18 September 1998

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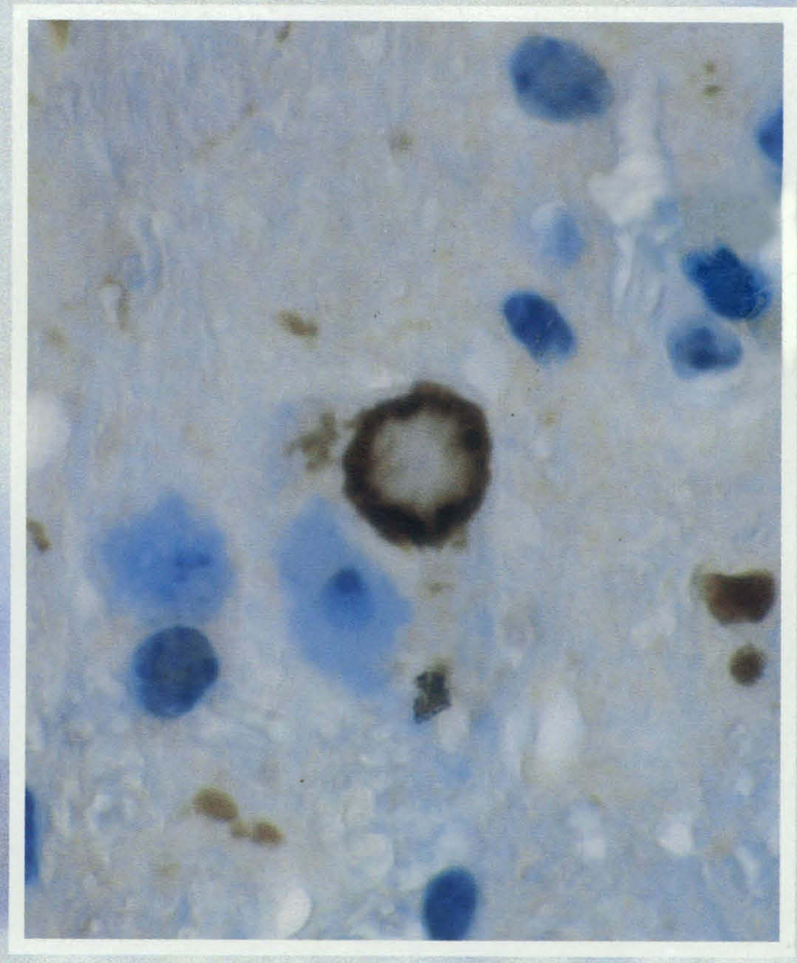

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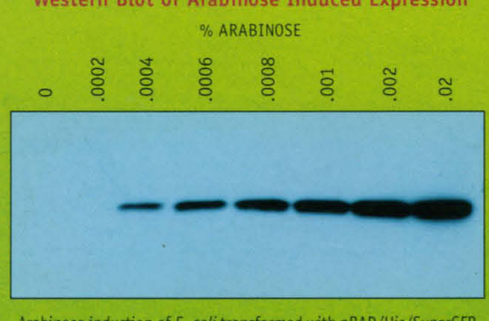

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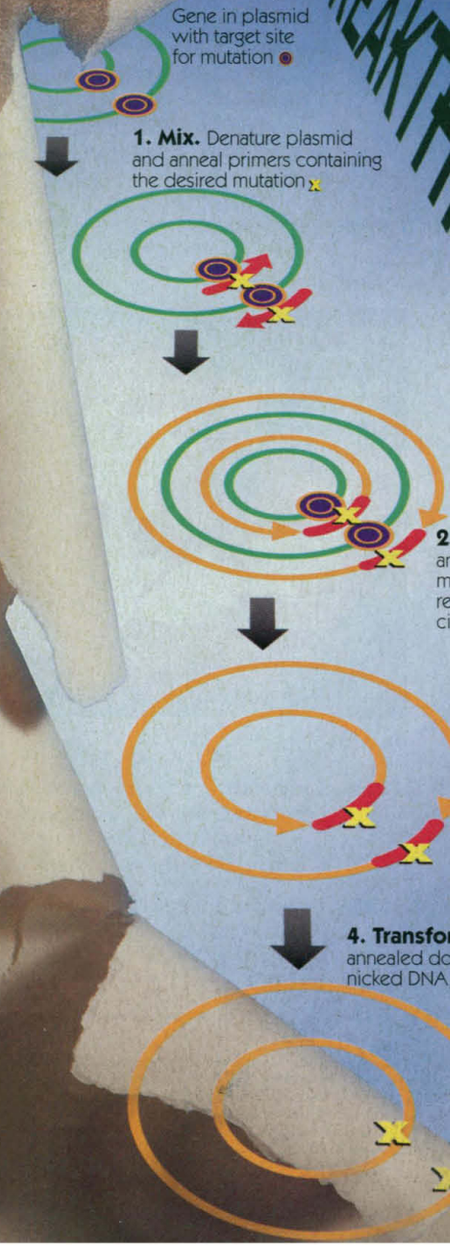

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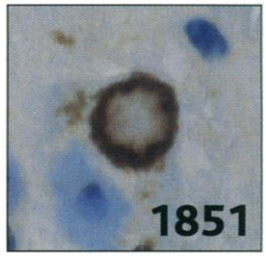

COVER In Lou Gehrig's disease [or amyotrophic lateral sclerosis (ALS)] the death of motor neurons causes muscles to atrophy. Many instances of ALS are caused by mutations in the enzyme superoxide dismutase (SOD1). Studies of mice expressing mutant SOD1 revealed that toxicity is independent of wild-type enzyme activity, but a common feature of ALS is intracellular aggregates of mutant SOD1 in motor neurons (brown staining) (image width ~50 micrometers). [Photo: L. I. Bruijn]

1775
Early American landfall

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150 YEARS • 1848-1998

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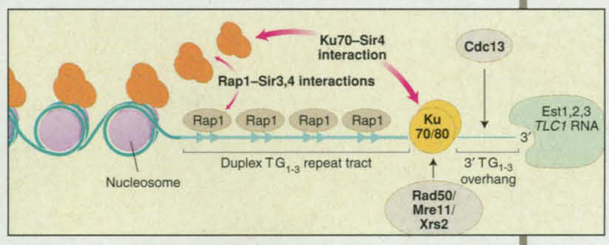
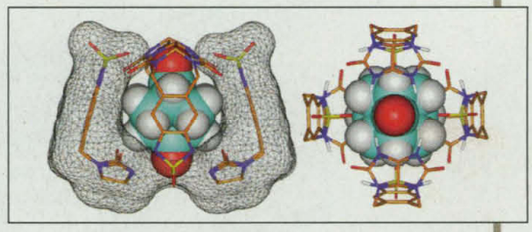


1818

Understanding telomeric function



1842

A fourfold molecular grip

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THE MJ RESEARCH NOTEBOOK

Volume VIII...No. 2 *A Bulletin of Technological Advance in Molecular Biology* *Summer 1998*

PCR-based Testing from a Suitcase? The Mobile Molecular Laboratory Makes It Quite Feasible...

The MML-0150 Mobile Molecular™ Laboratory

CONTAINS VIRTUALLY ALL EQUIPMENT NEEDED FOR DNA/RNA ANALYSIS

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WATERTOWN, Mass. — For the past 5 years, MJ Research has worked with a variety of investigators in an effort to develop field/mobile applications of PCR* and genetic testing. Many research efforts can be accelerated greatly if DNA amplification and analysis are conducted in the field, away from the regular laboratory. Assembling the equipment needed for such an endeavor is not easy, for most molecular instruments are not designed to be compact or lightweight, nor are they built for frequent shipment, nor do they operate on the wide variety of voltages and frequencies the world's power grid has to offer.

MJ Research has now addressed this problem. With experience gathered from supporting several expeditions, MJ has assembled a mobile lab that includes virtually all the instrumentation necessary (except micropipettors) to conduct genetic testing in field circumstances.

The incubator and thermal cycler is a rugged MJ Research MiniCycler™, which has a thermal range of -9° to 105°C. A mini gel box‡ with a casting tray and a variety of combs is supplied with a power supply‡ that can deliver 10, 60 or 120V. Pre-cast agarose gels with ethidium bromide are also available, and these fit into a lightweight transilluminator‡ that features an integral viewing hood and a matched Polaroid™ photodocumentation system. Also included is a microcentrifuge§ that can spin to 7000g, as well as a tube rack/chiller that can hold -20°C for 2 hours. Two 500ml bottles and storage areas are provided for reagents and supplies, including an area inside a foam cooler for cold storage during transport. All of this fits into a waterproof case with integral wheels to ease the 23kg burden of the apparatus, and the package can be checked as ordinary baggage on a jet airliner.

‡Made by Fotodyne Inc. of WI §Made by Denver Instrument Co. of CO

Bringing DNA Studies to High Schools

For years, high school biology teachers have lamented to MJ staffers how they would like to teach DNA methods to their students—but the cost of a DNA laboratory is beyond a high school's budget. Unfortunately, the fact is that precision instruments cannot be made cheaply, so one of the objectives with the mobile lab was to design a system where several schools in a district might *share* equipment, so cost constraints might be overcome. The MML-0150 is such an apparatus, perfect for teaching 8-10 students at a time.

NEED DNA CAPABILITY?

Many scientists outside of molecular biology wish to develop an ability to conduct DNA analysis, but they are at a loss at how to begin. A primary goal of the MJ design team was to create an easy-to-use DNA laboratory that might allow scientists to obtain, all at once, a set of matched instruments to conduct such research. Don't be fooled into thinking the compact size or low price means any compromise in function—rather, the MML-0150 contains virtually all the equipment you need to bring first-class molecular capabilities to any laboratory.

Harvard Group Beta Tests Mobile Lab While Investigating *Leishmania braziliensis*

BAHIA, Brazil – Scientists from the Harvard School of Public Health, in collaboration with Brazilian colleagues, have brought genetic analysis to remote areas, in order to better understand and fight one type of the disease leishmaniasis.

This vector-borne disease primarily affects poorer people in isolated areas. Unfortunately, effective means to control and treat this disfiguring skin condition have proven elusive. A big problem is that there are a number of variant strains of the intracellular parasite *Leishmania*, and the patterns of transmission and the disease manifestations vary greatly with strain.

The Harvard group, led by Prof. John David, used a mobile lab supplied by MJ Research to investigate *Leishmania* in the field. Using PCR* techniques, human infections were quickly diagnosed, and vector populations (i.e. sandflies) and various reservoir hosts (such as dogs) were tested as well. The efficacy of a new treatment was assayed, and PCR data in the field allowed specimen collection to be targeted precisely.

Dr. Marty Roper of Harvard offered many suggestions to improve the MML-0150. Among these were desires for a wider range of camera filters, a heated-lid option on the cycler, as well as the possibility of battery operation. MJ incorporated the first two but cannot the last. Power needs are just too great for batteries, but generators as light as 9kg can get the job done.

* PCR is covered by patents owned by Hoffmann-La Roche, Inc. & F. Hoffmann-La Roche Ltd. Users should obtain license to perform the reaction.

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GETTING TO THE SOURCE OF BLACK HOLES

A space interferometry program consisting of an 8-meter-diameter radio telescope in space and up to 40 ground-based telescopes from the Very Long Baseline Interferometry (VLBI) network provides a virtual telescope 25,000 kilometers in diameter with three times better resolution than previous radio interferometers. This international program requires five tracking stations and three data-correlating facilities to record simultaneously the radio signals from an extragalactic radio source at all of the telescopes and create an integrated, coherent radio image of the structure of the source near its core. Hirabayashi *et al.* (p. 1825; see the Perspective by Reid) have already seen exceptional detail in four images of such sources that show jetlike structures twisting and bending away from their cores. These jets are related to instabilities or precessing motions or both that are associated with a massive, spinning black hole at the core of these sources.

EARLY FISHING SITES

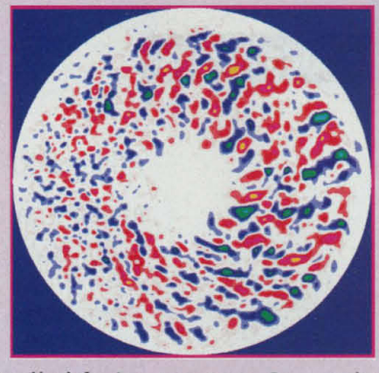
The earliest Paleo-Indian sites in the New World seem to indicate that most sustenance was based on hunting game, but many coastal sites that would provide a more detailed picture are now submerged. Sandweiss *et al.* (p. 1830) and Keefer *et al.* (p. 1833) describe two Paleo-Indian sites from coastal Peru that show evidence of a strong maritime-based sustenance economy (see the news story by Pringle). The sites are among the oldest in the New World and date to perhaps 12,000 years ago, considerably older than other evidence of maritime-based sustenance. One site contains possible evidence of early nets in younger levels, and both sites contain lithic artifacts derived from inland sources

CHANGING THE BULK OF THE PLANETS

The abundances of nonvolatile elements in the bulk of C1 carbonaceous chondrite meteorites have been assumed to represent the bulk composition from which all of the terrestrial planets formed in the solar nebula and subsequently evolved. Bertka and Fei (p. 1838) used the refined moment of inertia for Mars measured by Mars Pathfinder and recent high-pressure experiments on probable martian core phases to determine its bulk composition. They could not fit the data using a C1 chondrite accretion model. Instead, they suggest that the iron-silicon ratio in the solar nebula decreased with distance from the sun and thus each planet accreted a different proportion of iron to silicon. Given that this previously proposed hypothesis fits the new martian data better than the C1 chondrite hypothesis, models of planetary differentiation and core formation in our inner solar system will have to be revised to account for variation in iron-silicon ratio between the different planets versus a single iron-silicon ratio that has been assumed in the currently favored C1 chondrite model.

CLUES TO CONTROLLING PLASMA TURBULENCE

Stars are formed from a hot vigorously convecting plasma confined in a strong magnetic field undergoing fusion reactions. This model also forms the basis for many attempts at developing con-



trolled fusion reactors. One major problem has been the control of turbulence in the confined plasma. Turbulence hinders confinement and suppresses reactions. Lin *et al.* (p. 1835; see the Perspective by Burell) have explored the nature of turbulence and means to control it in such flows using a massively parallel computer simulation. The results show how small-scale zonal flows that regulate and turbulent transport develop and thus suggest ways to minimize turbulence.

FIRE POWER

Several phenomena, such as earthquakes and impact cratering, show a distinct power-law relation between size and frequency. This relation allows the occurrence of small events to be used to predict the occurrence of larger events. Malamud *et al.* (p. 1840) examined several large databases and found that natural forest fires also show such a relation, a finding that should improve the prediction and management of forest fires. The behavior is also captured in a simple cellular automata computer model of forest fires.

ONE OUT OF MANY

Complexation of two identical molecules (hosts) driven by the addition of a different molecule (a guest) is now well known. Using more host molecules becomes more difficult, however, because of the entropic penalties in organizing more components. Martin *et al.* (p. 1842) show that four identical molecules can be used to encapsulate and solvate adamantane suspended in dichloromethane. Weak interactions such as hydrogen bonding between the hosts and the guests and molecular curvature of the host had to be carefully tailored to direct such assembly.

OVERCOMING HUMORAL TRANSPLANT REJECTION

Because of the shortage of human organs available for transplant, the pig, whose physiology closely resembles humans, is being seriously considered as an organ donor. A major barrier to successful transplantation, however, is the humoral rejection of the donor organs that is initiated by natural production of antibodies in humans to certain carbohydrate moieties (called αGal epitopes) on the pig cells. These antibodies are thought to be produced because of exposure to similar epitopes in normal bacterial flora. In a mouse model, Bracy *et al.* (p. 1845) have surmounted this barrier by transducing some of the recipient's bone marrow cells to produce the enzyme, GT, that generates the carbohydrate. The recipient mice stop producing the natural antibodies, even in the face of constant bacterial challenge from the normal flora. If similar results could be obtained in a human system, this approach would remove a major obstacle to xenotransplantation.

REEXAMINING SOD'S ROLE IN ALS

Genes linked to the production of amyotrophic lateral sclerosis (ALS) encode a mutant form of an enzyme known as superoxide dismutase (SOD). This finding has led to the hypothesis that the neurodegeneration of motor neurons characteristic of the disease is linked to anomalous enzyme activity and the production of reactive oxygen species. Bruijn *et al.* (p. 1851; see the cover) now provide evidence

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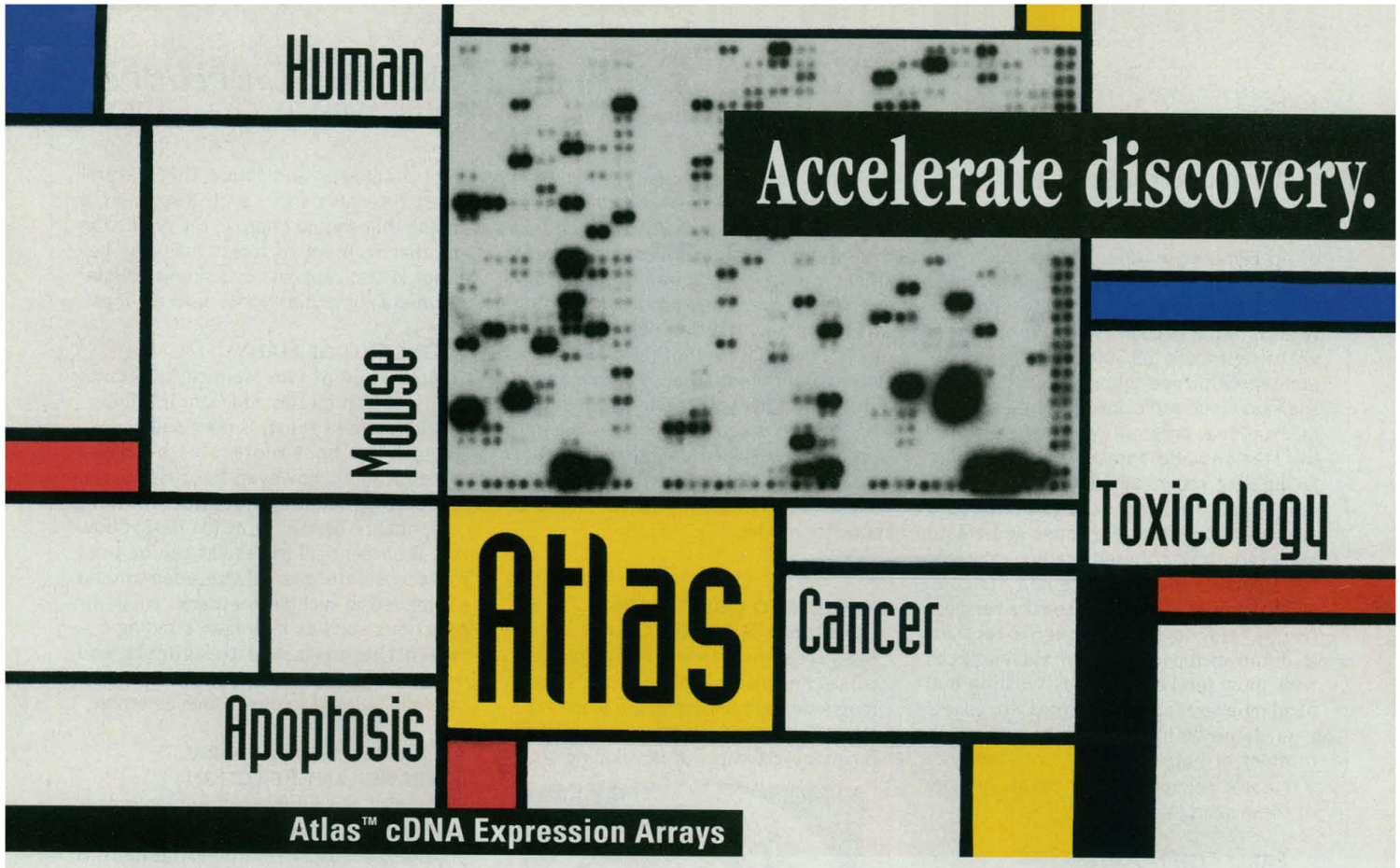

Illustration inspired by the art of Piet Mondrian (1872–1944).

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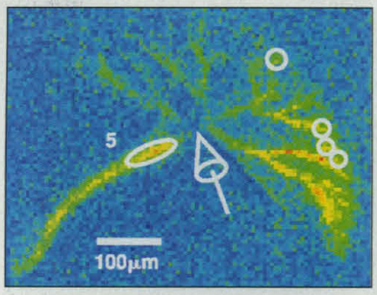
that challenges this hypothesis. Mice that completely lack endogenous SOD, and mice that possess six times the normal concentrations of SOD, all exhibit identical pathology in the presence of the mutant enzyme. These results suggest that therapies based on the replacement of SOD activity will be ineffective in treating ALS.

RECOVERING VELOCITY

Detecting moving visual stimuli presents the challenge of distinguishing a change in contrast due to motion of the stimulus from a change due to purely local patterns. Single and Borst (p. 1848) measured the intracellular concentration of calcium,



as an indicator of electrical activity, in the arbor of dendrites of single sensory neurons in the blowfly. They find that calcium fluctuates within individual dendrites in response to both types of contrast changes but that integration between the dendrites and the cell body effectively cancels out the responses due to local patterns while retaining the overall direction of motion. Furthermore, to maximize integrative efficacy, the fanlike dendritic arbor is oriented so that neurons sensitive to vertical motion have their fans aligned with the dorsal-ventral axis, whereas horizontally sensitive neurons have their arbors arrayed orthogonally.

ENTERING THE MEIOTIC CELL CYCLE

The mechanisms that control DNA replication during meiosis (the formation of gametes, which reduces chromosome number) are less well understood than those that control entry into mitotic S phase. In the yeast *Saccharomyces cerevisiae*, Dirick *et al.* (p. 1854) found that entry into meiotic S phase required the B-type cyclins Clb5 and Clb6 as does the mitotic regulatory mechanism. However, in meiosis, the protein kinase Ime2 was required rather than the related cyclin-dependent kinase Cdc28. Ime2 was required for degradation of the cyclin-dependent kinase inhibitor Sic1. The results indicate that meiotic cell cycles might have evolved from mitotic cycles with conserved roles for the cyclin B–cyclin-dependent kinase complexes. However, the Ime2 protein kinase might have functionally replaced the complex of Cdc28 with G_1-specific cyclins, which controls degradation of Sic1 at the transition from G_1 to S phase in mitotic cycles.

FERTILIN AND SPERM FUNCTION

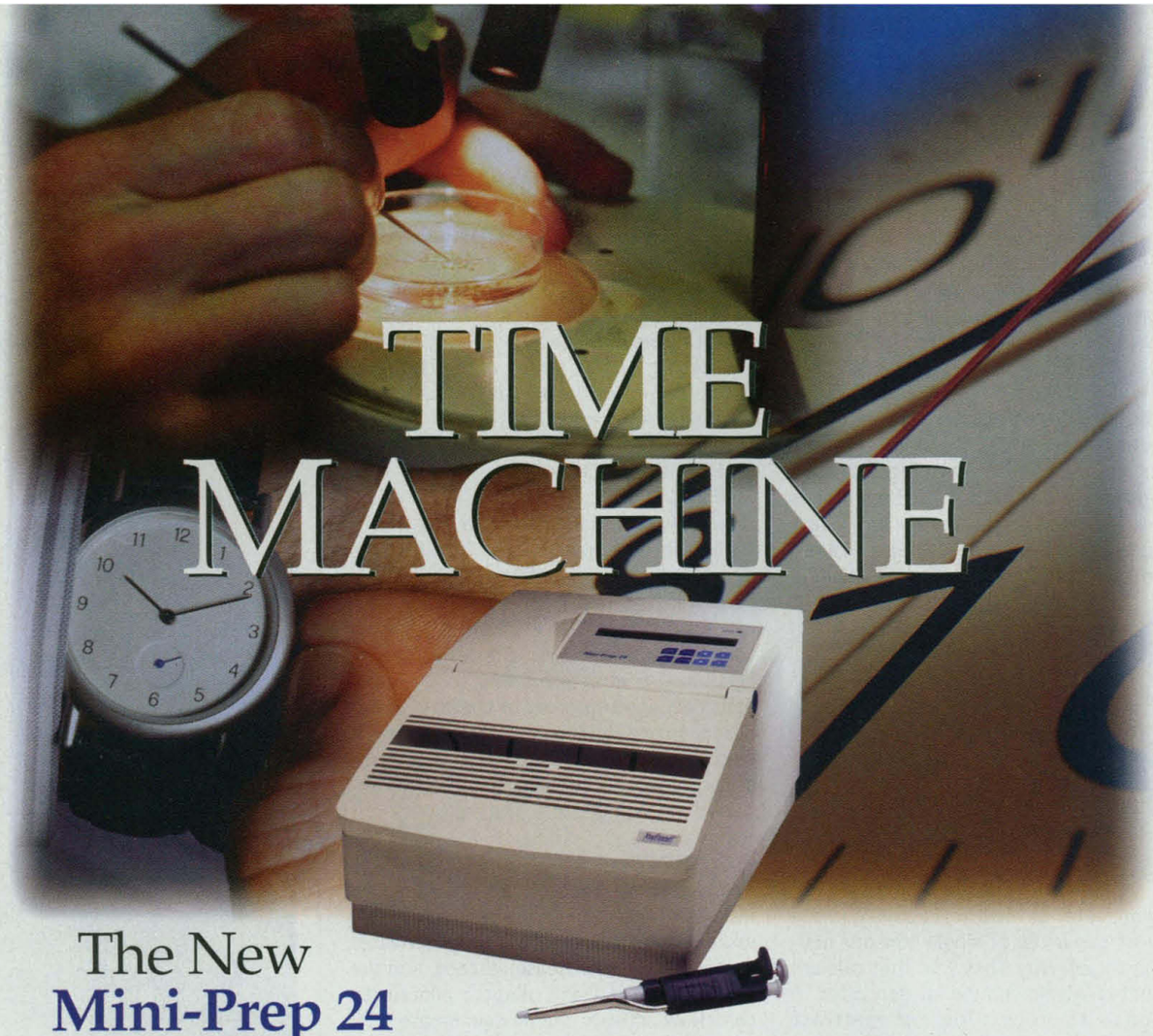
A multifunctional protein in the mammalian fertilization process, fertilin, was previously implicated in binding acrosome-reacted sperm to eggs. Using mice lacking fertilin β, Cho *et al.* (p. 1857) show that fertilin's functions are more diverse. Fertilin also affects binding to the zona pellucida, an outer coat of the egg. In addition, sperm lacking fertilin are deficient in making their way to the oviducts. Temporary adhesive interactions may be involved in the migratory process.

ACTIVATING ASK1 IN CELL DEATH

The cell death receptor Fas activates two independent apoptosis pathways. The more well-established pathway activates caspase 8 and a protease cascade, and the other uses the Daxx adaptor protein to somehow activate the protein kinase JNK, whose phosphorylation activity appears to be critical for apoptosis in certain cells. Chang *et al.* (p. 1860) found that Daxx removes the self-inhibition of apoptosis signal–regulating kinase 1 (ASK1), the first member of a kinase cascade. They hypothesize that Daxx brings ASK1 into the Fas receptor complex by binding to the amino-terminal domain of ASK1. This step removes the block on the kinase activity, and phosphorylation by ASK1 ultimately leads to the activation of JNK and cell death.

PROMOTING DENDRITES

Neurons respond to synaptic activity not only by forwarding the electrical signal but also by rearranging their growth to adapt to developing or changing signaling regimes. CPG15, a protein identified in the rat and *Xenopus laevis*, is induced in response to synaptic activity. Nedivi *et al.* (p. 1863) show by overexpressing the protein that it promotes growth of dendrites in projection neurons but has no effect on interneurons. The CPG15 protein appears to function in an intercellular signaling mechanism.



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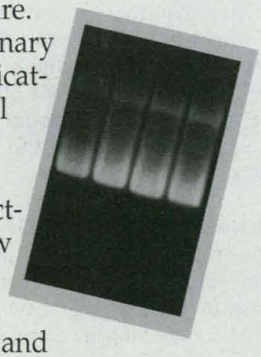

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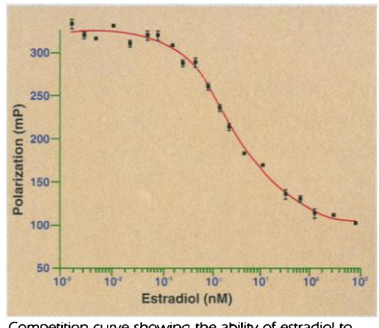

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Lundblad, J. R., *et al.*, Fluorescence polarization analysis of protein-DNA and protein-protein interactions, *Molec. Endocrinol.*, **10**, 607- 612 (1996).
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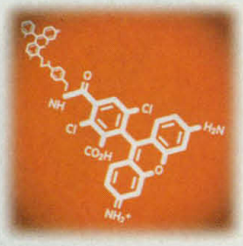

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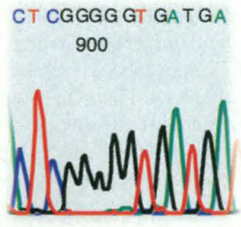

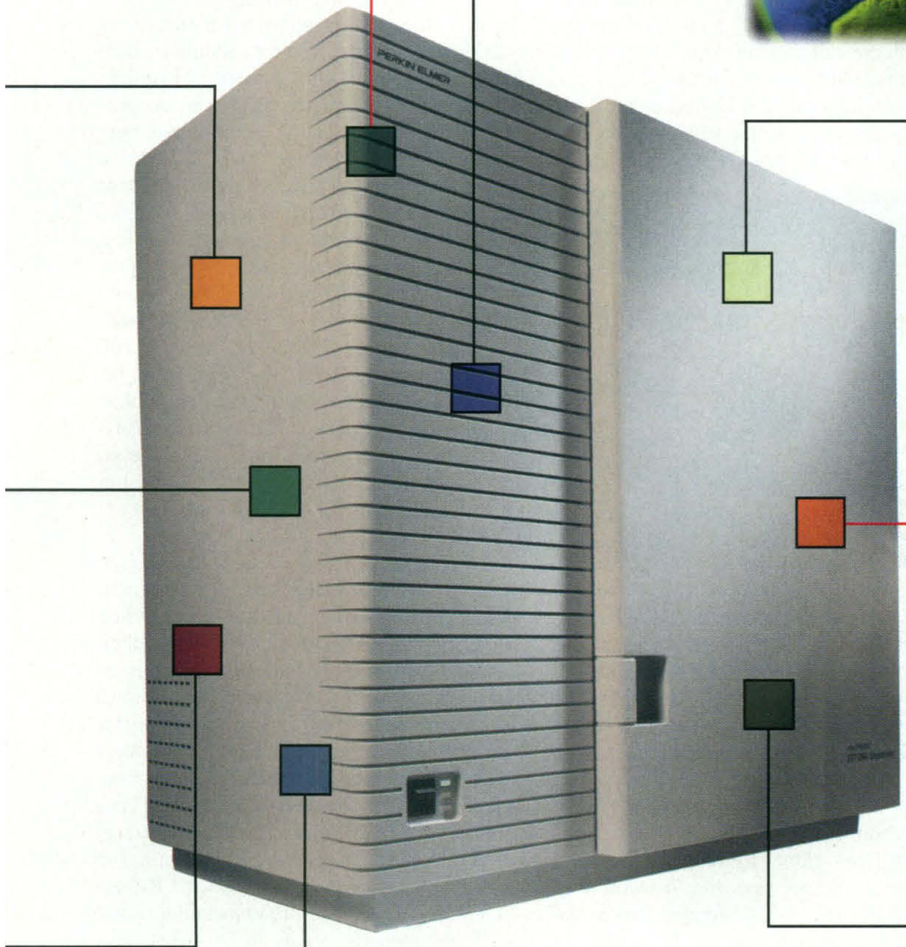

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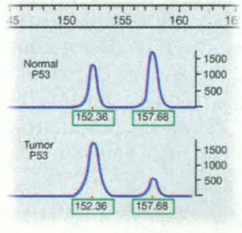

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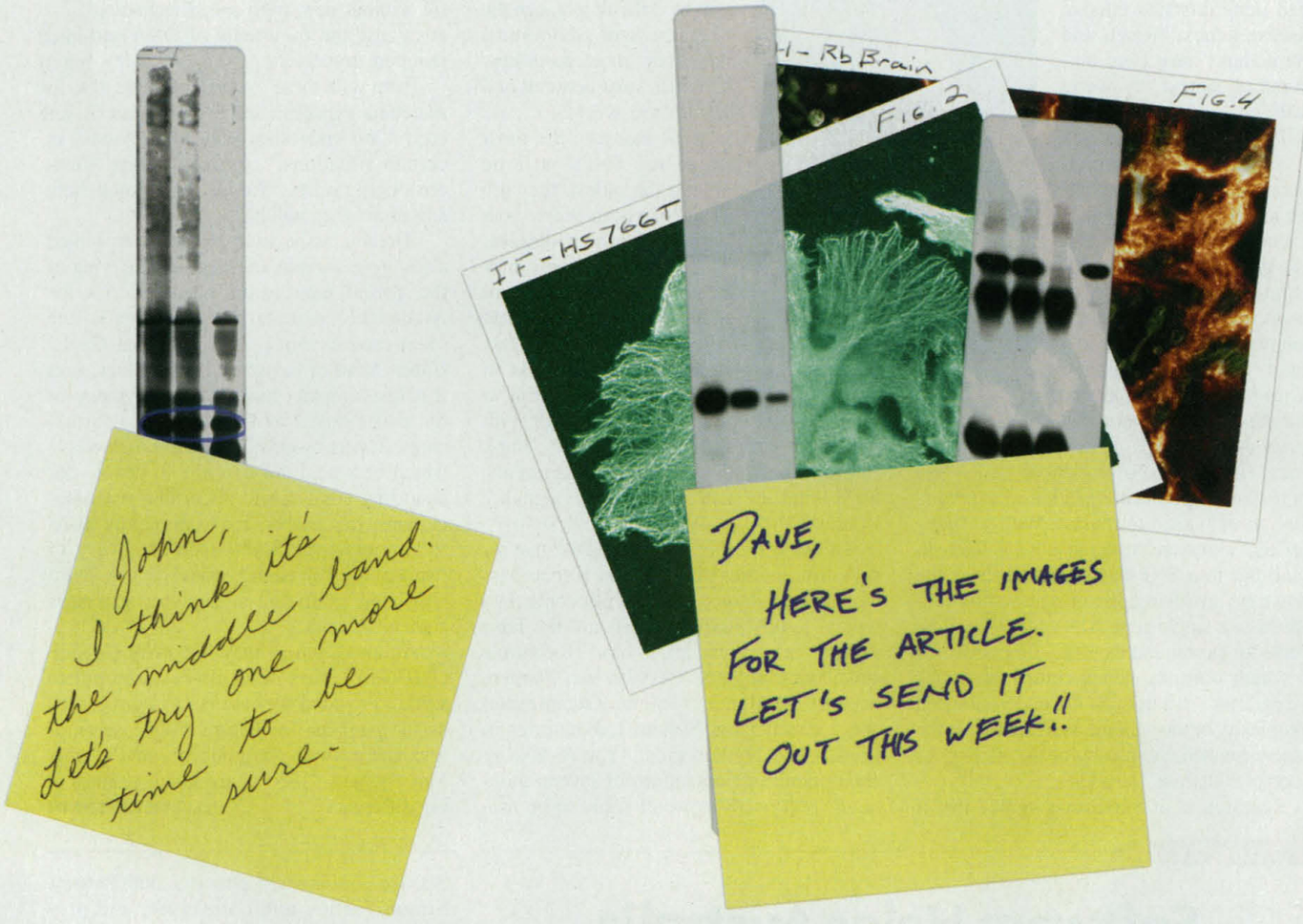

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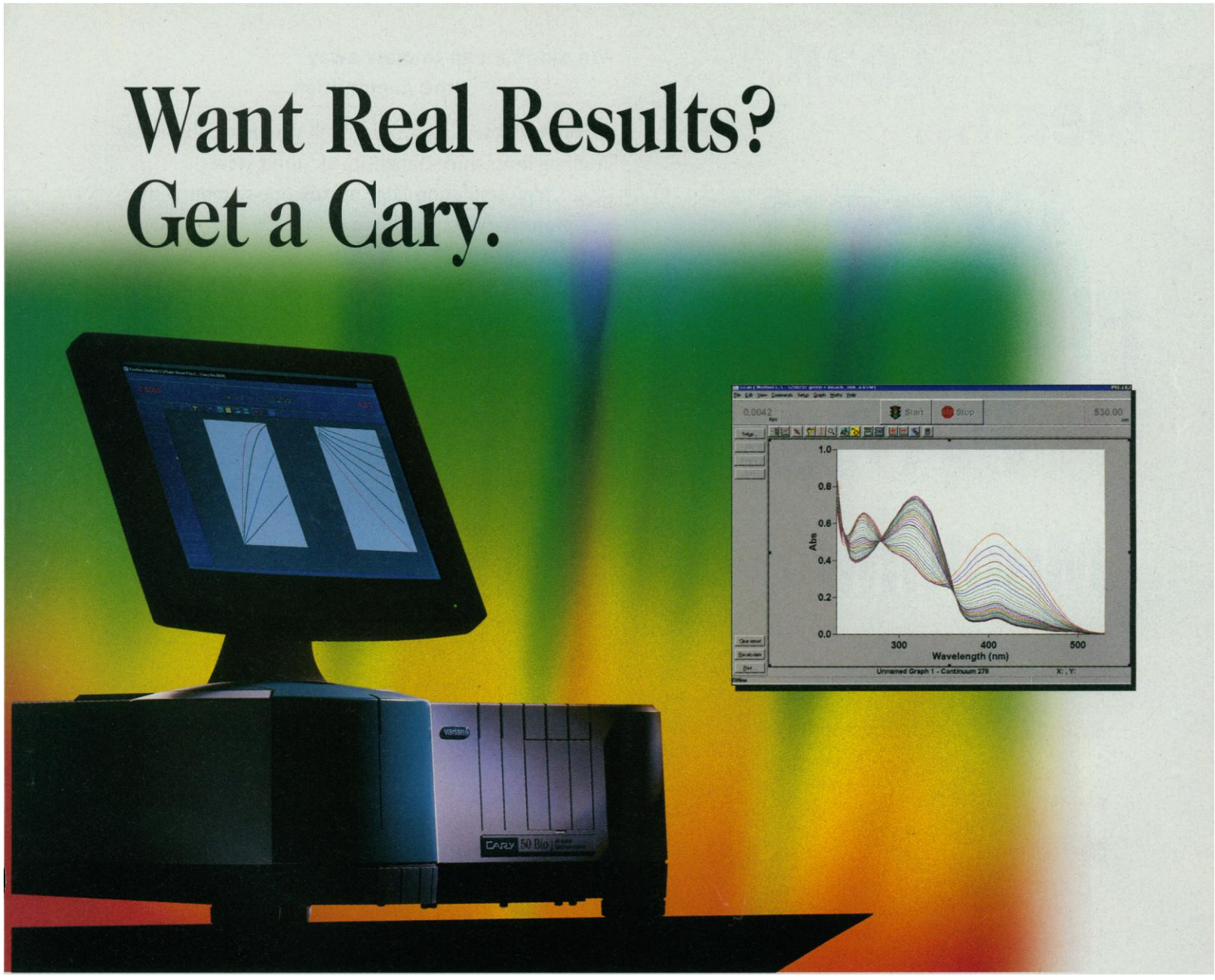

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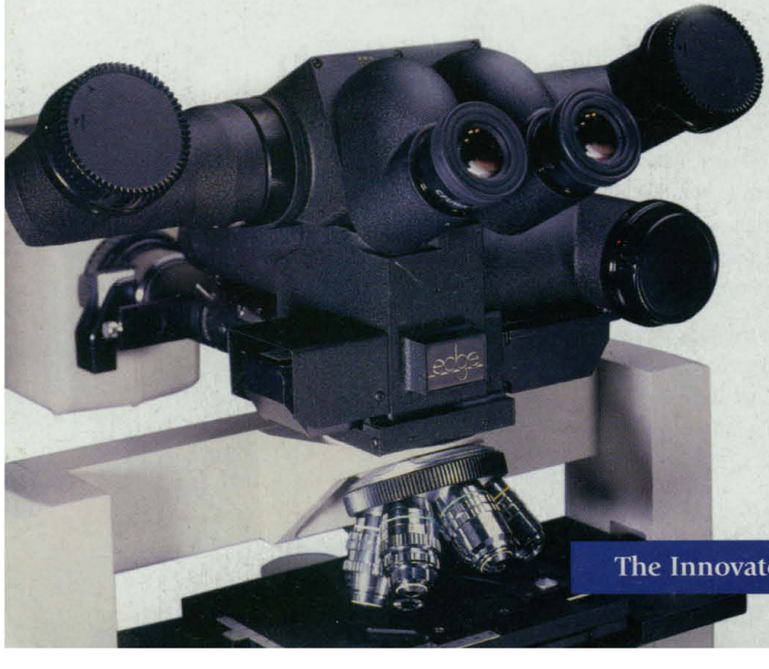

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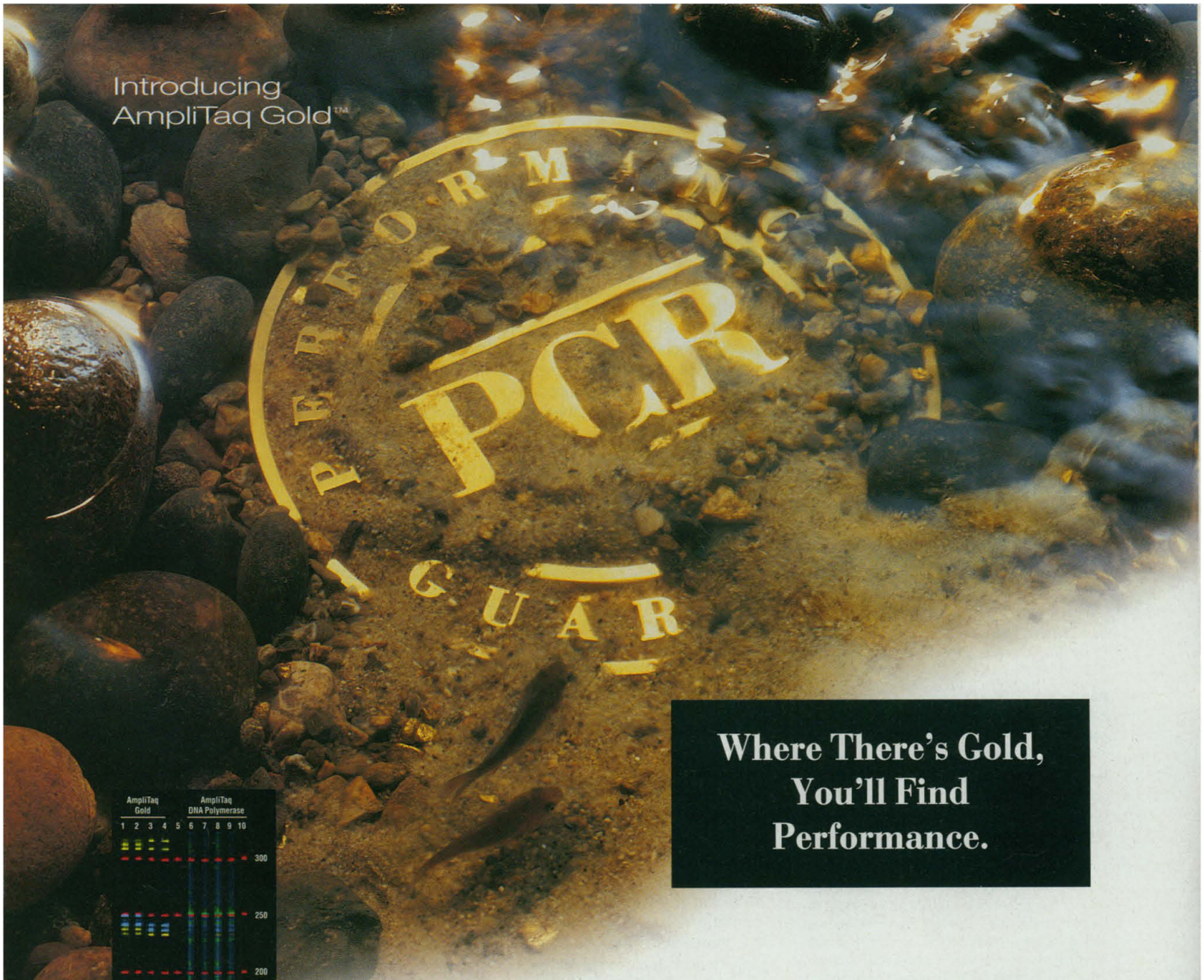

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