ANTICANCER BLOCKBUSTER? • RISE AND FALL OF THE SLIDE RULE

SCIENTIFIC AMERICAN

Bringing **DNA Computers** to Life

MAY 2006
WWW.SCIAM.COM

Quark Soup

PHYSICISTS RE-CREATE THE LIQUID STUFF OF **THE EARLIEST UNIVERSE**

Stopping **Alzheimer's**

Birth of **the Amazon**

Future **Giant Telescopes**

may 2006 contents

SCIENTIFIC AMERICAN Volume 294 Number 5

features

34A The original liquid universe

departments

Repliee, built by Hiroshi Ishiguro, Osaka University

columns

Cover image by Jean-Francois Podevin; photograph at left courtesy of the Intelligent Robotics Laboratory, Osaka University.

Scientific American (ISSN 0036-8733), published monthly by Scientific American, Inc., 415 Madison Avenue, New York, N.Y. 10017-1111. Periodicals postage paid at New York, N.Y., and at additional mailing offices. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 40012504. Canadian BN No. 127387652RT; QST No. Q1015332537. Publication Mail Agreement #40012504. Return undeliverable mail to Scientific American, P.O. Box 819, Stn Main, Markham, ON L3P 8A2. Subscription rates: one year $34.97, Canada $49 USD, International $55 USD. Postmaster: Send address changes to Scientific American, Box 3187, Harlan, Iowa 51537. **Reprints available:** write Reprint Department, Scientific American, Inc., 415 Madison Avenue, New York, N.Y. 10017-1111; (212) 451-8877; fax: (212) 355-0408. **Subscription inquiries: U.S. and Canada (800) 333-1199; other (515) 248-7684. Send e-mail to sacust@sciam.com** Printed in U.S.A.

Don't Rob the Cradle

Annually, diabetes costs the U.S. upward of $132 billion, autism costs more than $43 billion, and asthma's toll is $11.3 billion. Spending just $100 million in each of the next 20 years to understand better the origins of those conditions, if it would reduce their burden even fractionally, thus sounds like a bargain. Yet our national leaders now seem prepared to throw that opportunity away in favor of other priorities in the country's $2.7-trillion federal budget.

The program at risk is the National Children's Study, designed to ferret out the causes of a multitude of today's most dire and growing health risks, from autism, asthma and diabetes to violent behavior and childhood cancers. Mandated by Congress in the Children's Health Act of 2000, the study would follow 100,000 American children from before birth—and in some cases before conception—until their 21st birthdays. By signing up pregnant women and couples planning to conceive, the researchers could gather an unprecedented amount of information about the interplay between biology and environment that contributes to the children's development and health. Prospective studies of this type, such as the famous Framingham Heart Study that began in 1948, can represent the gold standard of epidemiological research because they are inherently unbiased. By collecting data about a large heterogeneous population in real time, before disease arises, they can test long-held but unproved hypotheses and amass a trove of evidence for investigators to sift through later.

Between 2000 and 2005 the National Institute of Child Health and Human Development spent $50 million to design and organize the project and to identify a nationwide network of researchers to conduct it. This year the scientists were to launch pilot study centers and in 2007 begin gathering data.

But in his 2006 budget, President George W. Bush slashed funding for the National Children's Study, and in his proposed 2007 budget, he eliminated its funding entirely and directed that the study be shut down. The White House rationale for spiking the project, according to budget director Joshua Bolten, is a need "to focus on national priorities and tighten our belt elsewhere."

Presumably children's health is a national priority, so perhaps the scuttling of the study is just one more gesture in the Kabuki theater of Washington budgetary politics. Presidents cut programs to look responsible, and Congress restores them to look generous. Maybe the National Children's Study is less dead than it seems and will soon have its full funding reinstated. But last year when Congress had the chance to fund the program more substantially for 2006, it declined to do so. That is a worrisome bellwether.

In its goals, scope and outcomes, this ambitious investigation could represent 20 Framinghams rolled into one. Smaller-scale studies might chip away at parts of the targeted health issues, but nothing else yet proposed could take its place. Moreover, the hard job of designing and organizing is already done. Just when we are poised to probe the origins of some of the most devastating conditions affecting American children and adults, it would be a fool's economy to squander the money and effort already spent by killing this effort in its cradle. Attention, Capitol Hill shoppers: Do you know a bargain when you see it?

THE EDITORS editors@sciam.com

RUBBERBALL PRODUCTIONS

How to Contact Us

EDITORIAL

For Letters to the Editors:
Letters to the Editors
Scientific American
415 Madison Ave.
New York, NY 10017-1111
or
editors@sciam.com
Please include your name and mailing address, and cite the article and the issue in which it appeared. Letters may be edited for length and clarity. We regret that we cannot answer all correspondence.

For general inquiries:
Scientific American
415 Madison Ave.
New York, NY 10017-1111
212-451-8200
fax: 212-755-1976
or
editors@sciam.com

SUBSCRIPTIONS

For new subscriptions, renewals, gifts, payments, and changes of address:
U.S. and Canada
800-333-1199
Outside North America
515-248-7684
or
www.sciam.com
or
Scientific American
Box 3187
Harlan, IA 51537

REPRINTS

To order reprints of articles:
Reprint Department
Scientific American
415 Madison Ave.
New York, NY 10017-1111
212-451-8877
fax: 212-355-0408
reprints@sciam.com

PERMISSIONS

For permission to copy or reuse material from *SA*:
www.sciam.com/permissions
or
212-451-8546 for procedures
or
Permissions Department
Scientific American
415 Madison Ave.
New York, NY 10017-1111
Please allow three to six weeks for processing.

ADVERTISING

www.sciam.com has electronic contact information for sales representatives of Scientific American in all regions of the U.S. and in other countries.

New York
Scientific American
415 Madison Ave.
New York, NY 10017-1111
212-451-8893
fax: 212-754-1138

Los Angeles
310-234-2699
fax: 310-234-2670

San Francisco
415-403-9030
fax: 415-403-9033

Detroit
Karen Teegarden & Associates
248-642-1773
fax: 248-642-6138

Midwest
Derr Media Group
847-615-1921
fax: 847-735-1457

Southeast and Southwest
Publicitas North America, Inc.
972-386-6186
fax: 972-233-9819

Direct Response
Special Aditions Advertising, LLC
914-461-3269
fax: 914-461-3433

Australia
IMR Pty Ltd.
Tel: +612-8850-2220
Fax: +612-8850-0454

Belgium
Publicitas Media S.A.
+32-(0)2-639-8420
fax: +32-(0)2-639-8430

Canada
Derr Media Group
847-615-1921
fax: 847-735-1457

France and Switzerland
PEM-PEMA
+33-1-46-37-2117
fax: +33-1-47-38-6329

Germany
Publicitas Germany GmbH
+49-211-862-092-0
fax: +49-211-862-092-21

Hong Kong
Hutton Media Limited
+852-2528-9135
fax: +852-2528-9281

India
Convergence Media
+91-22-2414-4808
fax: +91-22-2414-5594

Japan
Pacific Business, Inc.
+813-3661-6138
fax: +813-3661-6139

Korea
Biscom, Inc.
+822-739-7840
fax: +822-732-3662

Middle East
Peter Smith Media & Marketing
+44-140-484-1321
fax: +44-140-484-1320

The Netherlands
Insight Publicitas BV
+31-35-539-5111
fax: +31-35-531-0572

Scandinavia and Finland
M&M International Media AB
+46-8-24-5401
fax: +46-8-24-5402

U.K.
The Powers Turner Group
+44-207-592-8331
fax: +44-207-630-9922

On the Web

WWW.SCIAM.COM

UPDATED EVERY WEEKDAY

Visit **www.sciam.com/ontheweb**
to find these recent additions to the site:

Jurassic "Beaver" Is Largest Early Mammal Yet

A new fossil from China proves that the mammals that lived during the Jurassic era were more diverse than previously thought. The 164-million-year-old creature, dubbed *Castorocauda lutrasimilis*, had a tail like a beaver's, the paddling limbs of an otter, seallike teeth and probably webbed feet. And although most Jurassic mammals discovered thus far were tiny, shrewlike animals, *C. lutrasimilis* would have weighed in at approximately a pound. As such, it is the largest mammal from this time period on record.

COURTESY OF MARK A. KLINGLER *Carnegie Museum of Natural History*

Drug Found to Reverse the Ravages of Alzheimer's in Mice

Researchers have identified a compound that could significantly improve treatment of Alzheimer's disease. When administered to mice engineered to develop hallmarks of the disease, the drug reversed cognitive decline and reduced the two types of brain lesions—plaques and tangles—that occur in Alzheimer's patients.

New: The Scientific American Podcast

Join host Steve Mirsky each week as he explores the latest developments in science and technology through interviews with leading scientists and journalists.

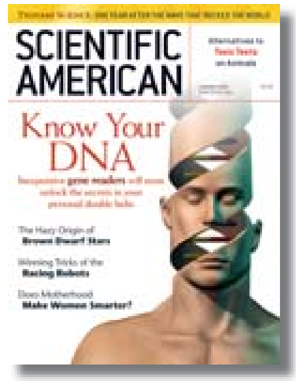
Ask the Experts

How do antibiotics kill bacterial cells but not human cells?

Harry Mobley, chair of the department of microbiology and immunology at the University of Michigan Medical School, explains.

Letters

EDITORS@SCIAM.COM



JANUARY'S ISSUE drew letters addressing articles that ranged from an exploration of how motherhood changes the structure of the female brain in "The Maternal Brain," by Craig Howard Kinsley and Kelly G. Lambert, to the sociopolitical and psychological factors that drive individuals to become suicide bombers in "Murdercide," by Skeptic columnist Michael Shermer.

The topic of animal experimentation, covered in "Saving Animals and People" [SA Perspectives] and "Protecting More than Animals," by Alan M. Goldberg and Thomas Hartung, generated the most heat and light in letters. Readers generally agreed that minimizing or eliminating animal testing wherever possible is a laudable goal; however, it is ethically acceptable to continue animal research if it is the only way to promote advances benefiting humanity. But to some, a "humans first" guideline rang hollow: Richard Dingman of Montague Center, Mass., wrote, "Just what is the 'ethical' basis for declaring that animal experimentation is preferable to testing on humans? The editors assume our acceptance of human superiority has an objective foundation so obvious that it need not be mentioned." The heartfelt debate goes on.

BRAIN GAIN

As a 41-year-old first-time father, I thoroughly enjoyed "The Maternal Brain," by Craig Howard Kinsley and Kelly G. Lambert. After witnessing my wife (who is also in her early 40s) go through various maternal changes, I was fascinated to learn about some of the mechanisms that might be at work. I was also overjoyed to learn that my apparent decrease in multitasking and cognitive skills may in fact be because of a relative increase in hers, quite possibly getting me off the hook for many a blunder.

The article also made me ponder why. I am a different man than I was before I became a father. Suddenly, I am interested in children (even those not my own) and am driven by protective and nurturing instincts I did not even know I had. And, it is safe to say, just about every parent agrees these feelings are different from what one feels with friendship or when falling in love. Even though a father does not experience pregnancy or lactation physically, does the paternal brain also undergo changes? I wonder how much research has been done beyond the paternal studies cited by the authors. Is my brain on fatherhood different? It sure "feels" different.

Andrew J. Anagnost
Portland, Ore.

ASSESSING DEADLY CERTITUDE

In "Murdercide" [Skeptic], Michael Shermer is once again dead-on (forgive the pun): it is inapt to think of suicide bombers as typical suicide victims. Rather than succumbing to despair and depression, they are committing what they consider affirmative acts of faith. In short, they are religious fanatics, hardly different from the murderers of abortion doctors, except that the latter zealots don't kill themselves as well.

Shermer cites Princeton University economist Alan B. Kreuger's finding that some countries that have spawned many terrorists (Saudi Arabia and Bahrain) are economically well off yet lack civil liberties, whereas poor countries that protect civil liberties are unlikely to spawn terrorists. That might be a good correlation, but a better factor than civil liberties is probably the degree of fundamentalist religious extremism present in a country. The murderers of 9/11 were Islamic jihadists first, citizens of their various nations second.

Kevin Padian
Kensington, Calif.

Decades ago, during the Vietnam War, Buddhist monks protested the war by burning themselves to death. I do not remember anyone analyzing in *Scien-*

tific American or the general press why they did so. It was obvious, and we had no great need to stop their self-immolation. Now the reason people resort to such radical action still seems obvious, but because they set out to harm others, the subject is worth analysis.

Reading the powerful antiwar speech given by British playwright Harold Pinter at his acceptance of the 2005 Nobel Prize for Literature, I wondered: Why do published opinions blame the social and political systems of those countries that produce the suicide bombers when the Iraq War can evoke such rage in people such as Pinter, who observe the war from their safe and comfortable homes?

Eugene Bercel
Naples, Fla.

SHERMER REPLIES: Padian is correct that these suicide bombers are jihadists first; that is so well known that I thought I'd add additional layers to the causal analysis of their motivations. To Bercel's point, the reason social scientists examine social and political systems (and psychological states as well) is that these are quantifiable variables that lend themselves to statistical analysis. This fact does not discount free will and the moral culpability in the choices terrorists make.

THE MORAL ANIMAL

A line in "Saving Animals and People" [SA Perspectives] was music to my ears: "But for the sake of people and animals alike, the development and acceptance of animal substitutes deserve enthusiastic support." Many of us could never accept the use of animals in experimentation as ethical, sound or even scientific.

Suzana Megles
Lakewood, Ohio

I was glad to see *Scientific American* discuss the effectiveness of animal testing for the benefit of humans. I hope that your influential publication continues to report on alternatives to animal testing in order to educate the scientific community as well as the public about this field and others with moral and ethical issues. People do not think enough about these debates, because they are not confronted with them in their day-to-day lives. It is the responsibility of the scientific community to engage in discourse about the ethics of their research and to get the public to think about these issues as well.

Daniel Bass
Providence, R.I.

CARY WOLINSKY

MULTIPLYING BENEFITS: The reduction of lab animal suffering has also yielded more rigorous safety tests.

DIPPING INTO DATA STREAMS

"Recognition Engines," by Gary Stix, could have offered valuable insight into IBM's new pattern-matching engine. Unfortunately, it suffers from major flaws that pretty much strip it of any interest.

The article attempts to explain the importance of IBM's work by showing how it can be applied to an application, such as spam filtering, and by comparing it in that context with what the reader must assume is the state of the art of pattern matching. Stix is, however, apparently not well informed about this: current spam-filtering technology is far more complex than he seems to think. In general terms, a battery of tests is applied to each incoming message, scores from each test are totted up, and the message is categorized as "spam" or "ham" (the latter a term for a legitimate message) by comparing the final score with a user-defined threshold. Stix presents an incorrect view of traditional pattern-matching techniques and, in discussing IBM's work, fails to explain to the reader what the company's labors are actually about. Instead he focuses on spam fighting, which, though perhaps more familiar to the average reader, is not a relevant application of this technology.

Dag-Erling Smørgrav
Linpro AS
Oslo, Norway

STIX REPLIES: The intention of the article was to show the difference between a conventional processor and the IBM design for a pattern-matching engine by using a simplified example for this complex technology. The article focused on a key aspect of the IBM design, the finite state machine that underlies the pattern-matching engine. It did not show—nor was it intended to demonstrate—all the relevant features of either spam filtering or other types of pattern matching. I chose spam filtering because it is an application to which many readers can relate. I also made the point that one of the characteristics of the IBM architecture is its programmability, which would allow it to be used for a range of applications, from processing Internet (XML) documents to, yes, even spam filtering.

ERRATUM The caption in the box "A Motorcycle That Steers Itself" ["Innovations from a Robot Rally," by W. Wayt Gibbs] incorrectly stated that a human rider turns a motorcycle by twisting the handlebars "in the turn direction." It should have said "in the opposite direction." Also, the statement that the Blue Team "invented a new approach that uses the front wheel alone to lean the bike through turns" should be clarified: the novel aspect of the team's robot was the automated system it employed to measure and adjust the motorcycle's heading, not wheel steering per se.

CLARIFICATION In "No More Gears," by Mark Fischetti [Working Knowledge], the gearbox shown on page 79 seemed to indicate that reverse has the same gear ratio as fourth gear. In cars, reverse usually has a ratio similar to that of first gear, because one usually reverses from a stationary position.

50, 100 & 150 Years Ago

FROM *SCIENTIFIC AMERICAN*

Brain and Behavior ▪ San Francisco Earthquake ▪ Strychnine's Trail

MAY 1956

THE HARDWIRED BRAIN—"How big a role does heredity play in behavior? In the lower vertebrates, at least, many features of visual perception—the sense of direction and location in space, the perception of motion and the like—are built into the organism and do not have to be learned. The whole idea of instincts and the inheritance of behavior traits is becoming much more palatable than it was 15 years ago, when we lacked a satisfactory basis for explaining the organization of inborn behavior. Every animal comes into the world with inherited behavior patterns of its species. Much of its behavior is a product of evolution, just as its biological structure is. —R. W. Sperry" [*Editors' note: Roger Wolcott Sperry was awarded the Nobel Prize in Physiology or Medicine in 1981.*]

DISLOYALTY TEST—"Last year President Eisenhower asked Detlev W. Bronk, president of the National Academy of Sciences, to look into the question of whether scientists accused of disloyalty should be allowed to do unclassified research under Government grants-in-aid or contracts. Bronk's committee held that scientific research should be judged on its own merits: a contribution to the cure of cancer 'would be no less beneficial to all humanity for having been made by a Communist.'"

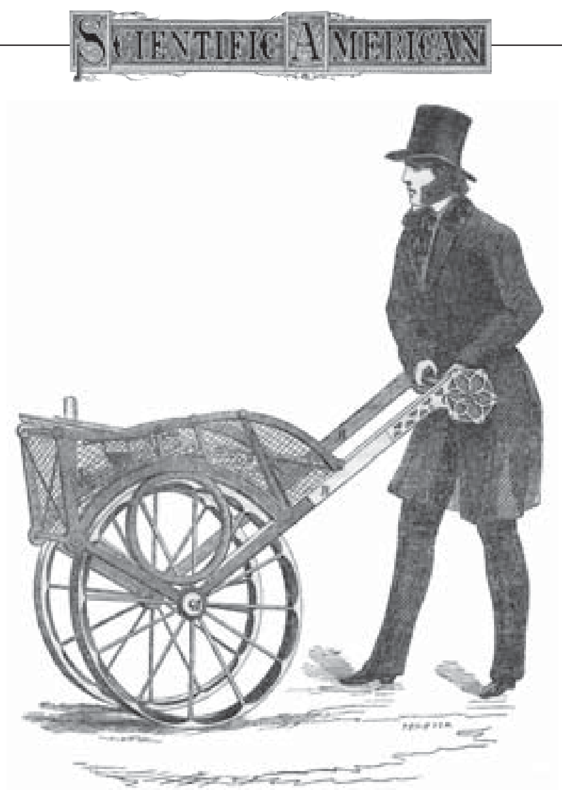
MAY 1906

SAN FRANCISCO AFTERMATH—"We may search all history in vain to find a dramatic parallel to that piteous spectacle of two hundred thousand half-naked and altogether homeless San Franciscans watching, in hopeless impotence, from the encircling amphitheater of the hills, the wiping off the earth of over twenty square miles of this their picturesque and passionately-loved capital city of the West! This is not the time for indulgence in the commonplaces of moralizing; but we feel that our record of this event would be incomplete without a reference to that spontaneous flood of practical generosity, which instantly rolled in upon the stricken people from every State and city of the Union. Capital and labor, railroad and factory, church and theater, all have joined hands; supplies and necessities are now pouring into the devastated city."

WAR AND DISEASE—"For nearly two centuries past, in wars that extended over any great period of time, on an average at least four men have perished from disease to every one who has died of wounds. These surprising figures are compared with the record made by the Japanese army in Manchuria, where only one died from sickness to every four and one-half men who died in battle. This complete reversal of the statistics of the leading nations of western civilization constitutes, according to Major Louis L. Seaman, the real triumph of Japan. These results were obtained by careful study of military sanitation and hygiene and by a most thorough bacteriological examination of the water along the line of march and in the vicinity of the camps."

MAY 1856

LAND SURVEYOR—"Our engraving illustrates the adaptation of a neat little pocket instrument for measuring surfaces as a land measuring instrument. The light ornamental wheels are linked by rods to the registering disks in the handle. In use the surveyor pushes the instrument before him over the surface of the ground. The use of the chain, with its tediousness, halts and starts, calculations and adjustments, is avoided, much time saved and errors prevented."



SURVEYING INSTRUMENT, better than the old-fashioned chain, 1856

CRIMINALS BEWARE—"The *Medical Times and Gazette* says, 'the finger of science points to the detection of the murderer by strychnine, and dissipates his visionary hopes; the grain of white powder, which he anticipates will carry his victim silently to the grave, excites, on the contrary, the most violent and characteristic convulsions; a minute fraction of a grain, lying on the animal membranes after death, will exhibit, under appropriate tests, a series of resplendent and iridescent rings of color to the chemist's view.'"

POLICY

Legislating Integrity

A SMALL ATTEMPT TO PREVENT POLITICAL MISUSE OF SCIENCE **BY PAUL RAEBURN**

Tucked inside the current funding bill for the Department of Health and Human Services is a little-noticed provision that regulates how the department handles science and scientific advice. None of the money in the bill can be used "to disseminate scientific information that is deliberately false or misleading," the provision says. And the department cannot ask candidates for its scientific advisory panels to disclose their political affiliation or voting history.

CAPITOL IDEA: Senator Richard Durbin of Illinois (*left*) inserted a provision in a funding bill and introduced legislation to prevent political meddling in science. He is shown with other Democratic senators gathered for an unrelated news conference in 2005.

TOM WILLIAMS *Roll Call Photos*

The provision, inserted by Senator Richard Durbin of Illinois, represents a tiny victory for critics of the Bush administration, who have become increasingly angry about what they see as the White House's misuse and abuse of science. They charge that the federal government widely dismisses or ignores scientific evidence or even, as one detractor puts it, manufactures uncertainty when the evidence challenges administration positions. Backers hope that, as the first legislation of its kind, the Durbin amendment will lead to broader efforts to regulate the use of science in this and future administrations.

When he introduced the provision, Durbin pointed to the example of William R. Miller, a professor of psychiatry and psychology at the University of New Mexico who was denied a position on the National Advisory Council on Drug Abuse after he said he had not voted for George W. Bush. "When the federal government seeks expert technical advice, it should look for the best possible expertise," Durbin said at the time. "It shouldn't limit itself to only those experts who voted for a particular candidate or who agree with the president's policy agenda."

Theoretically, the amendment outlaws the kind of activity that disturbs Durbin. "It basically says no one is allowed to ignore science for political purposes," says a Durbin staffer who spoke on condition of anonymity. But "the thing that's disappointing about the amendment is that it doesn't have any enforcement." That is, the department legally cannot violate the provision, but if it does—nothing happens. The amendment, therefore, is likely to have little effect. Nevertheless, Durbin and others see it as an important symbolic step.

The White House did not return calls seeking comment. But the administration did issue a lengthy response when this legislation was introduced. John H. Marburger III, director of the White House Office of Science and Technology Policy, stated then that the administration is "applying the highest scientific standards in decision-making" and that "the accusation of a litmus test that must be met before someone can serve on an advisory panel is preposterous." Marburger himself was appointed to his post despite being "a lifelong Democrat," he said.

With regard to the Miller case, Marburger argued that the National Institute on Drug Abuse had rejected Miller's appointment to the advisory panel on professional grounds, not for political reasons. Such incidents cited by critics represent only a few isolated cases among some 600 scientific committees in the Bush administration, he emphasized. And one of the most important science officials did not experience any meddling: at the annual meeting of the American Association for the Advancement of Science in February, Rita Colwell, who headed the National Science Foundation until 2004, said she had not come under any political pressure during her tenure.

Some of the administration's defenders point out that science and politics have always been strained bedfellows. This administration, they insist, is being unfairly singled out for criticism.

Sheila Jasanoff, a professor of science and technology studies at Harvard University who investigates the use of science in the federal government, disagrees. "Something different is going on in the Bush administration," she claims. Part of the problem is that it attempts to create controversy where none exists. "No matter how good the science is on anything, you can manufacture uncertainty," she says, citing the case of the Environmental Protection Agency giving undue weight to industry studies that question the herbicide atrazine's link to cancer.

Durbin's DHHS funding provision expires in September, at the end of the government's fiscal year. But Durbin has separately introduced legislation that tries to ensure that the federal government will avoid meddling with scientific evidence. It would prohibit censorship of research findings, protect whistle-blowers and keep scientific review out of the hands of the White House.

The legislation's prospects are uncertain. When the amendment was introduced, it attracted 12 cosponsors—all Democrats. Some Republicans have criticized the administration's handling of science, notably Representative Sherwood Boehlert of New York, chair of the House Committee on Science, who urged NASA to stop trying to intimidate James E. Hansen, perhaps the space agency's most famous climatologist. Nevertheless, the administration's critics see the legislation as the beginning of an effort to restore scientific integrity.

Paul Raeburn writes about science, policy and the environment from New York City.

ARM TWISTING?

Critics of the Bush administration point to headline instances as evidence of its abuse of science, most notably:

- **An attempt to alter an EPA report—in particular, to remove references to a National Academy of Sciences conclusion that humans were contributing to climate change (June 2003).**
- **The dismissal of two scientists from the President's Council on Bioethics after they disagreed with the administration over stem cell research and other issues (February 2004).**
- **The resignation of Susan F. Wood, former director of the Office of Women's Health at the Food and Drug Administration, after the agency overruled its scientific advisory panel and refused to approve over-the-counter sales of an emergency contraceptive known as Plan B, or the morning-after pill (August 2005).**
- **The charges by noted NASA climatologist James E. Hansen that the administration repeatedly tried to stop him from speaking publicly about climate change. Some of the pressure came from George C. Deutsch, a presidential appointee in the NASA public affairs office who later resigned over false academic credentials (January 2006).**

ECOLOGY

Mixing It Up

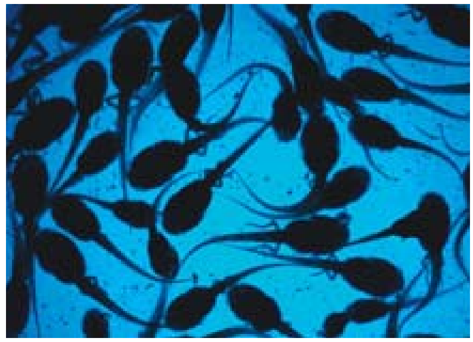
HARMLESS LEVELS OF CHEMICALS PROVE TOXIC TOGETHER BY DAVID BIELLO

One chemical alone may do no harm in low doses, but in conjunction with a few of its peers, even in doses that are individually safe, it can inflict serious harm. New research in frogs shows that a mixture of nine chemicals found in a seed-corn field in York County, Nebraska, killed a third of exposed tadpoles and lengthened time to metamorphosis by more than two weeks for the survivors.

Biologist Tyrone Hayes and his colleagues at the University of California, Berkeley, have spent the past four years testing four herbicides, two fungicides and three insecticides commonly used in American cornfields. Individually, the chemicals had little effect on developing tadpoles at low concentrations, such as about 0.1 part per billion. But when Hayes exposed them to all nine at the same low level in the laboratory—the lowest level actually found in the field—the future frogs fell prey to endemic infection. Those that survived ended up smaller than their counterparts raised in clean water—despite taking longer to mature into adults. "In humans, this is like saying, 'The longer you are pregnant, the smaller your baby will be,' which means the womb is no longer a nurturing environment," Hayes notes.

Hayes's study joins a growing body of work showing that chemicals in combination can produce a wide range of effects even at low concentrations. Rick Relyea of the University of Pittsburgh has shown in several studies that tadpoles exposed in their water to low levels of a single pesticide and the smell of a predator will face significantly higher mortality rates. For instance, about 90 percent of bullfrog tadpoles died from exposure to the pesticide carbaryl when the smell of predatory newts was present, whereas no tadpoles perished if exposed to each individually. The pesticide may be inducing a general stress in the tadpole that, when combined with another stressor, becomes deadly, Relyea argues.

It is not just pesticides that show a mixture effect. Phthalates—chemical softeners that make polymers flexible—can interfere with the sexual development of male rats. "We have males treated with phthalates where the testes are under the kidneys or floating around in the abdominal cavity," explains L. Earl Gray, Jr., a biologist at the Environmental Protection Agency and codiscoverer of this deformity, which has been dubbed phthalate syndrome. Gray has also found that various kinds of phthalates in combination either with one another or with certain pesticides and industrial effluents exert ever more powerful effects. For example, two phthalates at concentrations that on their own would not produce much deformity combined to create defective urethras (hypospadias) in 25 percent of exposed rats.



MIXED MESSAGE: Mixtures of pesticides in very low concentrations killed a third of tadpoles and disrupted the development of the survivors.

Besides adding to the issue of endocrine disruption—whether industrial chemicals are mimicking natural hormones—the findings on mixtures pose an incredible challenge for regulators. With tens of thousands of chemicals in regular use worldwide, assessing which combinations might prove harmful is a gargantuan task. "Most of the offices in the agency recognize that we cannot operate via the idea of 'one chemical, one exposure' to an individual anymore. We need to look at broader classes of compounds and how they interact," says Elaine Francis, national program director for the EPA's pesticides and toxics research program. But such testing has a long way to go to reach any kind of regulation, particularly given industry's qualms about the validity of existing research.

Marian Stanley, who chairs the phthalates panel for the American Chemistry Council, notes that at least one study showed that rodents suffering from phthalate malformations could still mate and have litters. "The additivity of phthalates alone are on end points that may not have any biological relevance," she says.

Nevertheless, evidence continues to accumulate that mixture effects are a critical area of study. In its National Water Quality Assessment, the U.S. Geological Survey found that a sampling of the nation's streams contained two or more pesticides 90 percent of the time. "The potential effects of contaminant mixtures on people, aquatic life and fish-eating wildlife are still poorly understood," states hydrologist Robert Gilliom, lead author of the study. "Our results indicate, however, that studies of mixtures should be a high priority."

HUMAN DISRUPTION

Besides affecting amphibians, endocrine disruption—chemical interference with hormonal cascades involved in development—may also be happening in humans. Shanna Swan of the University of Rochester has linked fetal exposure to phthalates and genital changes in 85 baby boys. "We found effects at levels that are seen in a quarter of the U.S. population," Swann says.

But whether the malformations stem from phthalates alone or in combination with other compounds remains unknown, because humans encounter many chemicals in mixture. To help sort out matters, a Johns Hopkins University study will look for the most common chemicals in people. Umbilical cord blood will be tested for a wide array of substances, from pesticides to phthalates to heavy metals, and the overall levels then correlated with the babies' characteristics at birth. Explains the study's leader, Lynn Goldman: "If we can identify some of these mixtures to which people are commonly exposed, then those might be the mixtures to look at more closely."

HEIDI AND HANS-JURGEN KOCH *Minden Pictures*

GEOLOGY

Chaos in the Crater

WELCOME TO VREDEFORT, A REAL BERMUDA TRIANGLE BY GRAHAM P. COLLINS

"**It's like being** in the Bermuda Triangle," says Rodger Hart of the iThemba Laboratory for Accelerator Based Science in South Africa. I take the compass to see for myself. At first the needle points in a steady direction, which for all I know could be magnetic north. But then I take a step forward, and the needle swings to a completely different quadrant. Another step, and yet another direction. Next I put the compass down against the large rock outcropping we are standing on. Now as I move the compass across the rock, with every few centimeters of motion the needle swings around.

The location is the center of the Vredefort Crater, about 100 kilometers southwest of Johannesburg. Vredefort is the oldest and largest impact remnant on the planet, created about two billion years ago when a 10-kilometer-wide asteroid slammed into the earth. Evidence of older collisions exists elsewhere, in South Africa and in Western Australia, but in those cases no geologic structure has survived the ravages of time.

Vredefort itself is not obviously a crater to the untrained eye. Geologists estimate the total crater size at 250 to 300 kilometers across, but the rim has long since been eroded away. The most obvious structure remaining is the Vredefort Dome, which is the crater's "rebound peak"—where deep rocks rose up in the crater's center after the impact.

According to Hart, the probable source of Vredefort's weird magnetism was a strong and chaotic magnetic field generated by currents flowing in the ionized gases produced at the height of the collision. Laboratory experiments confirm that impacts cause intense magnetic fields in that fashion. Scientists have calculated that a mere one-kilometer-wide asteroid, one tenth the size of Vredefort's, would create a field 1,000 times that of the earth's at a distance of 100 kilometers.

Vredefort's intense but random magnetism was not apparent from aerial surveys. Those analyses showed anomalously *low* magnetism over the crater, like a hole punched in the prevailing magnetic field. All the magnetic madness on the ground averages out to nothing when seen from too high up.

The results could have implications not only for earth geology but also for studies of Mars. The immense Martian basins Hellas and Argyre displayed virtually no magnetism when measured by the orbiting Mars Global Surveyor. The conventional explanation runs like this: When these craters formed around four billion years ago, the impacts wiped out the preexisting magnetization of the rocks. Therefore, at the time of their creation Mars must not have had a magnetic field, because that field would have been preserved in the magnetization of the basins' rocks when they cooled. Mars does not now have a magnetic field, but long ago it did. Thus, the standard explanation implies that Mars lost its field very early on.

INTENSE, RANDOM MAGNETISM in the Vredefort Crater occurs in rocks such as these brown granite boulders. The darker rock is pseudotachylite, which forms from melted granite.

SIMON BARBER *South African IMC*

But as Hart points out, if the Hellas and Argyre basins show the same properties as the Vredefort Crater, one cannot conclude anything about Mars's magnetic field when they were formed—it may have still been going strong. Mario Acuña, a principal investigator on the Mars Global Surveyor project, however, points out that data from smaller Martian craters of about Vredefort's size do not agree with Hart's scenario.

Back on earth, Hart has proposed a high-resolution helicopter survey of Vredefort's magnetism, from an altitude low enough to see the magnetic variations. That would produce a complete magnetic map—and make some sense of the crater's weirdness.

SHOCKED ROCKS

In the Vredefort Crater, the exceptionally strong and random magnetism exists only in "shocked" rocks—that is, rock that underwent intense pressure but did not melt. Rodger Hart of the iThemba Laboratory for Accelerator Based Science in South Africa, along with colleagues from the Paris Earth Physics Institute, suggests that the shocked rocks, which occur in thin layers, cooled rapidly, locking in a pattern of magnetization caused by the powerful, chaotic field generated at the time of impact. The unshocked rocks, in contrast, melted and formed larger pools that took days to cool down, preserving instead the weaker, more orderly natural magnetism of the earth.

ENERGY

Pumping Coal

COMING SOON TO THE U.S.: CLEANER DIESEL FROM DIRTY COAL **BY GUNJAN SINHA**

The U.S. is plump with coal. The country has one quarter of the world's reserves, and coal accounts for about 50 percent of the nation's electricity. To cut the reliance on oil imports, why not also use it to power cars and trucks or to heat homes, too?

That may happen soon. This year Waste Management and Processors, Inc. (WMPI), will break ground for the first U.S. coal-to-diesel production facility, in Gilberton, Pa. The plant will process 1.4 million tons of waste coal a year to generate approximately 5,000 barrels a day of diesel fuel. Other states, such as Illinois, Virginia, Kentucky, Wyoming and West Virginia, are also considering coal-to-liquid facilities.

Interest in the technology is certainly welcome news to WMPI president John Rich, who has been trying to finance such a facility for more than a decade. "Coal to liquids hadn't taken off, because the price of crude was at \$30 to \$40 a barrel," Rich says. Oil at about \$60 makes coal more attractive.

To create the fuel, coal is first mixed with oxygen and steam at high temperature and pressure to produce carbon monoxide and hydrogen. The second step, referred to as Fischer-Tropsch synthesis, uses a catalyst to transform the gas into a liquid synthetic crude, which is further refined. Along the way, mercury, sulfur, ammonia and other compounds are extracted for sale on the commodities market.

The type of technology required to gasify the coal depends on the starting material. Pennsylvania alone has an estimated 260 million tons of waste coal—coal discarded because of its low energy content. "For every

ISOLATION TO INNOVATION

Coal-to-liquid technology is not new, but it remains confined to the turf of political pariahs. The technology first emerged in Germany in the 1920s, and the Nazis refined the process to power their war machine. After the war, the fuel could not compete with the low cost of crude. During the next few decades, however, South Africa took over the reins. Faced with the constant threat of an oil embargo against its apartheid regime, the country tried to wean itself off oil imports. Today the nation's energy giant Sasol holds key patents on certain parts of the process.

two tons of coal mined, up to half ends up in the reject pile," Rich says. Existing nearby facilities are not equipped to burn it. WMPI will rely on approaches innovated by South African energy giant Sasol; those methods are optimized to work with energy-poor coal, which include lignite and bitumen.

The resultant fuel is cleaner than conventional, sulfur-free diesel. In comparison tests, DaimlerChrysler showed that the coal-derived fuel spews 10 percent of the carbon monoxide and hydrocarbons and 70 percent of the particulates. The firm had plans to unveil a demonstration vehicle with a tweaked V-6 engine in April that cuts nitrogen oxides and other emissions even further, says Stefan Keppeler, senior manager of fuels research at the company.

Though relatively clean at the tailpipe, the fuel is dirty at its source. A similar coal-based power plant discharges about four million tons of carbon dioxide a year. In some facilities, the greenhouse gas can be repurposed—it can be pumped into oil fields or, in the case of WMPI's plant, sold to the beverage industry. Unless scientists develop methods to sequester CO_2 and find other uses for the gas, the technology might languish, warns Rudi Heydenrich, business unit manager at Sasol. The gasification step is also expensive, accounting for two thirds of the cost of a facility. "You need a structure where there is government support to ensure sustainable economics in the long run," Heydenrich remarks.

Under the Bush administration's Clean Coal Power Initiative, a $100-million federal loan guarantee jump-started the new WMPI facility. The state of Pennsylvania also chipped in with tax credits and a plan to buy up to half the plant's output to power its vehicles. Investors may contribute the additional $500 million necessary to build the plant. The initial cost of the fuel is expected to be about $54 a barrel.

Coal is not the only source of synthetic

ROGER RESSMEYER *Corbis*

FILL 'ER UP: Coal can be converted into diesel fuel and compete with crude oil at about $60 a barrel.

diesel; the fuel can be derived from natural gas and more cheaply, too. In fact, Qatar and Nigeria are building gas-to-liquid plants, and Sasol estimates that by 2014, gas-to-liquid fuel may account for at least 5 percent of the global market. But the U.S. does not have nearly as much natural gas as coal. And considering the vast coal reserves in China, which is also considering the technology, coal-derived diesel seems likely to play a bigger role in helping to liberate some countries from dependence on oil imports.

Gunjan Sinha is based in Berlin.

SHEAR-THICKENING FLUID stiffens instantly when an object is dragged through it, enabling a vial of the liquid to be lifted. It can improve Kevlar's bullet-stopping power.

KATHY F. ATKINSON *University of Delaware Photo Services*

DEFENSE

Enhanced Armor

NEW SHIELDS TO FEND OFF EVOLVING BATTLEFIELD THREATS BY STEVEN ASHLEY

It's an all-too-familiar scene from the war in Iraq: A video shows a convoy of combat vehicles patrolling a dusty causeway. Suddenly, a huge detonation erupts next to one, often followed by a determined ambush. Over time, the guerrillas have steadily upgraded the lethality of their roadside bombs, suicide assaults and surprise attacks. This year, however, the U.S. military plans to field several new armor systems that should better defend its vehicles and personnel.

"The need to stop multiple, ever evolving threats is a tough problem," states Tony Russell, chief technology officer at Armor Holdings, a security products maker based in Jacksonville, Fla. "The systems we develop must defeat repeated armor-piercing bullet hits as well as the fragments and blast overpressures from explosives. And no one material—metal, composite, ceramic—is best at stopping every threat." Moreover, the armor has to be as light as possible. Successful solutions often mix several different substances to achieve the best result, Russell notes.

One of the least apparent recent improvements in armor has been the development of new, ultrahigh-hardness (UHH) steels. Such alloys are as much as 20 percent harder than the hardest off-the-shelf high-carbon steels, but they tend to be brittle and can crack when hit. Russell says that Armor Holdings has introduced an optimized version called UH56 steel, which is "hard enough to fracture armor-piercing ammo but tough enough not to crack with many impacts." UH56 is also easier to shape than many of its UHH cousins. The enhanced steels are being installed on many U.S. light-armored vehicles.

Researchers are also working on better transparent materials for windows, which are typically made from multiple laminations of bonded glass. As new threats loom, "the reaction is to add another layer of glass," explains Ron Hoffman of the University of Dayton Research Institute. But extra glass can make vehicles top-heavy, fuel-thirsty and sluggish.

One promising solution is to replace the glass with significantly cheaper and more effective aluminum oxynitride (ALON), a hard, sapphirelike material developed by industry, the U.S. Army and the U.S. Air Force. ALON offers better protection against armor-piercing projectiles at roughly half the weight and half the thickness of traditional glass-based transparent armor, Hoffman reports.

ALON has been around for years, but it has always been too expensive and too limited in size for vehicle windows. Engineers at Surmet, a ceramics maker in Burlington, Mass., have improved manufacturing processes involving the heating and compressing of ALON powders to make larger pieces of the material and to lower production costs significantly. Still, at around \$10 to \$15 per square inch, the optical ceramic costs more than military-grade glass (\$3 per square inch). Armor Holdings is expected to start installing the lightweight windows this year.

Body armor will soon be in for some significant enhancements as well. Standard-issue ballistic vests, which are reinforced by hard ceramic plate inserts, are massive and bulky but more protective than today's lighter-weight, multilayer fabric alternatives made of woven Kevlar and other high-strength fibers. A new technology called liquid armor may change that, however.

NEED TO KNOW: SHIELDS UP!

Electromagnetic armor is perhaps the most futuristic type of protection being explored. Engineers are developing it in response to shaped-charge weapons such as rocket-propelled grenades, in which a specially configured explosive forms a penetrating jet of molten copper that can bore its way through thick metal and ceramic armor. Current reactive armor—externally mounted explosives that break up the jets—is heavy and works only once.

Electromagnetic armor systems, in contrast, detect an oncoming projectile and rapidly generate an intense electric field, creating a powerful magnetic field that diverts charged particles in the hot, high-speed jet, which disrupts the warhead's intended effect. Electromagnetic armor should be ready within a few years, depending on the creation of lightweight power sources.

Liquid armor refers to "ballistic fabric infused with a shear-thickening fluid," a substance that stiffens temporarily less than a millisecond after impact, says Norman Wagner, a chemical engineer at the University of Delaware. Co-developed by Wagner's research group and a team led by Eric Wetzel at the U.S. Army Research Lab in Aberdeen, Md., shear-thickening fluid is a mixture of hard nanoparticles (often silica or sand) suspended in a nonevaporating liquid such as polyethylene glycol. Although the fluid adds only about 20 percent to the weight of the fabric, it greatly augments its resistance to puncture by high-speed projectiles. It also reduces the effect of blunt trauma by helping to transmit the impact energy to a larger portion of the ballistic fabric, Wagner explains. Certainly, in today's Iraq, allied forces need all the protection they can get.

NANOTECH

Light Work

BETTER SOLAR NANOTUBES TO SPLIT WATER FOR HYDROGEN **BY ERIC SMALLEY**

The path to the hydrogen economy is getting visibly brighter—literally. Nanotubes that break apart water molecules to liberate hydrogen can now do so more efficiently and could soon use the optical spectrum of sunlight.

In dissociating water with sunlight, engineers have available three technologies: One is solar cells, which hold the record for water-splitting efficiency but are comparatively expensive. Another approach uses microorganisms, which are inexpensive but so far produce only minuscule amounts of hydrogen. The third option is photocatalysis, which relies on momentarily freed electrons in a semiconductor. Electrons that encounter water molecules replace the electrons in the bonds between hydrogen and oxygen. They thus break water apart and generate hydrogen gas. Photocatalysts are potentially less expensive than solar cells and produce more hydrogen than microorganisms.

The trouble is, photocatalysts that split water must work in water, and those that do respond only to ultraviolet light, which makes up about 4 percent of sunlight. Materials that absorb the much more abundant visible portion of solar radiation tend to break down in water.

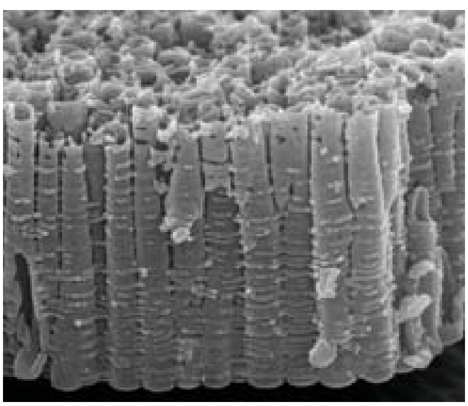
Scientists have turned to nanotubes of titanium dioxide to address efficiency. The tube form of the compound is about five times as efficient as the more typical film form, because the tubular shape enables electrons to stay free longer. Hence, an electron has a greater chance of splitting a water molecule.

Pennsylvania State University electrical engineer Craig Grimes and his team have pushed ultraviolet-to-hydrogen conversion efficiencies just beyond 12 percent using six-micron-long titanium dioxide nanotubes. The nanotubes generate 80 milliliters of hydrogen per hour per watt of ultraviolet light, a record for a photocatalyst-only system.

Now two teams, University of Texas at Austin chemist Allen Bard and his colleagues and the Penn State investigators, have begun formulating titanium dioxide nanotubes that respond to visible light. They have added carbon to titanium dioxide nanotubes to shift the wavelengths of light the tubes absorb to the visible portion of the spectrum. This shift as much as doubles the efficiency under an artificial mixture of ultraviolet and visible light, Bard says. The next step is coming up with a nanotube material that has a high efficiency in pure visible light.

The teams aim to boost the titanium dioxide nanotubes' water-splitting efficiency in visible light above the Department of Energy's 2010 goal of 10 percent. If the average U.S. rooftop were covered with a visible-light, 12 percent–efficient photocatalyst, it would generate the hydrogen equivalent of about 11 liters of gasoline a day, Grimes calculates.

Eric Smalley edits Technology Research News, *an online news service.*



NANOTUBES of titanium dioxide can be modified to respond to visible light in splitting water for hydrogen.

MAGGIE PAULOSE *Pennsylvania State University*

Welfare Woes

MIXED SUCCESS IN GETTING PEOPLE ON THEIR OWN FEET **BY RODGER DOYLE**

Unmarried women with children have long been at the core of the welfare controversy in the U.S. In 1984 Charles Murray, currently a fellow at the American Enterprise Institute, argued that the increasing generosity and availability of welfare—then called Aid to Families with Dependent Children (AFDC)—led to the growth of female-headed families. In 2004 there were almost 1.5 million births to unmarried women, a quarter of them teenagers. Since 2000 the number of unmarried women who gave birth for the first time has averaged at least 650,000 a year. Few have had the resources to rear a child properly.

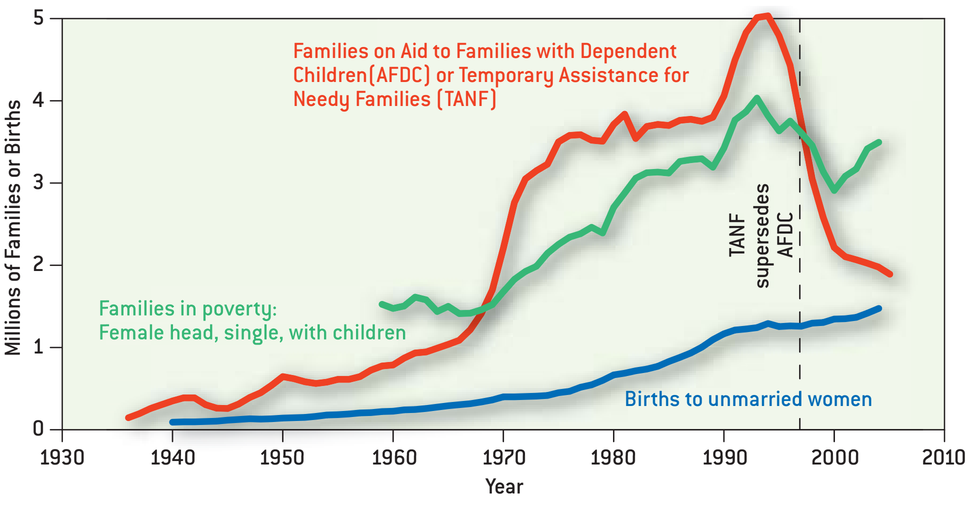
Murray's argument regarding the culpability of AFDC, though contradicted by dozens of independent studies, carried the day. In 1996 the U.S. replaced AFDC with the Temporary Assistance for Needy Families (TANF), which mandated a maximum of five years on the rolls, thereby encouraging recipients to join the paid workforce. Proponents have pointed to TANF's success in lowering welfare rolls, and indeed, as the chart illustrates, the number of welfare families declined dramatically. The levels achieved by mid-2005 are the lowest seen since 1969.

TANF, however, may not be the major reason for this development. According to one analysis, it accounted for about 20 percent of the decline; other factors, including a generally good economy and the Earned Income Tax Credit, a program that gives cash to low-income families, accounted for the rest. Another analysis attributes two thirds of the decline to TANF.

The chart also shows that the number of single mothers in poverty began falling well before TANF took effect and continued to drop until 2000, when the current upturn began. Still, the poverty level remains well below what it was before TANF. Not surprisingly, with such conflicting data, knowledgeable researchers, such as economist Rebecca Blank of the University of Michigan at Ann Arbor, have concluded that determining whether women and children are better off with TANF is not possible at this time.

Besides having stricter requirements, TANF also promotes marriage and discourages out-of-wedlock pregnancy, mainly through education and counseling. But like AFDC before it, TANF has not had any discernible effect on births to unwed mothers, whose numbers have increased almost every year since 1940, when tabulations began. Any program to "end welfare as we know it" must include a serious effort to reduce the number of unwed mothers, for they are the chief recipients of welfare.

Rodger Doyle can be reached at rodgerpdoyle@verizon.net



RODGER DOYLE

FAST FACTS: ON THE ROLLS

U.S. welfare recipients, June 2005:

Total families: 1,893,000

One-parent families: 1,019,000

Two-parent families: 32,000

Other (headed by grandparent, aunt, and so on): 842,000

Percent of recipients who were:

White, non-Hispanic: 37

Black: 39

Hispanic: 19

Native American: 2

Asian or Pacific Islander: 2

FURTHER READING

The Effects of AFDC on American Family Structure, 1940–1990. Steven Ruggles in *Journal of Family History*, Vol. 22, No. 3, pages 307–325; July 1997.

Welfare Reform: Effects of a Decade of Change. Jeffrey Grogger and Lynn Karoly. Harvard University Press, 2005.

Was Welfare Reform Successful? Rebecca M. Blank in *Economists' Voice*. Berkeley Electronic Press, March 2006. Online at www.bepress.com/ev

The Future of Children: The Landscape of Wealth, Poverty and Opportunities for Children. Duncan Lindsey. Oxford University Press (in press).

DATA POINTS: DEICING

Antarctica has lost a significant amount of ice in the past few years, find Isabella Velicogna and John Wahr of the University of Colorado at Boulder. They used measurements taken from April 2002 to August 2005 by the Gravity Recovery and Climate Experiment (GRACE). It consists of two orbiting satellites whose separation is affected by slight gravitational tugs caused by the shifting of mass on the earth's surface. The changes can be measured to an accuracy of one micron.

Percent of the earth's freshwater in Antarctica: 70

Percent of the earth's ice in Antarctica: 90

Cubic kilometers of ice lost annually during study period: 152

In gallons: 40 trillion

Time needed by U.S. to consume that amount of water: 3 months

Resulting contribution to annual rise in sea level: 0.4 millimeter

Margin of error: 0.2 millimeter

Percent of total sea-level rise during study period accounted for by Antarctic melting: 13

SOURCE: Science Express, *March 2*

AVIATION

Powering Off for Safety

Lifting the ban on cell phones during flights, a change being considered by the Federal Communications Commission, may be a bad idea: portable electronics can potentially interfere with GPS navigation, which has been increasingly used during landings. Carnegie Mellon University researchers stowed, with permission, a wireless frequency spectrum analyzer onboard 37 commercial flights in the eastern U.S. They found that passengers made one to four cell phone calls per flight. Moreover, the group discovered that other onboard sources (possibly DVD players, gaming devices or laptops) emitted in the GPS frequency, consistent with anonymous safety reports that these devices have interrupted the function of navigation systems. "There's enough to leave you feeling queasy about opening the floodgates to lots of other radiating sources," says M. Granger Morgan, co-author of a report published in the March *IEEE Spectrum*. If the ban were lifted, portable electronics would still have to comply with airline regulations that prohibit cockpit interference. *—JR Minkel*

CELL PHONES might interfere with GPS signals.

CREATAS/AGE FOTOSTOCK; ILLUSTRATION BY MATT COLLINS

ENTOMOLOGY

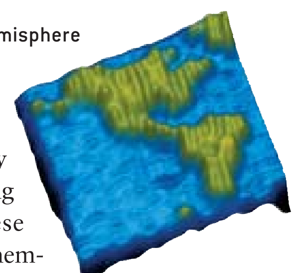
Cannibal Run

Millions of Mormon crickets swarm across western North America—not to devour crops, as do the more familiar locust hordes, but apparently to flee from one another. An international team studying a one-kilometer-long swarm in Idaho last year found that the flightless crickets were avid cannibals. When the scientists left food out for the insects, they clearly preferred meals high in protein and salt, nutrients the crickets are themselves rich in. Impairing cricket mobility (by gluing them to rocks) substantially increased the risk of cannibalization, suggesting that the insects swarm to escape death from behind. Although these forced marches are obviously dangerous for the crickets, apparently traveling alone is even more so, often quickly leading to death from predation. These findings, published online March 3 in the *Proceedings of the National Academy of Sciences USA*, could elucidate why locusts and other insects swarm. *—Charles Q. Choi*

NANOTECH

Origami from DNA

Strands of DNA can be folded into flat structures as elaborate as maps of the Americas. The DNA origami technique developed by California Institute of Technology computer scientist Paul Rothemund takes a long DNA and folds it repeatedly like a piece of string to create any desired shape, much like drawing a picture using a single line. Short DNAs are added to hold each fold in place. The results, revealed in the March 16 *Nature*, are origami forms up to roughly 100 nanometers wide made of about 200 pixels, in which each pixel is a short nucleotide chain. DNA's propensity for spontaneously lining up with matching sequences means these shapes will assemble themselves automatically if the molecules are sequenced properly. Designing structures takes about a day, using a computer program simple enough for a high school chemistry experiment. Scientists could create devices with such origami by attaching electronics or enzymes, and experiments have begun creating three-dimensional structures. *—Charles Q. Choi*



NANO ART: The Western Hemisphere as rendered by DNA.

PAUL ROTHEMUND

PHYSICS

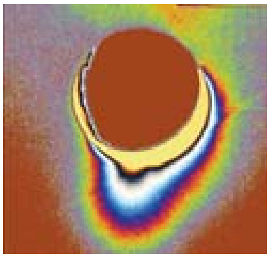
Artificial Gravity with Magnetism

Devices for simulating changes in gravity range from centrifuges to "vomit comets," but simple magnetism may offer the most versatile method. Living tissues are diamagnetic, meaning that they become magnetic in response to an external magnetic field. Researchers have used a powerful magnet to levitate frogs, effectively putting them in zero gravity; now the same Brown University group has varied and reversed the gravity felt by the single-celled paramecium, which senses gravity and swims against it. The scientists found that the cells keep swimming in magnetic fields that simulate up to 10 g's, at which point they tread water or poop out. The technique might serve to grow hard-to-produce tissues for medical research, says Brown physics Ph.D. candidate Karine Guevorkian, who presented the results at the March meeting of the American Physical Society. *—JR Minkel*

PLANETS

Cold Faithful

Ice geysers off the south pole of Saturn's moon Enceladus potentially hint at an underground ocean. In three flybys, the Cassini space probe detected a plume of ice and dust shooting thousands of kilometers high above the cracked, buckling crust. Most of the plume falls back down as snow to gild plains already littered with house-size ice boulders. The rest escapes the moon's gravity apparently to later make up Saturn's blue outermost E ring, some 300,000 kilometers wide. Like Yellowstone's Old Faithful, Enceladus's geysers are powered largely by deep-down heat, researchers believe. The heat within the moon that must be setting off the geysers may result from shifting, glacierlike tectonic plates and tidal forces. Such movement suggests that a liquid ocean might lie 10 meters or less below the icy surface. It might even be capable of supporting life, scientists speculate in the March 10 *Science*. *—Charles Q. Choi*



GEYSER erupts from Enceladus, as seen in false color by the Cassini probe.

VISION

Eyeing Redness

Color vision may have originated in humans and related primates to spot blushes on cheeks and faces pale with fear. Whereas birds' and bees' color receptors are evenly sensitive across the visible spectrum, two of the three kinds of color photoreceptors in humans and other Old World primates are both most sensitive to roughly 550-nanometer-wavelength light. California Institute of Technology neurobiologists suggest that this closeness in sensitivities is optimized toward detecting subtle changes in skin tone because of varying concentrations of oxygenated hemoglobin in the blood. This could help primates tell if a potential mate is rosy from good health or if an enemy is blanched with alarm. Supporting this idea, they say in their upcoming June 22 *Biology Letters* paper, is the fact that Old World primates tend to be bare-faced and bare-bottomed, the better to color-signal with. *—Charles Q. Choi*

SEEING RED in cheeks may explain why primate vision is sensitive to that color.

NASA/JPL/SPACE SCIENCE INSTITUTE (*top*); MITSUAKI IWAGO *Minden Pictures* (*bottom*)

BRIEF POINTS

- **Sleep on it: subjects pondering a complex decision and then distracted by puzzles made more satisfying choices than those who deliberated continuously. Evidently, the unconscious mind is better at plowing through information without bias.**

  Science, February 17

- **One concern about carbon nanotubes has been their toxicity—they can build up inside the body and damage organs. Special chemical modifications of the tube surface, however, enabled the nanotubes to be excreted intact in urine.**

  Proceedings of the National Academy of Sciences USA, February 28

- **First, the good news: treating mildly elevated blood pressure with drugs moderately cut the risk of hypertension later, perhaps by interfering with vascular processes that ultimately boost pressure.**

  New England Journal of Medicine online, March 14

- **Now, the bad: reducing blood levels of homocysteine, an amino acid thought to increase the likelihood of cardiovascular disease, by taking B vitamins failed to prevent heart attacks and stroke in high-risk patients.**

  New England Journal of Medicine online, March 12

SHAM Scam

The Self-Help and Actualization Movement has become an $8.5-billion-a-year business. Does it work? By MICHAEL SHERMER

According to self-help guru Tony Robbins, walking barefoot across 1,000-degree red-hot coals "is an experience in belief. It teaches people in the most visceral sense that they can change, they can grow, they can stretch themselves, they can do things they never thought possible."

I've done three fire walks myself, without chanting "cool moss" (as Robbins has his clients do) or thinking positive thoughts. I didn't get burned. Why? Because charcoal is a poor conductor of heat, particularly through the dead calloused skin on the bottom of your feet and especially if you scoot across the bed of coals as quickly as fire walkers are wont to do. Think of a cake in a 400-degree oven—you can touch the cake, a poor conductor, without getting burned, but not the metal cake pan. Physics explains the "how" of fire walking. To understand the "why," we must turn to psychology.

If you need to pay for someone's help, why is it called "self-help"?

In 1980 I attended a bicycle industry trade convention whose keynote speaker was Mark Victor Hansen, now well known as the coauthor of the wildly popular *Chicken Soup for the Soul* book series that includes the *Teenage Soul, Prisoner's Soul* and *Christian Soul* (but no *Skeptic's Soul*). I was surprised that Hansen didn't require a speaker's fee, until I saw what happened after his talk: people were lined up out the door to purchase his motivational tapes. I was one of them. I listened to those tapes over and over during training rides in preparation for bicycle races.

The "over and over" part is the key to understanding the "why" of what investigative journalist Steve Salerno calls the Self-Help and Actualization Movement (SHAM). In his recent book *SHAM: How the Self-Help Movement Made America Helpless* (Crown Publishing Group, 2005), he explains how the talks and tapes offer a momentary boost of inspiration that fades after a few weeks, turning buyers into repeat customers. While Salerno was a self-help book editor for Rodale Press (whose motto at the time was "to show people how they can use the power of their bodies and minds to make their lives better"), extensive market surveys revealed that "the most likely customer for a book on any given topic was someone who had bought a similar book within the preceding eighteen months." The irony of "the eighteen-month rule" for this genre, Salerno says, is this: "If what we sold worked, one would expect lives to improve. One would not expect people to need further help from us—at least not in that same problem area, and certainly not time and time again."

Surrounding SHAM is a bulletproof shield: if your life does not get better, it is your fault—your thoughts were not positive enough. The solution? More of the same self-help—or at least the same message repackaged into new products. Consider the multiple permutations of John Gray's *Men Are from Mars, Women Are from Venus—Mars and Venus Together Forever, Mars and Venus in the Bedroom, The Mars and Venus Diet and Exercise Solution*—not to mention the *Mars and Venus* board game, Broadway play and Club Med getaway.

SHAM takes advantage by cleverly marketing the dualism of victimization and empowerment. Like a religion that defines people as inherently sinful so that they require forgiveness (provided exclusively by that religion), SHAM gurus insist that we are all victims of our demonic "inner children" who are produced by traumatic pasts that create negative "tapes" that replay over and over in our minds. Redemption comes through empowering yourself with new "life scripts," supplied by the masters themselves, for prices that range from $500 one-day workshops to Robbins's $5,995 "Date with Destiny" seminar.

Do these programs work? No one knows. According to Salerno, no scientific evidence indicates that any of the countless SHAM techniques—from fire walking to 12-stepping—works better than doing something else or even doing nothing. The law of large numbers means that given the millions of people who have tried SHAMs, inevitably some will improve. As with alternative-medicine nostrums, the body naturally heals itself and whatever the patient was doing to help gets the credit.

Patient, heal thyself—the true meaning of self-help. SA

Michael Shermer is publisher of Skeptic *(www.skeptic.com) and author of* Science Friction.

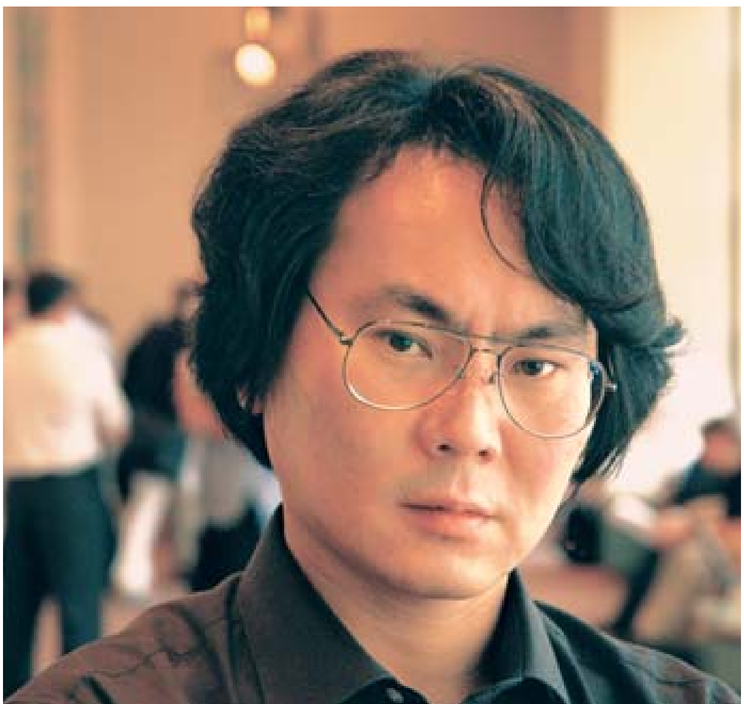
BRAD HINES

Page Intentionally Blank

Android Science

Hiroshi Ishiguro makes perhaps the most humanlike robots around—not particularly to serve as societal helpers but to tell us something about ourselves By TIM HORNYAK

At the 2005 World Exposition in Japan's Aichi prefecture, robots from laboratories throughout the country were on display. The humanoids came in all shapes and sizes: they moved on wheels, walked on two legs, looked like lovable little dolls or fantastic mechanical warriors. All, however, were instantly recognizable as artificial creations. Except one: it had moist lips, glossy hair and vivid eyes that blinked slowly. Seated on a stool with hands folded primly on its lap, it wore a bright pink blazer and gray slacks. For a mesmerizing few seconds from several meters away, Repliee Q1expo was virtually indistinguishable from an ordinary woman in her 30s. In fact, it was a copy of one.



TIM HORNYAK

HIROSHI ISHIGURO: ROBOTS' HUMAN TOUCH

- Creator of humanoid robot Repliee, modeled after a human newscaster.
- On how to develop more human-friendly robots: "We have to study cognitive science, psychology and neuroscience, maybe sociology. It's very important to integrate these different research areas."

To many people, Repliee is more than a humanoid robot—it is an honest-to-goodness android, so lifelike that it seems like a real person. Japan boasts the most advanced humanoid robots in the world, represented by Honda's Asimo and other bipedal machines. They are expected to eventually pitch in as the workforce shrinks amid the dwindling and aging population. But why build a robot with pigmented silicone skin, smooth gestures and even makeup? To Repliee's creator, Hiroshi Ishiguro, the answer is simple: "Android science."

Director of Osaka University's Intelligent Robotics Laboratory, Ishiguro has a high furrowed brow beneath a shock of inky hair and riveting eyes that seem on the verge of emitting laser beams. Besides the justification for making robots anthropomorphic and bipedal so they can work in human environments with architectural features such as stairs, Ishiguro believes that people respond better to very humanlike robots. Androids can thus elicit the most natural communication. "Appearance is very important to have better interpersonal relationships with a robot," says the 42-year-old Ishiguro. "Robots are information media, especially humanoid robots. Their main role in our future is to interact naturally with people."

Although Ishiguro grew up as a typical robot-model-building Japanese boy near Kyoto, he was more keen on philosophical questions about life than on inventing robots. Mild colorblindness forced him to abandon his aspirations of a career as an oil painter, and he was drawn to computer and robot vision instead. He built a guide robot for the blind as an undergraduate at the University of Yamanashi, and elements of his later humanoid Robovie went into the design of Mitsubishi Heavy Industries's new household communications robot, Wakamaru. A fan of the android character Data from the *Star Trek* franchise, he sees robots as the ideal vehicle to understand more about ourselves.

To emulate human looks and behavior successfully, Ishiguro yokes robotics with cognitive science. In turn, cognitive science research can use the robot as a test bed to study human perception, communication and other faculties. This novel cross-fertilization is what Ishiguro describes as android science. In a 2005 paper, he and his collaborators explained it thus: "To make the android humanlike, we must investigate human activity from the standpoint of [cognitive science, behavioral science and neuroscience], and to evaluate human activity, we need to implement processes that support it in the android."

One key strategy in Ishiguro's approach is to model robots on real people. He began research four years ago with his then four-year-old daughter, casting a rudimentary android from her body, but its few actuator mechanisms resulted in jerky, unnatural motion. With Tokyo-based robotics maker Kokoro Company, Ishiguro built Repliee also by "copying" a real person—NHK TV newscaster Ayako Fujii—with shape-memory silicone rubber and plaster molds. Polyurethane and a five-millimeter-thick silicone skin, soft and specially colored, cover a metal skeleton. Given clothing, a wig and lipstick, it is a near mirror image of Fujii.

REPLICATED: Ayako Fujii poses with her android clone, made for the 2005 Aichi Expo by Ishiguro's lab and Kokoro Company.

Appearance, though, is only part of human likeness. To achieve smooth upper-body movement in Repliee, Ishiguro equipped it with 42 small, quiet air servo-actuators. Because a fridge-size external air compressor powers the actuators, locomotion was sacrificed. Similarly, Ishiguro off-loaded most of the android's control elements and sensors. Floor sensors track human movement, video cameras detect faces and gestures, and microphones pick up speech. The result is a surprisingly good. "I was developed for the purpose of research into natural human-robot communication," Repliee says in velvety prerecorded Japanese, raising its arm in instantaneous response to a touch picked up by its piezoelectric skin sensors.

Humanlike robots run the risk of compromising people's comfort zones. Says Ishiguro collaborator Takashi Minato: "Because the android's appearance is very similar to that of a human, any subtle differences in motion and responses will make it seem strange." The negative emotional reaction is known as the "uncanny valley," first described in 1970 by Japanese roboticist Masahiro Mori. Repliee, though, is so lifelike that it has overcome the creepiness factor, partly because of the natural way it moves.

One of Ishiguro's android-science experiments demonstrates the importance of movement. He had subjects identify the color of a cloth behind a curtain after it had been pulled back for two seconds. Unknown to participants, Repliee was also behind the curtain, either motionless or exhibiting prelearned "micro movements" that people unconsciously make. When the android was static, 70 percent of the subjects realized that they had seen a robot. But when Repliee moved slightly, only 30 percent realized it was an android.

In a land where Sony Aibo robot dogs are treated like family, it is not surprising that the engineering students who work on Repliee daily have developed a special protectiveness for it. Gaze-direction experiments suggest that nonengineers can unconsciously accept androids on a social level, too. In these studies, subjects pausing to consider a thought looked away during conversations with both people and Repliee, leading Ishiguro and his associates to consider that the breaking of eye contact can be a measure of an android's human likeness. They see this as key to eliminating psychological barriers to robots playing everyday roles in society. (Less sophisticated androids are already at work in Japan: Saya, a robot with fewer sensors and limited movement that was developed by Hiroshi Kobayashi of Tokyo University of Science, has been a receptionist in the university's lobby for years.)

"An android is a kind of ultimate experimental apparatus and test bed," states Ishiguro collaborator Karl MacDorman, who has been examining possible links between the uncanny valley and fear of death. "We need more of them."

Although Ishiguro's automatons may even evolve to bipedalism, perhaps ironically, he is sure that androids will never be able to pass for human. There will be no need, say, for the elaborate *Blade Runner*–type "empathy tests." "Two seconds or 10 seconds of confusion is possible, but a whole day is not," Ishiguro remarks. "It's impossible to have the perfect android."

Still, he wants his next android, a male, to be as authentic as possible. The model? Himself. Ishiguro thinks having a robot clone could ease his busy schedule: he could dispatch it to classes and meetings and then teleconference through it. "My question has always been, Why are we living, and what is human?" he says. An Ishiguro made of circuitry and silicone might soon be answering his own questions. SA

Tim Hornyak is author of Loving the Machine: The Art and Science of Japanese Robots, *to be published in the U.S. in September by Kodansha International.*

the first few MICROSECONDS

In recent experiments, physicists have replicated conditions of the infant universe—with startling results

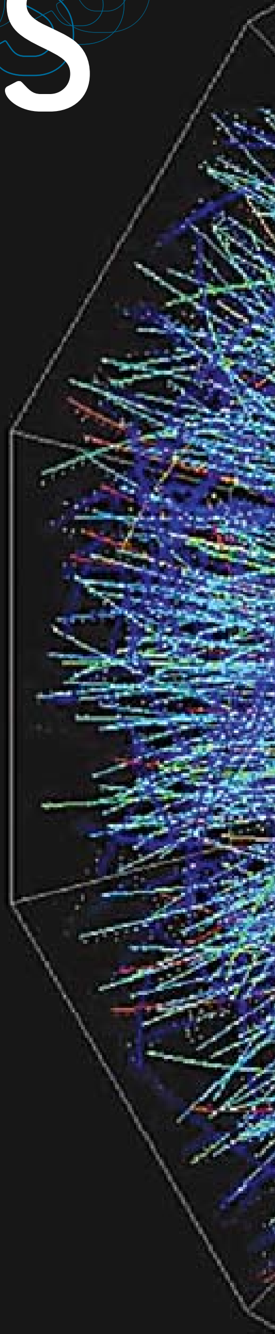
BY MICHAEL RIORDAN AND WILLIAM A. ZAJC

For the past five years, hundreds of scientists have been using a powerful new atom smasher at Brookhaven National Laboratory on Long Island to mimic conditions that existed at the birth of the universe. Called the Relativistic Heavy Ion Collider (RHIC, pronounced "rick"), it clashes two opposing beams of gold nuclei traveling at nearly the speed of light. The resulting collisions between pairs of these atomic nuclei generate exceedingly hot, dense bursts of matter and energy to simulate what happened during the first few microseconds of the big bang. These brief "mini bangs" give physicists a ringside seat on some of the earliest moments of creation.

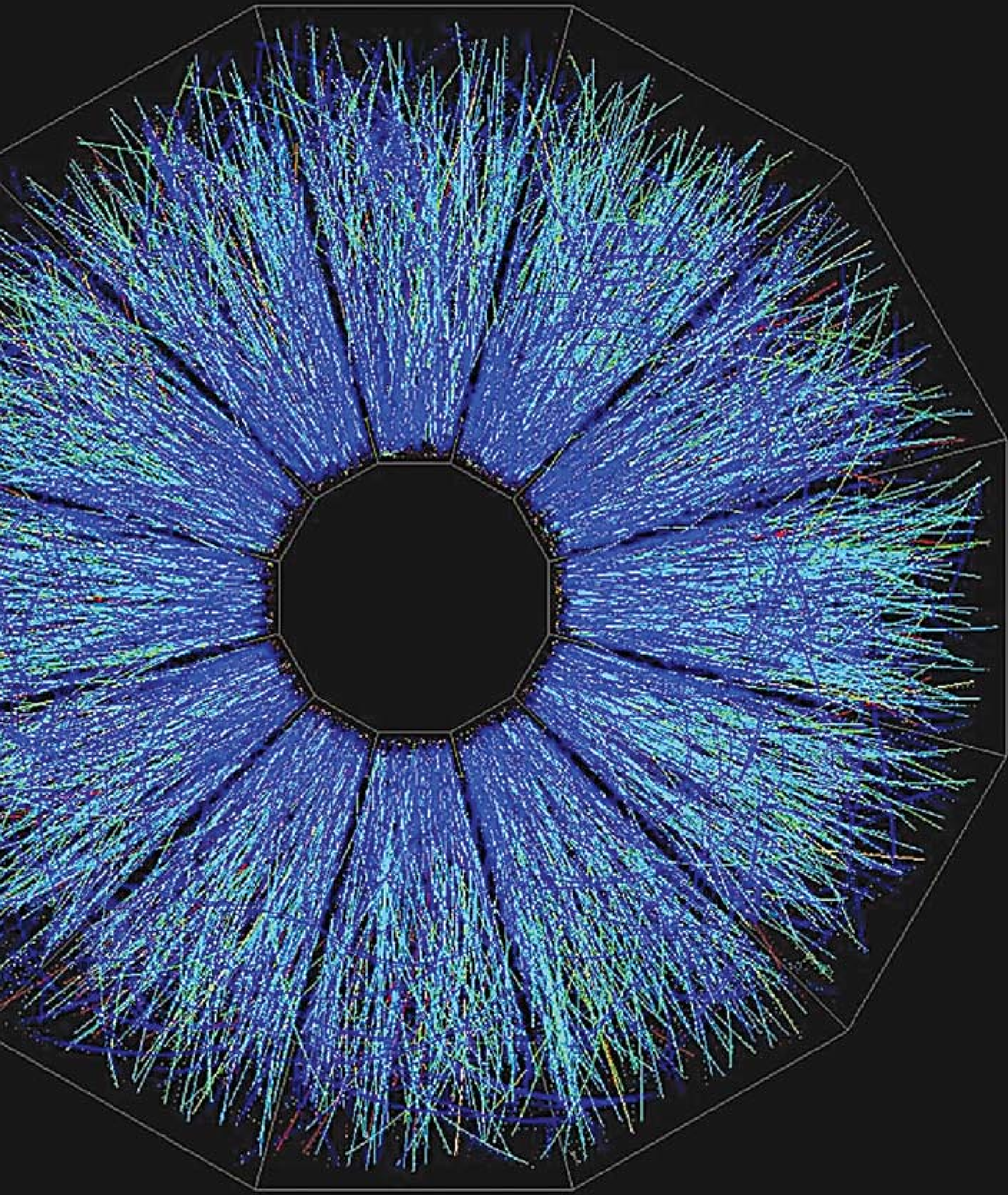
During those early moments, matter was an ultrahot, superdense brew of particles called quarks and gluons rushing hither and thither and crashing willy-nilly into one another. A sprinkling of electrons, photons and other light elementary particles seasoned the soup. This mixture had a temperature in the trillions of degrees, more than 100,000 times hotter than the sun's core.

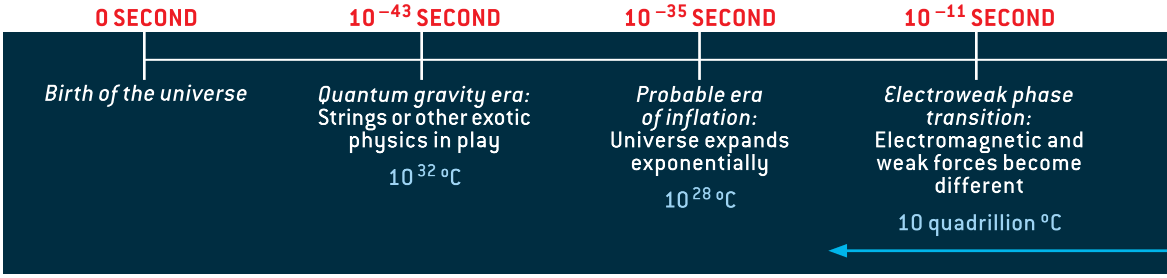
But the temperature plummeted as the cosmos expanded, just like an ordinary gas cools today when it expands rapidly. The quarks and gluons slowed down so much that some of them could begin sticking together briefly. After nearly 10 microseconds had elapsed, the quarks and gluons became shackled together by strong forces between them, locked up permanently within protons, neutrons and other strongly interacting particles that physicists collectively call "hadrons." Such an abrupt change in the properties of a material is called a phase transition (like liquid water freezing into ice). The cosmic phase transition from the original mix of quarks and gluons into mundane protons and neutrons is of intense interest to scientists, both those who seek clues about how the universe evolved toward its current highly structured state and those who wish to understand better the fundamental forces involved.

The protons and neutrons that form the nuclei of every atom today are



THOUSANDS OF PARTICLES streaming out from an ultrahigh-energy collision between two gold nuclei are imaged by the STAR detector at RHIC. Conditions during the collision emulate those present a few microseconds into the big bang.





COSMIC TIMELINE shows some significant eras in the early history of the universe. Experiments—SPS, RHIC and the future LHC—probe progressively further back into the first microseconds when the quark-gluon medium existed.

relic droplets of that primordial sea, tiny subatomic prison cells in which quarks thrash back and forth, chained forever. Even in violent collisions, when the quarks seem on the verge of breaking out, new "walls" form to keep them confined. Although many physicists have tried, no one has ever witnessed a solitary quark drifting all alone through a particle detector.

RHIC offers researchers a golden opportunity to observe quarks and gluons unchained from protons and neutrons in a collective, quasi-free state reminiscent of these earliest microseconds of existence. Theorists originally dubbed this concoction the quark-gluon plasma, because they expected it to act like an ultrahot gas of charged particles (a plasma) similar to the innards of a lightning bolt. By smashing heavy nuclei together in mini bangs that briefly liberate quarks and gluons, RHIC serves as a kind of time telescope providing glimpses of the early universe, when the ultrahot, superdense quark-gluon plasma reigned supreme. And the greatest surprise at RHIC so far is that this exotic substance seems to be acting much more like a liquid—albeit one with very special properties—than a gas.

Free the Quarks

IN 1977, when theorist Steven Weinberg published his classic book *The First Three Minutes* about the physics of the early universe, he avoided any definitive conclusions about the first hundredth of a second. "We simply do not yet know enough about the physics of elementary particles to be able to calculate the properties of such a mélange with any confidence," he lamented. "Thus our ignorance of microscopic physics stands as a veil, obscuring our view of the very beginning."

But theoretical and experimental breakthroughs of that decade soon began to lift the veil. Not only were protons, neutrons and all other hadrons found to contain quarks; in addition, a theory of the strong force between quarks—known as quantum chromodynamics, or QCD—emerged in the mid-1970s. This theory postulated that a shadowy cabal of eight neutral particles called gluons flits among the quarks, carrying the unrelenting force that confines them within hadrons.

What is especially intriguing about QCD is that—contrary to what happens with such familiar forces as gravity and electromagnetism—the coupling strength grows *weaker* as quarks approach one another. Physicists have called this curious counterintuitive behavior asymptotic freedom. It means that when two quarks are substantially closer than a proton diameter (about 10^{-13} centimeter), they feel a reduced force, which physicists can calculate with great precision by means of standard techniques. Only when a quark begins to stray from its partner does the force become truly strong, yanking the particle back like a dog on a leash.

In quantum physics, short distances between particles are associated with high-energy collisions. Thus, asymptotic freedom becomes important at high temperatures when particles are closely packed and constantly undergo high-energy collisions with one another.

More than any other single factor, the asymptotic freedom of QCD is what allows physicists to lift Weinberg's veil and evaluate what happened during those first few microseconds. As long as the temperature exceeded about 10 trillion degrees Celsius, the quarks and gluons acted essentially independently. Even at lower temperatures, down to two trillion degrees, the quarks would have roamed individually—although by then they would have begun to feel the confining QCD force tugging at their heels.

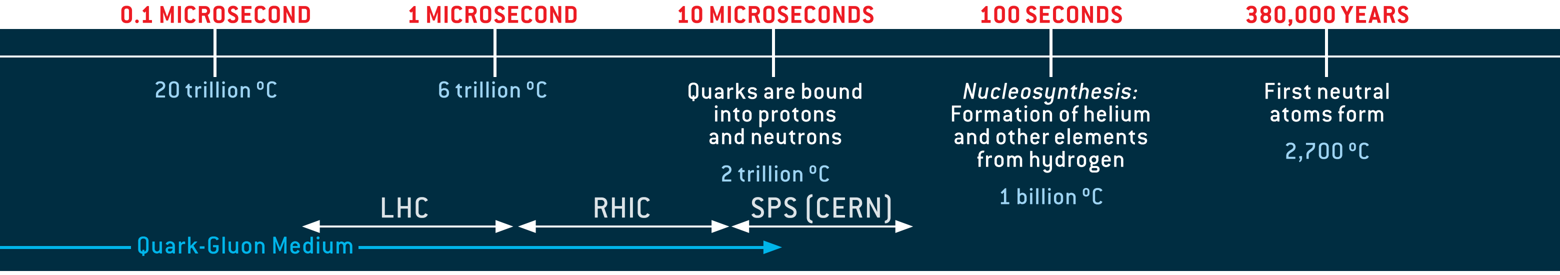
To simulate such extreme conditions here on earth, physicists must re-create the enormous temperatures, pressures and densities of those first few microseconds. Temperature is essentially the average kinetic energy of a particle in a swarm of similar particles, whereas pressure increases with the swarm's energy density. Hence, by squeezing the highest possible energies into the smallest possible volume we have the best chance of simulating conditions that occurred in the big bang.

Fortunately, nature provides ready-made, extremely dense nuggets of matter in the form of atomic nuclei. If you could somehow gather together a thimbleful of this nuclear matter, it would weigh 300 million tons. Three decades of experience colliding heavy nuclei such as lead and gold at high energies have shown that the densities occurring during these collisions far surpass that of normal nuclear matter. And the tem-

Overview/*Mini Bangs*

- In the first 10 microseconds of the big bang, the universe consisted of a seething maelstrom of elementary particles known as quarks and gluons. Ever since that epoch, quarks and gluons have been locked up inside the protons and neutrons that make up the nuclei of atoms.
- For the past five years, experiments at the Relativistic Heavy Ion Collider (RHIC) have been re-creating the so-called quark-gluon plasma on a microscopic scale by smashing gold nuclei together at nearly the speed of light. To physicists' great surprise, the medium produced in these mini bangs behaves not like a gas but like a nearly perfect liquid.
- The results mean that models of the very early universe may have to be revised. Some assumptions that physicists make to simplify their computations relating to quarks and gluons also need to be reexamined.

BROOKHAVEN NATIONAL LABORATORY/RHIC COLLABORATION (*preceding pages*); LUCY READING-IKKANDA (*timeline*)



peratures produced may have exceeded five trillion degrees.

Colliding heavy nuclei that each contain a total of about 200 protons and neutrons produces a much larger inferno than occurs in collisions of individual protons (as commonly used in other high-energy physics experiments). Instead of a tiny explosion with dozens of particles flying out, such heavy-ion collisions create a seething fireball consisting of thousands of particles. Enough particles are involved for the collective properties of the fireball—its temperature, density, pressure and viscosity (its thickness or resistance to flowing)—to become useful, significant parameters. The distinction is important—like the difference between the behavior of a few isolated water molecules and that of an entire droplet.

The RHIC Experiments

FUNDED BY the U.S. Department of Energy and operated by Brookhaven, RHIC is the latest facility for generating and studying heavy-ion collisions. Earlier nuclear accelerators fired beams of heavy nuclei at stationary metal targets. RHIC, in contrast, is a particle collider that crashes together two beams of heavy nuclei. The resulting head-on collisions generate far greater energies for the same velocity of particle because all the available energy goes into creating mayhem. This is much like what happens when two speeding cars smash head-on. Their energy of motion is converted into the random, thermal energy of parts and debris flying in almost every direction.

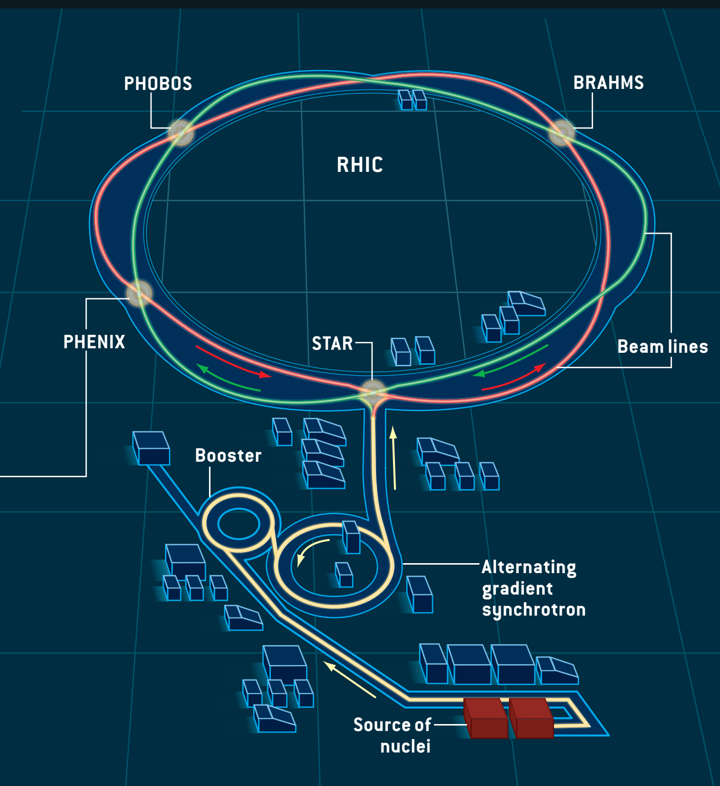
At the highly relativistic energies generated at RHIC, nuclei travel at more than 99.99 percent of the speed of light, reaching energies as high as 100 giga-electron volts (GeV) for every proton or neutron inside. (One GeV is about equivalent to the mass of a stationary proton.) Two strings of 870 superconducting magnets cooled by tons of liquid helium steer the beams around two interlaced 3.8-kilometer rings. The beams clash at four points where these rings cross. Four sophisticated particle detectors known as BRAHMS, PHENIX, PHOBOS and STAR record the subatomic debris spewing out from the violent smash-ups at these collision points.

When two gold nuclei collide head-on at RHIC's highest attainable energy, they dump a total of more than 20,000 GeV into a microscopic fireball just a trillionth of a centimeter across. The nuclei and their constituent protons and neutrons literally melt, and many more quarks, antiquarks (antimatter opposites of the quarks) and gluons are created from all the energy available. More than 5,000 elementary particles are

COLLIDING AND DETECTING PARTICLES

RHIC consists primarily of two 3.8-kilometer rings (*red* and *green*), or beam lines, that accelerate gold and other heavy nuclei to 0.9999 of the speed of light. The beam lines cross at six locations. At four of these intersections, the nuclei collide head-on, producing mini bangs that emulate conditions during the big bang that created the universe. Detectors known as BRAHMS, PHENIX, PHOBOS and STAR analyze the debris flying out from the collisions.

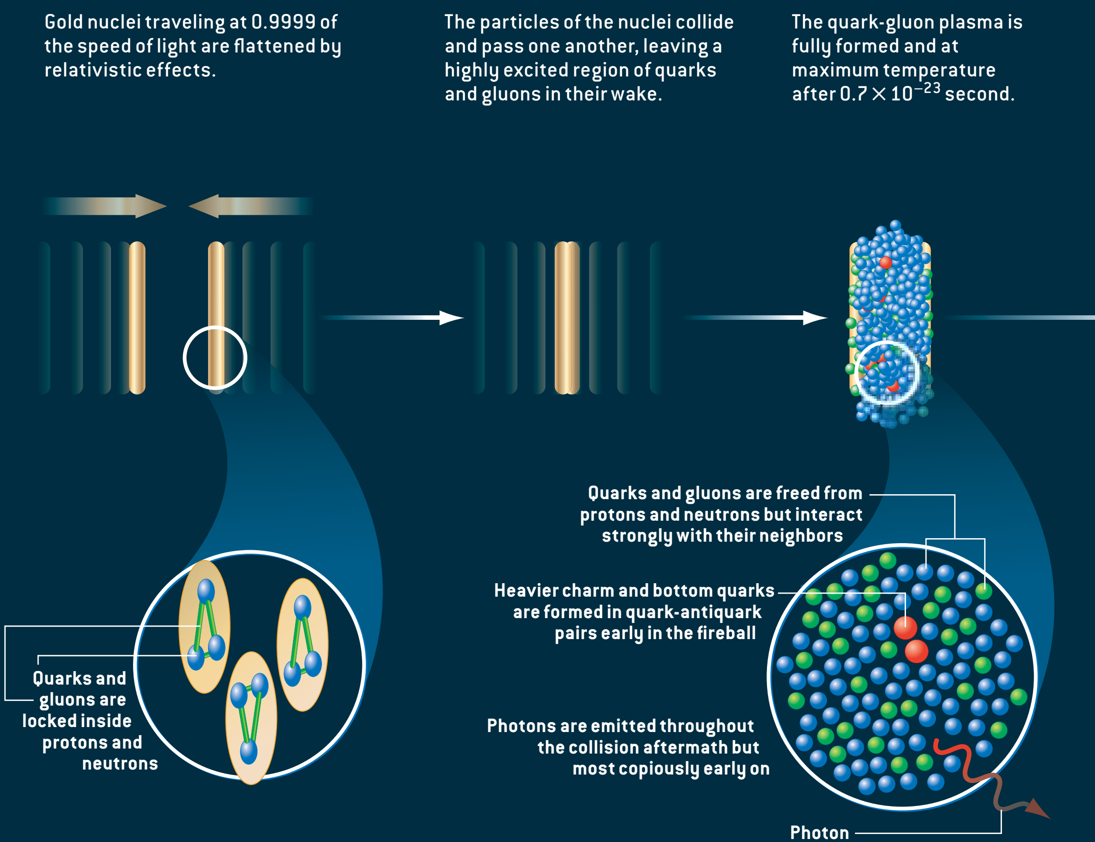
PHENIX experiment (shown here in partial disassembly during maintenance) searches for specific particles produced very early in the mini bangs.



BROOKHAVEN NATIONAL LABORATORY/RHIC COLLABORATION (*photograph*); LUCY READING-IKKANDA (*illustration*)

A MINI BANG FROM START TO FINISH

RHIC generates conditions similar to the first few microseconds of the big bang by slamming together gold nuclei at nearly the speed of light. Each collision, or mini bang, goes through a series of stages, briefly producing an expanding fireball of gluons (*green*), quarks and antiquarks. The quarks and antiquarks are mostly of the up, down and strange species (*blue*), with only a few of the heavier charm and bottom species (*red*). The fireball ultimately blows apart in the form of hadrons (*silver*), which are detected along with photons and other decay products. Scientists deduce the physical properties of the quark-gluon medium from the properties of these detected particles.



briefly liberated in typical encounters. The pressure generated at the moment of collision is truly immense, a whopping 10^{30} times atmospheric pressure, and the temperature inside the fireball soars into the trillions of degrees.

But about 50 trillionths of a trillionth (5×10^{-23}) of a second later, all the quarks, antiquarks and gluons recombine into hadrons that explode outward into the surrounding detectors. Aided by powerful computers, these experiments attempt to record as much information as possible about the thousands of particles reaching them. Two of these experiments, BRAHMS and PHOBOS, are relatively small and concentrate on observing specific characteristics of the debris. The other two, PHENIX and STAR, are built around huge, general-purpose devices that fill their three-story experimental halls with thousands of tons of magnets, detectors, absorbers and shielding [*see bottom box on preceding page*].

The four RHIC experiments have been designed, constructed and operated by separate international teams ranging from 60 to more than 500 scientists. Each group has employed a different strategy to address the daunting challenge presented by the enormous complexity of RHIC events. The BRAHMS collaboration elected to focus on remnants of the original protons and neutrons that speed along close to the direction of the colliding gold nuclei. In contrast, PHOBOS observes particles over the widest possible angular range and studies correlations among them. STAR was built around the world's largest "digital camera," a huge cylinder of gas that provides three-dimensional pictures of all the charged particles emitted in a large aperture surrounding the beam axis [*see illustration on page 35*]. And PHENIX searches for specific particles produced very early in the collisions that can emerge unscathed from the boiling cauldron of quarks and gluons. It thus provides a kind of x-ray portrait of the inner depths of the fireball.

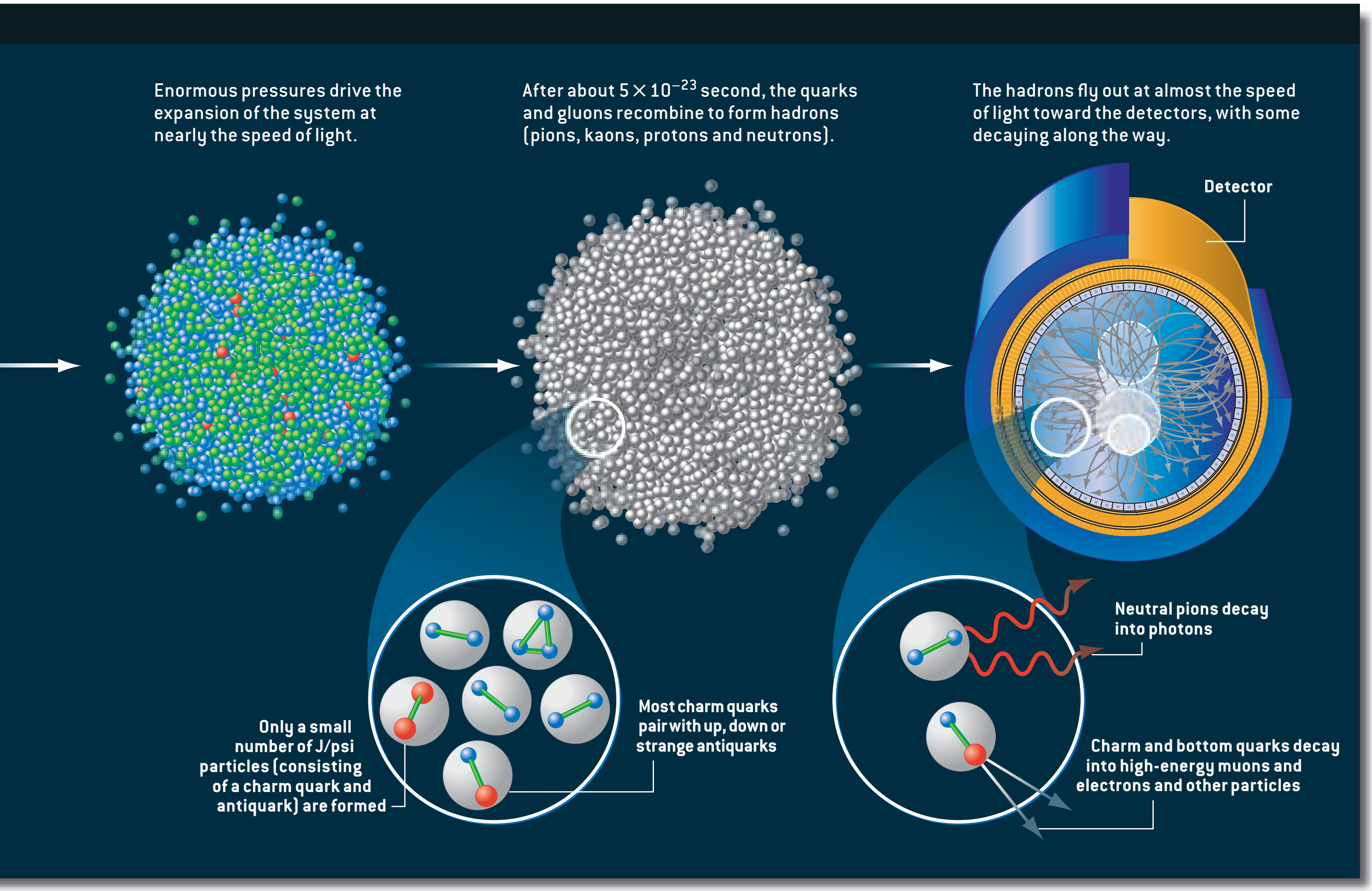
A Perfect Surprise

THE PHYSICAL PICTURE emerging from the four experiments is consistent and surprising. The quarks and gluons indeed break out of confinement and behave collectively, if only fleetingly. But this hot mélange acts like a liquid, not the ideal gas theorists had anticipated.

The energy densities achieved in head-on collisions between two gold nuclei are stupendous, about 100 times those of the nuclei themselves—largely because of relativity. As viewed from the laboratory, both nuclei are relativistically flattened into ultrathin disks of protons and neutrons just before they meet. So all their energy is crammed into a very tiny volume at the moment of impact. Physicists estimate that the resulting energy density is at least 15 times what is needed to set the quarks and gluons free. These particles immediately begin darting in every direction, bashing into one another repeatedly and thereby reshuffling their energies into a more thermal distribution.

Evidence for the rapid formation of such a hot, dense me-

LUCY READING-IKKANDA



dium comes from a phenomenon called jet quenching. When two protons collide at high energy, some of their quarks and gluons can meet nearly head-on and rebound, resulting in narrow, back-to-back sprays of hadrons (called jets) blasting out in opposite directions [*see box on next page*]. But the PHENIX and STAR detectors witness only one half of such a pair in collisions between gold nuclei. The lone jets indicate that individual quarks and gluons are indeed colliding at high energy. But where is the other jet? The rebounding quark or gluon must have plowed into the hot, dense medium just formed; its high energy would then have been dissipated by many close encounters with low-energy quarks and gluons. It is like firing a bullet into a body of water; almost all the bullet's energy is absorbed by slow-moving water molecules, and it cannot punch through to the other side.

Indications of liquidlike behavior of the quark-gluon medium came early in the RHIC experiments, in the form of a phenomenon called elliptic flow. In collisions that occur slightly off-center—which is often the case—the hadrons that emerge reach the detector in an elliptical distribution. More energetic hadrons squirt out within the plane of the interaction than at right angles to it. The elliptical pattern indicates that substantial pressure gradients must be at work in the quark-gluon medium and that the quarks and gluons from which these hadrons formed were behaving collectively, before reverting back into hadrons. They were acting like a liquid—that is, not a gas. From a gas, the hadrons would emerge uniformly in all directions.

This liquid behavior of the quark-gluon medium must mean that these particles interact with one another rather strongly during their heady moments of liberation right after formation. The decrease in the strength of their interactions (caused by the asymptotic freedom of QCD) is apparently overwhelmed by a dramatic increase in the *number* of newly liberated particles. It is as though our poor prisoners have broken out of their cells, only to find themselves haplessly caught up in a jail-yard crush, jostling with all the other escapees. The resulting tightly coupled dance is exactly what happens in a liquid. This situation conflicts with the naive theoretical picture originally painted of this medium as an almost ideal, weakly interacting gas. And the detailed features of the elliptical asymmetry suggest that this surprising liquid flows with almost no viscosity. It is probably the most perfect liquid ever observed.

THE AUTHORS

MICHAEL RIORDAN teaches the history of physics at Stanford University and at the University of California, Santa Cruz, where he is adjunct professor of physics. He is author of *The Hunting of the Quark* and co-author of *The Shadows of Creation*. *WILLIAM A. ZAJC* is professor of physics at Columbia University. For the past eight years, he has served as scientific spokesperson for the PHENIX Experiment at RHIC, an international collaboration of more than 400 scientists from 13 nations.

The Emerging Theoretical Picture

CALCULATING THE STRONG INTERACTIONS occurring in a liquid of quarks and gluons that are squeezed to almost unimaginable densities and exploding outward at nearly the speed of light is an immense challenge. One approach is to perform brute-force solutions of QCD using huge arrays of microprocessors specially designed for this problem. In this so-called lattice-QCD approach, space is approximated by a discrete lattice of points (imagine a Tinkertoy structure). The QCD equations are solved by successive approximations on the lattice.

Using this technique, theorists have calculated such properties as pressure and energy density as a function of temperature; each of these dramatically increases when hadrons are transformed into a quark-gluon medium. But this method is best suited for static problems in which the medium is in thermodynamic equilibrium, unlike the rapidly changing conditions in RHIC's mini bangs. Even the most sophisticated lattice-QCD calculations have been unable to determine such dynamic features as jet quenching and viscosity. Although the viscosity of a system of strongly interacting particles is expected to be small, it cannot be exactly zero because of quantum mechanics. But answering the question "How low can it go?" has proved notoriously difficult.

Remarkably, help has arrived from an unexpected quarter: string theories of quantum gravity. An extraordinary conjecture by theorist Juan Maldacena of the Institute for Advanced Study in Princeton, N.J., has forged a surprising connection between a theory of strings in a warped five-dimensional space and a QCD-like theory of particles that exist on the four-dimensional boundary of that space [see "The Illusion of Gravity," by Juan Maldacena; SCIENTIFIC AMERICAN, November 2005]. The two theories are mathematically equivalent even though they appear to describe radically different realms of physics. When the QCD-like forces get strong, the corresponding string theory becomes weak and hence easier to evaluate. Quantities such as viscosity that are hard to calculate in QCD have counterparts in string theory (in this case, the absorption of gravity waves by a black hole) that are much more tractable. A very small but nonzero lower limit on what is called the specific viscosity emerges from this approach—only about a tenth of that of superfluid helium. Quite possibly, string theory may help us understand how quarks and gluons behaved during the earliest microseconds of the big bang.

Future Challenges

ASTONISHINGLY, the hottest, densest matter ever encountered far exceeds all other known fluids in its approach to perfection. How and why this happens is the great experimental challenge now facing physicists at RHIC. The wealth of data from these experiments is already forcing theorists to reconsider some cherished ideas about matter in the early universe. In the past, most calculations treated the freed quarks and gluons as an ideal gas instead of a liquid. The theory of QCD and asymptotic freedom are not in any danger—no evidence exists to dispute the fundamental equations. What is up for debate are the techniques and simplifying assumptions used by theorists to draw conclusions from the equations.

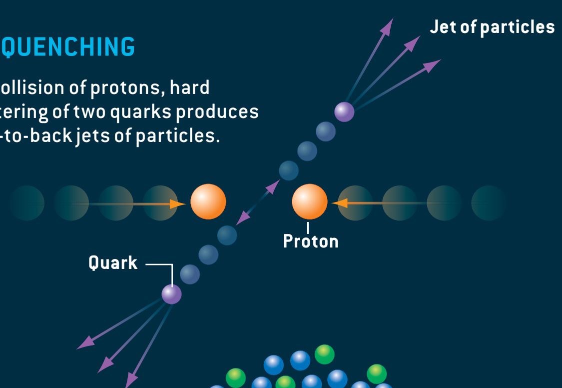
To address these questions, experimenters are studying the different kinds of quarks emerging from the mini bangs, espe-

EVIDENCE FOR A DENSE LIQUID

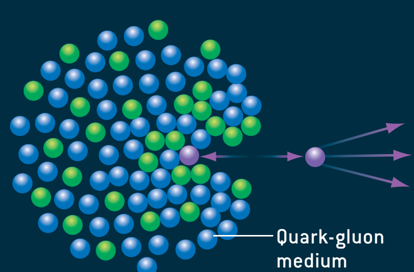
Two phenomena in particular point to the quark-gluon medium being a dense liquid state of matter: jet quenching and elliptic flow. Jet quenching implies the quarks and gluons are closely packed, and elliptic flow would not occur if the medium were a gas.

JET QUENCHING

In a collision of protons, hard scattering of two quarks produces back-to-back jets of particles.

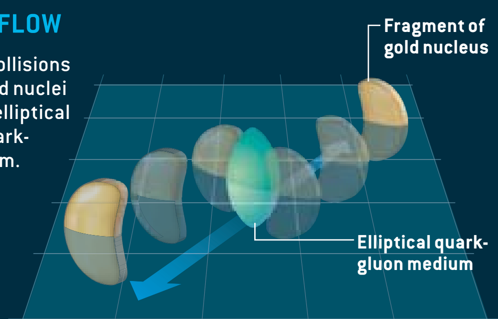


In the dense quark-gluon medium, the jets are quenched, like bullets fired into water, and on average only single jets emerge.

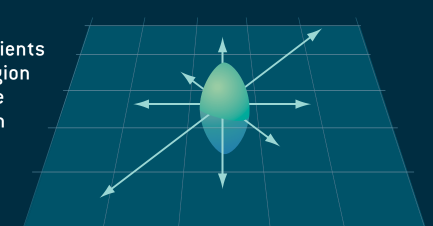


ELLIPTIC FLOW

Off-center collisions between gold nuclei produce an elliptical region of quark-gluon medium.



The pressure gradients in the elliptical region cause it to explode outward, mostly in the plane of the collision (*arrows*).



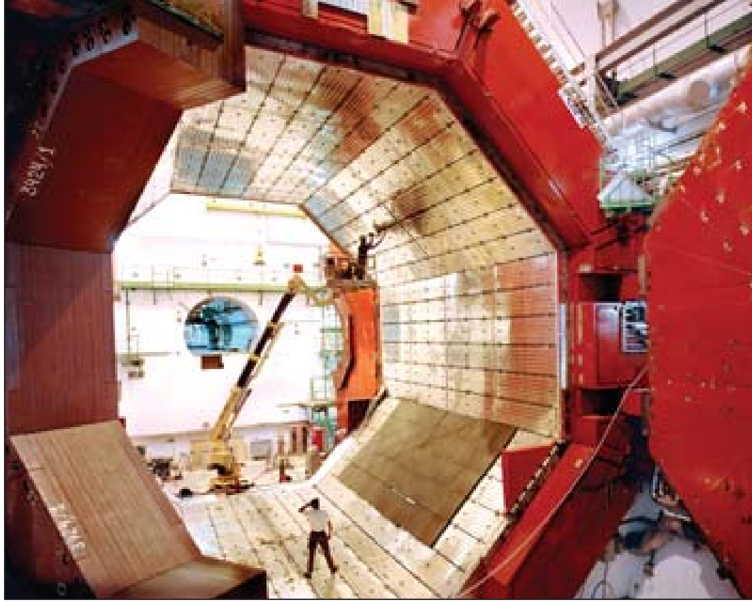
LUCY READING-IKKANDA

cially the heavier varieties. When quarks were originally predicted in 1964, they were thought to occur in three versions: up, down and strange. With masses below 0.15 GeV, these three species of quarks and their antiquarks are created copiously and in roughly equal numbers in RHIC collisions. Two additional quarks, dubbed charm and bottom, turned up in the 1970s, sporting much greater masses of about 1.6 and 5 GeV, respectively. Because much more energy is required to create these heavy quarks (according to $E = mc^2$), they appear earlier in the mini bangs (when energy densities are higher) and much less often. This rarity makes them valuable tracers of the flow patterns and other properties that develop early in the evolution of a mini bang.

The PHENIX and STAR experiments are well suited for such detailed studies because they can detect high-energy electrons and other particles called muons that often emerge from decays of these heavy quarks. Physicists then trace these and other decay particles back to their points of origin, providing crucial information about the heavy quarks that spawned them. With their greater masses, heavy quarks can have different flow patterns and behavior than their far more abundant cousins. Measuring these differences should help tease out precise values for the tiny residual viscosity anticipated.

Charm quarks have another characteristic useful for probing the quark-gluon medium. Usually about 1 percent of them are produced in a tight embrace with a charm antiquark, forming a neutral particle called the J/psi. The separation between the two partners is only about a third the radius of a proton, so the rate of J/psi production should be sensitive to the force between quarks at short distances. Theorists expect this force to fall off because the surrounding swarm of light quarks and gluons will tend to screen the charm quark and antiquark from each other, leading to less J/psi production. Recent PHENIX results indicate that J/psi particles do indeed dissolve in the fluid, similar to what was observed earlier at CERN, the European laboratory for particle physics near Geneva [see "Fireballs of Free Quarks," by Graham P. Collins, News and Analysis; Scientific American, April 2000]. Even greater J/psi suppression was expected to occur at RHIC because of the higher densities involved, but early results suggest some competing mechanism, such as reformation of J/psi particles, may occur at these densities. Further measurements will focus on this mystery by searching for other pairs of heavy quarks and observing whether and how their production is suppressed.

Another approach being pursued is to try to view the quark-gluon fluid by its own light. A hot broth of these particles should shine briefly, like the flash of a lightning bolt, because it emits high-energy photons that escape the medium unscathed. Just as astronomers measure the temperature of a distant star from its spectrum of light emission, physicists are trying to employ these energetic photons to determine the temperature of the quark-gluon fluid. But measuring this spectrum has thus far proved enormously challenging because many other photons are generated by the decay of hadrons called neutral pions. Although those photons are produced long after the quark-gluon fluid has reverted to hadrons, they all look the same when they arrive at the detectors.



ALICE DETECTOR will start operation at CERN's Large Hadron Collider in 2008. It will analyze collisions of lead nuclei involving about 50 times the energy of RHIC's mini bangs.

PETER GINTER

Many physicists are now preparing for the next energy frontier at the Large Hadron Collider (LHC) at CERN. Starting in 2008, experiments there will observe collisions of lead nuclei at combined energies exceeding one million GeV. An international team of more than 1,000 physicists is building the mammoth ALICE detector, which will combine the capabilities of the PHENIX and STAR detectors in a single experiment. The mini bangs produced by the LHC will briefly reach several times the energy density that occurs in RHIC collisions, and the temperatures reached therein should easily surpass 10 trillion degrees. Physicists will then be able to simulate and study conditions that occurred during the very first microsecond of the big bang.

The overriding question is whether the liquidlike behavior witnessed at RHIC will persist at the higher temperatures and densities encountered at the LHC. Some theorists project that the force between quarks will become weak once their average energy exceeds 1 GeV, which will occur at the LHC, and that the quark-gluon plasma will finally start behaving properly—like a gas, as originally expected. Others are less sanguine. They maintain that the QCD force cannot fall off fast enough at these higher energies, so the quarks and gluons should remain tightly coupled in their liquid embrace. On this issue, we must await the verdict of experiment, which may well bring other surprises. SA

MORE TO EXPLORE

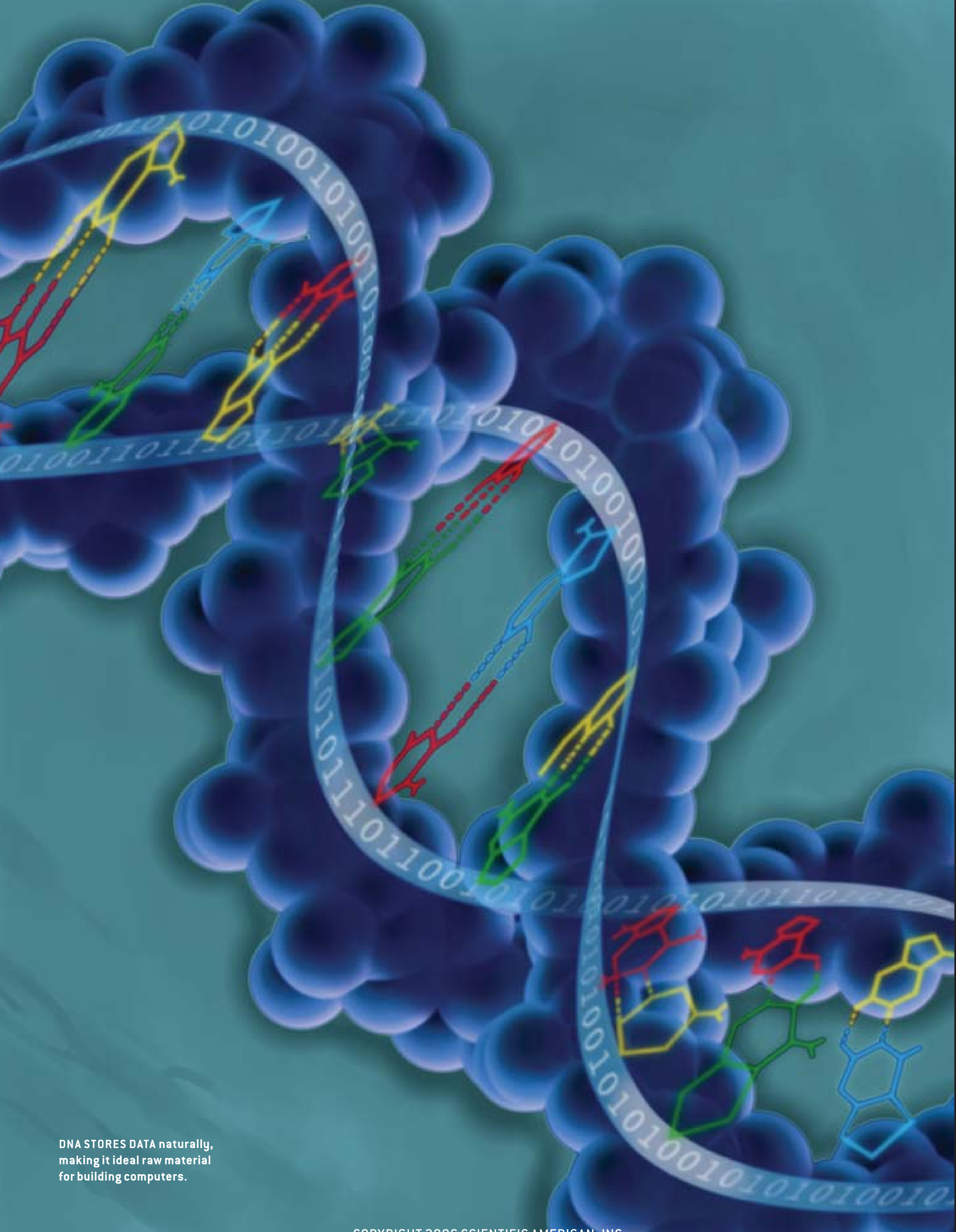
The Relativistic Heavy-Ion Collider: Creating a Little Big Bang on Long Island. Frank Wolfs in *Beam Line*, pages 2–8; Spring/Summer 2001. Online at **www.slac.stanford.edu/pubs/beamline/**

What Have We Learned from the Relativistic Heavy Ion Collider? Thomas Ludlam and Larry McLerran in *Physics Today*, Vol. 56, No. 10, pages 48–54; October 2003.

RHIC home page: **www.bnl.gov/RHIC/**

RHIC animations: **www.phenix.bnl.gov/WWW/software/luxor/ani/**

Web sites of the RHIC collaborations, which include links to research papers: **www.rhic.bnl.gov/brahms/; www.phenix.bnl.gov; www.phobos.bnl.gov;** and **www.star.bnl.gov**



DNA STORES DATA naturally, making it ideal raw material for building computers.

BRINGING DNA COMPUTERS TO LIFE

Tapping the computing power of biological molecules gives rise to tiny machines that can speak directly to living cells

By Ehud Shapiro and Yaakov Benenson

When British mathematician Alan Turing conceived the notion of a universal programmable computing machine, the word "computer" typically referred not to an object but to a human being. It was 1936, and people with the job of computer, in modern terms, crunched numbers. Turing's design for a machine that could do such work instead—one capable of computing any computable problem—set the stage for theoretical study of computation and remains a foundation for all of computer science. But he never specified what materials should be used to build it.

Turing's purely conceptual machine had no electrical wires, transistors or logic gates. Indeed, he continued to imagine it as a person, one with an infinitely long piece of paper, a pencil and a simple instruction book. His tireless computer would read a symbol, change the symbol, then move on to the next symbol, according to its programmed rules, and would keep doing so until no further rules applied. Thus, the electronic computing machines made of metal and vacuum tubes that emerged in the 1940s and later evolved silicon parts may be the only "species" of nonhuman computer most people have ever encountered, but theirs is not the only possible form a computer can take.

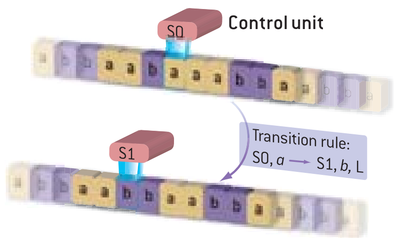
Living organisms, for instance, also carry out complex physical processes under the direction of digital information. Biochemical reactions and ultimately an entire organism's operation are ruled by instructions stored in its genome, encoded in sequences of nucleic acids. When the workings of biomolecular machines inside cells that process DNA and RNA are compared to Turing's machine, striking similarities emerge: both systems process information stored in a string of symbols taken from a fixed alphabet, and both operate by moving step by step along those strings, modifying or adding symbols according to a given set of rules.

These parallels have inspired the idea that biological molecules could one day become the raw material of a new computer species. Such biological computers would not necessarily offer greater power or performance in traditional computing tasks. The speed of natural molecular machines such as the ribosome is only hundreds of operations a second, compared

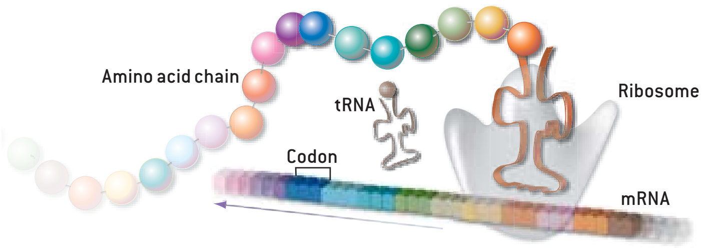
MATT COLLINS

COMPUTING MACHINES: CONCEPTUAL AND NATURAL

Mathematician Alan Turing envisioned the properties of a mechanical computer in 1936, long before molecule-scale machines within cells could be seen and studied. As the workings of nature's tiny automata were later revealed, striking similarities to Turing's concept emerged: both systems store information in strings of symbols, both process these strings in stepwise fashion, and both modify or add symbols according to fixed rules.



TURING MACHINE
This hypothetical device operates on an information-encoding tape bearing symbols such as "a" and "b." A control unit with read/write ability processes the tape, one symbol position at a time, according to instructions provided by transition rules, which note the control unit's own internal state. Thus, the transition rule in this example dictates that if the control unit's state is 0 (S0), and the symbol read is *a*, then the unit should change its state to 1 (S1), change the symbol to *b* and move one position to the left (L).



BIOLOGICAL MACHINE
An organelle found in cells, the ribosome reads information encoded in gene transcripts known as messenger RNAs (mRNAs) and translates it into amino acid sequences to form proteins. The symbolic alphabet of mRNA is made up of nucleotide trios called codons, each of which corresponds to a specific amino acid. As the ribosome processes the mRNA strand, one codon at a time, helper molecules called transfer RNAs (tRNAs) deliver the correct amino acid. The tRNA confirms the codon match, then releases the amino acid to join the growing chain.

LUCY READING-IKKANDA

with billions of gate-switching operations a second in some electronic devices. But the molecules do have a unique ability: they speak the language of living cells.

The promise of computers made from biological molecules lies in their potential to operate within a biochemical environment, even within a living organism, and to interact with that environment through inputs and outputs in the form of other biological molecules. A biomolecular computer might act as an autonomous "doctor" within a cell, for example. It could sense signals from the environment indicating disease, process them using its preprogrammed medical knowledge, and output a signal or a therapeutic drug.

Over the past seven years we have been working toward realizing this vision. We have already succeeded in creating a biological automaton made of DNA and proteins able to diagnose in a test tube the molecular symptoms of certain cancers and "treat" the disease by releasing a therapeutic molecule. This proof of concept was exciting, both because it has potential future medical applications and because it is not at all what we originally set out to build.

Overview/*Living Computers*

- Natural molecular machines process information in a manner similar to the Turing machine, an early conceptual computer.
- A Turing-like automaton built from DNA and enzymes can perform computations, receive input from other biological molecules and output a tangible result, such as a signal or a therapeutic drug.
- This working computer made from the molecules of life demonstrates the viability of its species and may prove a valuable medical tool.

Models to Molecules

ONE OF US (Shapiro) began this research with the realization that the basic operations of certain biomolecular machines within living cells—recognition of molecular building blocks, cleavage and ligation of biopolymer molecules, and movement along a polymer—could all be used, in principle, to construct a universal computer based on Turing's conceptual machine. In essence, the computational operations of such a Turing machine would translate into biomolecular terms as one "recognition," two "cleavages," two "ligations," and a move to the left or right.

Charles Bennett of IBM had already made similar observations and proposed a hypothetical molecular Turing machine in 1982. Interested in the physics of energy consumption, he speculated that molecules might one day become the basis of more energy-efficient computing devices [see "The Fundamental Physical Limits of Computation," by Charles H. Bennett and Rolf Landauer; SCIENTIFIC AMERICAN, July 1985].

The first real-world demonstration of molecules' computational power came in 1994, when Leonard M. Adleman of the University of Southern California used DNA to solve a problem that is always cumbersome for traditional computer algorithms. Known as the Hamiltonian path or the traveling salesman problem, its goal is to find the shortest path among cities connected by airline routes that passes through every city exactly once. By creating DNA molecules to symbolically represent the cities and flights and then combining trillions of these in a test tube, he took advantage of the molecules' pairing affinities to achieve an answer within a few minutes [see

"Computing with DNA," by Leonard M. Adleman; Scientific American, August 1998]. Unfortunately, it took him considerably longer to manually fish the molecules representing the correct solution out of the mixture using the laboratory tools available to him at the time. Adleman looked forward to new technologies that would enable the creation of a more practical molecular computer.

"In the future, research in molecular biology may provide improved techniques for manipulating macromolecules," Adleman wrote in a seminal 1994 scientific paper describing the DNA experiment. "Research in chemistry may allow for the development of synthetic designer enzymes. One can imagine the eventual emergence of a general purpose computer consisting of nothing more than a single macromolecule conjugated to a ribosomelike collection of enzymes which act upon it."

Devising a concrete logical design for just such a device, one that could function as the fundamental "operational specification" for a broad class of future molecular computing machines, became Shapiro's goal. By 1999 he had a mechanical model of the design made from plastic parts. We then joined forces to translate that model into real molecules.

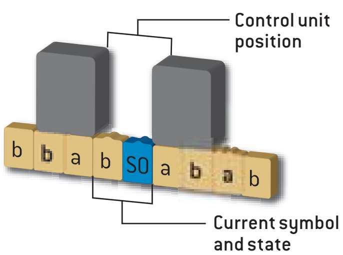
Rather than attacking the ultimate challenge of building a full-fledged molecular Turing machine head-on, however, we agreed to first attempt a very simplified Turing-like machine known as a finite automaton. Its sole job would be to determine whether a string of symbols or letters from a two-letter alphabet, such as "a" and "b," contained an even number of *b*'s. This task can be achieved by a finite automaton with just two states and a "program" consisting of four statements called transition rules. One of us (Benenson) had the idea to use a double-stranded DNA molecule to represent the input string, four more short double-stranded DNA molecules to represent the automaton's transition rules, or "software," and two natural DNA-manipulating enzymes, *Fok*I and ligase, as "hardware."

The main logical problem we had to solve in its design was how to represent the changing intermediate states of the computation, which consist of the current internal state of the automaton and a pointer to the symbol in the input string being

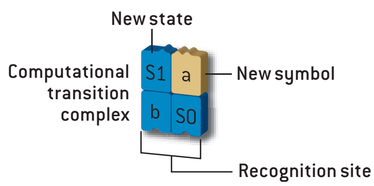
MOLECULAR TURING MACHINE MODEL

A Turing machine made of biomolecules would employ their natural ability to recognize symbols and to join molecular subunits together or cleave their bonds. A plastic model built by one of the authors (*right*) serves as a blueprint for such a system. Yellow "molecule" blocks carry the symbols. Blue software molecules indicate a machine state and define transition rules. Protrusions on the blocks physically differentiate them.

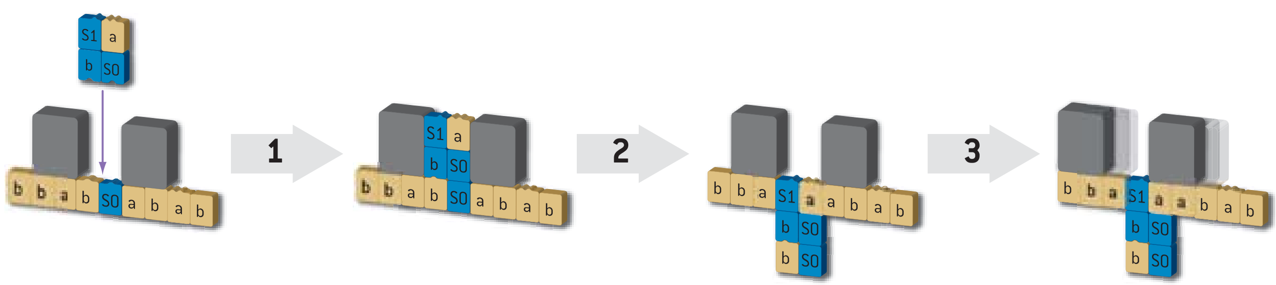
HOW IT WORKS



The machine operates on a string of symbol molecules. In its control unit position at the center, both a symbol and the machine's current state are defined.



One "computational transition" is represented by a molecule complex containing a new state and symbol for the machine and a recognition site to detect the current state and symbol. The example shown represents a transition rule: "If current state is S0 and current symbol is *b,* change state to S1 and symbol to *a,* then move one step to the left."



A free-floating computational transition complex slides into the machine's control unit (*1*). The molecule complex binds to and then displaces the current symbol and state (*2*). The control unit can move one position to the left to accommodate another transition complex (*3*). The process repeats indefinitely with new states and symbols as long as transition rules apply.

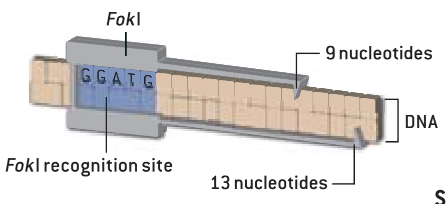
LUCY READING-IKKANDA (*illustrations*); WEIZMANN INSTITUTE OF SCIENCE (*photograph*)

BUILDING A MOLECULAR AUTOMATON

Because living organisms process information, their materials and mechanisms lend themselves readily to computing. The DNA molecule exists to store data, written in an alphabet of nucleotides. Cellular machinery reads and modifies that information using enzymes and other molecules. Central to this operating system are chemical affinities among molecules allowing them to recognize and bind with one another. Making molecules into a Turing-like device, therefore, means translating his concepts into their language.

A simple conceptual computer called a finite automaton can move in only one direction and can read a series of symbols, changing its internal state according to transition rules. A two-state automaton could thus answer a yes-no question by alternating between states designated 1 and 0. Its state at the end of the calculation represents the result.

Raw materials for a molecular automaton include DNA strands in assorted configurations to serve as both input and software and the DNA-cleaving enzyme *Fok*I as hardware. Nucleotides, whose names are abbreviated A, C, G and T, here encode both symbols and the machine's internal state.

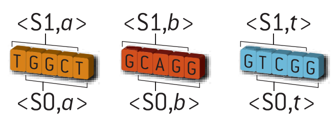


HARDWARE

The *Fok*I enzyme (*gray*) always recognizes the nucleotide sequence GGATG (*blue*) and snips a double DNA strand at positions 9 and 13 nucleotides downstream of that recognition site.

SOFTWARE

Transition rules are encoded in eight short double-stranded DNA molecules containing the *Fok*I recognition site (*blue*), followed by spacer nucleotides (*green*) and a single-stranded sticky end (*yellow*) that will join to its complementary sequence on an input molecule.



SYMBOL AND STATE

Combinations of symbols *a, b* or *terminator* (*t*) and machine states 1 or 0 are represented by four-nucleotide sequences. Depending on how the five-nucleotide sequence TGGCT is cleaved into four nucleotides, for example, it will denote symbol *a* and a state of either 1 or 0.

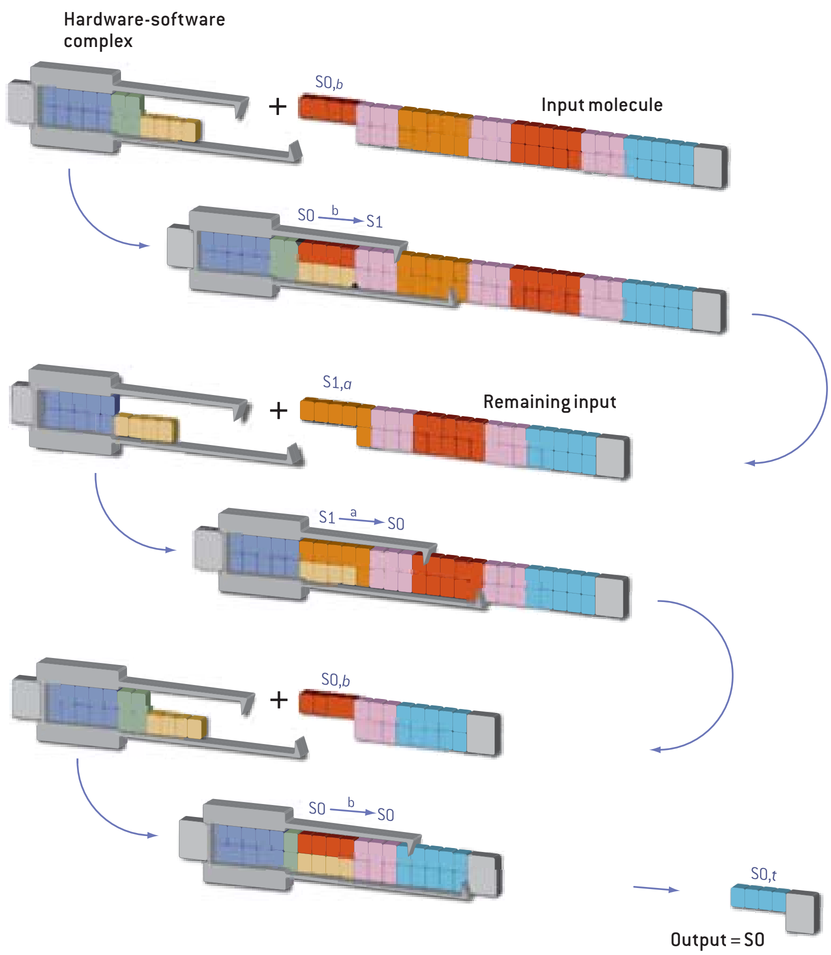
AUTONOMOUS COMPUTATION

A hardware-software complex recognizes its complementary state/symbol combination on the input molecule. The molecules join to form a hardware-software-input complex, then *Fok*I cleaves the input molecule to expose the next symbol.

A new hardware-software complex recognizes the next state and symbol on what remains of the input molecule.

Reactions continue until no rule applies or the terminator symbol is revealed.

In this example, computational cleavages leading to the final output (*far right*) have produced a four-nucleotide terminator symbol indicating a machine state of 0, the calculation's result.



LUCY READING-IKKANDA

processed. We accomplished this with a neat trick: in each step of the computation the enzymatic hardware was actually "digesting" the input molecule, cleaving the current symbol being processed and exposing the next one. Because the symbol could be cleaved in two different locations, each resulting version of it could represent, in addition to the symbol itself, one of two possible states of the computation. Interestingly, we discovered later that this last element was similar to a design that Paul Rothemund, a former student of Adleman, once proposed for a molecular Turing machine.

Remarkably, the resulting computer that our team announced in 2001 was autonomous: once the input, software and hardware molecules were placed in an appropriate buffer solution in a test tube, computation commenced and proceeded iteratively to completion without any human intervention.

As we tested this system, we also realized that it not only solved the original problem for which we had intended it—determining whether a symbol occurs an even number of times in a string—it could do more. A two-state, two-symbol finite automaton has eight possible symbol-state-rule combinations (2^3), and because our design was modular, all eight possible transition rules could be readily implemented using eight different transition molecules. The automaton could therefore be made to perform different tasks by choosing a different "program"—that is, a different mix of transition molecules.

In trying a variety of programs with our simple molecular automaton, we also found a way of further improving its performance. Among our tests was an omission experiment, in which the automaton's operation was evaluated with one molecular component removed at a time. When we took away ligase, which seals the software molecule to the input molecule to enable its recognition and cleavage by the other enzyme, *Fok*I, the computation seemed to make some progress nonetheless. We had discovered a previously unknown ability of *Fok*I to recognize and cleave certain DNA sequences, whether or not the molecule's two strands were sealed together.

The prospect of removing ligase from our molecular computer design made us quite happy because it would immediately reduce the required enzymatic hardware by 50 percent. More important, ligation was the only energy-consuming operation in the computation, so sidestepping it would allow the computer to operate without an external source of fuel. Finally, eliminating the ligation step would mean that software molecules were no longer being consumed during the computation and could instead be recycled.

The ligase-free system took our group months of painstaking effort and data analysis to perfect. It was extremely inefficient at first, stalling out after only one or two computational steps. But we were driven by both the computational and biochemical challenges, and with help and advice from Rivka Adar and other colleagues, Benenson finally found a solution. By making small but crucial alterations to the DNA sequences used in our automaton, we were able to take advantage of *Fok*I's hitherto unknown capability and achieve a quantum leap in the computer's performance. By 2003 we had an autonomous, programmable computer that could use its input molecule as its sole source of fuel [*see box on opposite page*]. In principle, it could therefore process any input molecule, of any length, using a fixed number of hardware and software molecules without ever running out of energy.

And yet from a computational standpoint, our automaton still seemed like a self-propelled scooter compared with the Rolls-Royce of computers on which we had set our sights: the biomolecular Turing machine.

DNA Doctor

BECAUSE THE TWO-STATE finite automaton was too simple to be of any use in solving complex computational problems, we considered it nothing more than an interesting demonstration of the concept of programmable, autonomous biomolecular computers, and we decided to move on. Focusing our efforts for a while on trying to build more complicated automata, however, we soon ran up against the problem recognized by Adleman: the "designer enzymes" he had yearned for a decade earlier still did not exist.

No known naturally occurring enzyme or enzyme complex can perform the specific recognitions, cleavages and ligations, in sequence and in tandem, with the flexibility needed to realize the Turing machine design. Natural enzymes would have to be customized or entirely new synthetic enzymes engineered. Because science does not yet have this ability, we found ourselves with a logical design specification for a biomolecular Turing machine but forced to wait until the parts needed to build it are invented.

That is why we returned to our two-state automaton to see if we could at least find something useful for it to accomplish. With medical applications already in mind, we wondered if the device might be able to perform some kind of simple diagnosis, such as determining whether a set of conditions representing a particular disease is present.

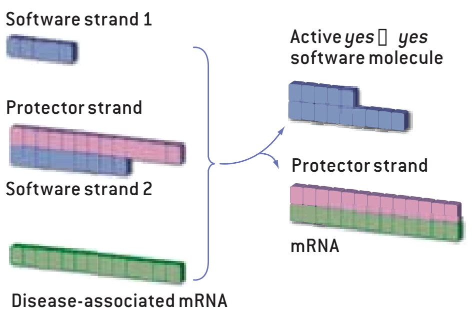
For this task, just two states suffice: we called one state "yes" and the other "no." The automaton would begin the computation in the *yes* state and check one condition at a time. If a condition on its checklist were present, the *yes* state would hold, but if any condition were not present, the automaton would change to the *no* state and remain that way for the rest of the computational process. Thus, the computation would

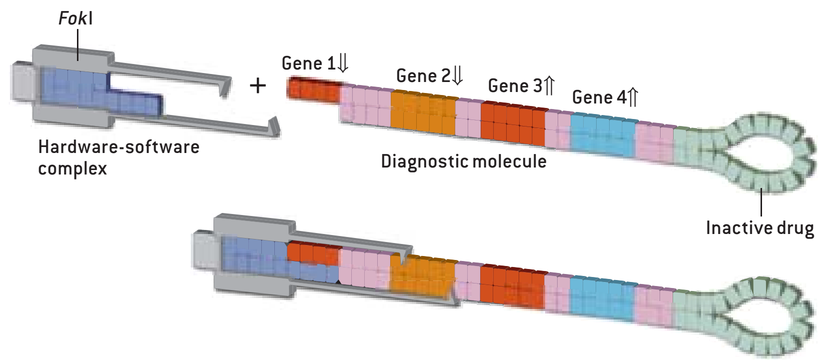
THE AUTHORS

EHUD SHAPIRO and *YAAKOV BENENSON* began collaborating to build molecular automata in 1999. Shapiro is a professor in the departments of computer science and biological chemistry at the Weizmann Institute of Science in Rehovot, Israel, where he holds the Harry Weinrebe Professorial Chair. He was already an accomplished computer scientist and software pioneer with a growing interest in biology in 1998 when he first designed a model for a molecular Turing machine. Benenson, just completing a master's degree in biochemistry at the Technion in Haifa, became Shapiro's Ph.D. student the following year. Now a fellow at Harvard University's Bauer Center for Genomics Research, Benenson is working on new molecular tools to probe and affect live cells.

DNA DOCTOR

Having shown that an automaton made from DNA and enzymes can perform abstract yes-or-no computations, the authors sought to give the device a practical query that it might face inside a living cell: Are indicators of a disease present? If the answer is yes, the automaton can output an active drug treatment. The basic computational concept is unchanged from the earlier design: complexes of "software" transition molecules and enzymatic "hardware" process symbols within a diagnostic molecule, cleaving it repeatedly to expose subsequent symbols. In addition, the new task requires a means for disease indicators to create input for the computation and mechanisms for confirming the diagnosis and delivering treatment.





INPUT

Gene transcripts called messenger RNAs (mRNAs) serve as disease indicators. By interacting with software molecules, mRNAs influence which of them is ultimately used in the computation. In this example, the two strands of a *yes* → *yes* transition molecule start out separated, with one bound to a single protector strand. The protector has a strong affinity for the disease-associated mRNA, however. If that mRNA is present, the protector will abandon its software strand to bind to the mRNA. The single software strands will then bind to one another, forming an active *yes* → *yes* transition molecule.

COMPUTATION

Complexes of transition-molecule software and *Fok*I enzymatic hardware process a series of symbols within the diagnostic molecule that represent underactivity (⇓) or overactivity (⇑) by specific genes. The automaton starts the computation in a *yes* state, and if all disease indicators are present, it produces a positive diagnosis. If any symptom is missing, the automaton transitions to *no* and remains in that state.

end in *yes* only if all the disease conditions held, but if one condition were not met the "diagnosis" would be negative.

To make this logical scheme work, we had to find a way to connect the molecular automaton to its biochemical environment so that it could sense whether specific disease conditions were present. The general idea that the environment could affect the relative concentrations of competing transition molecules—and thus affect the computation—had already been suggested in the blueprint for the molecular Turing machine. To apply this principle to sense disease symptoms, we had to make the presence or absence of a disease indicator a determinant of the concentration of software molecules that testify for the symptom.

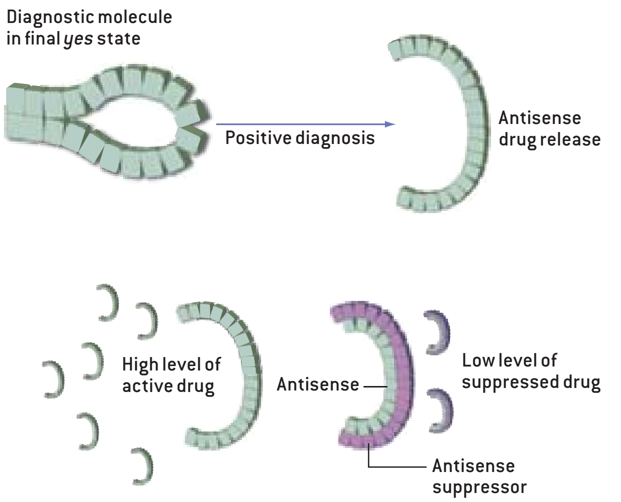
Many cancers, for example, are characterized by abnormal levels of certain proteins in the cell as a result of specific genes either overexpressing or underexpressing their encoded protein. When a gene is expressed, enzymes in the cell's nucleus copy its sequence into an RNA version. This molecular transcript of the gene, known as messenger RNA (mRNA), is then read by a structure called the ribosome that translates the RNA sequence into a string of amino acids that will form the protein. Thus, higher- or lower-than-normal levels of specific mRNA transcripts can reflect gene activity.

Benenson devised a system wherein some transition molecules would preferentially interact with these mRNA sequences. The interaction, in turn, would affect the transition molecules' ability to participate in the computation. A high level of mRNA representing a disease condition would cause the *yes* → *yes* transition molecules to predominate, increasing the probability that the computer would find the symptom to be present [*see box above*]. In practice, this system could be applied to any disease associated with abnormal levels of proteins resulting from gene activity, and it could also be adapted to detect harmful mutations in mRNA sequences.

Once we had both an input mechanism that could sense disease symptoms and the logical apparatus to perform the diagnosis, the next question became, What should the computer do when a disease is diagnosed? At first, we considered having it produce a visible diagnostic signal. In the molecular world, however, producing a signal and actually taking the next logical step of administering a drug are not that far apart. Binyamin Gil, a graduate student on our team, proposed and implemented a mechanism that enables the computer to release a drug molecule on positive diagnosis.

Still, our plan was not complete. Perhaps the central question in computer hardware design is how to build a reliable system from unreliable components. This problem is not unique to biological computers—it is an inherent property of complex systems; even mechanical devices become more unreliable as scale diminishes and the number of components increases. In our case, given the overall probabilistic nature of the computation and the imprecise behavior of biomolecular elements, some computations would inevitably end with a positive diagnosis even if several or all of the disease symp-

LUCY READING-IKKANDA



OUTPUT
After a positive diagnosis, final cleavage of the diagnostic molecule releases the treatment, a single-stranded so-called antisense DNA molecule (*top*). To compensate for diagnostic errors, the authors also created negative versions of the diagnostic molecules to perform parallel computations. When disease indicators are absent, these automata release a drug suppressor. With thousands of both types of diagnostic molecules computing simultaneously, the majority will make the correct diagnosis, and either the antisense molecule will outnumber its suppressors (*bottom*), or vice versa.

toms were absent, and vice versa. Fortunately, this probabilistic behavior is measurable and repeatable, so we could compensate for it with a system of checks and balances.

We created two types of computation molecules: one designed to release a drug when the computation terminates in the *yes* state, the other to release a suppressor of that same drug when the computation terminates in *no*. By changing the relative concentrations of the two types of molecules, we could have fine control over the threshold of diagnostic certainty that would trigger administration of an active drug.

Human physicians make this kind of decision whenever they weigh the risk to a patient of a possible disease against the toxicity of the treatment and the certainty of the diagnosis. In the future, if our molecular automaton is sent on a medical mission, it can be programmed to exercise similar judgment.

Dawn of a New Species

AS IT TURNED OUT, our simple scooter carried us much further than we had believed it could and in a somewhat different direction than we had first imagined. So far our biomolecular computer has been demonstrated only in a test tube. Its biological environment was simulated by adding different concentrations of RNA and DNA molecules and then placing all the automaton components in the same tube. Now our goals are to make it work inside a living cell, to see it compute inside the cell and to make it communicate with its environment.

Just delivering the automaton into the cell is challenging because most molecular delivery systems are tailored for either DNA or protein. Our computer contains both, so we are trying to find ways to administer these molecules in tandem. Another hurdle is finding a means of watching all aspects of the computation as they occur within a cell, to confirm that the automaton can work without the cell's activities disrupting computational steps or the computer's components affecting cellular behavior in unintended ways. And finally, we are exploring alternative means of linking the automaton to its environment. Very recent cancer research suggests that microRNAs, small molecules with important regulatory functions inside cells, are better indicators of the disease, so we are redesigning our computer to "talk" to microRNA instead of mRNA.

Although we are still far from applying our device inside living cells, let alone in living organisms, we already have the important proof of concept. By linking biochemical disease symptoms directly with the basic computational steps of a molecular computer, our test-tube demonstration affirmed that an autonomous molecular computer can communicate with biological systems and perform biologically meaningful assessments. Its input mechanism can sense the environment in which it operates; its computation mechanism can analyze that environment; and its output mechanism can affect the environment in an intelligent way based on the result of its analysis.

Thus, our automaton has delivered on the promise of biomolecular computers to enable direct interaction with the biochemical world. It also brings computational science full circle back to Turing's original vision. The first computing machines had to deviate from his concept to accommodate the properties of electronic parts. Only decades later, when molecular biologists began revealing the operations of tiny machines inside living cells did computer scientists recognize a working system similar to Turing's abstract idea of computation.

This is not to suggest that molecules are likely to replace electronic machines for all computational tasks. The two computer species have different strengths and can easily coexist. Because biomolecules can directly access data encoded in other biomolecules, however, they are intrinsically compatible with living systems in a way that electronic computers will never be. And so we believe our experiments suggest that this new computer species is of fundamental importance and will prove itself valuable for a wide range of applications. The biomolecular computer has come to life. SA

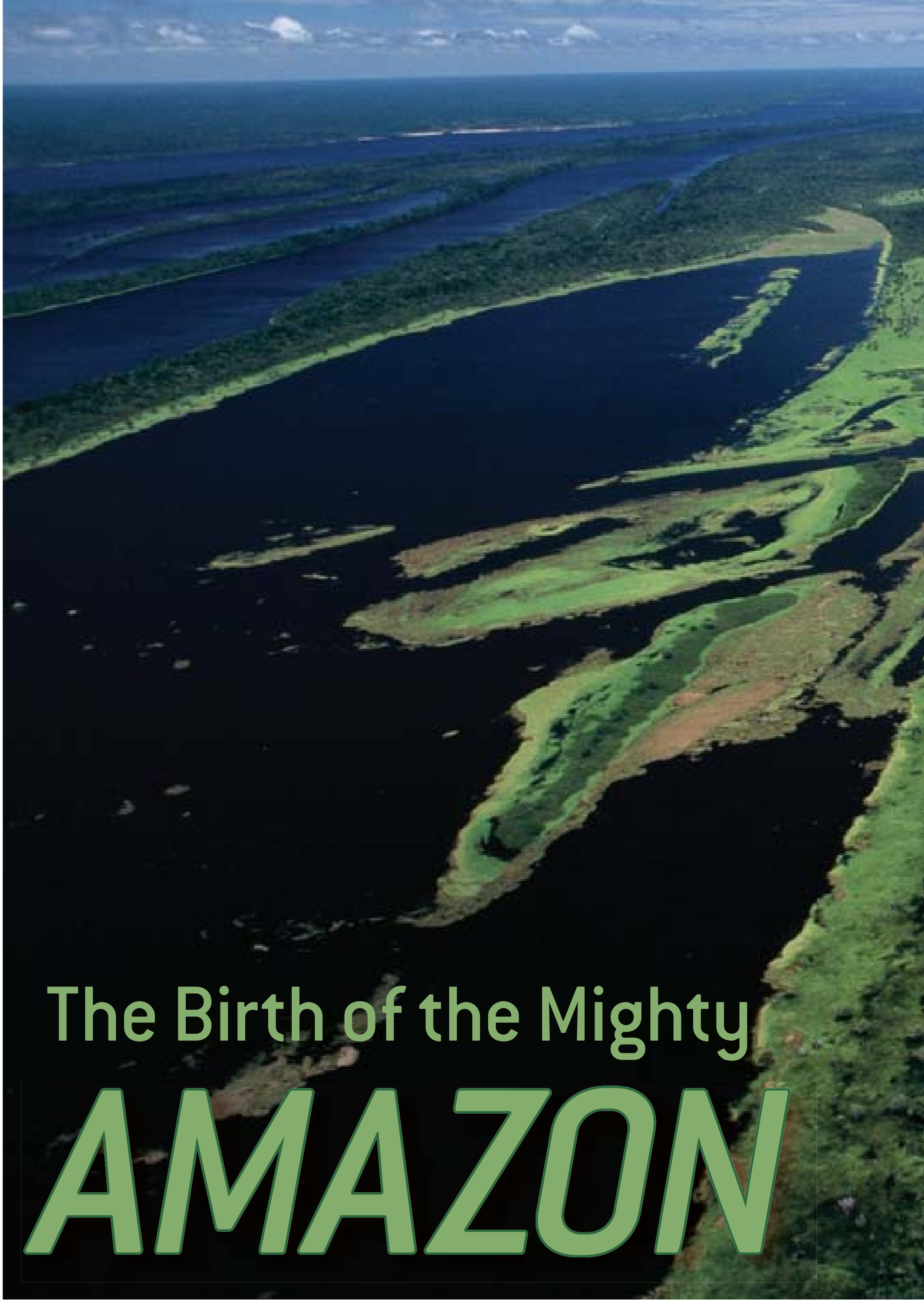
MORE TO EXPLORE

A Mechanical Turing Machine: Blueprint for a Biomolecular Computer. Presented by Ehud Shapiro at the 5th International Meeting on DNA Based Computers, Massachusetts Institute of Technology, June 14–15, 1999. **www.weizmann.ac.il/udi/press**

Programmable and Autonomous Computing Machine Made of Biomolecules. Y. Benenson, T. Paz-Elizur, R. Adar, E. Keinan, Z. Livneh and E. Shapiro in *Nature,* Vol. 414, pages 430–434; November 22, 2001.

An Autonomous Molecular Computer for Logical Control of Gene Expression. Y. Benenson, B. Gil, U. Ben-Dor, R. Adar and E. Shapiro in *Nature,* Vol. 429, pages 423–429; May 27, 2004.

INSIGHT INTO HOW THE WORLD'S LARGEST RIVER FORMED IS HELPING SCIENTISTS EXPLAIN THE EXTRAORDINARY ABUNDANCE OF PLANT AND ANIMAL LIFE IN THE AMAZON RAIN FOREST



The Birth of the Mighty AMAZON

By Carina Hoorn

Looking down at the Amazon River from above, an observer cannot help noticing that water dominates the landscape even beyond the sinewy main channel. The river, which extends from the Pacific highlands of Peru some 6,500 kilometers to Brazil's Atlantic coast, swells out of its banks and inundates vast swaths of forest during the rainy seasons, and myriad lakes sprawl across its floodplains year-round.

All told, the river nurtures 2.5 million square kilometers of the most diverse rain forest on earth. Until recently, however, researchers had no idea how long this intimate relation between river and forest has actually existed. The inaccessibility of this remote region, now called Amazonia, meant that long-held theories about the early days of the river and surrounding forest were speculative at best.

In the past 15 years new opportunities to study the region's rock and fossil records have finally enabled investigators to piece together a more complete picture of Amazonian history. The findings suggest that the birth of the river was a complicated process lasting millions of years and that the river's development

RICARDO AZOURY *Corbis*

JUNGLE ISLANDS of the Anavilhanas Archipelago, located on the Rio Negro near Manaus, Brazil, resemble the vast wetland that scientists now think inundated much of Amazonia between about 16 million and 10 million years ago.

greatly influenced the evolution of native plants and animals. Indeed, many researchers now contend that the incipient river nourished a multitude of interconnected lakes in the continent's midsection before forging a direct connection to the Atlantic Ocean; this dynamic wetland produced ideal conditions for both aquatic and terrestrial creatures to flourish much earlier than previously thought. The new interpretations also explain how creatures that usually live only in the ocean—among them dolphins—now thrive in the inland rivers and lakes of Amazonia.

Telltale Sediments

UNDERSTANDING HOW AND WHEN the Amazon River came to be is essential for uncovering the details of how it shaped the evolution of life in Amazonia. Before the early 1990s geologists knew only that powerful movements of the earth's crust forged South America's Andes and towering mountain peaks elsewhere (including the Himalayas and the Alps) primarily between about 23 million and five million years ago, an epoch of the earth's history known as the Miocene. Those dramatic events triggered the birth

ANCIENT ROCKS containing clues about Amazonia's early days, such as these buff-colored cliffs along Colombia's Caquetá River, protrude out of the dense rain forest only rarely.

COURTESY OF CARINA HOORN, REPRINTED FROM "FLUVIAL PALAEOENVIRONMENTS IN THE INTRACRATONIC AMAZONAS BASIN (EARLY MIOCENE-EARLY MIDDLE MIOCENE, COLOMBIA)," BY CARINA HOORN, IN *PALAEOGEOGRAPHY, PALAEOCLIMATOLOGY, PALAEOECOLOGY*, VOL. 109, NO. 1; MAY 1994. © ELSEVIER

of new rivers and altered the course of existing ones in Europe and Asia, and the experts assumed South America was no exception. But the specific nature and timing of such changes were unknown.

When I began exploring this mystery in 1988, I suspected that the best records of the ancient Amazonian environment were the massive deposits of mud, sand and plant debris stored in the trough that the mighty river now follows to the Atlantic. But getting to those sediments—long since solidified into mudstone, sandstone and other rocks—posed considerable challenges. A jungle big enough to straddle nine countries with differing laws does not yield its secrets easily. And the rocks forming the trough, which poke aboveground only rarely, usually do so along nearly inaccessible tributaries and tend to be covered by dense vegetation.

Along the hundreds of kilometers of waterways my field assistant and I surveyed in Colombia, Peru and Brazil, we encountered only a few dozen sizable outcrops. And often we had to wield a machete to cut away the foliage—once surprising a giant green anaconda and another time exposing the footprints of a jaguar. Even then, we could reach only the uppermost layers of the thick rock formation, which extends almost a kilometer below the surface in some locations.

Once the initial fieldwork was complete, my first conclusion was that the Amazon River did not exist before about 16 million years ago, the start of what geologists call the "Middle" Miocene. Most of the rocks we found that dated from earlier times consisted of reddish clays and white quartz sand that clearly had formed from the erosion of granites and other light-colored rocks in the continent's interior. This composition implied that the region's earlier waterways originated in the heart of Amazonia. I inferred—and other researchers later confirmed—that during the Early Miocene, rivers flowed northwest from low hills in the continental interior, and some eventually emptied into the Caribbean Sea.

The Amazonian landscape altered significantly soon thereafter when a violent episode of tectonic activity began pushing up the northeastern Andes. By about 16 million years ago in the rock record, the red and white sediments disappear. In their place we found intriguing alternations of turquoise-blue, gray and green clays, brown sandstone and fossilized plant matter called lignite. It was obvious that the dark particles of mud and sand were from a source other than light-colored granites. And distinctive layered patterns in the fossilized sediments indicated that the water that deposited them was no longer flowing north; instead it flowed eastward. My guess was that the rising mountains to the west shifted the drainage pattern, sending water east toward the Atlantic.

In support of this idea, later analysis of the sediment at Wageningen University in the Netherlands proved that many of the brown sand grains were indeed fragments of the dark-colored schists and other rocks that began washing away as the newborn Andes rose up. What is more, some of the pollen grains and spores I found in the clays and lignites came from conifers and tree ferns that could have grown only at the high altitudes of a mountain range. This pollen contrasted with that in the older Miocene sediments, which came from plants known to grow only in the low-lying continental interior. Drill cores of Miocene rocks in Brazil, which provided the only complete sequence of the change from reddish clays to the blue and brown sediments, further corroborated my conclusions.

Finally, scientists had undeniable evidence for when the budding Amazon River was born. But it soon became clear that the river did not establish its full grandeur until much later. In 1997 David M. Dobson, now at Guilford College in Greensboro, N.C., and his colleagues discovered that the Andean sand grains I found in Amazonia first began accumulat-

Overview/*Fresh Start*

- Many scientists have long assumed that a shallow sea covered Amazonia for much of its history and that the rain forest's current biodiversity evolved only recently.
- New research instead indicates that the rain forest was already flourishing by the time the Amazon River formed about 16 million years ago.
- The evolution of the modern forest now appears to have been influenced greatly by the long and dramatic birth of the river itself, which did not flow uninterruptedly across the continent until about 10 million years ago.

FROM SEA TO SEA?

Among modern Amazonia's most perplexing mysteries are the dolphins, stingrays and other typically marine creatures (*photographs*) that populate the rain forest's muddy, freshwater oases. A long-held theory suggests that a shallow sea crossed South America from north to south (*map below*) over much of the Miocene epoch, between 23 million and 10 million years ago, and that these animals descend from ocean-dwelling ancestors that migrated into the region via that waterway. Later, as the sea subsided, the species would have evolved to tolerate freshwater.


Amazon River dolphin (*Inia geoffrensis*)


Largespot river stingray (*Potamotrygon falkneri*)

FLIP NICKLIN *Minden Pictures* (*dolphin*); DANTE FENOLIO *Photo Researchers, Inc.* (*stingray*); RON MILLER (*maps*)

ing along the Brazilian coast only about 10 million years ago. That timing means the river took at least six million years to develop into the fully connected, transcontinental drainage system of today. Research into the geologic changes that occurred in that transition period has now illuminated the origins of the region's enigmatic, present-day fauna.

Seaway Skepticism

FOR DECADES, THE PREVAILING HYPOTHESIS about Miocene Amazonia held that a shallow sea swamped the region for much of that epoch. The discovery that the Amazon River took millions of years to mature did not contradict that view, because it left open the possibility that this sea barred the incipient river's path to the Atlantic.

Proponents of this hypothesis point out that a prolonged connection with the open ocean would also explain how dolphins, manatees, stingrays and other marine creatures made their way into the heart of the continent. Later, when the sea retreated, they would have evolved the ability to tolerate freshwater, which is why their descendants still thrive today in the forest's aquatic oases. Researchers in southern South America have also made convincing cases that shallow marine conditions existed in inland Argentina during the Miocene.

Such arguments make it tempting to believe the seaway scenario, but my colleagues and I have uncovered several lines of evidence that make it seem unlikely that such a connection dominated the landscape for long. Instead we think that the rock samples I collected from the Middle Miocene, representing the period from roughly 16 million to 10 million years ago, are relics of a primarily freshwater environment.

One of the most noticeable features of the Middle Miocene rock layers was their periodicity. Early on, I believed that this pattern developed as different kinds of sediments were deposited in dry versus wet seasons throughout the years—as is typical in wetlands fed by small rivers. During the dry season, soil particles and plant matter would have settled slowly to the bottom of the shallow lakes and swamps, eventually forming the blue clays and lignite. During the rainy season, engorged streams flowing from higher elevations to the west—perhaps even the incipient Amazon—would have carried the brown sands with them; moreover, the minerals typical of the Andean highlands appeared only in the sandstone layers.

Some investigators interpret the same deposits differently. Matti Räsänen of the University of Turku in Finland and his

Notes from the Field

Investigating in Amazonia is anything but easy, as my first days there back in 1988 illustrate. By finding and analyzing sedimentary rocks buried underneath the thick soil and vegetation, I hoped to elucidate the region's evolution.

Because the rocks I hunted were hundreds of kilometers apart, I would end up venturing along the margins of the many tributaries of the Amazon for weeks at a time. My base camp was the site of a former prison in Araracuara, a place so remote that escaped prisoners were thought to have no chance of survival. It is a good thing I had the help of my Indian field assistant, Aníbal Matapi.

HOORN (*right*) and her assistant, Aníbal Matapi.

One memorable day Aníbal and I puttered for hours by boat along Colombia's Caquetá River. To me, each bend in the river looked like the previous one, but Aníbal had spent his whole life in this part of the jungle; he knew exactly where we were. We stopped at an abandoned house to put up our hammocks for the night. The next day we would look for sediment outcrops near the Apaporis River, in an area locked off from the Caquetá by fearsome rapids. That rough water meant we would have to leave our boat behind and travel over land, carrying the motor with us.

Aníbal and I hiked across the hills toward the Apaporis and borrowed a smaller boat from the local Indians there; another group gave us shelter for the next few days while we searched for our prized outcrops. At first our hosts were friendly, but before long they seemed much less keen to have us around. Soon, the reason became clear. Another non-Indian was visiting the tribe, and we suspected he must be there to hide. The Colombian guerillas were active in the region at that time, and he was probably one of them. We were relieved to depart after accomplishing our objective: we had collected many kilograms of black clays and other ancient sediments.

Of all my journeys, the voyage to the Apaporis was the most difficult. But while we were doggedly digging for rock outcrops during the day and swinging in our hammocks at night, it seemed that time never passed in this remote place—and that a high-tech world was something in a parallel universe. *—C.H.*

colleagues contend that the alternating sediment types instead record the waxing and waning of ocean tides, which would have shifted the coastlines noticeably in the kind of shallow sea or estuary they think covered Amazonia at that time. The rising tides would have brought in the sands, and the mud and plant matter would have settled out as the tides receded. It is important to note, however, that tides can also occur in large freshwater lakes.

The strongest indications that freshwater dominated the landscape during the Middle Miocene emerged from the abundant fossils entombed in the outcrops. When Frank P. Wesselingh, now at the Natural History Museum (Naturalis) in Leiden, the Netherlands, accompanied me to Colombia in 1991, he unearthed a highly diverse population of fossil mollusks in the Middle Miocene rocks. Building on previous work by C. Patrick Nuttall, then at the British Museum in London, Wesselingh's detailed taxonomic studies of the mollusks, which represented about seven million years and dozens of sites throughout Amazonia, later revealed that most of the mollusks were adjusted to freshwater lakes; only a few species could have survived in a fully marine environment. A long-lived seaway such as that hypothesized by Räsänen would not have allowed such adaptation during the inundation; likewise, a salty sea would have wiped out any freshwater species that evolved before its existence.

A few years later, in 1998, Hubert B. Vonhof of the Free University Amsterdam, Wesselingh and their colleagues came to the same conclusion based on chemical signatures in the mollusks' shells. Mollusks grow their shells year by year from carbon, oxygen, strontium and other elements dissolved in the surrounding water. Hence, the composition of the growth bands in a single shell acts as a record of the water chemistry over the time the mollusk lived. And because the ratios of strontium isotopes—atoms of the same element with differing numbers of neutrons—are different for seawater than they are for freshwater, these ratios can serve as a monitor of salinity.

To the surprise of many scientists, the strontium signatures were relatively fixed over the large temporal and geographic extent of the mollusks studied, indicating not only that their habitat was predominantly freshwater but also that the wetland was probably a remarkably large, interconnected body of water. Current estimates suggest it covered about 1.1 million square kilometers and was roughly twice the size of the Great

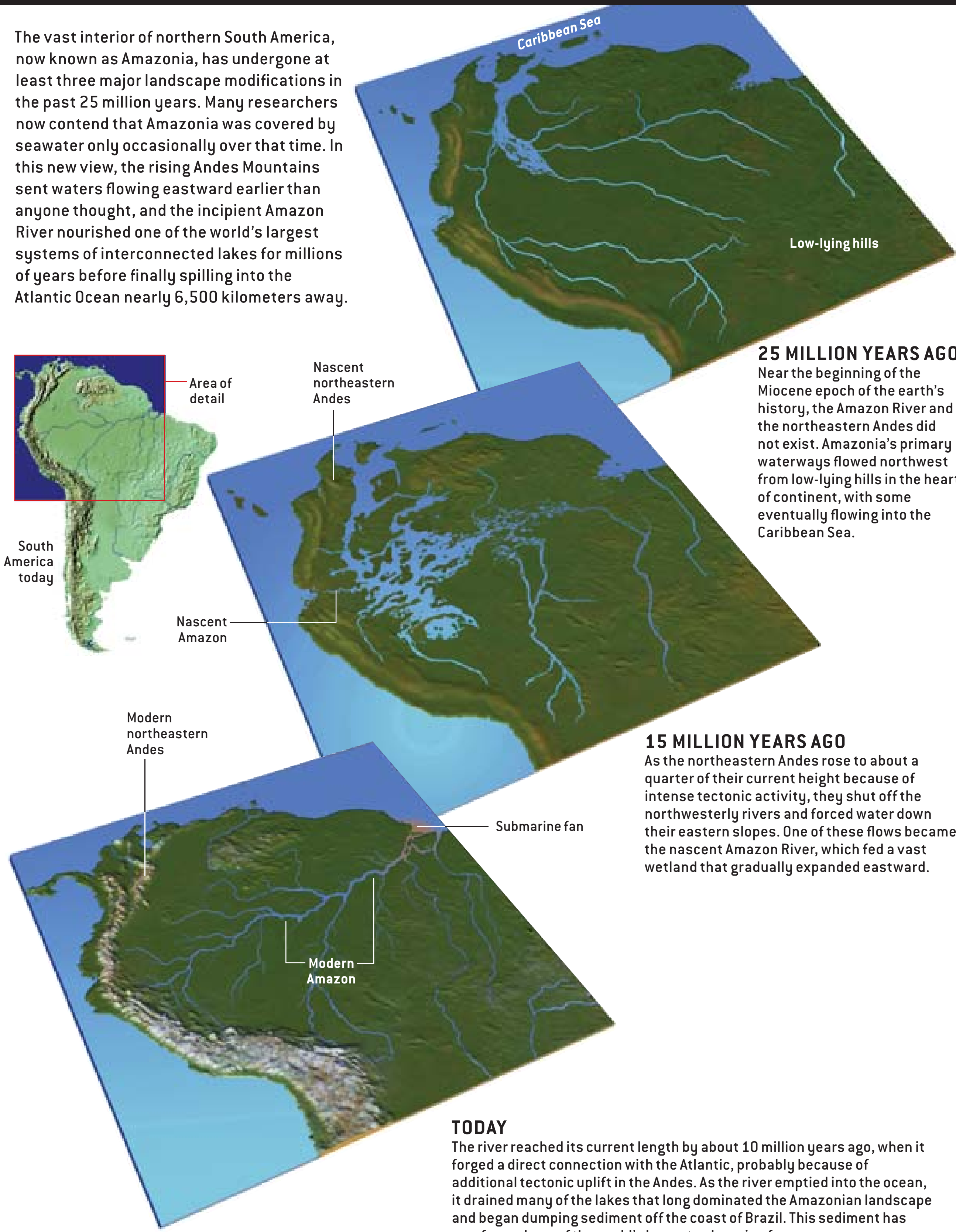
THE AUTHOR

CARINA HOORN is a geologist and pollen expert with the Institute for Biodiversity and Ecosystem Dynamics in Amsterdam, the Netherlands. She earned a doctorate from the University of Amsterdam in 1994 and a master's degree in science communication from Imperial College London in 2004. She has explored rivers in Amazonia, the Andes, the Himalayas and the Sultanate of Oman to identify the influence of these sedimentary environments on local vegetation. In addition to pursuing scientific research, Hoorn currently reports on new oil and gas exploration and production technologies for Shell in Rijswijk, the Netherlands.

S. B. KROONENBERG

THE TRANSFORMATION OF AMAZONIA

The vast interior of northern South America, now known as Amazonia, has undergone at least three major landscape modifications in the past 25 million years. Many researchers now contend that Amazonia was covered by seawater only occasionally over that time. In this new view, the rising Andes Mountains sent waters flowing eastward earlier than anyone thought, and the incipient Amazon River nourished one of the world's largest systems of interconnected lakes for millions of years before finally spilling into the Atlantic Ocean nearly 6,500 kilometers away.



25 MILLION YEARS AGO

Near the beginning of the Miocene epoch of the earth's history, the Amazon River and the northeastern Andes did not exist. Amazonia's primary waterways flowed northwest from low-lying hills in the heart of continent, with some eventually flowing into the Caribbean Sea.

15 MILLION YEARS AGO

As the northeastern Andes rose to about a quarter of their current height because of intense tectonic activity, they shut off the northwesterly rivers and forced water down their eastern slopes. One of these flows became the nascent Amazon River, which fed a vast wetland that gradually expanded eastward.

TODAY

The river reached its current length by about 10 million years ago, when it forged a direct connection with the Atlantic, probably because of additional tectonic uplift in the Andes. As the river emptied into the ocean, it drained many of the lakes that long dominated the Amazonian landscape and began dumping sediment off the coast of Brazil. This sediment has now formed one of the world's largest submarine fans.

RON MILLER

Evidence entombed in rocks about 16 million to 10 million years old—including sediment layers, pollen grains and fossil mollusks—suggests that true saline conditions rarely overtook Amazonia during the middle part of the Miocene epoch. Instead freshwater was the norm.

RHYTHMIC LAYERS of Middle Miocene sediment, now solidified into rock, are typical of those deposited in shallow wetlands fed by small rivers. During rainy seasons, engorged streams dump copious sand particles (*thin tan layers*) onto lake bottoms. During drier times, mud particles are most abundant; as they settle slowly, they form deposits of clay (*blue layers*) atop the sand.

POLLEN GRAINS abundant in Middle Miocene Amazonian rocks come from flowering plants, such as *Bombacaceae* (*left*) and *Caesalpinoideae* (*right*), that are known to have grown almost exclusively along tropical riverbanks. Rare occurrences of pollen from mangroves and of marine microorganisms in the same sediments confirm that saltwater invaded the region only briefly.

FRESHWATER MOLLUSKS, including *Pachydon* (*left*) and *Sioliella* (*right*), made up a vast majority of the Middle Miocene mollusks discovered at dozens of sites throughout Amazonia; only a few of the species found there could have survived in saltwater.

Lakes in North America—making it one of the largest and most enduring lake systems ever known.

Brief Invasions

DESPITE THE GROWING EVIDENCE against a long-lived seaway in Miocene Amazonia, the strontium signatures in the mollusks revealed that this enormous lake system did experience occasional salinity increases. Sea level is well known to have been higher in the Miocene than it is today, which makes it plausible that the rising Caribbean Sea could have surged southward along a narrow inland passage. Indeed, fossil plants and animals have confirmed the existence of short-lived connections with the ocean. Marine microorganisms and the pollen of mangroves—trees that thrive in salty seawater—turned up in my rock samples, but only rarely and over short time intervals. In all, the evidence implies that Amazonia was inundated at least twice when the vast wetland existed, between 16 million and 10 million years ago.

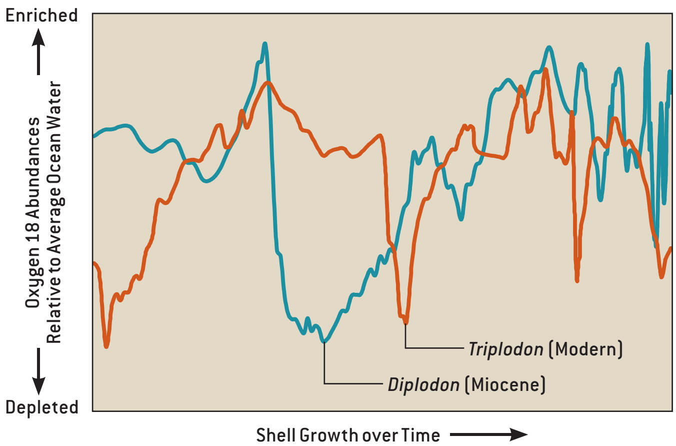
The best estimates indicate the marine incursions lasted on the order of thousands rather than millions of years at a time. And although they never increased the lake salinity to levels of the open ocean, they would still have given oceangoing animals a means for penetrating the heart of Amazonia. Detailed investigations of the history of particular creatures conclude, however, that the last major marine connection was probably severed when the Amazon was still a nascent river, long before the ancient wetland gave way to the transcontinental river of today. Molecular studies by Nathan R. Lovejoy, now at the University of Toronto at Scarborough, for example, indicated that the Amazonian stingrays, which are closely related to those now living in the Caribbean Sea, migrated inland sometime before about 16 million years ago.

Dolphin studies produced similar conclusions. In 2000 Insa Cassens and her colleagues at the Free University of Brussels in Belgium concluded that the pink river dolphins in present-day Amazonia are a relict of marine dolphin lineages that were common in the Early Miocene but went extinct soon thereafter, implying that the ones there now are a form that adapted to freshwater. And Eulalia Banguera-Hinestroza of the University of Valle in Colombia recently distinguished two genetically distinct groups of *Inia* dolphins, one in the Amazon and one in Bolivia, demonstrating that these groups have been separated for a considerable time; such a separation would not have occurred while a seaway still connected those regions.

Rain-Forest Antiquity

MOUNTING CLUES that the Amazon River basin of Miocene times was more lake than sea also forced scientists to take a new look at the history of the rain forest. One of the predominant theories about the source of Amazonian diversity was that it arose in the wake of the ice ages that have occurred over the past million years or so. The onset of arid conditions akin to those the ice ages bestowed on northern South America is one logical way an ancient rain forest could have shrunk into small, disconnected habitats. Many evolutionary biologists assume such separation is necessary to achieve biological

COURTESY OF CARINA HOORN (*sediment*); MARTIN KONERT *Free University Amsterdam* AND CARINA HOORN (*pollen grains*); FRANK P. WESSELINGH *Natural History Museum (Naturalis), Leiden* (*mollusks*)



OXYGEN IN MOLLUSK SHELLS such as those of 16-million-year-old *Diplodon* (*blue curve*) strongly suggests that the animals lived in a tropical floodplain lake. Specifically, *Diplodon*'s growth bands—the layers of shell that mollusks construct from elements dissolved in the surrounding water—show an alternating pattern of enrichment and depletion in a rare form of oxygen called oxygen 18. Such alternating patterns, which also occur in the modern Amazonian mollusk *Triplodon* (*red curve*), mean the animals experienced the wet and dry seasons typical of tropical rain forests; the curves would have been much flatter had the mollusks lived, for instance, in a salty sea.

JEN CHRISTIANSEN; SOURCE: RON J. G. KAANDORP *Free University Amsterdam*

richness: when small tracts of a once large habitat are cut off from one another, the theory goes, adjacent populations of a given species stop interbreeding; over time this reproductive isolation enables one population to diverge genetically from the others, eventually forming a whole new species. When the lands reconnect again in warmer times, the species remain distinct even when they live in overlapping territories.

But once again, the new findings tell a different tale. The same evidence that illuminated the lake ecosystem also suggests that many of the modern arrays of Amazonian plants and animals were actually flourishing millions of years ago. For instance, the full suite of pollen my assistants eventually extracted from the Miocene rocks represented an amazing diversity of vegetation. I identified 214 species. Many more species were excluded from the counts because I found only a single occurrence. Most of the more abundant pollen samples were from flowering plants common to riverbanks and similar in variety to those prospering in the forest today. In any case, the prolonged inundation by saltwater that others have proposed would have greatly limited the opportunities for these terrestrial species to dominate the region until much later, an observation that raises further doubt about a long-lived sea in Amazonia.

Reinforcing these pollen results is a new mollusk study indicating that the Miocene climate was capable of supporting a diverse rain forest. Ron J. G. Kaandorp of the Free University Amsterdam looked at the growth bands in mollusk shells from about 16 million years ago, this time studying chemical signatures of oxygen, an element that tracks rainfall abundances. The growth bands showed an alternating pattern of oxygen isotopes that was remarkably similar to those seen in modern Amazonian mollusks. In the modern shells, the alternating bands are well known to be the product of the wet and dry seasons that the forest depends on. Although the world was a warmer place during the Miocene, the presence of nearly identical oxygen signals in the ancient mollusks suggests that the climatic variation necessary to sustain a rainforest ecosystem was already in place when they were living—well before the ice ages of the past million years.

Species Explosion

IN LIGHT OF THE NEW EVIDENCE, a growing number of scientists agree that the Miocene wetland of the Amazon was a cradle of speciation where an evolutionary explosion took place. The uplift of the Andes started it all by triggering the birth of the Amazon River, among others, which went on to feed a vast wetland that dominated Amazonia for almost seven million years.

Marine invaders traveled into the region on a few occasions. The postincursion, freshwater environments of interconnected lakes turned out to be a perfect breeding ground for new aquatic animals such as mollusks, which developed into a highly diverse and populous fauna within a surprisingly short time—maybe as little as thousands of years. This environment was also ideal for small crustaceans called ostracods. Fernando Muñoz-Torres of Ecopetrol, a Colombian oil company, found that these ostracods—just like the mollusks—experienced explosive speciation during the same period. The shallow depth of the lakes and channels and partial isolation of some areas probably encouraged these high speciation rates.

Later, when the interconnected system of lakes made way for the full-blown Amazon River, most of the freshwater mollusks and ostracods—which needed quieter lake conditions—went extinct. At the same time, though, this changing landscape enabled a broader array of terrestrial plants and animals to evolve.

One of the most heartening discoveries from the recent geologic studies is that the Amazon flora and fauna are amazingly resilient. Over the 23 million years that the rain forest has existed, it has held strong—and even thrived—despite tremendous changes to the landscape: uplift of the eastern Andes Mountains, the birth of the Amazon River and inundation by seawater. Dare we hope that such resiliency will also help Amazonia survive the challenges that we humans are posing? SA

MORE TO EXPLORE

Origin and Evolution of Tropical Rain Forests. Robert J. Morley. John Wiley & Sons, 2000.

Seasonal Amazonian Rainfall Variation in the Miocene Climate Optimum. Ron J. G. Kaandorp, Hubert B. Vonhof, Frank P. Wesselingh, Lidia Romero Pittman, Dick Kroon and Jan E. van Hinte in *Palaeogeography, Palaeoclimatology, Palaeoecology,* Vol. 221, Nos. 1–2, pages 1–6; 2005.

New Contributions on Neogene Geography and Depositional Environments in Amazonia. Edited by C. Hoorn and H. B. Vonhof. *Journal of South American Earth Sciences,* Vol. 21, Nos. 1–2 (in press).

New understanding of the biology behind a successful cancer therapy may lead to a drug that can treat an array of solid tumors

Blockbuster

BY GARY STIX

From the time it was approved in 1998, Genentech's Herceptin—a drug in the vanguard of the first generation of so-called targeted therapeutics—has achieved an impressive track record for a subset of breast cancer patients. Some patients who take it live longer and the size of their tumors is kept under better control than if they had received standard chemotherapy alone.

To develop Herceptin, researchers at Genentech drew on investigations into the molecular workings of a cancer cell. Some breast cancer cells stud their exterior with a surfeit of receptors that join in pairs to trigger a cascade of signals that cause the cells to replicate uncontrollably, develop resistance to chemotherapy and encourage the growth of blood vessels that promote the spread of tumor cells.

But Herceptin (generically designated trastuzumab) is aimed only at 20 to 25 percent of breast cancer patients, those whose tumor cells bear excessive numbers of a receptor known as HER2 on the surface. It has not, moreover, been proved effective against other cancers. H. Michael Shepard, who headed the team at Genentech that developed Herceptin and who fought vigorously against efforts within the corporate ranks to kill the program, is now chief executive of a tiny start-up located less than a mile away from the biotech giant's South San Francisco headquarters. The company, called Receptor BioLogix, is trying to go Herceptin one better.

The Big Turnoff

SHEPARD RETURNED TO the business of researching receptors in 2003, after a post-Genentech hiatus that included stints at two small biotechs and time spent as a consultant

Dreams

HALT! A new drug candidate called Dimercept, depicted in white, couples with a receptor (*black*) on a cancer cell and thereby inhibits signals that tell the cell to replicate.

KEN EWARD *BioGrafx*

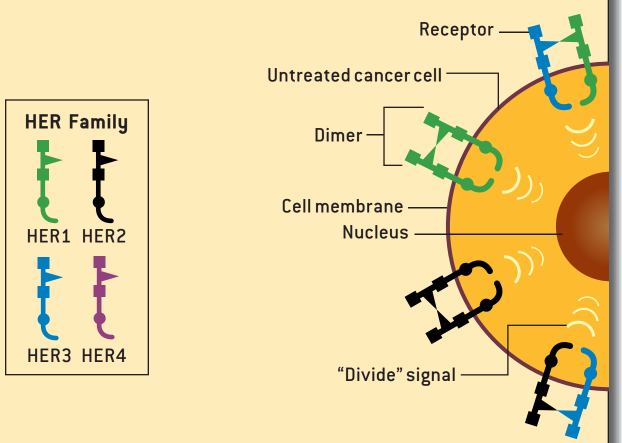
advising venture capitalists on new deals. His first push in that direction, although he did not realize it at the time, was a message on his answering machine from a former Genentech colleague, John Adelman. He knew Adelman, who had become a professor at the Vollum Institute at the Oregon Health & Science University, from the nights the two spent biding their time in the Genentech parking lot while each waited for their respective laboratory gels to finish processing. In his message on the machine, Adelman carried on about a new protein that could be a cure for breast cancer. Dubious, Shepard decided not to return the call.

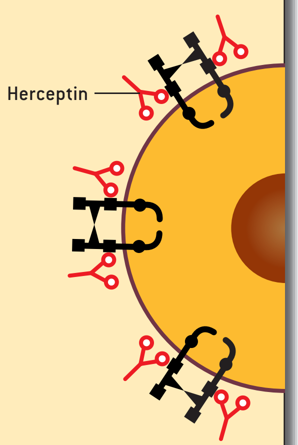
A mutual friend phoned later and urged Shepard to listen to Adelman's story. When Shepard phoned back, Adelman told him about Gail Clinton's laboratory at O.H.S.U., which had come up with a chemical compound that had some promising characteristics as a drug candidate. In the late 1990s a graduate student in Clinton's laboratory had found a distinctive form of the HER2 protein. Clinton and Adelman told the student, Joni Doherty, that the compound was an artifact and not worth researching further. Doherty disregarded the advice and sequenced the genetic material that encoded the protein.

The sequencing showed that the protein actually resembled a small piece of the receptor component that protrudes from the cell, the extracellular domain. It lacked the section that resides inside the cell and snakes across the cell membrane. And it included something that, at the time, was startling: When a cell needs a given protein, it transcribes the corresponding gene into a single strand of RNA and splices out copies of unneeded DNA segments termed introns. The resulting, spliced messenger RNA (mRNA) transcript then

HOW HERCEPTIN AND DIMERCEPT DIFFER

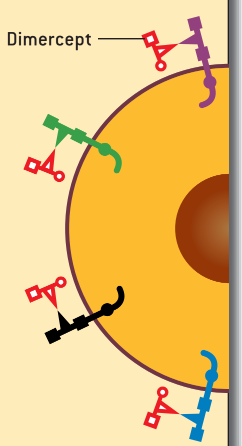
Cancer cells often display more cell-surface receptors of the HER family than normal cells do. When something causes receptor molecules to pair up, this "dimerization" leads the receptors to transmit signals that induce cancer cells to divide uncontrollably and metastasize. New therapies, including the breast cancer drug Herceptin and the experimental drug Dimercept, target solid tumors by hampering those signals, albeit in different ways.





HOW HERCEPTIN WORKS

Herceptin is a monoclonal antibody that acts on breast cancers with a surfeit of HER2 receptors, which can dimerize with copies of themselves. Binding by Herceptin curbs signaling primarily by HER2-HER2 pairs.



HOW DIMERCEPT WORKS

Dimercept inhibits both HER2 and other receptors in its family by linking to them at the site where they usually form dimers with copies of themselves or other family members. By inhibiting dimerization, this attachment can potentially prevent all known permutations of HER receptor pairs from emitting cell-replication signals into cells.

MELISSA THOMAS

serves as the template for making the protein. Doherty's protein, though, contained a part encoded by an intron. At one time, scientists disparaged introns as "junk" DNA. The Human Genome Project, though, underlined that differential inclusion or exclusion of introns can enable single genes to give rise to more than one type of protein.

The O.H.S.U. researchers wanted to know more about the function of their odd protein. It was not a receptor, but it acted as a decoy that imitated an aspect of receptor behavior. Normally a cell gets a message to begin the process of replication after a receptor joins physically, or "dimerizes," to another receptor. This pairing, in turn, sets off the transmission of chemical signals that induce the nucleus to trigger cell division. The drug candidate, originally called Herstatin, is now named Dimercept because it "intercepts" dimerization. The molecule sidles up to a receptor. The amino acids coded by the intron appear to initiate contact. A tiny arm that sticks out laterally from the protein interacts with a similar protruberance on the receptor and prevents the receptor from joining to another, thereby inhibiting the cascade of signals. What is more, Dimercept has this same effect not only on HER2 but on other receptors in the same family (the epidermal growth factor receptor family): HER1, HER3 and, possibly, HER4. The protein, made naturally in humans, is present mostly in fetal liver and kidney tissue, leading to the conjecture that it serves as a growth inhibitor in early development.

The ability to damp the activity of the entire complex of HER receptors explained the overexuberance of the message on Shepard's answering machine. Inhibiting all four receptors could in theory provide treatment for a population of breast cancer patients that does not respond to Herceptin as well as for patients with other types of solid tumors that emerge anywhere from the lung to the pancreas to the brain.

Pharmaceutical companies found out about the compound through published papers and patents. But O.H.S.U. decided initially not to license the compound. It was still smarting from being unable to share in the sales revenues for Gleevec, the blockbuster anticancer compound owned by Novartis Pharmaceuticals but co-developed with O.H.S.U. researcher Brian Druker. So, with the university's blessing, Adelman made the call to Shepard, who agreed to take on the task of starting the company in 2003 and who raised early seed funding.

Good Pickings

LAST YEAR Receptor BioLogix brought in more than $33 million, an especially large take for a biotech start-up, particularly one with a drug that has not reached human clinical trials. The job at Receptor BioLogix is not unlike the one Shepard performed at Genentech, although now he has responsibility for an entire operation. He is currently charged with transforming Dimercept from a laboratory curiosity to a drug ready for human clinical trials.

Although Dimercept stoppers the HER2 receptor, as does Herceptin, the two molecules are very different. The Genentech drug is a monoclonal antibody—an immune molecule that binds to only a single target, or antigen. Monoclonals are made by cultivating antibody-producing cells in the immune system of mice, extracting them from the animals' spleen, and then going through an elaborate process to "humanize" the antibodies to avoid immune reactions in human patients.

As a protein found naturally in the body, Dimercept does not elicit similar worries about immunogenicity. But the molecule brings its own challenges. Only 20 to 30 percent of the batches made so far are usable. "It doesn't make for a good manufacturing process if you have to throw away 80 percent of the stuff," Shepard says. Receptor BioLogix's dozen or so researchers are spending much of their time giving the molecule a full makeover. As inherited from O.H.S.U., Dimercept had 13 disulfide bridges, the linkages connecting amino acids called cysteines that hang off the main backbone of the molecule. "Some disulfide bonds get mixed up during production," Shepard notes. "We're trying to redesign it to make sure that doesn't happen."

Receptor BioLogix may ultimately have to confront the giant just over the hill.

Receptor BioLogix could ultimately find itself in a face-off with Shepard's former employer and perhaps other companies that are beginning to explore similar methods of inhibiting receptors. Genentech has already initiated clinical trials for a monoclonal antibody, called Omnitarg (pertuzumab), that impedes the HER2 receptor from dimerizing with other HER receptors, possibly providing some of the same benefits expected from Dimercept in treating a range of solid tumors. Dimercept's purported benefits appear to come from hampering all HER receptors from joining in any combination. But Mark Sliwkowski, a Genentech staff scientist, says that other HER receptors prefer to partner with HER2, so inhibiting it would interfere with the others as well.

Genentech thinks its molecule has its advantages. "There's very little data about what [Dimercept] does, where it's expressed, if it's expressed, why it's expressed, what its biological role is and what its therapeutic potential is," Sliwkowski comments. All things being equal, a monoclonal antibody such as Omnitarg may be preferable to Dimercept, he notes, because it stays in the body longer and so would require smaller and less frequent doses.

Shepard was involved during the 1980s with the invention of both Herceptin and Omnitarg, the latter being one of the other antibodies that was considered early on for targeting HER2 for breast cancer. In the end, Genentech stuck with the molecule that became Herceptin. With a sense of déjà vu, Shepard remembers the long list of reasons that critics, including some at Genentech, put forward about why monoclonal antibodies might not work. Similarly, he believes that the problems confronting Dimercept may find a solution. Receptor BioLogix is working on 15 variants of the original molecule produced in Clinton's laboratory. "There are lots of ways to shorten or lengthen the half-life of a molecule," Shepard says, while adding that dimerization that does not involve HER2 is an important event in certain cancers.

Whether Omnitarg or Dimercept, the concept of preventing dimers from forming on the surface of cancer cells may prove burdensome for other reasons. Mark Pegram, a professor of medicine at the University of California, Los Angeles, who has been contracted to test both the Receptor BioLogix and Genentech compounds, observes that both agents show promising anticancer activity in mice. The most imposing barrier to the success of these molecules as drugs, he remarks, will be development of new techniques to identify the subpopulation of patients who respond to them.

If Receptor BioLogix gets through the multitude of technical and clinical hurdles that straddle the path to an approved drug, it may have to confront its neighbor over the hill, not just in the marketplace. Receptor BioLogix's patent position is fairly strong because not many patents have been filed on proteins encoded with introns from the HER family of receptors. But if Dimercept gets nearer to market, Genentech might try to acquire rights to the drug or else come forth to defend its turf. "I suspect there's no limit to what they'll do," Clinton says. Already, at conferences, Genentech scientists have approached Clinton's colleagues and told them that they have researched variant HER proteins and that their labors led nowhere.

Worries about predations from the nearby giant are understandable. Other drugs, such as Erbitux, also interact with individual HER receptors, but none can tweak all four receptors, as Dimercept apparently does. If it works as envisaged, Dimercept, which might help patients who fall victim to a long list of solid tumors, could rake in billions of dollars of revenues a year. "The payoff is potentially huge," Shepard observes. No toxicity has been detected in mice, despite the protein's interaction with multiple receptors. The company hopes to start clinical trials in 2008. "I would say at this point, you just have to stay tuned. It's an absolutely different ball game in human trials; we won't know for a while," Clinton says.

For his part, Shepard remains in awe of the advances in molecular biology since the time he was a graduate student in the late 1970s. "Thirty years ago people weren't sure there was such a thing as receptors," he recalls. Today they name companies after them. SA

MORE TO EXPLORE

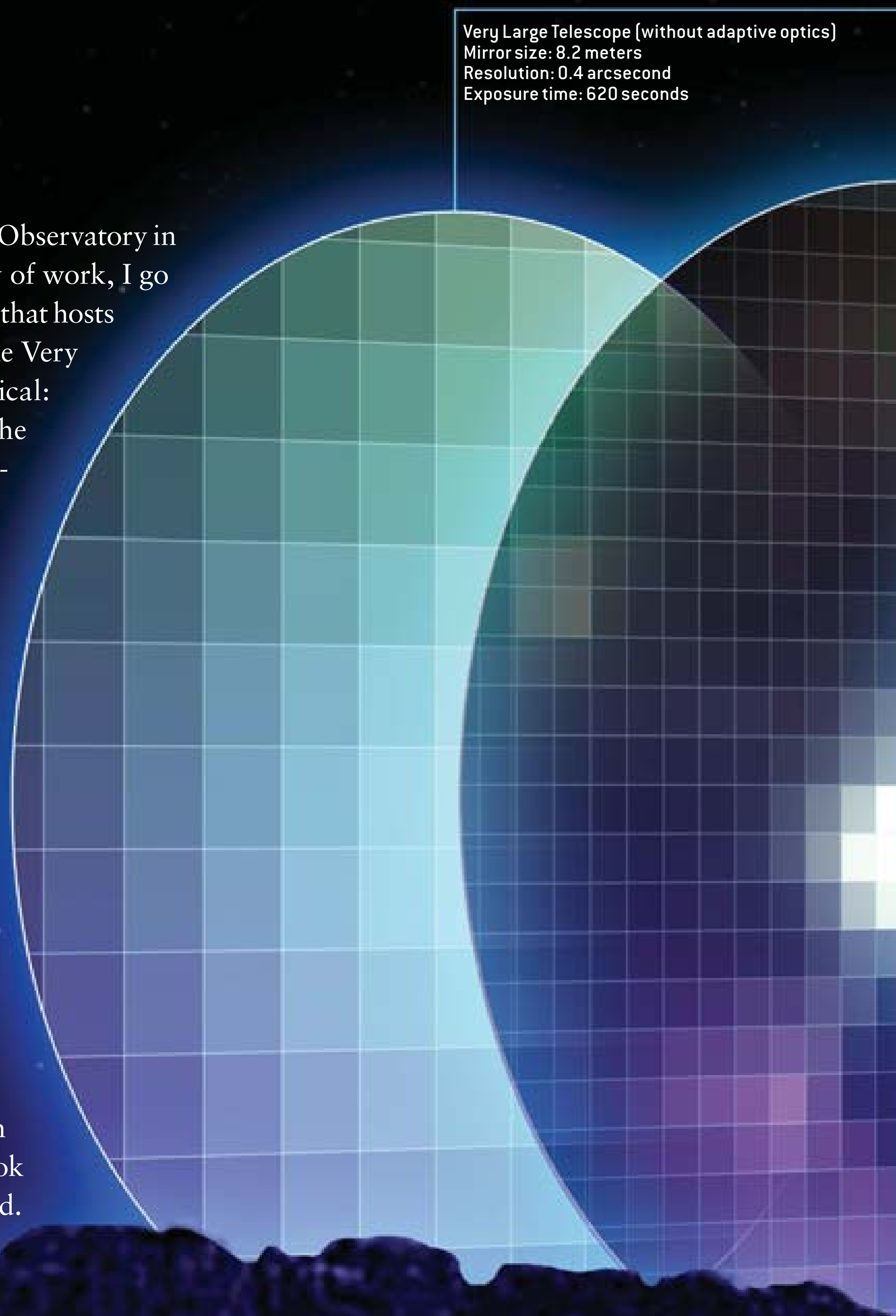
HER2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer. Robert Bazell. Random House, 1998.

The HER-2/Neu Receptor Tyrosine Kinase Gene Encodes a Secreted Autoinhibitor. Joni K. Doherty et al. in *Proceedings of the National Academy of Sciences USA,* Vol. 96, pages 10869–10874; 1999.

Herstatin, an Autoinhibitor of the Epidermal Growth Factor (EGF) Receptor Family, Blocks the Intracranial Growth of Glioblastoma. Julia A. Staverosky et al. in *Clinical Cancer Research,* Vol. 11, pages 335–340; January 1, 2005.

Giant Telescopes of the

The astronomical version of Moore's law says that telescopes double in size every few decades. But today's designers think they can build a telescope three, five or even 10 times bigger within a decade

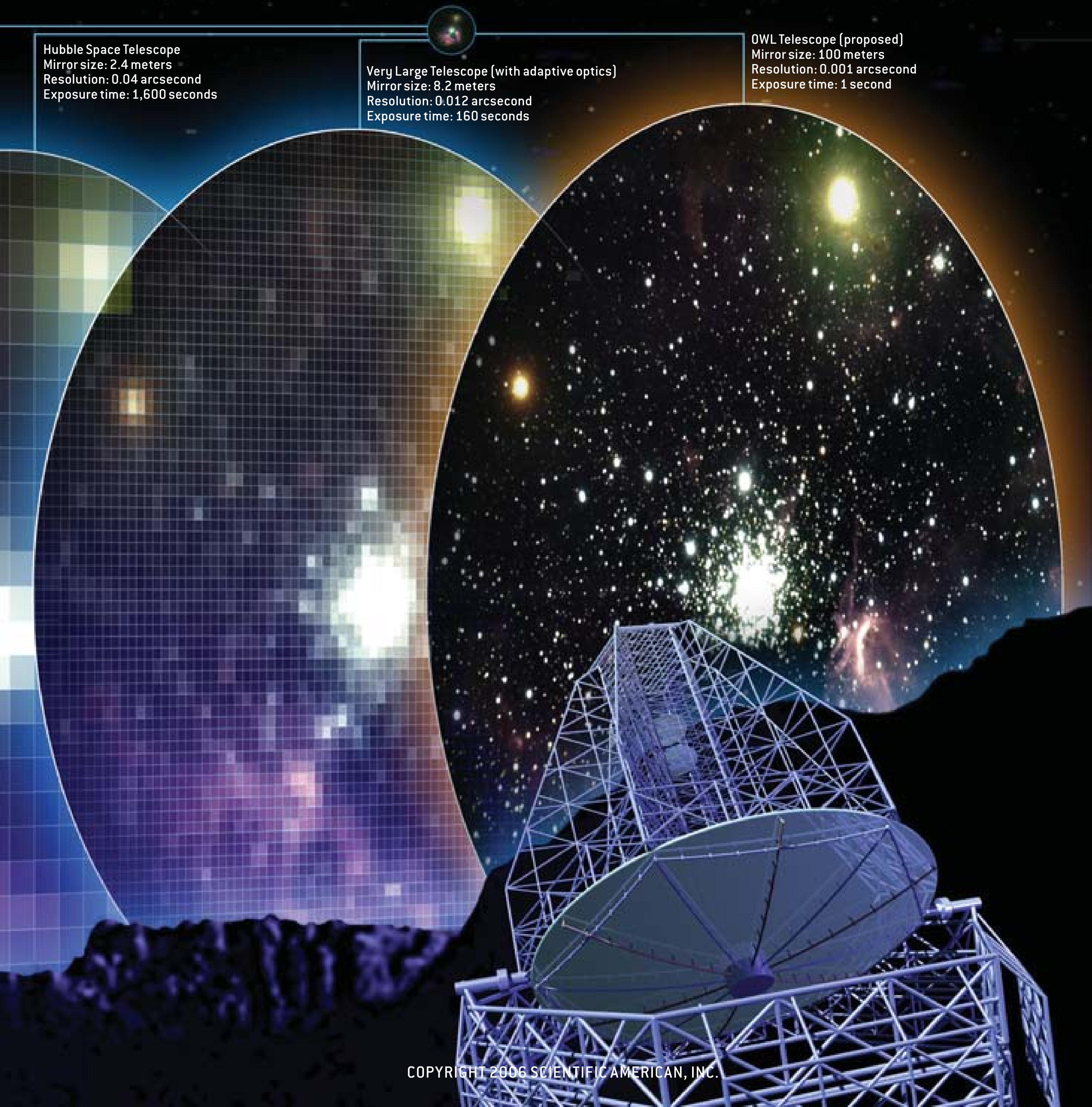


By Roberto Gilmozzi

Some of my best moments at Paranal Observatory in Chile are at night when, after a day of work, I go up "on deck," as we call the platform that hosts the four eight-meter-wide telescopes of the Very Large Telescope project (VLT). It is magical: the vast expanse of starry sky above, the smooth movements of the domes, the politically incorrect pleasure of smoking a pipe, the dark desert barely visible in its outline against the faintly opalescent horizon. As I stand there admiring the VLT, the most advanced set of telescopes in the world, its four 430-ton machines silently rotating in a complex ballet with the heavens, I reflect on how fortunate I am to be involved in such an awesome project. It is an achievement that all of humanity shares in. Like the other great telescopes of our day, such as the Keck Observatory, Hubble Space Telescope and Very Large Array, the VLT embodies the highest technologies that our civilization has to offer. If you traced the genesis of each part, you would find that, ultimately, it took millions of people to bring it into this world.

FROM INDISTINCT SMEAR TO SHIMMERING REGALIA: A large telescope equipped with adaptive optics has sharper vision than even the Hubble Space Telescope. (This simulation is based on a near-infrared VLT image of the star-forming region NGC 3603.)

FUTURE


Hubble Space Telescope
Mirror size: 2.4 meters
Resolution: 0.04 arcsecond
Exposure time: 1,600 seconds
Very Large Telescope (with adaptive optics)
Mirror size: 8.2 meters
Resolution: 0.012 arcsecond
Exposure time: 160 seconds
OWL Telescope (proposed)
Mirror size: 100 meters
Resolution: 0.001 arcsecond
Exposure time: 1 second

But astronomers never rest. The VLT had no sooner been built than many of us began to think about its successors, telescopes whose main mirrors would measure 25, 30 or even 100 meters in diameter. One concept that I have been deeply involved in designing is a behemoth called OWL (for its keen night vision and for being over*w*helmingly *l*arge) that would almost fill the whole Paranal deck with its 100-meter mirror.

Like all new scientific instruments, the eight- to 10-meter telescopes now in operation are not only answering the questions they were built for but also posing new, more profound and challenging ones that demand even larger instruments. Analyzing the composition of Earth-like planets in other star systems and looking for signs of life; studying the very first galaxies to form in the universe; understanding the nature of dark matter and dark energy; imaging the multitude of bodies in our own solar system that are not being studied by in situ spacecraft—all this drives astronomers toward a generation of giant optical telescopes with capabilities hundreds or thousands of times beyond what is available today. Various agencies in Europe have identified such a telescope as the highest priority in astronomy; for the U.S. National Academy of Sciences, it is second only to Hubble's successor, the James Webb Space Telescope (JWST). A number of projects are now on the drawing board, including OWL, the Thirty Meter Telescope (TMT) and the 24-meter Giant Magellan Telescope (GMT).

Historically, telescopes have followed their own version of Moore's law: each generation of telescope is about twice as large as the preceding one and takes several decades to build. This trend is illustrated particularly well by the "California progression" during the 20th century: the 2.5-meter Hooker telescope on Mount Wilson (1917), the five-meter Hale telescope on Mount Palomar (1948) and the twin 10-meter Keck telescopes on Mauna Kea, Hawaii (1993). Following this precedent, the next-generation telescope should be around 20 meters in diameter and start operations around 2025. Are those of us proposing 25-meter and even 100-meter telescopes by the middle of the next decade out of our minds? A closer look at the challenges of building a telescope may reassure you about astronomers' sanity. Not only is the need for larger ground-based telescopes pressing but, for the most part, the necessary technology already exists.

Scope for Improvement

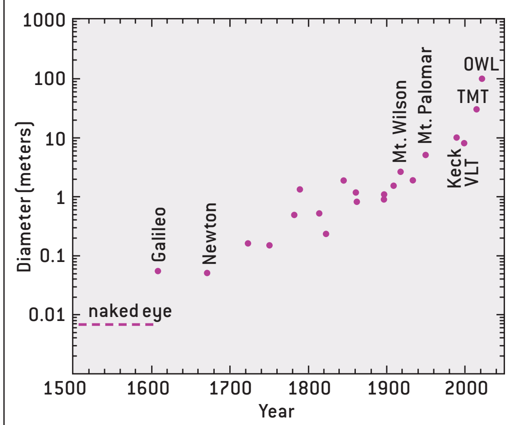
A BIG IMPETUS for defying the telescopic Moore's law is that astronomers are running out of other options for improving the ability of their devices to gather light. In a reflecting telescope, light first bounces off a primary mirror and then strikes a secondary mirror, which brings it to a focus at a convenient location, where you can view it with your eye, take a picture or splay it into a rainbow of colors for spectroscopic analysis. When astronomers talk about the size of a telescope, they are referring to the diameter of the primary mirror. Doubling it lets you see celestial bodies one quarter as bright or, equivalently, a body of a given brightness twice as far away.

Overview/*Very, Very Large Telescopes*

- In astronomy, size matters. Large telescopes can detect fainter objects and produce crisper images. Today's biggest telescopes for visible and near-infrared light have mirrors eight to 10 meters across, and researchers are now working on the next generation, ranging from 20 meters to an epic 100 meters.
- Though situated on the ground, the telescopes would be equipped with adaptive optics technology to undo the effects of atmospheric blurring. In fact, they would produce images sharper than those of the Hubble Space Telescope—and for less money. The new instruments could perform many tasks beyond the abilities of current ones, such as searching for Earth-size planets and analyzing the composition of any they find.

A TIMELINE OF TELESCOPES

Proposed telescopes such as OWL and TMT would continue the long historical trend of increasing aperture size.

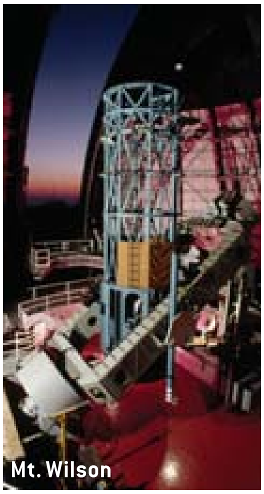


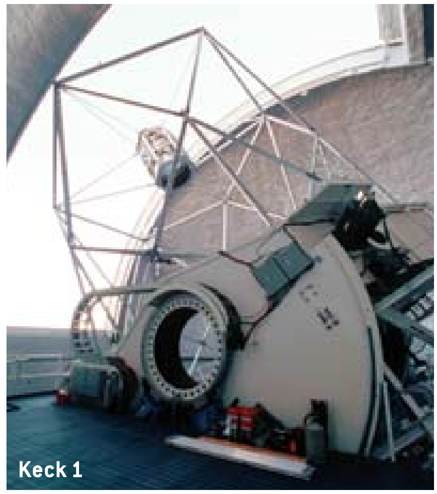
Over the past 50 years, telescopes have become more sensitive to faint bodies not just because of increases in diameter but also because of advances in detector technology. When it was built, the five-meter Hale telescope was equipped with photographic plates, which register only a few percent of the light falling on them. Today's electronic detectors are nearly 100 percent efficient—an improvement in sensitivity equivalent to a fivefold increase in diameter. In effect, then, the current generation of telescopes is actually 10 times bigger than its predecessors. For the next generation to make the same leap, now that so little room remains for further progress in detector efficiency, it would have to be 100 meters across.

Proponents of the various designs for future telescopes have had a friendly, if animated, debate about the largest diameter they can realistically achieve, but no one doubts the need to give the next generation an extra push in size. Traditionally, the size of new telescope designs has been limited by the ability to produce the mirror glass, cast it in the necessary shape and polish it. Visible light has a shorter wavelength than radio waves, so although radio dishes can be enormous, their requirements are much less stringent than those of optical mirrors, just as you need finer motor control to hold a grain of sand between your fingers than to carry a rock.

The five-meter Hale telescope has a

SLIM FILMS (*photocomposition*); EUROPEAN SOUTHERN OBSERVATORY (*NGC 3603*) (*preceding two pages*); MELISSA THOMAS (*this page*)





GUSTAVO TOMSICH *Corbis* (*Galileo*); JIM SUGAR *Corbis* (*Newton*); ROGER RESSMEYER *Corbis* (*Mt. Wilson, Mt. Palomar and Keck 1*)

paraboloidal mirror with a surface precision of 50 nanometers. If it were as wide as the Atlantic Ocean, the largest bump on its surface would be five centimeters high. To polish it, the builders used a wooden lapping tool covered with pitch; in the final stages, they buffed some areas by hand. The task took 11 years (admittedly with World War II in between), during which measurements of the shape were taken every two days.

Today's mirrors are shaped under computer control, greatly accelerating the schedule. The four 8.2-meter VLT mirrors were each polished in one year, with measurements taken almost continuously. Their surface quality equals or slightly exceeds that of the Hale, even though their shape (a hyperboloid, which produces the sharpest possible focus) is substantially more complex. So polishing is no longer the main stumbling block.

A bigger problem is fabricating the glass itself. To cast pieces of glass eight meters across, telescope builders have had to construct dedicated factories and climb up a tough learning curve, often making and breaking several mirrors before getting it right. Current procedures would not scale to even twice the size. Fortunately, Italian astronomer Guido Horn D'Arturo came up with the solution in 1932: a segmented mirror. The mirrors at the twin Keck telescopes, for example, are mosaics of 36 segments, each a hexagon 1.8 meters across. The hexagonal shape allows them to fit together to fill out a hyperboloidal surface. Each segment has a slightly different profile depending on its distance from the center of the mirror. In principle, such a design can be scaled up to whatever size. The downside is the need to align the pieces with subwavelength precision, to minimize the effect of the joints on image quality and to hold them together despite buffeting by the wind.

Like Keck, OWL and TMT would consist of hexagonal segments. The GMT designers have gone a different route: to minimize the downside of segmentation, they have chosen to build fewer but larger segments. Their telescope would be a mosaic of seven 8.4-meter circular mirrors (the first of which is already in fabrication, as a proof of principle) [see "Breaking the Mold," by W. Wayt Gibbs, Insights; Scientific American, December 2005]. The compromise of this approach is that it is hard to scale up any further.

Vision Quest

SENSITIVITY TO faint objects is only one of a telescope's desired features. Another is resolving power—the ability to discern fine details. In principle, a large telescope should be able to provide both. The larger a telescope is, the less its images are degraded by diffraction, a blurring that occurs when the incoming waves get cut off at the outer edge of the mirror. Until recently, however, diffraction has been a moot point for ground-based optical telescopes. Even at the most pristine sites, air turbulence blurs any feature smaller than 0.3 arcsecond. If you look at the giant star Betelgeuse (0.05 arcsecond across) through the $100-million Palomar five-meter telescope, all you see is a twinkling point of red light—which is brighter but no clearer than what you can see through a $300 20-centimeter backyard telescope or indeed with your naked eye.

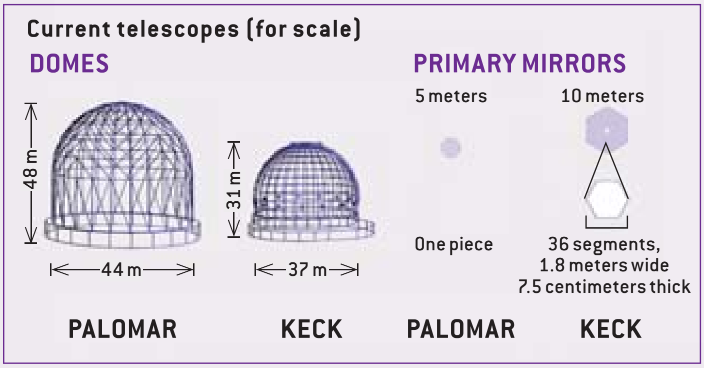
Orbiting telescopes have the opposite problem. They produce spectacularly high-resolution images but lack the sensitivity to see the faintest bodies, let alone split their light into multiple colors for compositional analysis. The diameter of the Hubble Space Telescope was limited by the size of the space shuttle to 2.4 meters, and even the JWST will have only a 6.5-meter mirror. The spectroscopic follow-up to these satellites' discoveries must be done from the ground.

THE AUTHOR

ROBERTO GILMOZZI is principal investigator of the OWL telescope design study. From 1999 through 2005, he was also director of the European Southern Observatory's Very Large Telescope Observatory at Cerro Paranal in Chile. His scientific interests include novae, supernovae and their remnants, the cosmic x-ray background, and the star-formation history of the universe.

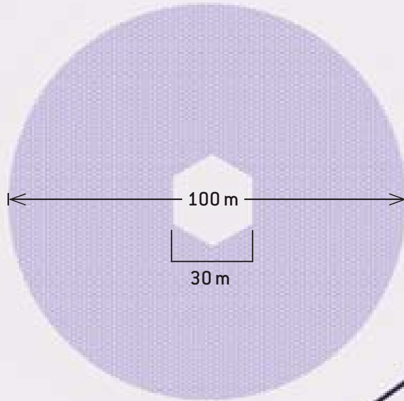
VISION FOR AN OWL

A 100-meter telescope would be 10 times as big as any optical instrument ever built, but a number of innovations would keep its cost to one billion euros ($1.2 billion)—cheaper than a space telescope. That price tag includes detectors and infrastructure as well as spare money to absorb cost overruns.



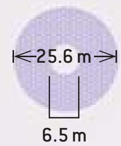
PRIMARY MIRROR

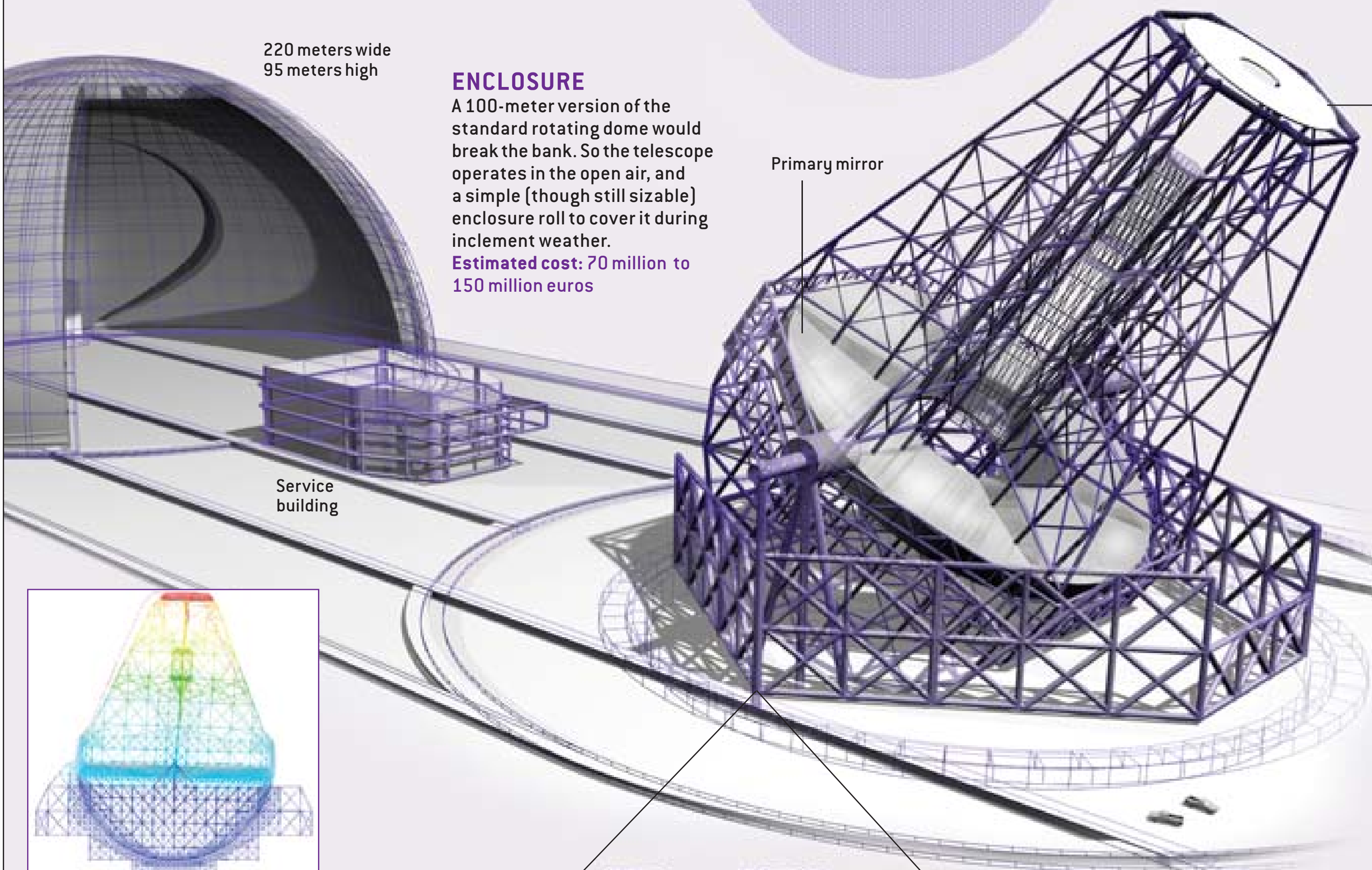
The primary mirror (which collects the starlight) consists of 3,048 hexagonal segments. To save money, they fill out a spherical surface rather than the usual paraboloid or hyperboloid.
Cost: 290 million euros



SECONDARY MIRROR

The secondary mirror (which redirects the starlight into the corrector) consists of 216 segments. To ease the mechanical requirements, it is flat rather than curved.
Estimated cost: 30 million euros





ENCLOSURE

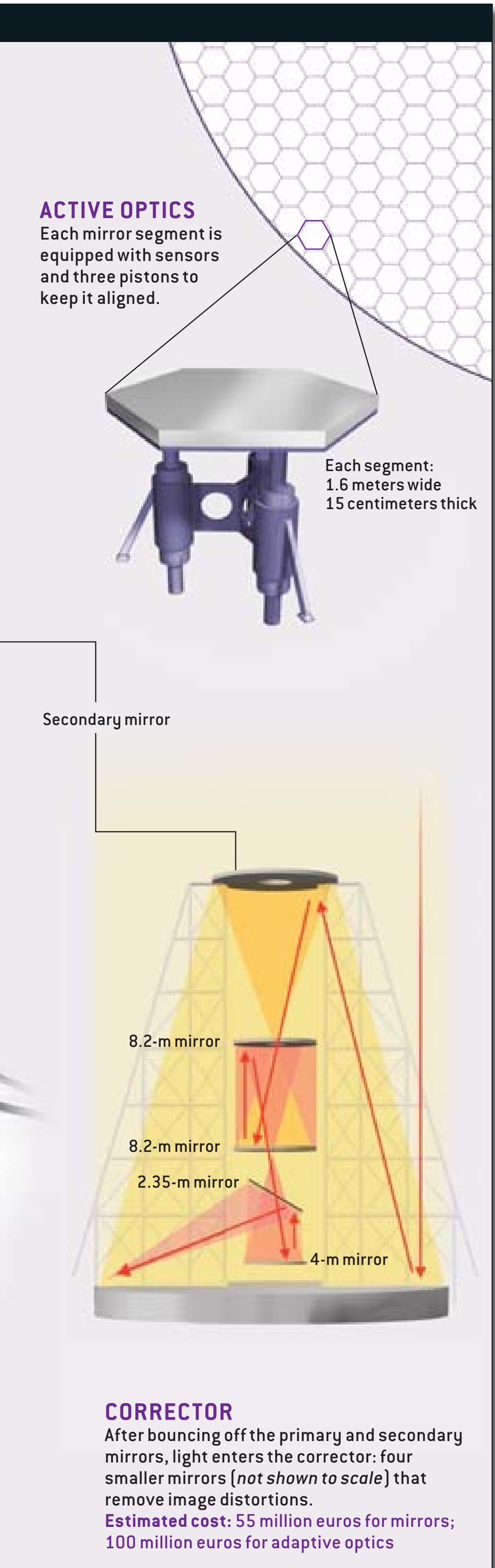
A 100-meter version of the standard rotating dome would break the bank. So the telescope operates in the open air, and a simple (though still sizable) enclosure roll to cover it during inclement weather.
Estimated cost: 70 million to 150 million euros

STRUCTURE

A truss framework distorts symmetrically when tilted toward the horizon, keeping the mirrors aligned. The horizontal displacement varies from 0 (*blue*) to 0.6 millimeter (*red*). Although the structure appears to screen out the mirror, it actually blocks only about 3 percent of the incoming light.
Estimated cost: 185 million euros

DRIVE MECHANICS

The telescope weighs nearly 15,000 tons—too heavy for standard telescope mounts. Instead it could be mounted on 300 friction drives (bogies) that roll on circular tracks.
Estimated cost: 30 million euros



DON FOLEY

This trade-off between sensitivity and resolution is not good enough for the next generation of telescopes, whose scientific goals require both at once. In an overnight exposure, a 100-meter telescope would be able to see celestial bodies a thousandth the brightness of anything astronomers have yet seen. Where current telescopes see a black patch of space, it would see a throng of dim objects. Without high resolution, all those objects would blend into one another.

A combination of high resolution and high sensitivity is also paramount for the detection of Earth-like planets. To see such a planet, which is less than a billionth as bright as its host star, astronomers have to block out the star using a small opaque disk known as a coronagraph. If the disk is too big, however, it also hides the planet. High resolution means that astronomers can get away with a smaller disk, extending the range of their planet hunts. The minimum size of a telescope that can survey our galactic neighborhood for planets in Earth-like orbits turns out to be about 80 meters. It could search a volume encompassing about 400 sunlike star systems and do spectroscopy of Earth-like planets, if present, of about 40 of them. A 30-meter instrument could survey a few dozen systems. To take a spectrum of any one of them, it would have to collect light for weeks, which may not be possible.

Evolve and Adapt

TO ACHIEVE THIS high resolution, the telescope will have to rely on adaptive optics to undo the distortions introduced by atmospheric turbulence. The idea is to monitor a reference star (which can be an artificial "star" created by shining a laser into the upper atmosphere) and adjusting the shape of a mirror to keep this star in focus. This mirror is either the secondary mirror or another, smaller one interposed between the secondary and the detectors. A thicket of small pistons, or actuators, push on the back of the mirror to fine-tune its shape.

This system enables a telescope to work at or close to its maximum resolving power, limited only by diffraction, as though the atmosphere were not even there. A 100-meter telescope should be able to see features 0.001 arcsecond across, which is 40 times better than Hubble can manage. Through it, Betelgeuse would appear not as a mere point of light but as a 3,000-pixel image offering a level of detail currently available only for nearby planets.

The technique is already used on many large telescopes, but for it to work on larger systems, it will have to be scaled up. That this is possible is not at all obvious: an adaptive-optics system on a 100-meter telescope would need more than 100,000 actuators. Today's systems have at most 1,000. The controlling computer must be capable of updating the shape of this mirror several hundred times a second, and processor technology is not yet up to the task.

Engineers are taking a staged approach, first building systems that operate at infrared wavelengths, which need fewer actuators because the effect of turbulence is less severe at longer wavelengths. They should also be able to take advantage of efforts to develop advanced adaptive optics for medicine, spaceflight, military surveillance and consumer electronics. An especially promising new technique is multiconjugate adaptive optics, which corrects for turbulence over a wide field of view, so that systems are not limited to the small patches of sky around a reference star [see "Three-Star Performance," by Graham P. Collins; Scientific American, May 2000]. The VLT is now deploying a demonstration of the multiconjugate method.

Interferometry, a technique that combines light from more than one telescope, can achieve an even higher resolution than the proposed large telescopes could [see "A Sharper View of the Stars," by Arsen R. Hajian and J. Thomas Armstrong; Scientific American, March 2001]. One such system operates at Paranal Observatory. The four VLT telescopes are located as far apart as 130 meters, so merging their light offers the same resolution as a single telescope 130 meters wide, providing exquisite details of the objects they study. But interferometers have their limitations. They can observe only a small field of view; using them is like looking through a drinking straw. Also, because of the complexity of their optics, they are able to utilize only a few percent of the light they collect, as opposed to 50 percent or more for a standard telescope, and in any case their total collecting area is only the sum of the component telescopes. In short, like space telescopes, they gain resolution by giving up sensitivity, so they are no substitute for a giant ground-based instrument.

Nuts and Bolts

AN ELEPHANT is not built like an ant. The weight of a creature goes up as the cube of its linear dimensions, whereas the ability of a skeleton to support weight goes up only as the square, so the elephant needs proportionately much bigger legs. What applies to large land mammals also applies to telescopes. All the advanced optical technology in the world hardly matters if the telescope cannot even support its own weight. Although radio astronomers have built steerable dishes up to 100 meters wide, the mechanical requirements of optical telescopes are substantially more demanding because they operate at much shorter wavelengths.

The telescope framework needs to be stiff enough to keep the mirrors precisely aligned with one another and to resist vibrations induced by the wind. Short stubby telescopes tend to be stiffer than long skinny ones, but they require that light be bent more strongly to be brought to a focus, complicating the optical design. Thus, engineers must strike a balance between mechanical and optical requirements. The VLT still jiggles in the wind somewhat, but the secondary mirror cancels the effects of these vibrations by moving in the opposite direction up to 70 times a second. OWL would do the same.

Another potential problem is that as the telescope tracks the heavens, its weight shifts, which can bend the instrument and cause its mirrors to move out of alignment. Most large telescopes today use the skeletal structure that engineer Mark Serrurier designed in the 1930s for Palomar. In it, the mirrors are each held by an open, boxlike frame of four triangular trusses. When tilted, the frames flex and the mirrors shift laterally, but because each mirror is held by the same type of frame, both mirrors shift by the same amount, keeping them closely aligned. OWL's design takes a similar approach but has the advantage that it can be built from a few standardized components, like Tinkertoys.

The total weight of the structure is 10,000 to 15,000 tons, depending on the final choice of the mirror material. In comparison, the Eiffel Tower weighed about 10,000 tons when it was built. As mammoth as it may seem, OWL would be proportionately much lighter than today's telescopes. If you scaled up one of the VLT unit telescopes, it would weigh half a million tons. Nevertheless, to move 10,000 tons with the requisite precision is a challenge of its own. Options that engineers are considering include trainlike bogies using friction drives in each wheel, thin layers of oil on which the telescope would float (as the VLT units do), and magnetic levitation.

Breaking the Law

TECHNICALLY, THEN, astronomers are not insane to consider building telescopes up to 100 meters across. Whereas past increases in telescope size required a leap in the technological dark, future ones can draw on existing knowledge and expertise. For modern builders, a 100-meter-tall structure is actually fairly run-of-the-mill.

The main question at this point is cost. Historically, the price tag of a telescope has been proportional to the diameter of the main telescope mirror raised to the 2.6th power ($D^{2.6}$). So if the four eight-meter VLT telescopes cost about $100 million each, a 20-meter telescope would run about $1 billion—which is the most money anyone can hope to raise for a new telescope. A 100-meter telescope would be an eye-popping $70 billion. As long as this law of telescope cost holds, astronomers should seriously consider building multiple copies of a smaller telescope to reach a desired equivalent size: the cost would then go as D^2. For $1 billion we could buy 10 8.2-meter telescopes with an area equivalent to a single 26-meter telescope. Unfortunately, for the reasons described above, equivalence in size does not mean equivalence in capability. Used as ordinary telescopes, the array would have the sensitivity of a 26-meter instrument but the resolving power of an 8.2-meter one. Used as an interferometer, the array would offer higher resolution but lower sensitivity.

Fortunately, engineers think they can break the law. The key is the mass production of components, so that the cost per component decreases sharply. That, in turn, requires a novel approach to the optics. Instead of the usual hyperboloidal primary mirror, which would require that each mirror segment be custom-made according to its position within the mirror, a 100-meter telescope could have a spherical mirror, whose segments are all identical in shape. An assembly line could create the segments, all 3,048 of them, at the rate of one every two days. The trade-off is that a spherical shape introduces a distortion into the light. To compensate, the telescope would have to be equipped with a device known as a corrector, similar to the one that fixed the vision of Hubble. Even so, the system would be cheaper.

One of the major expenses of any telescope is the dome. Palomar has a dome comparable to St. Peter's Basilica in Rome, if somewhat less artistic. One reason it is so big is that the telescope mount is tilted to point at the North Star. That way, the instrument can track stars

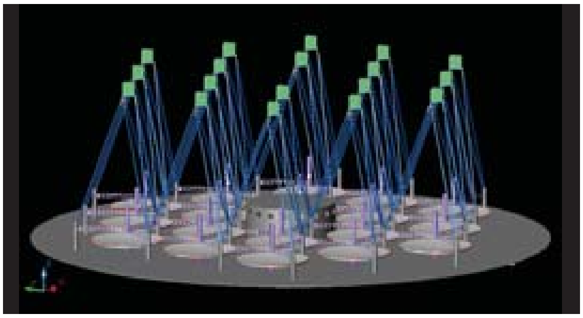
OTHER PROPOSED TELESCOPES

THIRTY-METER TELESCOPE (TMT)

Diameter:	30 meters
Estimated cost:	$700 million
Design:	Segmented hyperboloidal primary
Web site:	www.tmt.org

TODD MASON *Mason Productions* (*TMT*); PAUL HICKSON *University of British Columbia* (*LAMA*); TODD MASON *Mason Productions* AND CARNEGIE OBSERVATORIES (*GMT*); EURO50 PROJECT *Lund Observatory, Sweden* (*Euro50*)

LARGE-APERTURE MIRROR ARRAY (LAMA)

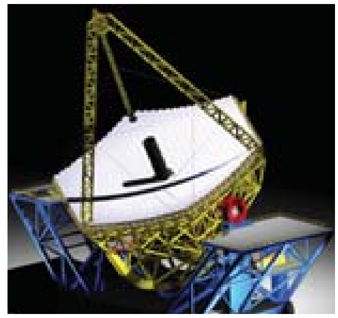


42 m (equivalent collecting area), 54 m (equivalent resolution)
$50 million
18 paraboloidal 10-m liquid-mercury mirrors, pointing up
www.astro.ubc.ca/LMT/lama

GIANT MAGELLAN TELESCOPE (GMT)

21.4 m (area), 24.5 m (resolution)
$500 million
Seven hyperboloidal 8.4-m mirrors on one mount
www.gmto.org

EURO50



50 m
$700 million
Segmented ellipsoidal primary
www.astro.lu.se/~torben/euro50

simply by spinning around its axis. Modern telescopes are supported by a more compact mount called altitude/azimuth (the term refers to motion in two dimensions rather than simple rotation around an axis). The disadvantage is a more complicated control mechanism, which computers have made feasible. But even with the altitude/azimuth system, a 100-meter telescope would require a hugely expensive dome. What is more, computer simulations suggest that such a monumental structure might create its own pocket of air turbulence. So OWL would merely have a sliding hangar to cover it during the day or in bad weather. The telescope would operate in the open air. It could handle a moderately strong wind, up to 15 meters a second (about 30 miles an hour). In fact, the constant breeze would reduce the air turbulence.

The cost of a 100-meter OWL would be around $1.2 billion. The TMT is currently estimated to run about $700 million, and the GMT around $400 million. A significant fraction of $1 billion is less than most space experiments, but it is still a very large amount of money. An international collaboration will probably be essential.

The Astronomical Panorama

THE PAST DECADE has been a golden age for astronomy, but we can expect even more to come by 2015. Innovative detectors and adaptive optics will extend the capacities of the present generation of eight- to 10-meter telescopes, much as new cameras and spectrometers have gotten more life out of Hubble. Interferometry will have progressed from exotic animal to workhorse, pursuing ever fainter objects and reaching submilliarcsecond resolution. JWST, specializing in infrared observations, will have been launched. The Atacama Large Millimeter Array will have started operation with dozens of dish antennas, providing a bridge between infrared and radio astronomy. Radio astronomers could be constructing the Square Kilometer Array project for the detection of low-frequency radio waves, a barely explored region of the electromagnetic spectrum.

With all these advances, do astronomers really need new, extremely large optical telescopes? The answer is a resounding yes. Crucial scientific problems, such as the study of extrasolar planets and the building blocks of stars and galaxies, cannot be tackled with smaller instruments. For visible and near-infrared light, ground-based telescopes offer higher resolution and sensitivity at lower cost than orbital observatories.

Deciding among the various approaches embodied by OWL, TMT and GMT will not be an easy task. Each has its pros and cons. Recently an international panel reviewing the OWL concept concluded that it is feasible but risky, both technically and financially. My colleagues and I, with the help of the wider astronomical community, are now putting together a smaller design, and a decision is expected by the end of the year. So the various projects may be converging. The TMT is itself a merger of several earlier designs.

Over the centuries, telescopes have gone from the size of a bedside table, to the size of a room, a house, a cathedral and now a skyscraper. Thanks to the advances of technology, we can build instruments able to see the first stars ever to be born in the universe and planets around other stars, including possibly sister planets of Earth. The question is no longer whether we can build giant telescopes or why we would want to, but when and how large. SA

MORE TO EXPLORE

OWL Concept Study. R. Gilmozzi and P. Dierickx in *ESO Messenger,* No. 100, pages 1–10; June 2000. Online at **www.eso.org/projects/owl/publications/2000_05_Messenger.htm**

Astrophysical Techniques. Fourth edition. C. R. Kitchin. Taylor & Francis, 2003.

Proceedings of Second Bäckaskog Workshop on Extremely Large Telescopes. Edited by A. L. Ardeberg and T. E. Andersen. *Proceedings of the SPIE,* Vol. 5382; July 2004.

The Light Brigade. Neil deGrasse Tyson in *Natural History,* Vol. 115, No. 2, pages 18–29; March 2006.

Exploring the Cosmic Frontier: Astrophysical Instruments for the 21st Century. ESO Astrophysics Symposia. Springer-Verlag (in press). **www.mpifr-bonn.mpg.de/berlin04/**

ALZHEIMER'S DISEASE gradually severs even one's oldest memories, but scientists are working on promising treatments. Some therapies could clamp the molecular cutting that appears to initiate the disorder; others could prevent the harmful effects that follow.

New research reveals strategies for blocking the molecular processes that lead to this memory-destroying disease

By Michael S. Wolfe

Shutting Down ALZHEIMER'S

The human brain is a remarkably complex organic computer, taking in a wide variety of sensory experiences, processing and storing this information, and recalling and integrating selected bits at the right moments. The destruction caused by Alzheimer's disease has been likened to the erasure of a hard drive, beginning with the most recent files and working backward. An initial sign of the disease is often the failure to recall events of the past few days—a phone conversation with a friend, a repairman's visit to the house—while recollections from long ago remain intact. As the illness progresses, however, the old as well as the new memories gradually disappear until even loved ones are no longer recognized. The fear of Alzheimer's stems not so much from anticipated physical pain and suffering but rather from the inexorable loss of a lifetime of memories that make up a person's very identity.

Unfortunately, the computer analogy breaks down: one cannot simply reboot the human brain and reload the files and programs. The problem is that Alzheimer's does not only erase information; it destroys the very hardware of the brain, which is composed of more than 100 billion nerve cells (neurons), with 100 trillion connections among them. Most current medications for Alzheimer's take advantage of the fact that many of the neurons lost to the disease release a type of chemical communicator (or neurotransmitter) called acetylcholine. Because these medicines block an enzyme responsible for the normal decomposition of acetylcholine, they increase the levels of this otherwise depleted neurotransmitter. The result is stimulation of neurons and clearer thinking, but these drugs typically become ineffective within six months to a year because they cannot stop the relentless devastation of neurons. Another medication, called memantine, appears to slow the cognitive decline in patients with moderate to severe Alzheimer's by blocking excessive activity of a different neurotransmitter (glutamate), but investigators have not yet determined whether the drug's effects last more than a year.

More than a decade ago few people were optimistic about the prospects for defeating Alzheimer's. Scientists knew so little about the biology of the disease, and its origins and course were thought to be hopelessly complex. Recently, however, researchers have made tremendous progress toward understanding the molecular events that appear to trigger the illness, and they are now exploring a variety of strategies for slowing or halting these destructive processes. Perhaps one of these treatments, or a combination of them, could impede the degeneration of neurons enough to stop Alzheimer's disease in its tracks. Several candidate therapies are undergoing clinical trials and have

TINA WEST

yielded some promising preliminary results. More and more researchers are feeling hope—a word not usually associated with Alzheimer's.

The Amyloid Hypothesis

THE TWO KEY FEATURES of the disease, first noted by German neurologist Alois Alzheimer 100 years ago, are plaques and tangles of proteins in the cerebral cortex and limbic system, which are responsible for higher brain functions. The plaques are deposits found outside the neurons and are composed primarily of a small protein called amyloid-beta, or A-beta. The tangles are located inside neurons and their branching projections (axons and dendrites) and are made of filaments of a protein called tau. The observation of these anomalies started a debate that lasted throughout most of the 20th century: Are the plaques and tangles responsible for the degeneration of brain neurons, or are they merely markers of where neuronal death has already occurred? In the past decade, the weight of evidence has shifted toward the amyloid-cascade hypothesis, which posits that both A-beta and tau are intimately involved in causing Alzheimer's disease, with A-beta providing the initial insult.

A-beta is a short peptide, or protein fragment, first isolated and characterized in 1984 by George G. Glenner and Cai'ne W. Wong, then at the University of California, San Diego. This peptide is derived from a larger protein called the amyloid-beta precursor protein, or APP. Molecules of APP stick through the cellular membrane, with one part of the protein inside the cell and another part outside. Two protein-cutting enzymes, or proteases—beta-secretase and gamma-secretase—carve out A-beta from APP, a process that occurs normally in virtually all cells in the body. The reason why cells make A-beta is unclear, but current evidence suggests that the process is part of a signaling pathway.

A portion of the A-beta region of APP is inside the membrane itself, between its outer and inner layers. Because membranes are composed of water-repelling lipids, the regions of proteins that pass through membranes typically contain water-repelling amino acids. When A-beta is cut out of APP by beta- and gamma-secretase and released into the aqueous environment outside the membrane, the water-repelling regions of different A-beta molecules cling to one another, forming small soluble assemblies. In the early 1990s Peter T. Lansbury, Jr., now at Harvard Medical School, showed that at high enough concentrations, A-beta molecules in a test tube can assemble into fiberlike structures similar to those found in the plaques of Alzheimer's disease. The soluble assemblies as well as the fibers of A-beta are toxic to neurons cultured in petri dishes, and the former can interfere with processes critical to learning and memory in mice.

These findings supported the amyloid-cascade hypothesis, but the strongest evidence came from studies of families at especially high risk of getting Alzheimer's. Members of these families carry rare genetic mutations that predestine them for the disease at a relatively young age, typically before 60. In 1991 John A. Hardy, now at the National Institute on Aging, and his colleagues discovered the first such mutations in the gene that encodes APP, specifically affecting the areas of the protein in and around the A-beta region. Soon afterward, Dennis J. Selkoe of Harvard and Steven Younkin of the Mayo Clinic in Jacksonville, Fla., independently found that these mutations increase the formation of either A-beta in general or a particular type of A-beta that is highly prone to forming deposits. Moreover, people with Down syndrome, who carry three copies of chromosome 21 instead of the normal two copies, have a much higher incidence of Alzheimer's in middle age. Because chromosome 21 contains the APP gene, people with Down syndrome produce higher levels of A-beta from birth, and amyloid deposits can be found in their brains as early as age 12.

Researchers soon discovered other connections between Alzheimer's disease and the genes that regulate the production of A-beta. In 1995 Peter St. George-Hyslop and his colleagues at the University of Toronto identified mutations in two related genes dubbed *presenilin 1* and *2* that cause very early and aggressive forms of Alzheimer's, typically appearing when the carrier is in his or her 30s or 40s. Further studies showed that these mutations increase the proportion of A-beta that is prone to clumping. We now know that the proteins encoded by the *presenilin* genes are part of the gamma-secretase enzyme.

Thus, of the three genes known to cause Alzheimer's early in life, one encodes the precursor to A-beta and the other two specify components of a protease enzyme that helps to manufacture the harmful peptide. Furthermore, scientists have found that people carrying a certain variation in the gene encoding apolipoprotein E—a protein that helps to bring together the A-beta peptides in assemblies and filaments—have a substantially elevated risk of developing Alzheimer's later in life. A variety of ge-

Alzheimer's disease destroys the very hardware of the brain.

Overview/*New Hope for the Old*

- Scientists have focused on the hypothesis that a peptide called amyloid-beta (A-beta) triggers the disruption and death of brain cells in Alzheimer's patients.
- Investigators are now developing drugs that could inhibit the production of A-beta and therapies that could stop the peptide from harming neurons.
- Several drug candidates are already in clinical trials to determine if they can slow or halt the relentless mental decline caused by Alzheimer's.

netic factors most likely play a role in the onset of the disease, with each contributing in a small way, and mouse studies indicate that environmental factors may also affect the disease risk (exercise, for example, may lower it).

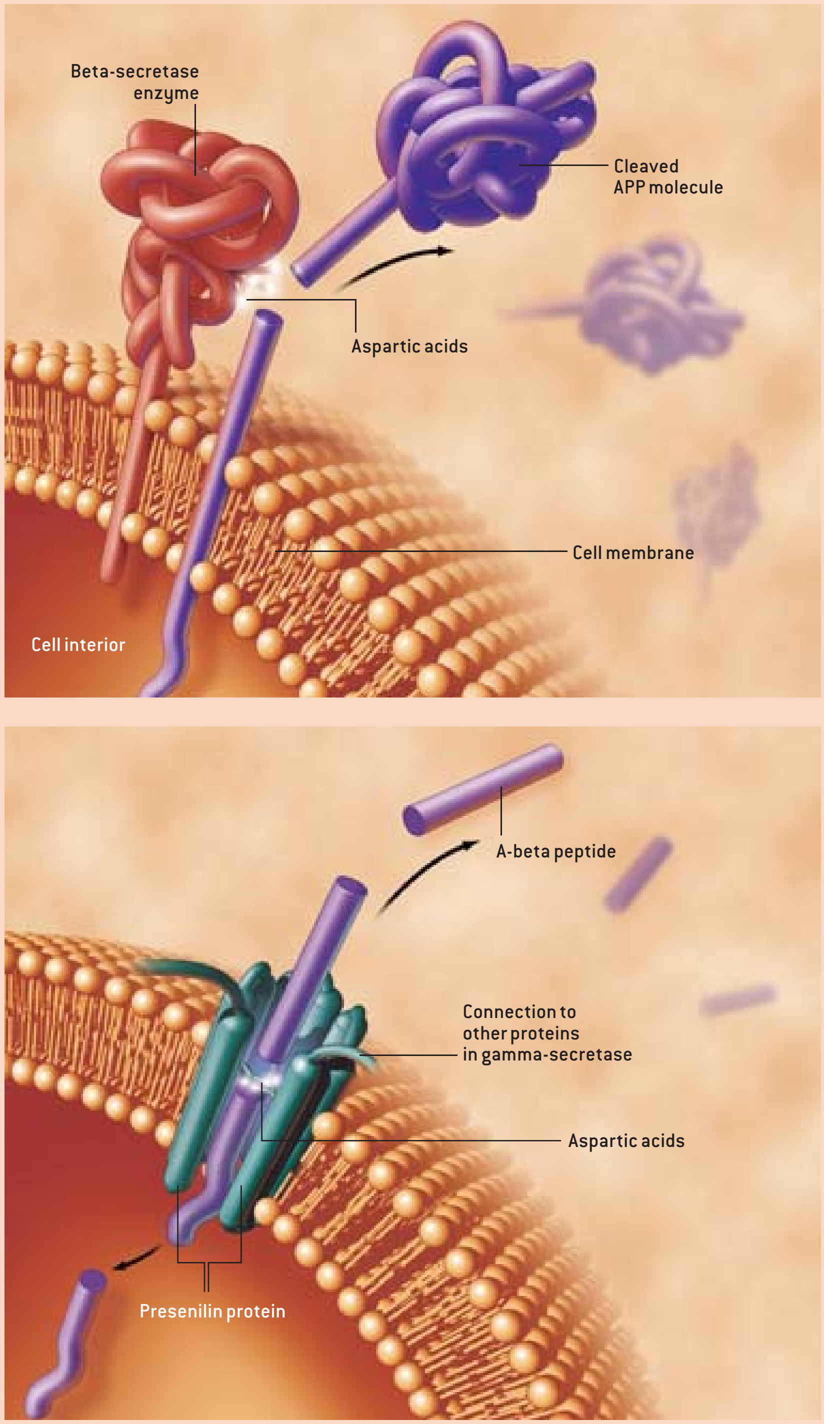
Scientists still do not understand exactly how the soluble assemblies and insoluble filaments of A-beta disrupt and kill neurons. The evidence suggests, though, that aggregates of A-beta outside a neuron can initiate a cascade of events that include the alteration of the tau proteins inside the cell. In particular, the A-beta aggregates can ultimately change the cellular activity of enzymes called kinases that install phosphates onto proteins. The affected kinases add too many phosphates to tau, changing the proteins' chemical properties and causing them to form twisted filaments. The altered tau proteins somehow kill the neuron, perhaps because they disrupt the microtubules that transport proteins and other large molecules along axons and dendrites. Mutations in the *tau* gene itself can also generate tau filaments and cause other types of neurodegenerative diseases besides Alzheimer's. Thus, the formation of tau filaments is apparently a more general event leading to neuronal death, whereas A-beta is the specific initiator in Alzheimer's disease.

Clamping the Molecular Scissors

GIVEN THE CRITICAL role of A-beta in the disease process, the proteases that produce this peptide are obvious targets for potential drugs that could inhibit their activity. Protease inhibitors have proved very effective for treating other disorders such as AIDS and hypertension. The first step in the formation of A-beta is initiated by beta-secretase, a protease that clips off the bulk of APP just outside the cellular membrane. In 1999 five different research groups independently discovered this enzyme, which is particularly abundant in brain neurons. Although beta-secretase is tethered to the membrane, it closely resembles a subset of proteases found in the aqueous environments inside and outside cells. Members of this subset—which includes the protease in-

THE UNKINDEST CUT

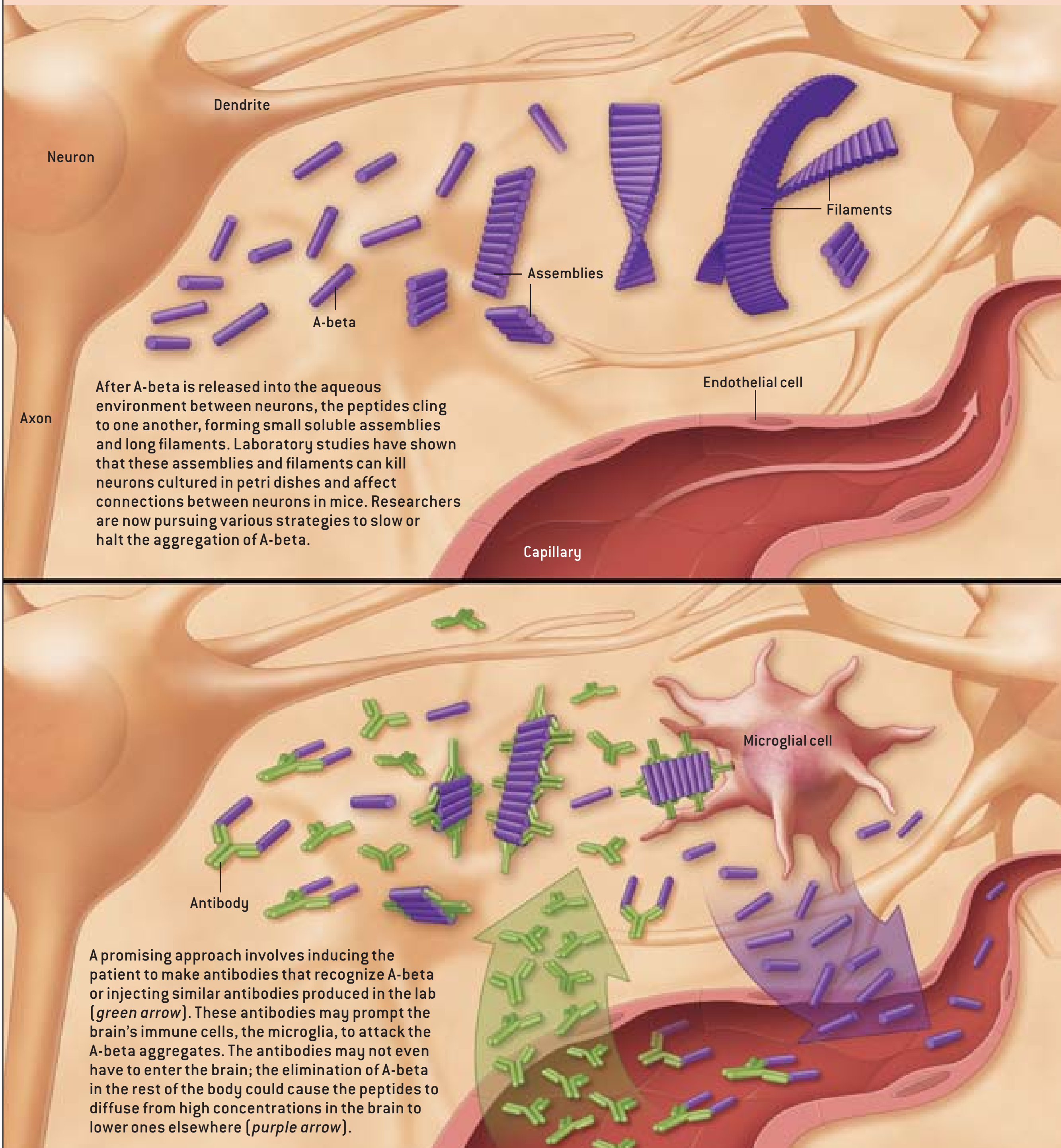
According to the amyloid-cascade hypothesis, Alzheimer's begins with the excessive buildup of amyloid-beta (A-beta), which is carved from the amyloid-beta precursor protein (APP). In the first step (*top*), an enzyme called beta-secretase cuts APP outside the cellular membrane with the help of aspartic acids that make water molecules more reactive. Then the presenilin protein, a component of the gamma-secretase enzyme, cuts the remaining stump inside the membrane, releasing A-beta (*bottom*). Some promising drugs inhibit the activity of gamma-secretase; others cause the enzyme to cut APP at a different location, producing a shorter, less harmful form of A-beta.



TAMI TOLPA

UNCLOGGING THE BRAIN

One strategy for fighting Alzheimer's is to clear toxic aggregates of A-beta from the brain.



After A-beta is released into the aqueous environment between neurons, the peptides cling to one another, forming small soluble assemblies and long filaments. Laboratory studies have shown that these assemblies and filaments can kill neurons cultured in petri dishes and affect connections between neurons in mice. Researchers are now pursuing various strategies to slow or halt the aggregation of A-beta.

A promising approach involves inducing the patient to make antibodies that recognize A-beta or injecting similar antibodies produced in the lab (*green arrow*). These antibodies may prompt the brain's immune cells, the microglia, to attack the A-beta aggregates. The antibodies may not even have to enter the brain; the elimination of A-beta in the rest of the body could cause the peptides to diffuse from high concentrations in the brain to lower ones elsewhere (*purple arrow*).

TAMI TOLPA

volved in replicating HIV, the virus that causes AIDS—use aspartic acid, a type of amino acid, to catalyze the protein-cutting reaction. All proteases use water to cut their respective proteins, and enzymes in the aspartyl protease family employ a pair of aspartic acids to activate a water molecule for this purpose.

Because beta-secretase clearly falls into this family, researchers were able to exploit the vast knowledge about these proteases, leading to a very detailed understanding of this enzyme and how it might be shut down. Indeed, investigators already know the three-dimensional structure of beta-secretase and have used it as a guide for computer-based drug design of potential inhibitors. Genetic studies suggest that blocking the enzyme's activity will not lead to harmful side effects; deletion of the gene encoding beta-secretase in mice eliminated A-beta formation in the rodents' brains without causing any apparent negative consequences. For the moment, however, beta-secretase inhibitors are not yet ready for clinical trials. The main challenge is to develop potent compounds that are small enough to effectively penetrate the brain. Unlike blood vessels in other parts of the human body, capillaries in the brain are lined with endothelial cells that are very tightly packed. Because there are few gaps between the cells, the protease inhibitors must be able to pass through the cell membranes to reach the brain tissues beyond, and most large molecules cannot breach this so-called blood-brain barrier.

The enzyme called gamma-secretase performs the second step in the formation of A-beta, cutting the stump of APP remaining after the cleavage by beta-secretase. Gamma-secretase accomplishes the unusual feat of using water to cut the protein inside the otherwise water-hating environment of the cellular membrane. Two important clues proved essential to our understanding of this protease. First, Bart De Strooper of the Catholic University of Louvain in Belgium found in 1998 that genetically deleting the *presenilin 1* gene in mice greatly reduced the cutting of APP by gamma-secretase, demonstrating that the protein encoded by the gene is essential to the enzyme's function. Second, my laboratory, then at the University of Tennessee at Memphis, discovered that compounds in the same chemical category as the classical inhibitors of aspartyl proteases could block gamma-secretase cleavage of APP in cells. This result suggested that gamma-secretase, like beta-secretase, contains a pair of aspartic acids essential for catalyzing the protein-cutting reaction.

Based on these observations, we hypothesized that the presenilin protein might be an unusual aspartyl protease stitched into the fabric of cell membranes. While I was on sabbatical at Harvard in Selkoe's lab and in collaboration with Weiming Xia, we identified two aspartic acids in presenilin predicted to lie within the membrane and demonstrated that they are both critical to the gamma-secretase cleavage that produces A-beta. Subsequently, we and others showed that the inhibitors of gamma-secretase bind directly to presenilin and that three other membrane-embedded proteins must assemble with presenilin to allow it to catalyze. Today gamma-secretase is recognized as a founding member of a new class of proteases that apparently wield water within cellular membranes to accomplish their biochemical tasks. Better yet, the inhibitors of gamma-secretase are relatively small molecules that can pass through membranes, enabling them to penetrate the blood-brain barrier.

A variety of genetic factors most likely play a role in the onset of the disease.

Two years ago I spoke to my youngest son's fifth-grade class about the work in my lab, explaining about amyloid and how we hoped to block the responsible enzymes to discover new medicines for Alzheimer's. One boy interrupted: "But what if that enzyme is doing something important? You could hurt somebody!" This concern, recognized by a 10-year-old, is very real: the potential of gamma-secretase as a therapeutic target is tempered by the fact that this enzyme plays a critical role in the maturation of undifferentiated precursor cells in various parts of the body, such as the stem cells in bone marrow that develop into red blood cells and lymphocytes. Specifically, gamma-secretase cuts a cell-surface protein called the Notch receptor; the piece of Notch released from the membrane inside the cell then sends a signal to the nucleus that controls the cell's fate.

High doses of gamma-secretase inhibitors cause severe toxic effects in mice as a consequence of disrupting the Notch signal, raising serious concerns about this potential therapy. Nevertheless, a drug candidate developed by pharmaceutical maker Eli Lilly has passed safety tests in volunteers. (This kind of test is called a phase I clinical trial.) The compound is now poised to enter the next level of testing (phase II) in patients with early Alzheimer's. Moreover, researchers have identified molecules that modulate gamma-secretase so that A-beta production is blocked without affecting the cleavage of Notch. These molecules do not interact with gamma-secretase's aspartic acids; instead they bind elsewhere on the enzyme and alter its shape.

Some inhibitors can even specifically curtail the creation of the more aggregation-prone version of A-beta in favor of a shorter peptide that does not clump as easily. One such drug, Flurizan, identified by a research team headed by Edward Koo of the University of California, San Diego, and Todd Golde of the Mayo Clinic in Jacksonville, has shown considerable promise in early-stage Alzheimer's patients and is already entering more advanced (phase III) clinical trials that will include more than 1,000 such subjects across the country.

Clearing the Cobwebs

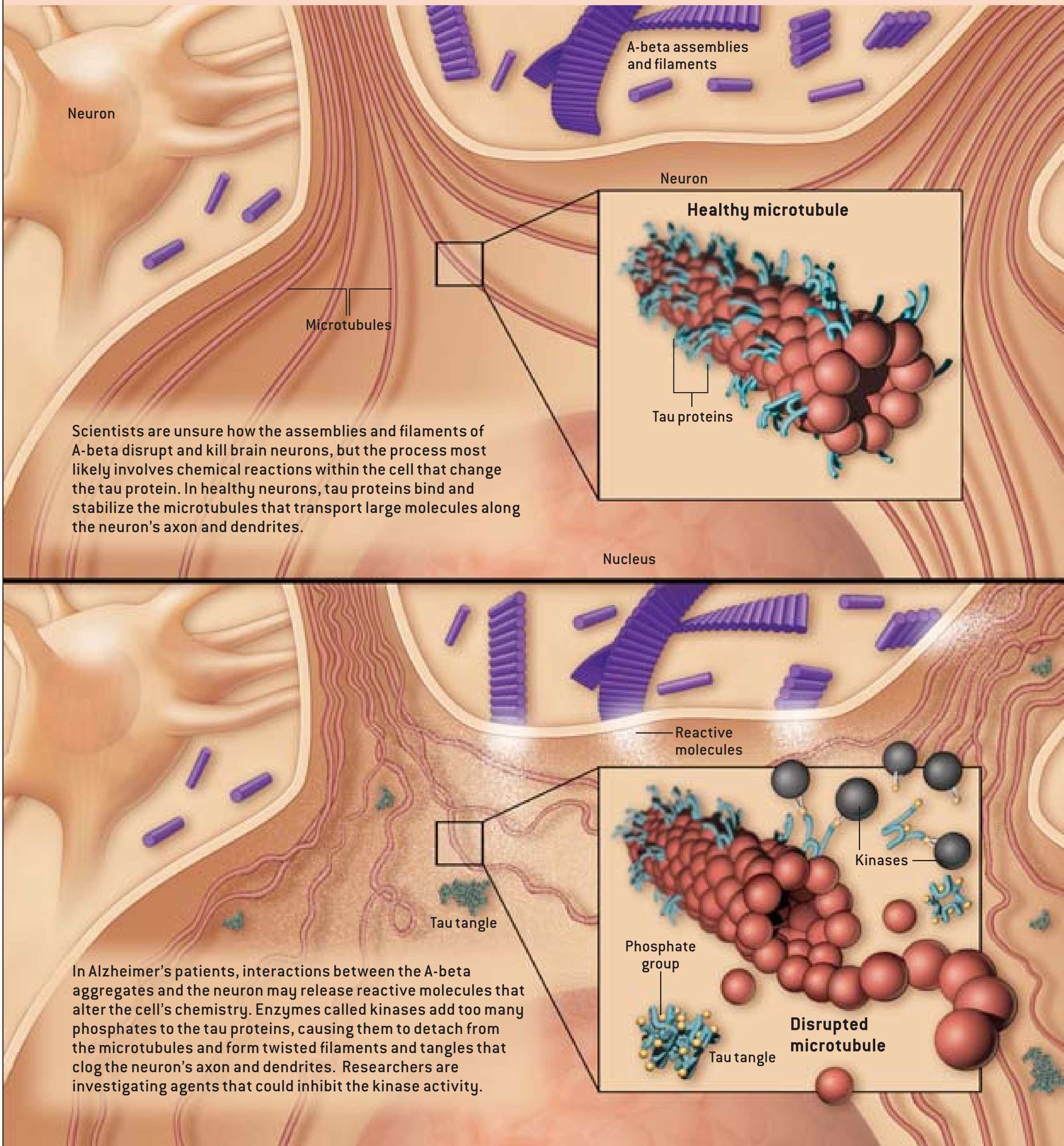
ANOTHER STRATEGY for combating Alzheimer's is to clear the brain of toxic assemblies of A-beta after the peptide is produced. One approach is active immunization, which involves recruiting the patient's own immune system to attack A-beta. In 1999 Dale B. Schenk and his colleagues at Elan Corporation in South San Francisco made a groundbreaking discovery: injecting A-beta into mice genetically engineered to develop amyloid plaques stimulated an immune response

THE AUTHOR

MICHAEL S. WOLFE is associate professor of neurology at Brigham and Women's Hospital and Harvard Medical School, where his work has focused on understanding the molecular basis of Alzheimer's disease and identifying effective therapeutic strategies. He received his Ph.D. in medicinal chemistry from the University of Kansas. This past January he founded the Laboratory for Experimental Alzheimer Drugs at Harvard Medical School, which is dedicated to developing promising molecules into drugs for Alzheimer's disease.

THE FATAL BLOW

Researchers are also studying ways to block the later stages of the amyloid cascade in Alzheimer's patients.



TAMI TOLPA

that prevented the plaques from forming in the brains of young mice and cleared plaques already present in older mice. The mice produced antibodies that recognized A-beta, and these antibodies apparently prompted the brain's immune cells—the microglia—to attack aggregates of the peptide [*see box on page 76*]. The positive results in mice, which included improvements in learning and memory, quickly led to human trials.

Unfortunately, although the injection of A-beta passed initial safety trials, several patients in the phase II tests developed encephalitis—inflammation of the brain—forcing a premature halt to the study in 2002. Follow-up research indicated that the therapy might have caused the inflammation by prompting the T cells of the immune system to make overaggressive attacks on the A-beta deposits.

Nevertheless, the investigation confirmed that many patients produced antibodies against A-beta and that those who did showed subtle signs of improved memory and concentration.

The safety concerns about active immunization led some researchers to try passive immunization, which aims to clear the peptide by injecting antibodies into patients. These antibodies, produced in mouse cells and genetically engineered to prevent rejection in humans, would not be likely to cause encephalitis, because they should not trigger a harmful T cell response in the brain. A passive immunization treatment developed by Elan Corporation has already advanced to phase II clinical trials.

How active or passive immunization can remove A-beta from the brain is somewhat mysterious, because it is unclear how effectively the antibodies can cross the blood-brain barrier. Some evidence suggests that entry into the brain may not be required: sopping up A-beta in the rest of the body may lead to an exodus of the peptide from the brain, because molecules tend to move from high concentrations to lower ones. Although passive immunization now seems to hold the most promise, active immunization is not out of the running. Preliminary studies headed by my Harvard colleague Cynthia Lemere show that immunization with selected parts of A-beta, instead of the entire peptide, can stimulate the antibody-producing B cells of the immune system without triggering the T cells responsible for the encephalitis.

Other researchers are pursuing nonimmunological strategies to stop the aggregation of A-beta. Several companies have identified compounds that interact directly with A-beta to keep the peptide dissolved in the fluid outside brain neurons, preventing the formation of harmful clumps. Neurochem in Quebec is developing Alzhemed, a small molecule that apparently mimics heparin, the natural anticoagulant. In blood, heparin prevents platelets from gathering into clots, but when this polysaccharide binds to A-beta, it makes the peptide more likely to form deposits. Because Alzhemed binds to the same sites on A-beta, it blocks the heparin activity and hence reduces peptide aggregation. The compound has shown little or no toxicity even at very high doses, and the treatment has resulted in some cognitive improvement in patients with mild Alzheimer's. Phase III clinical trials for this drug candidate are already well under way.

Targeting Tau

AMYLOID, HOWEVER, is just one half of the Alzheimer's equation. The other half, the tau filaments that cause neuronal tangles, is also considered a promising target for preventing the degeneration of brain neurons. In particular, researchers are focused on designing inhibitors that could block the kinases that place an excessive amount of phosphates onto tau, which is an essential step in filament formation. These efforts have not yet resulted in candidate drugs for clinical trials, but the hope is that such agents might ultimately work synergistically with those targeting A-beta.

Researchers are feeling hope—a word not usually associated with Alzheimer's.

Investigators are also exploring whether the cholesterol-lowering drugs called statins, which are widely used to cut the risk of heart disease, could become a treatment for Alzheimer's as well. Epidemiological studies suggest that people taking statins have a lower risk of acquiring Alzheimer's. The reason for this correlation is not entirely clear; by lowering cholesterol levels, these drugs may reduce the production of APP, or perhaps they directly affect the creation of A-beta by inhibiting the activity of the responsible secretases. Phase III trials are trying to establish whether statins such as Pfizer's Lipitor can truly prevent Alzheimer's.

Another exciting recent development involves cell therapy. Mark Tuszynski and his colleagues at U.C.S.D. took skin biopsies from patients with mild Alzheimer's and inserted the gene encoding nerve growth factor (NGF) into these cells. The genetically modified cells were then surgically placed into the forebrains of these patients. The idea was that the implanted cells would produce and secrete NGF, preventing the loss of acetylcholine-producing neurons and improving memory. The cell-based therapy was a clever strategy for delivering NGF, a large protein that could not otherwise penetrate the brain. Although this study included only a handful of subjects and lacked important controls, follow-up research showed a slowing of cognitive decline in the patients. The results were good enough to warrant further clinical trials.

Although some of these potential therapies may not fulfill their promise, scientists hope to find at least one agent that can effectively slow or stop the gradual loss of neurons in the brain. Such a breakthrough could save millions of people from the inexorable decline of Alzheimer's disease and set the stage for regenerative medicine to restore lost mental functions.

Targeting A-beta may block the onset of Alzheimer's or retard it early in its course, but whether this strategy will treat or cure those with more advanced stages of the disease remains unclear. Still, researchers have good reason for cautious optimism. The recent spate of discoveries has convinced many of us that our quest for ways to prevent and treat Alzheimer's will not be in vain. SA

MORE TO EXPLORE

Decoding Darkness. Rudolph E. Tanzi and Ann B. Parson. Perseus Books Group, 2000.

Hard to Forget: An Alzheimer's Story. Charles Pierce. Random House, 2000.

Therapeutic Strategies for Alzheimer's Disease. Michael S. Wolfe in *Nature Reviews Drug Discovery*, Vol. 1, pages 859–866; November 2002.

More information can be found online at **www.alz.org** and **www.alzforum.org**

When

Slide Rules Ruled

Before electronic calculators, the mechanical slide rule dominated scientific and engineering computation

By Cliff Stoll

Two generations ago a standard uniform identified engineers: white shirt, narrow tie, pocket protector and slide rule. The shirt and tie evolved into a T-shirt sporting some software advertisement. The pocket protector has been replaced by a cell phone holster. And the slide rule has become an electronic calculator.

Take another look at that slide rule. Pull it out of the drawer you stashed it in 30 years ago or make one of your own [*see box on next page*]. You'll see why it was once so valuable.

Before the 1970s the slide rule, or slipstick, was as common as the typewriter or the mimeograph machine. A few seconds of fiddling let scientists and engineers multiply, divide and find square and cube roots. With a bit more effort, techies could also compute ratios, inverses, sines, cosines and tangents.

Inscribed with a dozen or more function scales, the slide rule symbolized the mysteries of arcane science. Truth is, though, two scales did most of the work, as many technical jobs boiled down to multiplication and division. A pianist might play most of the ivories on the keyboard, but rarely did any engineer use all the scales on his (almost never her) slide rule.

Some engineers, perhaps bucking for promotion, wielded slide rules made of exotic mahogany and boxwood; others sported rules fashioned from ivory, aluminum or fiberglass. Cheapskates—including this author—carried plastic ones. From the finest to the humblest, however, all slide rules were based on logarithms [*see box on page 85*].

Birth of the Slide Rule

JOHN NAPIER, a Scottish mathematician, physicist and astronomer, invented logarithms in 1614. His Canon of Logarithms begins: "Seeing there is nothing that is so troublesome to mathematical practice, nor doth more molest and hinder calculators, than the multiplications, divisions, square and cubical

BRAD DeCECCO

DO-IT-YOURSELF SLIDE RULE

You can build a working slide rule from paper and cellophane tape. Photocopying these plans onto thicker paper yields a reasonably robust calculating instrument. These construction plans are also available at www.sciam.com/ontheweb

a Cut here

c Cut here

CHRIS HAMANN AND NANCY SHAW

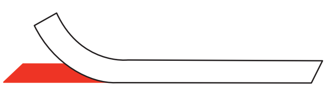
ASSEMBLY INSTRUCTIONS

1 Cut out the entire white panel (*a*). Cut along line between parts A and B (*b*), then remove excess (*c*).

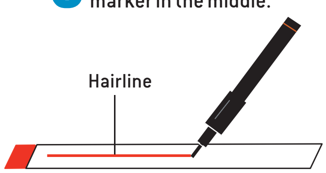
2 Fold part A along the dotted lines.

3 Slip part B into the folded part A.

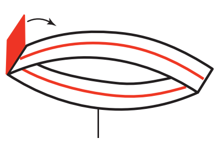
4 To make the cursor (the sliding window that is inscribed with a hairline), use the guides to the left to measure two pieces of transparent tape. Make one section the length of the black line and the other the length of the red line. Place the adhesive sides together.



5 Draw a line with a fine marker in the middle.

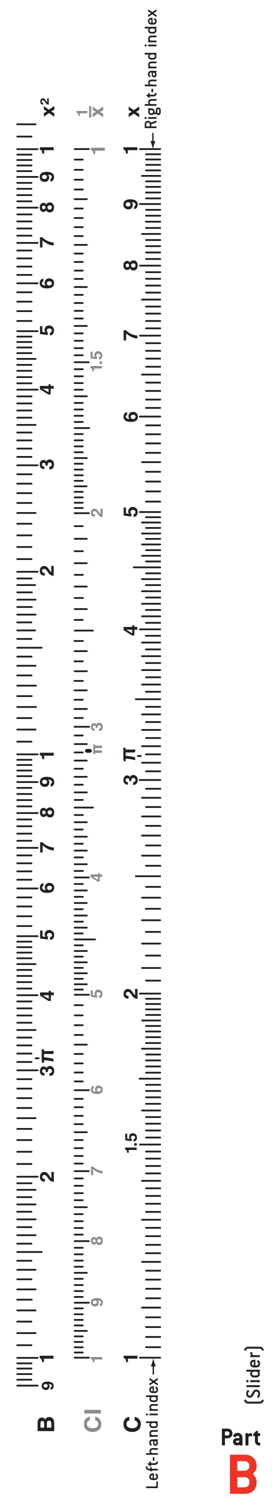


6 Wrap the folded tape around the slide rule for sizing. Use the adhesive end to complete the cursor. Slide cursor onto the rule.



Part **A**

b Cut here



Part **B**

extractions of great numbers, which besides the tedious expense of time are for the most part subject to many slippery errors, I began therefore to consider in my mind by what certain and ready art I might remove those hindrances."

Yes, logarithms—that horror of high school algebra—were actually created to make our lives easier. In a few generations, people will be equally shocked to learn that computers were also invented to make our lives easier.

So how did Napier's logarithms work? Listen to the inventor: "Cast away from the work itself even the very numbers themselves that are to be multiplied, divided, and resolved into roots, and putteth other numbers in their place which perform much as they can do, only by addition and subtraction, division by two or division by three."

Which is to say that by using logs, multiplication simplifies into sums, division becomes subtraction, finding a square root turns into dividing by two, and figuring a cube root becomes dividing by three. For example, to multiply 3.8 by 6.61, you look up the logarithms of those numbers in a table. There you will find 0.58 and 0.82. Add these together to get 1.4. Now go back to the table and find the number whose log is 1.4 to get a close approximation of the answer: 25.12. Begone ye slippery errors!

Napier's invention revolutionized mathematics—mathematicians adopted it immediately to speed their calculations. German astronomer Johannes Kepler used these modern logarithms to calculate the orbit of Mars at the start of the 17th century. Without their assistance, he might never have discovered his three laws of celestial mechanics. Henry Briggs, England's most eminent mathematician of the time, traveled to Scotland just to meet Napier. He introduced himself with: "My lord, I have undertaken this long journey purposely to see your person, and to know by what engine of wit or ingenuity you came first to think of this most excellent help unto

SLIDE RULE was invented by English minister William Oughtred in 1622. Robert Bissaker constructed the first slide rule whose slide fit into a slot in a fixed stock in 1654 (*bottom*). Henry Sutton's slide rule (*top*) was an early circular rule (circa 1663).

SCIENCE MUSEUM/SCIENCE AND SOCIETY PICTURE LIBRARY

HOW TO USE A SLIDE RULE

First, get your hands on a slide rule. The top stationary scale usually has the A scale; the B and C scales reside on the central slider. The D scale sits on the bottom stationary scale. The left-hand index is on the slider—it is the farthest left digit 1 on the C scale. At the extreme right of the slider, you will find another number 1 on the C scale—that is the right-hand index. Finally, the mobile cursor contains the hairline.

To multiply two numbers, move the slider until the left-hand index points to the first number on the D scale. Now slide the cursor hairline over so it points to the second number on the C scale. The answer will appear under the hairline on the D scale. So to multiply 2 times 4, adjust the C scale until the left-hand index points to 2 on the D scale. Move the hairline to rest over the 4 on the C scale. You'll find the answer, 8, right under the hairline on the D scale .

If your calculation extends off the end of the slide rule, use the right-hand index. So to multiply 7 times 6, set the right-hand index over 7 on the D scale and the hairline over 6 on the C scale. Read 4.2 on the D scale and then remember that the slippery decimal point must be shifted one place to the right to give the correct answer, 42.

To divide, set the hairline over the dividend on the D scale. Then shift the slider until the divisor lies under the hairline (and right next to the dividend). The quotient will be under the index. For example, let's divide 47 by 33. Move the cursor so that the hairline points to 4.7 on the D scale. Move the slider until 3.3 on the C scale rests under the hairline. Now the left-hand index sits adjacent to the answer, 1.42.

Want to find the square of a number? You will not need to move the slider. Just place the hairline over a number on the D scale. Look up at the A scale, where the hairline points to the square. So, right above 7 on the D scale, you will find 4.9 on the A scale. Slip the decimal point to the right to get the answer, 49.

To determine square roots, there is no need to move the slider. But notice that the A scale is divided into two parts: the left half runs from 1 to 10, and the right half goes from 10 to 100. To find the square root of any number between 1 and 10, place the hairline over the number on the left side of the A scale and read out the square root from the D scale. Use the right half of the A scale to take the square root of numbers between 10 and 100. When you write numbers in scientific notation, those with even exponents (such as 1.23×10^4) will be found on the left side of the A scale; those with odd exponents (such as 1.23×10^3) are on the right.

You can discover quite a few shortcuts—for instance, the cursor works as a short-term memory in chaining calculations. Or try using the CI scale to prevent calculations from running off the end of the slipstick.

You will find additional scales on your homemade slide rule. The K scale is used for cubes and cube roots; the S and T scales give sines and tangents. The L scale gives the logarithm of a number on the D scale.

Try these on your homemade slipstick. With a bit of practice, you may be surprised at its ease of use and its utility. *—C.S.*

OTIS KING, a London engineer, wrapped several feet of scales around a pocket-size cylinder in 1921 to achieve a portable slide rule with impressive resolution.

astronomy … I wonder why nobody else found it out before, when, now being known, it appears so easy." Briggs recognized genius; Napier went on to invent the decimal point and calculating rods (known as Napier's bones) and to lay the groundwork for Isaac Newton's calculus.

Napier had simplified computational tasks, but ready access to books of log tables was crucial to the procedure. So in 1620 mathematician Edmund Gunter of London marked a ruler with logarithms, which let his calculating colleagues find logs without a trip to the library. Gunter drew a number line in which the positions of numbers were proportional to their logs. In his scale, succeeding numbers are spread out on the left and squashed together at the right end. Two numbers could now be multiplied by measuring the distance from the beginning of the scale to one factor with a pair of dividers, then moving them to start at the other factor and reading the number at the combined distance.

Around 1622 William Oughtred, an Anglican minister in England, placed two sliding wooden logarithmic scales next to each other and created the first slide rule. A few years later he made a circular slide rule. Not that Oughtred crowed about his achievements. As one who loved pure mathematics, he probably felt that his invention was not worth much. After all, mathematicians created equations; they did not apply them. (This is still true today: making money often means finding an application for what someone else has developed.)

"Multiplication just required lining up two numbers and reading a scale."

For whatever reason, Oughtred failed to publish news of his invention, but one of his students, Richard Delamain, claimed in a 1630 pamphlet to have come up with the circular slide rule. More engineer than mathematician, Delamain was delighted with its portability, writing that it was "fit for use on Horse backe as on Foote."

Denied credit for his invention, Oughtred was outraged. He rallied his friends, who accused Delamain of "shamelessnesse" and being the "pickpurse of another man's wit." The argument would continue until Delamain's death, serving neither man much good. Oughtred later wrote, "This scandall hath wrought me much prejudice and disadvantage."

Look Ma, No Logs!

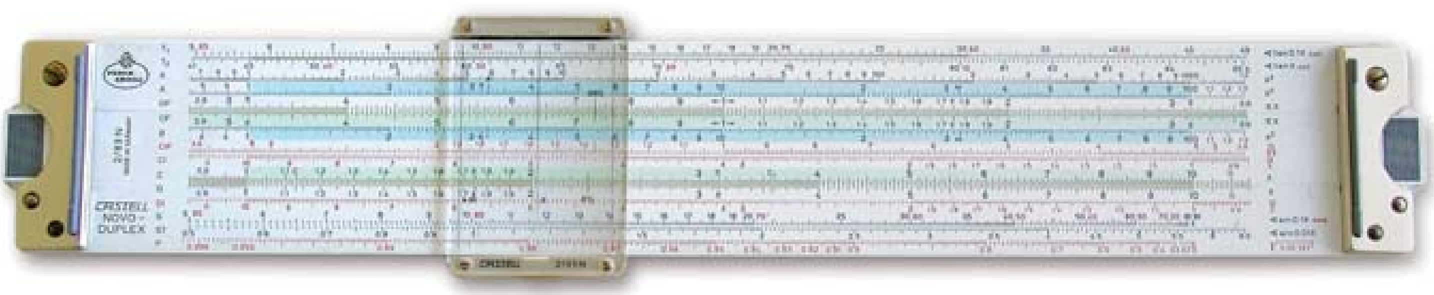
WITH OUGHTRED'S INVENTION in hand, no one needed a book of logarithms or even had to know what a log was. Multiplication just required lining up two numbers and reading a scale. It was quick and eminently portable. The slide rule would automatically "cast away numbers."

A wonderful idea, yet slide rules took two centuries to catch on. As late as 1850, British mathematician Augustus De Morgan lamented the resistance: "For a few shillings, most persons might put into their pockets some hundred times as much power of calculation as they have in their heads."

The slide rule was improved and extended during the first half of the 1800s. In a lecture before the Royal Society in 1814, Peter Roget (the creator of the thesaurus) described his invention, the log-log slide rule. With this tool, he could easily calculate fractional powers and roots, such as 30.6 to the 2.7th power. The utility of the log-log rule, however, was not appreciated until 1900, when chemists, electrical engineers and physicists began to face increasingly complex mathematics.

It took a 19-year-old French artillery lieutenant—Amédée Mannheim—to popularize the slide rule. In 1850 he chose the four most useful scales and added a movable cursor (a sliding pointer to line up numbers on the scales). Within a few years the French army adopted his device. When the Prussian infantry is attacking, who has time to aim a cannon using long division?

In time, European engineers, surveyors, chemists and astronomers carried Mannheim's improved slide rule. After World War I, American scientists began to adopt them. All



FABER-CASTELL 2/83N slide rule is considered by some to be the finest and most beautiful slide rule ever made.

WWW.VINTAGECALCULATORS.COM (*top*); FABER-CASTELL AG (*bottom*) but the cheapest slide rules displayed squares and roots; most also computed cubes, cube roots, inverses, sines and tangents. Sophisticated ones might include hyperbolic functions to let electrical engineers calculate vectors or help structural engineers find the shape of catenary curves, which are important elements in suspension bridges, for instance. To pry more precision out of their slipsticks, manufacturers added magnifiers to better judge positions on scales, inscribed ever finer tick marks and built longer slide rules. They mapped Napier's logarithms onto circles, spirals, disks and cylinders.

In 1921 London engineer Otis King spiraled a five-foot-long logarithmic scale around an inch-diameter cylinder that could fit in a pocket. Engineers marveled at its four digits of precision. For even more exactitude, a scientist might invest in Fuller's Rule, the granddaddy of high-precision slide rules. A 41-foot logarithmic helix snakes around the exterior of a foot-long cylinder; by using a special indicator, it gives the precision of an 83-foot scale, letting users do arithmetic with five digits of resolution. The elaborate contraption might be mistaken for an engraved rolling pin.

With few alternatives, techies adapted to slipsticks. In turn, slide-rule makers inscribed additional marks to speed calculations. Typically you could find pi, pi/4, the constant *e* (the base of "natural" logarithms) on the scales, and occasionally cursor marks to convert inches to centimeters or horsepower to watts. Specialized slide rules appeared with molecular weights for chemists, hydraulic relations for shipbuilders and radioactive decay constants for atom bomb designers.

By 1945 the log-log duplex slide rule had become ubiquitous among engineers. With nearly a dozen scales on each side, it would let users raise a number to an arbitrary power as well as handle sines, cosines and hyperbolic trigonometry functions with ease. During World War II, American bombardiers and navigators who required quick calculations often used specialized slide rules. The U.S. Navy designed a generic slide rule "chassis," with an aluminum body and plastic cursor, into which celluloid cards could be inserted for specialized calculations of aircraft range, fuel use and altitude.

By the 1960s you could not graduate from engineering school without a week's instruction in the use of a slipstick. Leather-cased slide rules hung from belts in every electrical engineering department; the more fashionable sported slide-rule tie clips. At seminars, you could tell who was checking the speaker's numbers. High-tech firms gave away slide rules imprinted with company trademarks to customers and prospective employees.

High Noon for the Slipstick

CONSIDER THE ENGINEERING achievements that owe their existence to rubbing two sticks together: the Empire State Building; the Hoover Dam; the curves of the Golden Gate Bridge; hydromatic automobile transmissions; transistor radios; the Boeing 707 airliner. Wernher Von Braun, the designer of the German V-2 rocket and the American Saturn 5 booster, relied on a rather plain slide rule manufactured by the German com-

Logarithm Log

A bit fuzzy about logarithms? Here is a short summary: If $a^x = m$, then x, the exponent, can be said to be the logarithm of m to the base a. Although a can be any number, let us focus on common logarithms, or the logs of numbers where $a = 10$. The common log of 1,000 is 3 because raising 10 to the third power, 10^3, is 1,000. Conversely, the antilog of 3 is 1,000; it is the result of raising 10 to the third power.

Exponents do not have to be integers; they can be fractions. For example, $10^{0.25}$ equals about 1.778, and $10^{3.7}$ equals about 5,012. So the log of 1.778 is 0.25, and the log of 5,012 is 3.7.

When you express everything in terms of 10 to a power, you can multiply numbers by just adding the exponents. So $10^{0.25}$ times $10^{3.7}$ is $10^{3.95}$ ($10^{0.25+3.7}$). What does $10^{3.95}$ equal? Look up the antilog of 3.95 in a log table, and you'll find 8,912, which is indeed about equal to the product of 1.778 and 5,012. (Common logs can be found by entering "log (*x*)" into Google, for example, or by consulting log tables in libraries.)

Just as multiplication simplifies to addition, division becomes subtraction. Here is how to divide 759 by 12.3 using logs. Find the logs of 759 and 12.3: 2.88 and 1.09. Subtract 1.09 from 2.88 to get 1.79. Now look up the antilog of 1.79 to get the answer, 61.7.

Need to calculate the square root of 567.8? Just determine its log: 2.754. Now divide that by 2 to get 1.377. Find the antilog of 1.377 for the answer: 23.82.

Naturally, complications arise. Log tables list only the mantissa—the decimal part of the log. To get the true logarithm, you must add an integer (called the characteristic) to the mantissa. The characteristic is the number of decimal places to shift the decimal point of the associated number. So to find the log of 8,912, you would consult a log table and see that the log of 8.912 is 0.95. You would then determine the characteristic of 8,912, which is 3 (because you must shift the decimal point three places to the left to get from 8,912 to 8.912). Adding the characteristic to the mantissa yields the true common log: 3.95.

Because common logs are irrational (a number expressed as an infinite decimal with no periodic repeats) and log tables have limited precision, calculations using logs can provide only close approximations, not exact answers.

Logarithms show up throughout science: Chemists measure acidity using pH, the negative log of a liquid's hydrogen ion concentration. Sound intensity in decibels is 10 times the log of the intensity divided by a reference intensity. Earthquakes are often measured on the Richter scale, which is built on logarithms, as are the apparent brightness magnitudes of stars and planets.

Finally, logs pop up in everyday usage. Many graphs that depict large numbers employ logarithmic scales that map numbers by orders of magnitude (10, 100, 1,000 and so forth)—the same scales that appear on slide rules. —*C.S.*

"COMPUTERS" used to refer to humans who spent their time calculating numbers. This 1953 advertisement foreshadowed the changes that would occur when electronic calculators and digital computers began to come into more common use.

pany Nestler. Indeed, the Pickett company made slide rules that went on several Apollo missions, as backup calculators for moon-bound astronauts. Soviet engineer Sergei Korolev used a Nestler rule when he designed the Sputnik and Vostok spacecraft. It was also the favorite of Albert Einstein.

THE AUTHOR

CLIFF STOLL is best known for breaking up a ring of hackers during the early days of the Internet, as described in his book *The Cuckoo's Egg.* His other books are *High Tech Heretic: Why Computers Don't Belong in the Classroom* and *Silicon Snake Oil.* Stoll received a doctorate in planetary science from the University of Arizona and now makes Klein bottles and teaches physics to eighth graders. In his previous life, he worked at the Space Telescope Science Institute, the Purple Mountain Observatory in China, the Kitt Peak National Observatory, the Keck Observatory and the Harvard-Smithsonian Center for Astrophysics. Stoll and his wife live in Oakland, Calif.; the log of the number of their children is about 0.301, and they have almost $10^{0.4772}$ cats. The author would like to thank Regina McLaughlin, Bob Otnes and Walter Shawlee for their help with this article.

Yet slide rules had an Achilles' heel; standard models could typically handle only three digits of precision. Fine when you are figuring how much concrete to pour down a hole but not good enough for navigating the path of a translunar space probe. Worse yet: you have to keep track of the decimal place. A hairline pointing to 3.46 might also represent 34.6, 3,460 or 0.00346.

That slippery decimal place reminded every competent engineer to double-check the slide rule's results. First you would estimate an approximate answer and then compare it with the number under the cursor. One effect was that users felt close to the numbers, aware of rounding-off errors and systematic inaccuracies, unlike users of today's computer-design programs. Chat with an engineer from the 1950s, and you will most likely hear a lament for the days when calculation went hand-in-hand with deeper comprehension. Instead

"The slide rule helped to design the very machines that would render it obsolete."

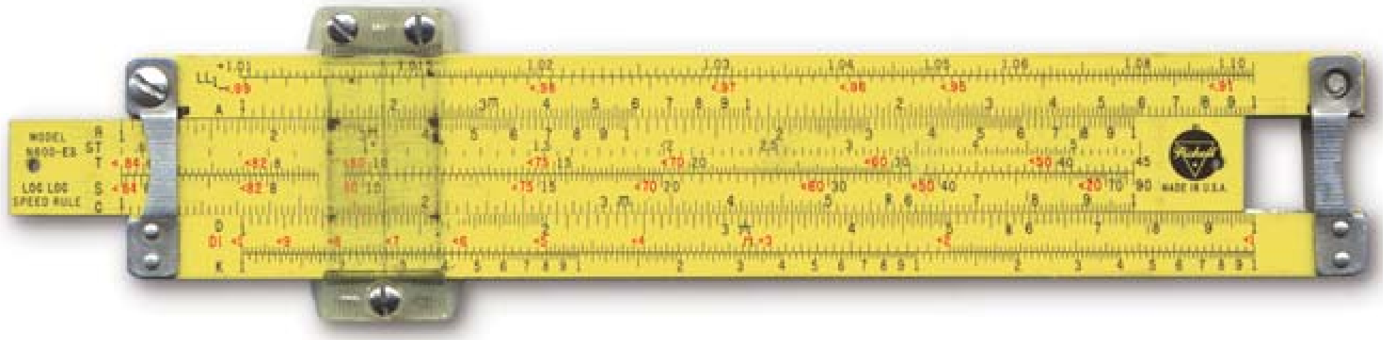
of plugging numbers into a computer program, an engineer would understand the fine points of loads and stresses, voltages and currents, angles and distances. Numeric answers, crafted by hand, meant problem solving through knowledge and analysis rather than sheer number crunching.

Still, with computation moving literally at a hand's pace and the lack of precision a given, mathematicians worked to simplify complex problems. Because linear equations were friendlier to slide rules than more complex functions were, scientists struggled to linearize mathematical relations, often sweeping high-order or less significant terms under the computational carpet. So a car designer might calculate gas consumption by looking mainly at an engine's power, while ignoring how air friction varies with speed. Engineers developed shortcuts and rules of thumb. At their best, these measures led to time savings, insight and understanding. On the downside, these approximations could hide mistakes and lead to gross errors.

Because engineers relied on imperfect calculations, they naturally designed conservatively. They made walls thicker than need be, airplane wings heavier, bridges stronger. Such overengineering might benefit reliability and durability, but it cost dearly in overconstruction, poorer performance and sometimes clumsy operation.

The difficulty of learning to use slide rules discouraged their use among the hoi polloi. Yes, the occasional grocery store manager figured discounts on a slipstick, and this author once caught his high school English teacher calculating stats for trifecta horse-race winners on a slide rule during study

IBM CORPORATION



PICKETT N600-ES slide rule traveled with the NASA Apollo spacecraft to the moon as a backup calculator.

hall. But slide rules never made it into daily life because you could not do simple addition and subtraction with them, not to mention the difficulty of keeping track of the decimal point. Slide rules remained tools for techies.

The Fall of the Slide Rule

FOR THE FIRST HALF of the 20th century, gear-driven mechanical calculators were the main computational competitors to slide rules. But by the early 1960s, electronics began to invade the field. In 1963 Robert Ragen of San Leandro, Calif., developed the Friden 130—one of the first transistorized electronic calculators. With four functions, this desktop machine amazed engineers by silently calculating to 12 digits of precision. Ragen recalls designing this electronic marvel entirely with analog tools: "From the transistor bias currents to the memory delay lines, I fleshed out all the circuitry on my Keuffel & Esser slide rule." The slide rule helped to design the very machines that would ultimately render it obsolete.

By the late 1960s you could buy a portable, four-function calculator for a few hundred dollars. Then, in 1972, Hewlett-Packard built the first pocket scientific calculator, the HP-35. It did everything that a slide rule could do—and more. Its instruction manual read, "Our object in developing the HP-35 was to give you a high-precision portable electronic slide rule. We thought you'd like to have something only fictional heroes like James Bond, Walter Mitty or Dick Tracy are supposed to own."

HP-35 POCKET CALCULATOR sounded the death knell for the slide rule. Introduced by Hewlett-Packard in 1972, the $395 handheld device combined large-scale integration circuits (six chips in all) with a light-emitting diode display. It was powered by batteries or an AC adapter.

Dozens of other manufacturers soon joined in: Texas Instruments called their calculator product the "Slide Rule Calculator." In an attempt to straddle both technologies, Faber-Castell brought out a slide rule with an electronic calculator on its back.

The electronic calculator ended the slipstick's reign. Keuffel & Esser shut down its engraving machines in 1975; all the other well-known makers—Post, Aristo, Faber-Castell and Pickett—soon followed suit. After an extended production run of some 40 million, the era of the slide rule came to a close. Tossed into desk drawers, slide rules have pretty much disappeared, along with books of five-place logarithms and pocket protectors.

Today an eight-foot-long Keuffel & Esser slide rule hangs on my wall. Once used to teach the mysteries of analog calculation to budding physics students, it harkens back to a day when every scientist was expected to be slide-rule literate. Now a surfboard-size wall hanging, it serves as an icon of computational obsolescence. Late at night, when the house is still, it exchanges whispers with my Pentium. "Watch out," it cautions the microprocessor. "You never know when you're paving the way for your own successor." SA

MORE TO EXPLORE

A History of the Logarithmic Slide Rule and Allied Instruments. Florian Cajori. First published in 1909. Reprinted by Astragal Press, 1994.

Slide Rules: Their History, Models and Makers. Peter M. Hopp. Astragal Press, 1999.

Basic slide-rule instructions: **www.hpmuseum.org/srinst.htm**

Interactive slide-rule simulation: **www.taswegian.com/SRTP/JavaSlide/JavaSlide.html**

Peter Fox offers an explanation of logarithms and slide rules at **www.eminent.demon.co.uk/sliderul.htm**

The Oughtred Society, dedicated to the preservation and history of slide rules and other calculating instruments: **www.oughtred.org**

Slide-rule discussion forum: **groups.yahoo.com/group/sliderule**

Walter Shawlee's Sphere Research's Slide Rule Universe sells slide rules and related paraphernalia: **www.sphere.bc.ca/test/sruniverse.html**

ERIC MARCOTTE (*top*); RICK FURR (*bottom*)

WORKINGKNOWLEDGE

ROBOT MOWERS

Cutting Work

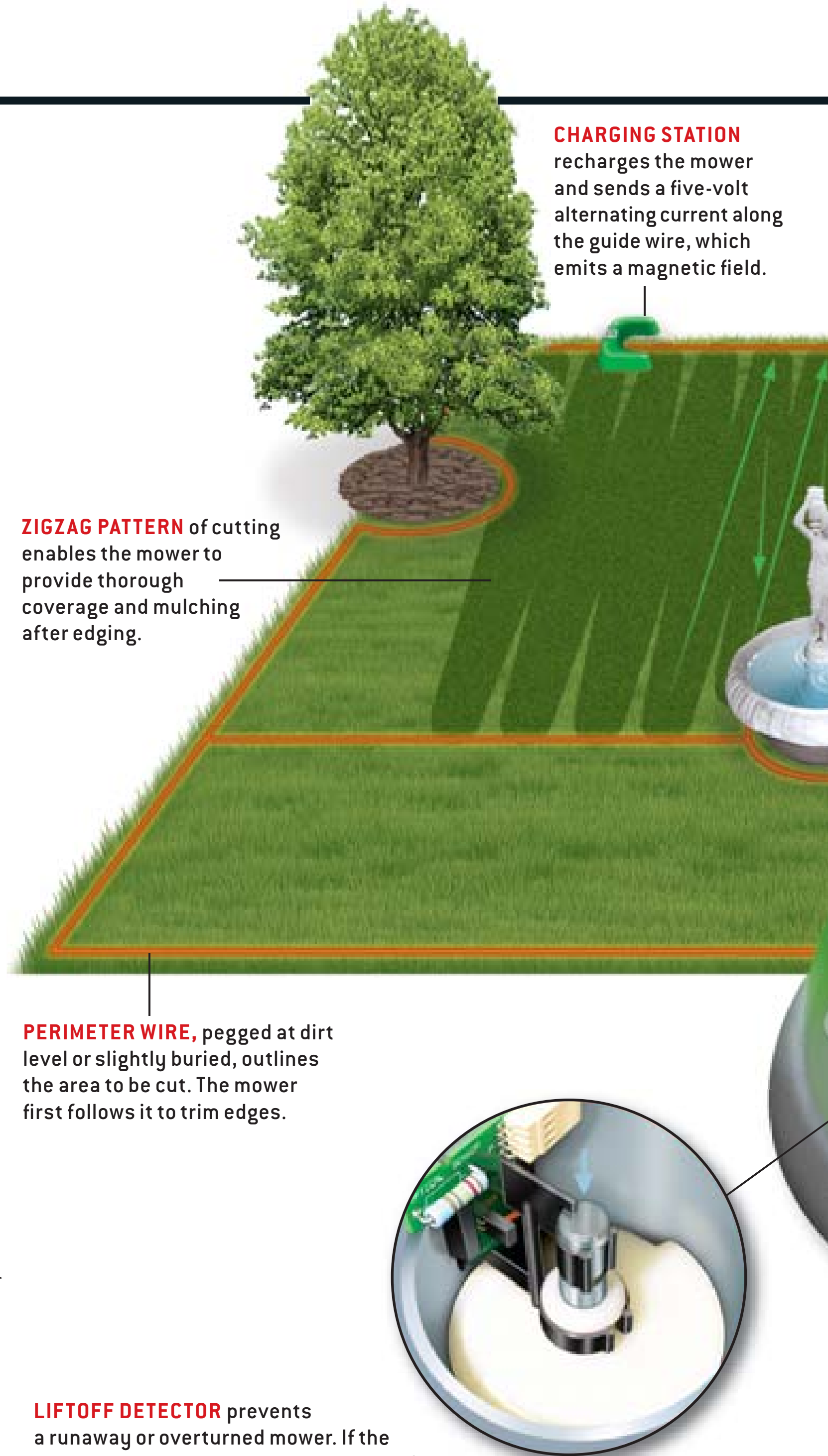
Autonomous lawnmowers have been around for several years, but after improving through hard knocks (some of them into trees), the newest generation is gaining popularity.

Of course, a human must set the stage, by outlining a yard with a dirt-level guide wire and by programming the robot with dates and times for cutting. After that, though, the electric mowers will start themselves, cut and return to base for recharging as needed, all on their own. Contrary to myth, they do not store maps of the territory or consult the Global Positioning System; they simply track where they are in relation to the guide wire [*see illustrations*].

Batteries are a key factor. Most units use lead-acid technology because it can provide the high power output needed for thick grass and is inexpensive. But the best mowers still cover only about 6,000 square feet per charge; half an acre will take four sessions. The machines also need two to three hours to complete those 6,000 square feet, crisscrossing and doubling back over their own paths to ensure they do not miss spots and for thorough mulching. That means the mower is on the lawn a lot, "but you're not out there pushing it, so why do you care?" notes Roy Tamir, technical expert at Systems Trading Corporation in Dallas. The company manages the RoboMower line, the biggest U.S. seller, made by Friendly Robotics in Israel.

Some prospective customers with large lawns balk at a bot mowing almost every other day to keep up. But the routine requires a change in mind-set; instead of a person shoving a mower through high grass and raking every weekend, the bots venture out more frequently and therefore only have to snip the tips of blades each time, which, turf experts add, leads to a healthier lawn. Despite all the activity, manufacturers say recharging costs only a few dollars a month.

Homeowners may find the frequent forays a nuisance (although the bots can cut at night). Owners may have to push a mower into tight corners or use the robot's manual controller. And they do still have to pick up sticks and debris that can ruin any mower's blades. Then there's the price: $1,500 or more. But busy people may be willing to pay for extra hours of free time. And the dog may make a new friend. —*Mark Fischetti*



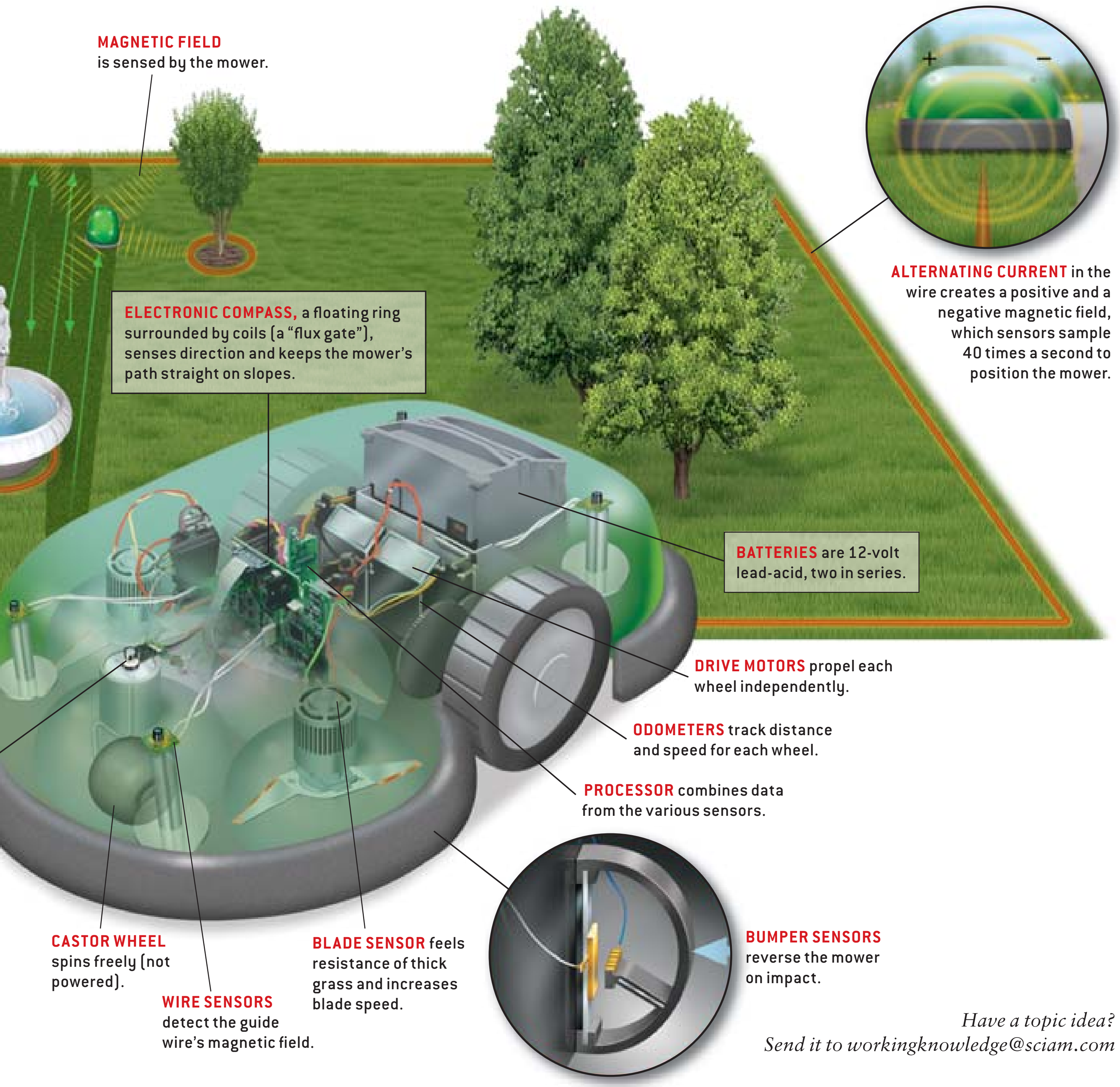
KENT SNODGRASS *Precision Graphics*; SOURCE: SYSTEMS TRADING CORPORATION

DID YOU KNOW...

▯ NEW ANGLE: Robot mowers follow a counterintuitive pattern of zigzags to cover a lawn [*see illustration on opposite page*]. Manufacturers made prototypes that cut rows, back and forth, as most people do. But the inability of the compass to determine a perfectly parallel path, and slippage on slopes or wet grass, left islands undone. The course follows a precessing triangle scheme that eventually covers all spots several times over.

▯ VACUUMS, TOO: Small robot vacuums that clean floors or short-pile carpet can be programmed ahead of time, return and dock for recharging on their own, and follow byzantine coverage patterns. There is no guide wire, though; to navigate, they reflect infrared or ultrasound beams off walls, objects and floors (the last to sense a stairway). Most look like a four-inch-thick Frisbee on wheels and underneath have a beater brush, spinning wand (for wall edges) and a suction slit. Models sell for $200 to $1,700. Some makers offer similarly styled units that wash floors.

▯ SITTIN' BY THE POOL: Automatic pool cleaners resemble a large, hard-shell bowling ball bag that crawls along the pool floor and walls, sweeping up sand, pebbles, leaves and scum. Powered by an electric cord, an impeller draws water through a filter while rotating scrub brushes scour surfaces. Other models have water jets that expel debris through a hose to the pool's filter system.



Have a topic idea?
Send it to workingknowledge@sciam.com

What Makes a Revolution?

INGREDIENTS FOR ENVIRONMENTAL AWAKENING **BY MARGUERITE HOLLOWAY**

FIELD NOTES FROM A CATASTROPHE: MAN, NATURE, AND CLIMATE CHANGE
by Elizabeth Kolbert
Bloomsbury Publishing, 2006 ($22.95)

In the 1990s the inhabitants of Shishmaref, an Inupiat village on the Alaskan island of Sarichef, noticed that sea ice was forming later and melting earlier. The change meant that they could not safely hunt seal as they had traditionally and that a protective skirt of ice no longer buffered the small town from destructive storm waves. Shishmaref was being undone by a warming world. To survive, the villagers recently decided to move to the mainland. Soon Shishmaref on Sarichef will be gone.

Pithy and powerful, the opening of Elizabeth Kolbert's book about global warming, *Field Notes from a Catastrophe,* echoes that of another book that also originated as a series of articles in the *New Yorker* magazine. Rachel Carson's *Silent Spring* starts in much the same way, with a fable about a town that lived in harmony with its surroundings and that fell silent. The question is, Can *Field Notes* galvanize a national movement to curb global warming in the same way *Silent Spring* sparked one to curb the use of pesticides?

Silent Spring's success as a transformative force came about because of Carson's scientific authority, the way she shaped her argument, the immediate nature of the threat, and the many movements afoot in American society in 1962. Carson was a scientist, and she had credibility when she described how synthetic chemicals, DDT in particular, affect living things. That authority convinced her readers and withstood critics and attacks by the chemical industry. Carson's writing was direct and her rhetoric carefully chosen, as her biographer Linda Lear and other scholars have noted. Carson appreciated Americans' fears about nuclear fallout: something invisible was contaminating their food. She made clear DDT's similar qualities: "No witchcraft, no enemy action had silenced the rebirth of new life in this stricken world. The people had done it themselves." Concerned that her audience might be solely women—mothers worried about the health of their children—she also spoke directly to hunters, outdoorsmen. She deliberately sought, and got, the widest possible reach.

Although Carson was describing something people could not see in their food, she was writing about something they could viscerally understand: they saw pesticides being sprayed. They could connect their health with their surroundings, and that kind of connection can lead to powerful activism. It did after *Silent Spring.* It did in the late 1970s in Woburn, Mass., as Jonathan Harr describes in *A Civil Action,* the story of families whose children were dying of leukemia. It did in 1978 at Love Canal in New York State. It continues to do so in communities around the world. If we can see the problem—in our family, in our neighborhood, in the natural world we are intimate with—it is not necessarily easier to tackle, but it becomes more immediate, more mobilizing.

Just as important as Carson's creden-

SEEING A PROBLEM makes it personal. Katrina prompted many Americans to wonder about climate change—even though no single hurricane's ferocity can be attributed to global warming.

JIM REED *Corbis*

tials, her literary brilliance and the tangibility of her topic was the time at which she was writing. In the 1960s Americans were energetically exercising their freedom of transformation. As Adam Rome, an environmental historian at Pennsylvania State University, has written, the environmental movement that blossomed after *Silent Spring* owed a great deal to the Democratic agenda set in the mid-1950s, to the growing activism of middle-class women, and to a counterculture raised in fear of the bomb and the planet's end. The power of *Silent Spring* lay in what people and politicians did with it.

Field Notes from a Catastrophe is not arriving on a similar scene. There is not much widespread U.S. protest about anything—not about the war with Iraq, not about the administration's links to oil and other industry, not about the diminishing of our civil rights. It is strangely quiet here. Americans are also burned out on environmental catastrophism. Many people have noted that with each new catastrophe that has not appeared—the extinction of nearly everything by the end of last year and food shortages, to mention two examples—doomsayers have lost more of their clout and their audience. The problems grow, but apathy has set in.

Kolbert is also writing about something most of us cannot see clearly. Despite reports of melting glaciers, changing ecology, shorter winters and other critical indicators, global warming remains hard to grasp. We can see breast cancer cases on Long Island. We can see high asthma rates in inner cities. And we can see nongovernmental organizations struggling on those fronts. We are not good at seeing big, wide and far away; our sense of scale has not evolved in tandem with the scale of our lives.

And yet. After Katrina, newspapers around the country explored the question of whether there was a link between the ferocity of the hurricane and global warming. (Answer: No one hurricane's force can be attributed to global warming, but trends of increasing intensity might, in time.) Maybe climate change is becoming more personal to more Americans—those in the lower 48.

Kolbert's book contributes more important images for us to personalize. Fairbanks, Alaska, is losing its foundation; as the permafrost melts, huge holes are opening in the earth, under houses, in front yards. Twenty-two English butterfly species have shifted their ranges to the cooler north. The Dutch are busy developing amphibious houses. Burlington, Vt., has tried to reduce energy consumption and has been only modestly successful; without national political will, any one plan hits a wall.

Field Notes has scientific authority as well. Kolbert is not a scientist, but she reports regularly on science, and she may well have talked to every researcher on the planet studying global warming. There are names and characters in *Field Notes* that even a climate-change obsessive may not have seen in other press articles or books. It can get dizzying at times. Yet the enduring impression is of deep, sober, rooted authority—the same impression *Silent Spring* conveys. The book is a review of the scientific evidence and of the failure of the politicians we chose. The details are terrifying, and Kolbert's point of view is very clear, but there is no rhetoric of rant here. She is most directly editorial in the last sentence of the book, and by that point, she has built the case.

Other books on global warming have not had much widespread social or political effect. There have been many—and even *Field Notes* arrives at the same time as *The Winds of Change,* by Eugene Linden (Simon & Schuster), and *The Weather Makers,* by Tim Flannery (Atlantic Monthly Press). In 1989 the much celebrated *The End of Nature,* by

Bill McKibben, for example, catalyzed debate—is nature really ending?—but not a national movement.

Perhaps *Field Notes* can't make a movement where there's little concentrated activist juice. But something about this book feels as though it might. For a friend of mine, Kolbert's *New Yorker* series was an awakening—the first time, she said, she really understood what was happening and why we must act. Let's hope this powerful, clear and important book is not just lightly compared to *Silent Spring*. Let's hope it is this era's galvanizing text. SA

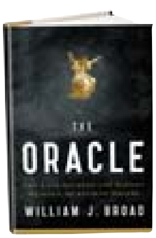
Marguerite Holloway, a contributing editor at Scientific American, *teaches journalism at Columbia University.*

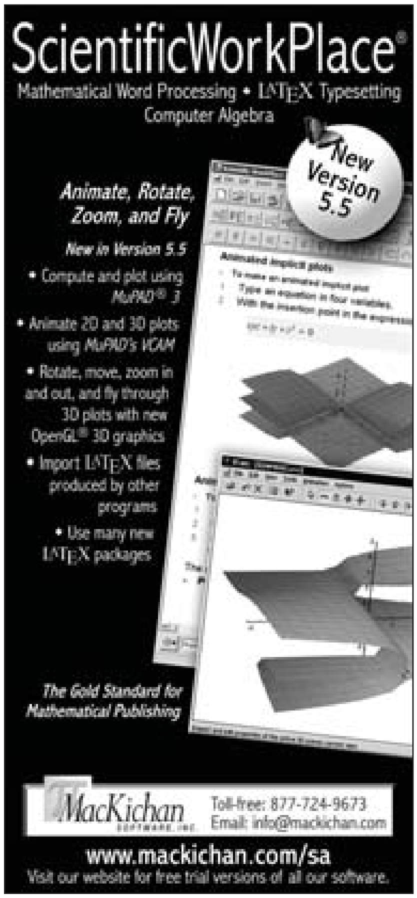
THE EDITORS **RECOMMEND**

THE ORACLE: THE LOST SECRETS AND HIDDEN MESSAGE OF ANCIENT DELPHI

by William J. Broad. Penguin Press, 2006 ($25.95)

The Oracle of Delphi, human mistress of the god Apollo, had the power to communicate his prophecies and advice. Accounts from the time describe how she breathed in vapors rising from the temple floor before communing with the god. But modern scholars have long discounted these reports. Broad, a writer at the *New York Times*, tells the story of scientists who worked from subtle clues scattered through the ancient literature and the landforms near Delphi to uncover evidence that explains the oracle's powers. They discovered that the vapors actually existed—they were petrochemical fumes that contained a hallucinogenic gas, which rose through cracks in the earth into the oracle's chamber. A fascinating account in its own right, the story also allows Broad to weave in the modern debate between science and religion.





The Proof Is on the Painting

MIXING DRINKS AND CULTURE IS AN ART **BY STEVE MIRSKY**

Like an examiner for the National Transportation Safety Board analyzing a plane crash, I'm trying to identify the factors that led to a recent calamity at the Milwaukee Art Museum. First, in retrospect, it's probably a bad idea to use an art museum for any kind of all-you-can-drink event.

When the event is dubbed Martinifest—unlimited martinis for $30—the idea becomes even more questionable. Next, add a suspicious martini recipe, which included vodka and "drink mix," according to the *Milwaukee Journal Sentinel*. This situation is a classic example of experts assuming that their proficiency extends to other areas—Milwaukeeans, there's no shame in accepting your status as beer connoisseurs and consulting a specialist for the preparation of other alcoholic beverages.

In addition, the event was run by Clear Channel, the radio/billboard/concert-promoter giant, also working outside its area of expertise in an art museum. Finally, cram about 1,900 people into a space meant for about 1,400. Here's the capsule summary from the *Journal Sentinel:* "People threw up, passed out, were injured, got into altercations and climbed onto sculptures." Which is either really bad management or a fairly banal example of postmodernism.

Fortunately, the worst-offended pieces were sturdy sculptures. But as a service to other art museums possibly planning all-you-can-drink boozefests, I got in touch with Jennifer Mass, a chemist and senior scientist at the Winterthur Museum & Country Estate in

Winterthur, Del., to find out about the dangers that drunken revelry poses to objets d'art such as the paintings sometimes found in your better museums.

Consider the three major categories of hazardous materials. The first is ethanol, the drinkable kind of alcohol. "Paintings are typically varnished with triterpenoid resins," Mass explains. "Ethanol would be an extremely aggressive solvent for those materials. Typically what happens after museum parties where alcohol is involved—which is always a bad idea to begin with—is that you get drips that wind up on paintings. And what you see is kind of a frosted appearance to the varnish. The varnish is actually starting to dissolve."

Hors d'oeuvres also pose a danger. Imagine some indiscriminately flung meats and cheeses. "Some of the materials that we have in foods, like proteins and carbohydrates, are also used in paintings," Mass says. "And then cleaning becomes a real problem, because the same solvent that would remove the food would also remove some of the original paint."

The acid test, literally, comes when paintings encounter—how to put this delicately—an ipecascade. "You've got the low pH from the stomach acid, combined with digestive enzymes, combined with the alcohol," Mass points out. "It would be extremely damaging to an object of art. We use enzyme treatments to *clean* objects of art, so that is something that is going to be an incredibly aggressive mixture."

Ah, but if the painting needed to be cleaned anyway, might a barf bath actually be a positive? "Too many unknown materials are going to be in someone's stomach contents," Mass speculates. "You could wind up eating right through the original varnish and attacking a painting with that mixture. So I can't say that it would start the job for you." Bottom line: do not allow your priceless masterpieces to be emetically sealed.

So how close to the art should people get at museum parties that include snacks and snifters? "We tend to keep people out of the rooms where there are original objects of art when there's food and drink involved," Mass says. "What a concept. And if there are pieces that are too large to be moved, then they should be roped off." Because it's far better to be roped off than ralphed on. SA

Join host Steve Mirsky on the Scientific American Podcast, *available through iTunes or at www.sciam.com/podcast*

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

How do salt and sugar prevent microbial spoilage?

—K. Rajyaguru, Libertyville, Ill.

Mickey Parish, chair of the nutrition and food science department at the University of Maryland, explains:

Salt (usually sodium chloride) and sugar (generally sucrose) interfere with microbial growth in several ways to block decay in food.

The most notable way is through simple osmosis, resulting in dehydration. The salt or sugar, whether in solid or dissolved form, attempts to reach equilibrium with the salt or sugar content of the food product with which it is in contact. This action has the effect of drawing available water from within the food to the outside and inserting salt or sugar molecules into the food interior. The result is a reduction of the so-called water activity (a_w), a measure of unbound, free water molecules in the food that are necessary for microbes to survive and reproduce. The a_w of most fresh foods is 0.99, whereas the a_w required to halt growth of most bacteria is roughly 0.91. Yeasts and molds usually survive with even lower amounts of water.

Microorganisms differ widely in their ability to resist salt- or sugar-induced reductions of water content. Most disease-causing bacteria do not grow below 0.94 a_w (roughly 10 percent sodium chloride concentrations), whereas most molds that spoil foods grow at levels as low as 0.80, corresponding to highly concentrated salt or sugar solutions.

In addition to dehydrating food, salt and sugar interfere with a microbe's enzyme activity and weaken its DNA molecular structure. Sugar may also provide an indirect form of preservation, by serving to accelerate the accumulation of antimicrobial compounds from the increase of certain other organisms. Examples include the conversion of sugar to ethanol in wine by fermentative yeasts and the transformation of sugar to organic acids in sauerkraut by lactic acid bacteria.

The practice of adding salt or sugar, or both, to food has ancient roots and has many names. Among them are salting, salt or sugar curing, and corning (pieces of rock salt are sometimes called corns—hence the name "corned beef").

Curing may utilize solid crystals of salt or sugar or solutions in which salt or sugar is mixed with water. For instance, brine is the term for salt solutions used in pickling. Examples of foods preserved with salt or sugar are bacon, salt pork, sugar-cured ham, fruit preserves, and jams and jellies. Curing has numerous permutations and may include additional preservation techniques, such as smoking, or ingredients such as spices. These processes not only prevent spoilage of foods but also serve to inhibit or prevent growth of food-borne pathogens such as *Salmonella* or *Clostridium botulinum*.

Why do bubbles form if a glass of water is left alone for a while?

—D. Teyp, Buenos Aires, Argentina

Rick Watling, a meteorologist at the National Oceanic and Atmospheric Administration, offers this answer:

The bubbles come from gases in the water. Atmospheric gases such as nitrogen and oxygen can dissolve in water. The amount present depends on the temperature of the water and the atmospheric pressure at the air-water interface. Colder water and higher pressure allow more gas to dissolve; conversely, warmer water and lower pressure permit less gas.

When you draw a glass of cold water from your faucet and let it to come to room temperature, nitrogen and oxygen slowly exit the solution, with tiny bubbles forming and coalescing at sites of microscopic imperfections on the glass. If the atmospheric pressure happens to be falling as the water warms, the equilibrium between gas molecules leaving and joining the air-water interface becomes unbalanced and tips in favor of them leaving the water, which in turn causes even more gas to come out of solution. SA

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

MATT COLLINS