systems?" We think the question is a good one, and we'd like to take a moment to answer it.

No Lateral Chromatic Aberration

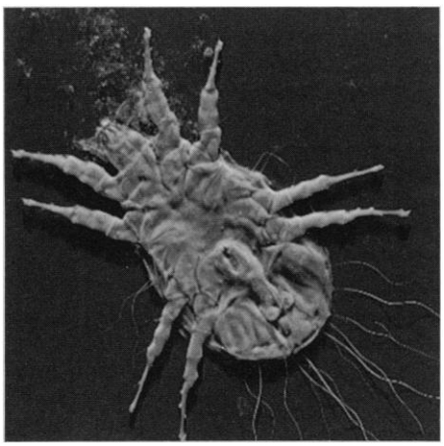
One of the basic problems in laser-scanning lies in the fact that UV-epiflourescence objectives are designed to maximize UV transmission, but are made achromatic only for visible wavelengths. When a laser beam is scanned through an objective, this inherent limitation causes lateral chromatic aberration — a situation in which the objective focuses the UV laser illumination off to the side with respect to the visible fluorescence detection spot. *(See Figure 1).* As the laser beam is scanned off-axis in this way, both signal intensity and resolution decrease *(Wells, 1990),* effectively limiting the useful field of view.

The ACAS is designed with a laser beam fixed in position along its entire optical axis, and builds confocal images by scanning a sample over the stationary laser beam (instead of scanning a beam across the sample). This method — called "stage-scanning" — eliminates the lateral chromatic aberration inherent in laser-scanning systems.

What does this mean to you?

Simply that, with the ACAS, signal intensity and resolution are independent of location. The ACAS 570*C*, like all other ACAS models, offers consistent high-resolution imaging at *all* points within the field, an important consideration when quantitating fluorescence at various locations within the sample.

In addition, because the ACAS is a stage-scanning system, it can scan an entire sample (up to 2 cm x 2 cm) with the same quality as a high magnification image. A laser-scanning system, on the other hand, is limited to collecting data strictly from the field of view visible through the oculars. The virtually unlimited field of view offered by the ACAS stage-scanning method can be an especially important advantage when working with whole embryos, other large samples, or when searching for rare events.



3-D SFP reconstruction of a series of confocal sections of macerated male Tyrophagus Longier (Astigmata Acari) *mite. Stained with acid fuchsin embedded in HEINZE medium. Sample size 720x720 microns. (Courtesy of Dr. Manfred G. Walzl, Univ. of Vienna, Austria)*

No Axial Chromatic Aberration

In addition to lateral chromatic aberration, laser-scanning confocal systems also can suffer from axial chromatic aberration — a vertical displacement of the UV laser illumination spot in relation to the point of visible fluorescence detection. *(See Figure 2).*

Because all objectives used in laser-scanning confocal microscopes focus UV excitation light at a different depth than visible detection light, the signal originating from the point of excitation will not be in proper focus for detection. This situation results in a marked loss of sensitivity, which worsens as the user selects thinner and thinner optical slices for confocal imaging.

The ACAS 570*C* corrects for this aberration by utilizing a multi-lens optical element in the excitation beam path to compensate exactly for the different focal depths of UV and visible light. This optic is mounted on a precision slide and can easily be moved into two positions: one for UV excitation, and one for visible excitation. In each case, the excitation and detection volumes become precisely aligned and, thus, the image you see is truly "confocal."

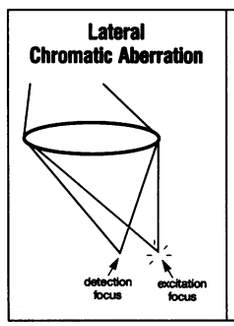


Figure 1

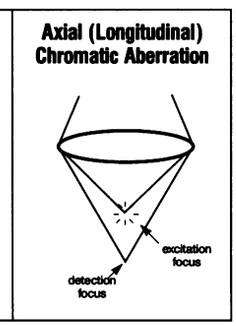


Figure 2

Is Faster Necessarily Better?

We've already mentioned some of the advantages of the on-axis ("stage scanning") method used by the ACAS 570*C*: no chromatic aberrations, unlimited size of field, and signal intensity and resolution independent of position within the field. But, what about the disadvantages?

The one we hear most often from other confocal companies has to do with speed. Because the ACAS 570*C* moves the specimen to build a confocal image point by point, gathering an image can require six seconds to three minutes, depending upon the size of the scanned area. Compared with laser scanning systems, this appears to be a relatively long time at first glance. But, is it really?

While a laser scanner can form an image in one to four seconds, nearly all biological samples require *multiple scans* before the signal-to-noise ratio becomes good enough to produce a publication-quality image. Thus, the real time for image acquisition on laser-scanning confocal systems may be *one minute or longer.*

While the ACAS' stage-scanning method results in a slower single-pass speed, it offers exceptional image quality and other opportunities not afforded by off-axis laser-scanning confocal units.

By using an AOM (Acousto-Optic Modulator), the ACAS flashes its laser beam only at the precise location of each pixel. Because the sample is not illuminated at any other time or location, sensitive specimens suffer *significantly less photobleaching and less photodamage.* This feature allows the use of photosensitive dyes that are not usable with other instruments.

In addition, the ACAS can accommodate very dim samples by utilizing a laser illumination system that can flash up to 256 times at each pixel location. This exclusive "single-scan averaging" feature produces exceedingly high signal-to-noise ratios in one pass. As a result, unlike laser scanners, the ACAS never needs to average multiple scans (and, therefore, users never need to deal with misregistration problems that can result from such operations).

As an additional advantage for confocal quantitation of kinetic events, the ACAS 570*C* can be set to acquire point data as quickly as 10 µsec per point, and line data from two to 400 points in timeframes as fast as 10 msec per line.

The Right Choice

We think all these reasons provide a pretty good answer as to why the ACAS 570*C* is the leader in UV-visible confocal microscopy (and has been for years). If you agree, give us a call. We'll be happy to tell you more about the exciting advantages of the line of ACAS products. There's one to fit every need.

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Wells, K. Sam, et al. "Chromatic aberrations in fluorescence LSCM measurements," Handbook of Biological Confocal Microscopy, *James B. Pawley, ed. (Plenum Press: New York, 1990.)*

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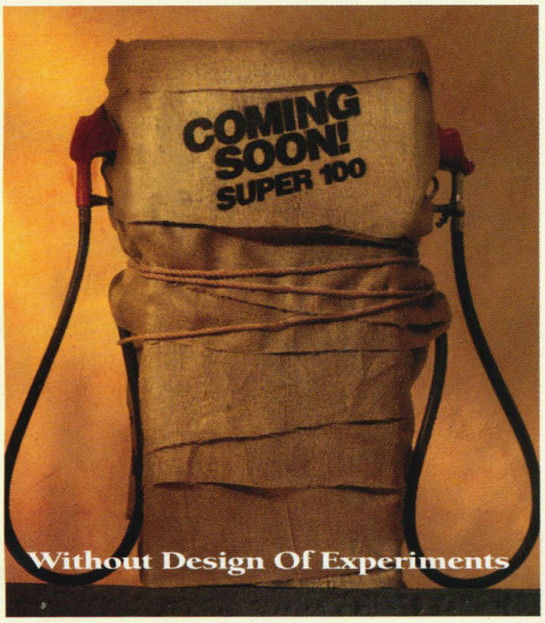

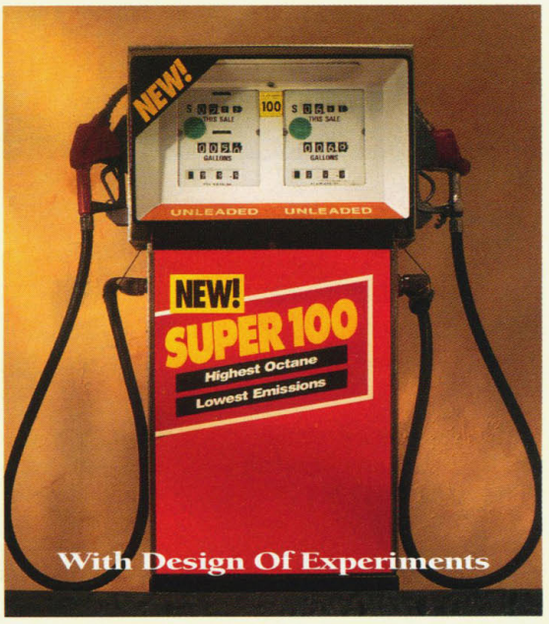

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As a complementary characterization technique to Edman Protein Sequencing — Apolipoprotein Al mutation Arg60 causes autosomal dominant amyloidosis; Ludwig Institute, London, UK; *Proc. Natl. Acad. Sci., USA,* **89,** 7389-7393 (1992).

Characterization of recombinant proteins — Analysis of recombinant human ciliary neurotrophic factor (CNTF) by laser desorption time of flight mass spectrometry; Regeneron Pharmaceuticals, NY; presented at the Sixth Protein Society Symposium.

Verification of synthetic peptides, looking for deletions, additions and protecting groups that have not been removed — Optimized solid phase peptide synthesis of a 41 amino acid residue peptide sequence of GP41 envelope glycoprotein with significant high sensitivity against HIV-1 antibody positive sera; University of Tübingen, Germany; presented at the 22nd European Peptide Symposium.

Characterization of variant proteins — Characterization of lysyl oxidase and TRAMP, distinct proteins that co-purify from porcine skin; Edinburgh University, UK; *Matrix*, in press.

Monitoring of enzymatic and chemical reactions — Studying advanced glycation processes using matrix assisted laser desorption; C.N.R. Padova, Italy, Policlinico University, Italy and Finnigan MAT, presented at Sixth Protein Society Symposium.

Characterization of glycoproteins and native oligosaccharides cleaved from glycoproteins — Glycobiology Institute, Oxford University, UK; *Glycoconjugate J.,* **9** 1-12 (1992).

Analysis of oligonucleotides — Matrix assisted laser desorption of oligonucleotides; California Institute of Technology; presented at 40th ASMS Conference on Mass Spectrometry.

Detection of peptides eluting from RP-HPLC — Predominant naturally processed peptides bound to HLA-DR1 are derived from MHC-related molecules and are heterogeneous in size; Harvard University, Cambridge, USA; *Nature* **358**, 764-768 (1992).

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Science in Japan

日本の科学

In the 6 years since *Science* last prepared a special issue on Japan (*Science*, 18 July 1986) the Japanese economy has continued to grow at a rate that is the envy of the world. For the Japanese scientific community, however, change has been uneven. Two different trends are obvious: The universities are changing very slowly, while industry is changing rapidly, building ever more sophisticated basic research laboratories. *Science*'s reporters take a look at these trends in the pages that follow, sketch the scientific geography of Japan, and meet a sample of Japan's diverse research scientists.

Science also asked several of Japan's own scientists and policy makers to describe the strengths and weaknesses of Japanese science and to describe particular areas of Japanese research. Their accounts appear on pages 581-630, preceded by a description of the early history of Japanese science from distinguished guest author, His Imperial Highness Akihito, Emperor of Japan. A celebrated scientist in his own right, the Emperor looks at the early history of Japanese science in the period before his great-grandfather, the Emperor Meiji, opened Japan to an influx of foreign learning.

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