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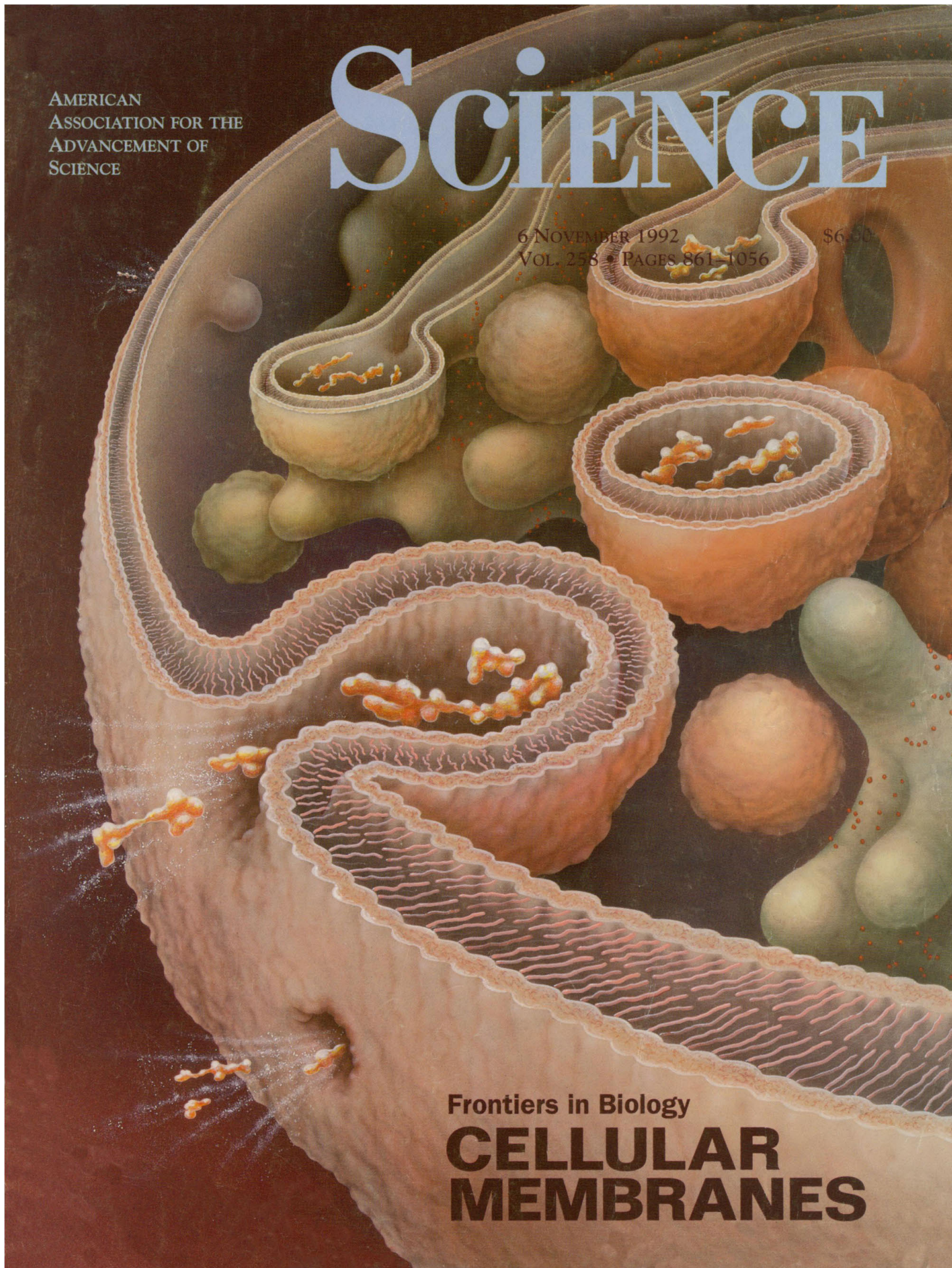
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Frontiers in Biology

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MEMBRANES**



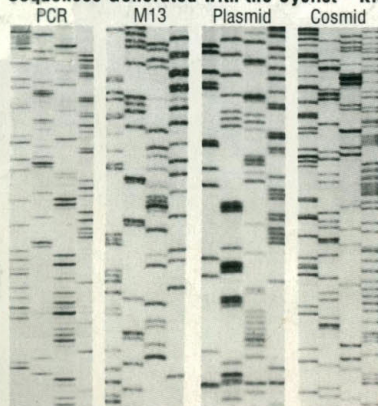
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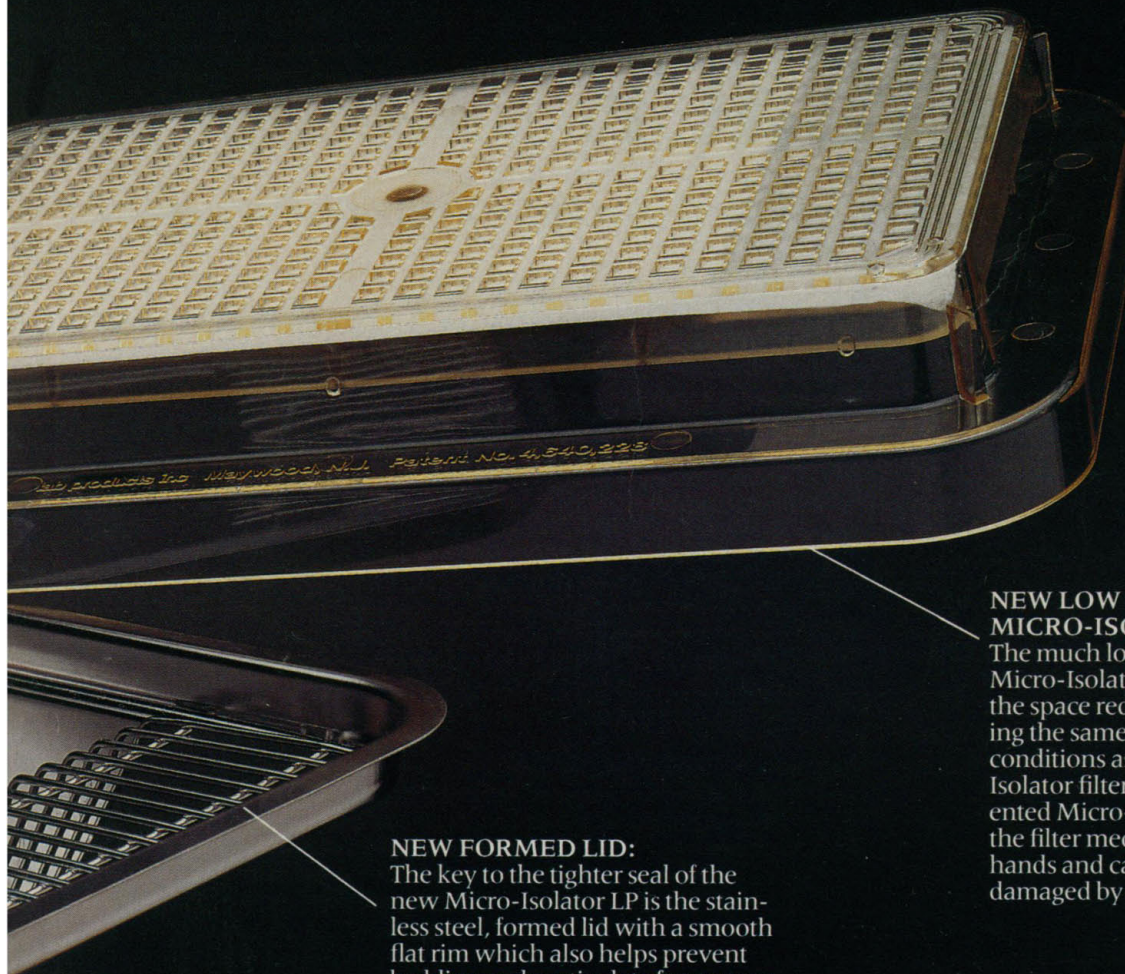
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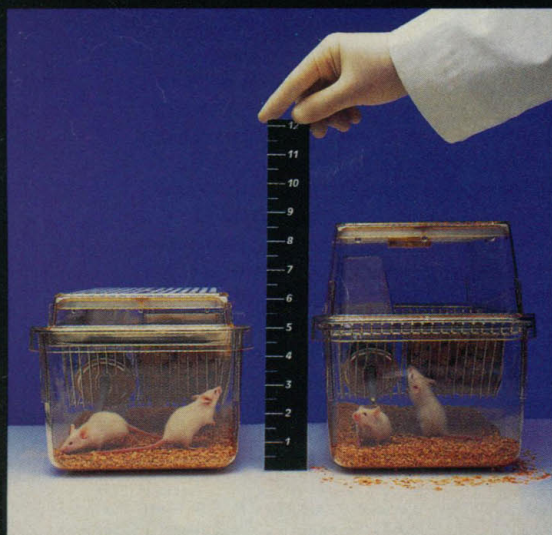
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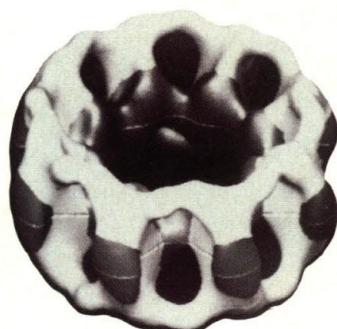
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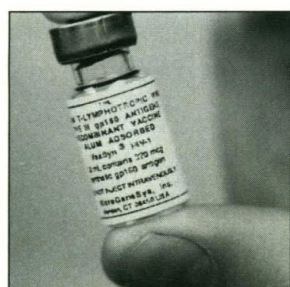
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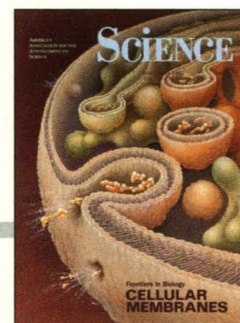
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COVER

Illustration of a plasma membrane and the interior of a cell. Secretory vesicles containing proteins bud from the Golgi apparatus in the interior of the cell and fuse with the plasma membrane; transport vesicles bud from the rough endoplasmic reticulum (with associated ribosomes shown as orange dots) and fuse with the Golgi

apparatus. The central role of the cellular membrane in diverse aspects of cell biology is the focus of this year's Frontiers in Biology issue. See the Editorial and the special section of Articles beginning on page 917. [Illustration: Tomo Narashima, New York]



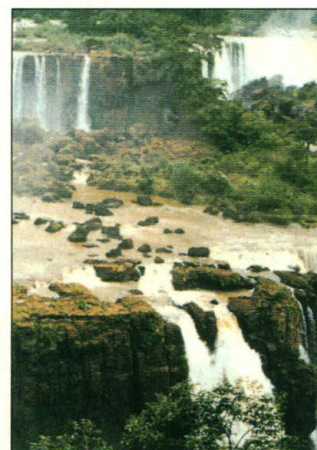
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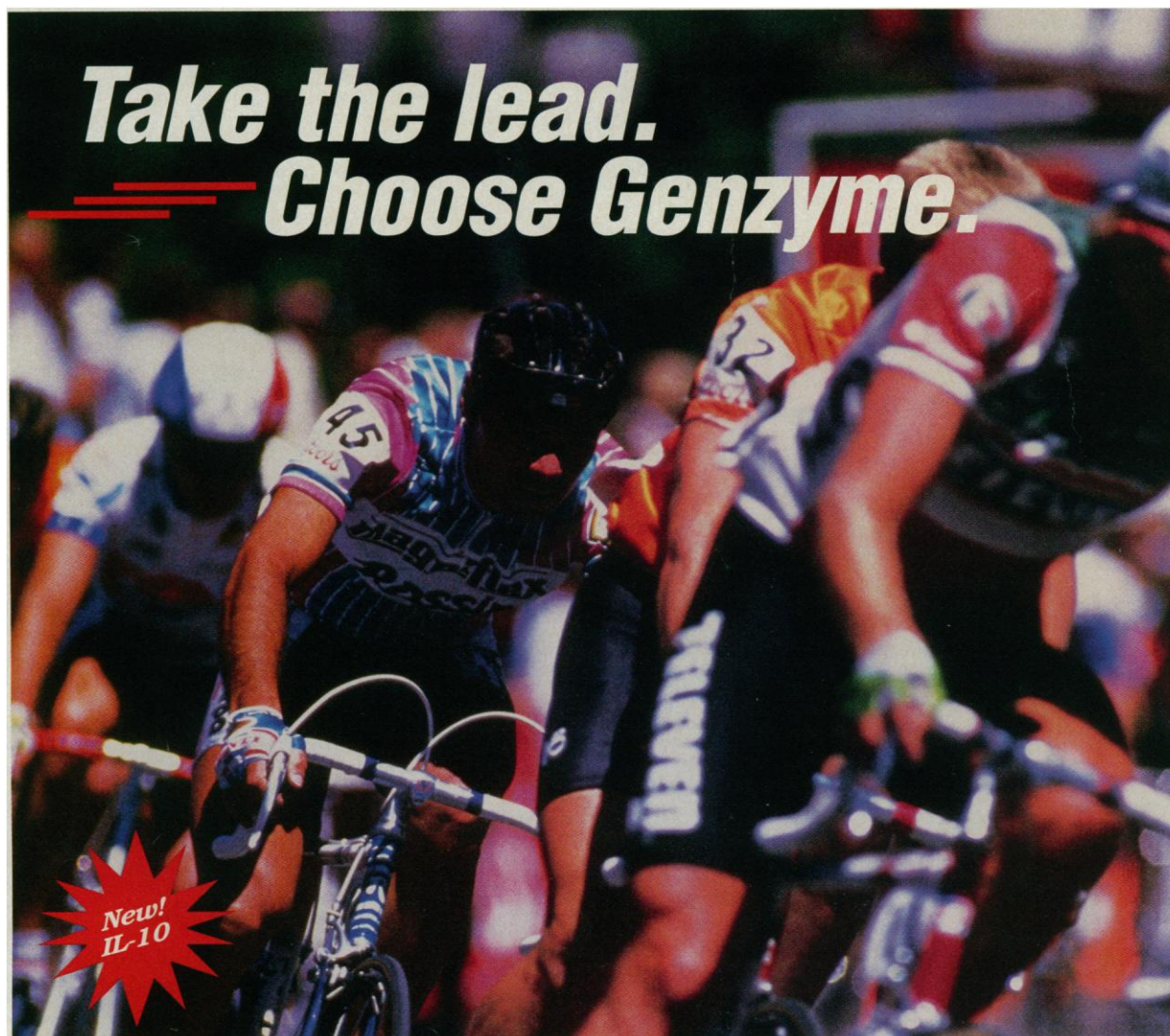


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Elementary origins

Some meteorites when dissolved in acid leave an insoluble residue of silicon carbide particles that are isotopically anomalous. They not only contain odd abundances of silicon and carbon isotopes but also yield anomalous xenon and almost pure neon-22. Brown and Clayton (p. 970) present calculations that indicate that such distributions can only be generated in the most massive carbon stars. Previous theories have contended that neon-22 directly condensed from low-mass asymptotic-giant-branch stars, but it appears that the neon comes from decay of condensed radioactive sodium-22. The authors refer to the isotope data as a kind of "cosmic chemical memory" that contains the evolutionary history of these stars.

Elemental images

Electron microscopes can be used to map distributions of chemical elements as well as to make images at high magnification, but the electrons in the imaging beam can damage the sample under study. Radiation damage is less of a problem with x-rays, but getting chemical sensitivity has been difficult. Ade *et al.* (p. 972) report the use of an x-ray microscope to record x-ray absorption near-edge spectra over a region 0.01 square micrometer in area. High-contrast maps of polymer blends and the DNA distribution in chromosomes were made with a spatial resolution of 55 nanometers.

An old breakup

Before South America and Africa separated in the breakup of Gondwanaland, a large flood

Altering signal transduction in nitrogenase

In the nitrogenase enzyme complex, the molybdenum-iron (MoFe)-protein, in which dinitrogen is reduced to ammonia, obtains its electrons from the iron (Fe)-protein. Other electron sources are ineffective, apparently because the MoFe protein transfers the electron back. The Fe-protein avoids this through a molecular switch; it undergoes a conformational change during electron transfer associated with the hydrolysis of bound magnesium adenosine triphosphate (MgATP), its energy source. This conformational change provides a signal that is transduced from the MgATP binding site and exposes the iron-sulfur cluster at which electron transfer to the MoFe-protein occurs. Wolle *et al.* (p. 992) propose a mechanism in which aspartate-125 (Asp¹²⁵) is part of the signal pathway. The recently solved x-ray structure of Fe-protein is highly homologous to that of the guanosine triphosphatase p21^{ras}, in which the analogous Asp⁵⁷ residue participates in conformational changes. Mutation of Asp¹²⁵ to glutamate allows both MgATP and MgADP to cause the conformational switch to occur and relaxes the requirement for Mg binding. A mechanism is proposed in which the ADP molecule moves to a position that blocks the pathway for reversed electron flow.

volcanic event occurred. Renne *et al.* (p. 975) used argon dating and previous paleomagnetic measurements to date the Paraná flood volcanic rocks in South America at 133 million years old. This volcanic event lasted less than 1 million years. The authors propose that Tristan da Cunha hot spot in what is now the south Atlantic uplifted and weakened the continental lithosphere, initiating an intense period of flood volcanism. The dating also puts this volcanic event after most estimates of the date of the Jurassic-Cretaceous boundary, a major extinction event.

Could still be active

Cooling of Mars' lithosphere should cause it to still be seismically active. Marsquakes were not detected by the Viking seismometer, but this instrument had poor sensitivity. Golombek *et al.* (p. 979) estimated the seismic activity of the planet by measuring the total slip over exposed surface

faults, such as grabens and rifts. This analysis was calibrated against a similar analysis for the moon, for which seismic data are available. Seismic events equivalent to magnitude three and four earthquakes should be frequent enough to be readily detectable with Apollo-class seismometers.

Heat shock stabilized

Heat shock proteins (Hsps), which are synthesized more rapidly by cells in response to environmental stresses such as high temperature, are hypothesized to somehow protect other proteins from thermal damage. Martin *et al.* (p. 995) used a heat-sensitive mutant of mitochondrial Hsp60 to show that Hsp60 can prevent the denaturation of dihydrofolate reductase that was introduced into yeast mitochondria. Such protection was reproduced in vitro with the bacterial homolog of Hsp60, GroEL. These heat shock specialists protect other

proteins from heat-induced deactivation by binding to them and thereby preventing their irreversible aggregation.

Resistance reductase

Certain genotypes of maize can be infected by the fungus *Cochliobolus carbonum*. This fungus produces a cyclic tetrapeptide, HC toxin, which is inactivated in resistant maize that contain dominant *Hm1* allele by HC toxin reductase (HCTR). Johal *et al.* (p. 985) generated and cloned several *Hm1* alleles by transposon-induced mutagenesis to determine if this gene encodes HCTR or regulator of its expression. The wild-type gene shares homology with dihydroflavonol-4-reductase genes of maize, petunia, and snapdragon, suggesting that *Hm1* encodes a reductase.

A pathway for plague

Fleas infected with *Yersinia pestis*, the causative agent of plague, can transmit this organism to humans through skin bites. Soedeinde *et al.* (p. 1004) show that a surface protease, Pla, helps *Y. pestis* infect internal organs. One millionfold times more mutant bacteria that lack the *pla* gene (*pla*⁻) are needed to cause death than wild type when injections are made under the skin of mice. However, lethal doses are similar for intravenous injections. Because the *pla* mutants establish local infections under the skin, the role of Pla protease may be in overcoming barriers to bacterial spread; Pla acts as a plasminogen activator, which could help the bacteria overcome fibrin and plasmin barriers. The protease can also specifically cleave complement C3 and thus reduce chemoattraction of immune cells to the site of infection.

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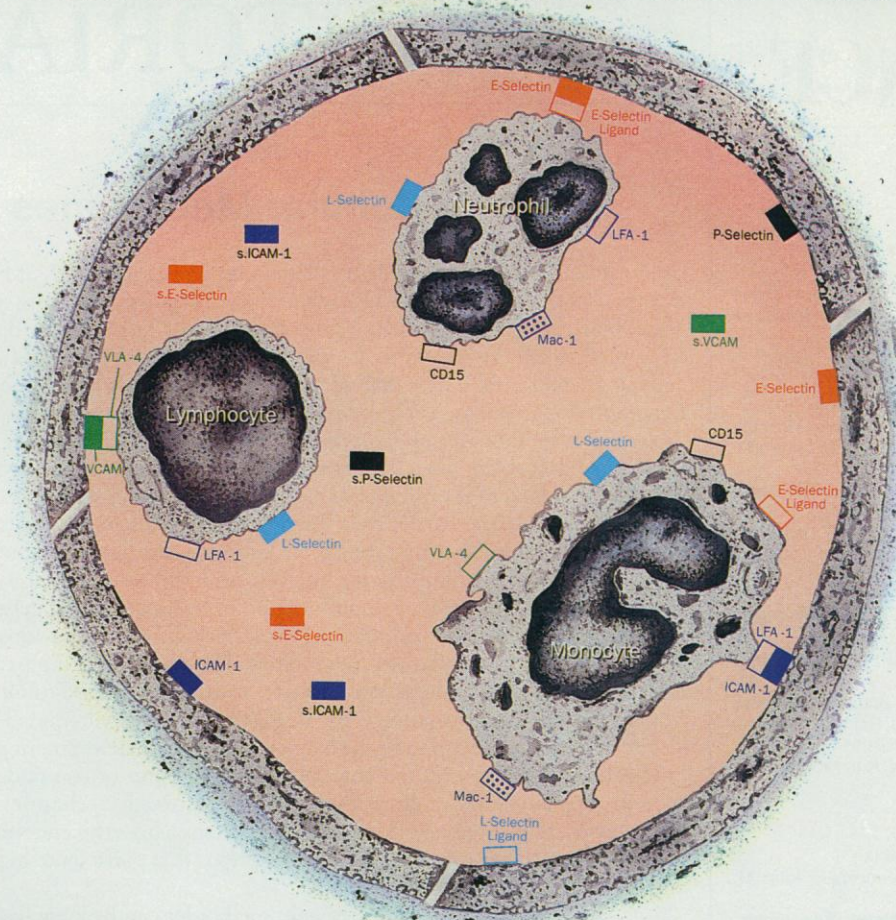
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Gearing, A.J.H. et al, In Press, Annals N. Y. Acad. Sci.

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- Current reports have suggested a role for intracellular adhesion molecule 1 (ICAM-1) in the progression of human malignant melanoma and other cancers. Stage I, II and III patients with histologically diagnosed malignant melanoma had significantly increased serum levels of circulating ICAM-1, (cICAM-1). We suggest that elevated levels of serum cICAM-1 may be of diagnostic and prognostic importance in patients with malignant cutaneous melanoma.◄◄

Harning, R. et al, Cancer Research (1991) 51, 5003-5005.

On-going studies into inflammatory diseases cite soluble adhesins as an area of potential importance....

- Studies have shown differences in intensity related to age and to particular inflammatory conditions (Such as rheumatoid arthritis, systemic lupus erythematosus, metastatic cancer, and acute urolithiasis) of both ICAM-1 and VLA (unpublished).◄◄

Seth, R. et al, The Lancet (1991) 338, 83-84.

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Diseases where Cytokines are important may also have a role for adhesins....

- Tumour necrosis factor, interleukin-1 and γ -interferon cause the release of soluble ICAM-1.◄◄

Giavazzi, R. et al, Cancer Research (1992)

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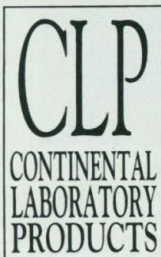


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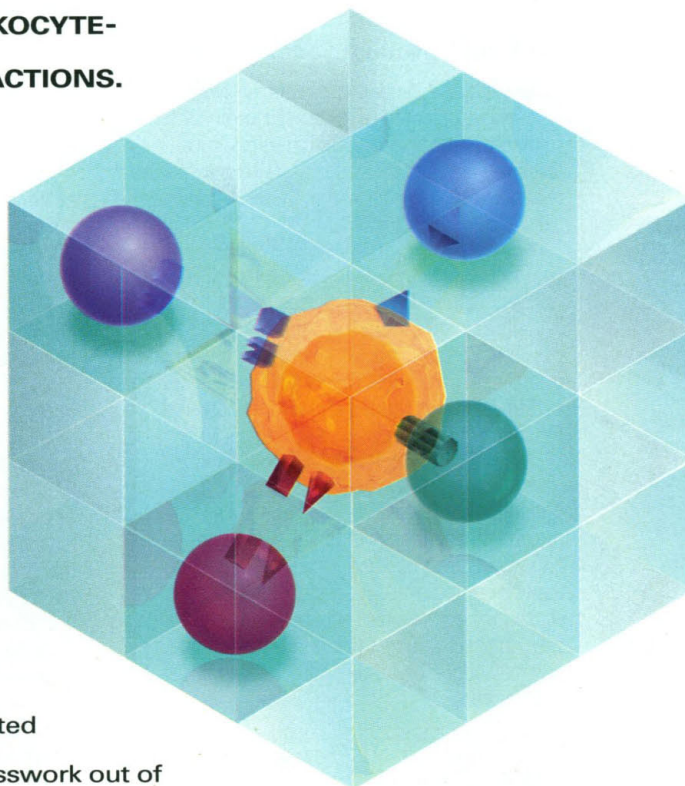
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Why the ACAS 570C is The Leader in UV-Visible Confocal Microscopy

From time to time, Meridian Instruments is asked a relatively simple question — “What makes your stage-scanning ACAS 570C 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-epifluorescence 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 570C, 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.

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 570C 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.”

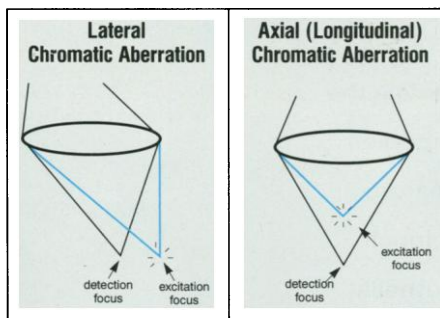


Figure 1

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 570C: 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 570C 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 570C can be set to acquire point data as quickly as 10 μ sec per point, and line data from two to 400 points in timeframes as fast as 10 msec per line.

The Right Choice

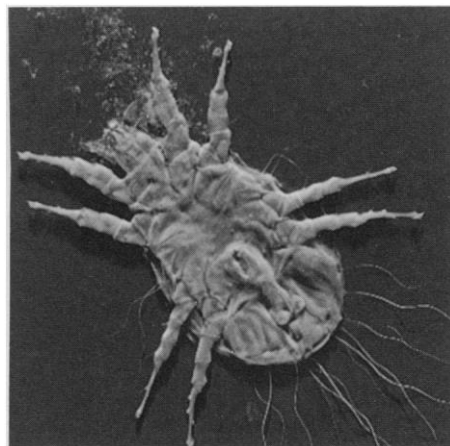
We think all these reasons provide a pretty good answer as to why the ACAS 570C is the leader in UV-visible confocal microscopy (and has been for years). If you agree, give us a call. We'll be happy to tell you more about the exciting advantages of the line of ACAS products. There's one to fit every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

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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. Walz, Univ. of Vienna, Austria)

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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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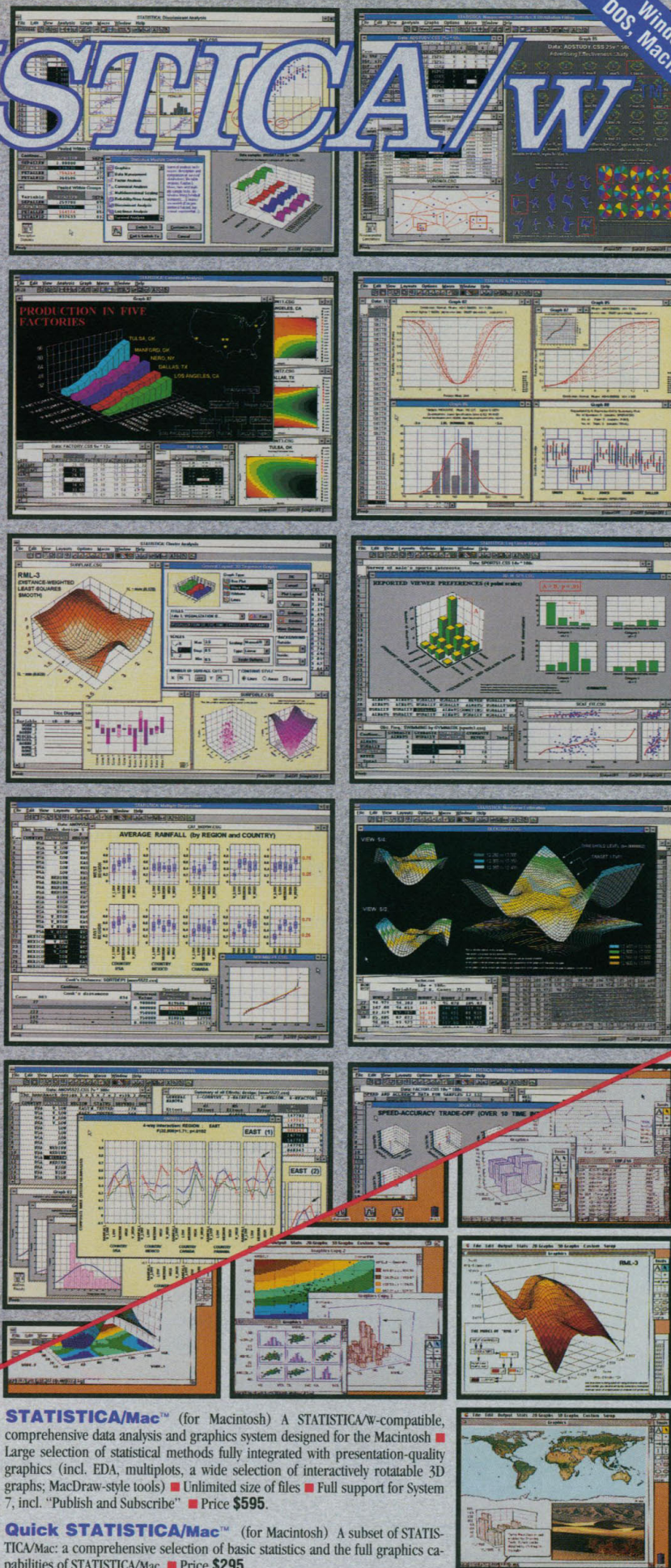


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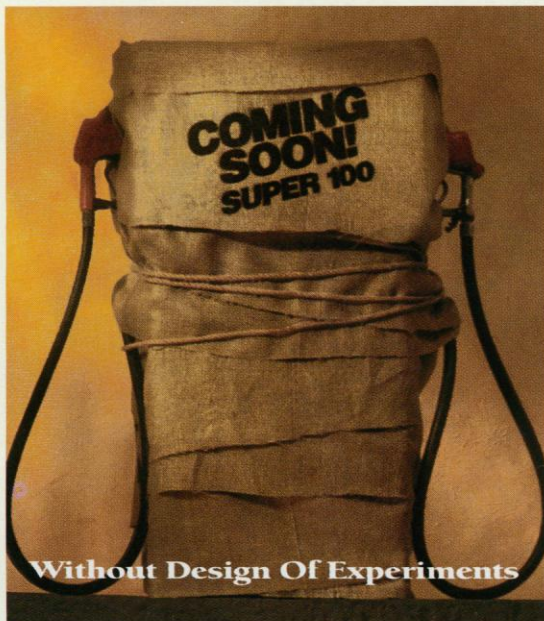
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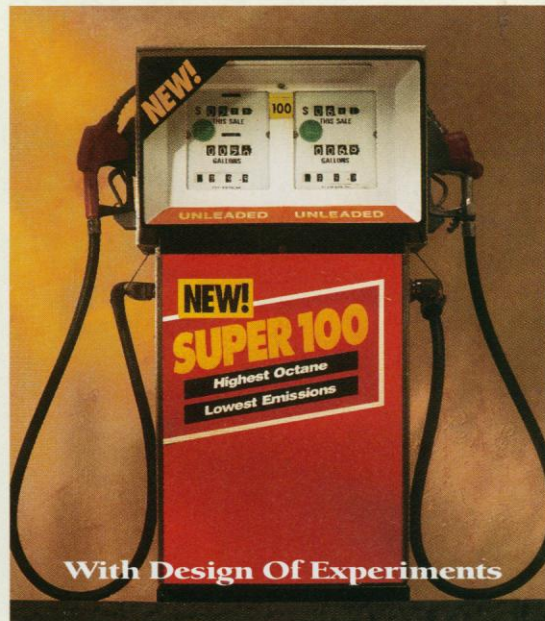
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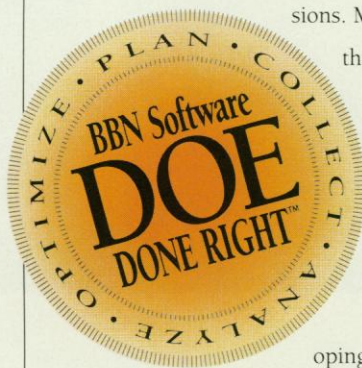
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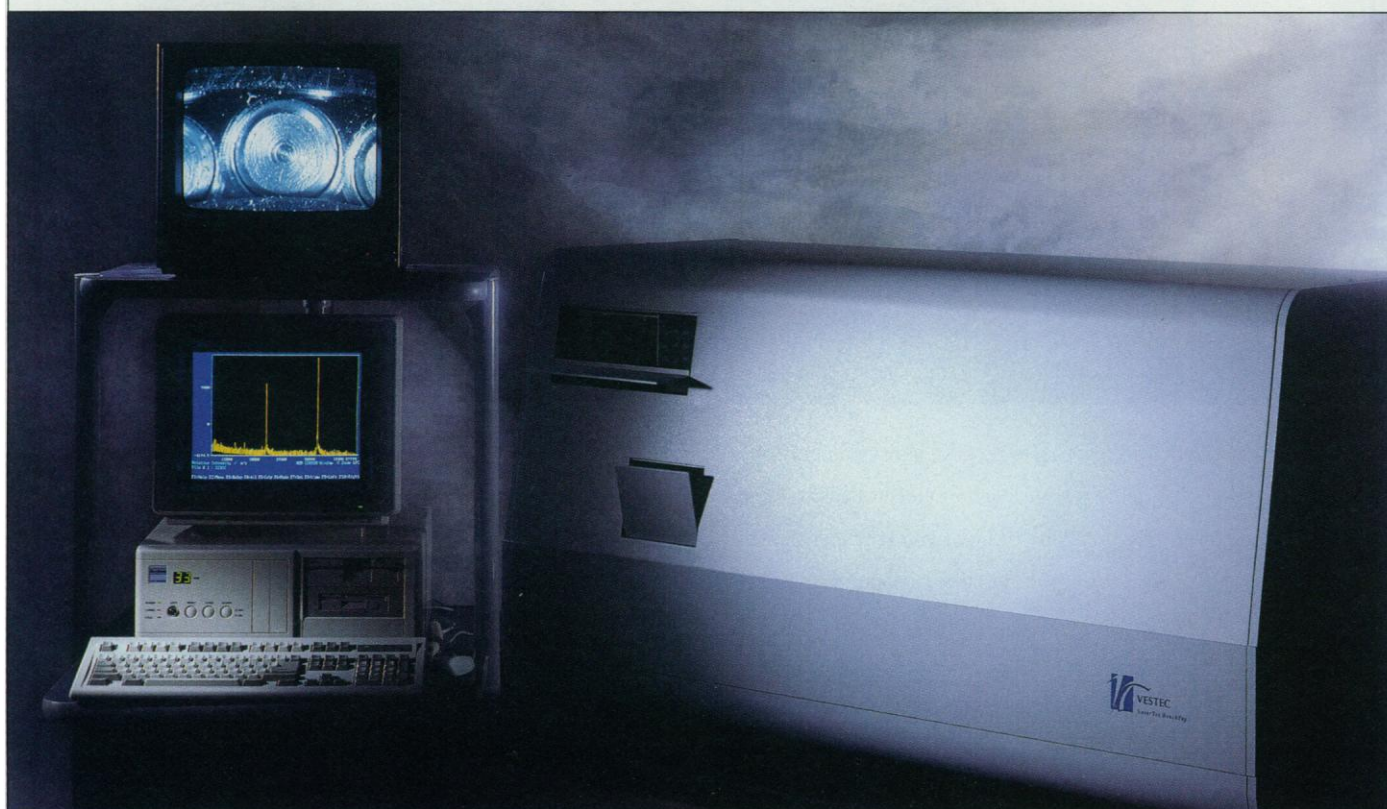
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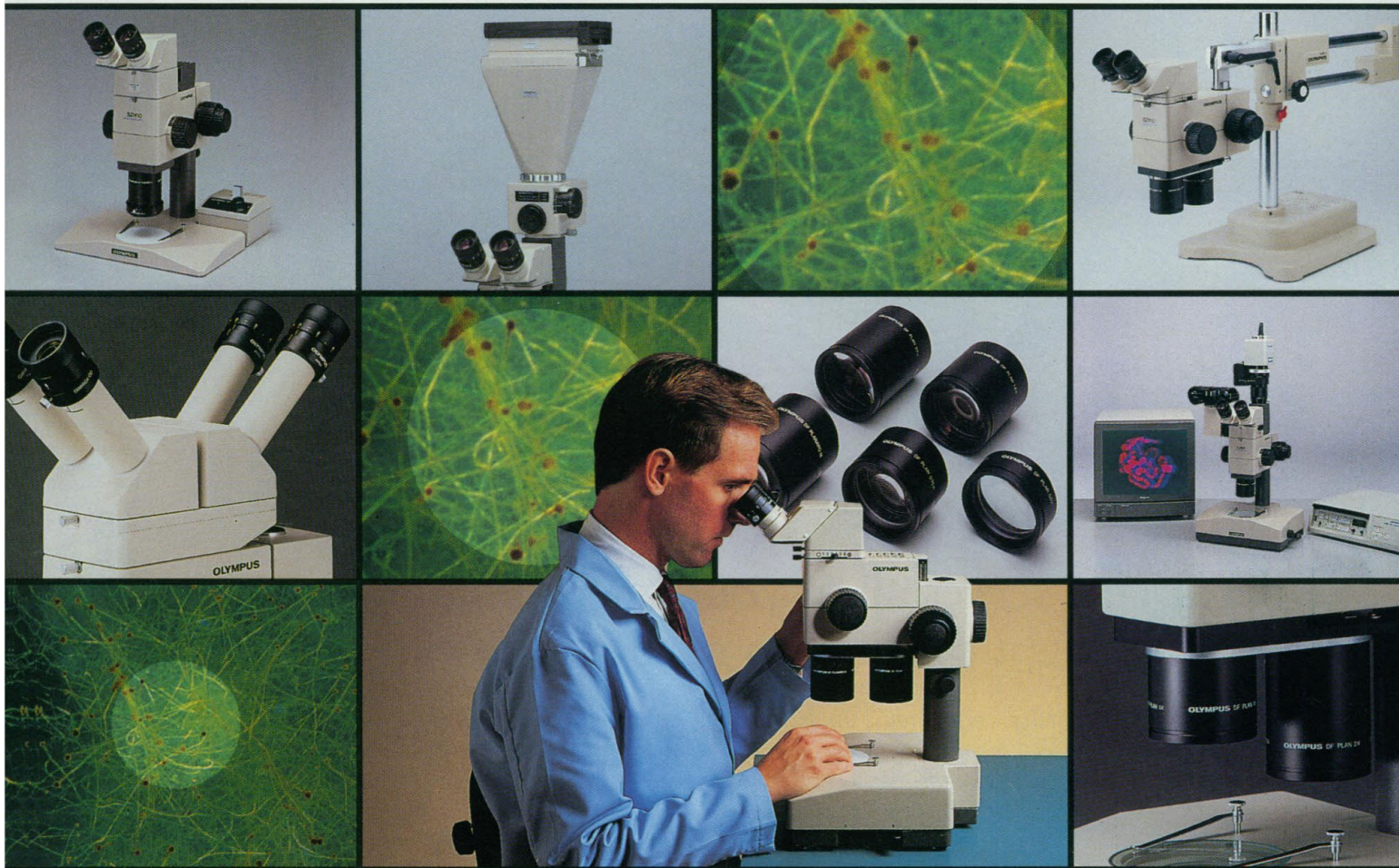
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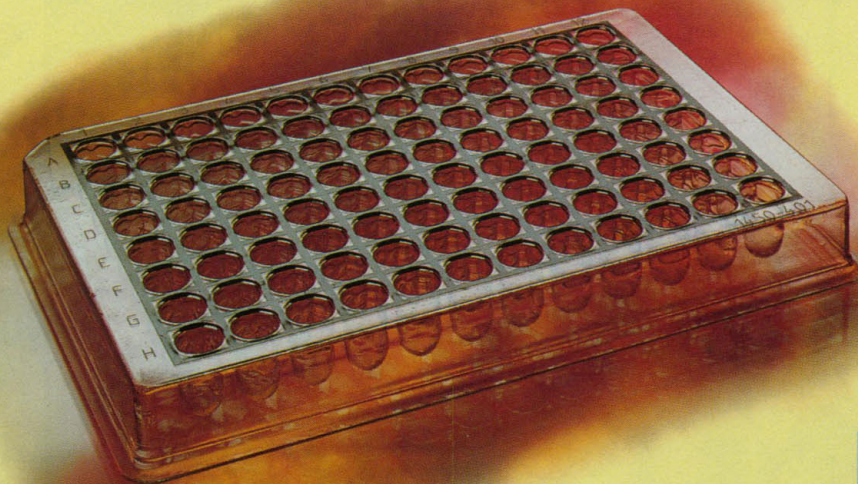
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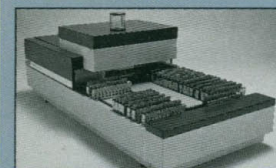
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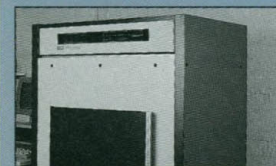


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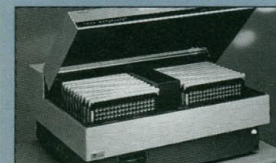
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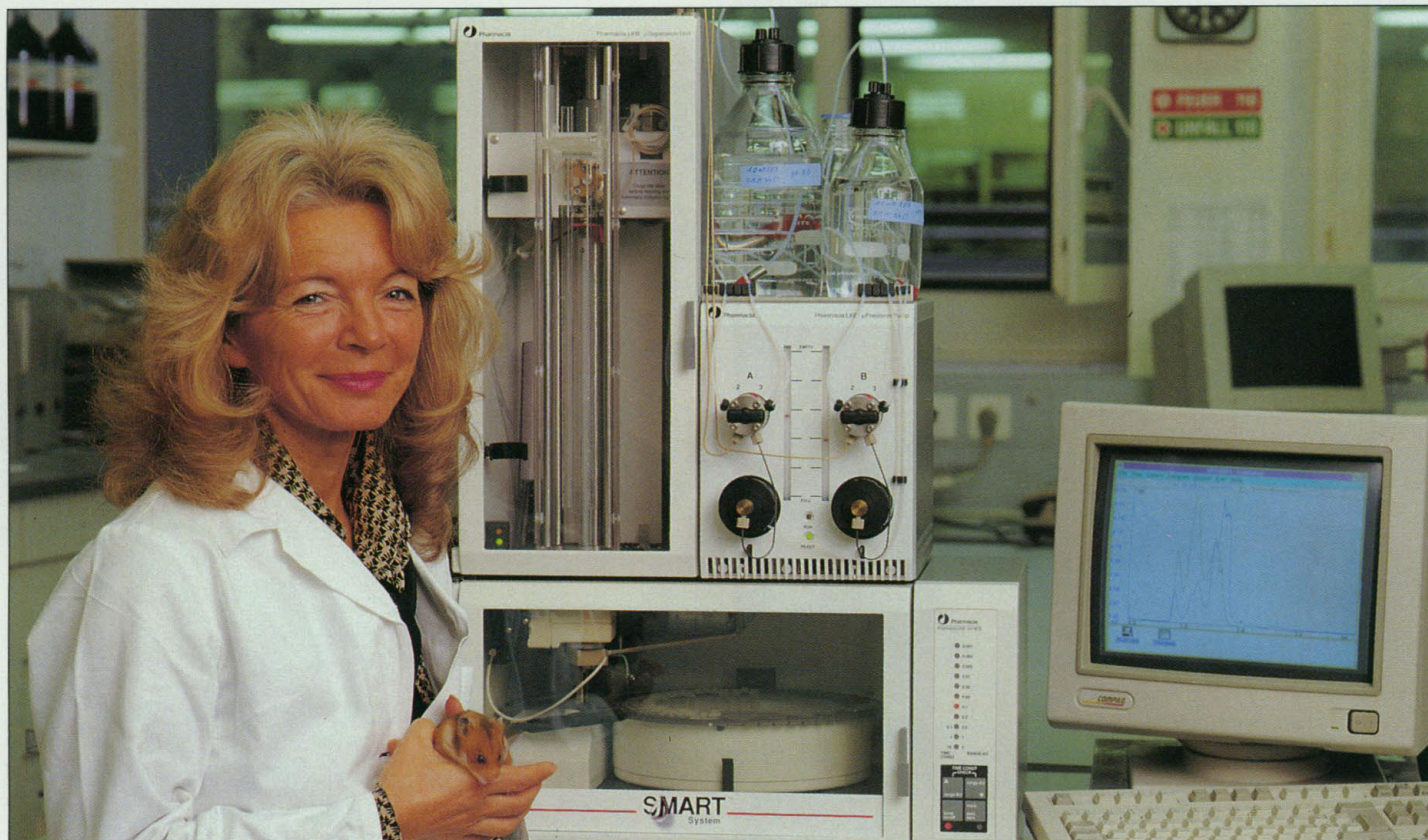
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Ulrike Hennes and colleagues at F. Hoffmann-La Roche in Basel, Switzerland, are investigating the effect of new cholesterol lowering drugs on populations of Golden Syrian male hamsters fed fat-rich diets.

Typically, one group of hamsters was fed a diet and another received the diet and a drug. After 15 days, both groups were sacrificed and their serum separated and assayed for lipoprotein and cholesterol levels.

However, the requirement for 500-1000 µl of plasma meant sacrificing several animals for each determination point. Furthermore, due to inter-individual variations, large numbers of hamsters were needed to assess the respective response with sufficient statistical certainty.

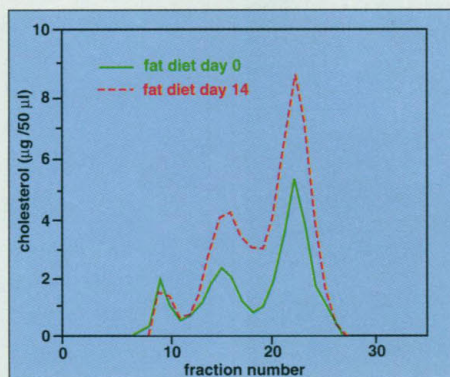
Ulrike and her colleagues then turned to SMART™ System. SMART System is a new micropurification system that recovers and purifies biologically active material present in ng and µg amounts. (With their system, the group usually recovered more than 98% of the cholesterol they applied in lipoprotein fractions.)

When samples of lipoproteins were separated on SMART System, a mere 80 µl of blood extracted from a single living hamster provided all the information Ulrike Hennes and her colleagues needed⁽¹⁾. Plasma samples from several animals were no longer necessary. In addition, SMART System further reduced the number of experimental animals needed because

the researchers could now monitor individual hamsters throughout a particular treatment period. So not only do Hoffmann-La Roche save a considerable number of experimental animals, they also get more valuable results.

Ulrike is very happy and the hamsters are naturally delighted.

1. Changes of lipoprotein patterns in hamsters under different metabolic states analysed following separation by micropreparative chromatography on SMART™ System from multiple micro plasma samplings. *Science Tools Vol. 36 No. 1 (1992)*, Hennes, U., Gross, W., Edelmann, A.



Effect of fat diet on lipoprotein pattern of an individual hamster after 14 days. SMART™ System. Superose® 6 PC 3.2/30 gel filtration column. Sample size: 20 µl. Adapted from (1).

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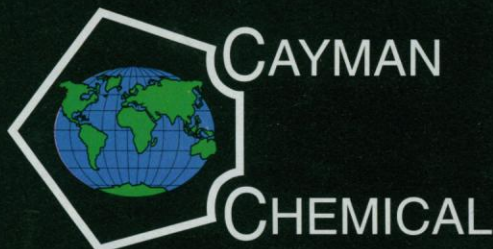
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Taormina (I), May 17-18

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B. Barlogie (USA) and F. Dammacco (I)
Evian (F), June 3-5

"Inhibin and Inhibin-Related Proteins"

H.G. Burger (AUS)
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D. Corda and S. Garattini (I)
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M.L. Aubert and P.C. Sizonenko (CH)
Geneva (CH), Sept. 30 - Oct. 2

"The Challenge of Biotechnology: from Laboratory Diagnosis to Clinical Therapy"

S.A. Aaronson (USA) and R. Verna (I)
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"Molecular Basis of Endocrine Diseases"

C. Pavía (E)
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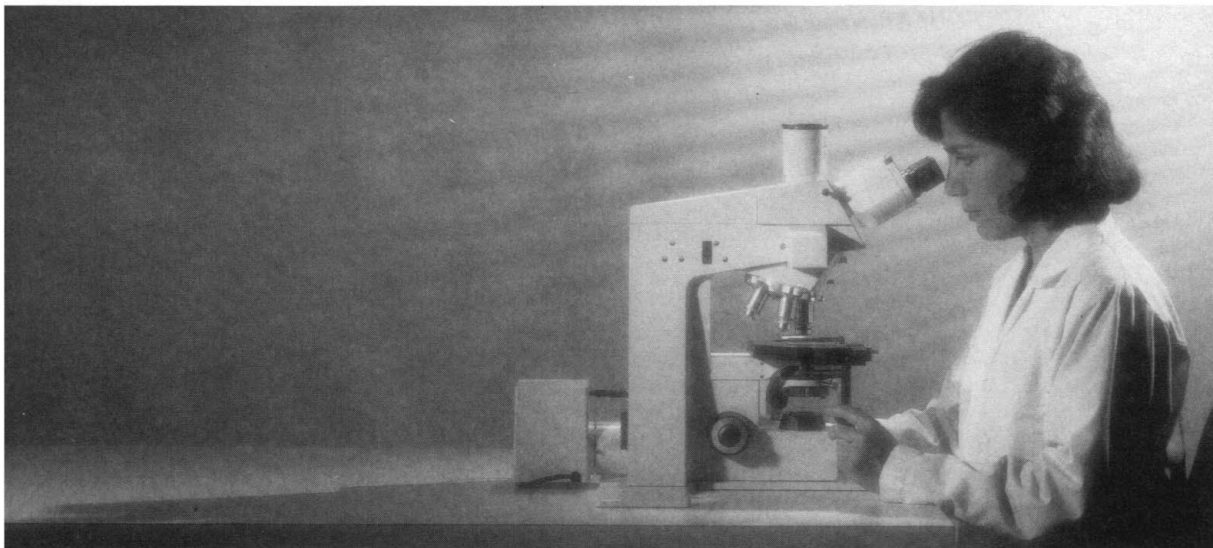
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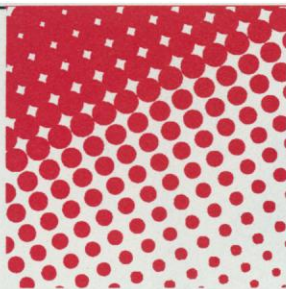
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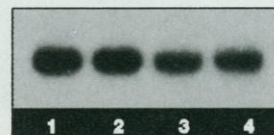
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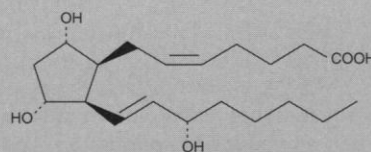
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Oxidative stress may have finally become a defined clinical entity that can be measured by immunoassay. Peroxidation of tissue phospholipids by oxygen radicals is the likely mechanism of injury in the hypoxic/reperfusion injuries associated with stroke, myocardial infarction, near-drowning and brief cardiac arrest. Unfortunately, the magnitude of a given oxidative insult has been difficult to quantify. Earlier efforts in this field concentrated on the reactive aldehydes that result from the fragmentation of oxidized fatty acids. Detection of malondialdehyde and other reactive aldehydes is the basis for a number of current tests for peroxidative tissue injury. However, the reactivity of these aldehydes with a variety of nucleophiles *in vivo* leads to a large family of different protein and DNA adducts, which can be nearly impossible to isolate and measure. The uncertain production profile in different tissues makes quantitation and interpretation difficult. Now a new enzyme immunoassay that detects and quantifies 8-isoprostanes may



8-isoprostane α
 (8-epi prostaglandin F_{2α})

make the measurement of oxidative injury more accurate.

8-isoprostanes are a group of cyclopentane-containing lipids that bear a close structural resemblance to the prostaglandins. The isoprostanes were discovered in 1990 by J.D. Morrow and L.J. Roberts^{1,2} at Vanderbilt University as an artifact in their samples drawn for the determination of eicosanoid content. While using GC/MS to determine the concentration of the major plasma Prostaglandin D₂ metabolite 11β-PGF_{2α}, the researchers noted the the PGF content of their samples seemed to increase in a linear fashion with respect to storage time. Closer inspection revealed that the newly generated PGF-like material was in fact an isomer with identical mass which resulted from lipid peroxidation in the stored samples. More interesting was the

observation that in rats ingesting carbon tetrachloride, the acute hepatitis resulting from oxidative metabolism of the xenobiotic was accompanied by a sharp increase in the plasma 8-isoprostane level. Using fast atom bombardment techniques, R.C. Murphy and his colleagues³ at the National Jewish Center in Denver were able to obtain mass spectra of the 8-isoprostane still attached to the 2-position of glycerol in the rat liver phospholipids. Subsequent hydrolysis by PLA₂ released the free isoprostane that was detected in the blood. These results indicated that a known oxidative assault on tissues (in this case by the trichloromethane radical) was accompanied by a corresponding increase in plasma isoprostanes.

Cayman Chemical Company of Ann Arbor, Michigan, who synthesized and supplied the authentic 8-isoprostane to the Vanderbilt group, has now developed a sensitive and specific enzyme immunoassay for this substance. For more information, call 313-662-6756 or fax 313-662-6896.

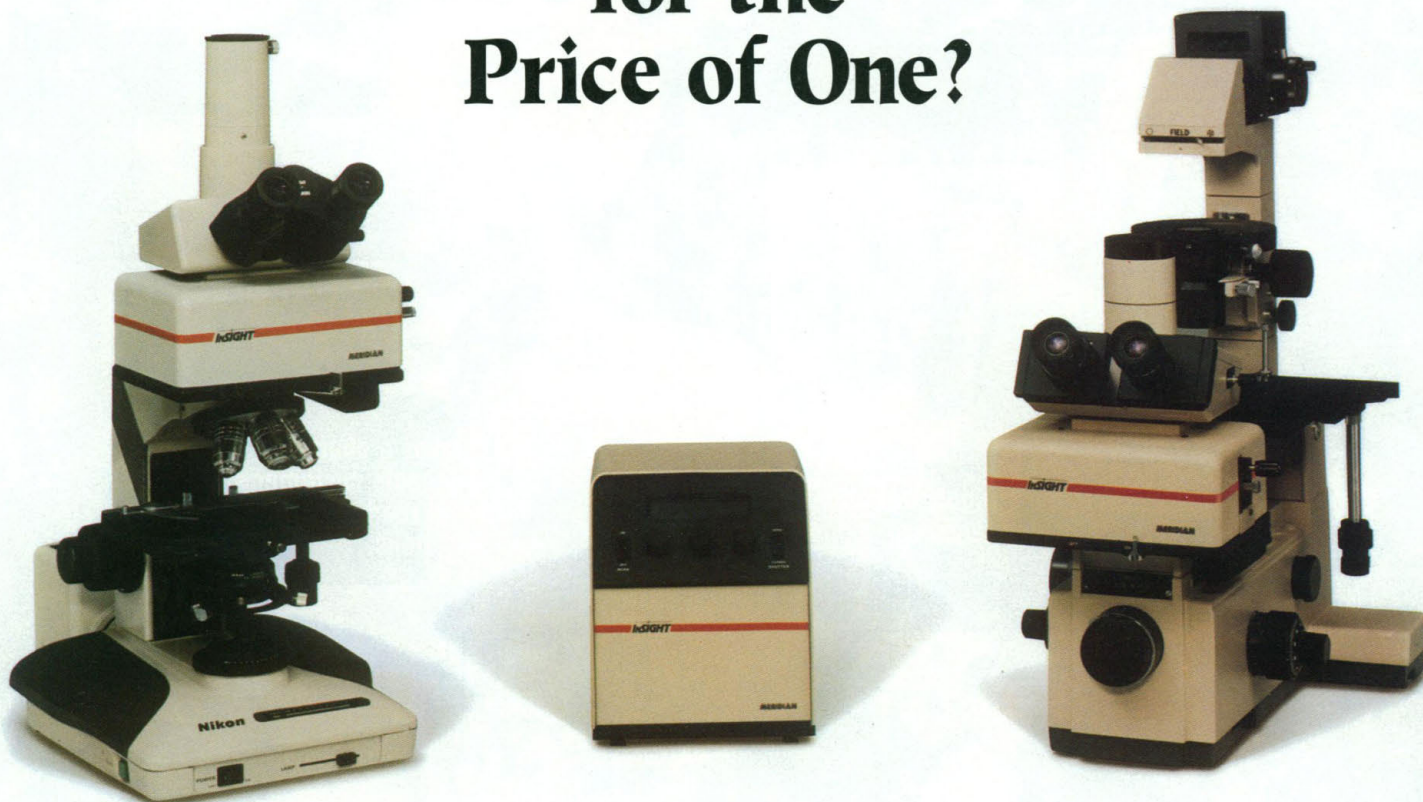
1. *Proc. Natl. Acad. Sci. USA* (1990) 87, 9383-9387
2. *Anal. Biochem.* (1990) 184, 1-10
3. Personal Communication

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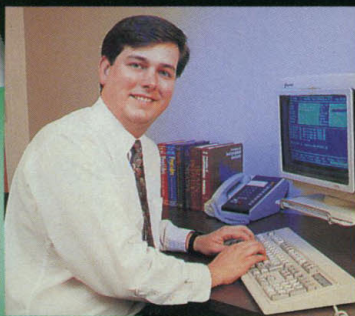
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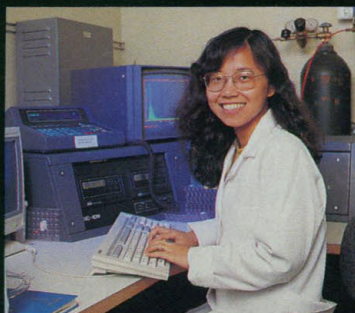
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