23 June 2000

Science

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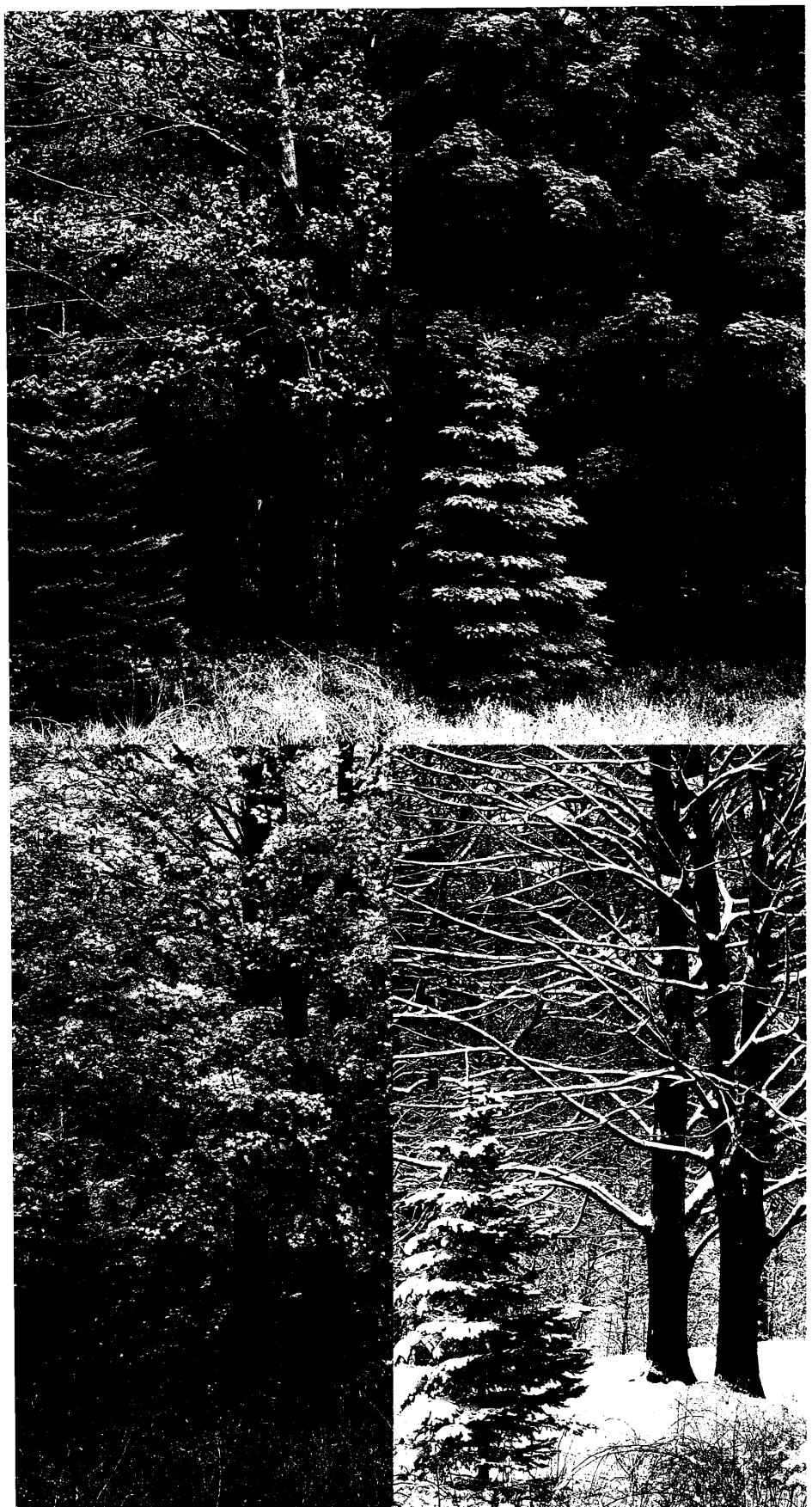
Pages 2085–2272 $8

AIDS Research in Africa

American Association for the Advancement of Science



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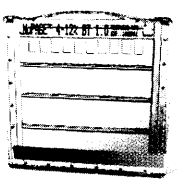

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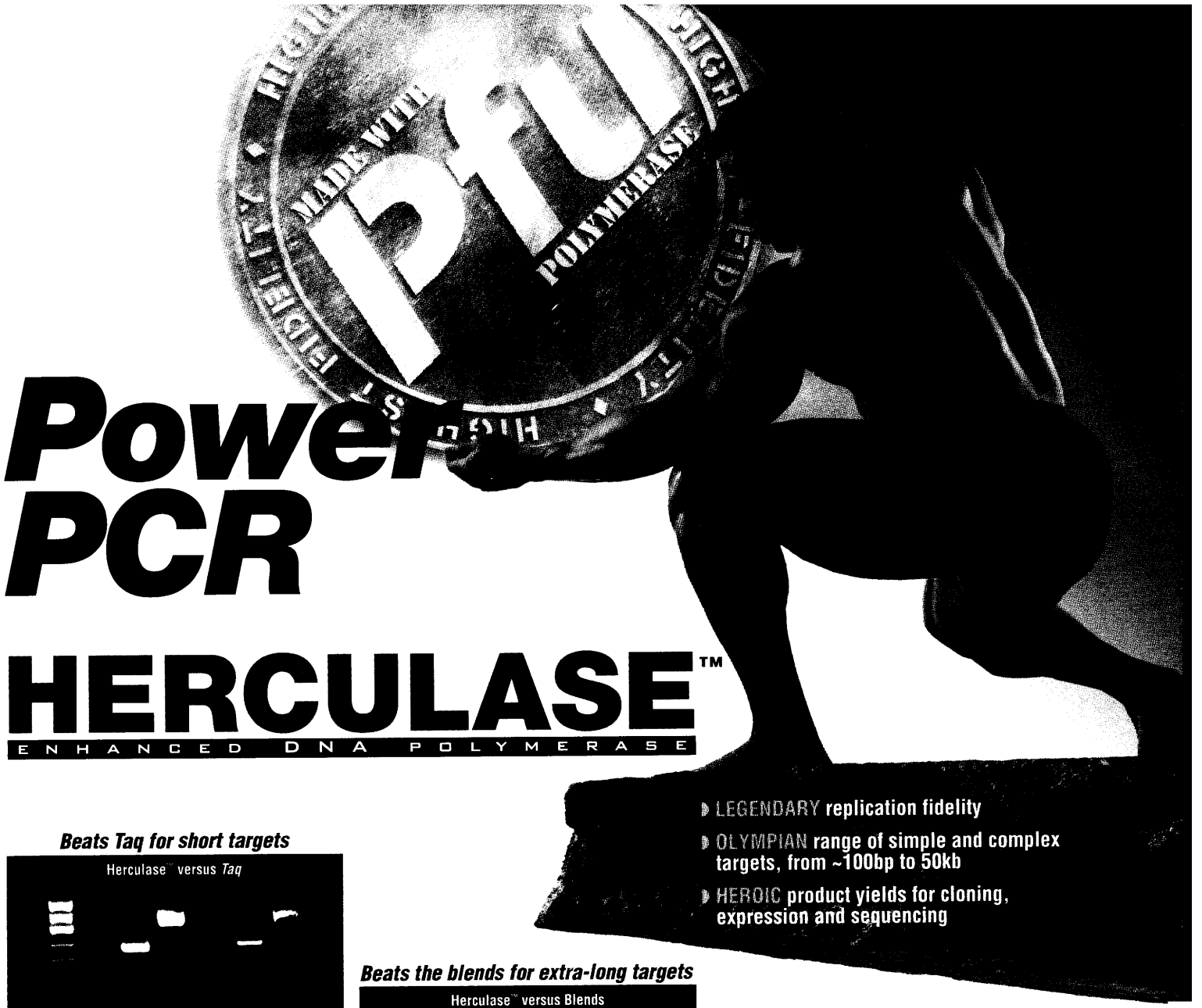

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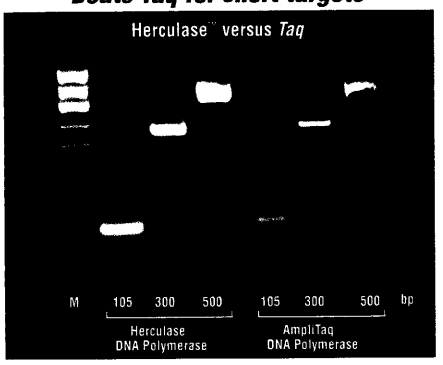

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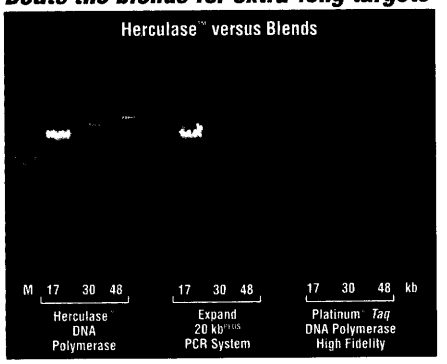

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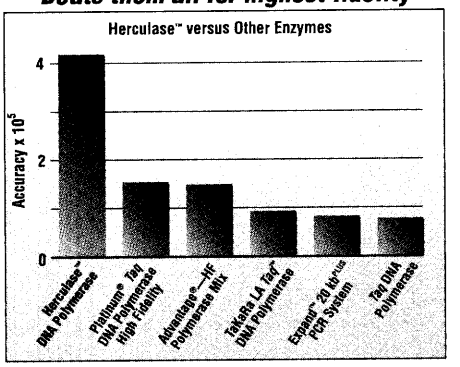

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VOLUME 288 23 JUNE 2000 NUMBER 5474

Science

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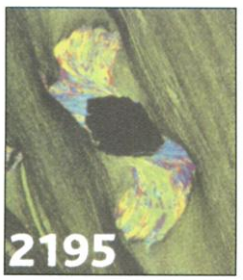
COVER These children in Mtubatuba, South Africa, will be growing up in a country where HIV infection rates are soaring. Their future, like that of children throughout much of sub-Saharan Africa, is clouded by the social, economic, and political consequences of the HIV/AIDS epidemic. A special section, beginning on page 2149, looks at AIDS research in Africa, the researchers who are conducting it, and the policy challenges that must be faced to blunt the epidemic. [Photo: Malcolm Linton]

2116
Critical periods for learning



Grain strain reflects mountain uplift

NEWS

NEWS OF THE WEEK

NEWS FOCUS

AIDS RESEARCH IN AFRICA

NEWS

VIEWPOINTS

See also Editorial on p. 2129.

RESEARCH

REPORTS

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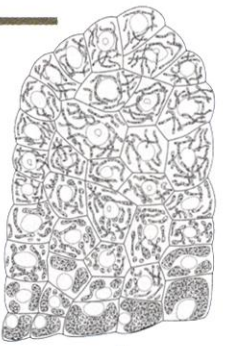

2138
Crucial organelles

2202
Feathery features in ancient gliders

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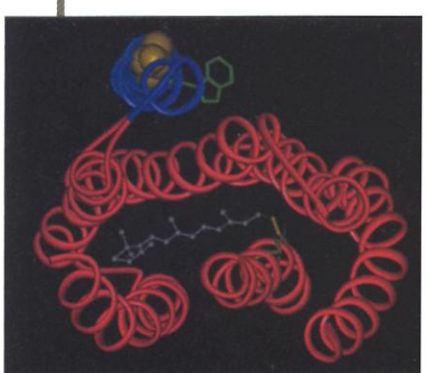
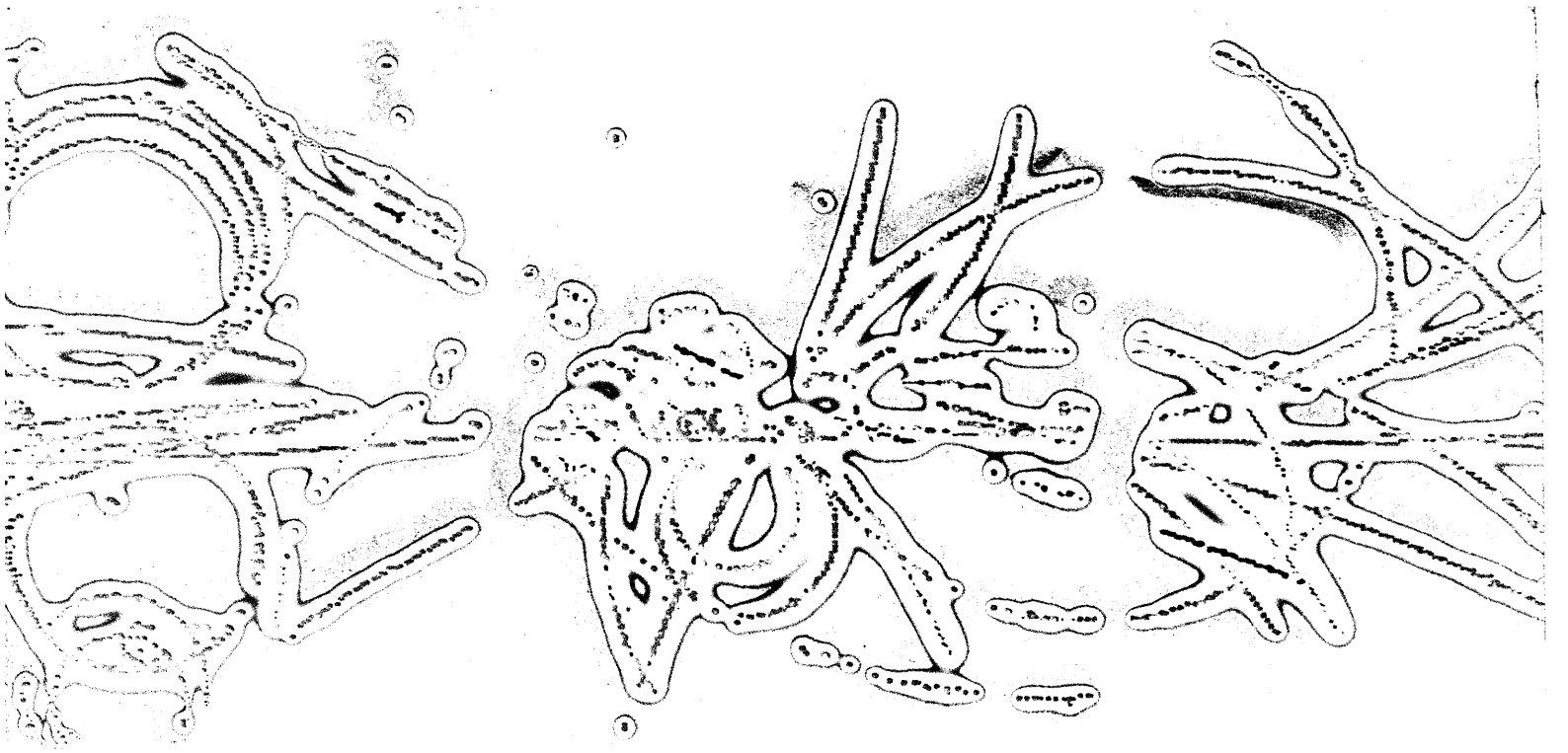


2209
The path of light



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BENT-CORE LIQUID CRYSTALS

In smectic liquid crystals, the molecules (or "mesogens") organize into layers, and in some cases the molecules adopt a particular orientation or polarization within the layers. Polarization is more likely if the molecules have a net chirality, and the design of ferroelectric liquid crystals (in which layer polarizations are all aligned) usually has relied on chiral molecules. Recently, it was shown that even achiral molecules, if they adopted a "bow" shape, could form antiferroelectric alignments (see the Perspective by Lubensky). Walba *et al.* (p. 2181) have now designed bow-shaped achiral mesogens that can adopt a ferroelectric alignment by paying careful attention to how the molecules interact between layers. Pratibha *et al.* (p. 2184) show that achiral bent-core mesogens can be added to an anisotropic smectic liquid crystal to convert the uniaxial material into an orthogonal biaxial smectic liquid crystal, which has been seen previously only in polymeric systems. These results suggest that dissolving bent-core molecules into lipid bilayers may produce unusual membrane order structures.

MAKING STRONGER POLYMERS

Polypropylene and polyethylene are among the most widely used plastics in the world, with applications ranging from food packaging to artificial knees. Recent advances in organometallic catalyst development have allowed a high level of control over the properties of the polymers. Chaffin *et al.* (p. 2187) report that synthesis using such metallocene catalysts leads to a much higher interfacial strength in layered materials. As a result, the layers are more difficult to separate by mechanical means than those synthesized by means of conventional catalysts, an advantageous property for multicomponent composites, which are important in many advanced applications of the polymers.

NEARBY ASTEROIDS

Near-Earth asteroids (NEAs) are fragments that have departed from the main asteroid belt, and now cross Earth's orbit, and thus have the potential to collide with us. Bottke *et al.* (p. 2190) combined numerical simulations of NEA orbits with observations of NEAs from the Spacewatch telescope to estimate the number and distribution of NEAs. They conclude that there are about 750 NEAs with diameters of about 1 kilometer and that the observational surveys have not yet detected many of the NEAs that are in highly eccentric and highly inclined orbits.

THE STRAIN IN GRAINS

The rate of mountain building is usually described by macroscopic structures such as folds and faults, but with improvements in microanalysis techniques, it is possible to use microscopic structures within the rock fabric to define more accurately the rate of deformation (strain rate). Müller *et al.* (p. 2195; see the Perspective by Ramsay) used the orientation of millimeter-long curved fibers of calcite, chlorite, and quartz around pyrite grains (called strain fringes) from a thrust fault in the Northern Pyrenees along with Rb-Sr dating of the fibers to determine the strain history of the orogeny. In particular, they noted a sudden increase in the strain rate over a short interval of 2 million years in which the deformation changed from gravitational collapse to horizontal crustal shortening.

LOW LATITUDE UPS AND DOWNS

The warm climate of the last 12,000 years (the Holocene epoch) has been relatively stable compared to that of the last glacial period, but it is becoming clear that the Holocene has not been without its own thermal ups and downs. The magnitude, timing, and nature of low latitude climate variability is the subject of work by deMenocal *et al.* (p. 2198). Using a marine sediment core drilled off the coast of West Africa, they show that numerous episodes of abrupt cooling occurred in surface waters, synchronously with millennial-scale variations in the North Atlantic.

ABOUT THE ORIGIN OF FEATHERS

The earliest well-developed feathers have been described in *Archaeopteryx*, a Late Jurassic bird (circa 145 Ma). On the basis of younger fossils, there are suggestions that earlier forms of feathers may have developed in theropod dinosaurs. Jones *et al.* (p. 2202; see the news story by Stokstad) now suggest that a Late Triassic (220 Ma) archosaur (a primitive reptile) had several long feathers extending from its body. The feather-like appendages seem to preserve the calamus (the hollow base of the feather), rachis (shaft), and barbs. The purpose of these feather-like features is unclear as is their relation to the later feathers seen in birds.

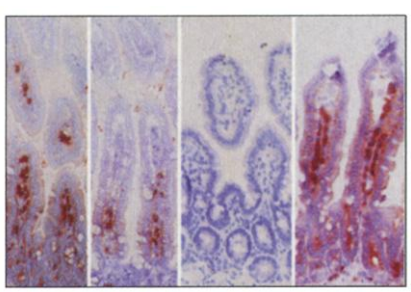
REMODELING ON THE RUN

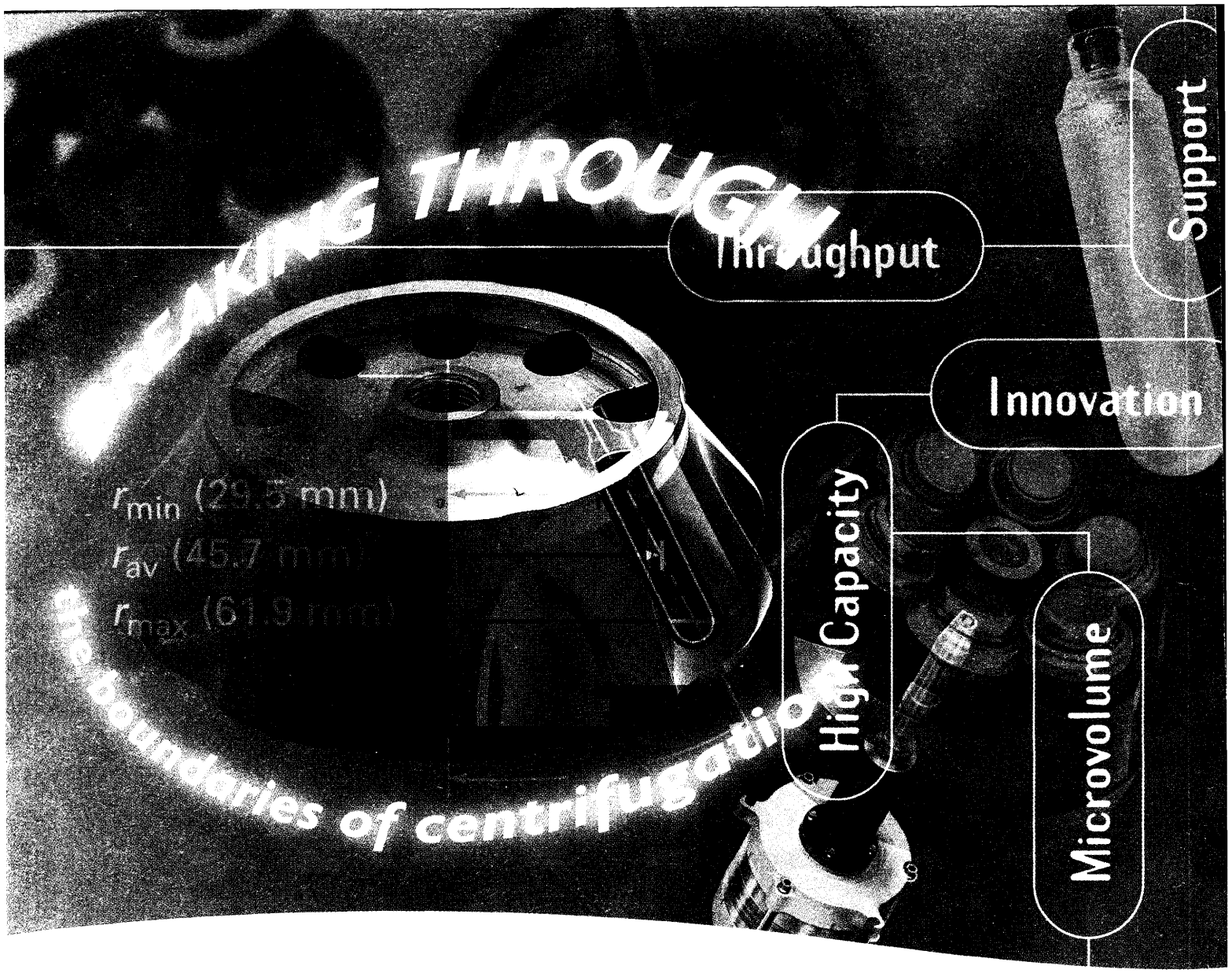
Choreographed cell migration forms the basis for normal development of a variety of structures. In the tiny worm *Caenorhabditis elegans*, the hermaphroditic gonad forms in the path laid down by its lead cell, which migrates back and forth along the body. Nishiwaki *et al.* (p. 2205; see the Perspective by Hardin) have now identified a protein, MIG-17, that is a component of the surrounding basement membranes and is critical for correct pathfinding by this leading cell. Because activity is dependent on an intact metalloprotease domain, the results suggest that MIG-17 may remodel the basement membrane in the course of pathway guidance.

CONTINUED ON PAGE 2095

GUT REACTION

The large intestine is home to a vast and complex microbial community that is present throughout the life of the human host, and that is important to normal bowel function. Mammals produce large quantities of immunoglobulin A (IgA) from the gut wall to prevent the flora from becoming invasive and to maintain the symbiosis. Despite the volume of IgA produced, little is known about it. Macpherson *et al.* (p. 2222) have discovered that these nonpathogenic organisms stimulate specific anti-commensal IgA from large numbers of B1 cell–derived plasma cells in the lamina propria of intact, healthy guts, even in the absence of T cell help or of any particular tissue organization. This capacity appears to be an evolutionarily primitive form of specific immune response.





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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 2093

SEEING THE LIGHT

Rhodopsin is a G protein–coupled receptor that is activated by light to induce the enzymatic cascade leading to vision. Isomerization of the 11-*cis* chromophore to all-*trans* triggers the visual transduction process. Borhan *et al.* (p. 2209) have trapped the photoisomerization intermediates and have traced changes in the interaction between the chromophore and the protein by photoaffinity labeling. They show that the isomerization occurs with minimal movement of the chromophore ring, giving a highly strained intermediate. This energy is used to flip the ring, which is accompanied by conformational changes in the protein.

EVOLUTION OF THE CIRCLE GAME

Archaebacteria represent a lineage distinct from prokaryotes and eukaryotes and can provide insights into the evolution of fundamental processes. Myllykallio *et al.* (p. 2212) have found evidence for a single origin of bidirectional replication in the circular genome of several Archaea and a region of termination of replication opposite it. The region surrounding the replication origin did not encode homologs of bacterial replication machinery, but had a cluster of eukaryotic-like enzymes that may function in initiation of replication. There was a lot of genetic variability in the region around the terminus, which is reminiscent of the genome shuffling seen in bacteria.

EVENTS AT THE CENTROMERE

At cellular mitosis, duplicated genetic material segregates by attaching to microtubules of the mitotic spindle. This association is facilitated by kinetochore proteins that bridge microtubules to regions in the DNA called centromeres. Takahashi *et al.* (p. 2215) show that in fission yeast, a histone-like protein called SpCENP-A is important for proper separation of duplicated chromosomes to occur. Its specific localization to centromeres depends on Mis6, another centromere-specific protein.

CHOOSING A HELPER

Immune responses can be mediated by cells (cell-mediated immunity) or through circulating factors like antibodies (humoral immunity), depending on whether naïve T cells differentiate into T helper 1 (T_H1) or T helper 2 (T_H2) cells. Li *et al.* (p. 2219) report that the small guanosine triphosphatase Rac2 increased the expression of interferon-γ (IFN-γ), a cytokine that promotes T cell differentiation, and that it appeared to signal through the mitogen-activated protein kinase p38 and the transcription factor NF-κB.

SELECTIVE MEMORY LOSS

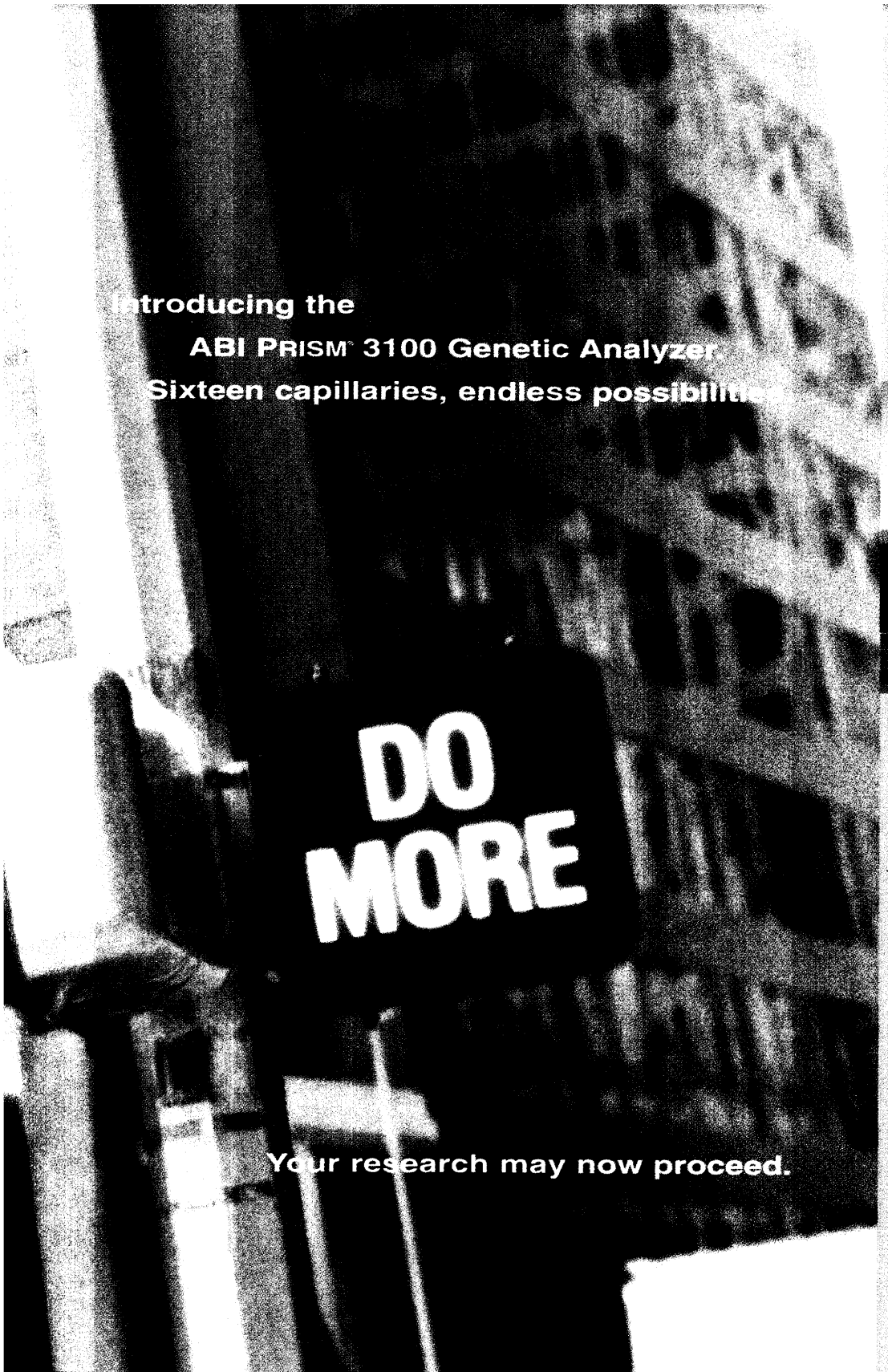
Learning and memory are accompanied by changes in gene expression in the brain. One of the greatest challenges in neuroscience is the elucidation of the signaling pathways that underlie these changes. A clue comes from the work of Garcia *et al.* (p. 2226), who show that mice deficient in a single transcription factor, NPAS2, are normal in a wide variety of behavioral tests but are impaired in a specific type of long-term memory, as revealed in a cued and contextual fear assay. Thus, NPAS2 is likely to regulate genes required for consolidation of long-term memory.

TECHNICAL COMMENT SUMMARIES

Time-Variable Cratering Rates?

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/288/5474/2095a

Studying the age distribution of spherules from Apollo 14 lunar soil samples, Culler *et al.* (Reports, 10 March, p. 1785) concluded that "over the last ~3.5 billion years [Gy], the cratering rate decreased by a factor of 2 to 3 to a low about 500 to 600 million years ago, then increased by a factor of 3.7 ± 1.2 in the last 400 million years." Hörz points out that the distribution data "might be consistent with a constant impactor flux" over the past 3 Gy if the time evolution of lunar soils is considered. He also notes that, because "lunar soils are the products of stochastic processes," a local sample "might not faithfully represent the average cratering history through geologic time." Muller *et al.* respond that "local effects can indeed distort the local record" and thus that measurements of material from other sites are currently under way. Meanwhile, they argue that, although Hörz's model is "an alternative interpretation of our data that deserves testing," analysis of the existing data at the improved precision allowed by the Culler *et al.* study strongly suggests variation in the impact rate over time.



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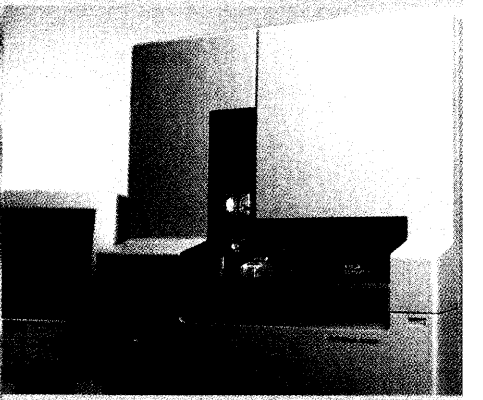

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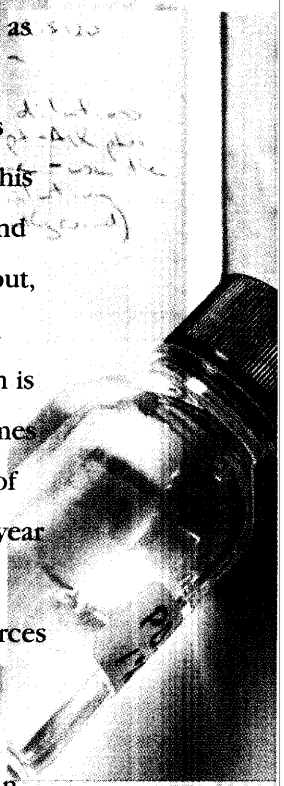
What if every time you came across a grim statistic about children in developing countries, you saw a face instead of a number? A set of real human eyes with a real human life. It could change the way you look at the world. Approximately four million of these children die each year from vaccine-preventable diseases. And here are some more faces to think about. A child in a developing country is 10 times more likely to die of a vaccine-preventable disease than a child living in the industrialized world. At least 20% of children (about 25 million infants per year) still do not have access to basic immunization services, with the lowest coverage in sub-Saharan Africa. But now for the first time in human history, a global partnership has been formed for the express purpose of helping every child in the world live free from vaccine-preventable disease. It's called the Global Alliance for Vaccines & Immunization. It represents a worldwide network of national governments, international development and finance organizations, philanthropic groups and the pharmaceutical industry. And here's how this alliance is going to change the world. To begin with, there's strength in numbers. Since GAVI is more than a single agency or organization, it can address the entire world immunization problem with a unified plan. Through such efforts, familiar killers like measles, diphtheria, tetanus, meningitis, hepatitis B and others can be controlled, if not wiped out. GAVI also stands behind the development and introduction of important new vaccines for diseases such as AIDS, tuberculosis and malaria. And it has established the Global Fund for Children's Vaccines to assist the poorest countries. This historic fund not only pays for vaccines and infrastructure, but through its financial clout, empowers countries to step up their own efforts. We know that global immunization is an investment that pays for itself many times over. But it can't be achieved without all of our support. 400 to 700 million dollars a year is needed to keep GAVI going. That, along with the expertise, brainpower and resources of people like you. Please join in the fight in any way you can. And perform a death-defying act of courage: Believe that you can make a difference in a child's life.



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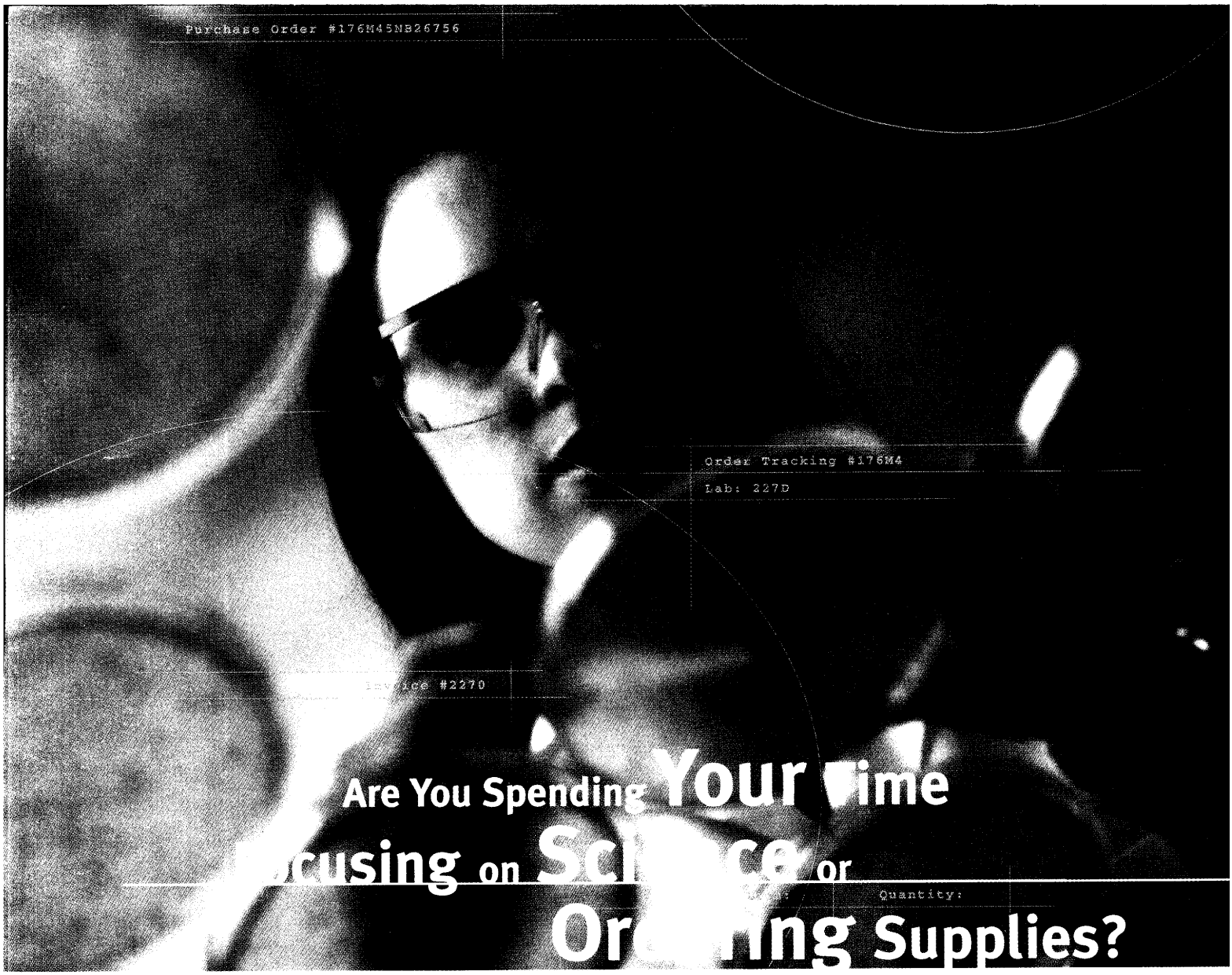

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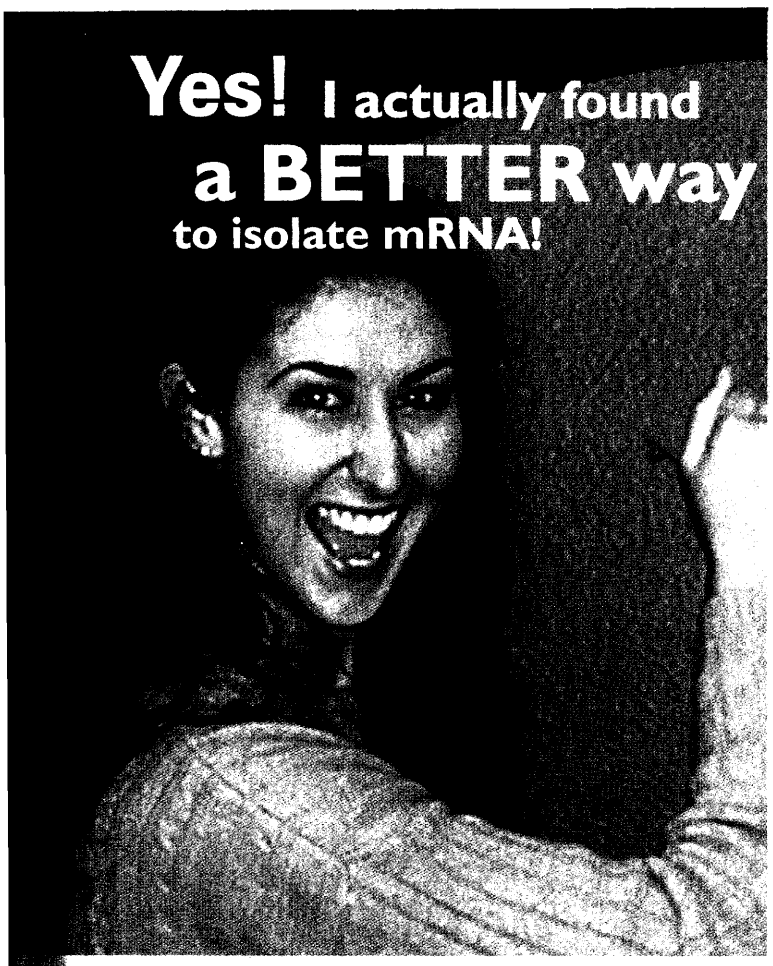

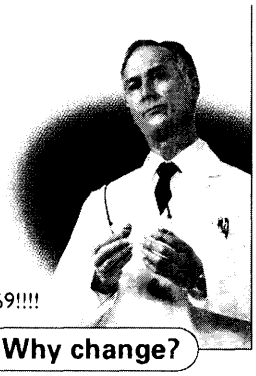

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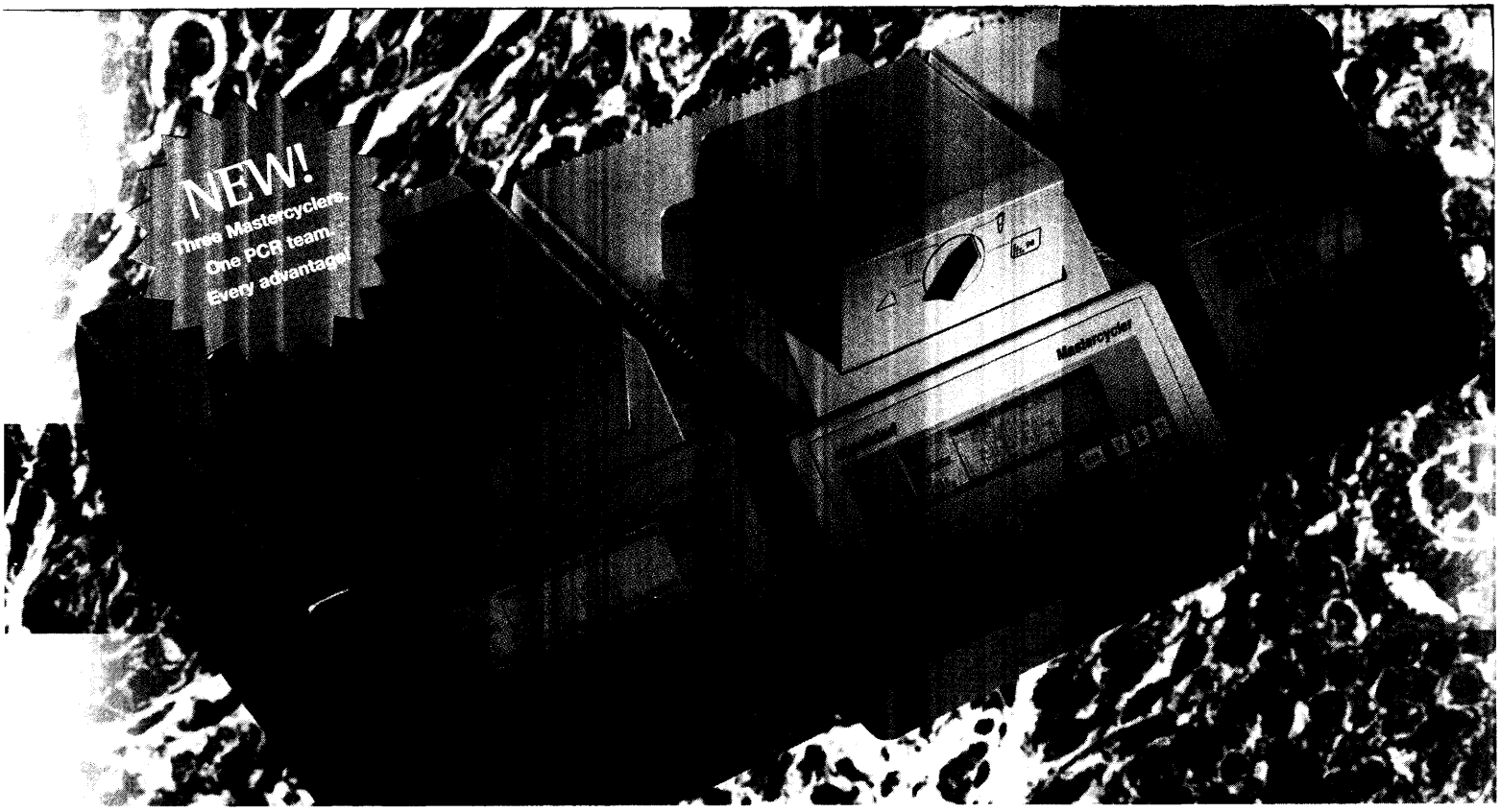

Background picture: squamous epithelium-of oral cavity, actin-*in situ* RT-PCR.

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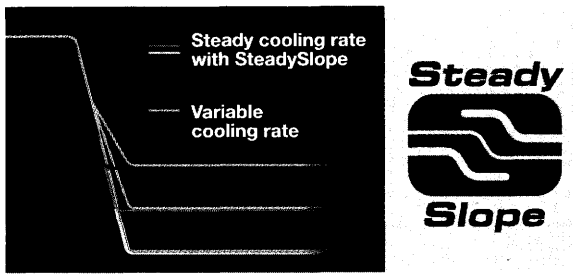

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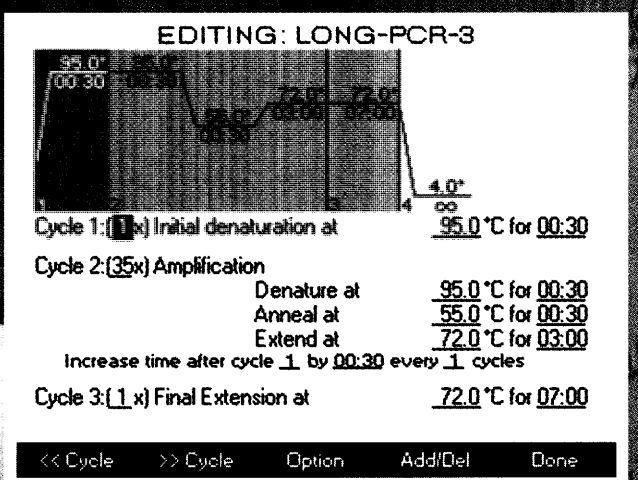

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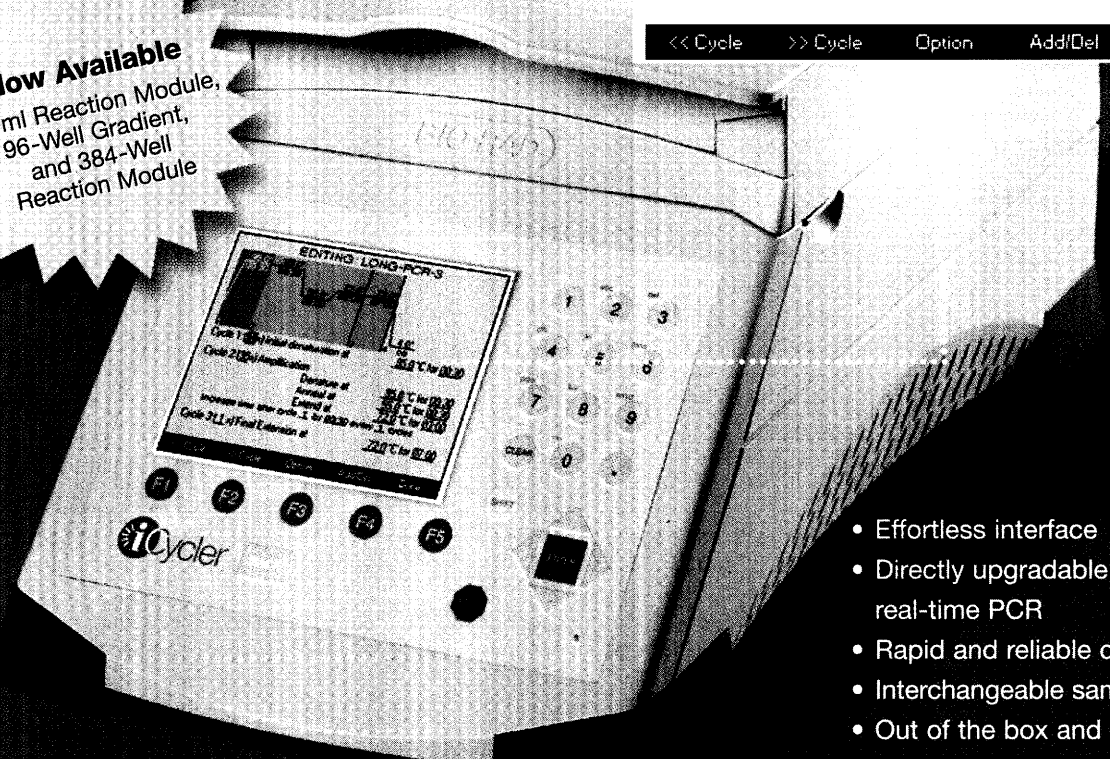

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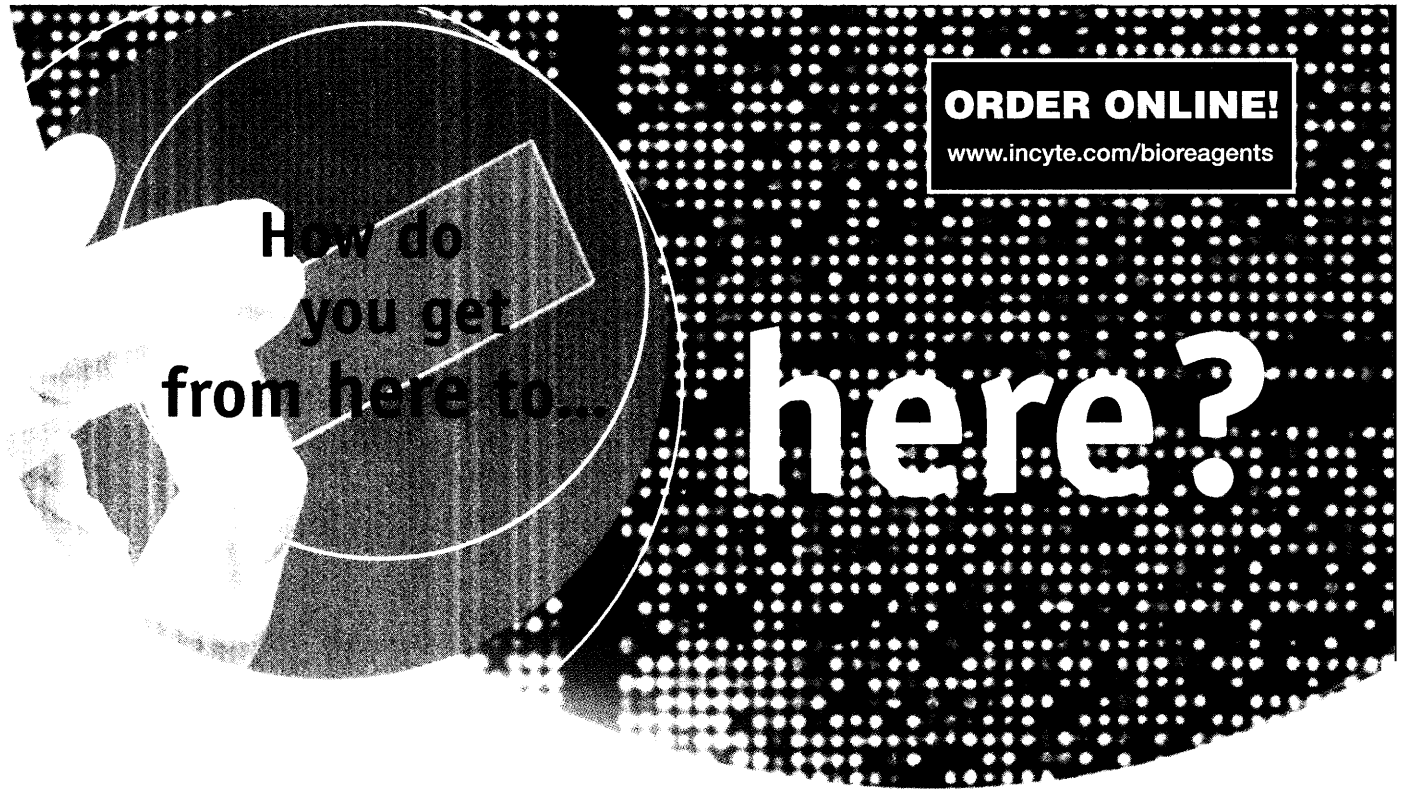

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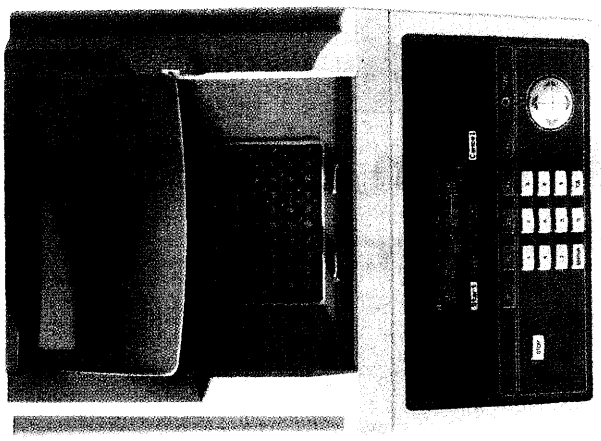
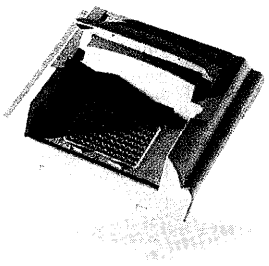
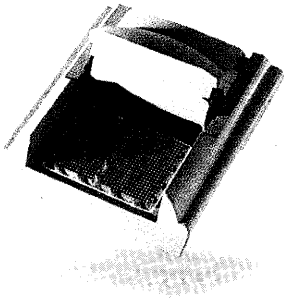
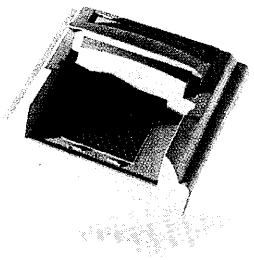




96-well 0.2 mL block



Dual 384-well 0.02 mL block



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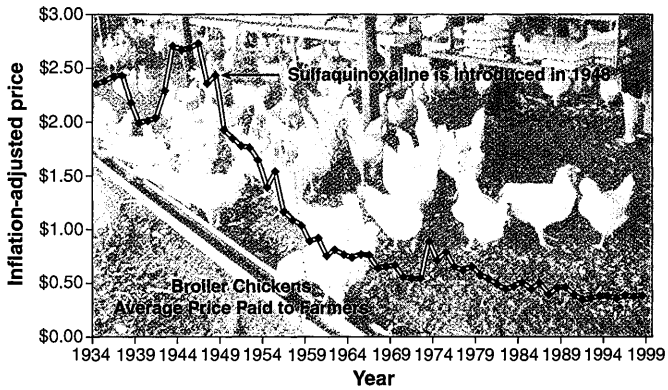

Average price received by farmers for broiler chickens (in dollars per live-weight pound) from 1934 to 1998. The data are adjusted for inflation and show prices in 1998 dollars (*4*, *5*). The arrow indicates sulfaquinoxaline's introduction in 1948 as a coccidiostat.

SOURCE: BACKGROUND IMAGE, USDA

valuable drugs in the treatment of microbial infections, although the emergence of resistance has reduced their usefulness. It may well be that the use of sulfonamides in the prevention of coccidiosis has accelerated the generation of resistance in medically relevant bacterial strains.

The history of sulfonamides is one of many examples that argue in favor of a strict separation of antibiotics for medical uses on the one hand, and for uses in animal nutrition or the mass treatment of livestock on the other. The latter uses often entail broad and uncontrolled exposure of the environment to antibiotics with consequences that are difficult to manage.

Jürgen Drews
Firnhaber Strasse 14, Feldafing D-82340, Germany. E-mail: drews@nigeons.com

fonamides in the prevention of coccidiosis; control of *Eimeria* infection is now largely dependent on monensin and related ionophores. However, a sea change in agricultural practice was precipitated by the introduction of sulfaquinoxaline and its analogs. Therefore, one might wonder if the sulfonamide class has benefited humankind more by the provision of plentiful and inexpensive dietary protein than by the cure of specific illnesses directly.

Manuel A. Navia
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References and Notes

1. J. Weijlard, M. Tishler, A. E. Erikson, *J. Am. Chem. Soc.* **66**, 1957 (1944).
2. L. C. Grumbles, J. P. Delaplane, T. C. Higgins, *Poult. Sci.* **27**, 605 (1948).
3. P. L. Long, *Br. Poult. Sci.* **25**, 3 (1984).
4. The data are from *Agricultural Prices* [U.S. Department of Agriculture, National Agricultural Statistical Service (NASS), Washington, DC]. Inflation correction factors to adjust the historical data to 1998 prices were listed at http://www.orst.edu/Dept/pol_sci/fac/sahr/sahr.htm, a Web site maintained by Robert C. Sahr (Oregon State University), which is part of the "Resources for Economists" Web site available at http://rfe.wustl.edu/EconFAQ.html
5. Thanks to D. Kennerson and K. Bruce of NASS for their assistance in obtaining the historical price data, and to H. Geer and R. Nolan for their advice on correcting these data for inflation.

Response

Navia raises an interesting point, quite apart from the medical uses of sulfonamide drugs. As to whether this class of drugs has perhaps been more beneficial in the provision of plentiful and affordable dietary protein than in the treatment of human diseases, I don't know the answer. As I pointed out in my Review article, however, sulfonamides were not only important as antibacterial drugs in their own right but also as the starting point for many structurally related but functionally diverse classes of drugs: diuretics, antidiabetic drugs, and antihypertensives. Sulfonamides continue to be

CORRECTIONS AND CLARIFICATIONS

News of the Week: "In contrast to Dolly, cloning resets telomere clock in cattle" by Gretchen Vogel (28 Apr., p. 586). The credit for the upper right photo should have read, "Peter Lansdorp, Terry Fox Laboratory, Vancouver."

Reports: "Rapid progression to AIDS in HIV$^+$ individuals with a structural variant of the chemokine receptor CX_3CR1" by S. Faure *et al.* (24 Mar., p. 2274). The values for the variables RR (relative risk) and *P* (probability) listed in Fig. 1B were incorrect. They should have been RR = 2.44 and $P = 0.016$, as stated in the text. And in Fig. 2, the black circles are data for the haplotype I249 M280, not I249 T280.

Random Samples: "Guinea worm banished from India" (17 Mar., p. 1917). The organism that nurtures Guinea worm eggs, *Cyclops*, is a crustacean (subclass Copepoda), not an aquatic insect.

Reports: "A piston model for transmembrane signaling of the aspartate receptor" by K. M. Ottemann *et al.* (10 Sept. 1999, p. 1751). In the legend for Fig. 4, the descriptions of the thick solid line and dashed line were reversed. The second sentence should have read, "Spectra in the presence (dashed line) and absence (thick solid line) of aspartate when the aspartate receptor is mixed with equimolar amounts of CheA and CheW."

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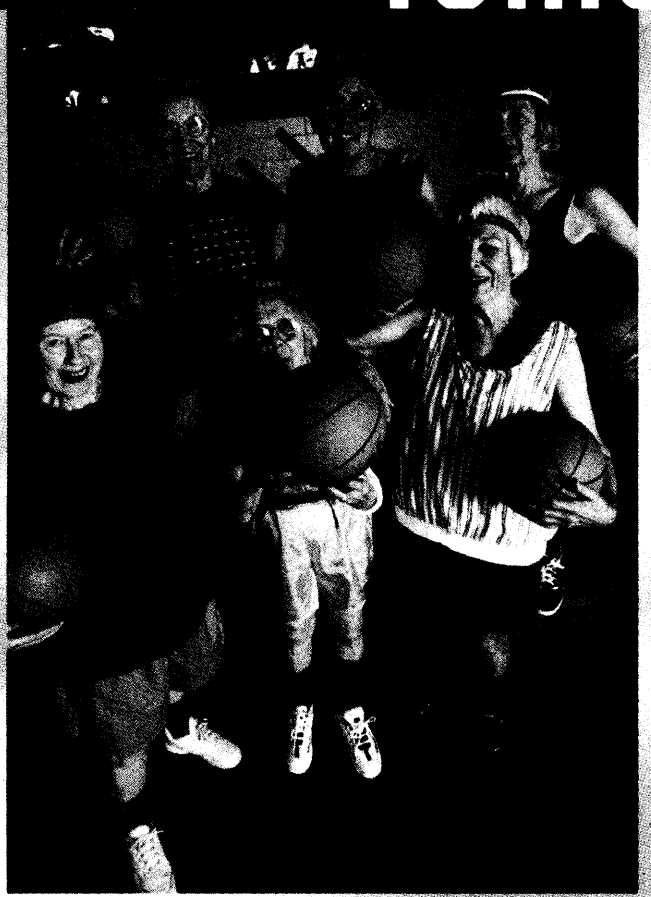

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