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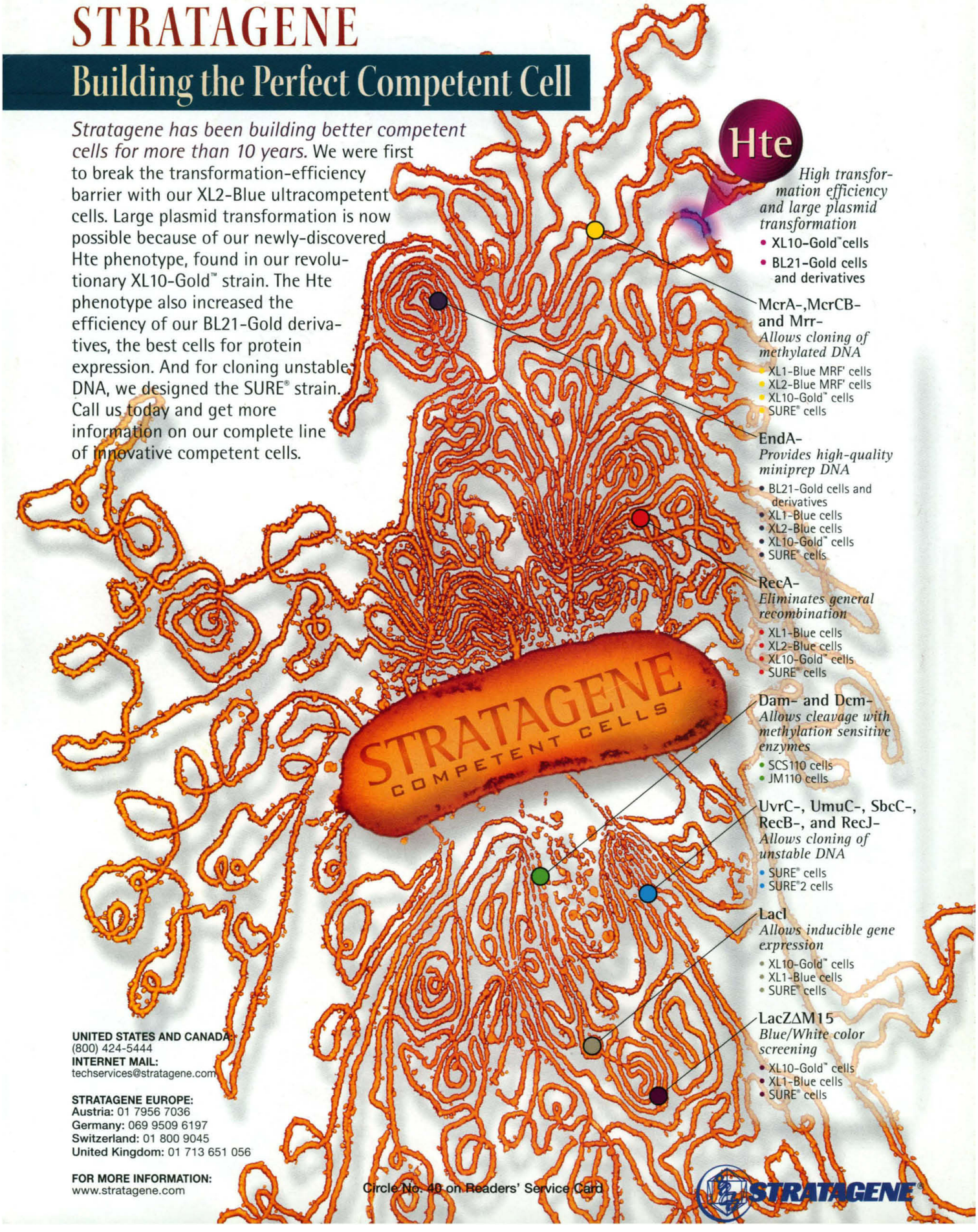

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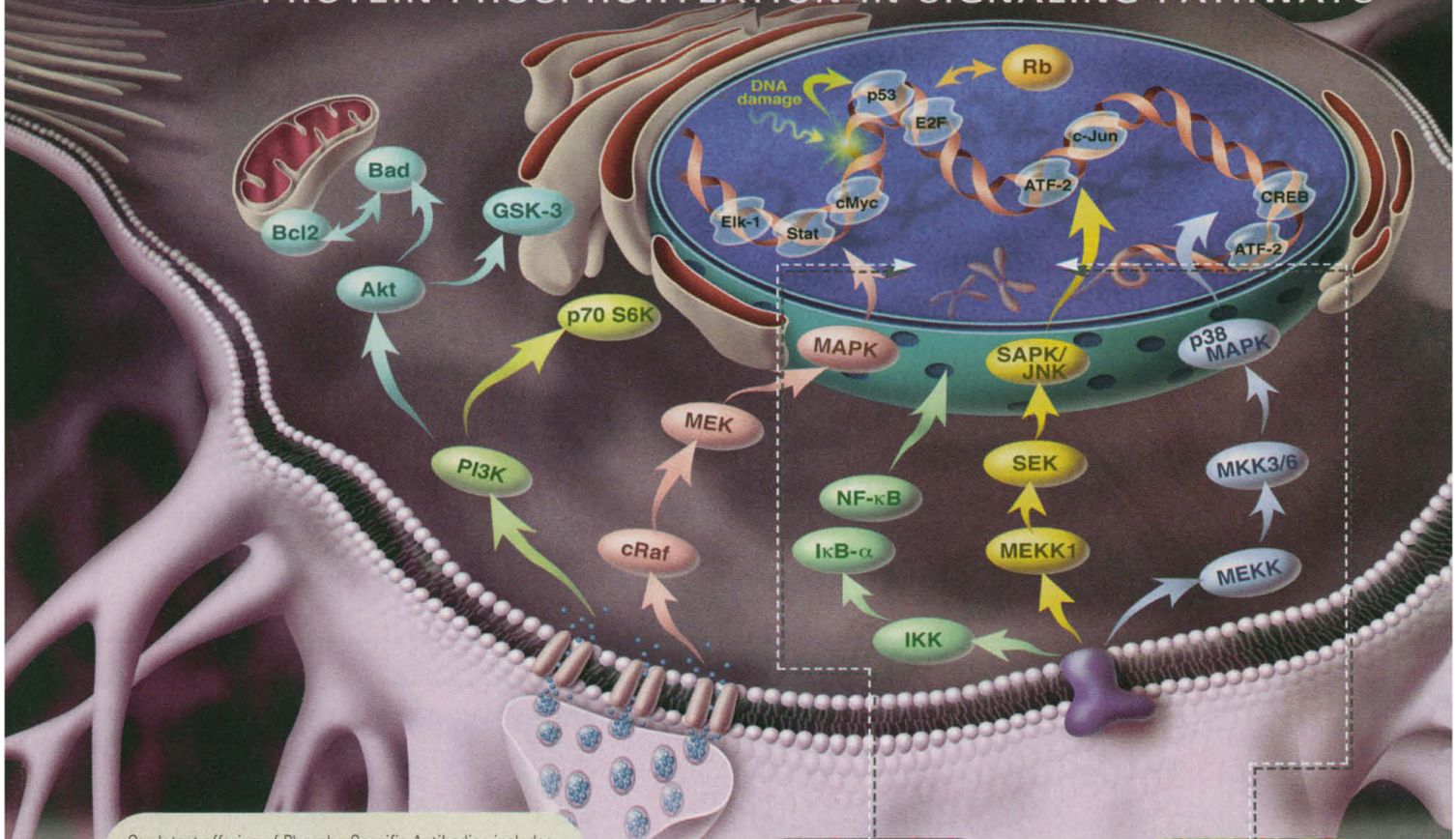

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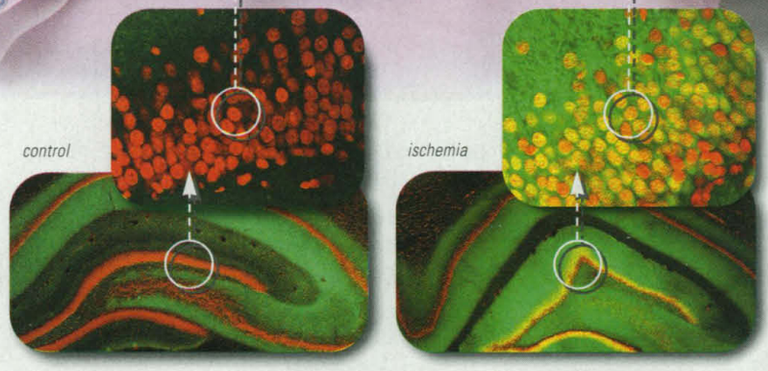

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Confocal images of immunostaining with Phospho-p44/42 MAP Kinase E10 Monoclonal Ab (green) and propidium iodide (red) in rat hippocampus from tissue sections of control and 15 minute transient cerebral ischemia followed by 30 minutes of reperfusion. Photo shows high resolution dentate gyrus (top) and low resolution hippocampus (bottom). Yellow represents overlay of red and green. (Provided by Dr. Bingren Hu, UCSD).

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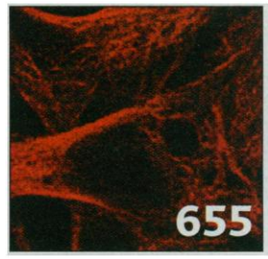

Cover Cellular distribution of active Src tyrosine kinases. β-Arrestins are proteins that bind to agonist-occupied G protein–coupled receptors and terminate receptor–G protein coupling, thus blocking signaling. However, when β-arrestins associate with c-Src they function as adapter proteins, linking G protein–coupled receptors to tyrosine kinase–dependent growth regulatory pathways. Image width ~50 μm. [Immunofluorescent micrograph: S. S. G. Ferguson and N. Bechard].

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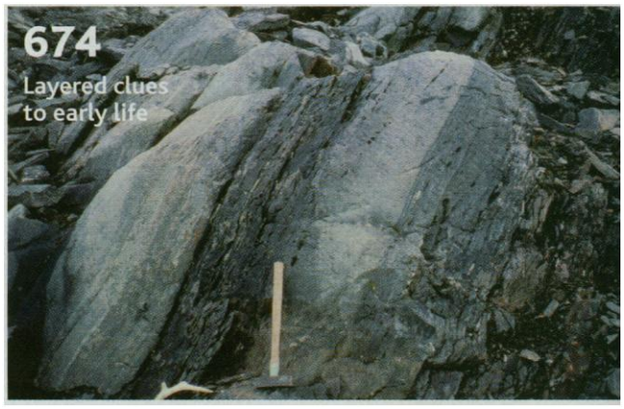

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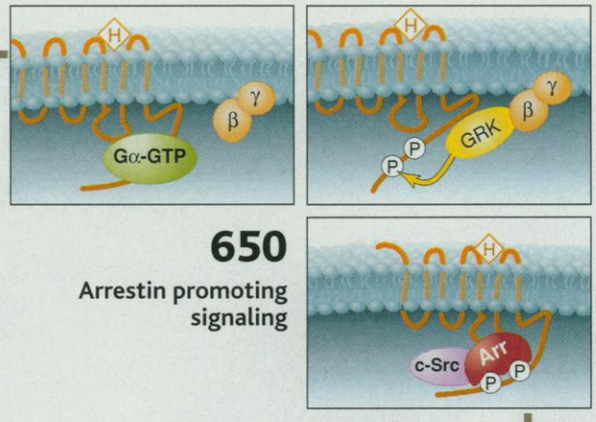

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** Clinical Chemistry 1998; 44:4 731-739*

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NANO-PENS

An atomic force microscope (AFM) tip, coated with alkane thiols, can write fine "lines" (as narrow as 30 nanometers) and "dots" of molecules on polycrystalline gold films. Piner *et al.* (p. 661) found that water from the air forms a meniscus between the AFM tip and the substrate, and this bridge allows alkane thiols to move continuously down the tip and decorate the gold surface. Although several factors control linewidth, the method could prove useful in patterning and modifying nanostructures.

TWO PHOTONS FROM ONE

In conventional fluorescent lamps, ultraviolet (UV) emission from hot mercury vapor excites the phosphor lining the tube, which then emits visible light. Although the conversion is efficient (about 90% on a per photon basis), the use of mercury poses environmental problems, and its vaporization leads to delay in turning on a fluorescent lamp. Wegh *et al.* (p. 663; see the news story by Antia) show that mercury can be replaced with an inert gas, xenon, by using a phosphor that combines rare-earth lanthanide atoms that can efficiently transfer the energy between each other. A quantum efficiency of nearly 200% can be achieved because this downconversion process creates two visible photons from a single high-energy UV photon.

RECYCLING RARE GASES

Argon in the mantle is released into Earth's atmosphere as basaltic magmas erupt. The accumulation of argon in the atmosphere (and its isotopic signature) can then be used to trace the amount of degassing over time. Sarda *et al.* (p. 666), however, provide evidence from a survey of argon and lead isotopes in basalts all along the Mid-Atlantic ridge that some atmospheric argon may be recycled back into the mantle, where it is poorly mixed. Rocks with low argon-40/argon-39 ratios, an indication of atmospheric argon usually attributed to atmospheric contamination, tend to contain radiogenic lead, an indication of recycled crustal material.

TRAPPED LITHOSPHERE POWERS ON

Measurements of the conductivity of the lithosphere (crust and the uppermost part of the mantle) can provide information about the composition and structural evolution of the subsurface that may not be obtained with other remote sensing techniques. Boerner *et al.* (p. 668) conducted a magnetotelluric survey (part of the LITHOPROBE Alberta Basement Transect) over the southern Archean Churchill Province and the adjacent, younger proterozoic terrane northeast of the province. Analysis and modeling of the data indicate that the Churchill Province lithosphere is more conductive than the adjacent proterozoic terrane. The higher conductivity may be due to the presence of hydrous minerals formed by metasomatism when the Churchill Province was tectonically trapped between two proterozoic subduction zones.

WEATHERING HEIGHTS

Mountain building (orogenic activity) leads to weathering and erosion. Patchett *et al.* (p. 671) use neodymium isotopes to trace the relation between orogenic activity and sedimentation since about 600 million years ago across North America. The data show that the Appalachain orogen was the dominant source of sediment from 450 to about 150 million years ago, even far from the orogen along the Arctic and northwestern coasts of the continent.

TRACES OF EARLY LIFE

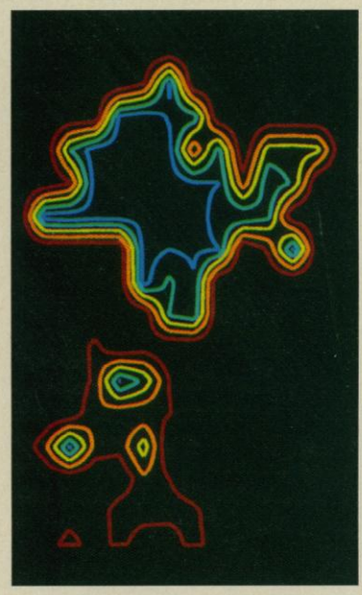
Most of Earth's oldest sedimentary rocks are metamorphosed, which has made it difficult to identify early fossils or determine when life on Earth began. The oldest fossils that have been found date to about 3500 million years ago. One common signature of life is the presence of carbon with a low carbon-13/carbon-12 ratio. Rosing (p. 674) reports such low ratios for graphite layers and globules in metamorphosed sedimentary rocks dated at about 3700 million years ago in Greenland.

UNDER ARRESTIN

The β-arrestin proteins function to "turn off" signaling through receptors coupled to heterotrimeric guanine nucleotide binding proteins (G proteins). Binding of β-arrestin to the receptor prevents further activation of G proteins and targets the receptor for sequestration by endocytosis. Luttrell *et al.* (p. 655; see the cover and the Perspective by Zuker) now show that β-arrestin also functions to promote mitogenic signaling from β_2 adrenergic receptors. The β-arrestin 1 protein binds the tyrosine kinase c-Src and brings that protein with it when it binds an activated receptor. Kinase activity of c-Src appeared to be enhanced by binding to β-arrestin 1, and inhibition of such recruitment of c-Src by β-arrestin inhibited β_2 adrenergic receptor–mediated activation of mitogen activated protein kinases. Arrestins thus have both positive and negative influences on signaling through G protein–coupled receptors.

A WIDER VIEW

The size of the receptive field of neurons in the visual cortex, traditionally determined from measurements of neuronal firing activity, is usually put at about 2° of visual angle. Intracellular recordings from single neurons made by Bringuier *et al.* (p. 695) show that the synaptic integration field, the



area where presentation of a visual stimulus causes subthreshold changes of postsynaptic responses, actually reaches up to 20° of visual angle. Thus, many more connections than previously thought influence the response of a single neocortical neuron. This result has important implications for the potential spatial and temporal integration capacity of the brain.

MYC AS IRONMASTER

The c-MYC protein is a transcription factor that controls the proliferation, differentiation, and death of cells, and its aberrant expression contributes to tumorigenesis. Wu *et al.* (p. 676) show that c-MYC coordinately regulates a gene expression

CONTINUED ON PAGE 603

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program controlling cellular iron metabolism. It represses transcription of the gene encoding H-ferritin, a protein that sequesters intracellular iron, and it activates transcription of the gene encoding iron regulatory protein–2, which increases the intracellular iron pool. Downregulation of H-ferritin was required for c-MYC–mediated cell transformation and stimulation of DNA synthesis, which suggests that this effect on iron metabolism is one of the ways in which c-MYC controls cell proliferation.

BUGS THAT ENERGIZE TERMITES

Spirochetes (slender, long bacteria with a flexible helical shape) are an unusually abundant and diverse component of the microbiota of the termite gut. Leadbetter *et al.* (p. 686) report the successful culturing of these bacteria and reveal their ability to form acetate from hydrogen and carbon dioxide in culture. Because the bulk of a termite's energy requirement is met by the oxidation of acetate, spirochetes are likely to play a major role in termite nutrition.

SENDING RAFTS TO T CELL RECEPTORS

When T cells bind antigen, other proteins soon arrive near the T cell antigen receptor (TCR). The key to this reorganization turns out to be costimulation. Viola *et al.* (p. 680; see the Perspective by Dustin and Shaw) found that lipid rafts bring in the signaling components that augment T cell signaling only in response to costimulation. Thus, a costimulatory signal from CD28 is not necessarily the summoning of a parallel signaling pathway that could join the TCR pathway in the nucleus. Costimulation may instead augment and sustain TCR signaling at the surface by initiating the reorganization of key cellular components to antigen-bound TCRs.

IMPROVED VIRUSES FOR GENE THERAPY

Hematopoietic stem cells (HSCs) are important targets for genetic treatment of many human diseases. However, they tend to be quiescent, which renders them resistant to retroviral vectors. Miyoshi *et al.* (p. 682) showed that a vector based on human immunodeficiency virus–type 1 could stably and highly efficiently transduce HSCs. These HSCs were then used to reconstitute nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice.

MITOCHONDRIAL MUTATIONS

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a genetic disease that is characterized by a wide spectrum of neurologic and muscular abnormalities. Patients with MNGIE show multiple deletions of mitochondrial DNA, but the disease is inherited in a Mendelian fashion and, therefore, is due to a defect in a nuclear gene. Nishino *et al.* (p. 689) show that the defective gene is *TP*, which encodes thymidine phosphorylase, a protein that regulates the availability of thymidine for DNA synthesis. This work may lead to new insights into nuclear control of mitochondrial DNA replication and potential new therapies for mitochondrial diseases.

RESTORING CIRCADIAN CLOCKS

Circadian rhythms control physiological activities during the course of the day in response to the day-light cycle in most organisms. Earnest *et al.* (p. 693) looked at metabolic activity in cell lines derived from one of the central controllers of the mammalian clock situated in the brain, the suprachiasmatic nucleus (SCN). These immortalized cells maintained a circadian rhythm in their activities in cell culture, and the cells could be transplanted into animals that had their SCN removed to restore circadian activities.

FLEXIBILITY OVER STABILITY

One of the difficulties in recreating early biochemistry is, of course, knowing only which molecules have survived and not which were available but did not survive. Beier *et al.* (p. 699) have synthesized a family of pentose-derived oligonucleotides that can plausibly be thought to have formed through the same chemical reactions that produced RNA. From their finding that all family members form stronger Watson-Crick base pairs than RNA, they propose that the survival of RNA did not result from maximization of double-stranded stability, but may in fact have balanced stability against flexibility.

AGAINST ANTIBIOTIC RESISTANCE

The ability of staphylococci to resist β-lactam antibiotics took away a powerful weapon against disease. Rosen *et al.* (p. 703) present a solution to the problem by redesigning an antibiotic so that it has strong antibacterial activity against resistant organisms but can release a side chain that had been causing animals to develop an immune response that would make the antibiotic toxic.

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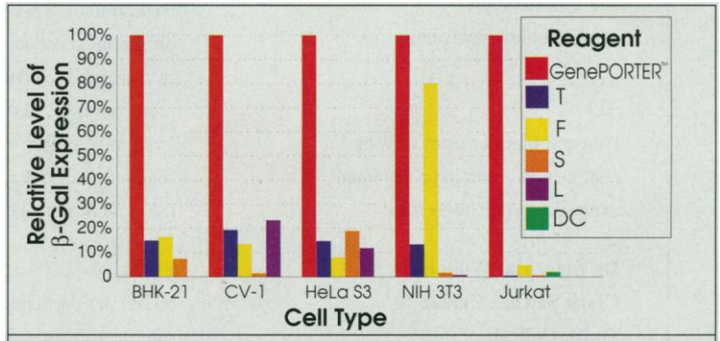

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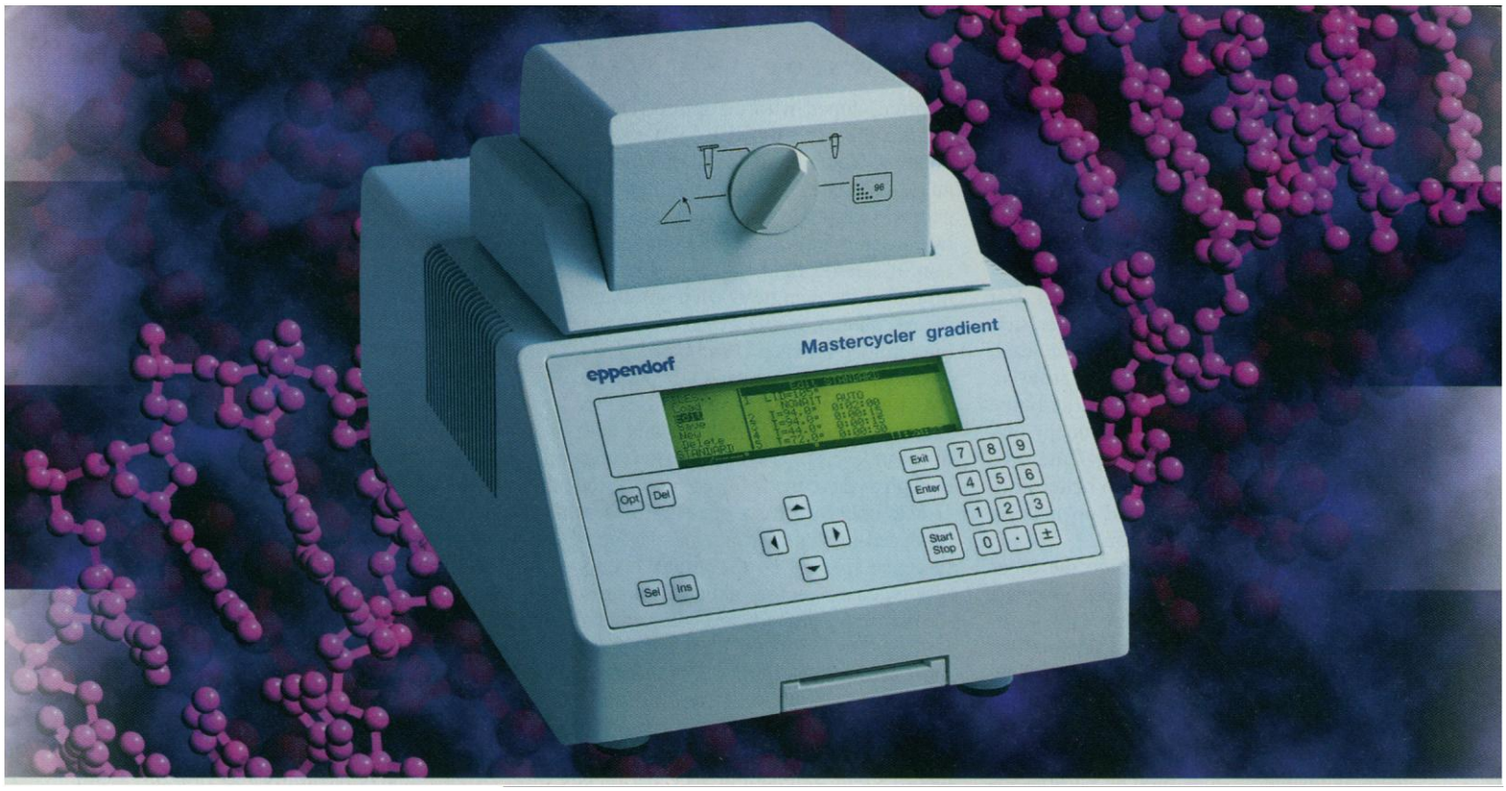

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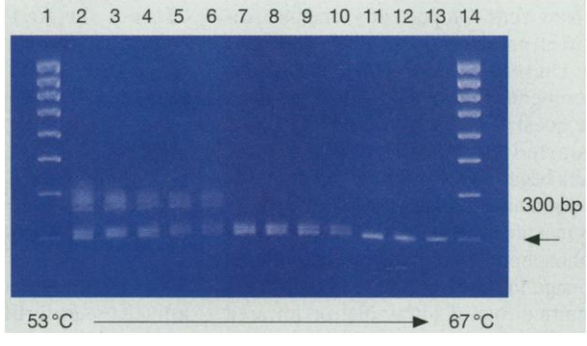

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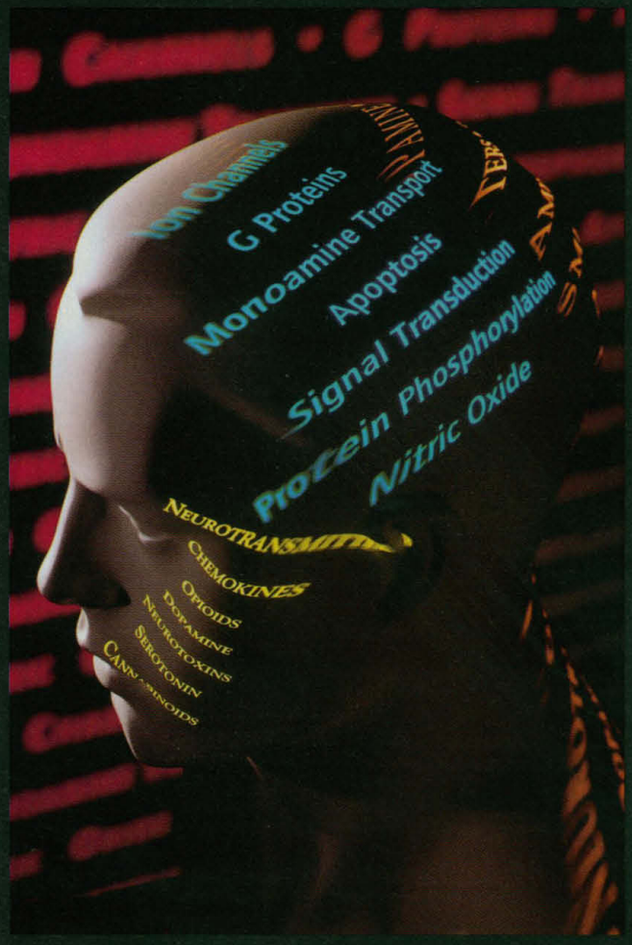

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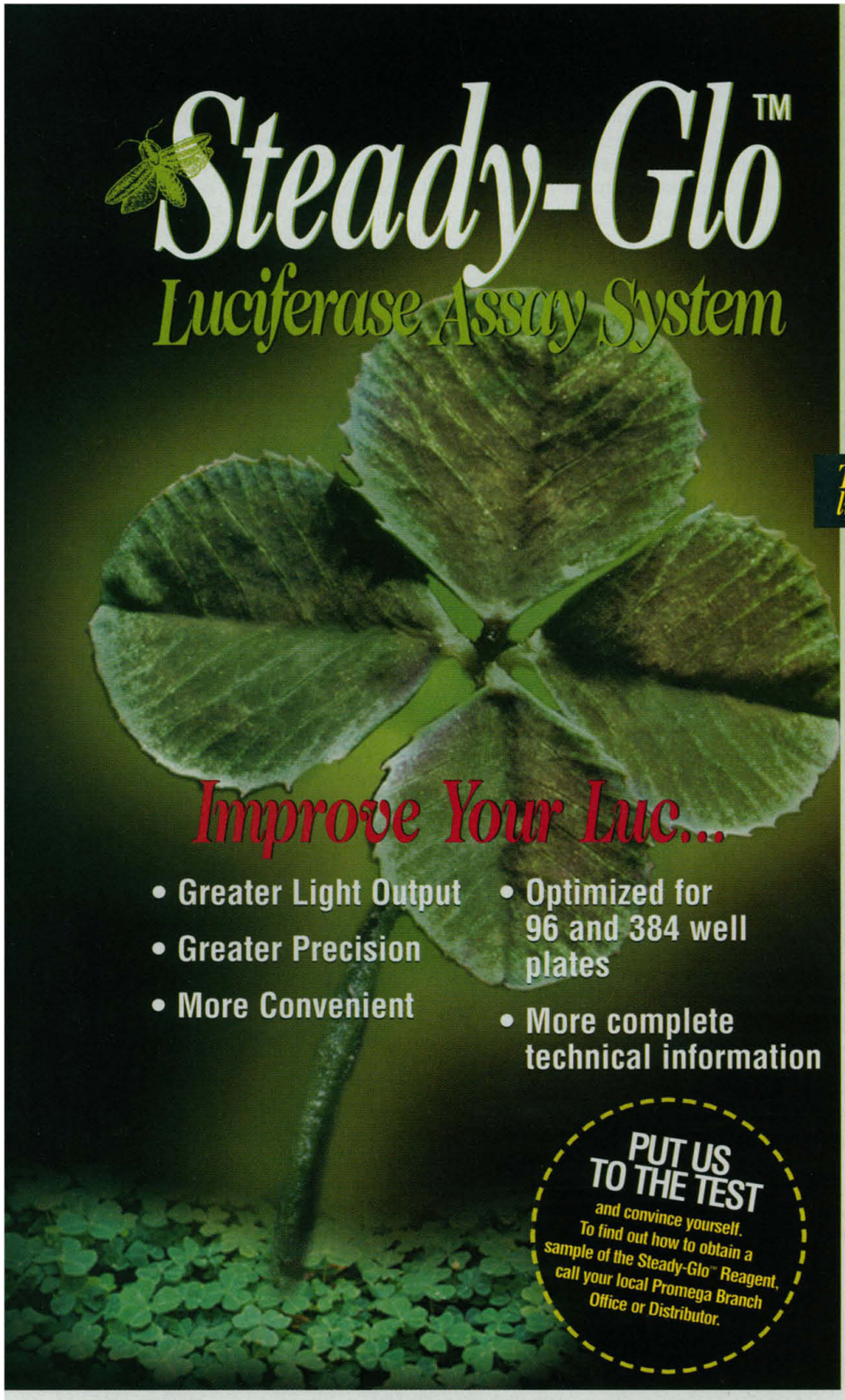

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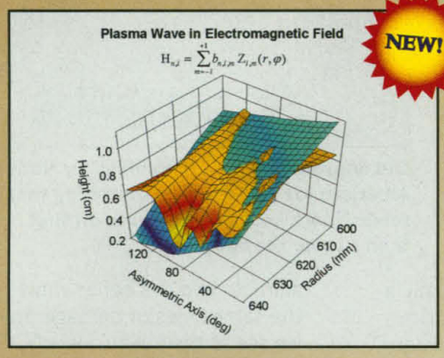

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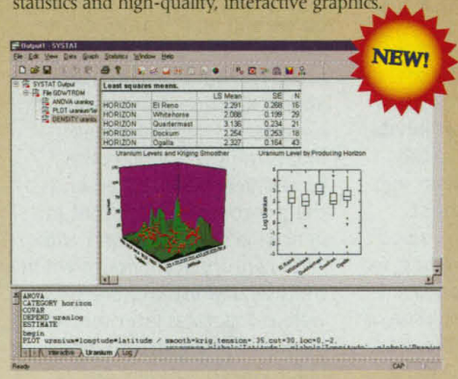

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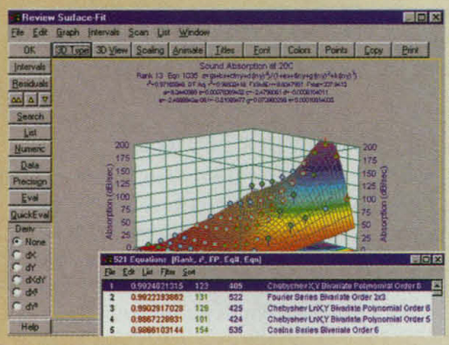

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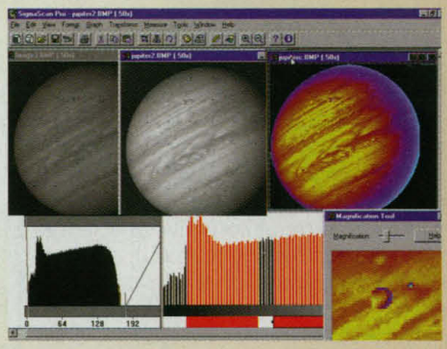

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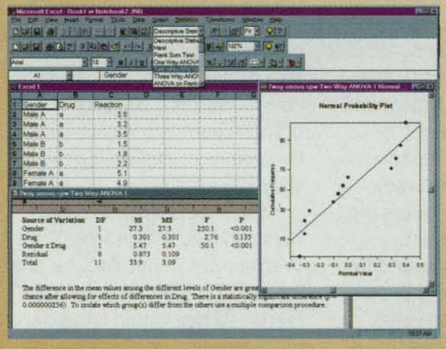

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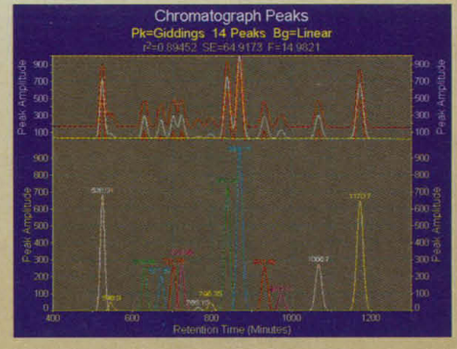

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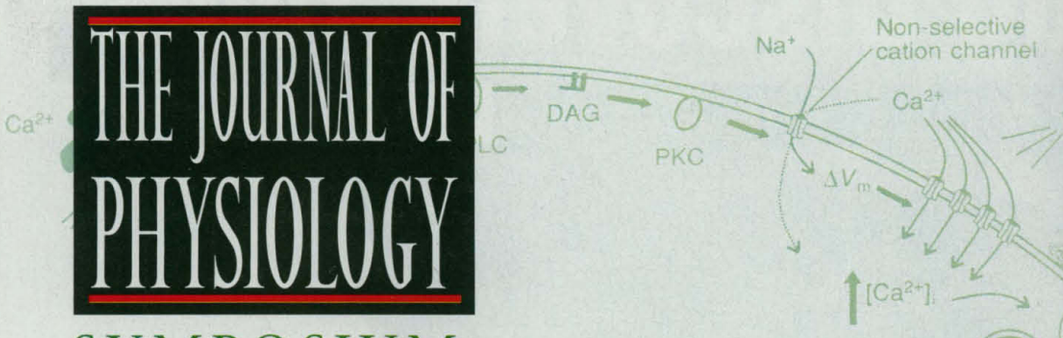

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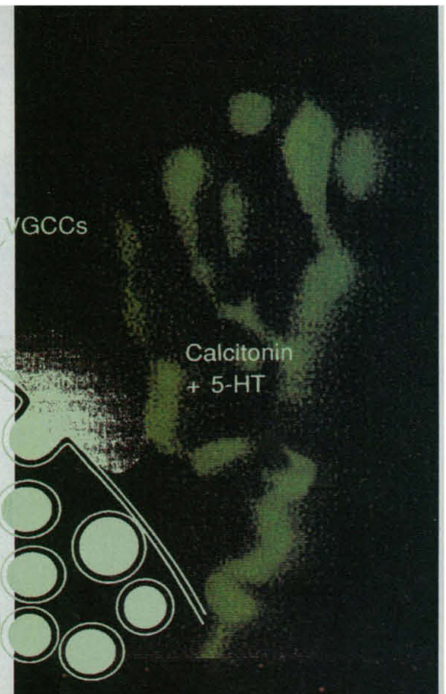

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The fusion complex of exocytosis and enveloped viral fusion

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Regulation of synaptic vesicle exocytosis

Pietro De Camilli
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Reformation of vesicles after exocytosis

George Augustine
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Jacopo Meldolesi
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Bertil Hille
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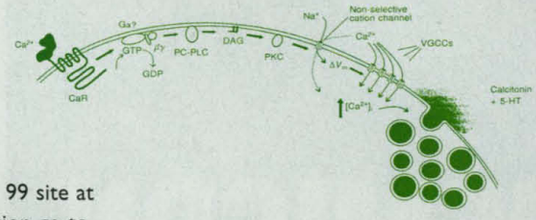
Stimulation of exocytosis without a calcium signal



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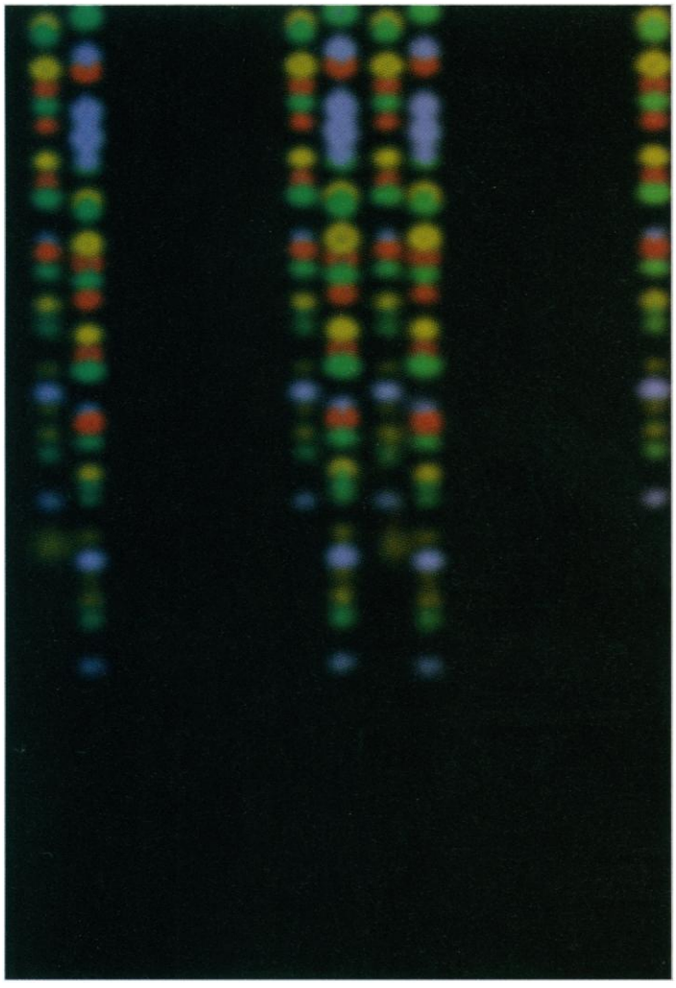

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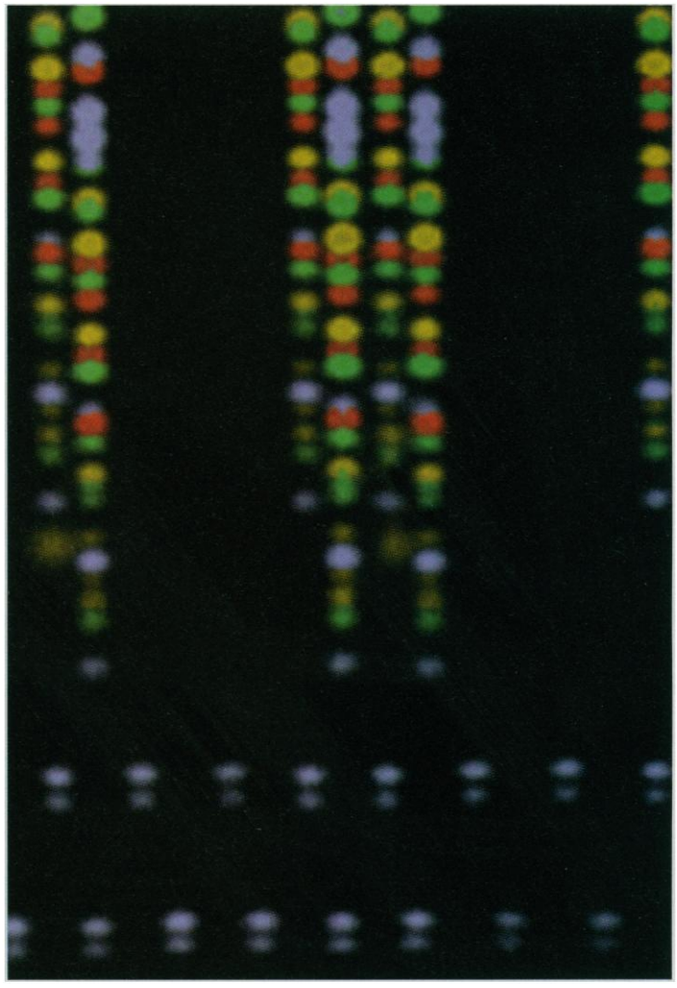

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