

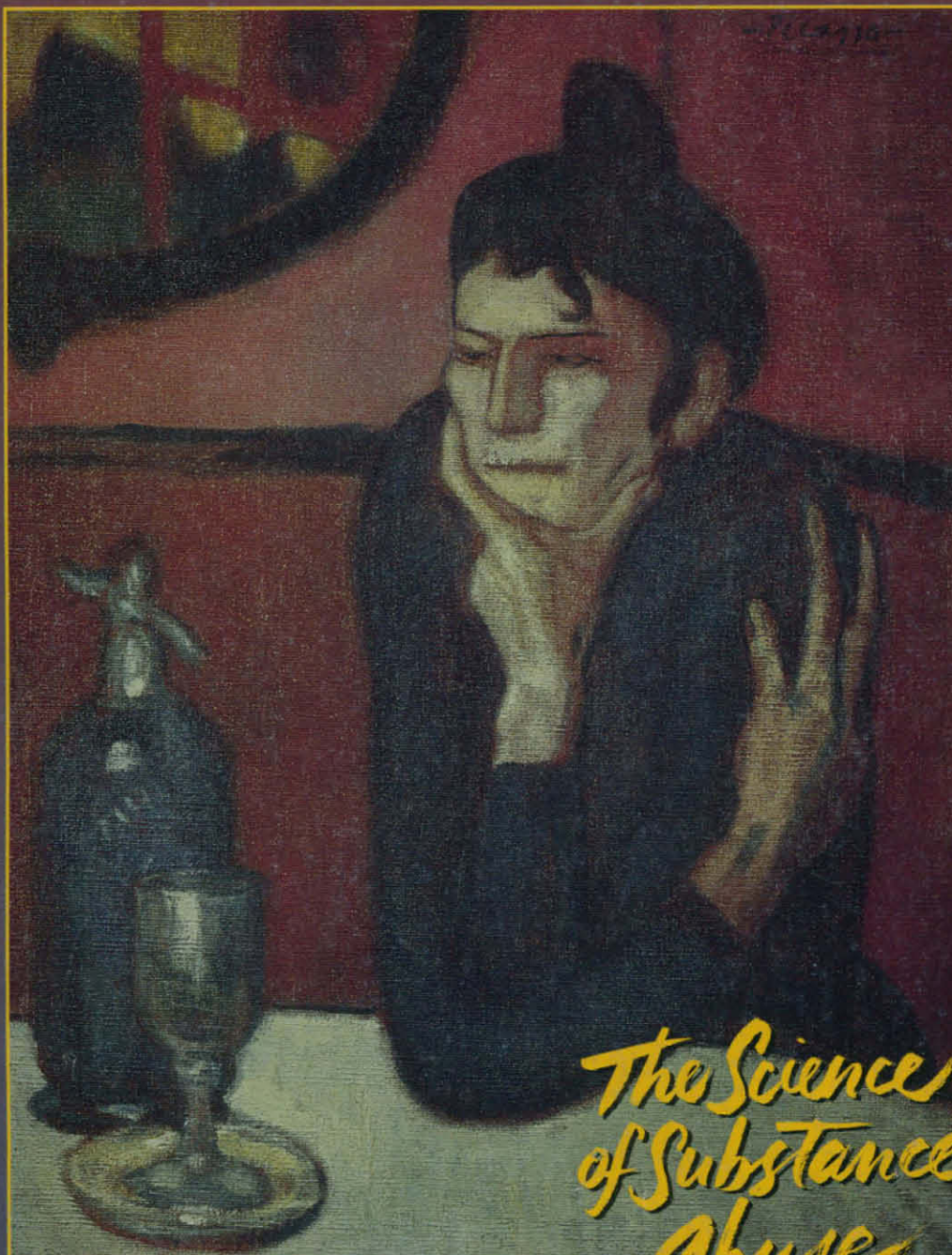


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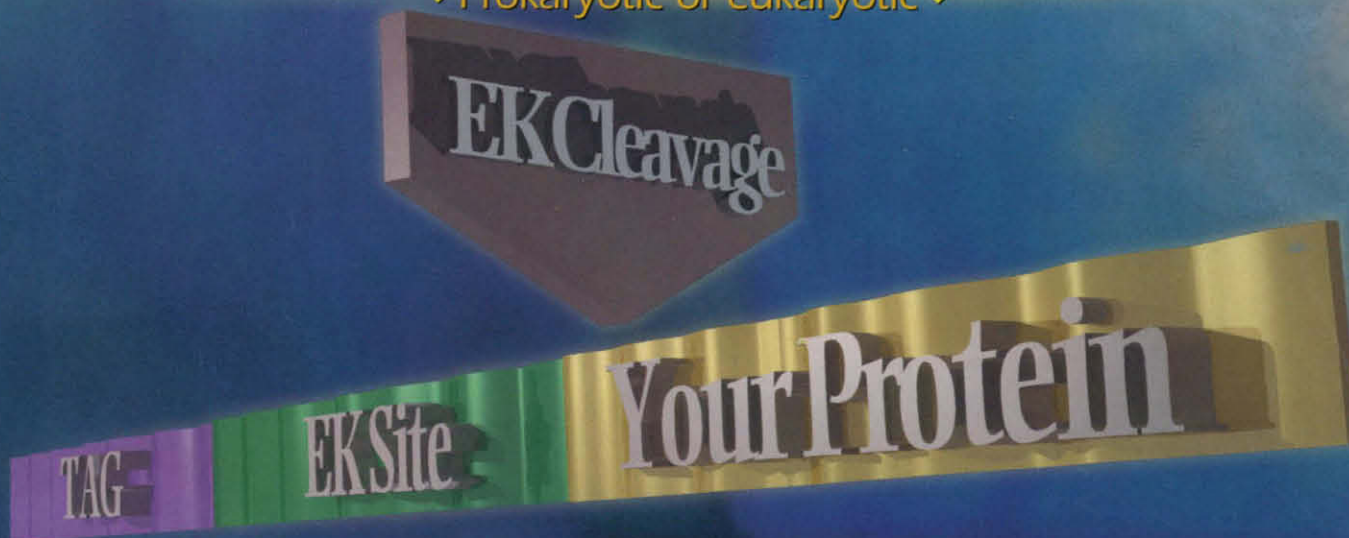


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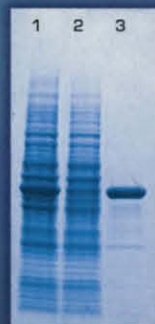
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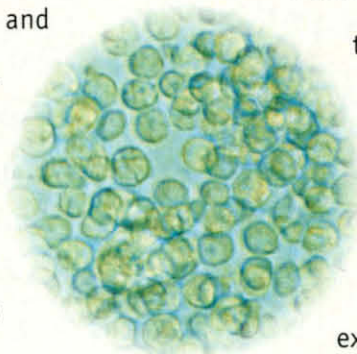
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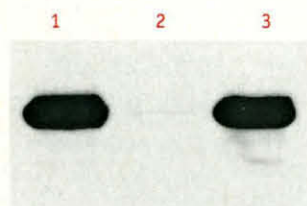
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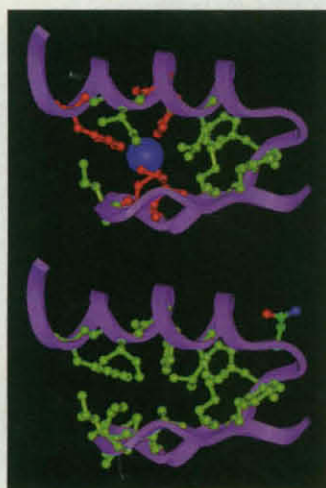
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De novo protein design

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COVER

Picasso's *The Absinthe Drinker* (1901). Absinthe, a concoction of distilled spirits and plant extracts, was a favorite narcotic in the Parisian cafes of the 19th century. Its intoxicating qualities, enjoyed by Toulouse-Lautrec and Modigliani among others, led to interdiction in France

in 1911. The editorial (p. 15), news stories (p. 35), and six articles (p. 45) discuss policy implications of findings about addictive substances, the biology of addiction, and new approaches to therapy. [Photo of painting: Erich Lessing/Art Resource; calligraphy by Bernard Maisner]



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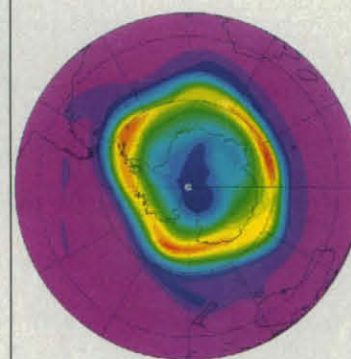
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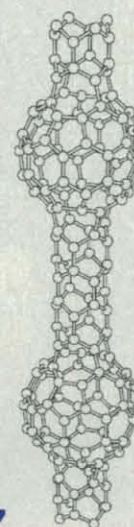
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Nanotubes for nanodevices

Indicates accompanying feature

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THIS WEEK IN SCIENCE

edited by PHIL SZUROMI

From defects to devices

Defects along carbon single-wall nanotubes (SWNTs) can produce abrupt changes in their local electrical characteristics. Collins *et al.* (p. 100; see the Perspective by Saito, p. 77) extracted SWNTs from bundles, or "ropes," of tubes (for distances up to 2 micrometers) with a scanning tunnel microscope tip, which adhered strongly to the end of the tube. As the tube was extracted, the conductivity could abruptly change upon slight movement (a few nanometers) from a response typical of graphite to one that was highly nonlinear and rectifying. Such abrupt "on-off" character could potentially be used in devices.

Extra deliveries

Rocks from the Lower Ordovician (dating from about 480 million years ago) found in Sweden contain abundant small meteorites compared with older and younger rocks. Schmitz *et al.* (p. 88) collected additional meteorite samples from these rocks and show using osmium isotopes and iridium concentrations that the influx of cosmic matter to the Earth increased at this time by about an order of magnitude. They speculate that the increased dust may be related to other evidence of a major impact or disruption of a meteorite parent body at this time.

Designer protein

A computational algorithm based on physical chemical potential functions and stereochemical constraints has been used to screen a large library of possible amino acid sequences against a design target. Dahiyat and Mayo (p. 82; see the Perspective by DeGrado, p. 80) screened 1.9×10^{27} combinations to obtain full sequence design 1 (FSD-1), a 28-residue protein that was designed to adopt a $\beta\beta\alpha$ motif

Winter ozone hole

The processes leading to the Antarctic ozone hole have been studied intensively, but because of technical difficulties in performing measurements during the polar winter, when little sunlight reaches the Antarctic, most measurements are constrained to latitudes below 75° throughout winter. Roscoe *et al.* (p. 93) present total ozone measurements at Faraday at 65°S throughout the winters of 1990, 1991, and 1994, and show that ozone depletion starts in June. Model calculations indicate that this is not an isolated phenomenon and that ozone destruction starts at the edge of the sunlit vortex in midwinter.

of a zinc finger domain. The solution structure indicates that the protein adopts the targeted fold.

Actively unresponsive

Under the wrong circumstances, T cells can be turned off, instead of on, by the antigen for which they are specific. Boussiotis *et al.* (p. 124) found that the resultant state of unresponsiveness, called anergy, is maintained by the presence of an activated small G protein, Rap1. Thus, the inability to respond to antigen is not only due to a break in the signaling pathway that culminates in the production of the cytokine interleukin-2, but to the active turning on of an alternative pathway.

Weighty factor

Body weight can be regulated by interactions of neuropeptides and their receptors. Agouti peptide, normally expressed in the skin where it regulates pigmentation, can cause obesity when overexpressed in mice. Agouti-related peptide (AGRP) shares some sequence similarity with Agouti, but, as shown by Ollmann *et al.* (p. 135), differs in expression and signaling properties. AGRP, normally expressed in the adrenal glands and the hypothalamus, binds a specific subset of the receptors available to Agouti. Overexpression of AGRP in mice affects body weight but not pigmentation.

CAML with two humps

The CAML protein (calcium-signal modulating cyclophilin ligand) was originally identified as interacting with cyclophilin B and thus thought to participate in the cellular actions of the immunosuppressant cyclosporin A and regulation of the transcription factor NF-AT in lymphocytes. Von Bülow and Bram (p. 138) have now identified another protein, called transmembrane activator and CAML-interactor, or TACI, that interacts with CAML. TACI is a member of the tumor necrosis factor receptor superfamily, and cross-linking of TACI with antibodies leads to activation of NF-AT and other transcription factors. Their results suggest the existence of unusual signaling mechanism in which interaction of the cell surface receptor TACI with CAML, which is found on intracellular vesicles, appears to be required for activation of NF-AT in response to TACI.

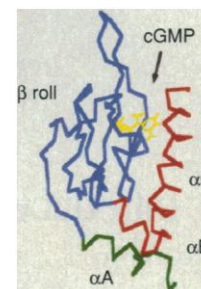
Heat shock proteins versus cancer

One of the most intractable problems in cancer treatment today is metastasis. Tamura *et al.* (p. 117) examined nonimmunogenic tumors of various histologic origins in a mouse model of metastatic cancer. They isolated the heat shock protein GP96, bound to random peptides from its cellular milieu, from either the primary tumor or a metastatic variant and injected it into mice that had well-established

tumors. Primary tumors as well as metastases regressed, and lifespan was extended.

Tuning channels

Cyclic nucleotide-gated ion channels in olfactory and retinal receptor cells are involved in the response to sensory stimuli. Varnum and Zagotta (p. 110) show that the amino-terminal



domain of the channel, which does not bind to the ligand but to the calcium sensor calmodulin, plays a direct role in "tuning" the channel-gating properties after ligand binding in response to intracellular calcium levels.

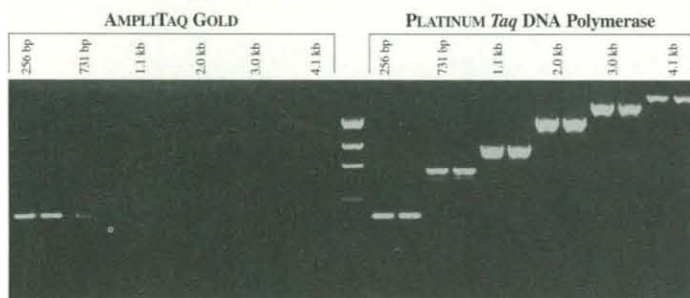
Oligomeric signal

The response of yeast to mating pheromone occurs through a complicated signaling pathway that has similarity to signaling pathways in vertebrates. Binding of the pheromone to its receptor activates a heterotrimeric guanine nucleotide-binding protein (G protein). The β subunit of the G protein apparently "talks" to a protein, Ste5, which serves as a scaffold for a series of protein kinases that propagate the signal. Inouye *et al.* (p. 103) show that oligomerization of Ste5 is necessary and sufficient for signaling. They define a protein domain within Ste5 that is required for interaction with the G protein and for dimerization. Similar domains occur in other proteins including BRCA1, the human breast cancer susceptibility-determining protein.

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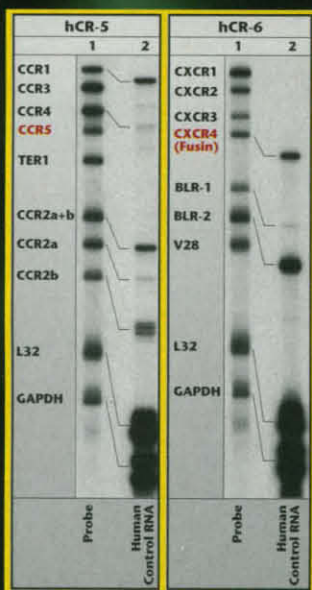
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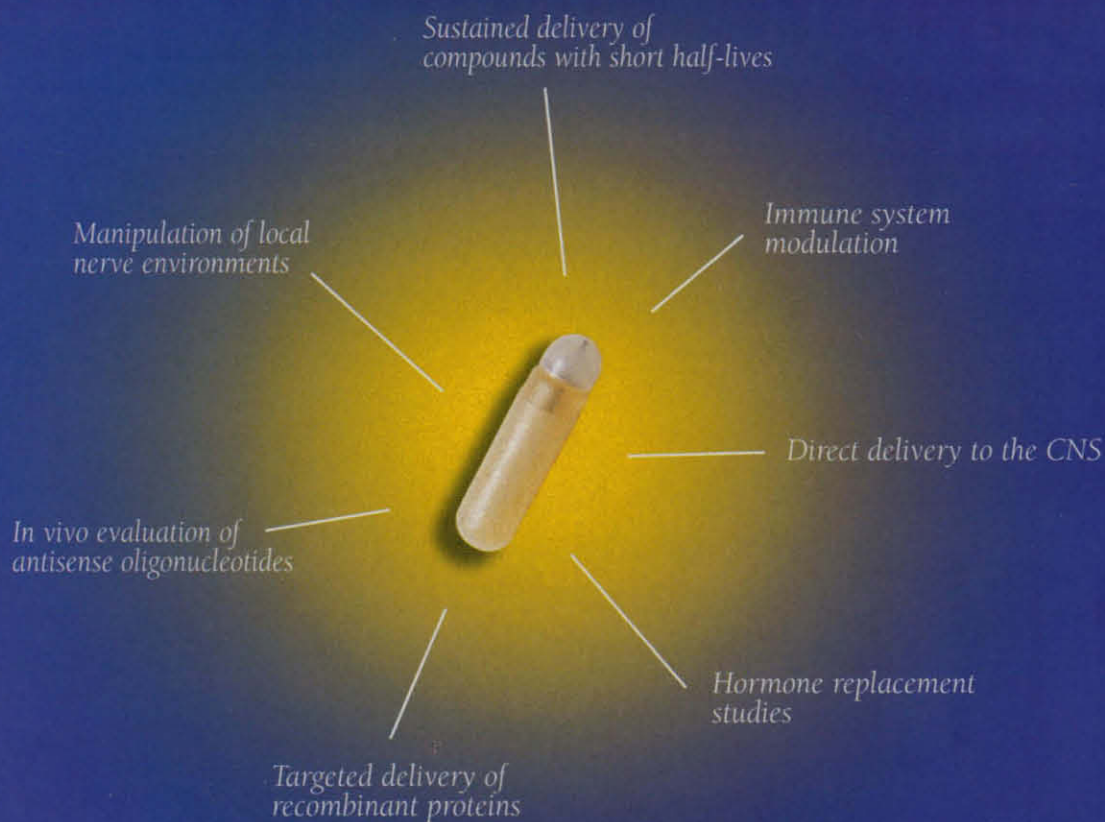
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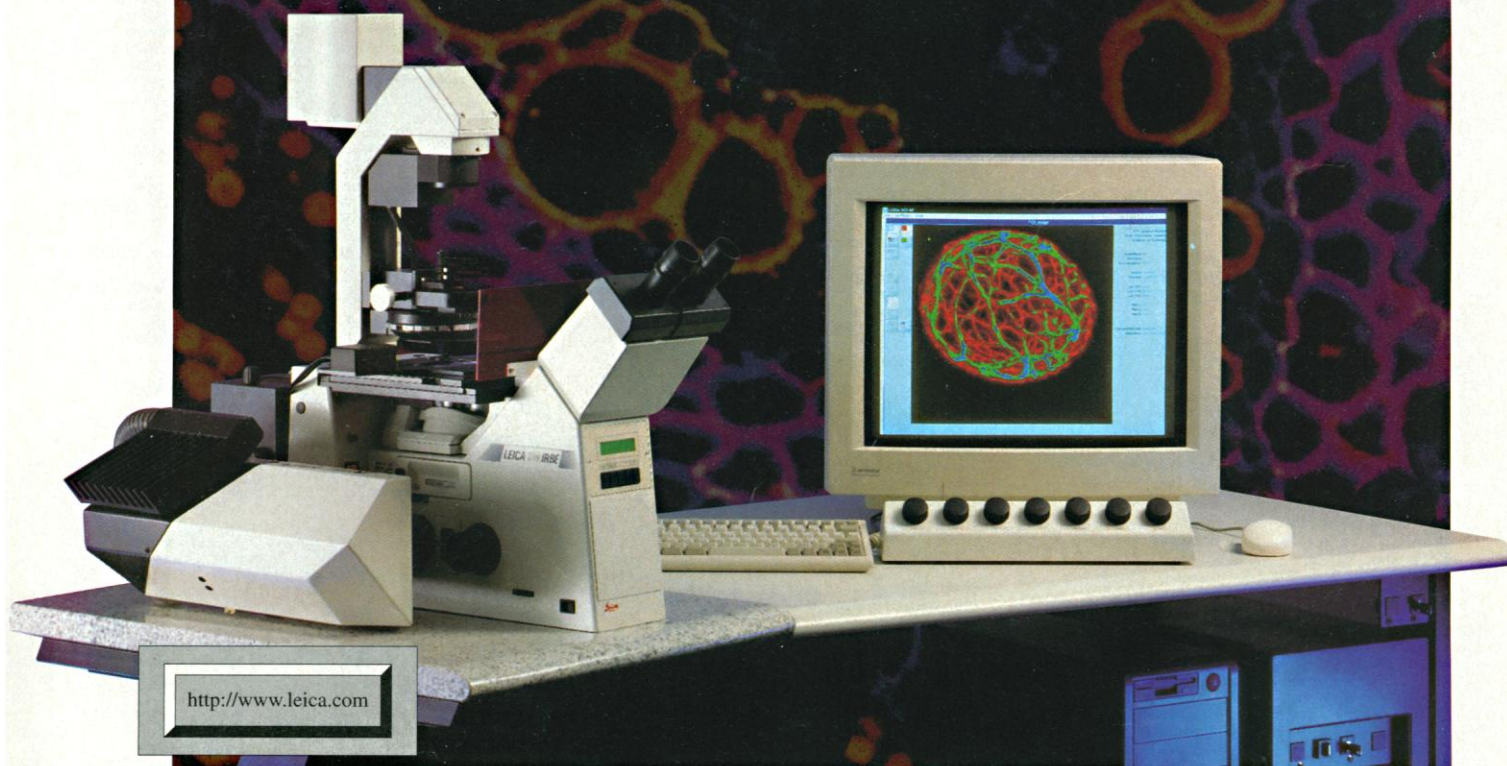
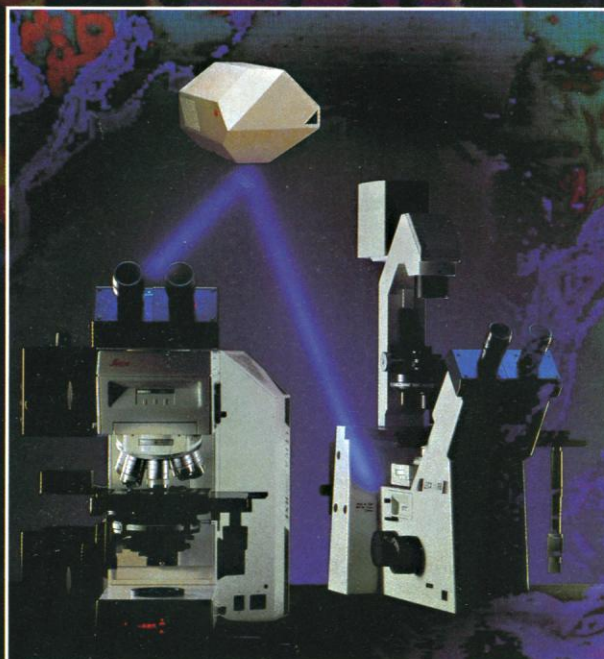
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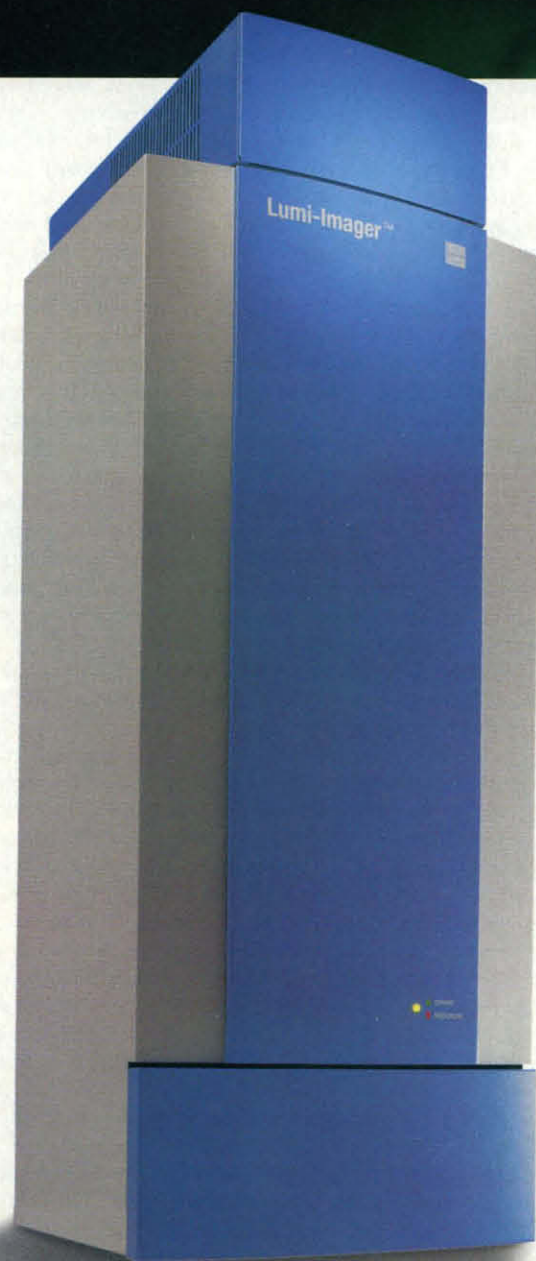
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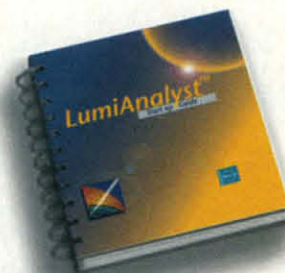


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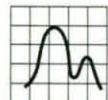
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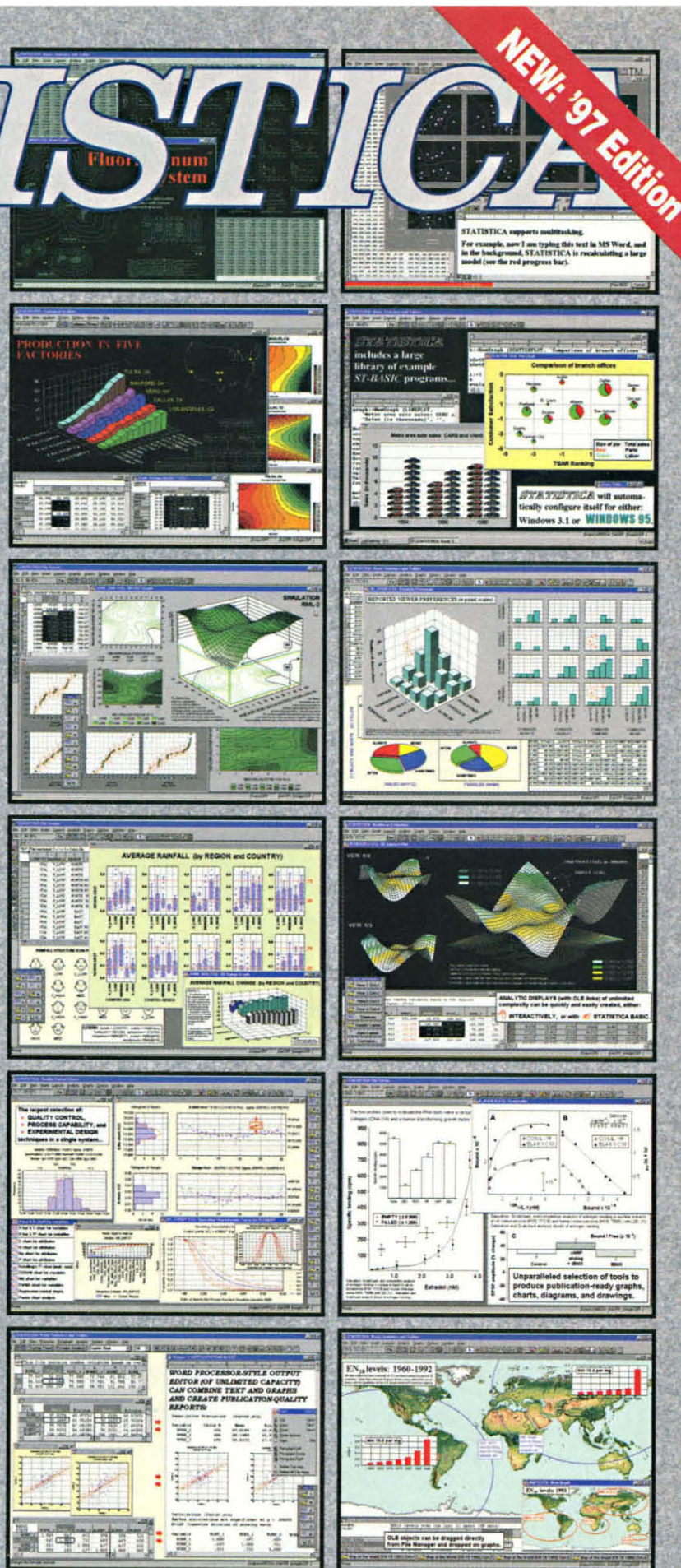
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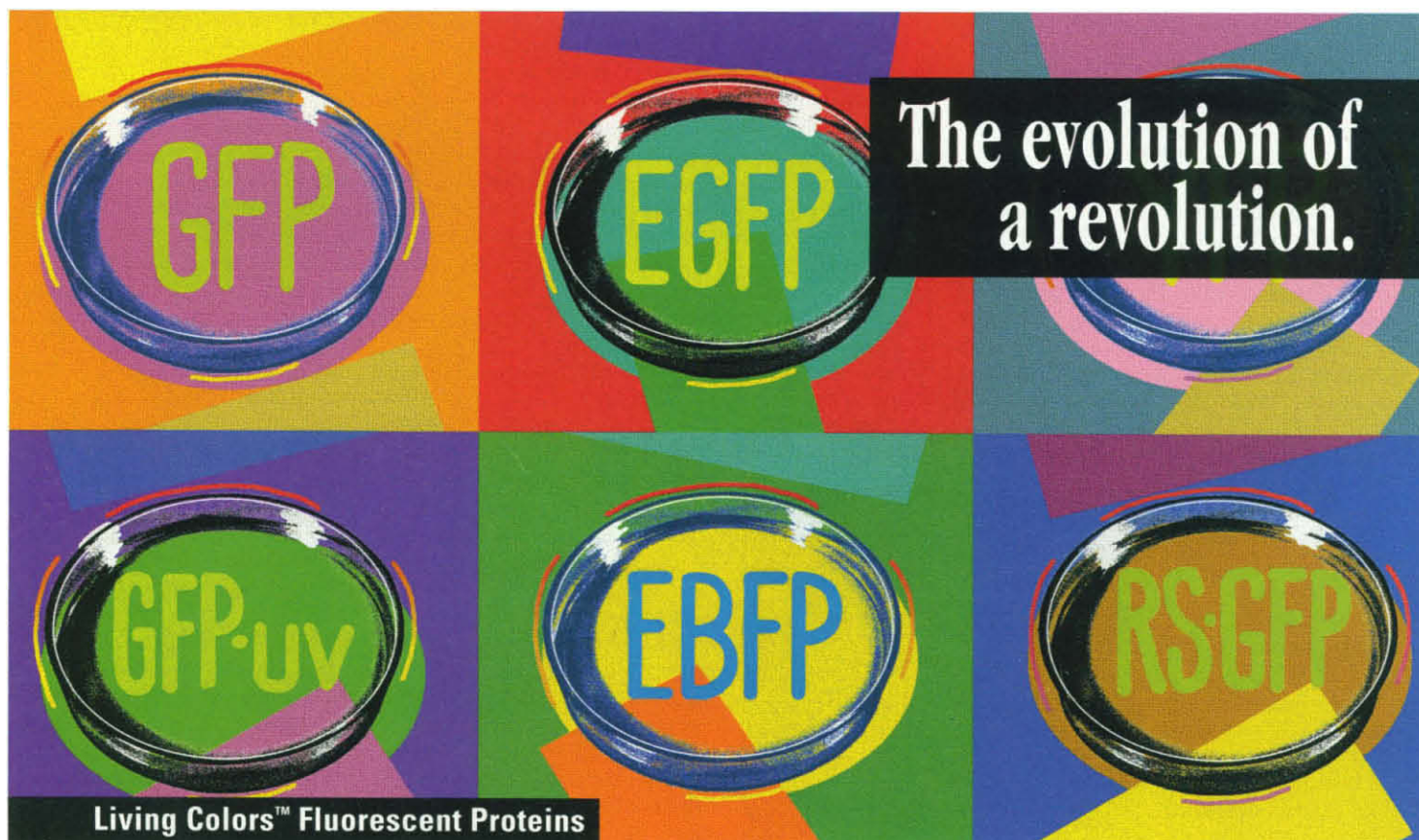
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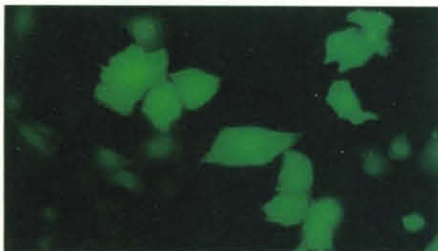




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Fig. 1. Sensitive detection of integrated HPV in SiHa cells using TSA-Direct (Cyanine 3 FISH). Biotinylated HPV-16 E6 DNA probe (1000 bp) hybridized to cultured SiHa cells. TSA fluorescence detection used Streptavidin-HRP followed by Cyanine 3 Tyramide. Slide counterstained with Hoechst 33342 (Molecular Probes, Inc.) and evaluated using separate tetramethylrhodamine and DAPI filters. Photo taken on KODAK 1000 speed film with 5 second (Cyanine 3 Tyramide) and 0.5 second (Hoechst 33342) double exposure using a 100X objective.

Fig. 1

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Figs. 2a-d. Comparison of HPV fluorescence detection using Cy™3-conjugated Streptavidin versus TSA-Direct (Cyanine 3 FISH). Biotinylated HPV-16 E6 DNA probe hybridized to cultured CaSki cells.

2a-b. Standard fluorescence detection carried out with Cy™3-conjugated Streptavidin (Jackson ImmunoResearch Laboratories, Inc.). TSA-enhanced fluorescence used Streptavidin-HRP followed by Cyanine 3 Tyramide. Slides counterstained with Hoechst 33342 (Molecular Probes, Inc.) and evaluated using a tetramethylrhodamine filter. Photos taken using KODAK 1000 speed film with a 1 second exposure using a 40X objective.

2c-d. Protocol same as above but counterstained slides evaluated using a multiband pass filter. Photos taken using KODAK 1000 speed film with a 1 second exposure using a 40X objective.

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Fig. 3a-b. Comparison of standard fluorescence detection using Cy™3-conjugated Streptavidin versus TSA-Direct (Cyanine 3). Courtesy of Kevin Roth, M.D., Ph.D., Washington University School of Medicine, St. Louis, MO. Bouin's fixed, paraffin embedded mouse intestinal tissue, deparaffinized and incubated with biotinylated wheat germ agglutinin. Sections incubated with Cy3-conjugated Streptavidin (3a) or with Streptavidin-HRP followed by Cyanine 3 Tyramide (3b). Wheat Germ Agglutinin labels intestinal epithelial cells at the base of the crypts.

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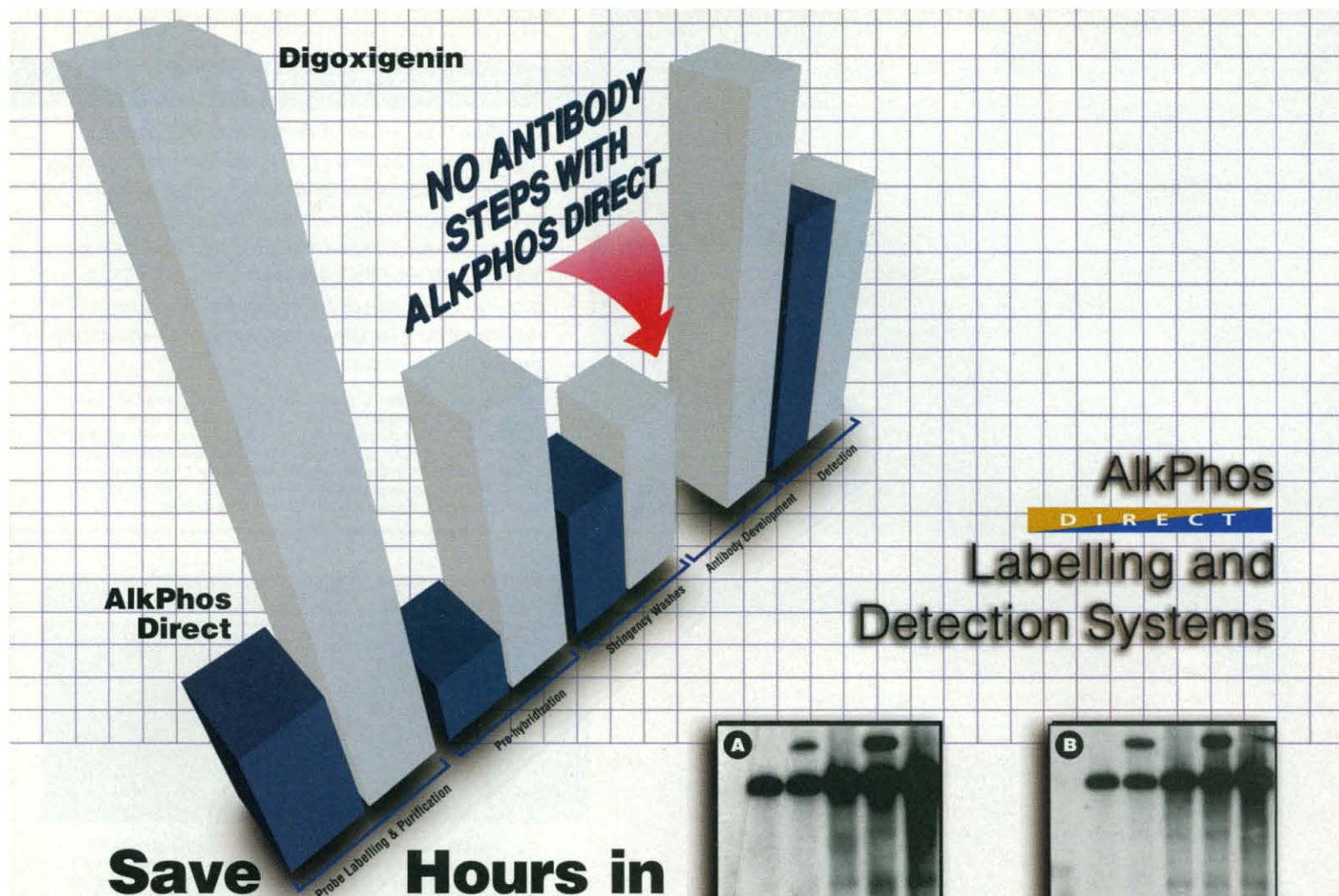
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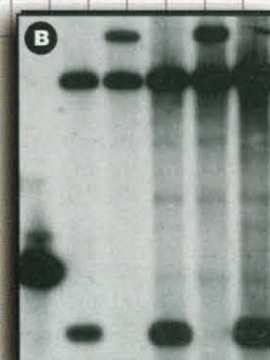
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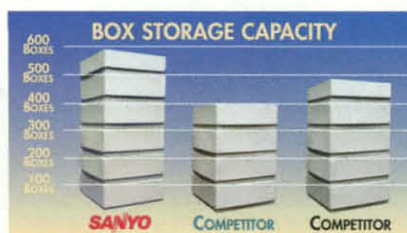
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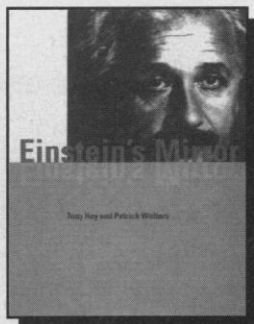
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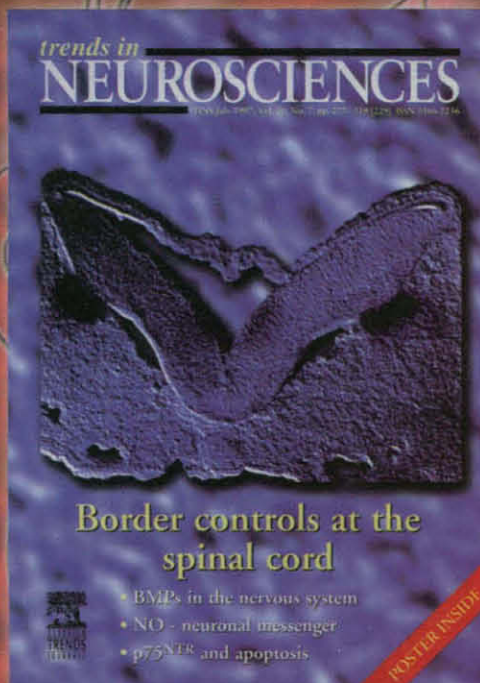
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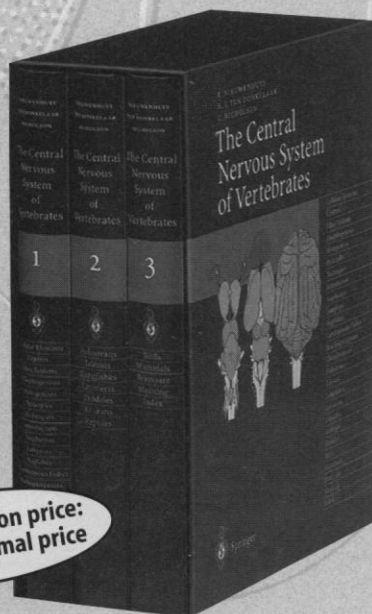
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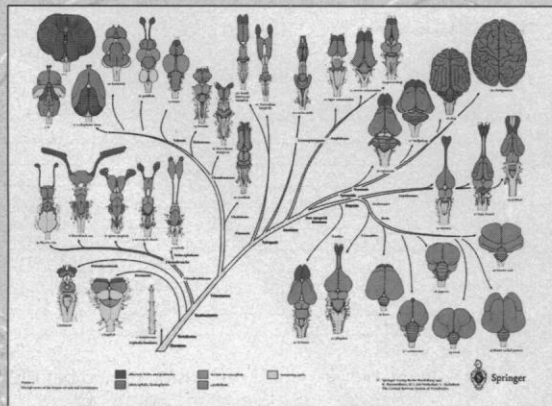


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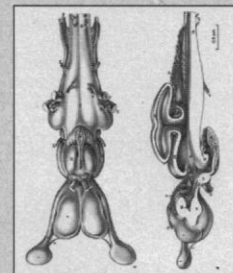
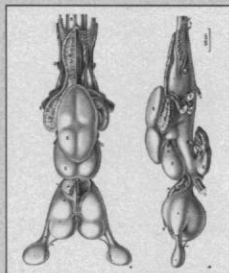
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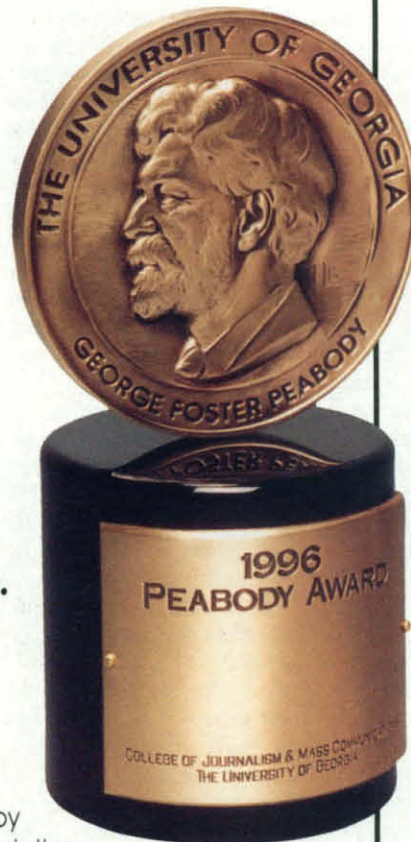
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Albert H. Teich, Stephen D. Nelson and Celia McEnaney, editors

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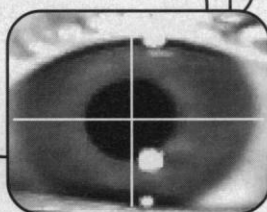


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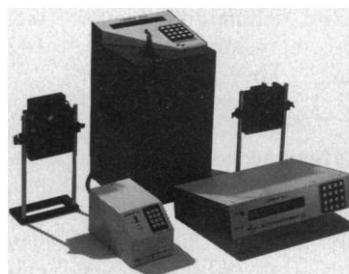
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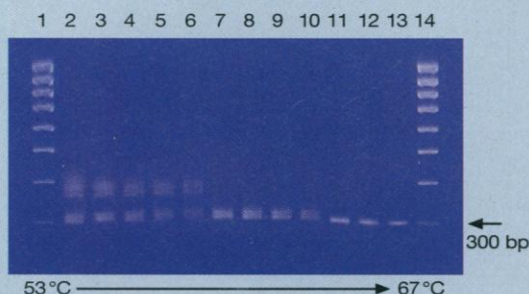
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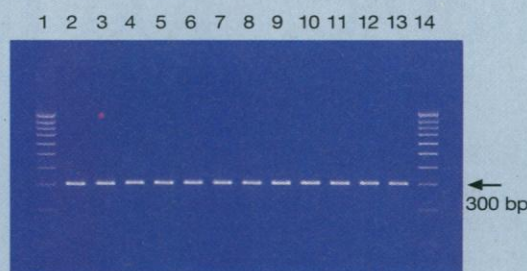
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● **Fig. 1:** Experimental determination of optimal annealing temperature: The calculated primer annealing temperature was 56.5 °C, the actual annealing temperature is 63.5 °C. The ribosomal spacer region of mycoplasmas from H9 cell cultures was amplified.

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● **Fig. 2:** Amplification shown in fig. 1 performed under optimized temperature conditions. In this experiment, the universal block was set to a **uniform temperature** in the annealing phase. The outstanding temperature

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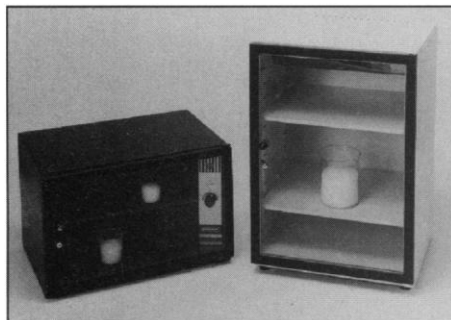
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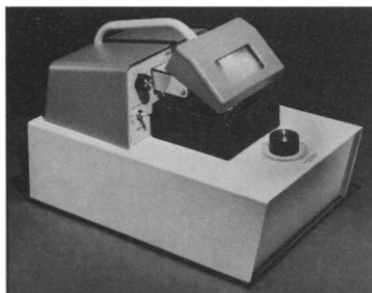
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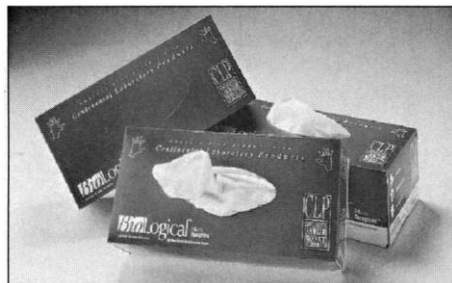
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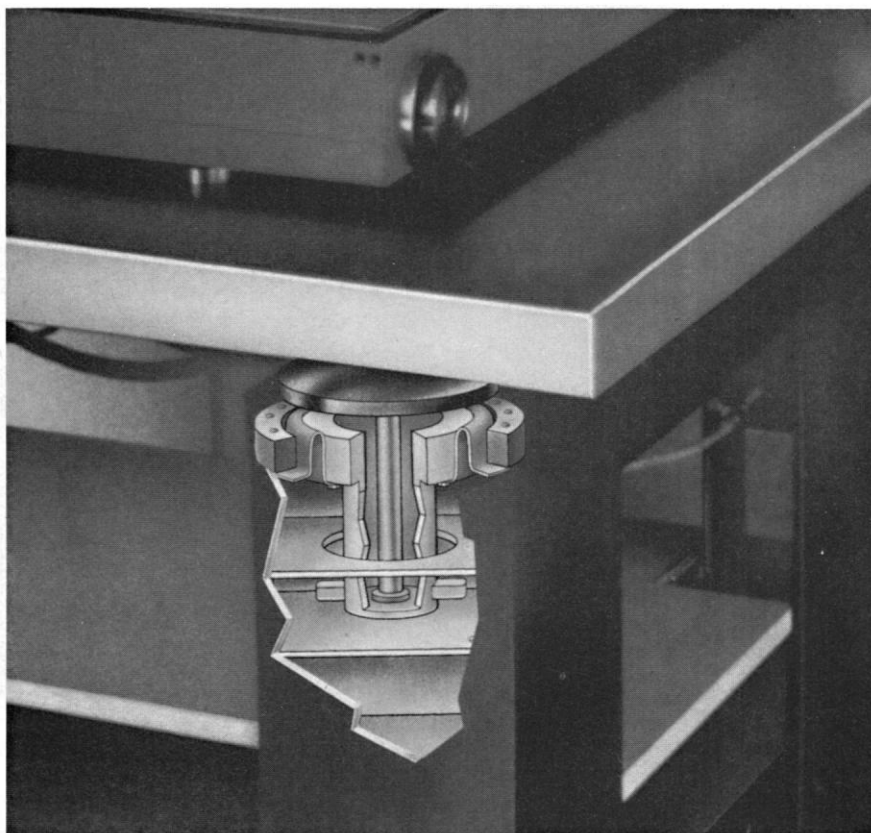
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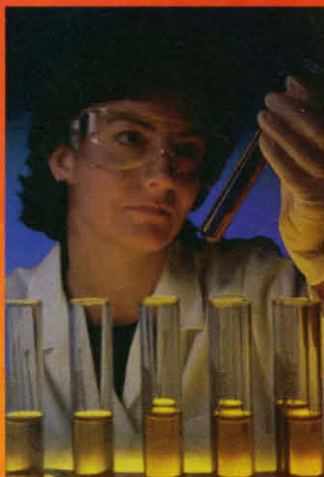
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