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Alternatives to **Toxic Tests** on Animals

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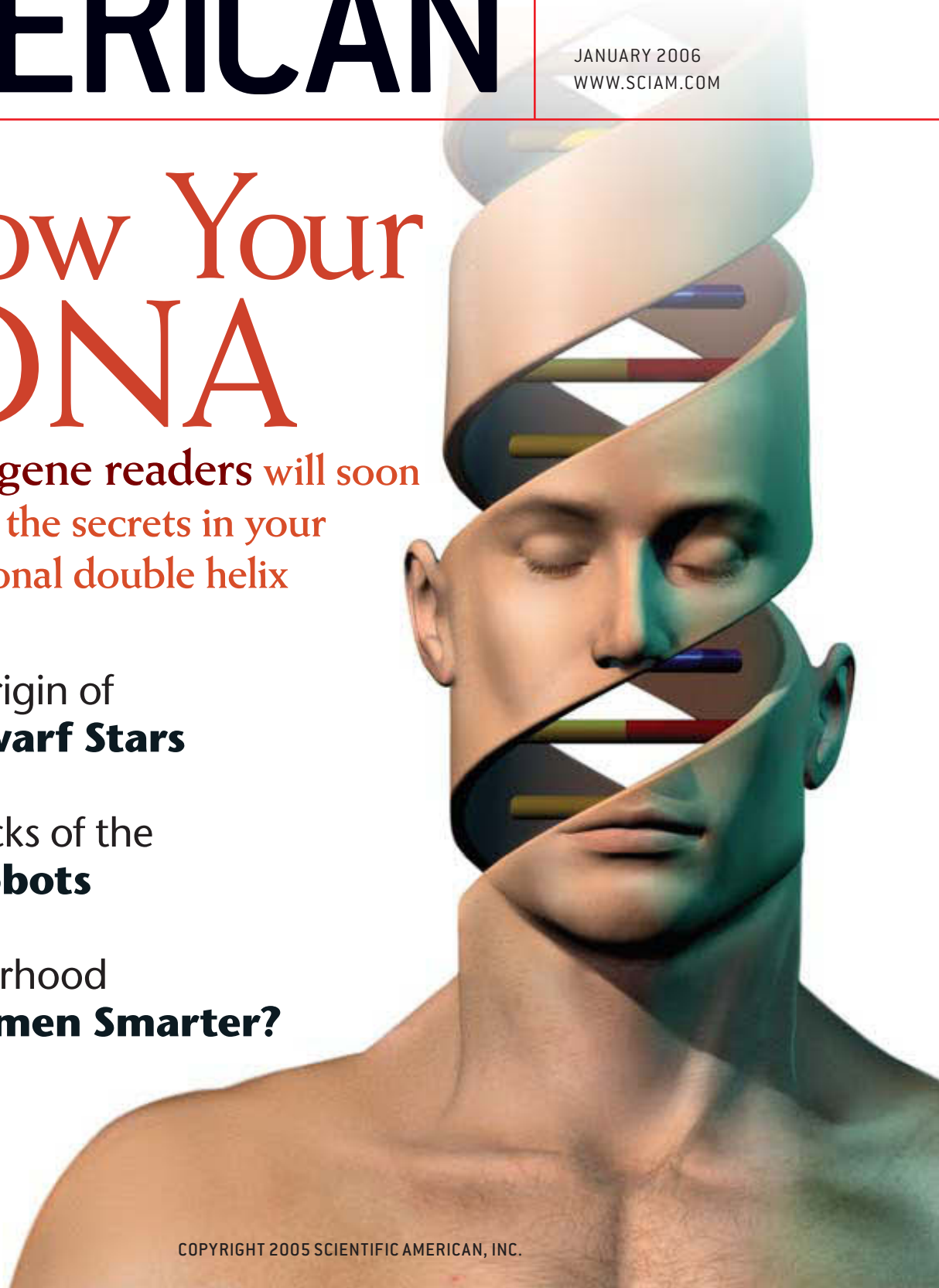

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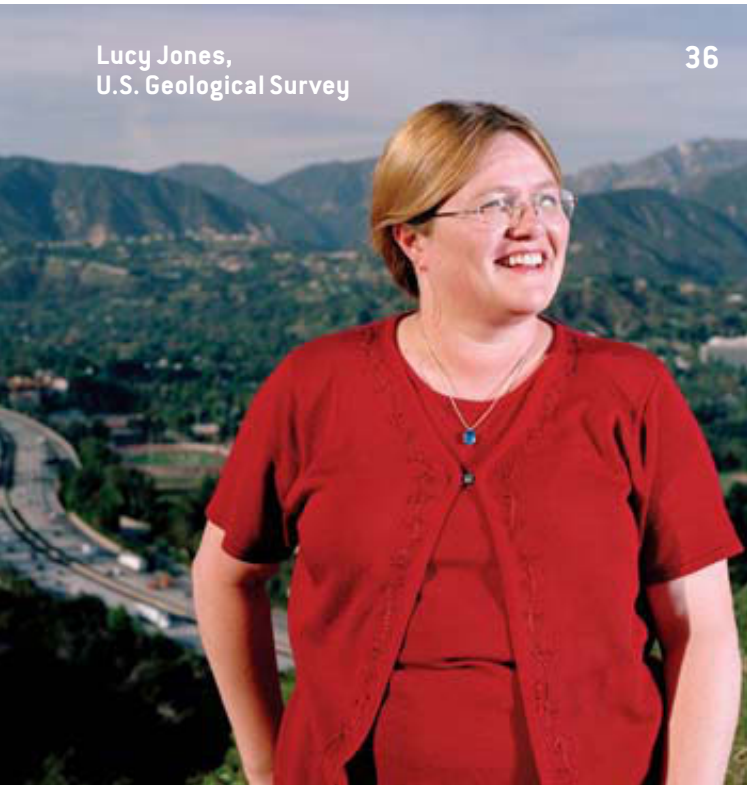

columns

Cover image by Kenn Brown; photograph at left by Brad Swonetz.

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Saving Animals and People

BEGINNING ON page 84 of this issue, scientists Alan M. Goldberg and Thomas Hartung describe recent advances in reducing, refining, and gradually replacing the use of animals in toxicology testing. Improvements in cell and tissue culture technologies, for example, allow a growing number of tests to be performed on human cells alone. Computer models, too, are becoming increasingly sophisticated, and many could one day become more accurate than trials in living animals as well as easier and less expensive.

HUMAN BLOOD CELL can sense toxins in vaccines or drugs, replacing traditional animal safety tests.

The article's story of efforts to advance science and animal welfare simultaneously contrasts with the extremism and thuggery that mar the debate over lab animal treatment. Those scientists who act blindly unconcerned about the numbers of animals they use or the cruelty of experimental conditions have no idea how monstrous they appear to some of the public.

On the other hand, their opponents can go to insane lengths. Ask the family in Newchurch, England, who for 30 years bred sterile guinea pigs for research—and who abandoned the business last month. A seven-year campaign of harassment, threats and firebombings by animal-rights extremists, culminating in the disinterment and theft of a relative's body from a church graveyard, achieved its desired effect.

Since the late 1990s, Huntingdon Life Sciences—a company that conducts testing of substances on animals mandated by the Environmental Protection Agency and the Food and Drug Administration—has become a proving ground for increasingly aggressive tactics by animal-rights militants. At an October 2005 hearing, a Senate committee listened to testimony about vandalism, harassment and threats against Huntingdon employees and financial institutions providing services to the company. (Observers have speculated that such acts of intimidation may have something to do with the unexplained last-minute decision in September by the New York Stock Exchange to postpone adding Life Sciences Research, the parent company of Huntingdon, to its listings.) One antiexperimentation witness at the hearing asserted that any means necessary were justified to spare animals' lives; he has previously embraced the idea of assassination to that end.

Use of animals in testing and in biomedical research continues to be necessary in many instances and is ethically preferable to experimenting on humans or forgoing cures that could save human lives. But for the sake of people and animals alike, the development and acceptance of animal substitutes deserve enthusiastic support.

In some instances, substitutes are already deemed as good or better than animals, but regulatory agencies have yet to catch up. In both the European Union and the U.S., scientists and companies wanting to use the new alternative tests complain that regulatory standards for proving a drug or chemical to be safe for humans force the continued use of animals. Thus, animal-loving Americans might turn their political energies toward lobbying the EPA and the FDA to speed validation of new methods so that they can be more widely employed. And animal advocates who want to influence business could consider investing in the small biotechs and large pharmaceutical companies that are working to develop alternatives to animals in research.

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EYE OF SCIENCE, REUTLINGEN, GERMANY; COURTESY OF THOMAS HARTUNG

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On the Web

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When NASA's infrared Spitzer Space Telescope snapped pictures of a distant quasar in the Draco constellation in October 2003, the photo shoot was only intended to calibrate the instrument. Those images, however, just may have provided a glimpse of the very first stars in the universe.

Mice Found to Woo Mates with Song

Mice may not sing for their supper, but male mice seem to sing to their prospective mates. Biologists made this discovery when they eavesdropped on male mice that had been exposed to the scent of female urine.

Brain Images Reveal Menstrual Cycle Patterns

For the first time, scientists have pinpointed an area of the brain involved in a woman's menstrual cycle. The research provides a baseline for understanding the emotional and behavioral changes that 75 percent of all women report experiencing before, during and after their period.

Ask the Experts

What causes a fever?

Peter Nalin, associate professor of clinical family medicine and director of the family practice residency program at Indiana University, explains.

SciAm Observations

A blog from the editors of *Scientific American*.

NASA/JPL-CALTECH/R. HURT (SSC)

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Letters

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SEPTEMBER'S SPECIAL ISSUE, "Crossroads for Planet Earth," focused on the unique near-term challenges of the next 50 years—and how our choices may well determine our species' ability not only to thrive but to survive far into the future.

Articles prescribed solutions—ranging from global to local, gradualist to radical—to tackle socioeconomic, demographic and environmental problems. And they drew a bounty of letters, laden with readers' prognostications, criticisms and alternative answers. But problem solving is a tricky business: to outline long-term fixes to current crises and trends, many authors had to valiantly venture onto that perilous tightrope that is forecasting the future. Ultimately, the portent of this issue was not gloom and doom but was summed up nicely by something Apple Computer visionary Alan C. Kay once observed: the best way to predict the future is to invent it.

HUMANITY AT THE CROSSROADS

Your special issue "Crossroads for Planet Earth" also could have been called "Crossroads for New Orleans." Everything covered—ending poverty, water and wealth, energy solutions, saving species, and the new face of disease—are now issues immediately faced by the people of the Gulf Coast.

If our leaders can find the will, we have the opportunity to rebuild this region as a model for the 21st century: with a living wage, green buildings, sustainable businesses and agriculture, reverence for nature, renewable energy and local decision making.

Katherine R. Silberman
Santa Barbara, Calif.

So many pages on the future, yet there is only a single paragraph on nuclear power. And that paragraph dismisses it! That is so unrealistic it is laughable. France gets a large percentage of its energy from nuclear power. If it were not for alarmists and ignorance, we could be well on our way to an energy glut. The whole issue reads like a utopian dream.

Kent Smith
Smethport, Pa.

Your omission of major agricultural soil management advances struck me as odd. Recent findings indicate that carbon lost from soil in agricultural land could have been the largest contributor to the measured rise in atmospheric carbon dioxide (CO_2) over the past two centuries, well ahead of the burning of fossil fuels (which is now becoming dominant). What is really interesting is that carbon loss from soil is largely reversible, with improved techniques such as no-tillage cropping and rotational grazing. That is, instead of agricultural land adding to the problem by some six gigatons of net CO_2 flux per year, it could actually sequester that much per annum, which would greatly mitigate its rise in atmospheric concentrations.

Matt Hagny
Wichita, Kan.

ERADICATING EXTREME POVERTY

Jeffrey D. Sachs's assertion that throwing more money at poverty in Africa would help solve the problem ["Can Extreme Poverty Be Eliminated?"] is not rational. The amount stolen by the thugs in charge is approximately equal to the amount of aid. According to Transparency International, 3 percent of the global GDP is lost to corruption.

When Sachs writes that climate and resources are to blame, he ignores Switzerland, which has water as its only resource, and Hong Kong and Singapore, which do not even have that. It is the establishment of democracy, capitalism and the rule of law that can make the difference. Only then can aid help. With these elements in place, private capital

would take advantage of low labor costs. This would raise the cost of labor, and workers' skills would develop to make the additional expense worthwhile.

Robert H. Black
Jacksonville, Fla.

SACHS REPLIES: Black is mistaken. The evidence strongly shows that Hong Kong and Singapore benefit from being small island economies on major trade routes, established as entrepôts. They are not models for development of tropical agricultural economies, such as those in Africa. Switzerland shows that a landlocked country can flourish if it is itself surrounded by rich nations, such as those in Europe, and serves as a long-standing land bridge between them.

The idea that aid has simply been stolen, when examined, is found to be a false generalization. Aid has often worked wonders—in the Green Revolution, the expansion of immunization coverage, the eradication of diseases, the spread of family planning. The key to success has been a core technology, quantitative targets, strong monitoring and evaluation. I agree that we should not write blank checks but rather operate aid programs on a rigorous business basis. We would save millions of lives every year, slow overall population growth and strengthen global security.

RUNNING ON FULL

In "Economics in a Full World," Herman E. Daly makes the extraordinary statement that "the well-being induced by an extra dollar for the poor is greater than that for the rich." He can prove that only if he can define "well-being" as an objective unit. Because that is not possible, he cannot prove his statement.

Richard D. Fuerle
Grand Island, N.Y.

DALY REPLIES: Most people feel that a leg amputation hurts Jones more than a pinprick hurts Smith. We make interpersonal comparisons of welfare or utility all the time on the democratic assumption that everyone has basically the same capacity for pleasure and pain. We do not need an objective "utilometer." Add to that the law of diminishing marginal utility of income (we satisfy our most pressing needs first), and it follows logically that an extra dollar of income is of more utility to the poor than to the rich.

USE IT AND LOSE IT?

In "Human Population Grows Up," Joel E. Cohen confuses what is with what can be. His question—"How many people *can* the earth support?"—is speculative, depending in part on how one defines human needs. But it is possible to answer the question "How many earths does it take to support today's population with current consumption patterns and current technology?" with ecological footprint accounts.

"Footprints" compare human demand on the biosphere in a given year with its available biological capacity in that year. Cohen correctly reports our conclusions: in 2001 humanity consumed nature's products 1.2 times faster than the biosphere could renew them. He incorrectly claims, however, that our accounting method exaggerates humanity's footprint because future energy systems could be less carbon-intensive. Although the adoption of such systems may reduce the footprint, our accounts document only what has occurred in the past, not the future.

Using less than the earth's regenerative capacity is a necessary condition for sustainability. Footprints show our failure to meet that goal for the past 20 years, putting our well-being at risk.

Mathis Wackernagel
Global Footprint Network
Oakland, Calif.

COHEN REPLIES: Wackernagel et al. converted fossil-fuel energy to land "by estimating the biologically productive area needed to sequester enough carbon emissions to avoid an increase in atmospheric CO_2." Although nuclear energy does not produce CO_2, Wackernagel charged it with the same demand for biologically productive area as energy from fossil fuel. This does not confuse what is with what can be but what is with what is not.

The difficulty is not the merits of fossil-fuel versus nuclear energy but the attempt to shoehorn the activities and demands of complex civilizations into a simple "biologically productive area." I question whether it is useful and reliable to claim to measure all human impacts on the earth at any time, past or future, by a single number of apparent but spurious precision.

ANSWERS to the December 2005 crossword.

ERRATUM In "Silicon Sniffer," by Steven Ashley [News Scan], the Sionex Corporation's name was misspelled "Scionex."

CLARIFICATIONS The photograph captioned "Deforestation in Washington State," on page 102 of "Economics in a Full World," by Herman E. Daly, depicts harvested and replanted private timberland bordering a national forest.

In "Can Extreme Poverty Be Eliminated?" by Jeffrey D. Sachs, the source of the data in the box "Extreme Poverty: Where We Stand," on page 61, was the United Nations Millennium Project Overview Report, not the World Bank's World Development Indicators.

150, 100 & 50 Years Ago

FROM *SCIENTIFIC AMERICAN*

Sargasso Theory ▪ Wright Skepticism ▪ Dismal Division

JANUARY 1956

SARGASSO SEAWEED—"Generations of scientists have sailed forth to study the Sargasso Sea. Contrary to what the seaweed might suggest, it is not a jungle teeming with life but one of the great oceanic deserts of the earth. Where do the weeds come from? Columbus theorized that the drifting weeds were torn loose from great submerged beds of plants near the Azores, but no such beds have ever been found. The floating Sargassum gives every evidence of growing, reproducing and living an independent life in the Sea where it is found. Many oceanographers now favor the theory that the great bulk of the seaweed in the Sargasso Sea is native to the Sea itself. Its forebears may have come from beds on the bottom, but it has now evolved the ability to live a free, floating existence on the surface."

JANUARY 1906

HEALTHY SKEPTICISM—"The Wright Aeroplane and Its Fabled Performances: A Parisian automobile paper recently published a letter from the Wright brothers to Capt. Ferber of the French army, in which statements are made that certainly need some public substantiation from the Wright brothers. If such sensational and tremendously important experiments [on airplane flight] are being conducted in a not very remote part of the country [Dayton, Ohio], on a subject in which almost everybody feels the most profound interest, is it possible to believe that the enterprising American reporter, who, it is well known, comes down the chimney when the door is locked in his face—even if he has to scale a fifteen-story sky-scraper to do so—would not have ascertained all about them and published them broadcast long ago? We certainly want more light on the subject." [*Editors' note: The Wrights briefly lifted their veil of secrecy to make a statement but delayed a public flight until August 1908.*]

SAFE-CRACKING—"Today the safe-breaker no longer requires those beautifully fashioned, delicate yet powerful tools which were formerly both the admiration and the despair of the safe manufacturer. For the introduction of nitroglycerine, 'soup' in technical parlance, has not only obviated onerous labor, but has again enabled the safe-cracking industry to gain a step on the safe-making one. The modern 'yeggman,' however, is often an inartistic, untidy workman, for it frequently happens that when the door suddenly parts company with the safe it takes the front of the building with it. The bombardment of the surrounding territory with portions of the Farmers' National Bank seldom fails to rouse from slumber even the soundly-sleeping tillers of the soil."

AUTOMOBILE ISSUE—"The annual automobile exhibition in New York City marks a distinct advance on its predecessors on every point of comparison. It is a matter of congratulation that the industry has now grown to such proportions that the manufacturers are enabled to turn out a standard car which is at once superior in construction and lower in price. In this issue, we illustrate and describe individual cars that represent the present progress in the art of automobile manufacture [*see illustration*]."

THE MOTOR CAR: Growing in influence, 1906

JANUARY 1856

WASTE OF NATIONS—"The division of labor, though it may bring to perfection the production of a country up to a certain point, is most deleterious in its effects upon the producers. To make pins to the best advantage, it may answer for a time to divide the operation into 20 parts. Let each man concentrate the whole of his attention on the one simple work, for instance, of learning to make pin heads, and on this ever let his time be consumed. It is astonishing the perfection and rapidity which he will acquire in performing the operation. But what is the result on the man? His powers of mind will dwindle, and his head become, for all practical purposes, after a number of generations, no larger than that of one of the pins he makes. He ceases to be a man, and becomes a mere tool."

NETWORKS

Virtual Jihad

THE INTERNET AS THE IDEAL TERRORISM RECRUITING TOOL **BY LUIS MIGUEL ARIZA**

If you read Arabic and want a degree in jihad, click on www.al-farouq.com/vb/. If you're lucky—the site disappears and reappears—you will see a post that belongs to the Global Islamic Media Front (GIMF). It announces the "Al Qaeda University of Jihad Studies." According to Ahmad al-Wathiq Billah, the GIMF "Deputy General Emir," students "pass through faculties devoted to the cause of the caliphate through morale boosting and bombings," and the site offers specialization in "electronic, media, spiritual and financial jihad."

The Internet has long been essential for terrorism, but what has surprised experts is the growth of such Islamist (radical Islam) and jihadist sites. Their continuing rise suggests that recruitment for a "holy war" against the West could proceed unabated, despite capture of key leaders.

According to Gabriel Weimann, a professor of communications at the University of Haifa in Israel, the number of all terrorist Web sites—those advocating or inciting terrorism or political violence—has grown from a dozen in 1997 to almost 4,700 today, a nearly 400-fold increase. (By comparison, the total number of Web sites has risen about 50- to 100-fold.) The enumeration includes various Marxist, Nazi and racist groups, but by far the dominant type, according to Weimann, is the Islamist-jihadist variety, which accounts for about 70 percent.

DENIS DOYLE *AP Photo*

MADRID BOMBINGS of March 11, 2004—here, at Atocha station—killed 192 commuters. The terrorists had downloaded jihadist documents, including one that called for attacking Spain.

FAST FACTS: SUICIDE BOMBERS

Suicide attacks in 2000: 43

In 2004: 163

In 2005: roughly one a day

Percent of all suicide bombings since 1968 that have occurred after September 11: 78

Number of active terrorist groups that have used suicide bombers: 35

Number that are Islamist-jihadist: 31

SOURCES: Scott Atran, Jean Nicod Institute, CNRS; Bruce Hoffman, RAND Corporation

The war in Iraq provides plenty of motivation for radicals, and the Internet appears to be facilitating them, even if legitimate governments shun them. "We are talking about groups that are opposed and persecuted all over the Arab and Muslim world, so the Internet becomes the only alternative to spread their messages," says Reuven Paz, director of PRISM (Project for the Research of Islamist Movements), a watchdog group in Herzliya, Israel. The spread "is like an attempt to create a virtual Islamic nation."

Scott Atran, a research director at the Jean Nicod Institute of the CNRS in Paris, studies the group dynamics of terrorists. He notes that the attackers of Madrid, London and Bali were autonomous groups, like "swarms that aggregate to strike and then vanish." The open, anarchic structure of the Internet supports this "chaotic dynamics" modus operandi as a way for militants to recruit new members and look for goals or inspiration. "Without the Internet, the extreme fragmentation and decentralization of the jihadi movement into a still functioning global network just would not be possible," Atran argues. "I think we can expect more independent attacks by autonomous groups because of the Internet."

Atran cites the Madrid train bombings on March 11, 2004, as a good example: a computer of one of the attackers showed evidence of systematic downloading from the same site that delivered a document entitled "Jihadi Iraq: Hopes and Dangers," which had circulated on the Net some months before the massacre. Among other charges, the document called for attacking Spain to force a withdrawal of that nation's troops from Iraq.

Atran, who has interviewed several radical jihadists, says that the Internet has spread a homogenized, flat notion of Islam, one that has little to do with Islamic tradition. The militants express a message of martyrdom for the sake of global jihad as life's noblest cause. "I was very surprised to find, from the suburbs of Paris to the jungles

of Indonesia, that people gave to me basically the same stuff, in the same words," Atran says.

Combating the problem might come at the expense of the freedom expected on the Internet. Weimann has argued that data mining could sniff out jihadists or remove information before would-be terrorists see it. Marc Sageman, a psychologist at the University of Pennsylvania and a former CIA officer, notes that the nature of Islamist-jihadist sites could be turned against them. "In jihad, with so many Web sites, you have many potential messages, and you do not know what is true," he remarks. This lack of authenticity, he notes, could serve as a basis for a misinformation campaign to foil jihadists.

Atran thinks it may be possible to fight the virulent ideas not just with a fist but also with an outstretched hand. The chat room could serve as a forum for life-affirming ideas as it does for terrorist ones. Convincing jihadists of alternative values would be a long process, he admits. But "I have seen groups of mujahedeens" transformed from fighters to community helpers. If that conversion works in physical space, he says, "I do not see any reasons why we cannot do that in cyberspace."

Luis Miguel Ariza is based in Madrid.

IMMUNITY

T Cells for Brain Cells

CAN AUTOIMMUNITY FEND OFF NEURODEGENERATION?

BY JR MINKEL

In 2002 a clinical trial of an experimental Alzheimer's vaccine was halted when a few patients began experiencing brain inflammation, a result of the immune system mounting an attack against the body. Now some researchers claim that inducing a mild autoimmune reaction could actually protect the central nervous system from a spectrum of neurodegenerative conditions, from glaucoma and spinal cord injury to Parkinson's and Alzheimer's disease. "This is a hot-button issue right now," says Howard Gendelman of the University of Nebraska Medical Center in Omaha.

It all started with glaucoma. Once thought to result primarily from high pressure in the eyeball constricting the optic nerve, the disease has lately come to be seen as a form of neurodegeneration, propagating from the injured optic nerve to healthy cells in the brain. Before monkey studies had demonstrated as much, neuroimmunologist Michal Schwartz of the Weizmann Institute in Rehovot, Israel, observed in the late 1990s that crushing a small portion of a rat optic nerve creates a large zone of sickened cells. She and her team also found that T cells, the immune system's attackers, gathered at these wounds.

Curious if the small accumulation was helpful or hurtful, the researchers injected different types of T cells into

GLAUCOMA, indicated by the clouding of the iris, is a form of neurodegeneration that could be stopped through a partial autoimmune response.

rats with optic nerve injury. Surprisingly, rats given T cells specific to myelin, the fatty sheath coating neurons, retained three times as many functional retinal ganglion cells as rats injected with other T cells. In subsequent experiments, rats

P. MARAZZI Photo Researchers, Inc.

genetically engineered to lack T cells, as well as rats insensitive to myelin autoimmune reactions, fared worse in glaucoma models than normal rats did.

Introducing antimyelin T cells to people would most likely cause brain inflammation, so Schwartz looked for a compound that would induce a weaker reaction. Copaxone, a peptide drug approved for the treatment of multiple sclerosis, fit the bill because the body's immune response against it also weakly targets myelin. And indeed, rodents vaccinated with Copaxone after insults to their optic nerves retained more retinal ganglion cells than untreated animals did.

Schwartz argues that the effect exploits a natural "protective autoimmunity" and has championed it as a more general measure for protecting the brain from disease. Too much autoimmunity causes brain disease, but too little may exacerbate the gamut of neurodegenerative conditions, she asserts. "It's a beautiful hypothesis," remarks Hartmut Wekerle of the Max Planck Institute for Neurobiology in Martinsried, Germany, but one that has split neuroimmunologists. "I think Schwartz's theory is right because it's been shown in a number of animal models," says Howard Weiner of the Center of Neurologic Diseases at the Brigham and Women's Hospital in Boston. "There's a reasonable chance it'll work in humans." In further support, Gendelman's group reported in 2004 that transferring Copaxone-specific immune cells to mice protects neurons in a model of Parkinson's disease.

The evidence is mixed, however. Spinal cord researcher Phillip Popovich of Ohio State University has been unable to mimic results from Schwartz's lab, in which transferred T cells protect spinal cord tissue. "We get what the conventional wisdom would expect: we get more problems," Popovich reports. The discrepancy probably results from subtle differences in the models employed, which implies that the effect is not robust enough to treat spinal cord injuries, he contends.

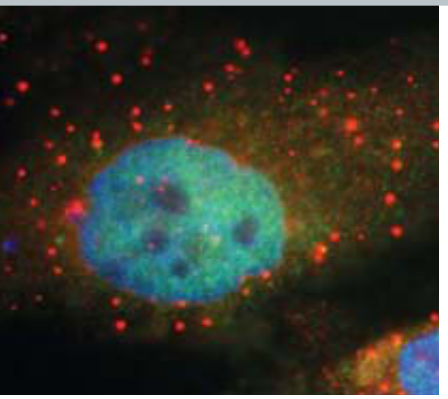
Mice have been cured of their versions of many diseases that still afflict humans, notes neuropathologist V. Hugh Perry of the University of Southampton in England. And unlike lab rat strains, individual people vary in their immune responses, creating the risk that vaccination will cause harmful autoimmune reactions, as occurred in the interrupted Alzheimer's trial. Perry acknowledges, however, that in some cases, "the regulation of inflammation is not as precise as it might be. If you can induce T cells to produce anti-inflammatory molecules, that may be a good thing."

Gendelman sees obstacles ahead before the great potential of protective autoimmunity, as he describes it, can be exploited. "How this occurs is a big black box," he says. The positive evidence has piqued some biotech interest, though: Israel's Teva Pharmaceutical Industries is investigating Copaxone and a similar peptide in models of glaucoma and several other neurodegenerative conditions. If the company moves ahead with clinical trials, that black box may open up.

JR Minkel is a frequent contributor.

BEATING GLAUCOMA WITH A VACCINE

Glaucoma, which afflicts an estimated 65 million people worldwide, is the leading cause of preventable blindness in the U.S. It has been thought to result from a buildup of pressure inside the eye that damages the optic nerve. But researchers know that glaucoma can persist or develop despite low intraocular pressure, notes Robert Weinreb, director of the Hamilton Glaucoma Center at the University of California, San Diego. A vaccine against glaucoma is therefore an appealing idea, he says: "It's begging for something that's not just an eyedrop." Rodent data suggest that a vaccine is possible, "but we need more data; we need a clinical trial."



P-BODIES (*red*), shown with a nucleus (*blue*), are organelles now known to be critical in protein making.

JOHN BLOOM

BIOLOGY

Un-Killing the Messenger

P-BODIES DO MORE THAN SERVE AS RNA TRASH BINS IN CELLS **BY CHARLES Q. CHOI**

For a cell to make proteins, the nucleus first has to issue instructions. Once these genetic memos outlive their usefulness, they end up deactivated in repositories known as processing bodies. Research now suggests that these P-bodies are less like junkyards and more like office centers, where messages are amassed, silenced and reactivated.

Messenger RNA, or mRNA, relays instructions archived in DNA to ribosomes, where it gets translated into proteins. Expunging outdated mRNAs is necessary, lest they interfere with newer orders, explains Roy Parker of the University of Arizona. In 2003 he and his team discovered that after they tagged six mRNA demolition enzymes

with fluorescent proteins, the enzymes all concentrated at the same points in yeast cells. Messenger RNAs that had been artificially made indigestible snarled at these spots, confirming that these P-bodies are where mRNAs go to die.

Early on, scientists suspected that P-bodies might play added roles, performing functions more complex than that of paper shredder. For instance, one RNA degrading protein found in yeast P-bodies, Dhh1p, was known for years as a key ingredient in granules in animal egg cells. These granules store mRNA from mothers to help generate proteins and drive much of the development in the early embryo. Neurons have mRNA storage granules as well, which are critical to memory formation. These granules, located near the synapses, release mRNA to make proteins that strengthen synapse connections.

In the past several months, Parker's experiments have confirmed suspicions about the handy nature of P-bodies. The organelles can, for instance, stockpile and deploy mRNA to make proteins. In the September 1, 2005, *Science,* Parker and his colleagues report that depriving yeast of glucose cut down protein manufacture, resulting in reduced numbers of ribosome complexes known as polysomes and increased mRNA delivery to P-bodies. But instead of simply being destroyed, mRNAs accumulated. When glucose was restored, the number of polysomes rose, and the mRNAs disappeared, indicating that they were reactivated.

In mammals, P-bodies "are clearly more complex," Parker says. He and his collaborators discovered that mammalian P-bodies concentrate Argonaute proteins 1 and 2, critical ingredients underlying the mechanism of RNA interference, by which cells employ small RNA sequences that inhibit or destroy specific mRNAs to modify their own behavior or defend against viral invasions. Nearly a third of the human genome may be regulated by RNA interference, explains molecular biologist John Rossi of the Beckman Research Institute of the City of Hope in Duarte, Calif., and the two teams' studies "show that P-bodies must be important to RNA interference."

The primordial role of P-bodies could be regulating translation by holding and releasing mRNAs. "Reusing old molecules is faster and more efficient than generating new ones," Rossi points out. Parker believes P-bodies' role as messenger shredder may have developed later, when cells might have found it beneficial to break down older mRNAs.

Much remains unknown about the mechanics of P-bodies and the range of biological processes they might influence. With his colleagues, Parker says he is developing a model in which P-bodies are the ancestors of many of the other mRNA storage granules "as a fundamental part of how cells control their genes."

Charles Q. Choi is a frequent contributor.

A TOOL FOR VIRUSES?

P-bodies could prove key to the life cycles of certain viruses. In a report appearing in the January *RNA,* Roy Parker of the University of Arizona and his colleagues at the University of California, Irvine, found that a retroviruslike element known as a retrotransposon appears to assemble its viruslike proteins at P-bodies in yeast. Retroviruses, such as HIV, might hijack the pool of deactivated mRNAs within P-bodies to use as genomic material for new viruses, Parker speculates. More broadly, John Rossi of the Beckman Research Institute of the City of Hope in Duarte, Calif., notes that viruses could interfere with P-bodies to modify host protein manufacture.

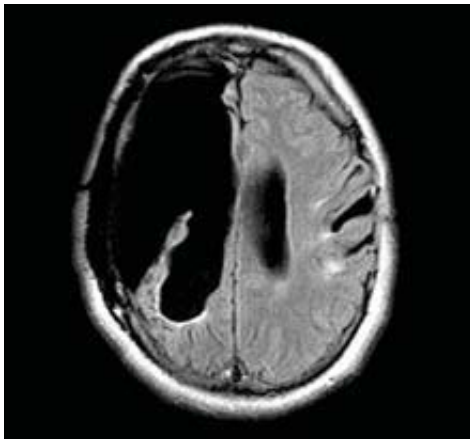
NEUROLOGY

Half-Brained Schemes

WHAT'S ALL THAT GRAY MATTER GOOD FOR, ANYWAY? BY PHILIP E. ROSS

New findings in neurology always seem to come with the caveat that there are subtleties that need to be explained. It is therefore refreshing to consider a big, fat unsubtlety: the size of our brains. At first glance, a big brain's function seems simple: to think big thoughts. And indeed, brain size does loosely correlate with intelligence, between species and, as recent MRI studies confirm, within our own. Yet some people who are missing brain parts remain just fine with what little they've got. The cases have multiplied since brain scans became routine.

Take the 50-something lawyer who, fearing Alzheimer's, came in for an MRI and got good news and bad news. He was fine, but his brain lacked a corpus callosum, the wrist-thick stalk that normally connects the brain's hemispheres. Still, he enjoyed a suc-



NEIL BORDEN *Photo Researchers, Inc.*

HALVING THE BRAIN of an epileptic child suppresses debilitating seizures without interfering with the development of normal intellectual abilities.

cessful practice and had a verbal IQ of around 130 and a nonverbal IQ above 90.

The patient exhibited subtle signs of abnormal behavior, says Warren S. Brown, a neuropsychologist who studies mind-body questions at the Fuller Theological Seminary in Pasadena, Calif.: "He just seemed odd—not remarkable, but he missed the point of social interaction." Brown adds that patients without a corpus callosum often do not get the point of jokes or understand pictures.

Of course, most brain abnormalities are found because neurologists had reason to look for them. To get around such bias, Elliott Sherr, a neurologist at the University of San Francisco, decided to study all the MRIs his university's hospital had taken. One in several thousand turned out to lack the corpus callosum. "Most times you'd get the 'Aha!' reaction," Sherr says. "So-and-so has had behavioral difficulties, and until then nobody had been able to put a finger on it." But for at least one patient, he adds, the finding had come as a complete surprise.

Equally illuminating are the patients whose corpus callosum has been surgically severed in an effort to control epileptic seizures. Michael S. Gazzaniga, director of the Center for Cognitive Neuroscience at Dartmouth College, observes that their unimpaired intelligence is inexplicable. "How come after splitting the brain, the overall cognitive capacity of the left hemisphere doesn't diminish?" he asks. "After all, half

NEED TO KNOW: HOBBIT'S BRAIN

A presumed dwarf form of *Homo erectus* raised the brain-intelligence question in late 2004. The skeletal remains, unearthed on the Indonesian island of Flores, were dubbed *H. floresiensis* by the discoverers, hobbits by the media, and a mistake by critics. The naysayers reasoned that because the creature's brain was no larger than a chimpanzee's, it could not have fashioned the highly sophisticated tools found nearby. Yet this conclusion ignores evidence that people who have a small brain, or even lack parts of their brain, can function normally.

of the cortex is no longer available to it."

Some evidence suggests that people born without a callosum benefit from enhanced development of subsidiary bridges between the hemispheres. Yet even this workaround cannot explain the competence of epileptic children who have had an entire hemisphere removed to control seizures. In one case, documented in 1975 by the late neuropsychologist Aaron Smith, a baby who underwent the operation grew up to finish college, get a responsible job, and score above average on intelligence tests. A study of many such children at the Johns Hopkins Children's Center found no intellectual deficits.

Then there are the people who just happen to have very small brains. Although a disproportionate number are mentally handicapped, many end up in the general school population, performing no worse than others on IQ tests. At least one celebrated intellectual, French writer Anatole France, had a brain just two-thirds the normal size. That puts him right in the middle of the range for *Homo erectus,* some 200,000 years ago.

Whatever benefit big brains provide, it has to be big itself to offset the huge metabolic cost of feeding the organ—some 20 to 25 percent of all calories consumed—as well as the dangers involved in giving birth to a big-headed baby. Two recent papers in *Science* conclude that two genes affecting brain size expanded through the population, under the influence of natural selection, well after modern humans emerged; one was under selection as recently as 5,000 years ago.

So if intellect isn't the point, what is a big brain for? Perhaps the extra capacity serves as backup in case we get hit on the head or lose too many neurons to the ravages of old age. Or maybe it archives the decades-long accumulation of knowledge that makes veteran hunter-gatherers more productive than novices. Another theory holds that the brain evolved to vent heat so we could hunt at high noon, when the lions slept. Finding the reason for humanity's swollen skull undoubtedly will take more brainpower.

CHEMISTRY

Clean and Green

SHORTER CARBON CHAINS MAKE STAIN BEATERS SAFER

BY REBECCA RENNER

Stain repellents confer easy-to-clean convenience to carpets and clothing thanks to substances called fluorosurfactants. Yet this benefit comes at a price: the processes used to make these surfactants—which are also used to improve paints and polishes—generate chemicals that have become pervasive in the environment. Of particular concern is perfluorooctanoic acid (PFOA), one of the most common fluorosurfactant breakdown products. Last July the science advisory board of the Environmental Protection Agency recommended that the EPA classify it as a "likely" human carcinogen. Canada has already banned some compounds that have the potential to break down to PFOA in the environment. Chemists, however, are now changing the structure of fluorosurfactants so that they do the job but are safer and do not accumulate in the environment.

GRAFFITI could be a thing of the past: fluorosurfactant coatings can cause paint to ball up, and new versions are environmentally safer.

JERRY COOKE *Corbis*

Fluorosurfactants basically consist of chains of carbon atoms surrounded by fluorine. Long rigid chains work best because they get many carbon-fluorine molecules to the surface, where they can do their jobs, and keep a large part of the chain embedded in a substrate. In stain repellents (the more demanding application), they pack tightly together so that their tips form an invisible protective armor. But chain length is also at the root of the environmental problem. Long-chain fluorosurfactants, based on a lineup of eight carbon atoms (C8), enter the

body more readily than shorter analogues, and they can break down to form PFOA. PFOA and other related long-chain fluorochemicals stick to blood proteins and masquerade as digestive acids. Consequently, they are difficult to eliminate, says environmental toxicologist Jonathan Martin of the University of Alberta in Edmonton.

Scott Mabury, a University of Toronto chemist, has done the most to link fluorosurfactants and their environmental consequences. Among the options to solve the problem, he suggests, are shortening the carbon-fluorine chains to make the chemicals less bioavailable. Indeed, 3M Company took this approach when it reformulated Scotchgard in 2001. Its change from C8 to C4, however, also caused some loss of performance, so 3M and other firms are continuing to look for more effective solutions.

To replace long-chain fluorosurfactants in polishes and paints, Omnova Solutions in Fairlawn, Ohio, has patented chemicals that consist of a long, flexible polymer backbone that bristles with small (C1 and C2) carbon-fluorine chains. The flexibility enables the short chains to reach the surface and to perform as well as or better than traditional C8 polishes and waxes. Tests show that these compounds neither accumulate in fish nor degrade during wastewater treatment, a process that appears to cause conventional fluorosurfactants to release long-chain chemicals. Omnova fluorosurfactants are now being used in industrial polishes and paints, which makes them easier to apply, and in antigraffiti coatings, which cause paint to ball up.

Chemists have also achieved some success with the tougher task of making short-chain stain repellents. University of North Carolina at Chapel Hill researchers hope to patent a new antistain chemical based on short chains they unveiled at the American Chemical Society meeting last August. They found a way to stiffen the C4 chains by propping them up with extra hydrocarbon groups. These achievements may only be scratching the surface of short-chain fluorosurfactants' potential.

Rebecca Renner writes frequently about toxicology from Williamsport, Pa.

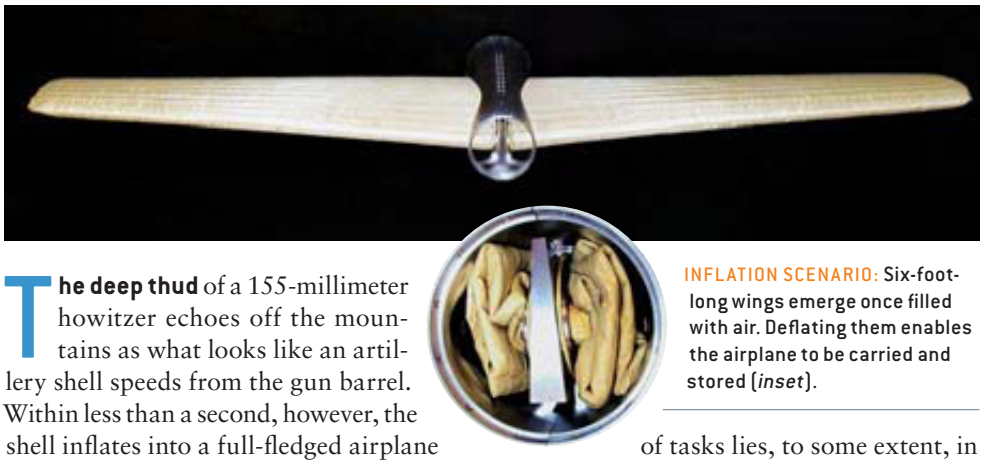
FLUORO FUNCTION

Fluorosurfactants work because they have a love-hate relationship with their chemical surroundings. Chains of carbon atoms surrounded by fluorine form the "hating end" and repel both water- and oil-based stains. The "loving end" of the molecule links up with hydrocarbon structures that anchor the chains to the rest of the coating. To repel stains, the terminal tips of millions of carbon-fluorine chains must reside at the surface. At lower concentrations, fluorosurfactants reduce surface tension, which, for instance, enables polishes and paints to be applied more easily and leave a smoother surface.

AERONAUTICS

Pumped-Up Performance

INFLATABLES FOR A GO-ANYWHERE WING AND A PLANE **BY SARAH TODD DAVIDSON**



INFLATION SCENARIO: Six-foot-long wings emerge once filled with air. Deflating them enables the airplane to be carried and stored (*inset*).

The deep thud of a 155-millimeter howitzer echoes off the mountains as what looks like an artillery shell speeds from the gun barrel. Within less than a second, however, the shell inflates into a full-fledged airplane with a six-foot wingspan. It soars through a smoke-filled sky toward a forest fire too hot and unpredictable for conventional airplanes to fly low and track.

It is just a matter of a few tweaks over the next year before inflatable vehicles should be able to fulfill such a role, say engineers at ILC Dover, an engineering company based in Delaware. Their goal is to have an unmanned aircraft that can be crumpled down and carried or stored in small spaces. Besides being able to fire them from howitzers, users could haul them around in backpacks or drop them from the air. Inflatable wings on otherwise normal airplanes would also allow engineers to double the craft's wingspan in flight. Such planes could fly to their destinations with the speed of their short wings, then extend their inflatables to burn less fuel while they loitered or slowed down for landing.

Inflatable wings passed a milestone in 2001, when inventors at the NASA Dryden Flight Research Center in Edwards, Calif., dropped a rigid aircraft from nearly 1,000 feet and two inflatable wings successfully deployed. But those wings lacked flight controls. So ILC began working to design actuators, which would be small, flexible and steerable, into the wings. Engineers are now building photovoltaic cells that can be scrunched when the wing is folded. When it unfolds, the cells provide power to onboard machinery.

"We have a number of different programs we are working on with this plane," says David Cadogan, the R&D manager at ILC. The potential for the plane to perform a variety of tasks lies, to some extent, in the fact that it can be scaled; it can range in size from 150 pounds down to 10, Cadogan says. A 100-pound version could carry various kinds of detection equipment, such as optical and infrared cameras, and ideally be operated by a single person.

For Bobby Jones, who helped to develop the wing while a student at the University of Kentucky and who now works on space suits at ILC, the groundbreaking aspect of the flying machine makes the project especially memorable. "I would talk about inflatable wings to people, and it would just be over their heads," he says.

In the long term, engineers at ILC and their collaborators at the University of Kentucky hope the wings will someday cut through the atmosphere of Mars. Engineers on the project say the technology is perfect for such a mission, where storage space on the flight to the planet is a scarce commodity.

ILC, which also designed the air bags that enabled the Mars rovers to land safely, is not the only firm interested in developing the technology. Vertigo, the Lake Elsinore, Calif., company that designed NASA's 2001 wings, continues to work on its version, which also includes a set of inflatables attached to a munition that can be fired from a howitzer. With several groups showing interest in the technology—including NASA, the Defense Advanced Research Projects Agency and companies that produce unmanned aerial vehicles—Cadogan might be aiming too low when he says the sky is the limit for these wings.

ILC DOVER (www.ilc.dover.com)

CRASH POSITION

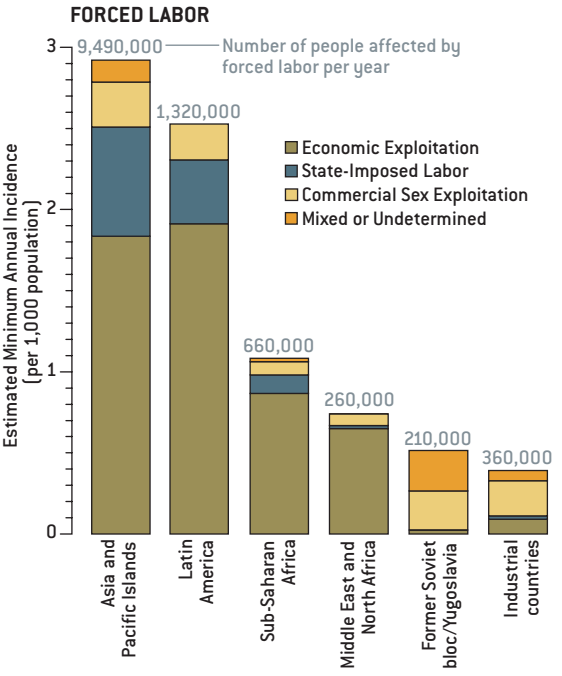
Inflatable aircraft not only save space but also are tough enough so that runways are not necessary. When the remote-controlled plane's time in the sky is over, the operator brings it home simply by crash-landing it. The impact does little to harm the robust wings, which are typically made of Vectran, a synthetic fiber stronger and more flexible than Kevlar. The operator can then just deflate the plane, roll it up and put it away.

BY THE NUMBERS

Modern Slavery

DESPITE ATTEMPTS TO END IT, FORCED LABOR THRIVES **BY RODGER DOYLE**

At least 12.3 million people are subjected to some form of forced labor. Meanwhile those who exploit them clear $44 billion in profits, rivaling the performance of the world's oil companies. These estimates come from a groundbreaking study conducted by the International Labor Organization (ILO), an arm of the United Nations. The ILO classifies forced labor into three categories: economic, state-imposed and sexual.



Economic exploitation, which accounts for 64 percent of the world total, occurs mostly in less developed countries and tends to affect the most marginalized, such as the lower castes of India and Pakistan and the indigenous peoples of Nepal and Brazil. Many of them are illiterate and understand little about their rights under the law. Hence, they are more likely to fall into servitude if they owe money to employers or landlords.

Economic exploitation persists in the U.S., primarily among illegal immigrants. For instance, California asparagus harvesters, mostly from Mexico, have had to work in substandard conditions for virtually nothing. Data from the Human Rights Center at the University of California, Berkeley, suggest that the U.S. has 10,000 or more forced laborers at any given time, mostly Chinese and Mexicans working in California, Florida, New York and Texas.

State-imposed exploitation accounts for 20 percent of the world total of forced labor. A chief concern is China's Reeducation through Labor program, which imprisons without trial those who have committed what the government characterizes as antisocial acts. The ILO is now negotiating with the Chinese about eliminating the program, which in early 2004 detained 260,000 people. One of the most extreme cases of forced labor comes from Myanmar (Burma), where the military can arbitrarily requisition the labor of entire villages.

Sexual exploitation accounts for 11 percent of the total, but in industrial and transition countries, it accounts for about half. Many victims are trafficked—that is, recruited, transported and sold. The fall of cold war barriers resulted in a resurgence of this practice. Enticed by promises of marriage, money or legitimate jobs, women and girls from Russia, Ukraine, Belarus and Poland are trafficked to western Europe. In the U.S., data from the Department of Justice suggest that 15,000 runaway youths are sexually exploited every year.

Forced labor has been an international concern at least since 1930, when the ILO, then under the League of Nations, issued its first convention against the practice. Although most ILO member states have ratified the organization's forced labor conventions, national laws are often too vague to be effective. As a result, most offenses are not prosecuted. According to Roger Plant, chief of the ILO's program to combat forced labor, the first priority is for member states to develop clear laws—and to commit the resources needed to enforce them.

Rodger Doyle can be reached at rodgerpdoyle@verizon.net

RODGER DOYLE; SOURCE: INTERNATIONAL LABOR ORGANIZATION; DATA FROM 1995 TO 2004

FURTHER READING

Hidden Slaves: Forced Labor in the United States. Human Rights Center, University of California, Berkeley, 2004.

Underidentification of Human Trafficking Victims in the United States. Elizabeth K. Hopper in *Journal of Social Work Research and Evaluation*, Vol. 5, No. 2, pages 125–136; Fall-Winter 2004.

Freedom Denied: Forced Labor in California. Human Rights Center, University of California, Berkeley, 2005.

A Global Alliance against Forced Labour. International Labor Organization, 2005.

DATA POINTS: CAFFEINE FIENDS

Caffeine boosts blood pressure in the short term, but habitual drinkers may not face the same risk. Researchers followed 155,594 American women over 12 years (from the ongoing Nurses Health Study) and found an inverted-J-shaped relation between high coffee intake and hypertension risk. Colas, however, demonstrated a linear correlation. Caffeinated soft drinks may harbor unidentified risk-boosting compounds, or perhaps the antioxidants in coffee protect the cardiovascular system.

Number in study who developed hypertension: 33,077

Number in the U.S. with hypertension: 50 million

Percent change in relative risk when the daily intake of coffee was:

Less than 1 cup: 0

1 cup: 6

2–3 cups: 0

4–5 cups: –7 to –9

6 or more cups: –9 to –12

Percent change when the daily intake of cola was:

Less than 1 cup: 0

1 cup: 9 to 13

2–3 cups: 11 to 24

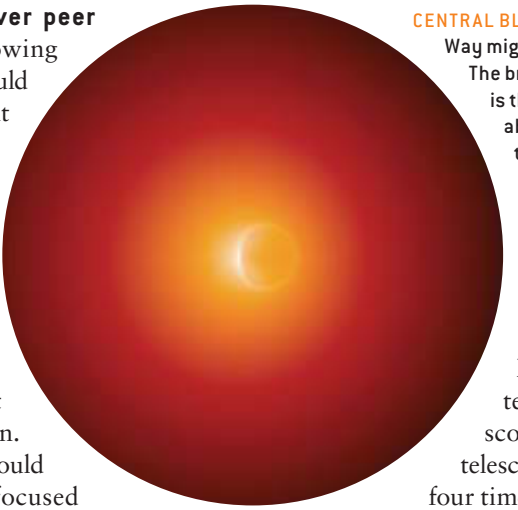
4–5 cups: 28 to 44

SOURCE: Journal of the American Medical Association, Vol. 294; *November 9, 2005. Data shown combine the results of two cohorts, which spanned slightly different periods.*

IMAGING

On the Horizon

Telescopes will never peer inside a light-swallowing black hole, but they could soon reveal the event horizon, the surface beyond which a black hole traps light permanently. The horizon would absorb light originating from behind a black hole, creating a shadow visible at high enough resolution. Around the shadow would be a bright ring of focused light, like the corona in an eclipse. Astronomers recently acquired the sharpest image yet of the object presumed to be our galaxy's central black hole, thanks to the Very Long Baseline Array, an 8,000-kilometer-wide system of 10 radio telescopes. Boosting such telescopes' resolution just four times should clarify the event horizon within the decade, according to a commentary published with the November 3, 2005, *Nature*.



CENTRAL BLACK HOLE of the Milky Way might look like this model. The bright area in the middle is the event horizon, which absorbs light behind it to create a shadow (*dark disk*) that is skewed because the hole is rotating.

—JR Minkel

MOLECULAR BIOLOGY

Protein by the Splice

The nucleus is not the only place where genetic instructions are pieced together. Messenger RNA, or mRNA, which conveys DNA instructions to the rest of the cell, is made of genetic sequences that, when spliced together properly, code for proteins. The many ways in which mRNA sequences can be woven back together help to create the body's vast diversity of proteins. Scientists thought that splicing took place only in the nucleus. Now, using fluorescent tags on splicing proteins in rat studies, molecular neurobiologist Jim Eberwine of the University of Pennsylvania and his colleagues have found that the process also occurs outside the nucleus—in particular, in dendrites, which are branches off neurons that help the cells receive electrical messages. Eberwine speculates that dendrites save mRNA in an unspliced form to ensure that the proteins they encode are not manufactured until needed. The findings appear in the November 15, 2005, *Proceedings of the National Academy of Sciences USA*.

—Charles Q. Choi

ANTHROPOLOGY

Descent in Europe

The ancient pioneers who brought farming to Europe roughly 7,500 years ago seem to have virtually disappeared genetically. Scientists extracted and analyzed mitochondrial DNA from 24 skeletons of the earliest known European farmers from 16 locations in Germany, Austria and Hungary. The investigators expected the maternally inherited DNA to resemble that of Europeans today, but in the November 11, 2005, *Science* they report a quarter of the Neolithic skeletons come from the N1a human lineage, to which only 0.2 percent of all humans now belong. These results strengthen the argument that modern Europeans largely descended from Paleolithic hunter-gatherers who arrived on the continent some 40,000 years ago. They later adopted farming from migrants who left the Fertile Crescent, where agriculture emerged about 12,000 years ago. Over time, the N1a lineage thinned out, perhaps as colonizing farmers intermarried with local women.

—Charles Q. Choi

COURTESY OF ERIC AGOL *University of Washington (top)*; ILLUSTRATION BY MATT COLLINS

CONSERVATION

Plight of the Condor

SAVING THE CONDOR might mean reintroducing seafood to the endangered predator.

Conservationists nurture the American condor on a diet of stillborn dairy calves, but weaning them onto marine meat might help them survive without human help. A team led by Stanford University scientists reconstructed dietary sources of recent and ancient condors by measuring carbon and nitrogen isotope concentrations in feather and bone remains. Condors seem to have mixed sea mammals into their diet after the last ice age, the researchers conclude. They also found signs of a second shift, from surf and turf back to land beasts alone, corresponding to the time when human settlers began hunting seal and whale. Reintroducing marine fare to condors' diets might create self-sustaining populations, the group suggests in the November 15, 2005, *Proceedings of the National Academy of Sciences USA*. —*JR Minkel*

ASTROPHYSICS

Biggest Losers

Black holes may be harder to make than once thought. When stars go supernova, theoretical calculations suggested that those about 25 times the sun's mass or more turn into black holes; meanwhile less massive stars become dense, whirling balls of neutrons. One such neutron star, in the Westerlund 1 star cluster and examined by NASA's Chandra X-ray Observatory, defies this calculation. Based on the size of the largest nearby stars, astronomers deduced that the neutron star's parent was among the biggest of them all—at least 40 solar masses. They suggest that extremely weighty stars might shed mass so effectively before they die that enough is left only for a neutron star. The findings, appearing in an upcoming *Astrophysical Journal Letters*, may severely limit the formation of black holes to stars between 25 and 40 solar masses. —*Charles Q. Choi*

PHYSICS

Underwater Speeding Violation

SUPER-DUPER SONIC: The group velocity of sound waves could be made to travel faster than light.

A simple mixture of beads and water could boost one property of sound waves past light speed. Experiments in 1982 demonstrated that the group velocity of a light pulse—based on the position of the peak of the pulse, not the individual waves—could exceed light speed. (Relativity remains unscathed because group velocity transmits no information in this case.) Now Joel Mobley of the University of Mississippi contends that an ultrasound pulse will disperse in a mix of water and plastic beads, so that the pulse's different frequencies vary greatly in speed. The sum of these components would create a faster-than-light, or superluminal, group velocity. Mobley's initial subluminal experiments support his calculations, he reported at the Acoustical Society of America meeting on October 19, 2005.

—*JR Minkel*

BRIEF POINTS

- **Scientists have discovered another appetite hormone called obestatin. Though closely related to the hunger hormone ghrelin, obestatin has the opposite effect and offers a new target in the fight against fatness.**

  Science, November 11, 2005

- **Emotional stress hampers problem solving, but propranolol, a beta blocker sometimes used to treat panic attacks, reversed the decline by interfering with the action of the stress hormone norepinephrine.**

  Society for Neuroscience meeting, November 2005

- **Where to put the cupholders? Rice University researchers made a single-molecule "car"—complete with a chassis, axles and buckyball wheels—that rolled on a gold surface when heated. At about four nanometers long, it is slightly wider than a strand of DNA.**

  Nano Letters, November 2005

- **A blood test can detect fragments of the mutant genes from cells of colon cancer at a stage when the disease can be treated, providing a possible alternative to colonoscopy.**

  Proceedings of the National Academy of Sciences USA, November 8, 2005

YVA MOMATIUK AND JOHN EASTCOTT *Minden Pictures (top)*; MEHAU KULYK *Photo Researchers, Inc. (bottom)*

"You should be very proud of me. It's an honor, and you will see the results, and everybody will be happy.... whatever you do, head high, with a goal, never be without [a] goal, always have a goal in front of you and always think, 'what for.'"
—Final letter to his wife by Ziad Jarrah, September 11 terrorist who crashed Flight 93 into a Pennsylvania field

Murdercide

Science unravels the myth of suicide bombers

By MICHAEL SHERMER

Police have an expression for people who put themselves into circumstances that force officers to shoot them: "suicide by cop." Following this lingo, suicide bombers commit "suicide by murder," so I propose we call such acts "murdercide": the killing of a human or humans with malice aforethought by means of self-murder.

The reason we need semantic precision is that suicide has drawn the attention of scientists, who understand it to be the product of two conditions quite unrelated to murdercide: ineffectiveness and disconnectedness. According to Florida State University psychologist Thomas Joiner, in his remarkably revealing scientific treatise *Why People Die by Suicide* (Harvard University Press, 2006): "People desire death when two fundamental needs are frustrated to the point of extinction; namely, the need to belong with or connect to others, and the need to feel effective with or to influence others."

Murderciders appear in posters like star athletes.

By this theory, the people who chose to jump from the World Trade Center rather than burning to death were not suicidal; neither were the passengers on Flight 93 who courageously fought the hijackers for control of the plane that ultimately crashed into a Pennsylvania field; and neither were the hijackers who flew the planes into the buildings.

The belief that suicide bombers are poor, uneducated, disaffected or disturbed is contradicted by science. Marc Sageman, a forensic psychiatrist at the Foreign Policy Research Institute, found in a study of 400 Al Qaeda members that three quarters of his sample came from the upper or middle class. Moreover, he noted, "the vast majority—90 percent—came from caring, intact families. Sixty-three percent had gone to college, as compared with the 5–6 percent that's usual for the third world. These are the best and brightest of their societies in many ways." Nor were they sans employment and familial duties. "Far from having no family or job responsibilities, 73 percent were married and the vast majority had children.... Three quarters were professionals or semiprofessionals. They are engineers, architects and civil engineers, mostly scientists. Very few humanities are represented, and quite surprisingly very few had any background in religion."

Joiner postulates that a necessary condition for suicide is habituation to the fear about the pain involved in the act. How do terrorist organizations infuse this condition in their recruits? One way is through psychological reinforcement. University of Haifa political scientist Ami Pedahzur writes in *Suicide Terrorism* (Polity Press, 2005) that the celebration and commemoration of suicide bombings that began in the 1980s changed a culture into one that idolizes martyrdom and its hero. Today murderciders appear in posters like star athletes.

Another method of control is "group dynamics." Says Sageman: "The prospective terrorists joined the jihad through preexisting social bonds with people who were already terrorists or had decided to join as a group. In 65 percent of the cases, preexisting friendship bonds played an important role in this process." Those personal connections help to override the natural inclination to avoid self-immolation. "The suicide bombers in Spain are another perfect example. Seven terrorists sharing an apartment and one saying, 'Tonight we're all going to go, guys.' You can't betray your friends, and so you go along. Individually, they probably would not have done it."

One method to attenuate murdercide, then, is to target dangerous groups that influence individuals, such as Al Qaeda. Another method, says Princeton University economist Alan B. Krueger, is to increase the civil liberties of the countries that breed terrorist groups. In an analysis of State Department data on terrorism, Krueger discovered that "countries like Saudi Arabia and Bahrain, which have spawned relatively many terrorists, are economically well off yet lacking in civil liberties. Poor countries with a tradition of protecting civil liberties are unlikely to spawn suicide terrorists. Evidently, the freedom to assemble and protest peacefully without interference from the government goes a long way to providing an alternative to terrorism."

Let freedom ring. SA

Michael Shermer is publisher of Skeptic *(www.skeptic.com). His latest book is* Science Friction.

BRAD HINES

Easing Jitters when Buildings Rumble

After natural disasters, an anxious public wants to see that someone understands the catastrophe. For California quakes, seismologist Lucy Jones does the job By DAVID APPELL

Lucy Jones is sitting in a tall chair in a conference room near her office in Pasadena, Calif. She is having makeup applied, preparing for a sit-down with a television crew from the National Geographic Channel. Only two days before, Hurricane Katrina had roared through New Orleans and other Gulf Coast areas, stranding and killing thousands. Images of destroyed homes, desperate crowds and—after Hurricane Rita—interminable evacuation traffic make it easy to imagine a catastrophe that could have an even bigger impact on the national psyche: a high-magnitude earthquake under Los Angeles or San Francisco. As a seismologist and scientist-in-charge for southern California for the U.S. Geological Survey (USGS), Jones has been thinking and talking about the possibility for most of her professional life.

BRAD SWONETZ

LUCY JONES: THE MOM IN SEISMOMETER

- **Impressed Californians after two 1992 earthquakes by doing press interviews while holding her toddler.**
- **Majored in Chinese literature, which helped her to become the first Western scientist to work in China after the normalization of relations in 1979.**
- **On earthquake danger: "The single biggest risk in Los Angeles is that building codes aren't retroactive."**

Jones takes the TV crew out to the nearby Eagle Rock fault under the La Loma Bridge in west Pasadena. It's not as famous as the San Andreas fault, but it suits the purposes of the program, which is about scientists' reactions to disaster movies. She explains to the camera that the worst-case scenario for Los Angeles is a big quake when the hot Santa Ana winds are blowing. These breezes from the east would spread fires created by breaks in natural gas lines and the arcing of power lines. "That could remove chunks of real estate," she says, then adds that California will not fall into the ocean. ("There's nowhere for it to fall to.")

A recent study by Jones's colleague Ned Field and others estimates that the losses from a major earthquake (about magnitude 7.5, perhaps a little smaller than the "Big One") under the Puente Hills fault in Los Angeles could total $250 billion and leave several thousand people dead, similar to the 1995 magnitude 6.9 Kobe earthquake in Japan. Another study finds that the San Francisco Bay Area has a 25 percent chance of getting hit with a magnitude 7 or greater earthquake in the next 20 years. Indeed, several years ago the Federal Emergency Management Agency (FEMA) had called such an earthquake one of the three most probable catastrophes threatening the U.S.—the other two were a terrorist attack in New York City and a direct hurricane strike on New Orleans.

The media like to tap Jones's expertise not just because she knows how to explain complicated geology but also because she knows how to soothe an anxious audience. "Lucy has the trust of the general public," says Tom Jordan, director of the Southern California

Earthquake Center in Los Angeles, "and they look to her for guidance about how citizens should prepare for and respond to earthquakes. She's both a media star and a respected authority." After the September 11 terrorist attacks and anthrax mailings, the *Los Angeles Times* called for "a Lucy Jones for bioterrorism" for the region, someone who can inspire trust and therefore encourage cooperation during emergencies.

Jones did not plan on becoming a practitioner of geophysical soothing. After completing her Ph.D. in geophysics at the Massachusetts Institute of Technology, she ended up in 1983 working for the USGS in southern California, where she had grown up. She made her scientific mark studying and applying the statistics of earthquakes. She found, for example, that only a small percentage of earthquakes will prove to be foreshocks. With fellow USGS seismologist Paul Reasenberg, she combined empirical data for aftershock sequences and derived rules for aftershock probabilities once a main shock has occurred (every earthquake has about a 5 percent chance of being followed by a larger one). She continues to analyze temblors statistically and frequently collaborates with her husband, Egill Hauksson, a seismologist at the California Institute of Technology.

SAN ANDREAS FAULT, here near San Luis Obispo, could produce a natural disaster worse than this past hurricane season.

TOM BEAN *Corbis*

But it is being a spokesperson after major quake events that has made Lucy Jones a household name in California. She began making media appearances after the 1986 Palm Springs earthquake but probably made the biggest impression on southern Californians by holding her toddler during television interviews after both the magnitude 6.1 Joshua Tree and magnitude 7.3 Landers earthquakes in 1992. A key attribute: "I have the ability to speak in sound bites, to get the succinct statement," she observes.

Over the years, as she has spoken to the press, she has learned that scientific accuracy is not the top priority after a serious quake—rather people want to be reassured. "People are far more afraid of earthquakes in proportion to the risk they actually pose to their lives," she says. Statistics from the National Safety Council show that an American's lifetime odds of dying in an earthquake is about one in 120,000—by comparison, dying in a transportation accident is 1,500 times more likely.

Jones says her ability to relieve anxiety was never intentional but is something she has thought about after the fact. "My theory is that people are afraid of earthquakes because they are out of [their] control. But seismologists give it a name and a number and a fault, and this puts it back in the box of controllable experiences. Even if an individual doesn't understand what happened, somebody does." In her move to a more explicitly comforting role, she thinks being a woman has helped—"I think that part of it is the female image in the situation. You feel better when Mommy tells you it's okay." After a second she adds, "It's the only time that being a woman in science has been a help!"

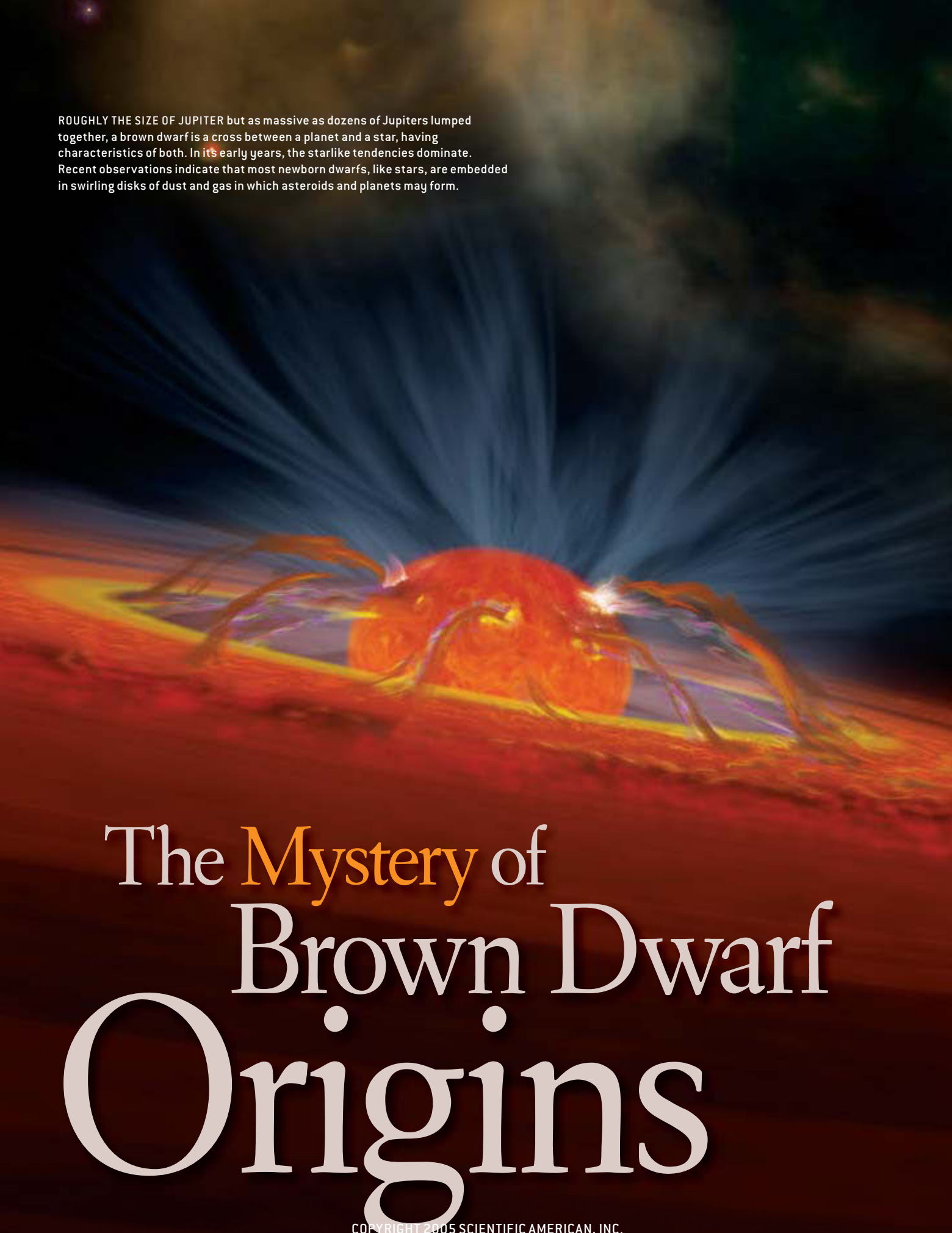
The reassuring approach that Jones embodies was missing in the recent hurricane relief efforts. "What happened to FEMA wasn't a surprise," she opines. "They have taken that agency and moved it into Homeland Security, told everybody in the agency that what they're working on is terrorism, and people with interest in natural disasters left [their jobs] if they could." She notes that in the current political climate "terrorism matters more than natural disasters." Jones worries that she and her colleagues have lost the attention of emergency managers, even though "a lot of the things you do in response to earthquakes are the same as you do in response to terrorism," such as training first responders and ensuring efficient communications channels.

Jones recently turned 50, and as she has progressed in her career she's become more involved in issues surrounding the earthquake threat in California. She just completed a term as chair of the California Seismic Safety Commission, a political appointment made by Governor Gray Davis. The commission, an independent board, advises state officials on matters affecting earthquake safety. Members review all legislation, such as those for construction codes, and offer their advice.

One issue revolved around a money-saving proposal to exempt community colleges from the Field Act, which requires stronger construction of schools. It costs 3 percent more to build tougher buildings, and one survey after an earthquake found the damage to Field Act buildings was only 0.3 percent of the value of a building versus 18 percent for non–Field Act buildings. Jones and the commission used such statistics to dissuade lawmakers from exempting the colleges, although Jones expects the bill to be resubmitted.

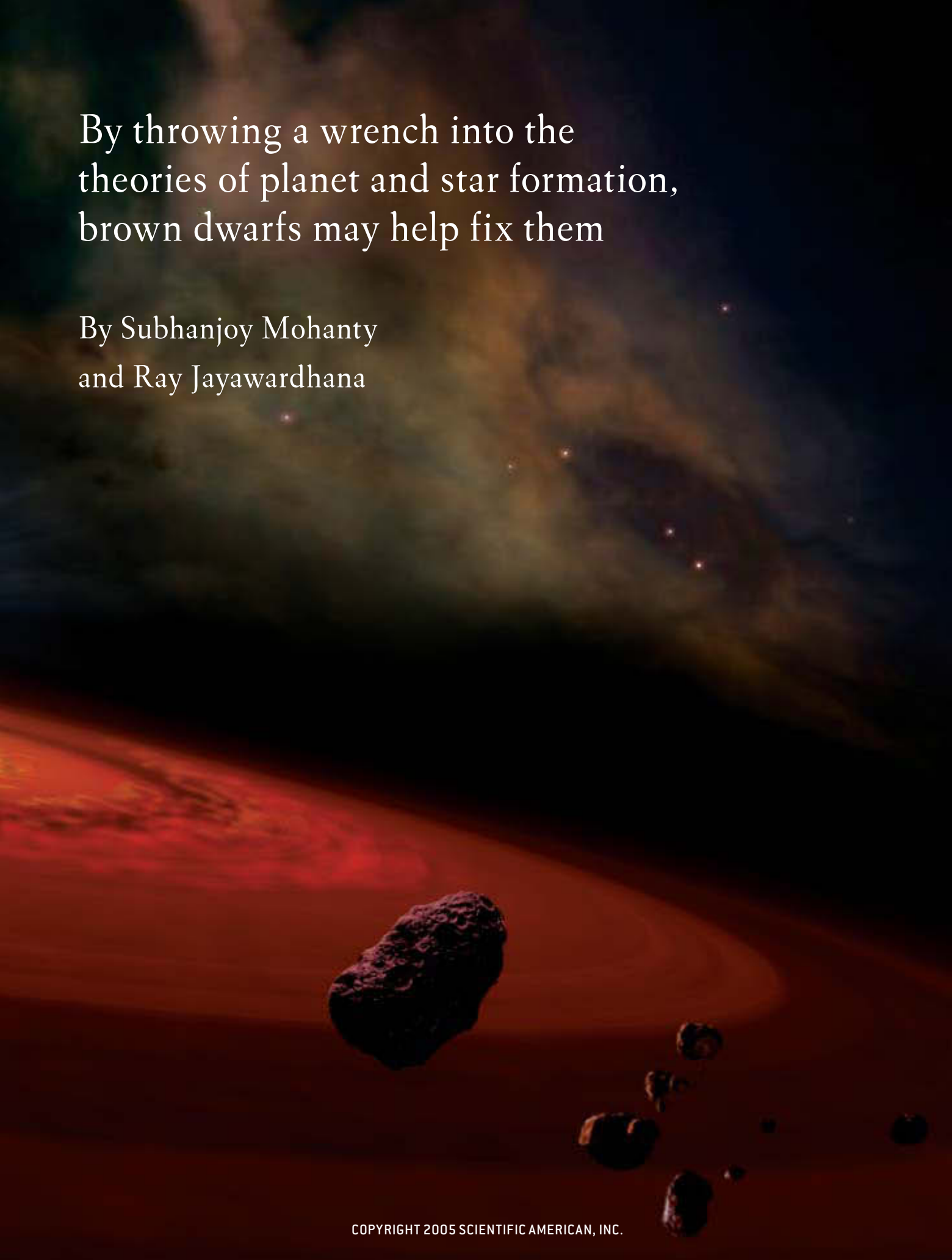
"It's a real eye-opening experience for me, to see how things don't help people until there's legislation about them," remarks Jones, who is also a member of the California Earthquake Prediction Evaluation Council, a body that examines specific predictions of temblors. Come the next midsize quake in California, or even the Big One, bet on Lucy Jones doing her part—not only explaining the science but also soothing the soul. SA

David Appell is based in Newmarket, N.H.



ROUGHLY THE SIZE OF JUPITER but as massive as dozens of Jupiters lumped together, a brown dwarf is a cross between a planet and a star, having characteristics of both. In its early years, the starlike tendencies dominate. Recent observations indicate that most newborn dwarfs, like stars, are embedded in swirling disks of dust and gas in which asteroids and planets may form.

The Mystery of Brown Dwarf Origins



By throwing a wrench into the theories of planet and star formation, brown dwarfs may help fix them

By Subhanjoy Mohanty
and Ray Jayawardhana

WHAT IS A PLANET? It seems such a simple question, but the answer keeps getting more and more confused. On the one hand, the line between planets and lesser bodies is notoriously hazy. Just last year astronomers identified a body larger than Pluto in the outermost solar system, rekindling the old debate over whether Pluto really qualifies as a planet and, if it does, why large asteroids do not. Even newspapers and museums have jumped into the fray. Less well known, though, is the muddle at the upper end of the planetary scale: the blurring of the divide between planets and stars.

The distinction used to be straightforward: a star shines by its own light, whereas a planet merely reflects the light of the star it orbits. In the more rigorous parlance of physics, stars are massive enough to undergo stable hydrogen fusion in their interiors over a sustained period, making them self-luminous. They form out of collapsing clouds of interstellar gas. Planets, on the other hand, are too puny and cold to initiate fusion. They are thought to congeal out of the debris floating around newborn stars; in short, they are leftover scraps of the star formation process.

In the past decade, however, astronomers have discovered a panoply of bodies that smear these boundaries. Straddling the mass range between planets and stars, sharing many characteristics with both but classifiable as neither, they yield fundamental insights into stellar and planetary formation and properties. These are the brown dwarfs. They span a mass range of 12 to 75 Jupiters: too light to attain the high central temperatures required to fuse ordinary hydrogen nuclei but heavy enough to fuse deuterium, a less common isotope of hydrogen. Newly formed brown dwarfs shine like feeble stars but quickly exhaust their deuterium supply and start to cool down like planets. The laws of physics imply that the size of young brown dwarfs (like that of stars) represents a balance between the inward pull of gravity and the outward push of thermal gas pressure. But older ones (like very massive planets) settle into an equilibrium between gravity and the quantum pressure exerted by densely packed electrons. The atmospheres of young brown dwarfs should closely resemble those of low-mass stars; as they cool, however, they should manifest the exotic meteorological phenomena, such as clouds, dust settling and precipitation, usually associated with planets.

Astronomers have identified hundreds of these peculiar beasts, both young ones in star-forming regions and older ones in the neighborhood of our solar system. Although the majority float through the galaxy independently (as stars do), a few inhabit orbits around stars (as planets do). It now appears that brown dwarfs could be nearly as numerous in our galaxy as sunlike stars [see "The Discovery of Brown Dwarfs," by Gibor Basri; SCIENTIFIC AMERICAN, April 2000]. As the ranks of these diminutive bodies have grown, however, a central mystery about them has come to the fore: How exactly do they form? The answer is crucial to understanding the processes at play in low-mass stars and giant planets and the differences between them.

Overview/*Brown Dwarfs*

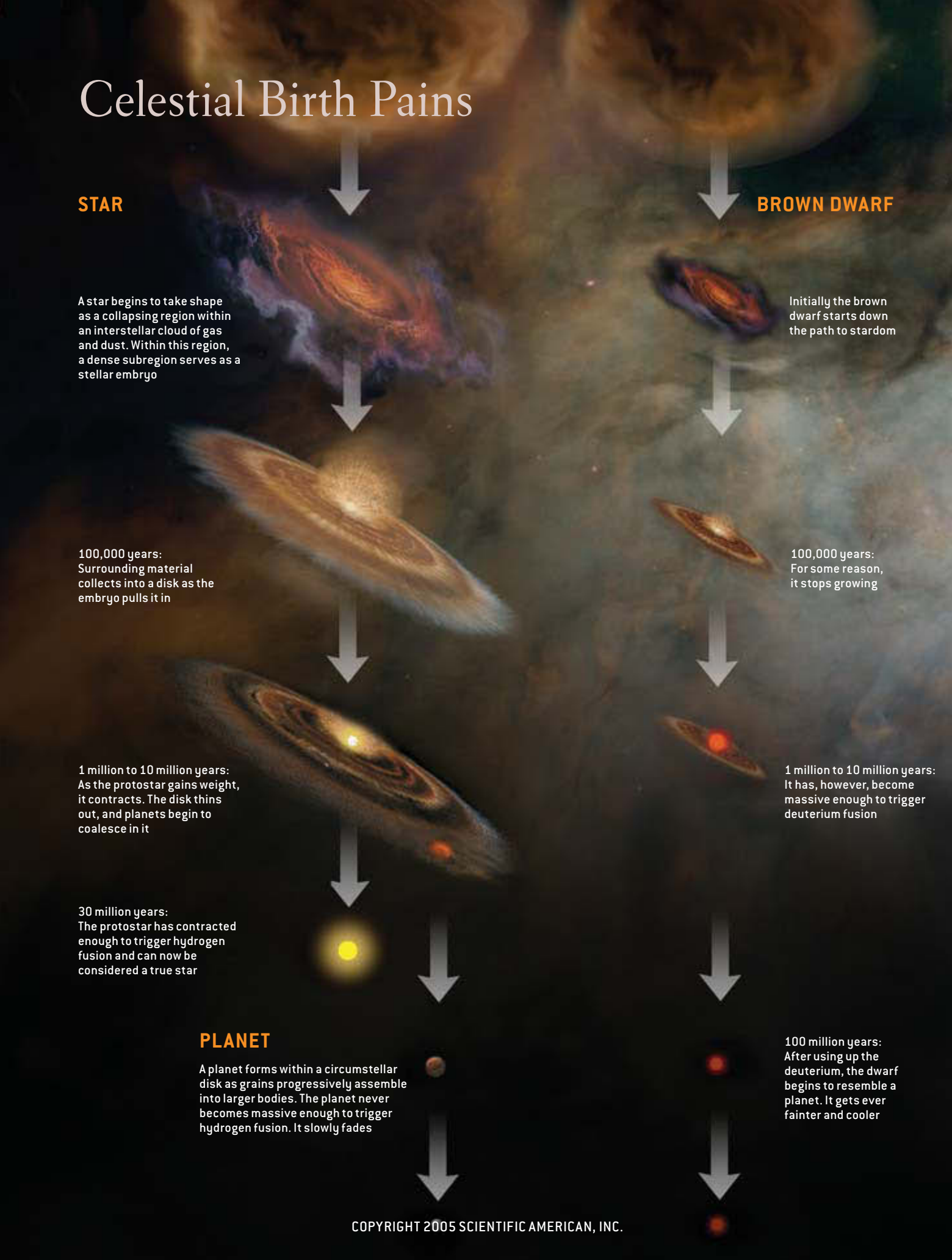
- Over the past decade, astronomers have discovered hundreds of brown dwarfs—"dwarf" meaning a small star, "brown" connoting a body that does not shine by sustained nuclear fusion. In terms of mass and other properties, they are a cross between mini-star and mega-planet.
- Having found them, astronomers must now figure out how they form. Brown dwarfs initially take shape in the same way that stars do, but something nips their growth in the bud. In one theory, the limiting factor is the puny size of their parent clumps, which in turn results from gas turbulence. In the second, it is gravitational interaction with nearby stellar embryos.
- Astronomers are beginning to test these theories by observing a range of brown dwarf properties. The resolution of this question will have broad implications for understanding both star and planet formation. It will also clarify what exactly distinguishes a star from a planet.

Cloudy Origins

IN TERMS OF MASS, brown dwarfs are intermediate between planets and stars, but in terms of origin, where do they fall? Do they form basically like planets or basically like stars? Planets are born in the disks of gas and dust girdling newborn stars. According to the most popular model, a gas-giant planet starts with the gradual agglomeration of dusty debris into larger and larger bodies. Once such a body reaches a few Earth masses in size, it undergoes runaway growth, sweeping up the surrounding gas at an accelerating rate. The entire process takes a few million years, over which time the disk gas also dissipates by either accreting onto the central star or getting blown out of the system altogether. So the amount of

DON DIXON (*preceding and opposite pages*)

Celestial Birth Pains



STAR

A star begins to take shape as a collapsing region within an interstellar cloud of gas and dust. Within this region, a dense subregion serves as a stellar embryo

100,000 years:
Surrounding material collects into a disk as the embryo pulls it in

1 million to 10 million years:
As the protostar gains weight, it contracts. The disk thins out, and planets begin to coalesce in it

30 million years:
The protostar has contracted enough to trigger hydrogen fusion and can now be considered a true star

PLANET

A planet forms within a circumstellar disk as grains progressively assemble into larger bodies. The planet never becomes massive enough to trigger hydrogen fusion. It slowly fades

BROWN DWARF

Initially the brown dwarf starts down the path to stardom

100,000 years:
For some reason, it stops growing

1 million to 10 million years:
It has, however, become massive enough to trigger deuterium fusion

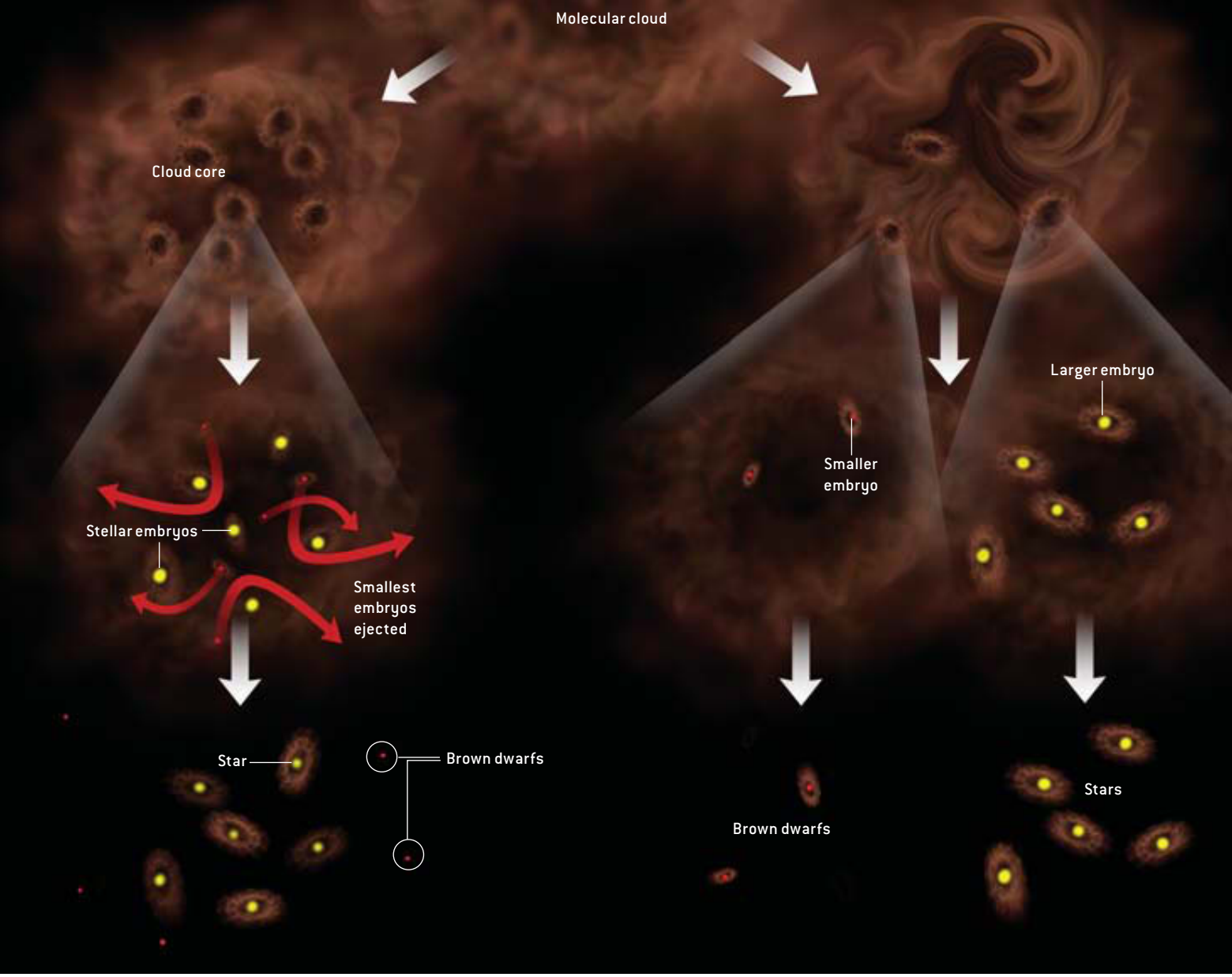
100 million years:
After using up the deuterium, the dwarf begins to resemble a planet. It gets ever fainter and cooler

Arrested Development

Brown dwarfs, like stars, form from stellar embryos embedded within larger clouds of gas and dust, but something prevents them from growing to stellar proportions. Astronomers have two competing theories.

EJECTION SCENARIO
Perhaps the embryos interact with one another. Those that happen to be smaller get thrown out of the cloud altogether, cutting them off from the material that fed their growth.

TURBULENCE SCENARIO
The cloud subregions (or "cores") that become stars can vary in size because of turbulent motions. Brown dwarfs are simply the low end of the range.



DON DIXON

gas available to build up a giant planet diminishes with time, limiting the heaviest objects that can arise to a mass of about 10 to 15 Jupiters. In that case, brown dwarfs cannot form in the same way that planets do. Observational surveys support this conclusion: most brown dwarfs are independent bodies, like stars, instead of bodies tethered to stars, like planets.

For these reasons, astronomers favor a more starlike formation scenario for brown dwarfs. Yet the classical picture of star formation does not quite work either. Decades of observations have established that stars form within so-called molecular clouds: vast agglomerations of cold gas and dust, each with enough material to form scores of suns. Within such a cloud some regions, known as cores, are denser than others. A sufficiently large and dense core can overcome the outward force of gas pressure to collapse under its own weight. The minimum mass a core must have to do so depends on proper-

ties such as temperature and is referred to as the thermal Jeans mass. From observations of molecular clouds, astronomers estimate a typical Jeans value of roughly one solar mass.

A typical core does not collapse all the way down to a single star. Instead its central, densest regions break up into smaller clumps. In 1976 theorists C. Low and Donald Lynden-Bell of the University of Cambridge calculated that the smallest such fragments could have masses as low as several Jupiters. More recent simulations by Alan Boss of the Carnegie Institution of Washington, taking magnetic fields into account, suggest that clumps of even one Jupiter mass may be possible. These fragments are stellar embryos: stars in the process of hatching, though not yet fully formed objects. Infalling gas from the core in which they are embedded rains down on them. Ultimately, the embryos sweep up most of the core material to become full-fledged stars. Because a collapsing core containing a solar mass of gas is divvied up among 10 or so embryos, the expected result is a handful of stars each with at least a tenth the mass of the sun.

What, then, accounts for brown dwarfs, which tip the scales at merely a few tens of Jupiters (a few hundredths of a solar mass)? Something must be preventing the initial stellar embryos from growing to stellar proportions. This mystery of how and why their growth is arrested, before they gather enough mass to ignite as stars, is at the heart of the current debate on brown dwarf genesis.

Theorists have proposed ways of resolving this quandary. In 2001 Bo Reipurth of the University of Hawaii at Hilo and Cathie Clarke of Cambridge suggested that brown dwarfs are the victims of sibling rivalry. In this scenario, the multiple embryos in a core compete to accrete matter, and the one that grows slowest is at the mercy of the others. Gravitational interactions eject it from the core, cutting it off from its reservoir of gas and leaving it permanently stunted. If that happens before the embryo has had time to attain stellar mass, the result is a brown dwarf. Brown dwarfs, then, are failed stars: no different from full-blown stars at birth but condemned to remain puny after being prematurely banished.

The next year a different hypothesis was put forward by Paolo Padoan of the University of California, San Diego, and Åke Nordlund of the University of Copenhagen. They questioned the usual assumption that star formation begins with cores containing at least one solar mass or more of material. Cores, they argued, can be even smaller because turbulent motion within the molecular cloud can trigger gravitational collapse. Simply put, a small core that would not collapse when left to its own devices can be induced to do so when compressed by turbulence. Brown dwarfs can then form directly from ultralow-mass cores. This turbulence scenario eliminates the need for a secondary mechanism (such as ejection) to stop embryos from growing. The dwarfs would not be losers in a struggle for resources; rather the resources were not there to begin with.

The two scenarios have distinct implications. In the turbulence scenario, the sequence of events is the same for stars and brown dwarfs; stars simply come from cores that happen to be larger, and brown dwarfs from cores that happen to be smaller. The range of turbulent velocities determines the relative proportion of small and large. The ejection scenario, on the other hand, attributes brown dwarfs to dynamical interactions that can toss an embryo out of the molecular cloud. It is the presence or absence of this additional mechanism that differentiates the two theories observationally. The turbulence picture predicts that whatever is true of low-mass stars should also be true of brown dwarfs, whereas the ejection hypothesis predicts that brown dwarfs will lose some of their starlike characteristics in the course of being ejected.

A Starlet Is Born

NEWBORN STARS, for instance, are surrounded by disks of leftover material. Over the course of millions of years, the disk material gradually drains into the nascent star, goes into making planets, moons, asteroids and comets, or is blown away. If the turbulence scenario is correct, young brown dwarfs, too, should have disks and maybe even planets [*see box on page 45*]. The ejection scenario predicts the opposite. If an embryo is ejected from a core, much of its surrounding disk should be stripped away in the process, as simulations by Matthew Bate of the University of Exeter in England and his colleagues have shown.

Similarly, stars often come in pairs. In the turbulence scheme, such binary systems should be nearly as common among brown dwarfs as among stars. The ejection process, however, would tear binaries apart, except perhaps when they were very tightly bound. Thus, widely separated binary dwarfs should be rare or nonexistent.

These properties offer ways to test the two scenarios. For example, astronomers can search for disks by their infrared radiation. Dust grains in a disk absorb light from the central star or brown dwarf and reemit the energy at longer wavelengths, making objects with disks appear brighter in the infrared than those without. Various astronomers, including us, have now surveyed large numbers of fledgling brown dwarfs in nearby young star–forming regions and clusters (where stars' ages can be estimated from their color and brightness), looking for this infrared excess. We find that disks are in fact ubiquitous around brown dwarfs that are a few million years

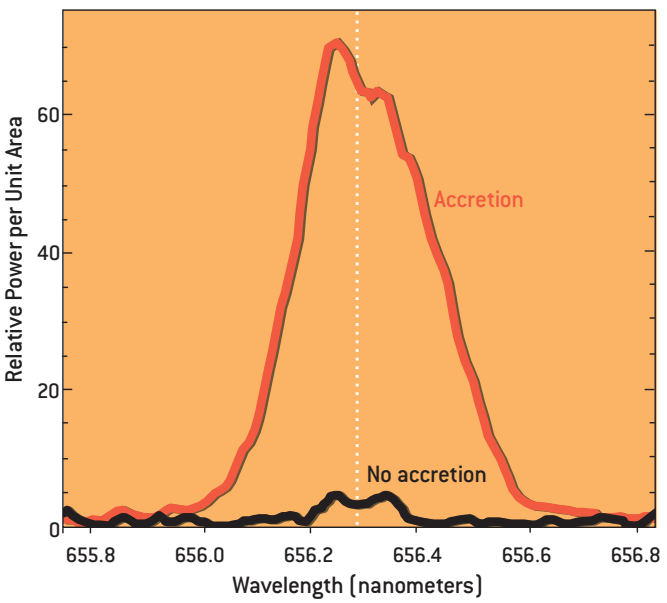
THE AUTHORS

SUBHANJOY MOHANTY and *RAY JAYAWARDHANA* have used some of the world's largest telescopes, such as the Keck, Subaru, Very Large Telescope and Magellan, to study ultralow-mass stars and brown dwarfs. Mohanty is a Spitzer Space Telescope postdoctoral fellow at the Harvard-Smithsonian Center for Astrophysics. He has also applied his statistical expertise to epidemiology and recently co-authored a paper for the *Journal of the American Medical Association* on Alzheimer's disease. Jayawardhana is professor of astronomy and astrophysics at the University of Toronto. He is a widely published science writer, a contributing editor to *Astronomy* magazine, and recipient of the 2003 Science Writing Award for a Scientist from the American Institute of Physics.

old. Of those surveyed, more than half evince infrared disk signatures, and the fraction may be as high as 80 percent among the very youngest objects. Indeed, in a young cluster of a given age, the percentage of brown dwarfs with disks is comparable to the percentage of stars with disks. In short, brown dwarfs are girdled by disks just as often as stars are, and their disk lifetimes are similar.

From infrared spectra, astronomers not only can determine that disks exist but also can estimate their shape and other properties. Around young stars, disks are found to range in shape. Some are flared—that is, thicker at the rim than in the center, like a concave lens. This shape naturally arises when dust and gas are well mixed. Other disks are relatively flat, presumably because dust grains have grown too large to be buoyed by the gas and have settled toward the midplane of the system. In many stellar disks, observers also have found the spectral signature of silicate emission, indicating that small dust grains on the disk surface have been strongly heated by the stellar radiation. Using the largest ground-based telescopes, as well as the Spitzer Space Telescope (the infrared counterpart to the Hubble), several groups, including ours, have recently shown that brown dwarf disks manifest the same properties.

Yet another way of identifying disks is to detect the telltale signs of disk material flowing onto the central object. Astronomers can certify ongoing accretion from the spectroscopic signatures of the various processes involved. For instance, spectral emission lines of hydrogen reveal high-velocity gas plunging in from the disk's inner edge, channeled in by magnetic fields. Lines of ionized calcium and excited helium are a sign of the high temperatures generated when gas crashes onto the stellar surface. Still other spectral lines hint at outflowing jets and winds, generated when magnetic fields threading the disk fling some of the inflowing disk material back out. Our group and others have recently detected all these signatures in the spectra of many newborn brown dwarfs [*see illustration below*]. These bodies accrete material at a tenth or hundredth of the rate that solar-mass stars do—a rate they can sustain for up to 10 million years.



SPECTRAL LINE OF HYDROGEN can reveal whether a brown dwarf has a gas disk. Hydrogen atoms at rest emit light at distinct wavelengths (*dotted line*), but when a gas is moving, this light gets smeared out into a range of wavelengths reflecting the range of velocities within the gas. Gas on the dwarf surface, being comparatively slow moving, generates a narrow spectral bump (*lower curve*). A broad hump (*upper curve*) is a telltale sign of gas plummeting in from a disk. Most young brown dwarfs appear to have disks, suggesting they form in much the same way full-fledged stars do.

Still Hope for Ejection?

IN A NUTSHELL, then, young brown dwarfs often have disks, with shapes similar to stellar ones; they accrete the disk gas the same way that young stars do; and their disks can be as long-lived as those of stars. So far, the mounting evidence all points to a remarkably similar infancy for both sunlike stars and brown dwarfs. At face value, this evidence supports the turbulence scenario. Nevertheless, the case is not yet closed. Whereas the ejection scenario does predict that brown dwarf disks should be truncated, it is still possible for ejected dwarfs to retain a small disk. Current observations probe only the inner disk regions: thus, although they reveal the presence of disks around brown dwarfs, they do not indicate the actual disk sizes and so cannot rule out ejection altogether. Ground-based radio telescopes, such as the Atacama Large Millimeter Array (ALMA) now under construction in Chile, should be able to probe the outer regions of brown dwarf disks and measure their sizes and masses, thereby testing the formation scenarios much more stringently. It may turn out that turbulence and ejection dominate in different regions of the galaxy.

Observations might also catch brown dwarfs in the very act of forming. Indeed, using the Spitzer Space Telescope, a group led by Neal Evans of the University of Texas at Austin recently identified what appear to be very small isolated cores with faint objects forming deep within them. If future observations confirm that these objects are brown dwarfs, it would greatly bolster the turbulence formation scenario.

The frequency of widely separated brown dwarf binaries is another test of the formation mechanism. Astronomers have so far seen a handful of them. If broader surveys find many more such tenuous systems, it would argue strongly against ejection, which would surely have torn them apart.

What astronomers learn about brown dwarf formation has broad ramifications for star and planet genesis in general. For example, knowing which of the two hypothesized mechanisms dominates could answer a question that astronomers have struggled with for a long time: What determines the relative number of stars of different masses? In the ejection scenario, it is the interactions among sibling stellar embryos. In the turbulence scenario, it is the range of turbulent velocities in the molecular cloud.

Similarly, the size and longevity of stellar disks, and thus the efficiency of planet formation, depend crucially on the role

LUCY READING-IKKANDA

Planets around Brown Dwarfs?

The discovery of disks of gas and dust around many young brown dwarfs brings up a fascinating question: Could they have planets, too? Could a planet orbit a body that itself is not much more than a planet? Apparently so. Gaël Chauvin of the European Southern Observatory and his colleagues recently discovered a probable five-Jupiter-mass companion orbiting a young brown dwarf at a distance of approximately 40 astronomical units (about as far from the dwarf as Pluto is from our sun). Our own observations (*image at right*) suggest that the companion could actually be closer to eight or 10 Jupiter masses, which is still smaller than the usual definition of a brown dwarf. What is more, observations hint that the companion has its own disk, which could be the raw material for satellites.

A DWARF'S DWARF: Infrared image shows a brown dwarf (*central disk*) orbited by an even smaller body (*arrowed*).

Until recently, the leading planet searches did not bother to look around low-mass stars, let alone brown dwarfs. That was partly a geocentric bias: to find a system like our solar system, astronomers thought they had to look around a sunlike star. But it was also because lower-mass stars are fainter and therefore harder to observe with the precision necessary to detect planets. Of the more than 150 giant planets spotted so far, only a few orbit stars much less massive than the sun, and even those stars are several times heavier than the heaviest possible brown dwarf.

Astronomers are now scrambling to explain the companion found by Chauvin and his colleagues. Low-mass stars have less massive disks than heavier stars do. The brown dwarf disks whose masses have been measured contain only a few Jupiters' worth of gas and dust in each. A recent paper by Gregory Laughlin and Peter Bodenheimer of the University of California, Santa Cruz, and Fred Adams of the University of Michigan at Ann Arbor argues that it would take longer for a planet to build up in such an emaciated system, and the disk would dissipate before the body could reach a large size. Thus, the companion seen by Chauvin probably did not form out of the brown dwarf's disk. Instead it is more likely that the companion itself formed just like a dwarf—out of a contracting cloud—so that the pair can be considered a petite binary-star system.

These restrictions on growth, however, apply only to giant planets. There is no reason asteroids and comets, or even Earth-mass planets, could not form in brown dwarf disks. In fact, the Spitzer Space Telescope has seen signs of growth and chemical processing of dust grains in some brown dwarf disks, perhaps marking the first tentative steps toward building up planets. Astronomers could look for the holes that planetary bodies might carve out in the disk. Or they might monitor the dwarf's light emission to see whether it periodically dims—the possible sign of a planet passing in front and blocking some of the light.

If they exist, planets around brown dwarfs would circle a sun that is not a sun at all. What about life on such planets? Because a brown dwarf is much cooler than our sun, the habitable zone around one would be quite small and close-in. Even this narrow zone would shrink as the dwarf cooled. *—S.M. and R.J.*

played by dynamical interactions in the stellar womb. If such interactions are frequent, as postulated in the ejection scenario, then planetary systems may be rare. But if turbulence is the chief mechanism for determining stellar masses, disks should be large and long-lived, implying that planetary systems resembling our solar system may be common.

Ironically, studying the formation of brown dwarfs calls into question the very definition of these objects. The dividing line between dwarfs and planets—12 Jupiter masses—is arbitrary; the formation theories set no such limit. In the ejection scenario, the stellar embryos that germinate within a molecular-cloud core can be as small as one Jupiter in mass. If they are ejected quickly enough, the result will be a planet-mass object. Similarly, in the turbulence scenario, chaotic gas motions can trigger the collapse of objects even smaller than the usual brown dwarf definition. Recent observations hint at the existence of isolated brown dwarfs with masses of just a few Jupiters. If verified, they would once again shake astronomers' idea of what a planet is. We instinctively seem to prefer clear boundaries in our view of the cosmos, with neatly pigeonholed categories, but nature is more canny, presenting us with a continuum of bodies and a messy degree of overlap.

As often happens in science, discoveries are made at the margins, where phenomena shade into one another and their most essential features become most apparent. It has taken the discovery of brown dwarfs—predicted in the 1960s but identified barely a decade ago—to give stellar astronomers a foil to understand what a star truly is. In the past few years, we have also taken a peek at their infancy, but the study of these Lilliputian bodies is itself in its formative period. Deciphering how they are forged promises to reveal much about the origins of both stars and planets. SA

SUBHANJOY MOHANTY, RAY JAYAWARDHANA AND NURIA HUÉLAMO

MORE TO EXPLORE

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Computer simulations of star and brown dwarf formation are available at **www.astro.ex.ac.uk/people/mbate/Research/Cluster/**

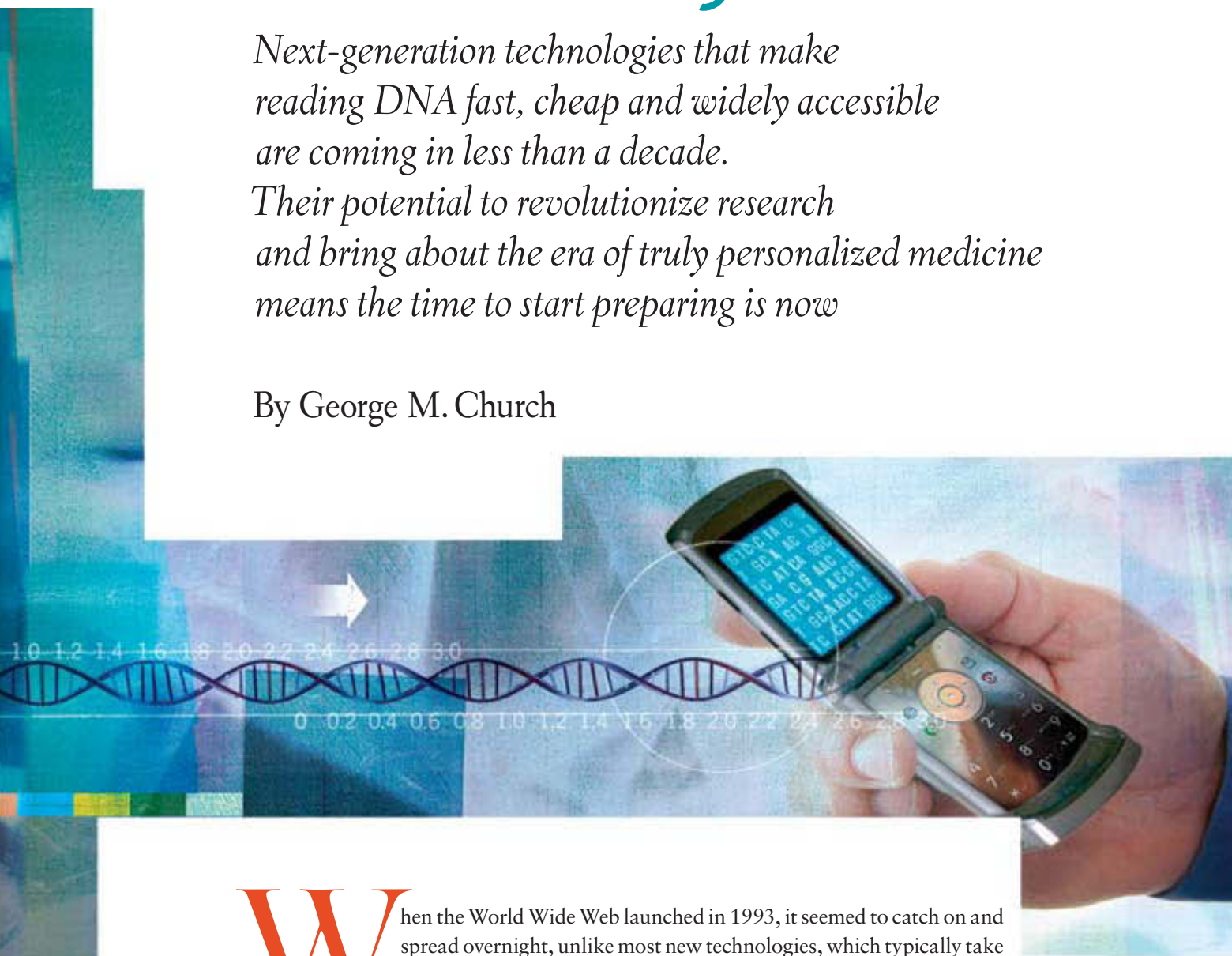
Fig. 107.

Fig. 70.

Genomes for ALL

Next-generation technologies that make reading DNA fast, cheap and widely accessible are coming in less than a decade. Their potential to revolutionize research and bring about the era of truly personalized medicine means the time to start preparing is now

By George M. Church



When the World Wide Web launched in 1993, it seemed to catch on and spread overnight, unlike most new technologies, which typically take at least a decade to move from first "proof of concept" to broad acceptance. But the Web did not really emerge in a single year. It built on infrastructure, including the construction of the Internet between 1965 and 1993, as well as a sudden recognition that resources, such as personal computers, had passed a critical threshold.

Vision and market forces also push the development and spread of new technologies. The space program, for example, started with a government vision, and only much later did military and civilian uses for satellites propel the industry to commercial viability. Looking forward to the next technological revolution, which may be in

biotechnology, one can begin to imagine what markets, visions, discoveries and inventions may shape its outcome and what critical thresholds in infrastructure and resources will make it possible.

In 1984 and 1985, I was among a dozen or so researchers who proposed a Human Genome Project (HGP) to read, for the first time, the entire instruction book for making and maintaining a human being contained within our DNA. The project's goal was to produce one full human genome sequence for $3 billion between 1990 and 2005.

We managed to finish the easiest 93 percent a few years early and to leave a legacy of useful technologies and methods. Their ongoing refinement has brought the street price of a human genome sequence accurate enough to be useful down to about $20 million today. Still, that rate means large-scale genetic sequencing is mostly confined to dedicated sequencing centers and reserved for big, expensive research projects.

The "$1,000 genome" has become shorthand for the promise of DNA-sequencing capability made so affordable that individuals might think the once-in-a-lifetime expenditure to have a full personal genome sequence read to a disk for doctors to reference is worthwhile. Cheap sequencing technology will also make that information more meaningful by multiplying the number of researchers able to study genomes and the number of genomes they can compare to understand variations among individuals in both sickness and health.

"Human" genomics extends beyond humans, as well, to an environment full of pathogens, allergens and beneficial microbes in our food and our bodies. Many people attend to weather maps; perhaps we might one day benefit from daily pathogen and allergen maps. The rapidly growing fields of nanotechnology and industrial biotechnology, too, might accelerate their mining of biomes for new "smart" materials and microbes that can be harnessed for manufacturing or bioremediation of pollution.

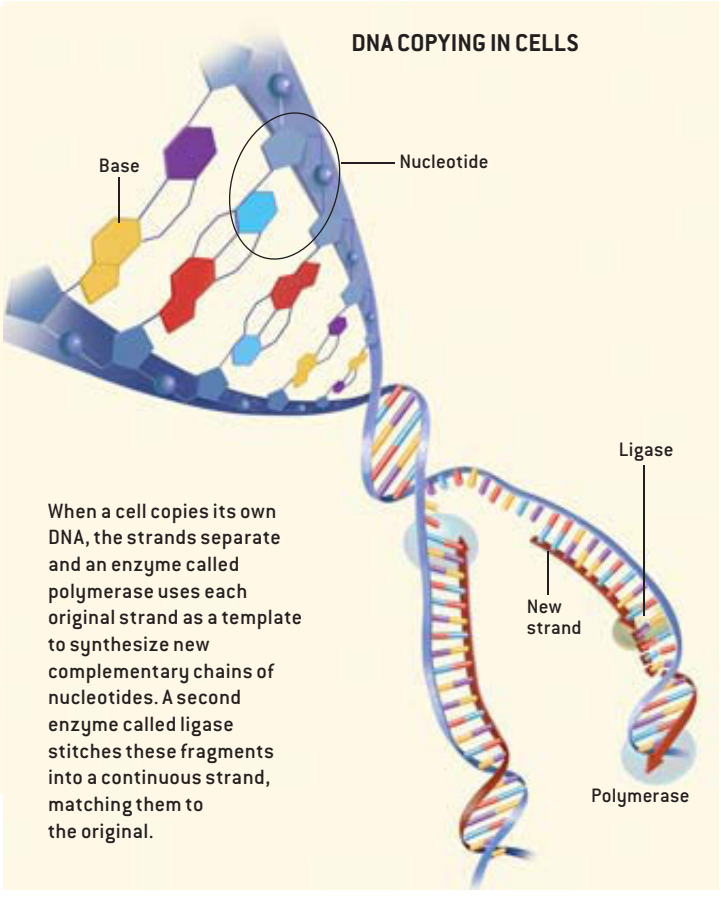
The barrier to these applications and many more, including those we have yet to imagine, remains cost. Two National Institutes of Health funding programs for "Revolutionary Genome Sequencing Technologies" challenge scientists to achieve a $100,000 human genome by 2009 and a $1,000 genome by 2014. An X Prize–style cash reward for the first group to attain such benchmarks is also a possibility. And these goals are already close. A survey of the new approaches in development for reading genomes illustrates the potential for breakthroughs that could produce a $20,000 human genome as soon as four years from now—and brings to light some considerations that will arise once it arrives.

Overview/*DNA Revolutions*

- Biotechnology's full potential may only be realized when its tools, such as genome-reading technology, are as inexpensive and accessible as personal computers today.
- New approaches to reading DNA reduce costs by cutting preparatory steps, radically miniaturizing equipment and sequencing millions of molecules simultaneously.
- Reaching the goal of low-cost sequencing will raise new questions about how abundant personal genetic information is best used and by whom. The Personal Genome Project is an attempt to begin exploring these issues.

READING DNA

Many techniques for decoding genomes capitalize on the complementary base-pairing rule of DNA. The genomic alphabet contains only four letters, elemental units called bases—adenine (A), cytosine (C), guanine (G) and thymine (T). They pair with each other (A with T; C with G) to form the rungs of the classic DNA ladder. The message encoded in the sequence of bases along a strand of DNA is effectively written twice, because knowing the identity of a base on one strand reveals its complement on the other strand. Living cells use this rule to copy and repair their own DNA molecules (*below*), and it can be exploited to copy (*1–2*) and label DNA of interest, as in the sequencing technique developed by Frederick Sanger in the 1970s (*3–4*) that is still the basis of most sequencing performed today.

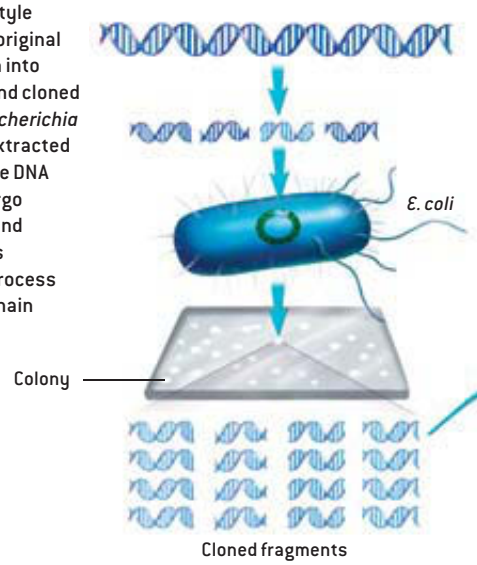


STUART BRADFORD (*preceding pages*); TERESE WINSLOW (*above*)

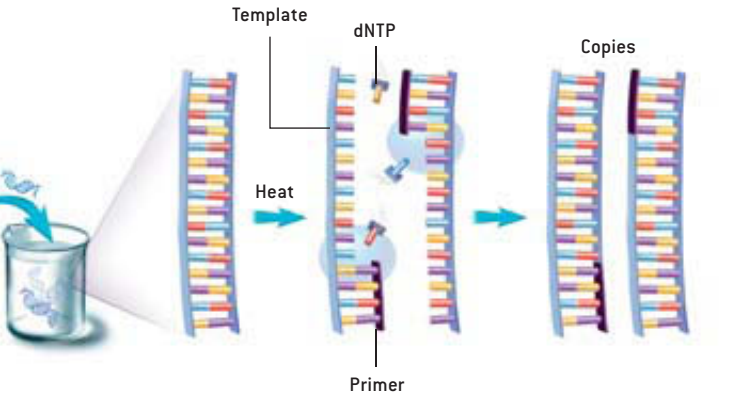
Reinventing Gene Reading

WITH ANY SEQUENCING METHOD, the size, structure and function of DNA itself can present obstacles or be turned

1 Before Sanger-style sequencing, an original DNA strand is broken into smaller fragments and cloned within colonies of *Escherichia coli* bacteria. Once extracted from the bacteria, the DNA fragments will undergo another massive round of copying, known as amplification, by a process called polymerase chain reaction (PCR).

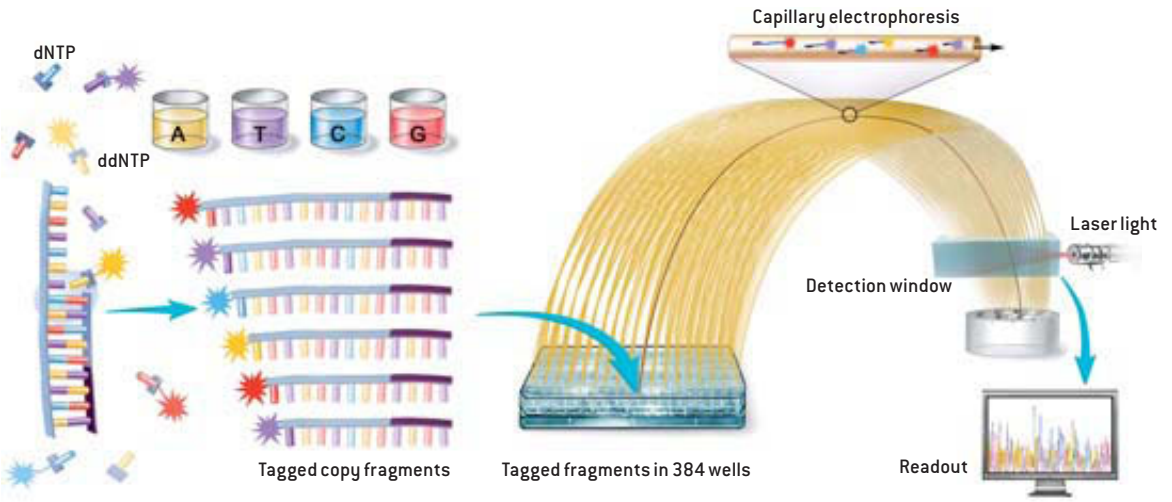


2 During PCR, fragments are heated so they will separate into single strands. A short nucleotide sequence called a primer is then annealed to each original template. Starting at the primer, polymerase links free-floating nucleotides (called dNTPs) into new complementary strands. The process is repeated over and over to generate millions of copies of each fragment.



3 Single-stranded fragments are next tagged in a process similar to PCR but with fluorescently labeled terminator nucleotides (ddNTPs) added to the mixture of primers, polymerase and dNTPs. Complementary strands are built until by chance a ddNTP is incorporated, halting synthesis. The resulting copy fragments have varying lengths and a tagged nucleotide at one end.

4 Capillary electrophoresis separates the fragments, which are negatively charged, by drawing them toward a positively charged pole. Because the shortest fragments move fastest, their order reflects their size and their ddNTP terminators can thus be "read" as the template's base sequence. Laser light activates the fluorescent tags as the fragments pass a detection window, producing a color readout that is translated into a sequence.



into advantages. The human genome is made up of three billion pairs of nucleotide molecules. Each of these contains one of four types of bases—abbreviated A, C, G and T—that represent a genomic alphabet encoding the information stored in DNA. Bases typically pair off according to strict rules to form the rungs in the ladderlike DNA structure. Because of these pairing rules, reading the sequence of bases along one half of the ladder reveals the complementary sequence on the other side as well.

Our three-billion-base-long genome is broken into 23 separate chromosomes. People usually have two full sets of these, one from each parent, that differ by 0.01 percent, so that an individual's personal genome can really be said to contain six billion base pairs. Identifying individual bases in a stretch of the genome requires a sensor that can detect the subnanometer-scale differences between the four base types. Scanning tunneling microscopy is one physical method that can visualize these tiny structures and their subtle distinctions. For reading millions or billions of bases, however, most sequencing techniques rely at some stage on chemistry.

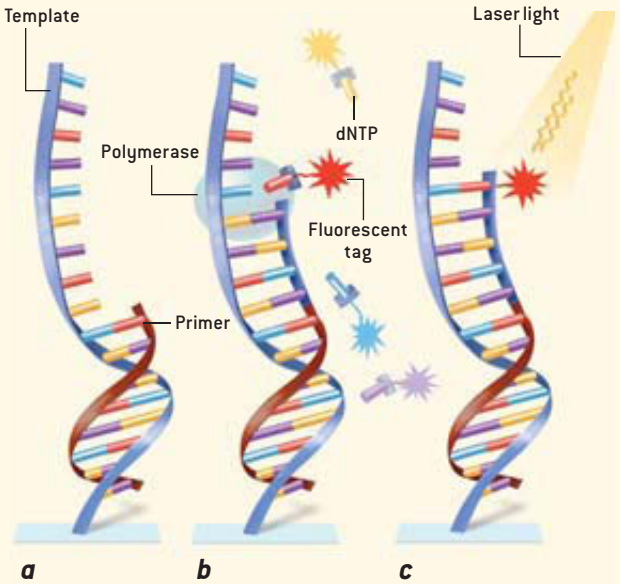
A method developed by Frederick Sanger in the 1970s became the workhorse of the HGP and is still the basis of most sequencing performed today. Sometimes described as sequencing by separation, the technique requires several rounds

SEQUENCING BY SYNTHESIS

Most new sequencing techniques simulate aspects of natural DNA synthesis to identify the bases on a DNA strand of interest either by "base extension" or "ligation" (*below*). Both approaches depend on repeated cycles of chemical reactions, but the technologies lower sequencing costs and increase speed by miniaturizing equipment to reduce the amount of chemicals used in all steps and by reading millions of DNA fragments simultaneously (*opposite page*).

BASE EXTENSION

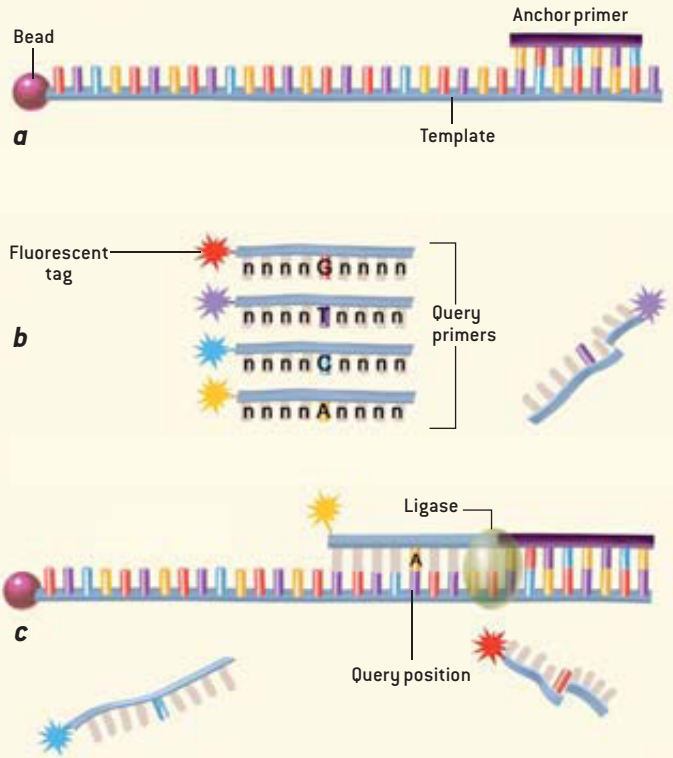
A single-stranded DNA fragment, known as the template, is anchored to a surface with the starting point of a complementary strand, called the primer, attached to one of its ends (*a*). When fluorescently tagged nucleotides (dNTPs) and polymerase are exposed to the template, a base complementary to the template will be added to the primer strand (*b*). Remaining polymerase and dNTPs are washed away, then laser light excites the fluorescent tag, revealing the identity of the newly incorporated nucleotide (*c*). Its fluorescent tag is then stripped away, and the process starts anew.



Pyrophosphate detection uses bioluminescence, instead of fluorescence, to signal base-extension events. A pyrophosphate molecule is released when a base is added to the complementary strand, causing a chemical reaction with a luminescent protein that produces a flash of light.

LIGATION

An "anchor primer" is attached to a single-stranded template to designate the beginning of an unknown sequence (*a*). Short, fluorescently labeled "query primers" are created with degenerate DNA, except for one nucleotide at the query position bearing one of the four base types (*b*). The enzyme ligase joins one of the query primers to the anchor primer, following base-pairing rules to match the base at the query position in the template strand (*c*). The anchor-query-primer complex is then stripped away and the process repeated for a different position in the template.



of duplication to produce large numbers of copies of the genome stretch of interest. The final round yields copy fragments of varying lengths, each terminating with a fluorescently tagged base. Separating these fragments by size in a process called electrophoresis, then reading the fluorescent signal of each terminal tag as it passes by a viewer, provides the sequence of bases in the original strand [*see box on preceding two pages*].

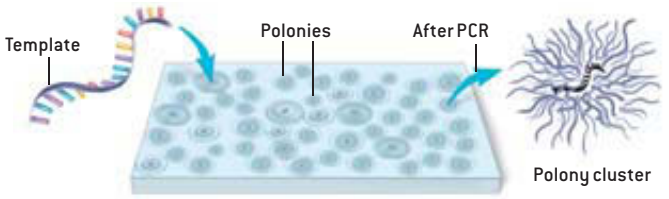
Reliability and accuracy are advantages of Sanger sequencing, although even with refinements over the years, the method remains time-consuming and expensive. Most alternative approaches to sequencing therefore seek to increase speed and reduce costs by cutting out the slow separation steps, miniaturizing components to reduce chemical volumes, and executing reactions in a massively parallel fashion so that millions of sequence fragments are read simultaneously.

Many research groups have converged on methods often lumped together under the heading of sequencing by synthesis because they exploit high-fidelity processes that living systems use to copy and repair their own genomes. When a cell is preparing to divide, for example, its DNA ladder splits into single strands, and an enzyme called polymerase moves along each

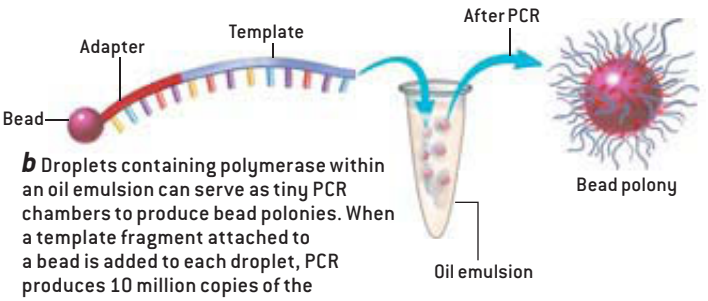
TERESE WINSLOW

AMPLIFICATION

Because light signals are difficult to detect at the scale of a single DNA molecule, base-extension or ligation reactions are often performed on millions of copies of the same template strand simultaneously. Cell-free methods (*a* and *b*) for making these copies involve PCR on a miniaturized scale.



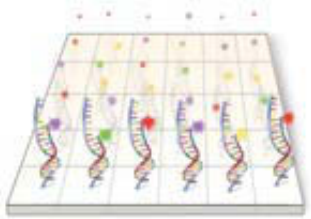
a Polonies—polymerase colonies—created directly on the surface of a slide or gel each contain a primer, which a template fragment can find and bind to. PCR within each polony produces a cluster containing millions of template copies.



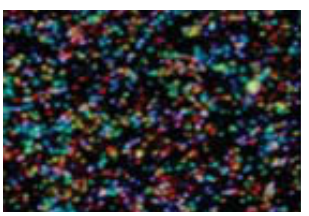
b Droplets containing polymerase within an oil emulsion can serve as tiny PCR chambers to produce bead polonies. When a template fragment attached to a bead is added to each droplet, PCR produces 10 million copies of the template, all attached to the bead.

MULTIPLEXING

Sequencing thousands or millions of template fragments in parallel maximizes speed. A single-molecule base-extension system using fluorescent-signal detection, for example, places hundreds of millions of different template fragments on a single array (*below left*). Another method immobilizes millions of bead polonies on a gel surface for simultaneous sequencing by ligation with fluorescence signals, shown in the image at right below, which represents 0.01 percent of the total slide area.



Single-molecule array



Bead polonies

BEAD POLONIES FROM JAY SHENDURE ET AL. IN *SCIENCE*, VOL. 309; SEPTEMBER 9, 2005. WITH PERMISSION BY AAAS

of these. Using the old strands as templates and following base-pairing rules, polymerase catalyzes the addition of nucleotides into complementary sequences. Another enzyme called ligase then joins these pieces into whole complementary strands while matching them to the original templates.

Sequencing-by-synthesis methods simulate parts of this process on a single DNA strand of interest. As bases are added by polymerase to the starting point of a new complementary strand, known as a primer, or recognized by ligase as a match, the template's sequence is revealed.

How such events are detected varies, but one of two signal types is usually involved. If a fluorescent molecule is attached to the added bases, the color signal it gives off can be seen using optical microscopy. Fluorescence detection is employed in both base-extension and ligation sequencing by many groups, including those of Michael Metzker and his colleagues at Baylor University, Robi Mitra of Washington University in St. Louis, my own lab at Harvard Medical School and at Agencourt Bioscience Corporation.

An alternative method uses bioluminescent proteins, such as the firefly enzyme luciferase, to detect pyrophosphate released when a base attaches to the primer strand. Developed by Mostafa Ronaghi, who is now at Stanford University, this system is used by Pyrosequencing/Biotage and 454 Life Sciences.

Both forms of detection usually require multiple instances of the matching reaction to happen at the same time to produce a signal strong enough to be seen, so many copies of the sequence of interest are tested simultaneously. Some investigators, however, are working on ways to detect fluorescent signals emitted from just one template strand molecule. Stephen Quake of the California Institute of Technology and scientists at Helicos Biosciences and Nanofluidics are all taking this single-molecule approach, intended to save time and costs by eliminating the need to make copies of the template to be sequenced.

Detecting single fluorescent molecules remains extremely challenging. Because some 5 percent are missed, more "reads" must be performed to fill in the resulting gap errors. That is why most groups first copy, or amplify, the single DNA template of interest by a process called polymerase chain reaction (PCR). In this step, too, a variety of approaches have emerged that make the use of bacteria to generate DNA copies unnecessary.

One cell-free amplification method, developed by Eric Kawashima of the Serono Pharmaceutical Research Institute in Geneva, Alexander Chetverin of the Russian Academy of Sciences, and Mitra when he was at Harvard, creates individual colonies of polymerase—polonies—freely arrayed directly on the surface of a microscope slide or a layer of gel. A single template molecule undergoes PCR within each polony, producing millions of copies, which grow rather like a bacterial colony from the central original template. Because each resulting polony cluster is one micron wide and one femtoliter in volume, billions of them can fit onto a single slide.

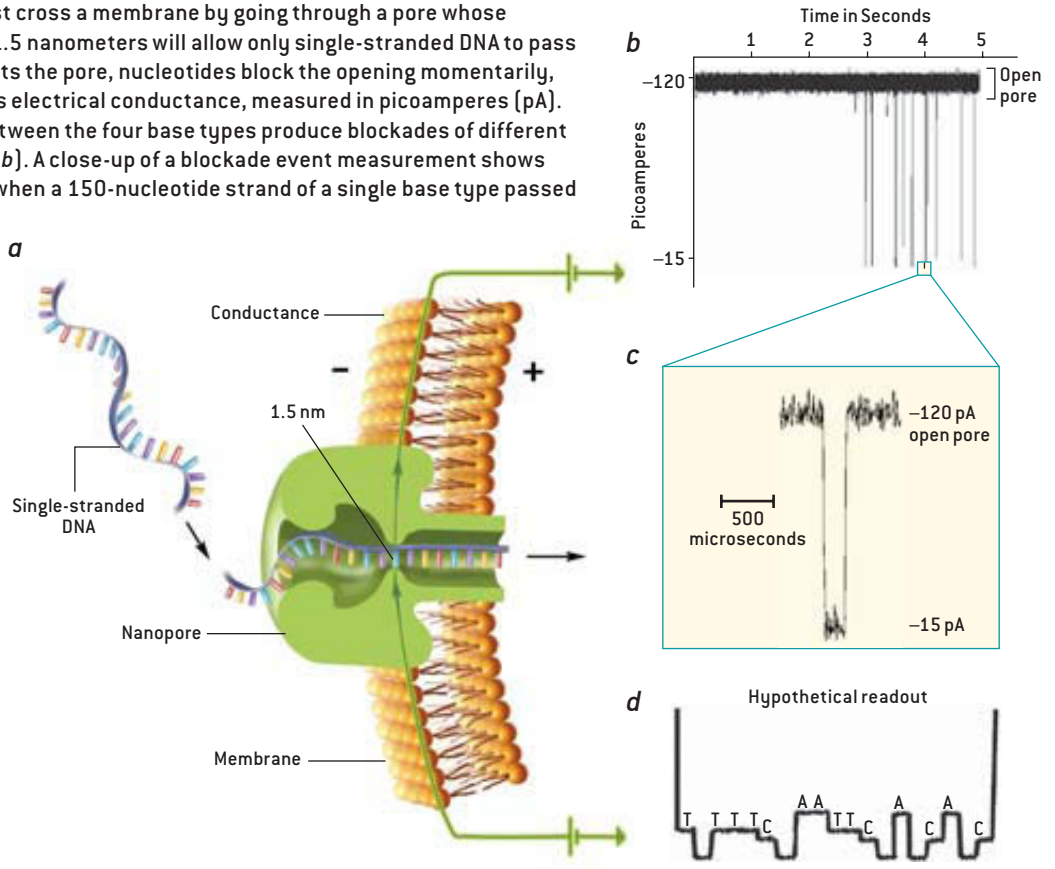
A variation on this system first produces polonies on tiny beads inside droplets within an emulsion. After the reaction millions of such beads, each bearing copies of a different template, can be placed in individual wells or immobilized by a gel where sequencing is performed on all of them simultaneously.

These methods of template amplification and of sequencing by base extension or by ligation are just a few representative examples of the approaches dozens of different academic and corporate research groups are taking to sequencing by synthesis.

Still another technique, sequencing by hybridization, also uses fluorescence to generate a visible signal and, like sequenc-

NANOPORE SEQUENCING

Like electrophoresis, this technique draws DNA toward a positive charge. To get there, the molecule must cross a membrane by going through a pore whose narrowest diameter of 1.5 nanometers will allow only single-stranded DNA to pass (*a*). As the strand transits the pore, nucleotides block the opening momentarily, altering the membrane's electrical conductance, measured in picoamperes (pA). Physical differences between the four base types produce blockades of different degrees and durations (*b*). A close-up of a blockade event measurement shows a conductance change when a 150-nucleotide strand of a single base type passed through the pore (*c*). Refining this method to improve its resolution to single bases could produce a sequence readout such as the hypothetical example at bottom (*d*) and yield a sequencing technique capable of reading a whole human genome in just 20 hours without expensive DNA copying steps and chemical reactions.



ing by ligation, exploits the tendency of DNA strands to bind, or hybridize, with their complementary sequences and not with mismatched sequences. This system, employed by Affymetrix, Perlegen Sciences and Illumina, is already in widespread commercial use, primarily to look for variations in known gene sequences. It requires synthesizing short single strands of DNA in every possible combination of base sequences and then arranging them on a large slide. When copies of the template strand whose sequence is unknown are washed across this array, they will bind to their complementary sequences. The best match produces the brightest fluorescent signal. Illumina also adds a base-extension step to this test of hybridization specificity.

One final technique with great long-term promise takes an entirely different approach to identifying the individual bases in a DNA molecule. Grouped under the heading of nanopore sequencing, these methods focus on the physical differences between the four base types to produce a readable signal. When a single strand of DNA passes through a 1.5-nanometer pore, it causes fluctuations in the pore's electrical conductance. Each base type produces a slightly different conductance change that can be used to identify it [*see box above*]. Devised by Dan Branton of Harvard, Dave Deamer of the University of California, Santa Cruz, and me, this method is in development now by Agilent Technologies and others with interesting variations, such as fluorescent signal detection.

Lowering Cost

EVALUATING THESE NEXT-GENERATION sequencing systems against one another and against the Sanger method illustrates some of the factors that will influence their usefulness. For example, two research groups, my own at Harvard and one from 454 Life Sciences, recently published peer-reviewed descriptions of genome-scale sequencing projects that allow for a direct comparison.

My colleagues and I described a sequencing-by-ligation system that used polony bead amplification of the template DNA and a common digital microscope to read fluorescent signals. The 454 group used a similar oil-emulsion PCR for

THE AUTHOR

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TERESE WINSLOW; SOURCES: "NANOPORES AND NUCLEIC ACIDS: PROSPECTS FOR ULTRARAPID SEQUENCING," BY DAVID W. DEAMER AND MARK AKESON, IN *TIBTECH*, VOL. 18; APRIL 2000. © 2000 ELSEVIER SCIENCE LTD. ALL RIGHTS RESERVED; AND "MOVING SMALLER IN DRUG DISCOVERY AND DELIVERY," BY DAVID A. LAVAN, DAVID M. LYNN AND ROBERT LANGER, IN *NATURE REVIEWS DRUG DISCOVERY*, VOL. 1, NO. 1; JANUARY 2002

amplification followed by base-extension sequencing with pyrophosphate detection in an array of wells. Both groups read about the same amount of sequence, 30 million base pairs, in each sequencing run. Our system read about 400 base pairs a second, whereas 454 read 1,700 a second. Sequencing usually involves performing multiple runs to produce a more accurate consensus sequence. With 43-times coverage (43×)—that is, 43 runs per base—of the target genome, 454 achieved accuracy of one error per 2,500 base pairs. The Harvard group had less than one error per three million base pairs with 7× coverage. To handle templates, both teams employed capture beads, whose size affects the amount of expensive reagents consumed. Our beads were one micron in diameter, whereas 454 used 28-micron beads in 75-picoliter wells.

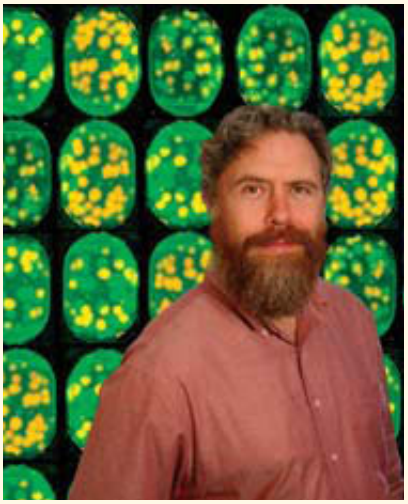
THE PERSONAL GENOME PROJECT

Every baby born in the U.S. today is tested for at least one genetic disease, phenylketonuria, before he or she leaves the hospital. Certain lung cancer patients are tested for variations in a gene called *EGFR* to see if they are likely to respond to the drug Iressa. Genetic tests indicating how a patient will metabolize other drugs are increasingly used to determine the drugs' dosage. Beginnings of the personalized medicine that will be possible with low-cost personal genomes can already be glimpsed, and demand for it is growing.

Beyond health concerns, we also want to know our genealogy. How closely are we related to Genghis Khan or to each other? We want to know what interaction of genes with other genes and with the environment shapes our faces, our bodies, our dispositions. Thousands or millions of data sets comprising individuals' whole genome *and* phenome—the traits that result from instructions encoded in the genome—will make it possible to start unraveling some of those complex pathways.

Yet the prospect of this new type of personal information suddenly becoming widely available also prompts worries about how it might be misused—by insurers, employers, law-enforcement agents, friends, neighbors, commercial interests or criminals.

No one can predict what living in an era of personal genomics will be like until the waters are tested. That is why my colleagues and I recently launched the Personal Genome Project (PGP). With this natural next step after the Human Genome Project, we hope to explore possible rewards and risks of personal genomics by recruiting volunteers to make their own genome and phenome data openly available.



GEORGE M. CHURCH, shown with images of fluorescent polonies, is one of a group of volunteers planning to open their genomes to public scrutiny.

These resources will include full (46-chromosome) genome sequences, digital medical records, as well as information that could one day be part of a personal health profile, such as comprehensive data about RNA and proteins, body and facial measurements, and MRI and other cutting-edge imagery. We will also create and deposit human cell lines representing each subject in the Coriell repository of the National Institute of General Medical Sciences. Our purpose is to make all this genomic and trait information broadly accessible so that anyone can mine it to test their own hypotheses and algorithms—and be inspired to come up with new ones.

A recent incident provides a simple example of what might happen. A few PGP medical records—my own—are already publicly available online, which prompted a hematologist on the other side of the country to notice, and inform me, that I was long overdue for a follow-up test of my cholesterol medication. The tip led to a change in my dose and diet and consequently to a dramatic lowering of at least one type of risk. In the future this kind of experience would not rely on transcontinental serendipity but could spawn a new industry of third-party genomic software tools.

The PGP has approval from the Harvard Medical School Internal Review Board, and like all human research subjects, participants must be informed of potential risks before consenting to provide their data. Every newly recruited PGP volunteer will also be able to review the experience of previous subjects before giving informed consent. The project's open nature, including fully identifying subjects with their data, will be less risky both to the subjects and the project than the alternative of promising privacy and risking accidental release of information or access by hackers.

Like the free data access policy established by the HGP, the openness of the PGP is designed to maximize potential for discovery. In addition to providing a scientific resource, the project also offers an experiment in public access and insurance coverage. In its early stages, private donors will help to insure a diverse set of human subjects against the event that they experience genetic discrimination as a consequence of the PGP. This charity-driven mechanism has the advantage of not needing to be profitable at first, but insurance companies may nonetheless be very interested in its outcome. *—G.M.C.*

Details of the PGP can be found at http://arep.med.harvard.edu/PGP/

JOHN SOARES

The best available electrophoresis-based sequencing methods average 150 base pairs per dollar for "finished" sequence. The 454 group did not publish a project cost, but the Harvard team's finished sequence cost of 1,400 base pairs per $1 represents a ninefold reduction in price.

These and other new techniques are expected very soon to bring the cost of sequencing the six billion base pairs of a personal genome down to $100,000. For any next-generation sequencing method, pushing costs still lower will depend on a few fundamental factors. Now that automation is commonplace in all systems, the biggest expenditures are for chemical reagents and equipment. Miniaturization has already reduced reagent use relative to conventional Sanger reactions one billionfold from microliters to femtoliters.

Many analytic imaging devices can collect raw data at rates of one billion bytes (a gigabyte) per minute, and computers can process the information at a speed of several billion operations a second. Therefore, any imaging device limited by a slow physical or chemical process, such as electrophoresis or enzymatic reaction, or one that is not tightly packed in space and time, making every pixel count, will be correspondingly more costly to operate per unit DNA base determined.

Another consideration in judging emerging sequencing technologies is how they will be used. Newer methods tend to have short read-lengths of five to 400 base pairs, compared with typical Sanger read-lengths of 800 base pairs. Sequencing and piecing together a previously unknown genome from scratch is therefore much harder with the new techniques. If medicine is the primary driver of widespread sequencing, however, we will be largely resequencing the human genome looking for minute variations in individuals' DNA, and short read-lengths will not be such a problem.

Accuracy requirements will also be a function of the applications. Diagnostic uses might demand a reduction in error rates below the current HGP standard of 0.01 percent, because that still permits 600,000 errors per human genome. At the other end of the spectrum, high-error-rate (4 percent) random sampling of the genome has proved useful for discovery and classification of various RNA and tissue types. A similar "shotgun" strategy is applied in ecological sampling, where as few as 20 base pairs are sufficient to identify an organism in an ecosystem.

Raising Value

BEYOND DEVELOPING these new sequencing technologies, we have much work to do in a short amount of time to get ready for the advent of low-cost genome reading. Software will be needed to process sequence information so that it is manageable by doctors, for example. They will need a method to derive an individualized priority list for each patient of the top 10 or so genetic variations likely to be important. Equally essential will be assessing the effects of widespread access to this technology on people.

From its outset, the HGP established a $10-million-a-year program to study and address the ethical, legal and social issues that would be raised by human genome sequencing. Participants in the effort agreed to make all our data publicly available with unprecedented speed—within one week of discovery—and we rose to fend off attempts to commercialize human nature. Special care was also taken to protect the anonymity of the public genomes (the "human genome" we produced is a mosaic of several people's chromosomes). But many of the really big questions remain, such as how to ensure privacy and fairness in the use of personal genetic information by scientists, insurers, employers, courts, schools, adoption agencies, the government, or individuals making clinical and reproductive decisions.

We have much work in a short time to get ready for LOW-COST GENOMES.

These difficult and important questions need to be researched as rigorously as the technological and biological discovery aspects of human genomics. My colleagues and I have therefore initiated a Personal Genome Project [*see box on preceding page*] to begin exploring the potential risks and rewards of living in an age of personal genomics.

When we invest in stocks or real estate or relationships, we understand that nothing is a sure thing. We think probabilistically about risk versus value and accept that markets, like life, are complex. Just as personal digital technologies have caused economic, social and scientific revolutions unimagined when we had our first few computers, we must expect and prepare for similar changes as we move forward from our first few genomes. SA

MORE TO EXPLORE

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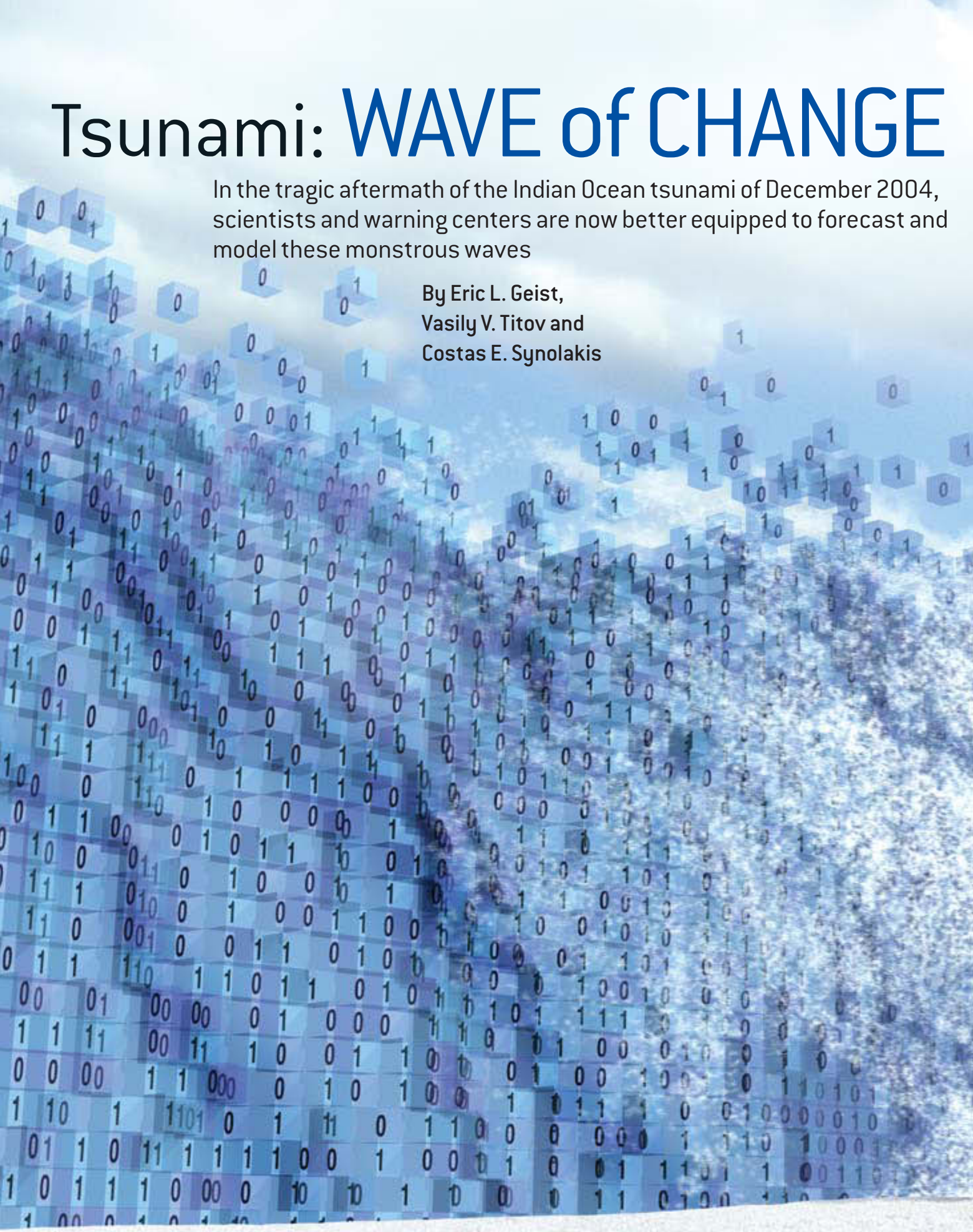
Tsunami: WAVE of CHANGE

In the tragic aftermath of the Indian Ocean tsunami of December 2004, scientists and warning centers are now better equipped to forecast and model these monstrous waves

By Eric L. Geist,
Vasily V. Titov and
Costas E. Synolakis



WALL OF WATER 30 meters high that battered shores in December 2004 has yielded improved computer simulations of tsunami behavior.

On December 26, 2004, a series of devastating waves attacked coastlines all around the Indian Ocean, taking the largest toll of any tsunami ever recorded. The surges decimated entire cities and villages, killing more than 225,000 people within a matter of hours and leaving at least a million homeless.

This shocking disaster underscored an important fact: as populations boom in coastal regions worldwide, tsunamis pose a greater risk than ever before. At the same time, this tsunami was the best documented in history—opening a unique opportunity to learn how to avoid such catastrophes in the future. From home videos of muddy water engulfing seaside hotels to satellite measurements of the waves propagating across the open ocean, the massive influx of information has reshaped what scientists know in several ways.

For one thing, the surprising origin of the tsunami—which issued from a location previously thought unlikely to birth the giant waves—has convinced researchers to broaden their list of possible danger areas. The new observations also provided the first thorough testing of computer simulations that forecast where and when a tsunami will strike and how it will behave onshore. What is more, this event revealed that subtle complexities of an earthquake exert a remarkably strong influence over a tsunami's size and shape. The improved models that have resulted from these discoveries will work with new monitoring and warning systems to help save lives.

Before the Big One

RESEARCHERS HAVE LONG KNOWN that the breeding grounds for nearly all tsunami-generating earthquakes are subduction zones. Marked by immense trenches on the seafloor, such areas form where one of the planet's outer shell of tectonic plates plunges underneath

another. Gravitational forces and the motion of viscous material deep within the earth's mantle work to keep the plates moving past each other, but friction in the shallow crust temporarily locks them together. As a result, stress builds up across the vast interface, or fault, between the two plates. Sometimes that stress is relieved suddenly in the form of a large earthquake. The bottom plate dives farther down, snapping the top plate violently upward—and the overlying seawater goes along for the ride. The size of the resulting tsunami depends on how much the seafloor moves. Once generated, the tsunami splits in two; one moves quickly inland while the second heads toward the open ocean.

In the eastern Indian Ocean, off the west coast of Sumatra, Indonesia, the India Plate slips below the Eurasia Plate along the Sumatra subduction zone. Southern parts of this fault zone have produced large (magnitude 9) earthquakes in the past, most recently in 1833; Kerry Sieh of the California Institute of Technology and his colleagues have found ancient coral reefs uplifted by these events. Experts were on the watch for another large shock there.

But they were puzzled when the tsunami-producing event of December 2004 originated in the upper part of this region, just northwest of Sumatra. Prior records had shown much slower motion along the offshore fault there, so it was unclear that stress could ever build up enough to result in such a violent tremor. Yet later analysis revealed that the magnitude 9 shock raised a 1,200-kilometer stretch of seafloor by as much as eight meters in some places as it unlocked a California-size area of the fault zone—displacing hundreds of cubic kilometers of seawater above normal sea level. As a result, investigators now are considering possible additional tsunami threats near Alaska, Puerto Rico and other similar subduction zones [*see box on opposite page*].

The Sumatra-Andaman shock began at 7:59 A.M. local time, and soon a global network of seismic stations alerted the Pacific Tsunami Warning Center in Ewa Beach, Hawaii. Although geophysicists there were some of the first people outside the region to learn of the earthquake, they had no way to confirm that a deadly tsunami was surging across the Indian Ocean until they got the first news bulletin of the catastrophe unfolding.

In the Pacific Ocean, where 85 percent of the world's tsunamis occur, remote sensors called tsunameters can detect a tsunami offshore and warn the Pacific center's scientists and those at a second center in Palmer, Alaska, before the waves make landfall [see "Tsunami!" by Frank González; SCIENTIFIC AMERICAN, May 1999]. But no such technology was in place for the Indian Ocean, and no established lines of communication existed to transmit a warning to people on the coast. Although the first waves took two hours or more to reach Thailand, Sri Lanka and many of the areas hardest hit, nearly everyone was taken by surprise.

In the Open Ocean

THAT DECEMBER DAY forever changed the world's appreciation for how much damage tsunamis can inflict, where they might strike and how utterly defenseless so many communities are. International groups have been scrambling to rectify the situation ever since [*see box on page 62*]. Meanwhile researchers have been digging through the clues this disaster left behind to sharpen their understanding of how tsunamis get started, propagate and then crash against the shores—and to better warn of the next one.

For 15 years, researchers in Japan and the U.S. have been developing computer models that simulate how a tsunami propagates through the open ocean. Before now, however, investigators had few observations to compare against their theories. All tsunami-propagation models require two key starting variables: an estimate of the location and area of deformed seafloor, which researchers base on the quake's magnitude and epicenter, and a measure of the height, or amplitude, of the displaced water. The latter can be inferred adequately for real-time forecasts only after making direct observations of tsunami waves in the open ocean.

But for previous major tsunamis, scientists just had measurements that tide gauges recorded near the coast or that surveyors later estimated from water damage on land. The main problem is that near shore, a tsunami's actual size is masked by additional waves generated as the tsunami bounces off seawalls, wraps around islands, or sloshes back and forth in a bay—all of which make for a very tangled signal.

By sheer coincidence, a trio of earth-monitoring satellites gave modelers the pristine, undistorted wave heights they needed for the Indian Ocean tsunami. The satellites happened to orbit over the region between two and nine hours after the earthquake, making the first radar measurements of a tsunami propagating across the open ocean. The results proved for the first time that—as suspected—a bump of water only half a meter high in the open ocean can truly transform into the towering surges that wreak so much destruction on land.

With a ground speed of about 5.8 kilometers a second, the satellites also provided the first continuous transect of tsunami amplitudes—that is, they monitored the waves continuously along their travel path rather than making measurements in a single spot, as tide gauges do. As it turns out, the modeled and mea-

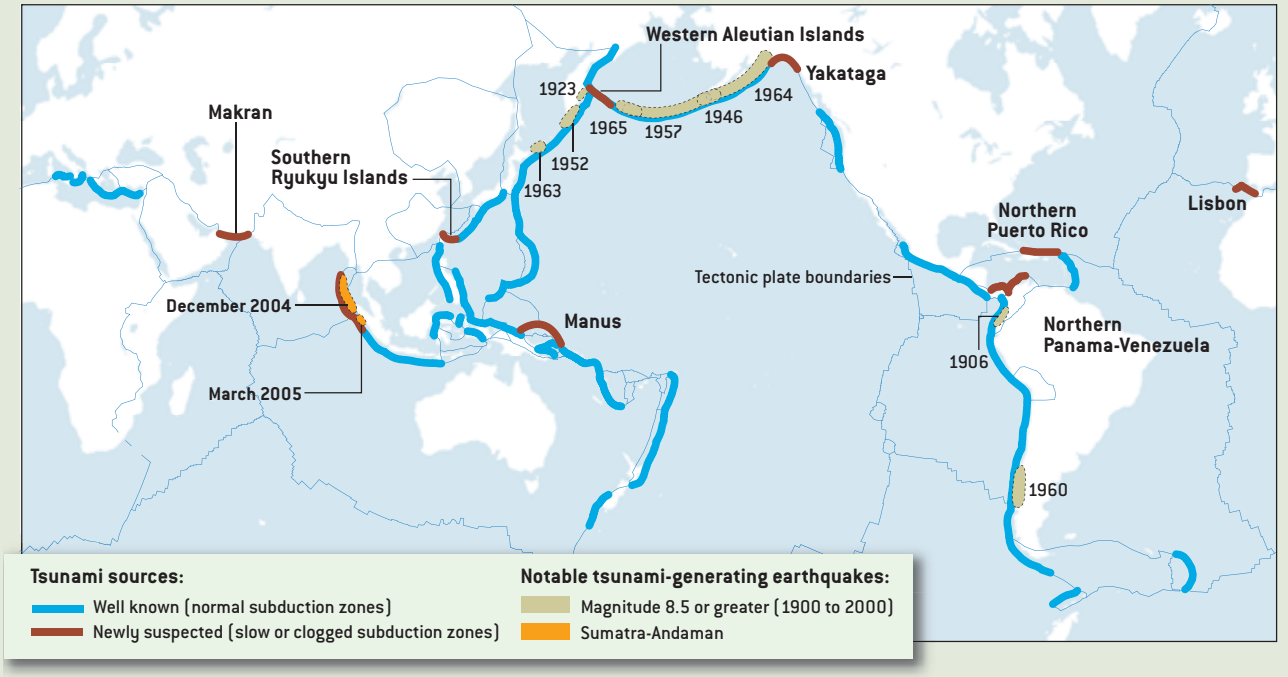
Overview/*Future Forecasts*

- In the wake of the catastrophic December 2004 tsunami in the Indian Ocean, a massive influx of information about the event has reshaped our understanding of such monster waves.
- From the new data, scientists have learned how to better forecast what areas could spawn a tsunami, where it will go and how far it will climb up on shore.
- The resulting improved computer models will work with new monitoring and warning systems to help save lives.

MATTHEW FREY *Wood Ronsaville Harlin, Inc. (preceding pages)*

RETHINKING TSUNAMI ORIGINS

The most notable tsunami-generating earthquakes of the past century (*tan ovals*) occurred where two tectonic plates meet head-on in so-called subduction zones (*blue lines*). One plate thrusts atop the other, raising tsunami waves along with it. But the part of the Sumatra-Andaman fault where the Indian Ocean disaster originated had no previous record of shocks larger than magnitude 8. When a magnitude 9 earthquake struck there in December 2004, followed three months later by another nearly as large at magnitude 8.7 (*orange ovals*), scientists began reassessing similar slow-moving faults for their tsunami potential. New areas of concern (*red lines*) also include those where bulky features on the seafloor may obstruct subduction, thus adding stress to the fault.



sured wave heights match each other quite well [*see box on next page*], validating general theories about how tsunamis move across the open ocean—and confirming that the current modeling paradigms are a useful tool for public safety, even for the largest tsunami.

Global Reach

THE GLOBAL SCOPE of the tsunami further corroborated that the models are sound for forecasting. Because a tsunami in the deep ocean moves along at about the same speed as a jet airliner (from 500 to 1,000 kilometers an hour), the first wave took less than three hours to travel from northern Sumatra and the Andaman Islands east to Myanmar (Burma), Thailand and Malaysia and west to Sri Lanka, India and the Maldives. Within 11 hours it had struck the South African coast 8,000 kilometers away, the farthest point away where a tsunami-related death was reported.

But the waves did not stop there. About the same time the tragedy made the news, scientists started getting records from tide gauge stations around the world. On its westward path, the tsunami curved around the southern tip of Africa and then split as it traveled northward through the Atlantic; one branch headed toward Brazil and the other toward Nova Scotia. On its eastward path, the tsunami sped through the gap between Australia and Antarctica and into the Pacific as far north as Canada. Not since the eruption of Krakatau volcano in 1883 had a tsunami been known to travel so far.

When the entire path of the tsunami played out on the National Oceanic and Atmospheric Administration's leading computer simulation, called MOST (short for *m*ethod *o*f *s*plitting *t*sunami), the simulated wave heights agreed quite well with the measurements at various tide gauge stations. What is more, the model revealed just *how* a tsunami manages to travel so far. A map of the simulated wave heights for the Indian Ocean event showed that they are highest along mid-ocean ridges. These ridges, which connect one ocean basin to the next, appear to channel the wave energy farther than it might otherwise travel. Knowing about this effect is helpful for forecasting because modelers can better estimate where the strongest wave energy is most likely to go.

Immediate Aftermath

FORECASTING HOW a tsunami will behave once it climbs ashore is a much greater challenge. As always occurs in tsunamis, the December event's waves gradually slowed down as they entered shallow water. By the time the ripples reached shore, the distance between

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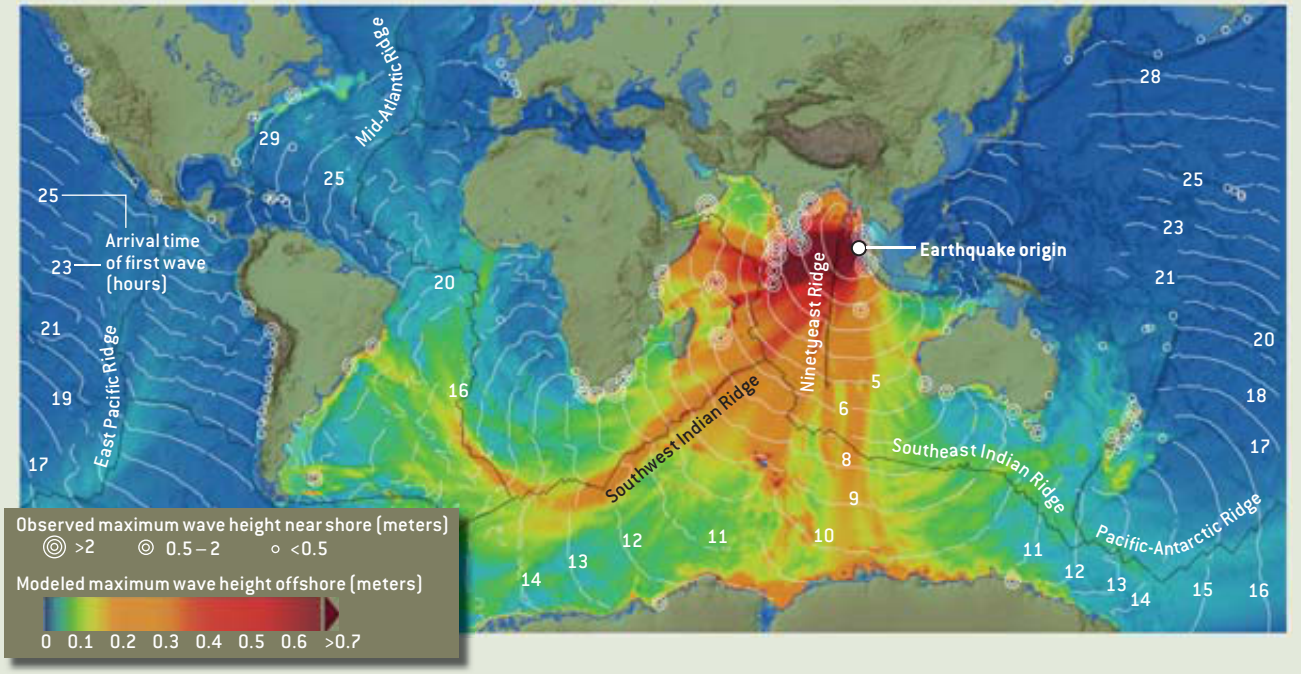
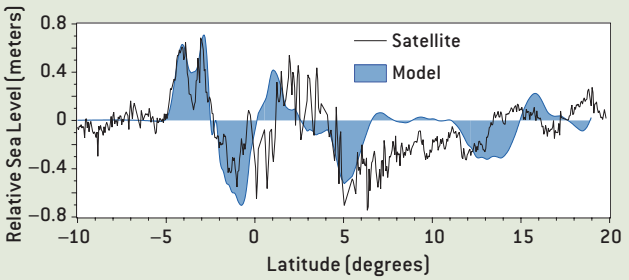
PREDICTING TSUNAMI BEHAVIOR

Observations from the December 2004 tsunami confirmed scientists' basic understanding of three key aspects of tsunami behavior: how large events propagate around the world, what the waves look like in the open ocean, and how far inland the waves will climb. Each image compares direct measurements with values calculated by the leading U.S. tsunami-forecasting model, called *m*ethod *o*f *s*plitting tsunami, or MOST.

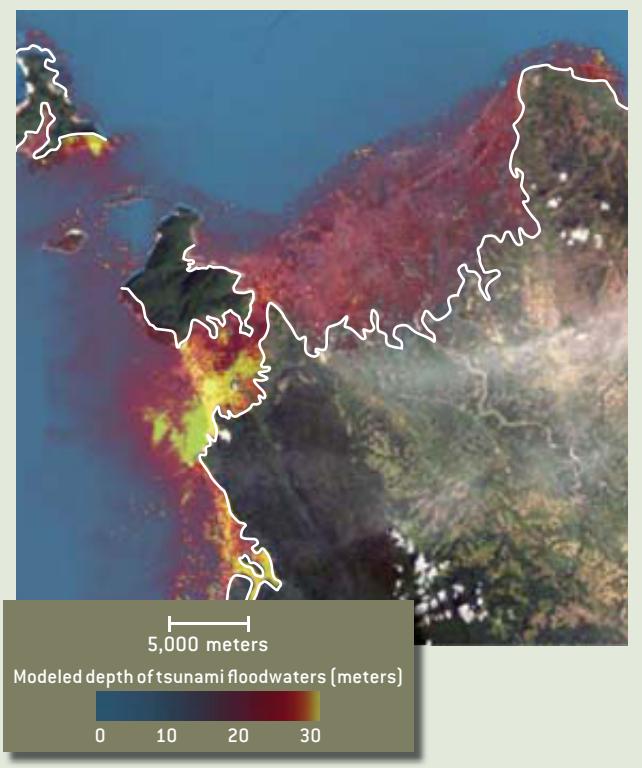


GLOBAL VIEW of the tsunami's path shows that the tallest offshore waves modeled (*warm colors*) correlate well with the tallest waves that tide gauges measured near the coasts (*largest circles*). The first wave (*white lines*) took nearly 30 hours to reach western Canada.



WAVE HEIGHTS in the open ocean—measured by the Jason-1 satellite as it flew over the Indian Ocean two hours after the earthquake that initiated the tsunami (*black lines*)—match the model's calculations (*blue areas*) better than expected. Peaks represent wave crests; dips are wave troughs.

TSUNAMI FLOODWATERS in some areas of northern Sumatra's Aceh province attained heights of 30 meters and surged up to 4.5 kilometers inland. Once again, areas that the model predicted would flood (*color overlay*) agree well with field measurements and satellite images after the event (*regions seaward of white line*).



VASILY V. TITOV

crests, which was hundreds of kilometers in the open ocean, had decreased to 15 or 20 kilometers. But with the fast water still pushing from behind, the wave peaks grew higher and higher, to more than 30 meters in Sumatra's Aceh province, the first region hit.

Still moving at about 30 to 40 kilometers an hour, the waves swept inland—more than four kilometers in parts of the city of Banda Aceh [*see box on opposite page*]. They receded just as violently, carrying far out to sea anything they picked up on the way in. Along all inundated shorelines, waves pounded the coasts for hours. And with 30 minutes or more between crests, many people haplessly returned to the beaches, only to be attacked by subsequent waves. The cumulative damage to the physical environment was so vast that it was visible to astronauts in space; it was also extremely varied.

Considering the many factors involved, how could models reliably predict such variation? Until the early 1990s, because of unresolved computational complexities, even the best simulations ended their calculations at the water's edge or just offshore. Investigators then used that last height to estimate how far inland a tsunami would climb. But the initial careful surveys of tsunami disasters suggested their estimates were way off. A tsunami that struck Nicaragua in 1992 was the first time scientists made comprehensive field measurements to compare with the model predictions. The flooding levels in some places were up to 10 times higher than what the models had predicted.

A race of sorts soon developed between U.S. and Japanese modelers seeking to describe the inundation more accurately, by calculating the entire evolution of the tsunami on dry land. Through a combination of large-scale laboratory experiments and field measurements from subsequent tsunamis, investigators refined the Japanese TUNAMI-N2 and the U.S. MOST models until they could match the inundation patterns of most past tsunamis quite well—as long as high-resolution data about the coastal and offshore topography were available.

JIMIN LAI AFP/Getty Images

TWISTED RAILWAY TRACKS near Sri Lanka's southwestern coast community of Sinigame mark where the December 2004 tsunami derailed an eight-car passenger train, killing an estimated 1,500 people.

These researchers did not know, however, that the models would work as well for the largest tsunamis. As it turned out, the models matched the Indian Ocean flooding better than expected, despite the relative lack of detail about the coastal landscape.

Post-tsunami surveyors in Indonesia and elsewhere quickly noted that predictions of floodwater depth alone could not always foretell the full impact of the tsunami. In many locales in Thailand and Sri Lanka, the tsunami depth on land was less than 4.5 meters, yet the devastation rivaled that in Aceh, where the water was six times deeper. Another shocking reality was that in Banda Aceh, the waves destroyed block after block of reinforced concrete structures that may have withstood the earthquake's shaking.

To account for the magnitude of the wreckage, Ahmet C. Yalciner of Middle East Technical University in Ankara, Turkey, and one of us (Synolakis) are devising new damage metrics—standards that coastal engineers can use to assess the force of tsunami waves on structures—that also consider powerful currents, which are much stronger in tsunami floodwaters than they are in normal tides and storm waves.

Shaking Surprises

ARGUABLY THE GREATEST scientific conundrum regarding the Indian Ocean tsunami is the earthquake itself. Even the magnitude of the earthquake is still debated, with some estimates as high as 9.3. Although the seismic shock was the largest since the 1964 Alaska earthquake, it has been a challenge to describe how the Sumatra-Andaman fault produced such a giant tsunami.

By any measure, this earthquake was amazingly complex. Typically the fault slip will be largest right at the start, near

THE AUTHORS

ERIC L. GEIST, VASILY V. TITOV and *COSTAS E. SYNOLAKIS* bring various types of expertise to the study of tsunamis. Geist is a research geophysicist with the U.S. Geological Survey in Menlo Park, Calif. He uses computer simulations to study how the inherent complexity of subduction zone earthquakes affects tsunami generation. Titov developed NOAA's premier computer model for forecasting tsunamis. He is senior modeler for that agency's Tsunami Research Program in Seattle and affiliate assistant professor at the University of Washington. Synolakis directs the University of Southern California Tsunami Research Center, which he founded in 1995. His current work involves field surveys of tsunami destruction, large-scale laboratory models of tsunami waves, and computer simulations of flooding along tsunami-prone coastlines, including those of California.

its origin. Yet in some cases, the fault break begins with a small amount of slip, suggesting that the earthquake will be small, then hits a weak or highly stressed part of the fault that lets loose violently, resulting in a much larger earthquake and tsunami. That is what happened in the 2004 tsunami. Such cases are challenging to analyze in time to make a useful warning.

NOAA's tsunami forecast models were put to the test for this perplexing event. Running the model with seismic data alone would have underestimated tsunami heights in the open ocean by a factor of 10 or more. Adding the first direct measurement of tsunami amplitude, which reached scientists from a tide gauge station at Cocos Island about three and a half hours after the earthquake occurred, improved the results dramatically. But something was still missing.

In the days following the earthquake, analyses of the shock's strong seismic waves indicated that the initial fault break sped northward from Sumatra at 2.5 kilometers a second. They also pinpointed the areas of greatest slip—and thus of the greatest tsunami generation. The problem for tsunami modelers was that none of these seismic solutions included enough overall fault motion to reproduce either the satellite observations of wave heights in the open ocean or the severe flooding in Banda Aceh.

The critical clue came from land-based stations that use the Global Positioning System (GPS) to track ground movements much slower than what seismic waves produce. Those measurements revealed that the fault continued to slip, albeit slowly, after it stopped emanating seismic energy. Although there is a limit to how slowly a fault can slip and still generate a tsunami, it is most likely that this often overlooked phenomenon, called after-slip, accounts for the surprising tsunami heights. If so, incorporating continuous GPS readings may be an important component of tsunami warning systems in the future.

Hit or Miss

THE SPECIFIC FACTORS in any given earthquake clearly exert fearsome controls on tsunamis. As if emphasizing this point, Planet Earth produced another

Warnings for the Future

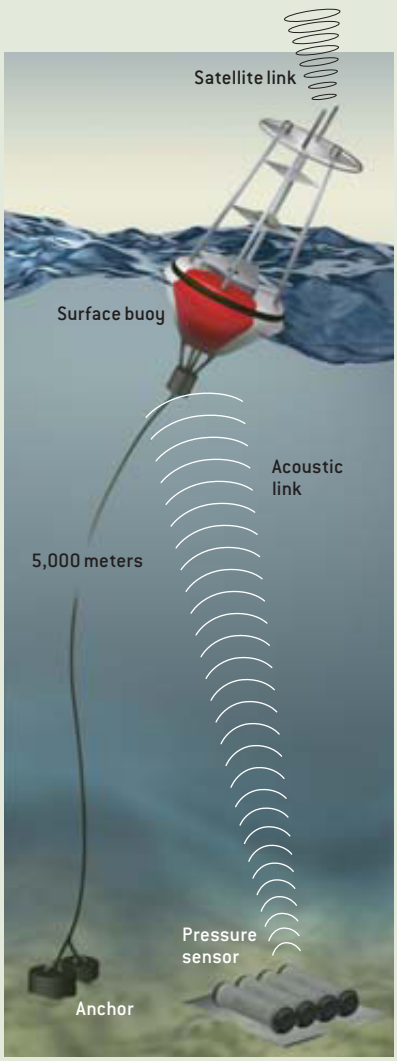
Before the December 2004 event, the Indian Ocean had no tsunami-warning system. Since then, several international groups, coordinated by UNESCO's Intergovernmental Oceanographic Commission, have raced to correct the problem. To achieve the monitoring capability that currently exists in the Pacific, the Indian Ocean needs three basin-wide technological components: an improved seismic network to locate large earthquakes, a minimum of five tsunameters (*right*) to detect tsunami waves as they travel across the open ocean (although 13 are needed to detect a tsunami in less than 30 minutes), and a real-time network of tide gauges near shore.

Key steps took place in the past year. Two seismic networks—one entirely new—now report automatically to the national earthquake centers in Indonesia and Malaysia; the latter will soon make its information available to the entire region. Four tide gauges have already been upgraded for tsunami monitoring—including one near Indonesia, which lies closest to major tsunami-generating faults. More than 20 additional installations and improvements are scheduled for the coming months.

It is unclear how and when the necessary tsunameters can be acquired, and political challenges must be overcome in certain countries before the seismic network can be completed, but UNESCO officials remain optimistic. If all goes well, a basic monitoring system should be operational by July. Computer models must then combine those measurements into accurate warnings.

Once warnings are available, they must still be disseminated to people on the coasts. Along most of the Indian Ocean's 66,000 kilometers of shoreline, the first wave will not arrive for two hours or more—enough time for most people to move inland after an alarm sounds. In places where tsunami waves will strike in an hour or less, an alarm may come too late. Residents must instead recognize natural signs—severe ground shaking and a receding ocean that often precede an incoming surge.

In both cases, swift evacuation to predesignated safe zones is essential. Local officials have already held practice drills in some parts of Thailand, Sri Lanka and Indonesia that were hit hard in 2004. *—C.E.S., E.L.G. and V.V.T.*



TSUNAMETER features a pressure sensor on the seafloor that sends an acoustic signal to a buoy at the surface when it senses a passing tsunami. The buoy then relays the warning via satellite to the officials responsible for sounding an alarm.

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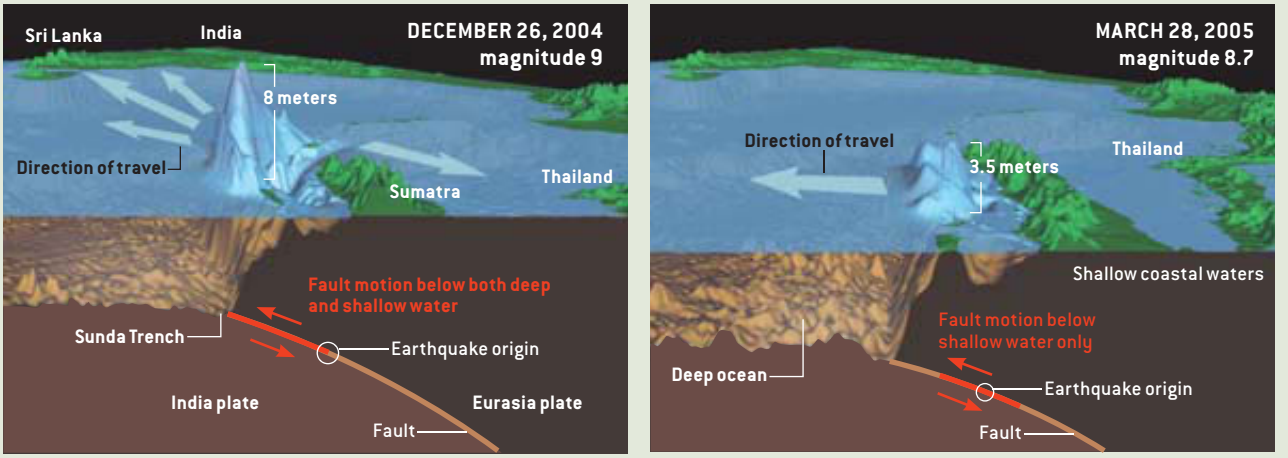
SHOCKING DIFFERENCES

On March 28, 2005, three months after the tsunami-generating earthquake of December 2004, a second large earthquake rocked the same fault. The initial waves the shocks generated were eight meters in December and 3.5 meters in March; they are exaggerated for comparison's sake in the diagrams below. Through detailed studies, researchers have uncovered four main reasons for this unexpected disparity.

First, the March shock released 1/15 the energy of its predecessor (it was a magnitude 8.7 shock; December's was greater than 9). It struck along a deeper portion of the fault (*red*), thereby limiting how much energy surged upward into the overlying water. It occurred underneath shallow water, so it raised a smaller volume of water; in December, part of the tsunami formed above the deep Sunda Trench. Finally, it struck about 100 kilometers farther south, so most of its eastbound waves struck Sumatra, which shielded Thailand and Malaysia, and its westbound waves headed out to sea; in December, both eastbound and westbound waves attacked nearby landmasses.



SOURCE: ERIC L. GEIST

huge temblor along the same fault on March 28, 2005. The initial break occurred an equivalent distance from the Sumatra coastline and at virtually the same depth below the seafloor as the December earthquake, and both shocks are among the top 10 largest recorded since 1900. Yet they produced radically different tsunamis.

Seeing the March earthquake flash on their computer screens as a magnitude 8.7, scientists at the Pacific Tsunami Warning Center and elsewhere expected the worst. Severe damage from strong ground shaking indeed occurred but without immediate reports of tsunami damage. When an international team (including one of us, Titov) surveyed the region two weeks later, they measured tsunami run-up heights as high as four meters—still potentially deadly. Some Indonesians said they learned from their first experience and ran inland when the ground shook. Better evacuation is only one reason the March tsunami did not take more lives.

Analysis of aftershocks from the December earthquake suggested to Andrew Newman of the Georgia Institute of Technology and Susan Bilek of the New Mexico Institute of Mining and Technology that the fault slipped near the deep trench that time and was thus under deeper water than the main part of the fault that slipped in March was. The December tsunami thus had more opportunity to gain height during its trip from deep water to shore. In addition, unlike the December tsunami, fault movement in March occurred below the islands of Nias and Simeulue, thereby limiting the amount of water the uplifting crust could displace.

A slight difference in the fault orientation meant that their tsunami waves proceeded in two different general directions. For the March earthquake, most of its eastbound waves smashed into the island of Sumatra, which blocked much of the wave energy from moving on toward Thailand and Malaysia. The westbound waves shot out into the open ocean to the southwest, largely missing Sri Lanka, India and the Maldives, all of which suffered terribly in December. These examples highlight the critical importance that even small variations in the location of an earthquake can make.

Despite the lingering scientific uncertainties that will probably always surround such complex phenomena, the new tsunami science is ready for implementation. The biggest challenge for saving lives is now applying the scientific findings to proper education, planning and warning. SA

MORE TO EXPLORE

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National Oceanic and Atmospheric Administration tsunami pages: **www.tsunami.noaa.gov/**

University of Southern California Tsunami Research Center: **http://cwis.usc.edu/dept/tsunamis/2005/index.php**

U.S. Geological Survey Tsunami and Earthquake Research: **http://walrus.wr.usgs.gov/tsunami/**

INNOVATIONS FROM A ROBOT RALLY

By W. Wayt Gibbs

This year's Grand Challenge competition spurred advances in laser sensing, computer vision and autonomous navigation—not to mention a thrilling race for the $2-million prize

THE MOST VALUABLE AND COMPLEX component in a modern vehicle typically is also the most unreliable part of the system. Driving accidents usually have both a human cause and a human victim. To certain engineers—especially those who build robots—that is a problem with an obvious solution: replace the easily distracted, readily fatigued driver with an ever attentive, never tiring machine.

The U.S. military, which has been losing soldiers to roadside bombs in Iraq for several years, is particularly keen on this idea. But by 2002 more than a de-

MACHINE ON A MISSION, Sandstorm swivels its laser-scanning "eye" (*inside silver dome*) to peer around a tight turn as it negotiates Beer Bottle Pass in the 2005 Grand Challenge race, followed by a DARPA chase vehicle. The autonomous Humvee drove the 132-mile course at an average speed of 18.6 miles an hour but was bested by a slightly faster robot.

An Endurance Race for Robots

Enthusiasm ran high among the 550-odd engineers from seven nations and 42 U.S. states who gathered in Pasadena, Calif., in August 2004 to hear DARPA officials lay down the rules for the 2005 Grand Challenge race. Many had already set aside day jobs and invested their own savings to begin work on a self-navigating ground vehicle, in hopes of earning a shot at the $2-million prize in October 2005. Few seemed discouraged by the results of the first Grand Challenge, held on March 13, 2004, when only 13 teams were able to field machines for the 142-mile course and none cleared the first mountain crossing (see "A New Race of Robots," by W. Wayt Gibbs; SCIENTIFIC AMERICAN, March 2004).

Sandstorm, constructed by the Red Team at Carnegie Mellon University, had traveled fastest and farthest in the 2004 event, driving at up to 36 miles an hour before straying off the edge of a narrow hairpin turn 7.4 miles into the route. But even as it fell far short of the goal, Sandstorm's performance set new records in off-road robotics and ignited the imagination of many of the roboticists, students and backyard mechanics here.

Ron Kurjanowicz, the DARPA program manager for the 2005 Grand Challenge, spelled out the rules. Any kind of traction-propelled vehicle could enter, but officials would disqualify any robot that interfered with another, damaged the environment or communicated with humans in any way during the race. The course, delineated by a computer-readable list of GPS waypoints, would be held secret until 4 A.M. on race day. "This year you should be prepared to drive 175 miles in 10 hours or less," Kurjanowicz said. The robots will have to negotiate many obstacles, Tether warned. "There are gullies, washouts, stopped vehicles, underpasses, utility towers. And on the morning of the race we're going to place several tank traps on the road," he said, showing a photograph of a scary-looking obstruction built from three crisscrossed iron girders.

"Our job is to look for crazy people with crazy ideas," Tether said, only half in jest, "and then to bring those ideas as quickly as possible from the 'far side' of technology to the near side. Looking at the crowd here today, I'd say we've done that."

MENAGERIE OF ROBOTS in the 2005 Grand Challenge included several that, like Team Cornell's Spider (*top*), were based on military vehicles. Many entrants adapted pickup trucks or SUVs in order to focus their efforts on inventing new software and sensors, such as Team DAD's 64-laser terrain scanner (*middle*). And some vehicles were designed from scratch, including Team Jefferson's Tommy (*bottom*).

cade of military-funded research on autonomous ground vehicles had produced only a few slow and clumsy prototypes.

So that year the Pentagon authorized its Defense Advanced Research Projects Agency (DARPA) to take an unconventional approach: a public competition with a $1-million prize. The next February DARPA director Anthony J. Tether announced that the Grand Challenge—the first long-distance race for driverless vehicles—would be held in the Mojave Desert in March 2004. When no robot completed that course, DARPA doubled the prize and scheduled a second running, through a different part of the desert, for October 2005.

The point of the Grand Challenge was not to produce a robot that the military could move directly to mass production, Tether says. The aim was to energize the engineering community to tackle the many problems that must be solved before vehicles can pilot themselves safely at high speed over unfamiliar terrain. "Our job is to take the technical excuse off the table, so people can no longer say it can't be done," Tether explained at the qualifying event held 10 days before the October 8 race.

Clearly, it can be done—and done in more than one way. This time five autonomous vehicles crossed the finish line, four of them navigating the 132-mile course in well under the 10 hours re-

Overview/*The Grand Challenge 2005*

- Five out of 23 competing robots successfully navigated a 132-mile course through the Mojave Desert in October 2005 as part of the DARPA Grand Challenge race. To qualify for the $2-million prize, the driverless vehicles had to finish in less than 10 hours. Four turned in elapsed times under 7.5 hours.
- The competition inspired numerous technical innovations that enable computer-controlled vehicles to move quickly over rough and unfamiliar terrain. The robotic entrants demonstrated advances in location tracking, road and obstacle perception, and high-speed path planning.
- These technologies may appear in future military, agricultural, industrial and even consumer vehicles. Some are already being commercialized.

DARPA (*preceding pages*); VAUGHN YOUTZ *Zuma/Corbis* (*this page, top*); DIGITAL AUTO DRIVE (*middle*); DARPA (*bottom*)

quired to be eligible for the cash prize.

More important than the race itself are the innovations that have been developed by Grand Challenge teams, including some whose robots failed to finish or even to qualify for the race. These inventions provide building blocks for a qualitatively new class of ground vehicles that can carry goods, plow fields, dig mines, haul dirt, explore distant worlds—and, yes, fight battles—with little or no human intervention.

"The potential here is enormous," insists Sebastian Thrun, director of Stanford University's Artificial Intelligence Laboratory and also head of its robot racing team. "Autonomous vehicles will be as important as the Internet."

From Here to There

IF ROBOTICS IS EVER to fulfill Thrun's bold prediction, it will have to leap technical hurdles somewhat taller than those posed by DARPA's competition. The Grand Challenge did define many of the right problems, however. To succeed in such a race, vehicles first have to plot a fast and feasible route for the long journey ahead. Next, the robots need to track their location precisely and find the road (if there is one) as well as any obstacles in their way. Finally, the machines must plan and maneuver over a path that avoids obstructions yet stay on the trail, especially at high speed and on slippery terrain.

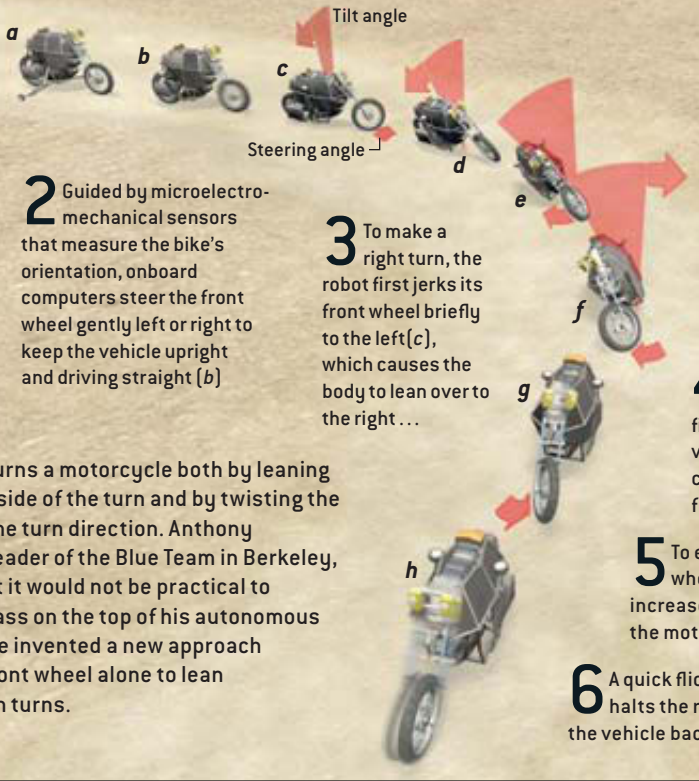
Two hours before the event began, DARPA officials unveiled the course by handing out a computer file listing 2,935 GPS waypoints—a virtual trail of bread crumbs, one placed every 237 feet on average, for the robots to follow—plus speed limits and corridor widths. Many teams simply copied this file to their robots unchanged. But some used custom-built software to try to rapidly tailor a route within the allowed corridor that could win the race.

The Red Team, based at Carnegie Mellon University, raised this mission-planning task to a military level of sophistication. In a mobile office set up near the starting chutes 13 route editors, three speed setters, three managers, a statistician and a strategist waited for the DARPA CD. Within minutes of its arrival, a "preplanning" system that the team had built with help from Science Applications International Corporation, a major defense contractor, began overlaying the race area with imagery drawn from a 1.8-terabyte database containing three-foot-resolution satellite and aerial photographs, digital-elevation models and laser-scanned road profiles gathered during nearly 3,000 miles of reconnaissance driving in the Mojave.

The system automatically created initial routes for Sandstorm and H1ghlander, the team's two racers, by converting every vertex to a curve, calculating a safe speed around each curve, and knocking the highest allowable speeds down to limits derived from months of desert trials at the Nevada Automotive Testing Center. The software then divided the course and the initial route into segments, and the manager assigned one segment to each race editor.

Flipping among imagery, topographic maps and reconnaissance scans, the editors tweaked the route to take tight turns the way a race driver would and to shy away from cliff edges. They

A MOTORCYCLE THAT STEERS ITSELF



1 When not in motion, the motorbike rests on retractable landing gear (*a*)

2 Guided by microelectromechanical sensors that measure the bike's orientation, onboard computers steer the front wheel gently left or right to keep the vehicle upright and driving straight (*b*)

3 To make a right turn, the robot first jerks its front wheel briefly to the left (*c*), which causes the body to lean over to the right . . .

4 . . . then straightens its wheel as the chassis continues to tip right (*d*), and finally steers right (*e*) to halt its fall. The vehicle holds this pose, in which the push of centrifugal force balances the pull of gravity, for the duration of the turn

5 To exit the turn, the robot kicks the front wheel even farther to the right (*f*), which increases the centrifugal force and rights the motorbike

6 A quick flick of the wheel to the left (*g*) halts the rotation of the chassis and puts the vehicle back on a straight heading (*h*)

A human rider turns a motorcycle both by leaning weight to the inside of the turn and by twisting the handlebars in the turn direction. Anthony Levandowski, leader of the Blue Team in Berkeley, Calif., knew that it would not be practical to move a large mass on the top of his autonomous motorbike, so he invented a new approach that uses the front wheel alone to lean the bike through turns.

GHOSTRIDER ran unassisted for 20 miles at a time in desert testing.

JOHN KOCON (*illustration*); ANTHONY LEVANDOWSKI (*photograph*)

The Race to the Starting Line

Forty-three robots rolled onto the infield of the California Speedway in Fontana, Calif., on September 28, 2005, for the Grand Challenge semifinals. Over the next eight days, each robot would get at least four chances to run a speed trial through the roughly two-mile course, which officials had cluttered with fence gates, parked cars, stacked tires and a tunnel that blocked GPS reception. Chris Urmson of the Red Team and Sebastian Thrun of the Stanford Racing Team surveyed the competition from the top of the grandstands. As they gazed at the gamut of robots ranging from a 275-pound minibike to a 15-ton military truck, Urmson broke into a grin. "This may be the coolest thing I have ever seen," he said.

The vehicles on display had been sifted from a much larger crop. DARPA accepted applications from 195 groups, including three high school teams, 35 university squads and all 15 finalists from the 2004 Grand Challenge. Many high-powered universities that sat out the first race—including Stanford, Cornell, Princeton, the University of California, Los Angeles, and the Massachusetts Institute of Technology—had entered in the second.

Only 118 teams made the first cut, based on a technical summary and a video of the vehicle in action. In May, DARPA officials visited each team for an on-site inspection and demonstration on a 220-yard (200-meter) zigzag course. The inspectors timed each robot and placed garbage cans in its path to test its obstacle-dodging abilities over three runs.

The more advanced teams sent their robots on a longer fourth run to show off the machines' driving skills. In Cedar Rapids, Iowa, Team Terramax's Oshkosh truck was able to back up and realign its eight-foot-wide body to squeeze around traffic cones with just inches to spare. At an old steel mill site in Pittsburgh, the Red Team's H1ghlander Hummer sped at 25 miles an hour over rubble-strewn road and shot through a railroad underpass.

From the first day of the qualifiers, it was clear that the technology had taken giant strides in the past 18 months. Eleven of the 43 contestants completed the obstacle course on their first try, and 25 robots had done so by the end of the trial—some hitting speeds over 40 miles an hour. Two of the finishers had crashed badly on some of their runs and were eliminated. DARPA sent the remaining 23 on to Primm, Nev., to take their shot at the $2-million prize.

CUT: M.I.T.'s Manticore (*top*) failed its on-site demonstration. IRV, built by Indy Robot Racing, flamed out on the straw bales in Fontana (*middle*). Team ENSCO was a contender for the prize until its Dexter robot (*bottom*) struck a boulder in the road at mile 81 of the race.

GRANT JORDAN (*top*); STEVEN WALLACE *Advanced Network Management Lab, Indiana University* (*middle*); SARAH WILKIN (*bottom*)

marked "slow" any sections near gates, washouts and underpasses; segments on paved roads and dry lake beds were assigned "warp speed."

The managers repeatedly reassigned segments so that at least four pairs of eyes reviewed each part of the route. Meanwhile, in a back room, team leaders pored over histograms of projected speeds and estimates of elapsed time. Team leader William "Red" Whittaker ordered completion times of 6.3 hours for H1ghlander and 7.0 hours for Sandstorm, and the system adjusted the commanded speeds to make it so.

Hitting the Road

ROADS CHANGE—desert roads more than most—so no map is ever entirely up-to-date. And even the perfect route is of no value unless the robot always knows where it is and where it needs to go next. Every vehicle in the Grand Challenge was equipped with differential GPS receivers. They are generally accurate to better than three feet, but overpasses and canyons block the GPS signal, and it sometimes shifts unpredictably.

Most teams thus added other tracking systems to their robots, typically inertial navigation systems that contain microelectromechanical accelerometers or fiber-optic gyroscopes. But two of the competitors created technologies that promise to be more accurate or less expensive, or both.

A team of high school students from Palos Verdes, Calif., found inspiration in the optical mouse used with desktop computers. They installed a bright lamp in their Doom Buggy robot and directed the white light onto the ground through optical tubing. A camera aimed at the bright spot picks up motion in any horizontal direction, acting as a two-dimensional odometer accurate to one millimeter. "We call it the GroundMouse," says team member Ashton Larson.

The Intelligent Vehicle Safety Technologies (IVST) team, staffed by professional engineers from Ford, Honeywell, Delphi and Perceptek, used a similar technique on its autonomous pickup truck. A radar aimed at the ground senses Doppler shifts in the frequency of the reflected beam, from which the robot then calculates relative motion with high precision. Whenever the vehicle loses the GPS fix on its position, it can fall back on dead-reckoning navigation from its radar odometer.

In the desert, even human drivers sometimes have difficulty picking out a dirt trail. It takes very clever software indeed to discriminate terrain that is probably road from terrain that is prob-

ably not. Such software, Tether says, "is a big part of what I call the 'secret sauce' that makes this technology work."

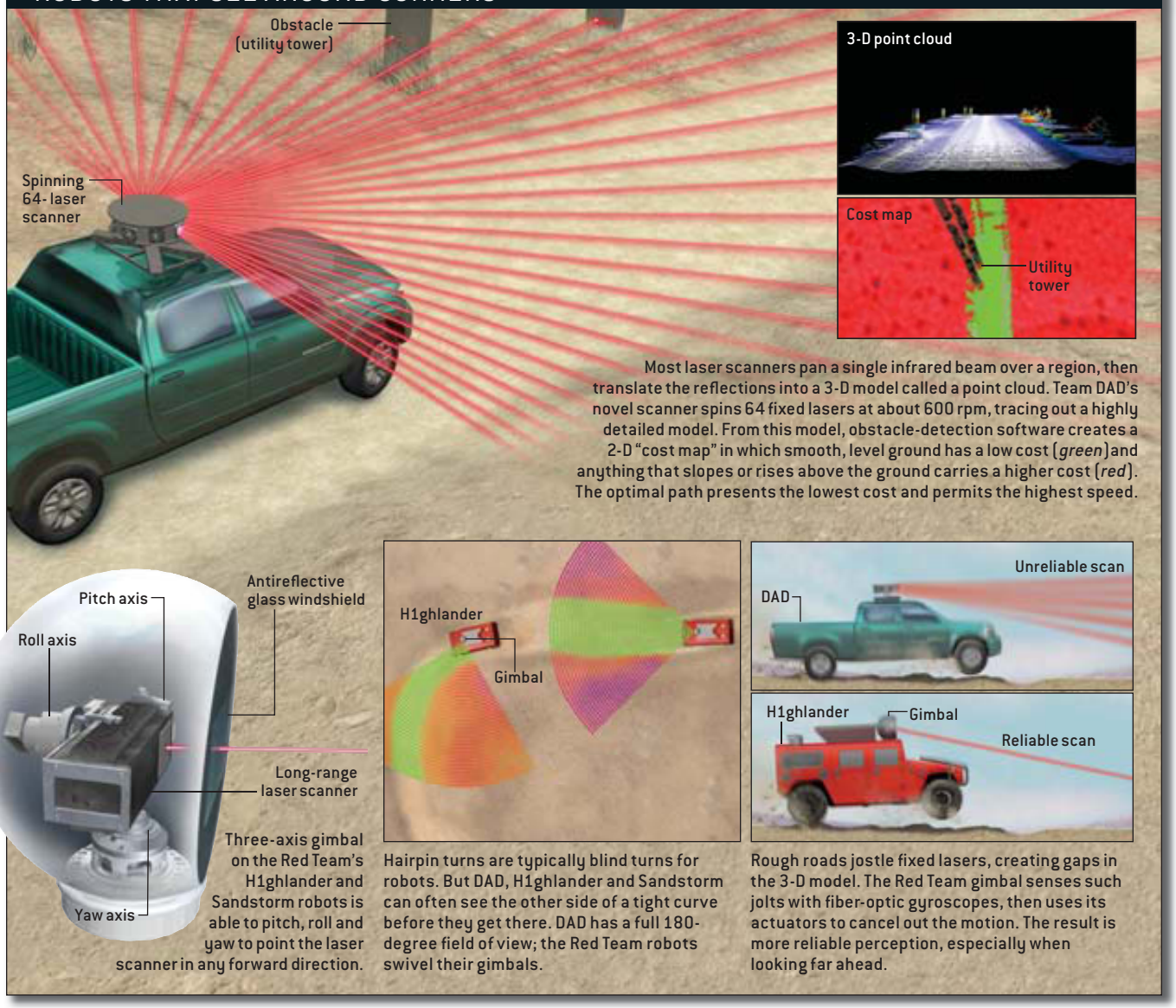
The experience of the Grand Challenge suggests that for robots, laser scanners provide the best view for this task. By rapidly sweeping an infrared laser beam across a swath of the world in front of the machine, a scanner creates a three-dimensional "point cloud" of the environment. A single laser beam cannot cover both distant objects and nearby road with sufficient fidelity, however, so a robot typically uses several in concert.

More lasers are not necessarily better. IRV, the Indy Robot Racing Team's autonomous Jeep, sported 11. But when the vehicle's sensors were knocked out of alignment, it ran over hay bales, caught fire and was eliminated during the qualification round. Without accurate calibration, laser scanners place obstacles in the wrong spot on the robot's internal map, drawing the vehicle into the very objects it is trying to avoid.

David Hall of Team DAD, a two-man operation from Morgan Hill, Calif., created a novel laser sensor that addresses the calibration problem by fixing 64 lasers inside a motorized circular platform that whirls 10 times a second [*see box below*]. A bank of fast digital signal processors, programmed in the low-level Assembly language, handles the flood of data. In prerace trials, the sensor was able to pick out obstacles the size of a person from up to 500 feet away.

The Red Team took a different but equally innovative approach with its two robots. Each carries a single long-range laser that can do the job of many, because it swivels, rolls and nods on top of an articulated arm called a gimbal. Protected by a dome and windshield that look like a giant eyeball on top of the robot, the laser can tilt up or down when the vehicle climbs or descends. As the robot approaches a turn, the gimbal swivels left or right, keeping its eye trained on the road.

ROBOTS THAT SEE AROUND CORNERS



JOHN KOCON (*illustrations*); JOSHUA ANHALT AND TUGRUL GALATALI, RED TEAM (*point cloud*); LUCY READING-IKKANDA AND RED TEAM (*cost map*)

Red Team engineers also mounted fiber-optic gyroscopes to each of the gimbal's three axes and linked them via a feedback system to actuators that stabilize the laser so that it holds steady even as the vehicle jumps underneath it. The team failed to integrate that stabilization capability with the robots' other systems in time to use it for the race. But both Motion Zero, a company just launched by the Blue Team in Berkeley, Calif., and HD Systems in Hauppauge, N.Y., are miniaturizing the technology and planning to market it for use in satellites, weapons systems and camera platforms.

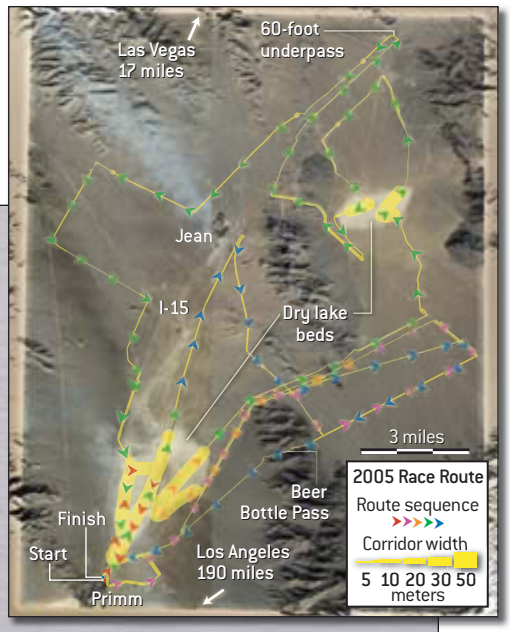
A Path to the Future

INDISPENSABLE AS lasers seem to be, they have their drawbacks. At $25,000 to more than $100,000 each, the price of long-range laser scanners is formidable. Other kinds of sensors, such as video cameras and radars, can see farther and cost less. Yet these have their own weaknesses, and they produce torrents of data that are infamously hard to interpret.

Many teams equipped their robots with a combination of sensors. But only a few succeeded in building systems that could integrate the disparate perspectives to deduce a safe and fast path ahead—and do so many times a second.

Team Terramax's 15-ton robotic Oshkosh truck completed the course thanks in part to a novel "trinocular" vision system designed by Alberto Broggi's group at the University of Parma in Italy. The program selects from among three possible pairs of cameras to get an accurate stereo view of the near, medium or distant terrain. The higher its speed, the farther out the robot peers.

After the competition, Thrun reflected that one of the key advantages of his Stanford team's Stanley robot, which won the race and the $2 million, was its vision-based speed switch. Stanley uses a simple but powerful form of machine learning to hit the gas whenever it spots a smooth road extending into the distance [*see box on opposite page*].



GRAND CHALLENGE COURSE began and ended in Primm, Nev. Over its 131.7 miles, the route (*sequence of colored arrows*) included two long underpasses, several railroad crossings and a mountain pass.

And the Winner Is ...

"Last year, the night before the race, I just kept thinking, 'Don't screw up, Sandstorm,'" recalls Chris Urmson, one the team's technical leaders. "This year, it's more a feeling of anticipation—like Santa Claus is coming."

At 4 A.M. plus 90 seconds, the course comes up on screens in the Red Team's route planning trailer. "Hmm, this is exciting," Alexander Gutierrez says as he scans the convoluted route.

Michael Montemerlo, lead programmer for the Stanford team, is looking at a similar display of the course on his laptop inside Stanley. "What the heck? There's all kinds of overlap—it keeps going in and out. There: there are the mountains, right at the end." Sebastian Thrun, the team leader, looks over his shoulder. "It's short," Thrun says. "That's sad."

H1ghlander is the first to launch into the rising dawn. If it sticks to its schedule—and in months of desert testing it always has—the vehicle will finish at 1 P.M. after a 6.3-hour run. Stanley starts five minutes later, followed by Sandstorm and the remainder of the 23 robots at five- to 10-minute intervals.

By 8:35 A.M. Team DAD's pickup with the spinning laser has passed IVST's truck and is gaining on Sandstorm. An hour later H1ghlander rolls through a 40-mile-an-hour dust storm, having widened its lead on Stanley by seven minutes. Stanley is meanwhile pulling farther ahead of Sandstorm, which the Red Team commanded to drive at a conservative 7.0-hour pace as part of a hare-and-tortoise strategy. Team ENSCO's Dexter, which started in the middle of the pack, is making great time.

As H1ghlander crosses the railroad and hits rolling terrain, it stops midway up a hill and slips back to the bottom, then climbs and falls again. On the third attempt it crests the hill, but clearly the robot's engine is flagging. Stanley catches up, and shortly past noon whoops erupt from the large crowd of Stanford and Volkswagen spectators as Stanley takes the lead.

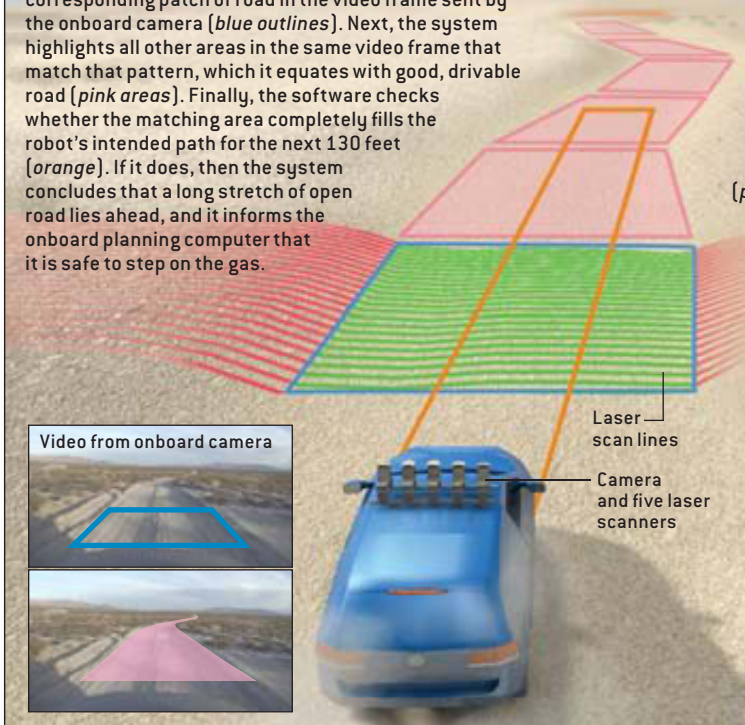
At 1:51 P.M. Stanley appears at the finish line, soon followed by H1ghlander and Sandstorm. Team Gray's KAT-5 arrives at sunset, as officials pause Terramax, which spends the night idling in the desert and completes its mission the next morning. After checking the robots' time logs, Tether of DARPA pronounces Stanley the Grand Challenge victor, by a margin of 11 minutes.

VICTORIOUS Stanley claimed the $2-million prize for Stanford with an elapsed time of 6.9 hours. Four other robots completed the course: Sandstorm in 7.1 hours, H1ghlander in 7.2, KAT-5 in 7.5, and Terramax in 12.9.

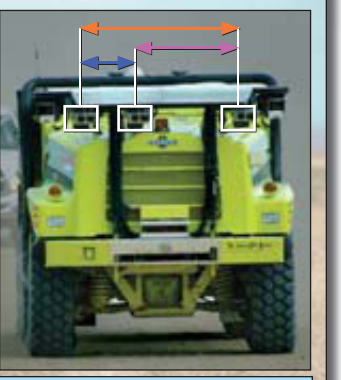
GENE BLEVINS *L.A. Daily News/Corbis (photograph);* W. WAYT GIBBS *(route map)* AND IKONOS *(satellite image)*

VISION LINKED TO SPEED

Smart speed switch, which helped Stanley win the 2005 Grand Challenge, combines laser and video sensors in a four-step process. First, the robot filters its laser data to identify a section of terrain ahead that is smooth and relatively flat (*green*). Second, a program finds the corresponding patch of road in the video frame sent by the onboard camera (*blue outlines*). Next, the system highlights all other areas in the same video frame that match that pattern, which it equates with good, drivable road (*pink areas*). Finally, the software checks whether the matching area completely fills the robot's intended path for the next 130 feet (*orange*). If it does, then the system concludes that a long stretch of open road lies ahead, and it informs the onboard planning computer that it is safe to step on the gas.



Trinocular Terramax (*right*) can build a 3-D stereo view of the world from any of three pairs (*arrows*) of color video cameras. The closest cameras (*purple*), used at slow speeds, can detect obstacles up to 50 feet away. At fast speeds the robot selects its widest pair (*orange*), which can pick up objects 65 to 165 feet ahead. The third pair (*pink*) offers a happy medium.



Terramax might first detect the pillars of an underpass with its long-range stereo cameras (*orange zone above*). As the vehicle slows, it will switch to medium- and then short-range camera pairs to make certain it notices all the obstacles in its video scene (*inset*).

Some of the innovations with the greatest reach, however, appeared on robots that never reached the finish line. The IVST team, for example, devoted desert trials to discovering the optimum sensor configurations for its Desert Tortoise in a variety of "contexts"—such as washboard trail, paved highway or interstate underpass. As the robot drives, explains team leader William Klarquist, "the vehicle chooses an appropriate context that switches off some sensors, switches on others, and reassigns the confidence that it places in each one." This technique should allow a robot to move from desert to, say, farmland and still perform well by loading a new set of contexts.

In IRV, the Indy Robot Racing Team demonstrated a "plug and play" system for sensors, a feature that is probably a prerequisite for the creation of an autonomous vehicle industry. The far-flung team of more than 100 engineers needed a way to swap sensors and software modules in and out of the robot easily as the group tested and refined the system. So they invented a network protocol (analogous to the hypertext transfer protocol on which the Web runs) for autonomous driving.

Each sensor on IRV plugs into a dedicated computer, which boils the raw data down to a set of obstacle coordinates and sizes, and then translates that into the network protocol. Every sensor computer broadcasts its obstacle list to all other sensors and to the robot's central path-planning computer. The standard makes removing a malfunctioning radar or upgrading a buggy vision algorithm as simple as a changing a tire.

With the dust hardly settled from the race, the next milestone for autonomous ground vehicles is not yet clear. DARPA's Tether points to military interest in convoys that use a human lead driver to send coordinates to a pack of robots behind. Whittaker aimed to have H1ghlander tending fences on his farm by the end of 2005, and by November he was already drafting proposals for a lunar mission. Both he and Thrun said they received lucrative offers from commercial investors in the days before the race. So whatever else happens, these robots will keep moving. SA

W. Wayt Gibbs is senior writer.

MORE TO EXPLORE

High Speed Navigation of Unrehearsed Terrain: Red Team Technology for Grand Challenge 2004. Chris Urmson et al. Carnegie Mellon University Technical Report CMU-RI-TR-04-37; June 2004.

Adaptive Road Following Using Self-Supervised Learning and Reverse Optical Flow. David Lieb, Andrew Lookingbill and Sebastian Thrun in *Proceedings of Robotics: Science and Systems I;* June 2005. Available online at **roboticsproceedings.org**

DARPA Grand Challenge Web sites: **www.darpa.mil/grandchallenge** and **grandchallenge.org**

JOHN KOCON (*illustrations*); SEBASTIAN THRUN *Stanford University* (*video frames*); V. ROSS JOHNSON AND SHAHN TORONTOW (*photograph, top right*); ALBERTO BROGGI *University of Parma* (*inset at bottom right*)

BEHAVIORAL CHANGES accompany motherhood in virtually all female mammals. New research suggests that hormone-induced alterations of the female brain may make mothers more vigilant, nurturing and attuned to the needs of their young, as well as improve their spatial memory and learning.

THE MATERNAL BRAIN

Pregnancy and motherhood change the structure of the female mammal's brain, making mothers attentive to their young and better at caring for them

By CRAIG HOWARD KINSLEY and KELLY G. LAMBERT

Mothers are made, not born. Virtually all female mammals, from rats to monkeys to humans, undergo fundamental behavioral changes during pregnancy and motherhood. What was once a largely self-directed organism devoted to its own needs and survival becomes one focused on the care and well-being of its offspring. Although scientists have long observed and marveled at this transition, only now are they beginning to understand what causes it. New research indicates that the dramatic hormonal fluctuations that occur during pregnancy, birth and lactation may remodel the female brain, increasing the size of neurons in some regions and producing structural changes in others.

Some of these sites are involved in regulating maternal behaviors such as building nests, grooming young and protecting them from predators. Other affected regions, though, control memory, learning, and responses to fear and stress. Recent experiments have shown that mother rats outperform virgins in navigating mazes and capturing prey. In addition to motivating females toward caring for their offspring, the hormone-induced brain changes may enhance a mother rat's foraging abilities, giving her pups a better chance of survival. What is more, the cognitive benefits appear to be long-lasting, persisting until the mother rats enter old age.

Although studies of this phenomenon have so far focused on rodents, it is likely that human females also gain long-lasting mental benefits from motherhood. Most mammals share similar maternal behaviors, which are probably controlled by the same brain regions in both humans and rats. In fact, some researchers have suggested that the development of maternal behavior was one of the main drivers for the evolution of the mammalian brain. As mammals arose from their reptile forebears, their reproductive strategy shifted from drop-the-eggs-and-flee to defend-the-nest, and the selective advantages of the latter approach may have favored the emergence of hormonal brain changes and the resulting beneficial behaviors. The hand—or paw—that rocks the cradle indeed rules the world.

Awash in Hormones

HALF A CENTURY AGO scientists found the first hints that the hormones of pregnancy spur a female mammal's ardor for

JUSTINE COOPER

its offspring. Starting in the 1940s, Frank A. Beach of Yale University showed that estrogen and progesterone, the female reproductive hormones, regulate responses such as aggression and sexuality in rats, hamsters, cats and dogs. Further pioneering work by Daniel S. Lehrman and Jay S. Rosenblatt, then at the Institute of Animal Behavior at Rutgers University, demonstrated that the same hormones were required for the display of maternal behavior in rats. In 1984 Robert S. Bridges, now at the Tufts Cummings School of Veterinary Medicine, reported that the production of estrogen and progesterone increased at certain points during pregnancy and that the appearance of maternal behavior depended on the interplay of the hormones and their eventual decrease. Bridges and his colleagues went on to show that prolactin, the lactation-inducing hormone, stimulated maternal behavior in female rats already primed with progesterone and estrogen.

Besides hormones, other chemicals affecting the nervous system appear to play a role in triggering motherly impulses. In 1980 Alan R. Gintzler of the State University of New York Downstate Medical Center reported increases in endorphins—painkilling proteins produced by the pituitary gland and the brain region called the hypothalamus—over the course of a rat's pregnancy, especially just before birth. In addition to preparing the mother for the discomfort of birth, the endorphins may initiate maternal behavior. Taken together, the data demonstrate that the regulation of this behavior requires the coordination of many hormonal and neurochemical systems and that the female brain is exquisitely responsive to the changes that occur with pregnancy.

Scientists have also identified the brain regions that govern maternal behavior. Michael Numan and Marilyn Numan of Boston College have shown that a part of the hypothalamus in the female brain, the medial preoptic area (mPOA), is largely responsible for this activity; creating a lesion in the mPOA or injecting morphine into the region will disrupt the characteristic behavior of mother rats. But other areas of the brain are also involved [*see box on opposite page*], and each of these sites is rife with receptors for hormones and other neurochemicals. Noted neuroscientist Paul MacLean of the National Institute of Mental Health has proposed that the neural pathways from the thalamus, the brain's relay station, to the cingulate cortex, which regulates emotions, are an important part of the maternal behavior system. Damaging the cingulate cortex in mother rats eliminates their maternal behavior. In his 1990 book *The Triune Brain in Evolution,* MacLean hypothesized that the development of these pathways helped to shape the mammalian brain as it evolved from the simpler reptilian brain.

Interestingly, once the reproductive hormones initiate the maternal response, the brain's dependency on them seems to diminish, and the offspring alone can stimulate maternal behavior. Although a newly born mammal is a demanding little creature, unappealing on many levels—it is smelly, helpless and sleeps only intermittently—the mother's devotion to it is the most motivated of all animal displays, exceeding even sexual behavior and feeding. Joan I. Morrell of Rutgers has suggested that the offspring themselves may be the reward that reinforces maternal behavior. When given the choice between cocaine and newly born pups, mother rats choose pups.

When given the choice between cocaine and newly born pups, mother rats choose pups.

Craig Ferris of the University of Massachusetts Medical School recently studied the brains of lactating mother rats using functional magnetic resonance imaging (fMRI), a noninvasive technique that tracks changes in brain activity. Ferris found that activity in the mother's nucleus accumbens, a site that is integral to reinforcement and reward, increased significantly when she nursed her pups. And Ronald J. Gandelman of Rutgers has shown that when a mother mouse is given the opportunity to receive foster pups—the mouse presses a bar in her cage, causing the pups to slide down a chute—the mother will keep pressing the bar until her cage fills with the squirming, pink objects.

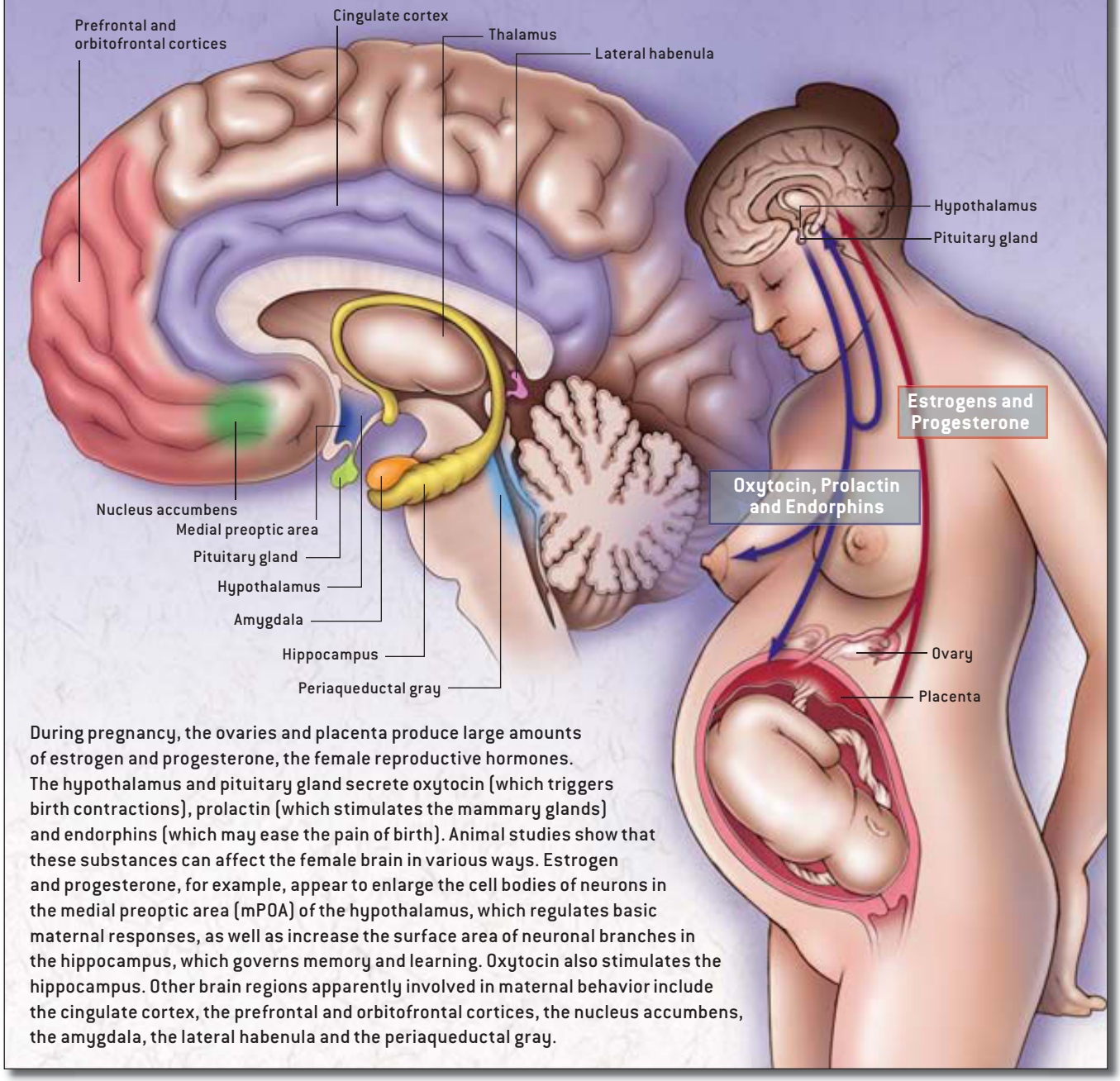
Several researchers have hypothesized that as suckling pups attach to their mother's nipples, they may release tiny amounts of endorphins in the mother's body. These natural painkillers may act somewhat like an opiate drug, drawing the mother again and again to contact with her pups. Suckling and pup contact also release the hormone oxytocin, which may have a similar effect on the mother. Lower mammalian species such as mice and rats, which most likely lack the lofty principles and motivations of humans, may care for their pups for the simple reason that it feels good to do so.

But what about the motivations of the human mother? Jeffrey P. Lorberbaum of the Medical University of South Carolina has used fMRI to examine the brains of human moms as they listened to their babies cry. The patterns of activity were similar to those of the rodent mothers, with the mPOA region

Overview/*Mother Wit*

- Studies of rodents have shown that the hormones of pregnancy trigger changes not only in the brain regions governing maternal behavior but also in areas that regulate memory and learning.
- These brain changes may explain why mother rats are better than virgins at navigating mazes and capturing prey.
- Researchers are now investigating whether human females also gain mental benefits from motherhood.

THINKING FOR TWO



During pregnancy, the ovaries and placenta produce large amounts of estrogen and progesterone, the female reproductive hormones. The hypothalamus and pituitary gland secrete oxytocin (which triggers birth contractions), prolactin (which stimulates the mammary glands) and endorphins (which may ease the pain of birth). Animal studies show that these substances can affect the female brain in various ways. Estrogen and progesterone, for example, appear to enlarge the cell bodies of neurons in the medial preoptic area (mPOA) of the hypothalamus, which regulates basic maternal responses, as well as increase the surface area of neuronal branches in the hippocampus, which governs memory and learning. Oxytocin also stimulates the hippocampus. Other brain regions apparently involved in maternal behavior include the cingulate cortex, the prefrontal and orbitofrontal cortices, the nucleus accumbens, the amygdala, the lateral habenula and the periaqueductal gray.

of the hypothalamus and the prefrontal and orbitofrontal cortices all lighting up. Furthermore, Andreas Bartels and Semir Zeki of University College London found that the brain areas that regulate reward became activated when human moms merely gazed at their children. The similarity between the human and rodent responses suggests the existence of a general maternal circuit in the mammalian brain.

Brain Changes

TO UNDERSTAND THE WORKINGS of this circuit, researchers have studied how the female brain changes at different reproductive stages. In the 1970s Marian C. Diamond of the University of California, Berkeley, provided some of the earliest evidence while investigating the cortices of pregnant rats. The outermost layer of the brain, the cortex receives and processes sensory information and also controls voluntary movements. Rats raised in enriched sensory environments, surrounded by wheels, toys and tunnels, typically develop more intricately folded cortices than rats housed in bare cages. Diamond, however, found that the cortices of pregnant rats from impoverished environments were just as complex as those of the female rats from enriched settings. She concluded that some combination of hormones and fetus-related factors were most likely stimulating the pregnant rats' brains.

Two decades later, after studies demonstrated the importance of the mPOA to maternal behavior, investigators began

TAMI TOLPA

looking for changes to that brain region. In the mid-1990s Lori Keyser, a researcher in one of our laboratories (Kinsley's) at the University of Richmond, showed that the cell bodies of the neurons in the mPOA of pregnant rats increase in volume. What is more, the length and number of dendrites (the signal-receiving branches extending from the cell body) in mPOA neurons increase as the pregnancy progresses. The same changes were also observed in female rats treated with a pregnancy-mimicking regimen of progesterone and estradiol, the most powerful of the natural estrogens. These neuronal alterations typically accompany a rise in protein synthesis and activity. In essence, the hormones of pregnancy "rev up" the mPOA neurons in anticipation of birth and the demands of motherhood. The nerve cells are like thoroughbreds straining at the starting gate, awaiting their release for the race. After birth, the mPOA neurons direct the mother's attention and motivation to her offspring, enabling her to care for, protect and nurture her progeny with the panoply of behaviors known collectively as maternal.

Maternal behavior encompasses many facets beyond the direct care of offspring, however, so it occurred to us that other brain regions might also undergo changes. For instance, a mother rat has to take risks to tend her nest and young. She must frequently leave the relative safety of the nest to forage for food, making herself and her helpless offspring more vulnerable to predators, because if she stays in the nest, she and her brood will slowly starve. We can predict two cognitive changes that would improve the mother rat's cost-benefit ratio. First, an enhancement of her foraging skills—for example, the spatial ability used for navigating her environment—would minimize the amount of time she is away from the nest. Second, a diminution of the rat's fear and anxiety would make it easier for her to leave the nest, allow her to forage faster, and steel her for confrontations with her hostile surroundings.

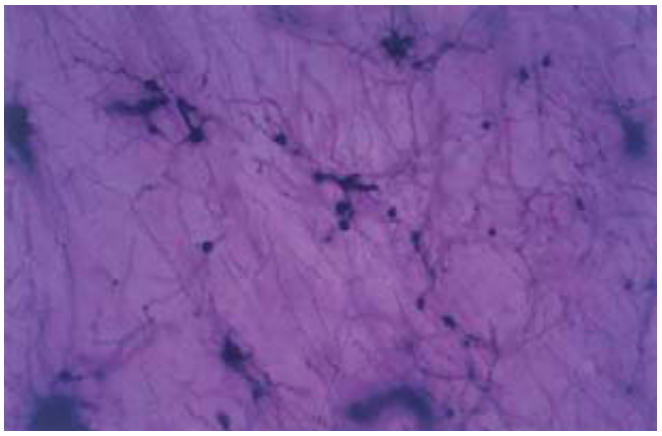
In 1999 we found support for the first prediction by showing that reproductive experience enhanced spatial learning and memory in rats. Young females that had experienced one or two pregnancies were much better than age-matched virgin rats at remembering the location of a food reward in two different kinds of mazes: an eight-arm radial maze [*see top illustration in box on page 78*] and a dry-land version of the Morris water maze, a large, circular enclosure with nine baited food wells. The improved foraging abilities were observed in both lactating females and mothers at least two weeks removed from weaning their young. Furthermore, virgin females provided with foster young performed similarly to lactating females. This result suggests that simply the presence of offspring can provide a boost to spatial memory, perhaps by stimulating brain activities that alter neuronal structures or by prompting the secretion of oxytocin.

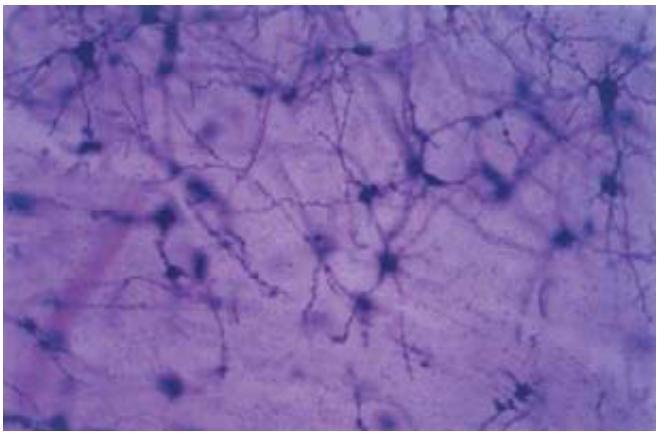
Are other features of the mothers' hunting skills also enhanced? Recent work by undergraduates Naomi Hester, Natalie Karp and Angela Orthmeyer in Kinsley's lab has shown that mother rats are faster than virgins at capturing prey. Slightly food-deprived mother and virgin rats were each placed in a five-foot-square enclosure bedded with wood chips, in which a cricket was hidden. The virgins took an average of nearly 270 seconds to find the cricket and eat it, compared with just more than 50 seconds for the lactating females. Even when the virgin females were made hungrier or when the sounds of the crickets were masked, the mother rats were still able to get to the prey more quickly.

Regarding the second prediction, Inga Neumann of the University of Regensburg in Germany has repeatedly documented that pregnant and lactating rats suffer less fear and anxiety (as measured by levels of stress hormones in their blood) than virgin rats when confronted with challenges such as forced swimming. Jennifer Wartella, while in Kinsley's lab, confirmed and extended these results by examining rat behavior in the five-foot-square enclosure; she found that mother rats were more likely to investigate the space and less likely to freeze up, two hallmarks of boldness. In addition, we found a reduction in neuronal activity in the CA3 region of the hippocampus and the basolateral amygdala, two areas of the brain that regulate stress and emotion. The resulting mitigation of fear and stress responses, combined with the enhancements in spatial ability, ensures that the mother rat is able to leave the security of the nest, forage efficiently and return home quickly to care for her vulnerable offspring.

It appears that hormonal fluctuations ramp up neural activity during pregnancy.

Alterations of the hippocampus, which regulates memory and learning as well as emotions, appear to play a major role in causing these behavioral changes. Some fascinating work by Catherine Woolley and Bruce McEwen of the Rockefeller University showed ebb-and-flow variations in the CA1 region of the hippocampus during a female rat's estrous cycle (the equivalent of the human menstrual cycle). The density of dendritic spines—tiny, thornlike projections that provide more surface area for the reception of nerve signals—increased in this region as the female's levels of estrogen rose. If the relatively brief hormonal fluctuations of the estrous cycle produced such striking structural changes, we wondered, what would happen to the hippocampus during pregnancy, when estrogen and progesterone levels remain high for an extended period? Graciela Stafisso-Sandoz, Regina Trainer and Princy Quadros in Kinsley's lab examined the brains of rats in the late stages of pregnancy, as well as females treated with pregnancy hormones, and found the concentrations of CA1 spines to be denser than normal. Because these spines direct input to their associated neurons, the big rise in density during pregnancy





CELL BODIES of neurons from the mPOA of a virgin female rat (*left*) are much smaller than those from a pregnant rat (*right*). The hormones of pregnancy appear to "rev up" the mPOA neurons, boosting their protein synthesis and activity in anticipation of the demands of motherhood.

may contribute to the enhanced ability of the mothers to navigate mazes and capture prey.

Oxytocin, the hormone that triggers birth contractions and milk release, also appears to have effects on the hippocampus that improve memory and learning. Kazuhito Tomizawa and his colleagues at Okayama University in Japan have reported that oxytocin promotes the establishment of long-lasting connections between neurons in the hippocampus. Injections of oxytocin into the brains of virgin female mice improved their long-term memory, presumably by increasing enzyme activity that strengthened the neuronal connections. Conversely, injecting oxytocin inhibitors into the brains of mother rats impaired their performance on memory-related tasks.

Other researchers have focused on motherhood's effects on glial cells, the connective tissue of the central nervous system. Gordon W. Gifford and student collaborators in Kinsley's lab have examined astrocytes, star-shaped glial cells that provide nutrients and structural support for neurons. They found that the astrocytes in the mPOA and hippocampus of late-pregnant, lactating and hormone-treated female rats were significantly more complex and numerous than those in virgin rats. Again, it appears that hormonal fluctuations ramp up neural activity during pregnancy, modifying neurons and glial cells in critical brain regions to enhance learning and spatial memory.

Do any of these cognitive benefits extend beyond the lactational period? Jessica D. Gatewood, working with other students in Kinsley's lab, has reported that mother rats up to two years old—equivalent to human females older than 60—learn spatial tasks significantly faster than age-matched virgin rats and exhibit less steep memory declines. At every age tested (six, 12, 18 and 24 months), the mothers were better than the virgins at remembering the locations of food rewards in mazes. And when we examined the brains of the mother rats at the conclusion of testing, we found fewer deposits of amyloid precursor proteins—which seem to play a role in the degeneration of the aging nervous system—in two parts of the hippocampus, the CA1 region and the dentate gyrus.

Recent work by Gennifer Love, Ilan M. McNamara and Melissa Morgan in our other lab (Lambert's), employing a different strain of rat and testing conditions, has confirmed that long-term spatial learning is enhanced in older mother rats. What is more, the investigators gauged the boldness of the rats using a maze shaped like a plus sign, with two open arms that rodents typically avoid because they are elevated and exposed, offering no hiding places [*see bottom illustration in box on next page*]. At most of the ages through 22 months that were tested, the mother rats spent more time in the fear-evoking open arms of the maze than the virgin rats did. When the brains of the mother rats were examined, researchers found fewer degenerating cells in the cingulate, frontal and parietal cortices, regions that receive considerable sensory input. These results suggest that the repeated inundation of the female brain with the hormones of pregnancy, coupled with the enriching sensory environment of the nest, may mitigate some of the effects of aging on cognition.

The Human Connection

DO HUMAN FEMALES RECEIVE any similar cognitive benefits from pregnancy and motherhood? Recent studies indicate that the human brain may undergo changes in sensory regulatory systems that parallel the alterations in other animals. Alison Fleming of the University of Toronto at Mississauga has shown that human mothers are capable of recognizing many of their infants' odors and sounds, possibly because of enhanced sensory abilities. She and her colleagues found that mothers with high postbirth levels of the hormone cortisol were more attracted to and motivated by their babies' scents and were better able to recognize their infants' cries. The results indicate that cortisol, which typically rises with stress and

THE AUTHORS

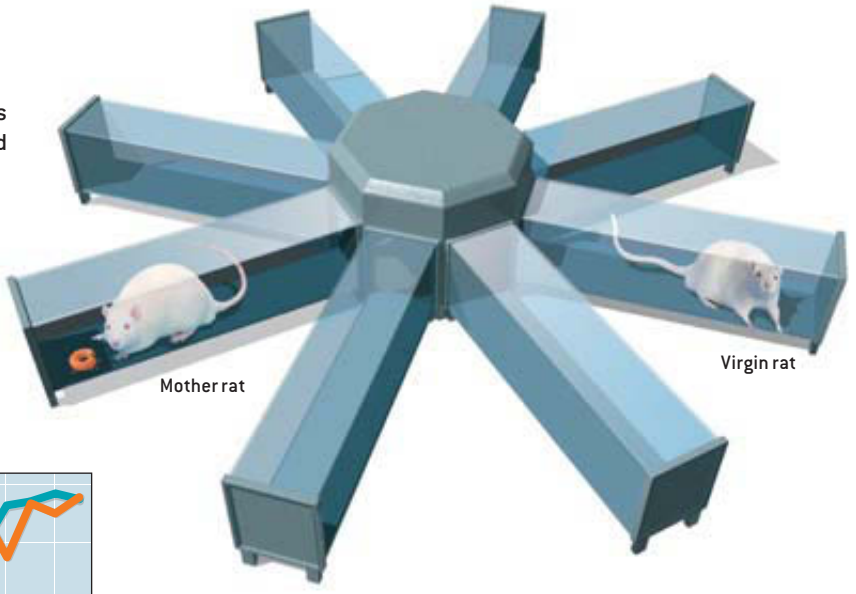
CRAIG HOWARD KINSLEY and *KELLY G. LAMBERT* have spent more than a decade investigating the effects of pregnancy and motherhood on the female brain. Kinsley is MacEldin Trawick Professor of Neuroscience in the department of psychology and Center for Neuroscience at the University of Richmond. Lambert is professor of behavioral neuroscience and psychology, chair of the department of psychology and co-director of the Office of Undergraduate Research at Randolph-Macon College.

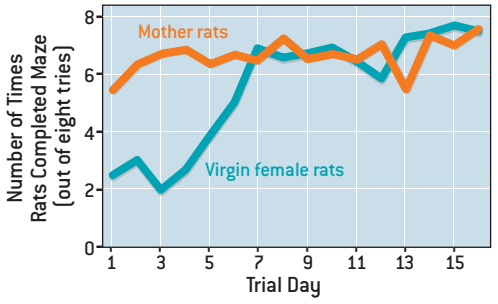
MOTHER KNOWS BEST

Recent experiments indicate that reproductive experience enhances spatial learning and memory in rats while alleviating fear and stress. These behavioral changes can improve a mother rat's foraging abilities, giving her pups a better chance of survival.

EIGHT-ARM RADIAL MAZE

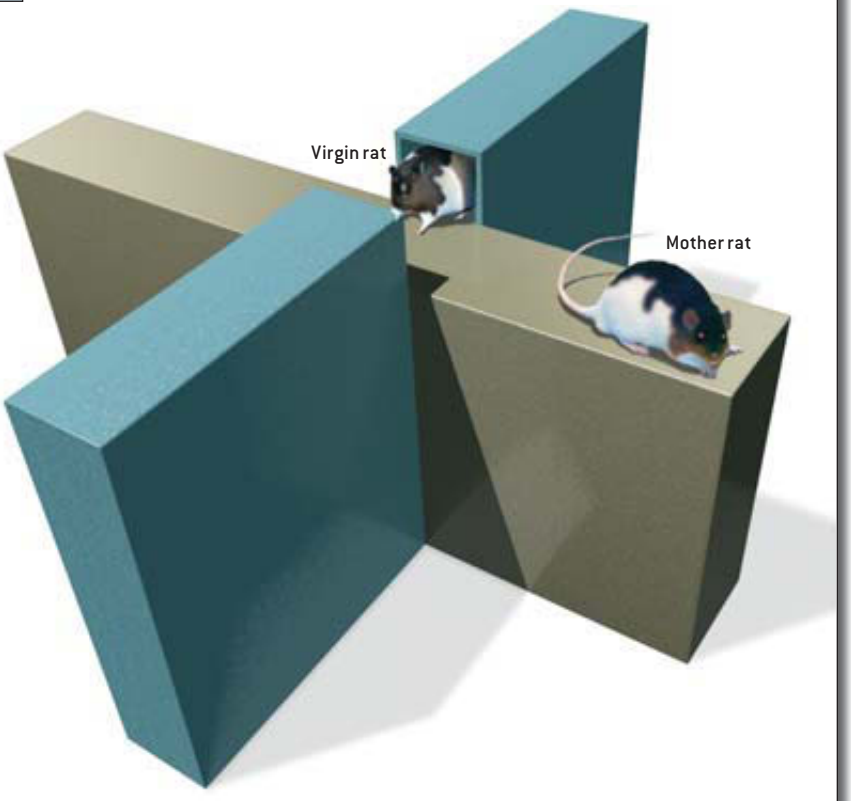
First the researchers familiarized the rats with a radial maze in which food baits were initially placed in all eight arms, then in only four, then in two, and finally in just one. Then the investigators measured how well the rats remembered which arm remained baited. Mother rats who had experienced two or more pregnancies were mostly successful in completing the maze (that is, finding the bait within three minutes) from the first day of testing; the virgin female rats did not match their success until the seventh day.

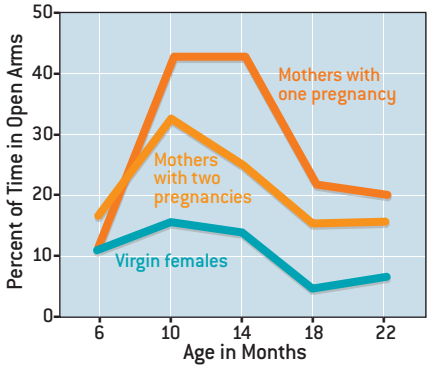




ELEVATED PLUS MAZE

In this maze, which was shaped like a plus sign and raised four feet above the floor, researchers measured how much time the rats spent in the two open arms, which rodents tend to avoid because they are elevated and exposed (unlike the maze's two closed arms). At nearly every age, the mother rats were bolder than the virgins, spending more time in the fear-evoking open arms.





SLIM FILMS

can have a negative impact on health, may have a positive effect in new mothers. By raising cortisol levels, the stress of parenting may boost attention, vigilance and sensitivity, strengthening the mother-infant bond.

Other studies have pointed to a possible long-term effect of motherhood. As part of the New England Centenarian Study, Thomas Perls and his colleagues at Boston University found that women who had been pregnant at or after the age of 40 were four times more likely to survive to 100 than women who had been pregnant earlier in life. Perls interpreted the data to suggest that women who became pregnant naturally in their 40s were probably aging at a slower pace. We would add, however, that pregnancy and the subsequent maternal experience may have enhanced the women's brains at a crucial period when the menopause-induced decline in reproductive hormones was just starting. The cognitive benefits of motherhood may have helped offset the loss of the memory-protecting hormones, leading to better neural health and increased longevity.

Is it possible that motherhood provides an edge to women as they compete with others for limited resources? Unfortunately, scientists have conducted little research comparing the learning or spatial memory abilities of human mothers and nonmothers. A 1999 study led by J. Galen Buckwalter of the University of Southern California showed that pregnant women had below-normal results on several verbal memory tests but that their scores rebounded soon after they gave birth. This study, however, was small (only 19 subjects) and found no significant changes in general intelligence. In her book *The Mommy Brain,* journalist Katherine Ellison documents many instances wherein the skills acquired through parenting might also aid women in the workplace. Successful leadership requires sensitivity to employee needs and a sustained vigilance of impending challenges and threats. But can these skills transfer from the nursery to the boardroom?

Investigators have begun to focus on one skill that is traditionally associated with motherhood: the ability to multitask. Do changes in the maternal brain allow mothers to balance competing demands—child care, work, social obligations and so on—better than nonmothers? Scientists do not yet know the answer, but studies indicate that the human brain is remarkably plastic: its structure and activity can change when a person is confronted with a challenge. Arne May and colleagues at the University of Regensburg found structural changes in the brains of young women and men who had learned how to juggle three balls in the air; the regions devoted to perception and the prediction of movement expanded after the subjects learned how to juggle, then contracted after they stopped practicing. Likewise, perhaps alterations occurring in the maternal brain enable the mother to juggle the demands of parenthood successfully.

Animal studies show that mother rats are particularly good at multitasking. Experiments in Lambert's lab have demonstrated that mother rats nearly always beat virgins in competitions that involve simultaneously monitoring sights, sounds, odors and other animals. In a race to find a preferred food (Froot Loops), rats who had experienced two or more pregnancies were the first to attain the treat 60 percent of the time. Rats who had given birth just once won the prize 33 percent of the time, compared with only 7 percent for the virgin rats.

Finally, what about the paternal brain? Do fathers who care for offspring gain any mental benefits? Studies of the common marmoset, a small Brazilian monkey, may provide some insights. Marmosets are monogamous, and both parents participate in the care of their offspring. In collaboration with Sian Evans and V. Jessica Capri of Monkey Jungle in Miami, Fla., Anne Garrett from Lambert's lab tested mother and father marmosets on a "foraging tree" in which the monkeys had to learn which containers held the most food. Parents—both mothers and fathers—outperformed nonparents in the test. This result supported earlier studies that examined a mouse species (*Peromyscus californicus*) in which the male contributes significantly to parental care. In Lambert's lab, Erica Glasper and other students found that father mice, like mothers, had an advantage in the dry-land maze; Ashley Everette and Kelly Tu showed that the fathers were quicker to investigate novel stimuli, such as Lego blocks, than their bachelor counterparts were.

Mother rats nearly always beat virgins in competitions that involve multitasking.

In summary, reproductive experience appears to promote changes in the mammalian brain that alter skills and behavior, particularly among females. For the female, the greatest challenge from an evolutionary perspective is to ensure that her genetic investment flourishes. Maternal behaviors have evolved to increase the female's chances of success. This does not mean that mothers are better than their virgin counterparts at every task; in all likelihood, only the behaviors affecting the survival of their offspring would be enhanced. Still, many benefits seem to emerge from motherhood as the maternal brain rises to the reproductive challenge placed before it. In other words, when the going gets tough, the brain gets going. SA

MORE TO EXPLORE

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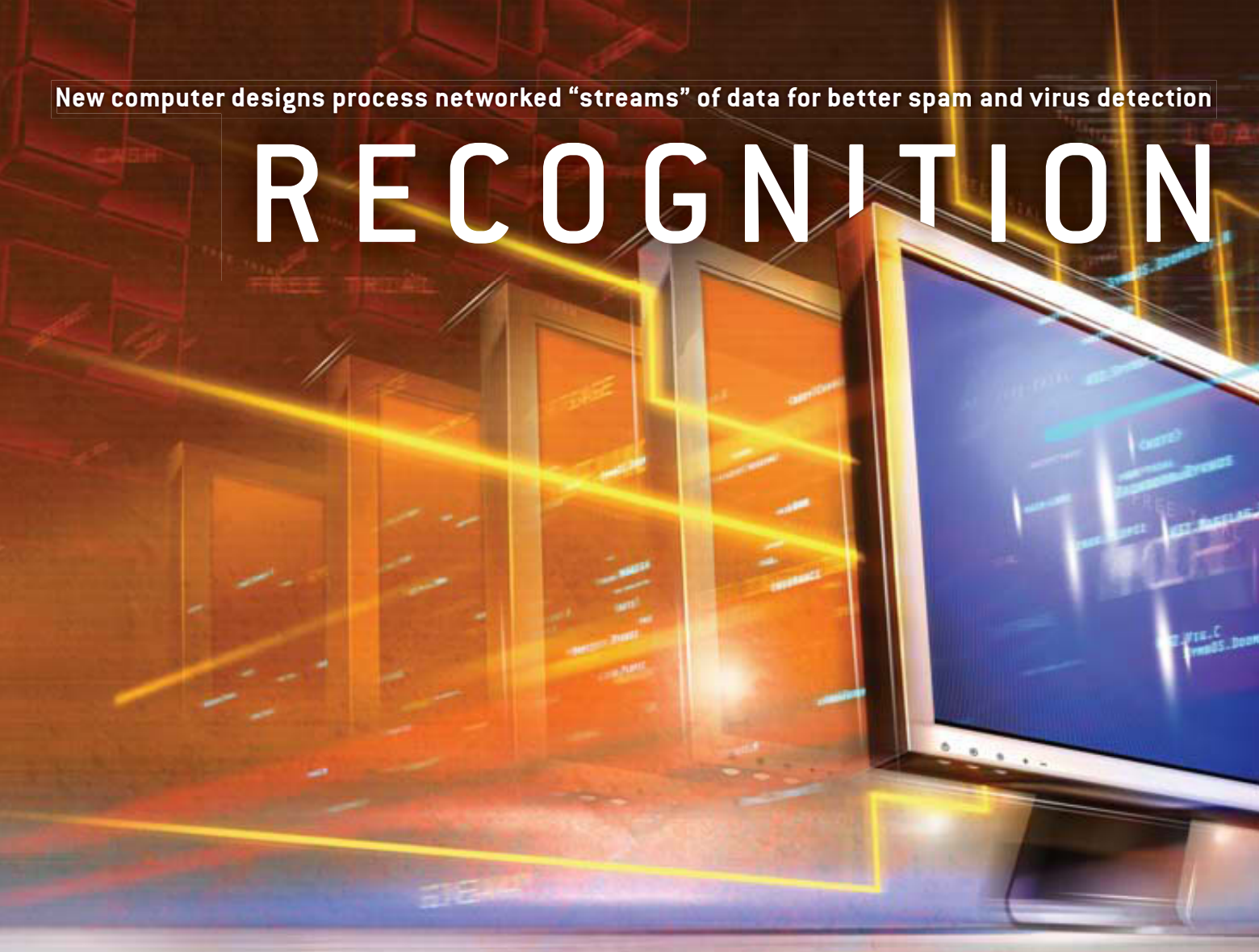
New computer designs process networked "streams" of data for better spam and virus detection

RECOGNITION



The computer industry survived for much longer than it should have on the assurance that faster processors every few years would cover a multitude of sins—the inefficiency and bloated size of application software being some of the worst transgressions. That luxury appears to be fading as power consumption has skyrocketed and the circuit boards on which the microprocessors sit threaten to transmute themselves into space heaters. Intel (where the hallowed Moore's law has reigned) and other hardware makers have responded by designing computers to run multiple processors at slower speeds.

Multiprocessors come with their own baggage, however. First, writing software that apportions computational tasks among several processors remains an unwanted burden for many programmers. Moreover, a number of the fastest-growing networking applications—from virus scanning to reading Web documents encoded in extensible markup language (XML)—do not lend themselves readily to parallel processing.

Determining whether a message contains a word that denotes spam, such as "lottery" or "Viagra," requires evaluation of consecutive parameters: Is the word "lottery" followed later in the document by the word "payout"? Distributing this task among an array of processors is asking for trouble. Instead engineers have begun to embrace a more specialized role for coprocessors. The main microprocessor retains its responsibility as chief dispatcher for key operating system functions. Meanwhile designs for processors that perform spam and virus hunting or XML processing have taken a page from graphics processing, which has long had its own specialized units. In recent years, so-called intrusion-detection accelerator engines have often taken over some of the work from increasingly overburdened central processing units (CPUs). A few academic and industrial laboratories have even begun to advance this concept one step further by accommodating all types of "streamed" information that move over a network. In essence, they have created a general-purpose stream processor that can be readily reprogrammed and can handle multiple applications, whether it be guarding a firewall or compressing files.

Pattern-Matching Engine

THE IBM ZURICH Research Laboratory has netted Nobel Prizes for the creation of the scanning tunneling microscope and high-temperature superconductivity. It has also served as a nexus for developing network hardware and software. At Hot Chips, a conference put on by the Institute of Electrical

RYAN ETTER

and Electronics Engineers that took place in August 2005 at Stanford University, Jan van Lunteren of IBM Zurich gave a presentation on a stream processor—a "pattern-matching engine" for catching viruses, spam and other bad actors—that he developed along with colleague Ton Engbersen.

IBM's processor emerged from earlier research on how to move data through the Internet's network computers, called routers. Van Lunteren, a native of the Netherlands, worked during the late 1990s at IBM Zurich on improving techniques for efficiently looking through the data tables of routers to find the forwarding information for data packets traveling through a network. Routers have to examine tens of millions of packets a second and inspect tens of thousands of entries in their databases to procure the next link on the network before sending packets out of one of multiple output ports. Van Lunteren devised a hash function for searching routing tables. This mathematical formula produces a number, or hash index, that indicates in a table lodged in the processor hardware where the relevant output port is that connects to the link that in turn will move the packet to the next router on the network.

Van Lunteren designed an algorithm based on a hash function—the Balanced Routing Table, or BaRT, search—that compresses dramatically the number of bits needed to store the routing tables in memory. BaRT, which could find its way into a number of IBM products, can handle 25 million packets a second and might eventually take care of four times that amount of data traffic.

Routing table searches require only a look at a short string of data in the initial part of the packet, the header that tells a packet where to go. With the avalanche of spam, viruses and other so-called malware, however, network processors now also have to read much more deeply inside the contents of the packet itself for telltale signs that a sender is up to no good. Similarly, reading document-encoding languages such as XML also places high demands on network hardware. The hash function that van Lunteren devised for routing became essential for IBM's stream processor.

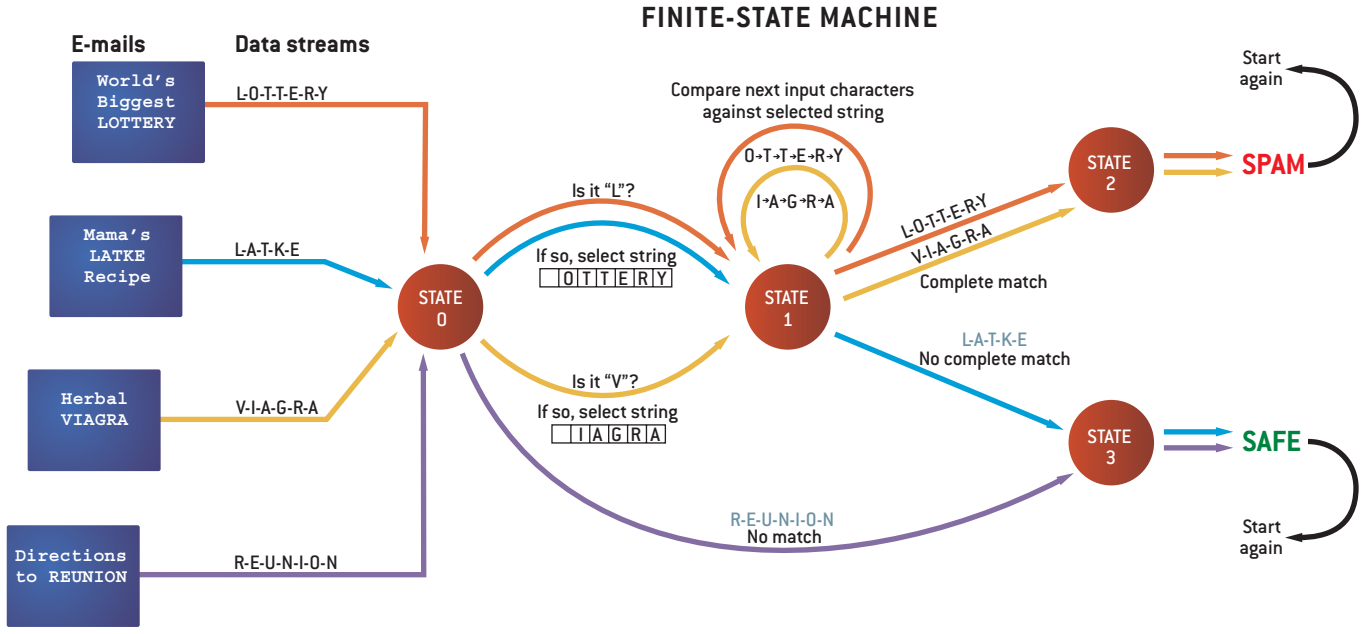
Beyond von Neumann

CONVENTIONAL PROCESSORS require multiple instructions to deal with XML codes or to look for malware, creating a bottleneck in which tens of clock cycles are needed to handle a single character. Despite many refinements, the average CPU still relies largely on an architecture initiated in the 1940s by the great mathematician John von Neumann as well as computer pioneers J. Presper Eckert and John Mauchly.

MATCHING MANY VS. COMPARING ONE BY ONE

Finite-state machines process data streams by matching each input character simultaneously against many different characters indicative of spam that are stored in memory. A conventional von Neumann machine, in contrast, must evaluate the characters stored in memory one by one.

In state 0, the finite-state machine initially compares character "L" against two others, "L" and "V," to determine whether it can be the first letter of "LOTTERY" or "VIAGRA," two stored words that denote spam. Once a match occurs, the machine switches to state 1, checking successive input characters against a stored character string, either "OTTERY" or "IAGRA." If it finds a complete match for one of the two strings, the machine moves to



The von Neumann architecture, as it is called, fetches an instruction from an address in memory and executes it, and a program counter is updated with the address of the next instruction to be performed. The cycle then repeats itself, unless explicitly told otherwise by an instruction that requires the processor to jump to another place in the program. If the processor confronts a task with any degree of complexity—for instance, evaluation of whether a particular character is legal in XML coding—it must grind through multiple instructions and clock cycles to complete the task.

Van Lunteren and Engbersen borrowed a conceptual scheme from the earliest years of computing, a finite-state machine that is rooted in the work of computing pioneer Alan M. Turing. A finite-state machine is a basic description of how any computing machine operates: how it performs operations in a discrete series of steps and assumes a finite list of internal states at any one time. On an abstract level, even the von Neumann architecture can be characterized as a finite-state machine. But the type of finite-state machine designed by van Lunteren and Engbersen distinguishes itself from a CPU that relies on the von Neumann architecture because it forgoes inclusion of a program counter.

Unlike the von Neumann namesake, van Lunteren and Engbersen's finite-state machine can evaluate multiple things simultaneously in a single cycle, instead of considering just one, as happens in the process that is controlled by the program counter. That is one of the reasons finite-state machines have been deployed for years in graphics processors and voice-recognition systems and in hardware design. Finite-state machines, however, have not lent themselves to being reprogrammed readily, thus sacrificing the flexible, general-purpose quality of the von Neumann–based CPU.

Yet the bottleneck posed by the sequential nature of conventional CPUs has begun to diminish some of the distinctions between the two types of processors. The IBM finite-state hardware, for one, can be reprogrammed with a software update if new viruses proliferate or if the XML standard changes.

The design of van Lunteren and Engbersen's processor relies on a state diagram, a type of graph that consists of circular nodes, or states, and links between nodes that represent transitions from one state to another. A subway turnstile is a form of finite-state machine. Its initial node is a state called "locked." Insertion of a coin is indicated in the graph by a line that traces a "transition" from the current state to an "unlocked" node. Passing through the turnstile is another line that marks a transition back to the locked node.

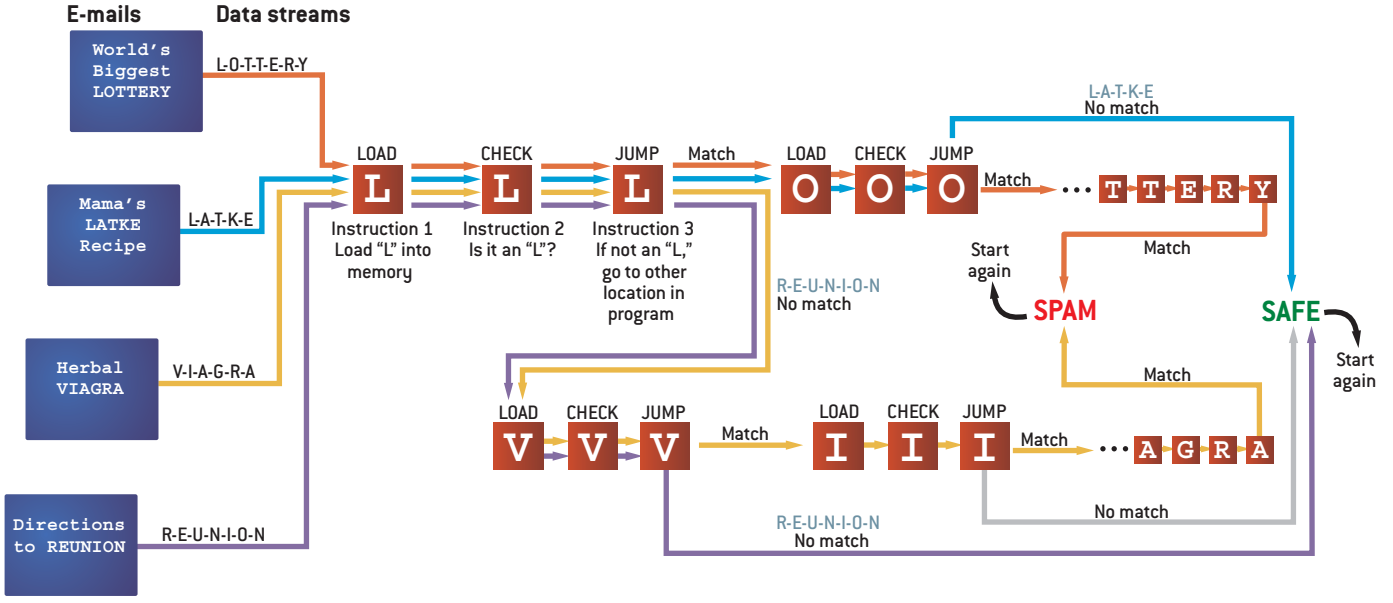
In IBM's finite-state machine, a given state may link more than two nodes. In an actual stream-processing application, a node might have links to many others, and each link would be assessed at the same time before a decision is made to move to the next state in the diagram. In looking for spam in an incoming stream of data, the processor would read from

MELISSA THOMAS

state 2, indicating detection of a word found in spam messages. If no match occurs, as with the word "LATKE," the hardware shifts to state 3, suggesting that no spam is lurking. If the initial input letter does not jibe with words in memory, such as the "R" in "REUNION," the machine proceeds directly from state 0 to state 3.

In the typical von Neumann architecture, each input character can be tested only against one stored character at a time. Moreover, three and sometimes more instructions, and thus multiple processor cycles, are required for each character—one to load the character, another to check whether it is the desired character, and the third to jump to another location in the program if it is not the character being sought.

VON NEUMANN ARCHITECTURE



memory the word "lottery." It could evaluate not only whether the character "o" followed an "l" in an arriving string of characters but also whether a spam message may have inserted an underscore character—"l_o"—to try to fool a spam blocker. As part of the same search, executed in a single processor cycle, it could look for the "l" in "lottery" as well as for the "V" in "Viagra" and many other characters in its memory. In a conventional processor, each of those steps would have to be executed sequentially [*see box on these two pages*].

At least in the laboratory, applying a finite-state machine to streaming applications improves performance substantially. Van Lunteren reported at Hot Chips that IBM's finite-state machine can process characters at up to 20 gigabits a second for viruses, spam and other applications, 10 to 100 times faster than a conventional processor. A key enabling tool was BaRT. In many finite-state machines, storing rules for carrying out the transitions in a state diagram consumes a large amount of memory. IBM can store in its finite-state machine hardware up to 25,000 characters in less than 100 kilobytes of memory, as little as $^{1}/_{500}$ the requirements for some other finite-state machines. The efficiency of the algorithm devised originally for routing tables allows for a linear increase in memory needs: if the number of transition rules rises from one to 10, memory demands go up by a comparable factor. In many other finite-state machines, a similar increment would require 100 times more space.

IBM already offers the finite-state machine technology for custom applications—licensed through its engineering and technology services group—and it is evaluating the processor for a number of products. IBM is not alone in adopting this idea. Universities and other companies have also developed programmable finite-state machines. John Lockwood, a professor at Washington University in St. Louis, co-founded a company called Global Velocity to commercialize such a processor. Van Lunteren says that the IBM design is special because of its ability to handle a wide range of applications, becoming a general-purpose processor for any stream-processing application. The sophistication of these coprocessors may continue to evolve as critical tasks such as stream processing stray further and further from the control of the central processing unit. This work ensures that the legacy of Turing and von Neumann will coexist a few centimeters away on the same circuit board. SA

MORE TO EXPLORE

The Alphabets, Words and Languages of Finite State Machines. This explanation of how finite-state machines work can be accessed at **www.c3.lanl.gov/mega-math/workbk/machine/mabkgd.html**

Global Velocity is a company that has developed similar processing concepts to the IBM team: **www.globalvelocity.com/index.html**

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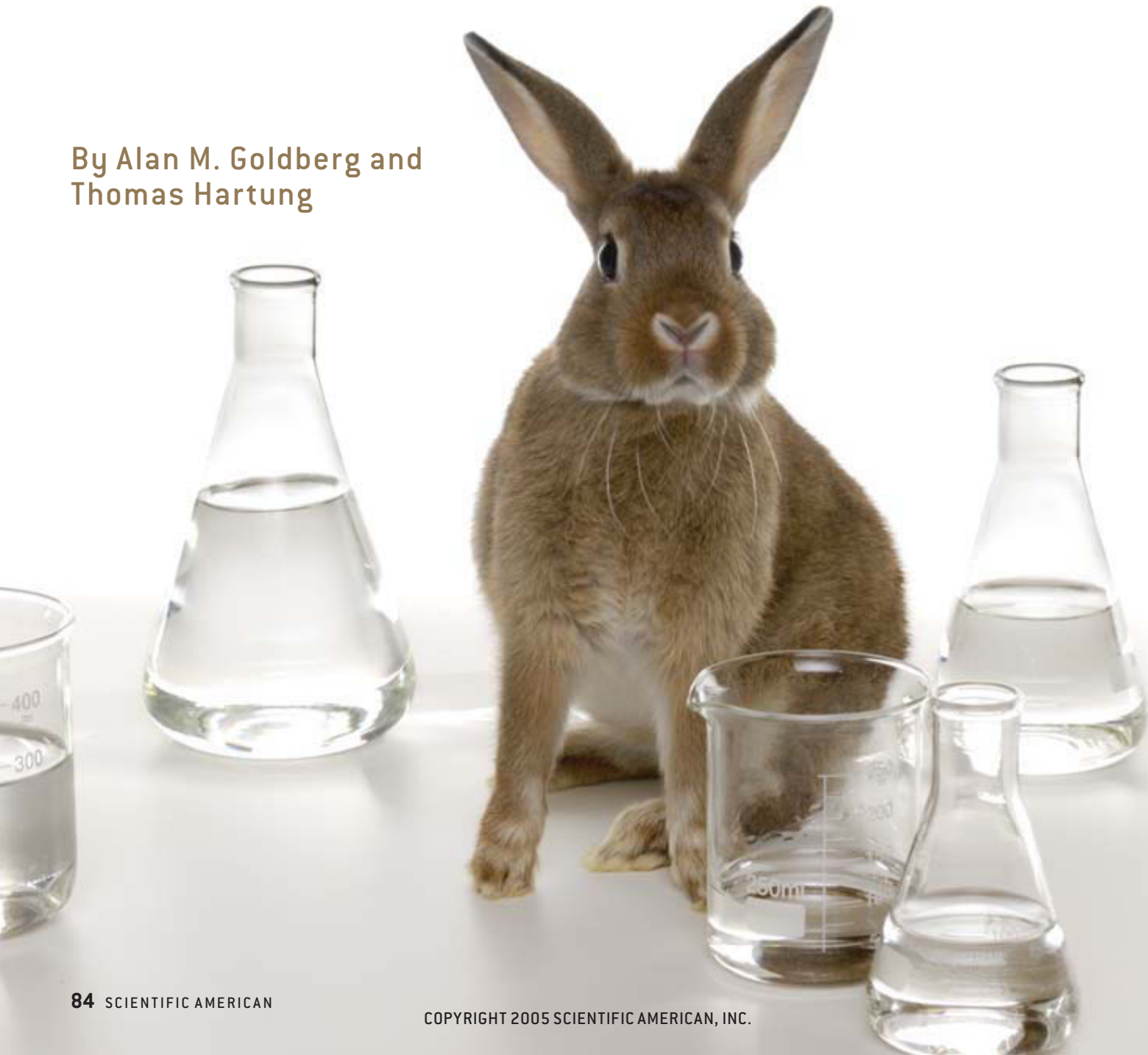
PROTECTING MORE THAN ANIMALS

Reducing animal suffering often has the unexpected benefit of yielding more **RIGOROUS SAFETY TESTS**

By Alan M. Goldberg and Thomas Hartung



FOR SEVERAL MONTHS IN 1999, A FLUFFY SEVEN-FOOT BUNNY WITH FLOPPY EARS and large, doleful eyes chased presidential candidate Al Gore around the campaign trail. Gore's crime: as vice president, he had initiated a chemical toxicity testing program that would cause the suffering or death of close to a million animals. To most observers, though, such a testing program seemed long overdue.

Two years earlier the group now called Environmental Defense had pointed out that adequate information exists on the safety of perhaps only a fourth of 100,000 commonly used chemicals, and both the Environmental Protection Agency and the trade group now known as the American Chemistry Council had come to agree. Gore had brought together all the interested parties—environmental activists, regulators and manufacturers—to initiate a program for performing minimal safety tests on the 2,800 chemicals that the U.S. produced or imported at more than one million pounds a year. A public Web site would post the information obtained.

The giant rabbit did emphasize an underlying truth: millions of animals are sacrificed annually in routine toxicity tests, and future programs could drastically increase these numbers. The EPA has drawn up a priority list of some 80,000 chemicals on which basic safety information must be gathered; in addition, its ambitious Children's Health Initiative seeks to examine subtle phenomena such as the long-term effects of exposing a fetus to a chemical. Another EPA effort focuses on the neurological consequences of lead, mercury and similar poisons for reproduction and development. Across the Atlantic, the program for Registration, Evaluation and Authorization of Chemicals (REACH) will evaluate the safety

A small community of scientists scattered around the world has for decades been seeking ways to resolve the conflict between SAFETY AND HUMANENESS.

of 30,000 chemicals produced or traded in Europe at more than one metric ton a year. In 2001 the U.K.'s Medical Research Council calculated that this program alone will require $11.5 billion, 40 years and more than 13 million animals. All in all, current programs envisage using hundreds of millions of animals and tens of billions of dollars just to determine the safety of existing substances. And every year industry adds thousands of chemicals to the inventory.

The two of us belong to a small community of scientists scattered around the world, in industry, academia and government, that has for decades been seeking ways to resolve the conflict between safety and humaneness. Gore's program offered us a chance to demonstrate our wares. At a request from Environmental Defense, one of us (Goldberg) brought together researchers from Johns Hopkins University, Carnegie Mellon University and the University of Pittsburgh to examine how the program could achieve its goals with fewer animals.

The program was to collect a minimal amount of information, called the Screening Information Data Set, which the Organization for Economic Cooperation and Development (OECD) recommends for evaluating the potential hazard from a chemical. This battery of tests typically requires 430 animals for each chemical. Fortunately, the OECD, which seeks to harmonize scientific and other rules of 30 industrial countries, including the U.S., accepts certain innovative protocols for the data-set battery that require fewer animals. Using the organization's guidelines and also redesigning a few protocols so that experimenters can extract multiple results from single tests, we demonstrated that the number of animals could be reduced by 80 percent—to 86 animals—with no loss of information.

Long maligned by animal activists as being an apology for animal research and derided by many scientists as being motivated by soppy sentiment, the science of alternatives to animal testing has nonetheless found a footing on the narrow ridge where animal welfare meets rigorous science. The field is changing the ways in which chemical and biological products are developed and tested for safety.

Overview/*The New Toxicology*

- Safety testing of household, agricultural and other chemicals as well as medical products traditionally uses many millions of animals every year in protocols that are often painful.
- New methods involving cell and tissue cultures, noninvasive imaging, or plain statistics are greatly reducing the need for, and the suffering involved in, animal testing.
- The new toxicology is more rigorously based on scientific evidence and can save time and money.

Reduction, Refinement, Replacement

LEGAL REQUIREMENTS for testing vary widely around the world. In the European Union, for instance, since 2003 no cosmetic can be sold if the finished product or any ingredients were tested on animals, provided that validated alternatives exist. Complete bans on animal testing of cosmetic ingredients should be in place by 2009. In contrast, the Food and Drug Administration, which regulates cosmetics in the U.S., requires only that certain safety data be available should the need arise after marketing. Over time, the FDA has developed guidelines for dealing with complaints about safety; these require, in particular, the controversial Draize eye test. The protocol asks for placing the substance in the eyes of albino rabbits to measure the reaction induced.

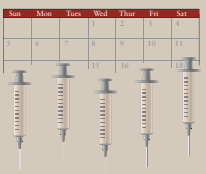
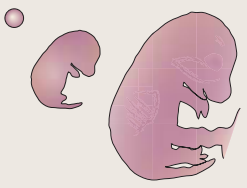
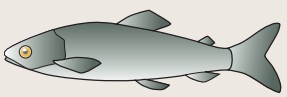
Both the EPA and its European counterparts, on the other hand, specify the methodology for evaluating agricultural chemicals. The testing of a single pesticide consumes a minimum of two years and approximately 10,000 animals of several species. Scientists first decide whether or not the chemical is absorbed through the skin, whether it can be inhaled, or whether it might leave a residue on food crops and thereby be ingested. For each route, various questions—such as the period for which someone might be exposed, how much of the substance he or she might absorb, and how it might be distributed in the body—need to be answered for individuals of different ages, including fetuses.

If the product does not enter the bloodstream, investigators need worry only about the consequences of topical application. If the compound is absorbed in the bloodstream, however, then its effects and those of all its metabolites on many different organs must be checked. In the standard procedure, researchers feed the substance to rats, mice, dogs or other mammals throughout their life span and look for impaired functioning of various organs or for cancers and other ailments. They also observe a set of offspring of these animals throughout their lives. More targeted tests may be incorporated into this regimen or done separately.

In reality, representatives of nine multinational companies revealed to Goldberg that all the firms use petri dish or nonmammalian tests, usually involving fish or worms, to decide if a chemical is safe enough to produce. Only then do they perform the life-span feeding studies—to satisfy the company's lawyers and regulatory agencies. The table on the opposite page lists the complete battery of animal tests commonly

CARY WOLINSKY (*preceding pages*)

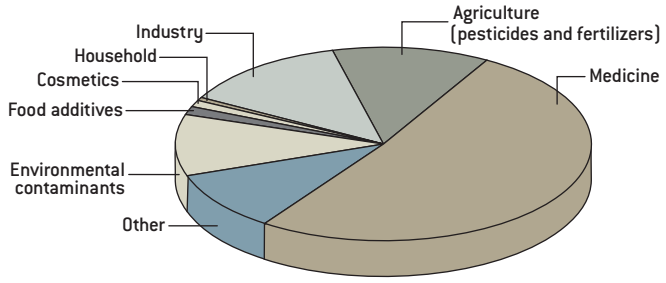
A FLEDGLING SCIENCE MATURES

	TRADITIONAL SAFETY TESTS	ALTERNATIVES
	**TOXICOKINETICS** measures absorption, distribution, metabolism and excretion of chemicals. A chemical is fed to animals, from which blood, urine and feces are collected; the animals are then killed to locate 100 percent of the parent compound and its metabolites in organ systems	Industry has partly replaced the tests with in vitro and in silico methods. The OECD has approved an in vitro approach for skin absorption
	**TOPICAL TOXICOLOGY** evaluates the effects of chemicals on skin, eyes and, occasionally, oral and vaginal mucous membranes. A compound is placed on the membrane, which is examined for reddening, blistering or corrosion	The OECD has accepted alternatives for corrosion, phototoxicity and sensitization; ECVAM validation studies are in progress for skin and eye irritation, allergic reactions and photogenotoxicity
	**ACUTE SYSTEMIC TOXICITY** determines the effects of ingesting a substance one or more times within 24 hours, with the consequences measured within 14 days. The classic LD_{50} involves administering different doses of the substance to six or seven cohorts of animals to determine the average amount needed to kill half a cohort. It typically requires 140 animals	The OECD has approved a tiered testing strategy requiring an average of 16 animals; the ECVAM is developing a strategy that uses no animals. The ECVAM and ICCVAM are jointly examining an in vitro approach to determine a starting dose for LD_{50} studies that could reduce animal numbers to six per chemical
	**REPEAT DOSE/CHRONIC TOXICITY** tests measure the failure of an organ system to perform its normal function under the continuous influence of a chemical. Many animal methods are in use; they involve administering multiple doses over time to the organism and evaluating the outcome	No tests have been formally validated. Approaches in use include measuring specific cell functions and gene array outcomes as well as noninvasive animal studies, including MRI, PET scans and biophotonics
	**DEVELOPMENTAL/REPRODUCTIVE TOXICOLOGY** measures the effects of chemical exposure on sperm and eggs, fetal development, and the ability to reproduce, as well as any delayed effects after pubescence. Female animals are treated with a compound, and reproductive outcome is measured. Similar tests on males measure male reproductive health	Industry uses noninvasive whole-animal studies and several in vitro approaches; the ECVAM has validated three embryo toxicity methods; other methods are in prevalidation stages
	**CARCINOGENESIS/MUTAGENESIS** studies measure the potential for a compound to produce tumors. In theory, animals are exposed to the compound throughout their lifetimes, and resulting tumors are evaluated; in fact, animals studies are rare because of the expense	Many laboratories use the Ames Bacterial Mutagenesis Assay and other in vitro tests, which monitor mutation in a bacterium or cell; several ECVAM validation studies are under way
	**ECOTOXICOLOGY** measures the environmental effects of chemicals. Being relatively recent, these studies began by using "alternative" targets, such as fish, algae and water fleas	Germany and Sweden have accepted a fish egg test for effluents; the ECVAM has validated a strategy to reduce fish use by 60 percent
	**BIOLOGICALS TESTING** measures the quality of vaccines and other drugs of biological origin and checks for contamination by fever-producing bacterial toxins (pyrogens). Usually a vaccine or drug is administered to a group of animals, and the target disease is introduced to this group and to another, unprotected, group to compare the resultant illness	For pyrogens, one blood test (LAL) is in use, and new cytokine assays have undergone validation. The ECVAM has validated statistical techniques for reducing animal numbers and refinements for reducing suffering during vaccine testing

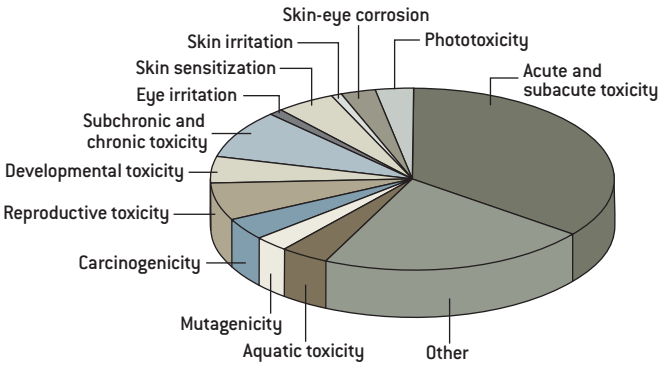
OECD = Organization for Economic Cooperation and Development
ECVAM = European Center for the Validation of Alternative Methods
ICCVAM = Interagency Coordinating Committee on the Validation of Alternative Methods

EMILY COOPER

Use of Animals in Testing Products



Use of Animals in Testing Chemicals



NUMBER OF ANIMALS required for various testing purposes ranges widely. Roughly half the animals in product testing are used for controlling the quality of medical products such as vaccines (*top*). Estimating the toxicity of a chemical (*bottom*) requires an array of highly specific tests, of which acute toxicity—resulting from the accidental ingestion of a large quantity of a substance—takes up the highest proportion of animals. Data in both charts pertain to the 15 member countries of the European Commission in 2002, which used 10.7 million animals that year. No such breakdowns are available for the U.S.

required for evaluating the safety of a chemical or drug. Government regulators overwhelmingly request the traditional animal tests partly because some of the best alternatives are industry secrets but also because they trust the animal tests, which have, by and large, protected the public in the past.

Only recently are regulators becoming more open to considering alternatives. The concept dates back to 1959, when William Russell and Rex Burch of the Universities Federation of Animal Welfare in the U.K. decreed the "three Rs"—reduction, refinement and replacement—as means of reducing the animal suffering inherent in many studies. Alternatives can no longer be cleanly assigned to one or another of the three Rs, but they remain useful guides.

Reduction means designing experiments so that they yield adequate information with the least number of animals. For instance, tests of acute systemic toxicity measure the consequences, as observed within 14 days, of ingesting a substance one or more times within 24 hours. The most widely accepted measure of acute toxicity is the lethal dose 50 percent, or LD_{50}: the amount of a substance required to kill half the test animals. To determine the lethal dose, experimenters formerly injected or fed a specific amount of the chemical to each animal in a group of 10 males and 10 females. Using six or seven such groups, each receiving a different dose, they would count the dead.

Experimenters gradually came to see this test (forgive the pun) as overkill and sought more streamlined protocols. Since 1989 statistical sophistication has allowed the LD_{50} to be obtained with 45 animals, and now the OECD accepts a protocol that measures the lethal dose with, on average, 16 animals. A recently completed transatlantic study promises to further reduce this number to about six animals per substance.

In another example, noninvasive imaging techniques familiar from clinical medicine—x-rays, nuclear magnetic resonance and positron-emission tomography—can reveal distinctions among a vast array of normal and altered states of animal organs. These techniques allow researchers to follow a single animal through the course of the experiment as an alternative to the traditional procedure: starting with a set of animals and killing one at each stage to determine the status of, say, its liver. Such imaging allows better control of the data and also reduces animal use in such experiments by up to 80 percent.

A more futuristic kind of imaging, biophotonics, developed by Christopher H. Contag and Pamela R. Contag of Stanford University, falls more neatly into the realm of refinement: designing experiments so that they involve less animal suffering. A researcher adds the gene for the *luciferase* enzyme to, for example, a cancerous cell and inserts the cell into an animal. The enzyme confers the ability to produce "firefly" light, ensuring that the cancer cell and all its daughters glow. Easily measured by specialized instrumentation, the photons allow researchers to monitor the cancerous growth under the influence of various chemical and pharmaceutical agents—long before the animal has developed a palpable tumor. The procedure truly eliminates pain and distress and can be adapted to study a wide variety of diseases in their incipient stages.

Another valuable refinement technique, especially useful in vaccine testing, involves defining a "humane end point," so that a painful study ends as soon as the relevant data have been collected. For instance, if an animal's body temperature drops

THE AUTHORS

ALAN M. GOLDBERG and *THOMAS HARTUNG* are toxicologists who were moved by the animal suffering they witnessed to seek alternatives. Goldberg has a doctorate in pharmacology from the University of Minnesota and is professor of toxicology at Johns Hopkins University, where he directs the Center for Alternatives to Animal Testing. He edits the book series Alternative Methods in Toxicology, has served on numerous government and other panels and has received several awards, most recently from the Society of Toxicology. Hartung has a doctorate in biochemical pharmacology from the University of Constance in Germany and an M.D. in toxicology from Tübingen University. He served as chief executive officer of the Steinbeis Technology Transfer Center and currently heads the European Center for the Validation of Alternative Methods. Goldberg has consulting arrangements with Xenogen Corporation in Alameda, Calif.; Hartung's alternative pyrogen assay is licensed by a nonprofit group to Charles River Laboratories in Massachusetts.

EMILY COOPER; SOURCE: EUROPEAN COMMISSION JOINT RESEARCH CENTER

below a certain point, it never recovers; the test can then be halted with no loss of data to spare the creature a long-drawn-out death. If an animal vaccinated against rabies and infected with the virus begins to circle, that is a sure sign that the vaccine has failed, and the animal can be humanely killed, relieving it of hours of agony. Even better, technicians testing the efficacy of many vaccines can these days just check the level of antibodies after infecting it, instead of waiting for the animal to develop overt signs of disease. Refinement also includes using medications and anesthetics to reduce pain and distress.

Yet a further class of refinement substitutes species lower in the evolutionary ladder, in the belief that they suffer less. During the past few years, the zebra fish and the nematode *Caenorhabditis elegans* have become popular for observing the development of the nervous system under the influence of chemicals. In both these species, scientists have established the function of all essential genes: if a chemical turns a gene on or off, researchers know how the change will affect protein production and cellular metabolism. And simply washing a chemical over a gene array—a one- by two-inch chip containing, say, all 9,000 relevant genes of the zebra fish—allows researchers to see which genes the substance activates.

Most recently, some firms have begun to produce chips of human genes, including those believed to control the cellular response to toxicity. This technology, which will reach its pinnacle in the future—because interpreting the chip's message still remains a great challenge—exemplifies the most glamorous R, replacement.

The Third R

REPLACEMENT MEANS entirely eliminating the use of whole animals in testing. Most such alternatives owe their existence to society's tremendous progress toward cheap, fast and efficient technologies, rather than to a quest for humaneness per se. For instance, most analyses of hormones, such as the pregnancy test, which once involved long-drawn-out methods on live animals, are now accomplished by alternative (chemical or immunological) means.

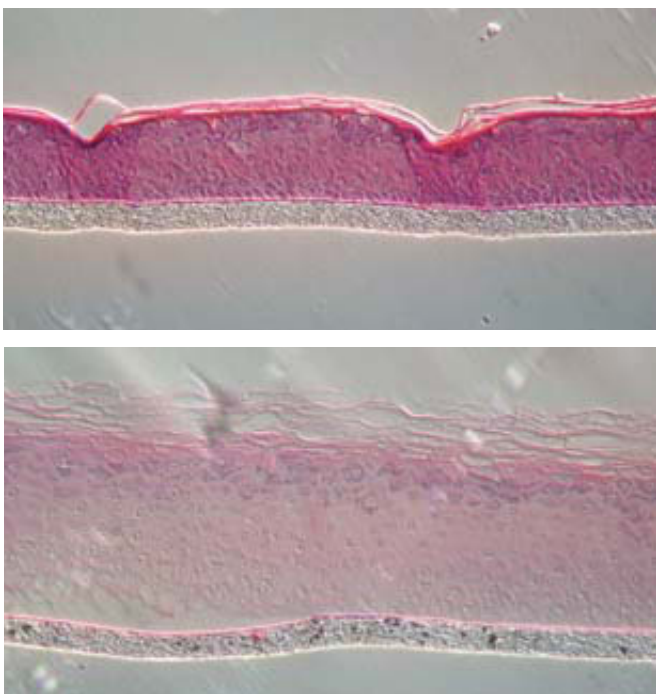
An early example of replacement was the serendipitous discovery in the 1970s of an alternative to the pyrogen test by Henry Wagner of Johns Hopkins University. This procedure checked for the presence of fever-producing bacterial contaminants by injecting a substance into rabbits and taking their body temperature 24 hours later. Wagner was developing very short-lived radioisotopes as means of diagnostic imaging in humans, and he needed to ensure that they were free of bacterial toxins—but the radioisotopes would be inactive by the time the rabbit test provided results. Wagner knew that Frederick Bang, also at Johns Hopkins, had shown that the hemolymph (essentially, the blood) of the horseshoe crab reacted to the most important bacterial toxins in a predictable and measurable manner. The FDA quickly gave permission to use this "*Limulus* amebocyte lysate," or LAL, test for detecting pyrogens.

More recently, Albrecht Wendel of the University of Constance in Germany and one of us (Hartung) have demonstrated that bacterial toxins can be detected by their property of provoking leukocytes in human blood to release proteins called cytokines, some of which signal the brain to induce a fever. Thus, simply checking for cytokines in human blood reveals the presence of all relevant toxins, overcoming several limitations of the LAL test.

Finding certain replacements—such as for the Draize test, which is extremely painful for the rabbits, because the eye is such a sensitive organ—has, however, required a focus on animal welfare. A decade ago some researchers began to perform the test on fresh eyeballs from slaughterhouses instead of on living rabbits. Although scarcely an aesthetic improvement, the alternative eliminated pain as well as the use of extra animals. In Germany, the fine membrane separating the yolk of a hen's egg from the albumen often serves as a substitute for the cornea in these tests.

In the 1980s the Johns Hopkins Center for Alternatives to Animal Testing, which Goldberg directs, funded research on how different chemicals affect two-dimensional tissue cultures of human corneal cells. (An earlier bunny-suit campaign, against the Draize eye test, had led the Cosmetic, Toiletry, and Fragrance Association to found the center, which is part of the Bloomberg School of Public Health.) Based in part on these studies, several companies have now produced three-dimensional tissues that very accurately mimic the outer surfaces of the human eye—allowing experimenters to check not only for irritation but also for subtle structural changes.

Indeed, researchers can nowadays grow a large variety of human cells from the skin, lung, eye, muscle, mucous membranes and other organs. Even more exciting is reconstituted



SYNTHETIC SKIN can replace the shaved back of live rabbits in tests of corrosivity of different substances. This commercial "skin" has been subjected to water (*top*) and an alkali (*bottom*) for three minutes.

MATTEK

The ultimate replacements may be "in silico"—COMPUTER MODELS of interacting organ systems that trace the effects of drugs.

tissue—three-dimensional constructions of specialized cells cultivated on a support system. In addition to the eye, these artificial tissues have been developed for the skin, lung, gastrointestinal tract, and linings of the mouth and vagina. Widely adopted in industry, they have replaced animals for a vast array of tests. (A need remains, however, for a practical three-dimensional culture for organs such as the liver.)

Most important, cell and tissue cultures enable researchers to see the biological mechanisms by which a chemical acts in a way that was never possible with whole animals. Investigators can now model in vitro the series of biochemical processes initiated by a chemical. In the future, such studies will allow scientists to predict the functional consequences—alterations of genes, changes to cell growth, and so on—of exposing a cell in the human body to a chemical. Even more, multiple tissues cultured within a single chamber, a system recently developed by AP Research in Baltimore, can mimic such complex interactions as the transformation of one chemical into another by the metabolic activity of an organ, which in turn affects other organs. These developments, albeit in their infancy, have the potential to eliminate animals in studies of toxicodynamics: the chain of events by which a chemical is distributed, metabolized and excreted.

Perhaps the ultimate replacements will be not so much in vitro as "in silico": the pharmaceutical industry is beginning to use computer models of interacting organ systems to study the effects of drugs. Charles DeLisi of Boston University and others are seeking backers for the Virtual Human Project, a futuristic venture in distributed computing similar in scale to the Human Genome Project. The virtual human may one day simulate the human response to biological, physical and chemical stresses, obviating the need for animal studies.

BLOOD LEUKOCYTE releases proteins called cytokines in the presence of fever-producing bacteria. Simply testing for cytokines in a patient's blood allows such "pyrogenic" bacteria to be detected, replacing a rabbit test and an older alternative.

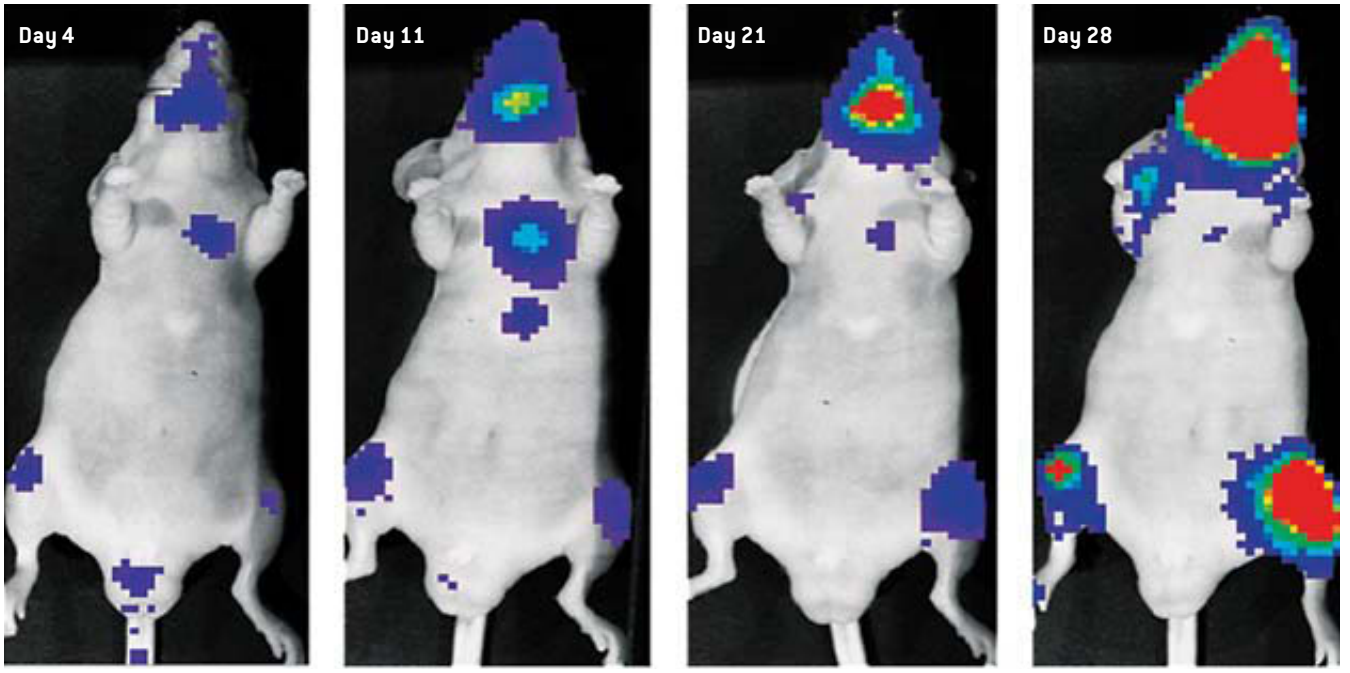
Convincing Skeptics

AT PRESENT, HOWEVER, the discovery of new alternatives remains a fitful and uncertain process. Finding funds for research specifically directed at alternatives has been difficult, at least in the U.S. The National Toxicology Program, which coordinates all toxicological testing programs within the federal government, together with the National Institutes of Environmental Health Sciences, provides the bulk of government funding for alternatives. Although the U.S. government's agencies are interested in humane science, they have spent less than $10 million over the past decade on validating alternatives for regulatory use. In contrast, the E.U. has spent more than $300 million in the same period on alternative methods and validation studies, and its member governments have individually invested millions—Germany alone exceeding $100 million—in the search for alternatives. (Both the U.S. and the E.U. do, however, spend many millions of dollars on research that might one day lead to alternatives.)

The efficacy of any new alternative must be proved before regulatory agencies can accept it. In the U.S., the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), made up of representatives of 15 federal agencies, appoints panels of independent experts to review the available literature, including protocols submitted by companies, to assess the validity of a test. Depending on its regulatory mandate, each agency then independently decides whether or not to accept a test. Since its inception in 1997, ICCVAM has evaluated 16 alternative methods, six of which have been adopted by regulatory authorities, whereas the others are undergoing recommended improvements. In the past, a proved test could take a decade or more to become widely adopted, but since ICCVAM's inception this delay is much reduced.

As initiated in Europe, validation of an alternative is similar in concept and complexity to clinical trials. Just as clinical trials are "evidence based" and need to rigorously demonstrate that a drug is effective, validation trials must also prove that an alternative test does the job it is designed for. The concept of scientific validation gained broad international consensus at an OECD workshop in Solna, Sweden, in 1996. In accordance with the so-called Solna Principles, the European Center for the Validation of Alternative Methods (ECVAM), and also

EYE OF SCIENCE, REUTLINGEN, GERMANY; COURTESY OF THOMAS HARTUNG



BIOPHOTONICS, the use of photons of light to detect and measure biological changes in living animals, demonstrates the progress of cancer in a mouse. The cancer is rendered visible (*colored areas*) long before the animal has developed a palpable tumor (*not shown*). Such techniques enable researchers to examine the effects of experimental drugs in a humane way.

ICCVAM, undertakes a set of "prevalidation" studies to assess the potential of an alternative and to iron out glitches with its protocol. In Europe, if the test passes, ECVAM then usually lines up several laboratories in different countries, each of which subjects a large spectrum of coded substances to the alternative test. Often the laboratories simultaneously evaluate many potential alternatives to a given animal test. A body of about 35 scientists representing the 25 member countries, the European Commission, academic associations, industry, and animal welfare groups judges the results of the trial; ICCVAM is present as an observer. If an alternative proves able to reliably gauge the relevant property of the substances, and its results are consistent and reproducible across laboratories, the committee formally pronounces it valid.

In a recent validation trial, for instance, 10 laboratories spent three years studying six alternatives for the pyrogen test, checking their ability to ferret out the fever-producing substances from 190 unmarked samples. Five tests made it to the review stage, now under way. Since its inception in 1991, ECVAM has completely validated 17 alternatives; nine more are in the last stage of peer review; another 25 are undergoing final trials or analysis. By law, an alternative must be used in Europe once it is validated, but in practice delays of several years are still common. As European regulators become more accustomed to the new methods, however, they are quicker to accept them.

The replacement effort faced a major setback in the early 1990s, when six large validation trials for alternatives to the Draize eye test failed. The outcome was puzzling, since some of the alternatives were being used in the cosmetics industry without apparent problems. Having reviewed other data, we now understand why the alternatives failed: their results were being compared with those of the Draize test itself, which, it turns out, yields many false positives. ICCVAM and ECVAM are now jointly reviewing existing information on the Draize test and its alternatives. The study will form the basis of a statement of validity or, if necessary, another validation trial of Draize alternatives, and this time we are reasonably confident of success.

Gore's bunny once collapsed from the heat and had to be revived by the candidate's campaign aides. The incident provides an apt metaphor: the animals' supposed enemies coming to the rescue. Alternatives devised by science can, if fully implemented, greatly reduce animal use. Academic and industry estimates agree, for instance, that existing alternatives can cut the number of animals needed for the European REACH program by 70 percent, and a similar figure most likely prevails for the EPA's priority list. More prosaically, alternatives can save millions and possibly billions of dollars and cut years, if not decades, off testing schedules—while yielding more rigorous and pertinent data. The new science can then better protect not only the creatures it was designed to help but also the rest of us. SA

MORE TO EXPLORE

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Altweb: **Alternatives to Animal Testing: http://altweb.jhsph.edu**

European Center for the Validation of Alternative Methods: **http://ecvam.jrc.cec.eu.int/index.htm**

XENOGEN

CONTINUOUSLY VARIABLE TRANSMISSION

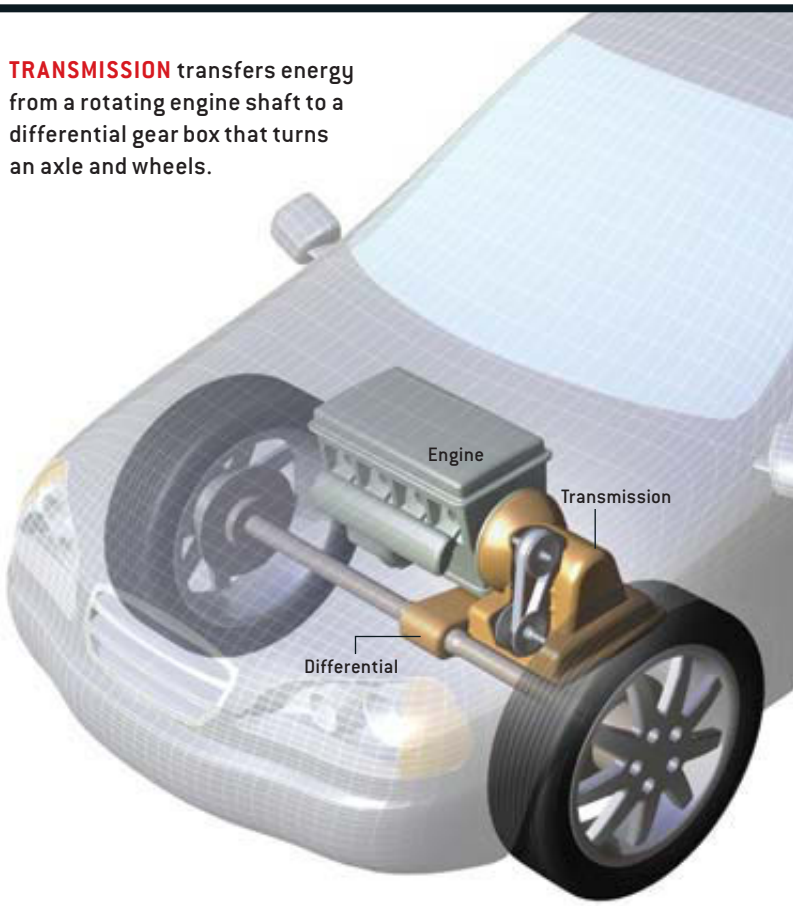
No More Gears

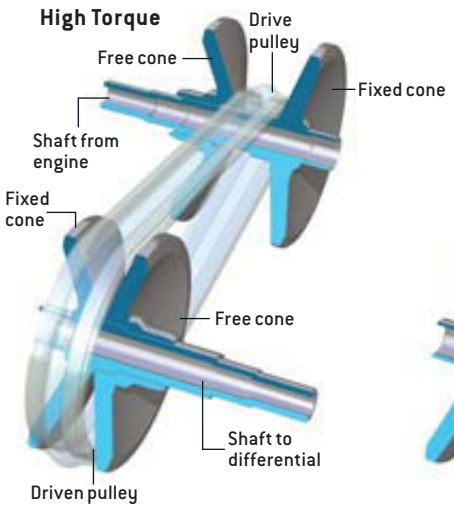
A car's engine can rev wildly, but the vehicle will not move until the driver puts it in gear. For a century, a box of gears called the transmission has transferred engine power to the wheels. In manual designs, the driver shifts the gears to deliver different torques. In automatics, hydraulics or servomotors do the work. A radically different scheme known as continuously variable transmission (CVT) has lurked in the background for 50 years, however, and has recently made inroads in small and midsize cars and in hybrid vehicles.

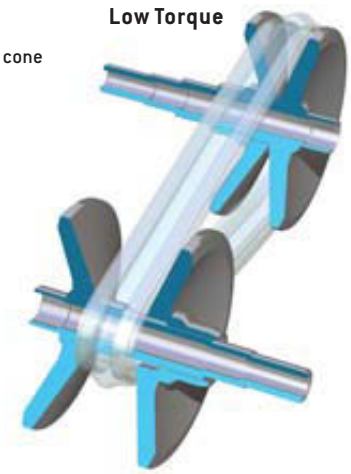
Several CVT configurations exist, all of which replace gears entirely. The dominant scheme utilizes two pairs of movable cones, under computer control, connected by a tough steel belt [*see illustrations*]. Instead of a fixed number of gear ratios provided by a typical five-speed manual or four-speed automatic, CVTs offer continuous change in the degree of torque transfer—the equivalent of an infinite number of gear ratios. As the car accelerates, the driver feels no lurch because no step occurs from one ratio to the next. The variable transfer speed also allows the engine to operate near its optimum output range over a variety of wheel speeds, improving fuel efficiency. The gearstick has positions for park, reverse, neutral and drive. That's it.

CVTs have caught on in part because of improvements in the belt and cone materials. "It has required a lot of know-how," says Hendrik De Leeuw, CVT product manager at supplier Bosch in Farmington Hills, Mich. "The efficiency gains occur primarily at lower vehicle speeds and during acceleration and deceleration," notes John German, energy expert at American Honda Motor in Ann Arbor. When cruising at higher speeds, he observes, "there is a fair amount of friction loss in the belt itself." Some skeptics also claim belts struggle to accelerate big cars quickly. But De Leeuw says CVTs will continue to move into larger cars; Nissan is using them in its Murano sports wagon. Still, the hottest market is in Asia, where most people drive small cars in traffic-congested areas. Other automakers remain dubious, at least for the U.S. market. In 2004 General Motors ended its brief use of CVTs in the Saturn Vue in favor of new, six-speed automatic transmissions that offer smaller gear steps and energy losses, states spokesman Nick Richards. —*Mark Fischetti*

TRANSMISSION transfers energy from a rotating engine shaft to a differential gear box that turns an axle and wheels.







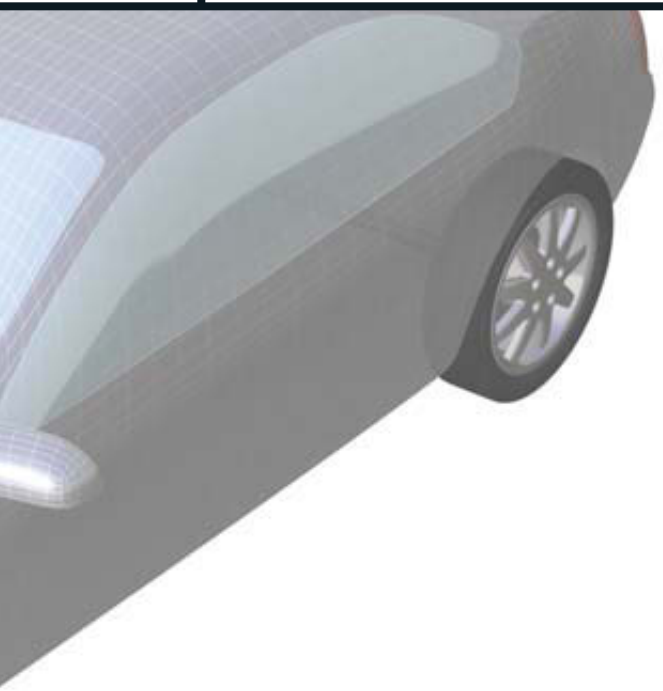
GEORGE RETSECK; SOURCE FOR CVT AND BELT: BOSCH

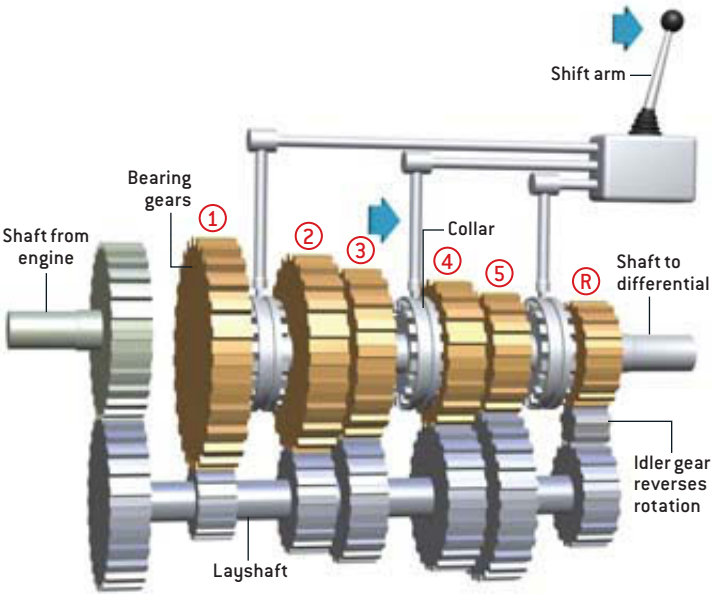
DID YOU KNOW...

LOCKED UP: Although CVTs offer significant fuel-economy gains during slow and stop-and-go driving, automatic transmissions can be as efficient at higher speeds. Also, in both designs, the transmission's torque converter may lock the engine shaft into the differential shaft to the axles when cruising at certain speeds, reducing hydraulic losses in the converter.

DA VINCI'S RIDE: In 1490 Leonardo da Vinci sketched a mechanism for continuously varying power between two rods. In the 1880s and 1930s European and American patents, respectively, were filed for CVTs. Dutch inventors Hub van Doorne and Wim van Doorne designed a CVT in 1958. Their company, DAF, produced the first practical CVT car. The brothers later started Van Doorne Transmissie, now owned by Bosch, to make CVTs. In 1989 the Subaru Justy became the first U.S. production model with the technology.

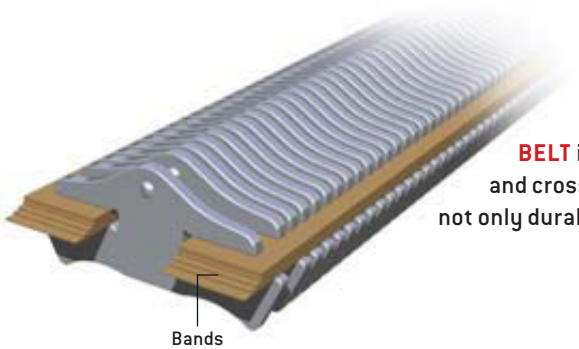
OXYMORON: Some manufacturers offer an "automatic manual" transmission for consumers who like the ease of an automatic but occasionally want the fun of shifting gears. The driver can push a lever that puts the automatic into manual mode. He or she then moves the gear-select stick left to cause a downshift, for example, and right for an upshift. There is no clutch pedal; the stick movement simply tells the automatic's actuators to engage. BMW also makes a CVT with a "sports mode" that allows the driver to "shift."





GEARS in the layshaft of a manual transmission (*five-speed shown*) are turned by the engine. They subsequently move bearing gears that spin freely. Pushing the shift arm into "first" inserts a collar on the differential shaft into the first bearing gear, and they rotate together. Pulling the arm back places the collar into the second gear. Separate shift arms engage third and fourth gear and fifth gear and reverse. Lower gears create higher torque at slower wheel speed.

CONES replace gears in a continuously variable transmission. The engine shaft turns a drive pulley that pushes a belt. The belt turns a driven pulley that spins the shaft to an axle. In each pulley, a hydraulic actuator under computer control moves the free cone closer or farther from the fixed cone. For high torque (*far left*), equivalent to low gear, the drive cones widen and the belt slides down, while the driven cones tighten and the belt slides up. For low torque and high speed (*near left*), the opposite movements occur. In between, a continuous, or infinite, number of "gears" are possible.



BELT is made of thin steel bands and cross members that provide not only durability but also flexibility.

Topic suggested by readers Kim Olsen and Len Baumann. Send ideas to workingknowledge@sciam.com

Getting a Rational Grip on Religion

IS RELIGION A FIT SUBJECT FOR SCIENTIFIC SCRUTINY? BY GEORGE JOHNSON

BREAKING THE SPELL: RELIGION AS A NATURAL PHENOMENON
by Daniel C. Dennett
Viking (Penguin), 2006 ($25.95)

If nowhere else, the dead live on in our brain cells, not just as memories but as programs—computerlike models compiled over the years capturing how the dearly departed behaved when they were alive. These simulations can be remarkably faithful. In even the craziest dreams the people we know may remain eerily in character, acting as we would expect them to in the real world. Even after the simulation outlasts the simulated, we continue to sense the strong presence of a living being. Sitting beside a gravestone, we might speak and think for a moment that we hear a reply.

In the 21st century, cybernetic metaphors provide a rational grip on what prehistoric people had every reason to think of as ghosts, voices of the dead. And that may have been the beginning of religion. If the deceased was a father or a village elder, it would have been natural to ask for advice—which way to go to find water or the best trails for a hunt. If the answers were not forthcoming, the guiding spirits could be summoned by a shaman. Drop a bundle of sticks onto the ground or heat a clay pot until it cracks: the patterns form a map, a communication from the other side. These random walks the gods prescribed may indeed have formed a sensible strategy. The shamans would gain in stature, the rituals would become liturgies, and centuries later people would fill mosques, cathedrals and synagogues, not really knowing how they got there.

With speculations like these, scientists try to understand what for most of the world's population needs no explanation: why there is this powerful force called religion. It is possible, of course, that the world's faiths are triangulating in on the one true God. But if you forgo that leap, other possibilities arise: Does banding together in groups and acting out certain behaviors confer a reproductive advantage, spreading genes favorable to belief? Or are the seeds of religion more likely to be found among the memes—ideas so powerful that they leap from mind to mind?

In *Breaking the Spell: Religion as a Natural Phenomenon,* Daniel Dennett, director of the Center for Cognitive Studies at Tufts University, has embarked on another of his seemingly impossible quests. His provocatively titled book *Consciousness Explained* made a persuasive effort to do just that. More recently, in *Freedom Evolves,* he took on free will from a Darwinian perspective.

This time he may have assumed the hardest task of all—and not just because of the subject matter. Dennett hopes that this book will be read not just by atheists and agnostics but by the religiously faithful—and that they will come to see the wisdom of analyzing their deepest beliefs scientifically, weeding out the harmful from the good. The spell he hopes to break, he suggests, is not religious belief itself but the conviction that its details are off-limits to scientific inquiry, taboo.

"I appreciate that many readers will be profoundly distrustful of the tack I am taking here," he writes. "They will see me as just another liberal professor trying to cajole them out of some of their convictions, and they are dead right about that—that's what I am, and that's exactly what I am trying to do."

HAMLET exemplifies the way we continue to experience the presence of those who are important to us even after they die. Such "spirits" may have provided the earliest impetus for religion. (Laurence Olivier in a 1948 production.)

BETTMANN/CORBIS

This warning comes at the end of a long, two-chapter overture in which Dennett defends the idea that religion is a fit subject for scrutiny. The question is how many of the faithful will follow him that far.

For those who do not need to be persuaded, the main draw here is a sharp synthesis of a library of evolutionary, anthropological and psychological research on the origin and spread of religion. Drawing on thinkers such as Pascal Boyer (whose own book is called *Religion Explained*) and giving their work his own spin, Dennett speculates how a primitive belief in ghosts might have given rise to wind spirits and rain gods, wood nymphs and leprechauns. The world is a scary place. What else to blame for the unexpected than human-like beings lurking behind the scenes?

The result would be a cacophony of superstitions—memes vying with memes—some more likely to proliferate than others. In a world where agriculture was drawing people to aggregate in larger and larger settlements, it would be beneficial to believe you had been commanded by a stern god to honor and protect your neighbors, those who share your beliefs instead of your DNA. Casting this god as a father figure also seems like a natural. Parents have a genetic stake in giving their children advice that improves their odds for survival. You'd have less reason to put your trust in a Flying Spaghetti Monster.

At first this winnowing of ghost stories would be unconscious, but as language and self-awareness developed, some ideas would be groomed and domesticated. Folk religion would develop into organized religion, Dennett suggests, somewhat the way folk music bloomed into the music of today. The metaphor is hard to resist. "Every minister in every faith is like a jazz musician," he writes, "keeping traditions alive by playing the beloved standards the way they are supposed to be played, but also incessantly gauging and deciding, slowing the pace or speeding up, deleting or adding another phrase to a prayer, mixing familiarity and novelty in just the right proportions to grab the minds and hearts of the listeners in attendance."

Like biological parasites, memes are not necessarily dependent on the welfare of their hosts. One of the most powerful fixations, and one that may have Dennett flummoxed, is that it is sacrilegious to question your own beliefs and an insult for anyone else to try. "What a fine protective screen this virus provides," he observes, "permitting it to shed the antibodies of skepticism effortlessly!"

Asides like this seem aimed more at fellow skeptics than at the true believers Dennett hopes to unconvert. A better tack might be for him to start his own religion. Meanwhile his usual readers can deepen their understanding with another of his penetrating books. SA

George Johnson, a 2005 Templeton-Cambridge Journalism Fellow in Science and Religion, is author of Fire in the Mind: Science, Faith, and the Search for Order *and six other books.*

THE EDITORS **RECOMMEND**

THE APE IN THE TREE: AN INTELLECTUAL AND NATURAL HISTORY OF *PROCONSUL*

by Alan Walker and Pat Shipman. Belknap Press of Harvard University Press, 2005 ($26.95)

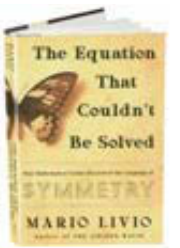
Proconsul, an ape of the Miocene epoch found in the fossil record of East Africa, "is the best candidate we know of for the last common ancestor of both modern apes and humans, the very trunk of that forking, branching tree that is so fascinating because it is the record of our own origins." Walker, professor of anthropology at Pennsylvania State University, has spent years finding *Proconsul* fossils and piecing together the story of this ancient ape.

His is the voice in this book, recounting what it is like to do fieldwork in the harsh conditions of East Africa and recording the trail of detective work and analysis that led to his conclusions about the ape's place in evolution. "We now know," he says of that place, "that *Proconsul* in its various species anchored the hominoid lineage between 21 and 14 million years ago, revealing our beginning as primitive and in some ways monkeylike creatures." Shipman, also a professor of anthropology at Pennsylvania State University, is his wife and the writer of most of the book because, Walker says, "she is a better writer than I am." It is a felicitous combination.

THE EQUATION THAT COULDN'T BE SOLVED: HOW MATHEMATICAL GENIUS DISCOVERED THE LANGUAGE OF SYMMETRY

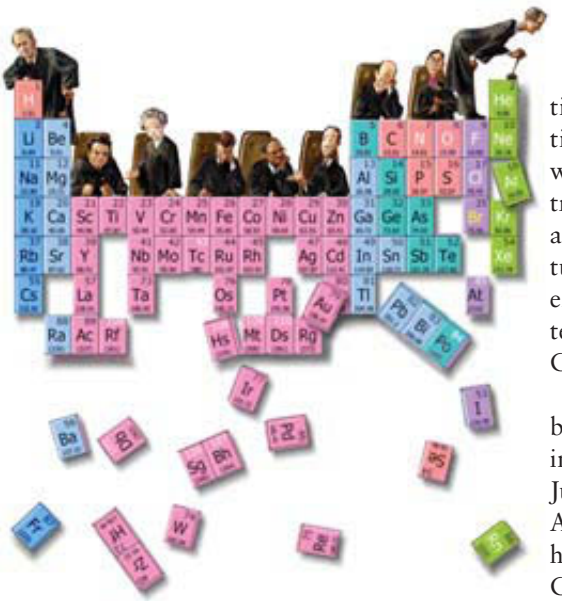
by Mario Livio. Simon & Schuster, 2005 ($26.95)

The so-called quintic equation resisted solution for three centuries, until two brilliant young mathematicians independently discovered that it could not be solved by any of the usual methods—and thereby opened the door to a new branch of mathematics known as group theory. This book is the story of these two early 19th-century mathematicians—a Norwegian, Niels Henrik Abel, and a Frenchman, Evariste Galois, both of whom died tragically, Galois in a duel at the age of 20. Livio, an astrophysicist now at the Space Telescope Science Institute and author of *The Golden Ratio,* interweaves their story with fascinating examples of how mathematics illuminates a wide swath of our world.



And Science for All

THE SECOND LAW TRUMPS THE TENTH AMENDMENT **BY STEVE MIRSKY**



Sam Alito—not the town across the Golden Gate Bridge from San Francisco, that's Sausalito—is the new nominee for associate justice of the U.S. Supreme Court. Harriet Miers had been the nominee, but she thought *Marbury v. Madison* had something to do with New York Knick point guard Stephon Marbury and his home court of Madison Square Garden.

Despite her lack of experience in constitutional law, Miers was defended by some commentators who posited that corporate law experience would come in handy when the court hears business cases. Fair enough. But surely the court will hear more and more cases involving science and technology, too. Therefore, I'd like to suggest a few science-related questions that members of the Senate Judiciary Committee might ask Supreme Court nominees:

1. What's the difference between RNA and the NRA?

2. It has been said that gravity is not just a good idea, it's the law. Is gravity indeed the law? Is gravity indeed a good idea in a land of rampant obesity?

3. What's the second law of thermodynamics? What's the third law of motion? Who's on first?

4. A related question. In his confirmation hearings, Chief Justice John Roberts compared being a judge with being a baseball umpire. Is it time for the instant replay in baseball? And does antediluvian refer to baseball prior to the *Flood* decision?

5. Do you believe in spontaneous human combustion, or do you refuse to answer on the grounds that you might incinerate yourself? (The kids, they love that one.)

6. In commenting on the death penalty, Justice Antonin Scalia said, "For the believing Christian, death is no big deal." Is death, in fact, a big deal? And if death isn't a big deal, why is murder?

7. Original *Law and Order,* or *Law and Order: Criminal Intent?*

8. Le Chatelier's principle holds that if you kick a chemical system that has settled into a dynamic equilibrium, it will react by adopting a new equilibrium. Is kicking a system in equilibrium a violation of the Eighth Amendment's prohibition of cruel and unusual punishment?

9. How can you have deregulation that lowers product safety standards at the same time as tort reform that limits awards for injuries from unsafe products and still keep a straight face?

10. Are you a strict constructionist, holding that the Constitution is a "dead" document? If so, would it be unconstitutional to transport the original Constitution across state lines in a car but constitutional to do so by horse? Also, the element helium was discovered after the Constitution was written. Can I still use it in balloons?

11. If Justice Ruth Bader Ginsburg leaves Washington, D.C., heading west at 60 miles per hour and Justice Anthony Kennedy leaves Los Angeles heading east at 70 miles per hour, will they meet before Justice Clarence Thomas asks a question?

12. Einstein showed with relativity that different observers, depending on their relative motion, may see two events as being simultaneous or as one preceding the other. Does that, like, blow your mind? And how should it come into play when evaluating eyewitness accounts?

13. Would you use Microsoft Word to write an opinion in a case involving Microsoft?

14. In the recently concluded Scopes-like trial of *Kitzmiller v. Dover School District,* one of the defendants claimed not to know the source of the funds for 60 copies of an intelligent-design book, which he admitted to only having glanced through, for the school library. He was then confronted with his own canceled check. Should such a defendant face charges of perjury or, despite the Eighth Amendment implications, be forced to actually read the book? SA

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

Why does skin wrinkle with age? How can you slow or prevent this process?

Suzan Obagi, assistant professor of dermatology at the University of Pittsburgh and director of the Cosmetic Surgery and Skin Health Center, offers this answer:

Wrinkles arise from physical shifts that occur naturally as we grow older—and they are exacerbated by outside influences, such as exposure to sun or tobacco smoke.

As we age, we gradually lose our collagen, a protein fiber that makes our skin firm; as a result, skin becomes thinner and more fragile. We also begin to lose the elastin that gives skin its elasticity and its glycosaminoglycans, or GAGs, which enable it to hold moisture. The result is drier skin with wrinkles that don't go away. Such changes, however, occur slowly and account for only a small amount of our furrows.

The effects of sun, tobacco smoke and pollution, for example, speed up the process. They can thicken parts of our skin, which is why we end up with lesions, skin cancer, freckles and sun spots. These factors can also exaggerate the normal loss of elasticity and firmness. The result is rough, uneven, patchy skin, with deeper creases than growing older by itself would cause.

Keeping skin smooth as long as possible means taking care of it. Every day apply a sunscreen of at least SPF 35, preferably one that contains zinc or titanium. After reaching the age of 25, use Retin-A, a vitamin A derivative with the generic name tretinoin, as an antiaging cream. It is a prescription agent that has been used for more than 30 years with excellent results. Although your skin might peel or flake at first, over time the tretinoin reduces fine lines, the size of pores and brown spots. If tretinoin treatment is not enough, peels and lasers can help build collagen and improve the skin's appearance. Because the regular sloughing off of skin tells the body to make more collagen, the laser treatments, which go a little deeper, boost that response in the skin.

What causes humidity?

—W. Chowanski, Camarillo, Calif.

Jeffrey Hovis, a science and operations officer at the National Oceanic and Atmospheric Administration's National Weather Service in Charleston, W.V., explains:

Humidity describes the amount of water in the air, which varies as part of a never-ending cycle of evaporation and condensation. Water on the earth's surface—in lakes, rivers and oceans—evaporates as water vapor. The air continues to absorb the water until it cannot hold it anymore, at which point the water vapor can condense into clouds and return to the earth as rain or snow.

Relative humidity, which TV forecasters often mention, compares the amount of moisture in the air with the total that it could hold. Warm air can carry more water than cool air can. Regardless of temperature, air that bears half as much moisture as it could conceivably contain has a relative humidity of 50 percent. Weather reporters focus on this factor because people feel uncomfortable when high relative humidity accompanies high temperature. That discomfort results because the human body relies on evaporation for cooling. When the air is already saturated, our skin cannot shed sweat.

Meteorologists also measure the air's dew point, the temperature at which saturation occurs. For a good example of this effect, think of a glass of iced tea on a muggy day. Remember that warm air can hold more moisture than cold air. When the air around the tea cools, it reaches its dew point and leaves water on the outside of the glass. In the atmosphere, air that reaches the dew point forms clouds. Instead of condensing on a glass, however, water in air may form on dust particles. When enough air falls below the dew point, it results in a cloud of dust and water that is heavy enough, and precipitation falls. SA

For a complete text of these and other answers from scientists in diverse fields, visit www.sciam.com/askexpert

MATT COLLINS