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Do-It-Yourself
**Black Holes:**
Physics Gets Ready

MAY 2005
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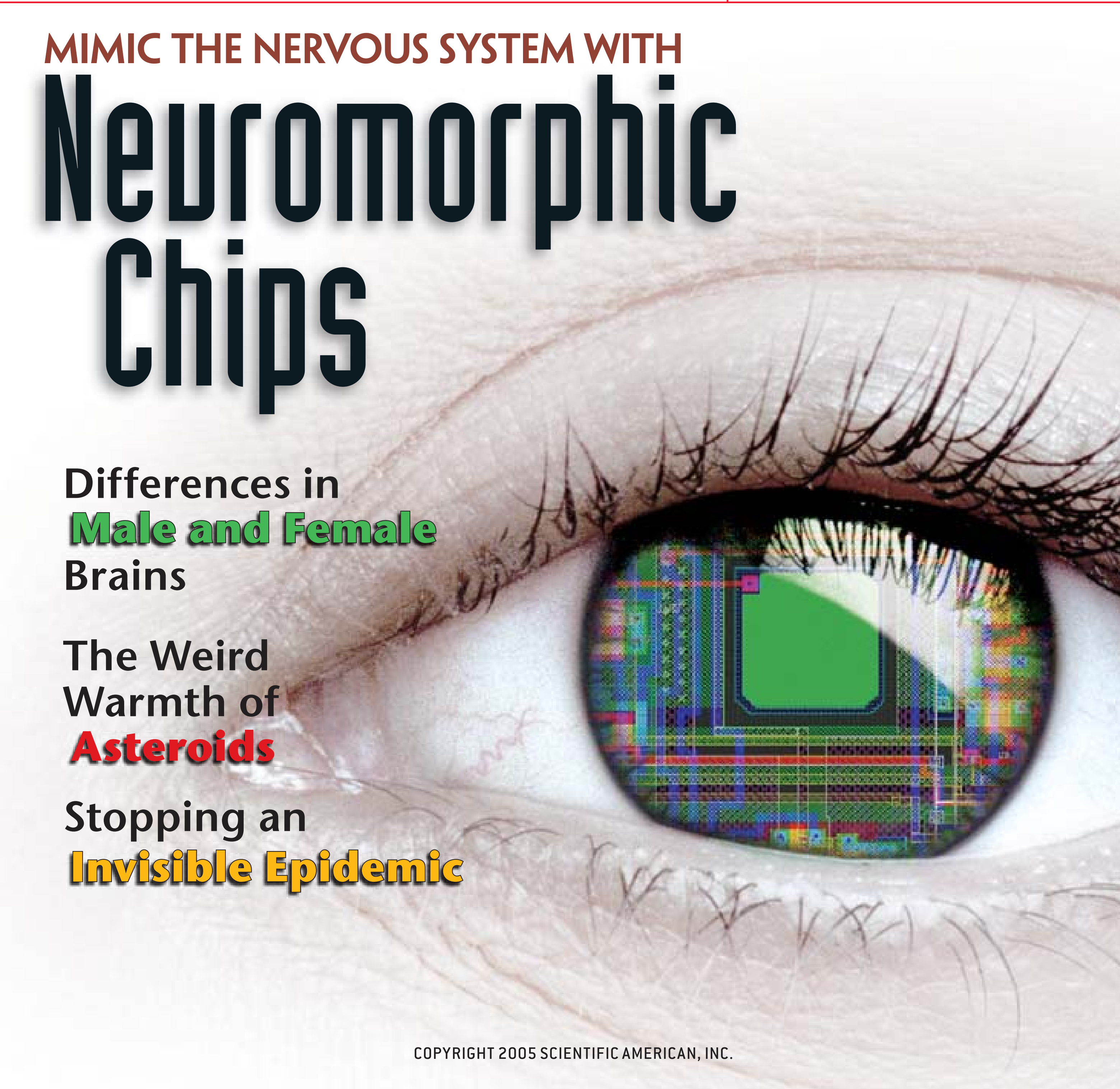

MIMIC THE NERVOUS SYSTEM WITH

## Neuromorphic Chips

Differences in **Male and Female** Brains

The Weird Warmth of **Asteroids**

Stopping an **Invisible Epidemic**

may 2005

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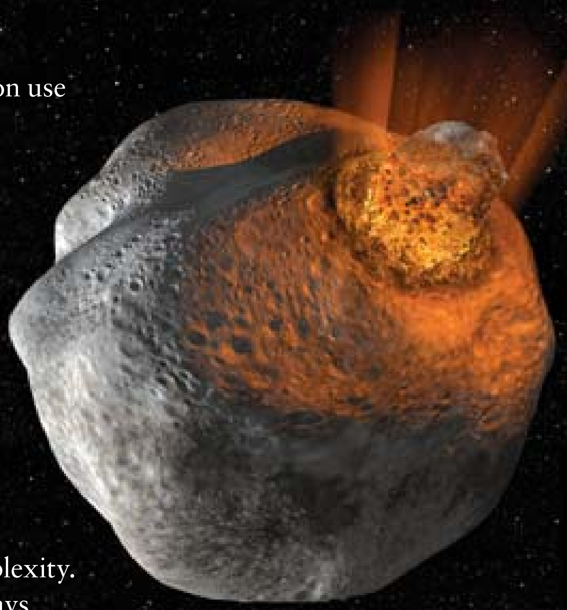
SCIENTIFIC AMERICAN Volume 292 Number 5

## features





80 When very small worlds collide

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Rita Charon, Columbia University 38



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**Cover image by Stone (*eye photograph*), Kareem Zaghloul (*retina layout*) and Jen Christiansen (*photoillustration*); photograph at left by Flynn Larsen.**

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# SA Perspectives

## Human Inventory Control

**It was inevitable** that the radio tags that let cars breeze through toll plazas would get placed on, or in, people. The sole elementary school in a California town 50 miles northwest of Sacramento raised hackles far and wide this past January when it tagged students with the same technology used to determine the whereabouts of cattle and to keep tabs on toilet paper rolls at Wal-Mart. The Brittan Elementary School in Sutter required the seventh- and eighth-grade students to wear a badge that sported a name, a photograph and a radio tag containing identification data that could be read automatically at attendance time. Purportedly, the radio-equipped badges would have also helped improve safety and prevent vandalism.

STUDENT obeys the rules.

The situation in Sutter quickly turned incandescent. One tagged student returned from school and told her parents that she felt like a piece of supermarket produce, according to a report in the *Los Angeles Times*. Parents staged a protest. The American Civil Liberties Union and other groups jumped in. After the local company that developed the technology reacted to the controversy by withdrawing from the project, the school abandoned it in mid-February.

The radio tags deployed in Sutter are, like all new technology, neither inherently good nor bad. Their value, of course, depends on how they are used. Tags could help detect a container shipped into the Port of Baltimore carrying a dirty bomb. In Brazil, businessmen have of their own accord taken more drastic steps than those imposed at Brittan Elementary. In response to that country's rash of kidnappings, forty of them have gone so far as to implant radio-tracking chips under their skin. The company that imports the chips from the U.S. told the Brazilian daily *O Globo* that it has a 2,000-person waiting list.

But, unlike the Brazilian *empresários,* students in Sutter had no choice in the matter. They faced the threat of expulsion if they showed up in the morning without badges strung around their necks. A seventh-grade classroom was clearly the wrong place to implement radio tags that convey precarious implications for individual privacy. The Brittan school board may have had the best intentions, but tagging junior high kids becomes a form of indoctrination into an emerging surveillance society that young minds should be learning to question.

Public education and debate about the proper framework for protecting electronic privacy is desperately called for because we are beginning to see the floodgates open. The U.S. government is pushing aggressively ahead with plans for radio tags in passports, which will store personal information and be readable remotely by anyone, whether a customs official at a desk or a terrorist standing nearby. The Department of Homeland Security has already strapped more than 1,700 immigrants applying for permanent residency with ankle bracelets to prevent those who may be ordered for deportation from fleeing. The respite for the student-tagging business, moreover, may be short-lived. InCom, the company that outfitted Sutter students, has received calls from many other school districts interested in implementing similar programs.

Some segments of U.S. society have always had a visceral aversion to a national identity card. Those instincts are sound and should be reinforced. Widespread adoption of human-tracking devices should never be embraced without serious and prolonged discussion at all levels of society.

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MAX WHITTAKER *AP Photo*

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# On the Web

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## Brain Study Bolsters Case for Smart Bantam Human Species

**When scientists announced** last fall that they had unearthed bones belonging to a miniature human species, *Homo floresiensis*, that lived on the island of Flores in Indonesia as recently as 13,000 years ago, the find made front-page news around the world. But controversy followed on the heels of those claims.

Several paleoanthropologists countered that the small-bodied, small-brained specimen was not a new species but rather an *H. sapiens* individual afflicted with a pathological condition. And in November the bones were transported to the lab of one such dissenter—Teuku Jacob, a paleoanthropologist not involved in the original research—despite objections by some members of the discovery team, sparking a heated custody battle.

Late February marked the return of most of the remains to their repository at the Indonesian Center for Archaeology in Jakarta, nearly two months later than promised. Whether Jacob's study of the bones will yield publications in peer-reviewed journals remains to be seen. Meanwhile an examination of the brain morphology of the Flores hominid reportedly upholds the new species interpretation.

COURTESY OF KIRK E. SMITH *Mallinckrodt Institute of Radiology, Washington University*

## Starless Galaxy Said Found

**Astronomers recently** have discovered what is believed to be the first dark galaxy ever detected, a starless mass of spinning matter located some 50 million light-years away in the Virgo cluster of galaxies.

## Ask the Experts

**How are tattoos removed?**

Dermatologist **Joshua L. Fox,** director of Advanced Dermatology's Center for Laser and Cosmetic Surgery in New York City, explains.

# Letters

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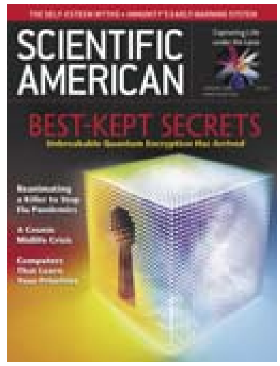


**IF A THEME EMERGED from the January issue, it was health and well-being, including the valuable insights gained by researchers who have resurrected the deadliest flu in history—a plague that is still less than a human lifetime in the past. Writes Laurence Garvie of McMinnville, Ore., "I was told that at the age of two I nearly died of the 1918 influenza. In the 86 years since then I have never had the flu. I have often wondered if this early attack immunized me."**

**The most fertile soil for reader response proved to be the provocative article on the "myth" of self-esteem, which questioned the notion that boosting students' self-esteem improves grades and behavior. William F. Bertolette of Baton Rouge, La., also gleaned from the story "the great word 'floccinaucinihilipilification' (meaning 'the action or habit of estimating as worthless'), which also describes the attitude of so many New Orleans Saints fans." Nevertheless, we've estimated our reader comments on this article and others as anything but inutile.**

## ON GUARD

**The article** "Immunity's Early-Warning System," by Luke A. J. O'Neill, dealt effectively with one component of the innate immune system, namely the Toll-like receptors. It ignored, however, another crucial component: a class of carbohydrate-binding proteins known as lectins, present, for example, in our blood serum and the lining of our lungs, as well as on the surfaces of macrophages. Such lectins serve as immediate defense agents against invading viruses, bacteria, fungi and parasites.

The best-studied example is the mannose-binding lectin, which specifically recognizes the sugar coats of infectious organisms, combines with them and leads to the infection's elimination from the blood serum.

**Nathan Sharon**
Weizmann Institute of Science
Rehovot, Israel

**Immunity's** early-warning system consists not only of membrane-bound Toll-like receptors on the cell surface but also of an important intracellular group of receptors named NALPs and NODs.

NOD2, one of the most prominent, recognizes muropeptides, which are building blocks for bacterial cell walls, and triggers signaling pathways characterized by the activation of the transcription factor NF-κB and the production of proinflammatory cytokines.

**Mario Albrecht**
Max Planck Institute for Informatics
Saarbrücken, Germany

*O'NEILL REPLIES: Toll-like receptors (TLRs) are indeed not the only proteins involved in innate immunity. Mannose-binding lectin and the NOD family are clearly important for the initial response to pathogens but were not covered in my article for reasons of space and clarity. Also, the literature on TLRs is more extensive, and their targeting by new drugs is more advanced.*

## RETURN OF THE FLU

**I was greatly intrigued** by "Capturing a Killer Flu Virus," by Jeffery K. Taubenberger, Ann H. Reid and Thomas G. Fanning. In 1952, as a research physician at the Philadelphia Naval Hospital, I led a medical ward that handled the naval victims of a new flu epidemic—eventually called influenza A-prime. This experience impelled me to work at the Armed Forces Institute of Pathology to review and study the materials available there concerning the 1918 flu pandemic.

Unfortunately, I was unaware of Johan Hultin's work to recover the 1918 flu virus among the Inuit in 1951; my own efforts to understand what had been going on in the 1918 event were considerably constricted. The visible effects on the lungs, as described by Taubenberger et al., clearly accounted for the quick suffocation death in many cases. But in some cases of early death, this lung manifestation was not so obvious. In these instances, I was inclined to attribute death to a massive innate immune response, such as that discussed in the same issue by Luke A. J. O'Neill in "Immunity's Early-Warning System."

Both articles gave me a sense of déjà vu, as I recalled my long night vigils, reviewing slide after slide, trying to spin some coherent theory of what the 1918 pandemic had been, despite the obvious limits inherent in my youthful exploration of this ever fascinating subject.

**Jordan Scher**
New York City

## RUNNING ON SELF-ESTEEM

**We learned from** Roy F. Baumeister, Jennifer D. Campbell, Joachim I. Krueger and Kathleen D. Vohs ["Exploding the Self-Esteem Myth"] that self-esteem bears little relation to academic progress and social development. In February we learned from Claude Steele ["Performance without Anxiety," by Sally Lehrman; Insights] that negative stereotyping (surely resulting in a lack of self-esteem) is the subtle cause of many problems and failures. Are these articles contradictory?

**Cress Kearny**
Oakland, Calif.

**It is difficult** to differentiate between ego and self-esteem, but they are entirely different. Good looks can result in an inflated ego. Self-esteem comes from being ethical. Regrettably, ethics are not taught in any school that I know of. People who live by a code of ethics are the happiest and most content of all.

**Bob Wilson**
Franklin, N.C.

**The authors report** that bullies are surer of themselves than other children. If so, then what is their motivation for bullying? What need is being fulfilled? Why would a confident and self-assured person not be "big" enough to help and protect those he perceives as weak?

**Don Cosby**
Fort Lauderdale, Fla.

*BAUMEISTER REPLIES: There is no contradiction between our article and Steele's comments: loss of self-esteem is not the primary mediator of the effects of negative stereotyping. Wilson points out a major challenge facing our society. Instilling ethics is not easy. I think the self-esteem movement believed it had found an alternative route to making people become good citizens. But it hasn't. In answer to Cosby's question, children may bully others for pragmatic benefits, because they enjoy it or they think others do not give them the respect they deserve. For a lengthier discussion of this issue, see my 1997 book* Evil: Inside Human Violence and Cruelty.

SMUG AND SMASHING: Boosting self-esteem is not likely to enhance performance.

## HUBBLE'S TROUBLES

**"A Bad Fix for Hubble,"** by Steven Ashley [News Scan], states that NASA is set to launch in 2011 "Hubble's replacement," the James Webb Space Telescope (JWST). Although JWST will be an exciting and important element in NASA's Origins program, it is *not* a "replacement" for the Hubble Space Telescope. Unlike the Hubble, the JWST will be optimized for a particular task (examining early galaxies whose light is significantly redshifted to infrared) and will have a mission possibly as short as five years, after which it will not be repairable because of its distance from the earth. The Hubble's considerable scientific versatility and its impact on the general public make it vital that one of the dozens of planned shuttle missions should be devoted to the repair and upgrade of this singular instrument.

**Lyle Crawford**
Victoria, B.C.

## NURTURING NURSING

**As a physician,** I read with great interest "Nurses in Short Supply," by Rodger Doyle [By the Numbers], who states correctly that "now, when virtually all professions are open to women, nursing has become a relatively unattractive career choice." I wish to emphasize that the female makeup of medical school classes is now typically 50 percent. Some years ago my academic adviser pointed out a trend: the best female science students had moved toward medicine and away from nursing. Recently I have noticed that many students are avoiding more challenging math and science courses, too—but those areas of basic research provide the foundations for medical advances.

No one disagrees with the need to improve nurses' salary and working conditions, but there is also a need to motivate all talented students toward mastery of college-level math, physics, chemistry and biology. Only then can we attain the health care system we all desire.

**Stuart Oserman**
Chicago Medical School, Rosalind Franklin University of Medicine and Science

**ERRATA** In the table on page 45 of "Immunity's Early-Warning System," by Luke A. J. O'Neill, the name of the company studying ANA245 was misspelled. The correct name is Anadys, not Anandys.

On page 37A of "You, Robot," by Chip Walter [Insights], the graph plotting computer intelligence incorrectly shows a lone blue dot denoting a computer as smart as a human.

MELISSA SZALKOWSKI

# 150, 100 & 150 Years Ago

FROM *SCIENTIFIC AMERICAN*

## Ecology of Disease ▫ Coal Cornucopia ▫ Baleful Moon

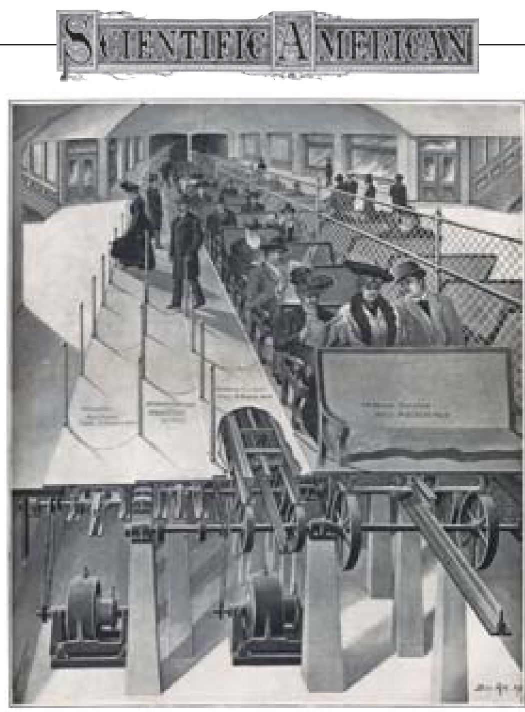
### MAY 1955

**GERM THEORY**—"A new look at the biological formulation of the germ theory seems warranted. We need to account for the peculiar fact that pathogenic agents sometimes can persist in the tissues without causing disease and at other times can cause disease even in the presence of specific antibodies. During the first phase of the germ theory the property of virulence was regarded as lying solely within the microbes themselves. Now virulence is coming to be thought of as ecological. Whether man lives in equilibrium with microbes or becomes their victim depends upon the circumstances under which he encounters them. This ecological concept is not merely an intellectual game; it is essential to a proper formulation of the problem of microbial diseases and even to their control. —René J. Dubos"

**INSULIN**—"In the history of protein chemistry the year 1954 will go down as a landmark, for last year a group of investigators finally succeeded in achieving the first complete description of the structure of a protein molecule. The protein is insulin, the pancreatic hormone which governs sugar metabolism in the body. The achievement was due largely to the efforts of the English biochemist Frederick Sanger and a small group of workers at Cambridge University. When Sanger commenced his investigation in 1944, it appeared that the key to insulin's activity as a hormone lay in its structure, for it contained no special components that might explain its specific behavior."

### MAY 1905

**COAL RESOURCES**—"The report of the Royal Commission on the amount of coal still available below the surface of Great Britain comes as a flat contradiction of those alarmists who take pleasure in telling us that, within such and such a limited time, we shall have dug all the coal out of the earth, and shall have to depend upon some other kind of fuel. The conclusion is that if coal were to be mined at the average rate per year of the past thirty-four years, there is enough coal available to last for over six hundred years to come. If this condition may be taken as representative, the exhaustion of the world's coal supply will take place at such a remote date that it need give us no concern."




**MOVING PLATFORMS,** a proposal for mass transit, 1905

**ARCHDEACON AIRPLANE**—"M. Ernest Archdeacon, a Frenchman, recently conducted some experiments in raising an aeroplane by means of a powerful 60-horse-power automobile. The aeroplane was loaded with a weight equivalent to that of a man. The aeroplane rose gracefully to a height of about 100 feet, after which the rope was cut, and the aeroplane, on account of the breaking of one of the planes of its rudder, suddenly fell, breaking itself in pieces. The aeroplane was of the type employed by the Wright brothers in this country; that is, with a guiding aeroplane placed in front."

**PEOPLE MOVER**—"The proposal was to build a continuous moving platform across Manhattan Island, under 34th Street, with a loop at each end. The platform was to be built with moving sections, traveling at the respective speeds of three, six and nine miles per hour [*see illustration*]. The Rapid Transit Commission voted against the proposal, the objections being directed against its appropriation of a thoroughfare which, because of its contiguity to the new Pennsylvania Railroad station, would form the most important cross-town link in the future complex system of subway transportation in New York."

### MAY 1855

**LUNAR INFLUENCE**—"Some scientific men have come to the conclusion that the moon exercises no influence whatever on the weather, crops, or anything else on the earth, while others as positively affirm that it does. The opinions or popular belief of different nations—savage and civilized—with respect to the moon's influence is something very remarkable. What effect the moon has upon crops we cannot tell, but many of our farmers firmly believe that the times of planting and sowing must be in accordance with the moon's phases. There must be some foundation for such wide-spread opinions; but their truthfulness we have heard denied over and over again."

news SCAN

PUBLIC HEALTH

# Cooping Up Avian Flu

BUYING TIME TO ARM FOR A PANDEMIC IS POSSIBLE—MAYBE **BY CHRISTINE SOARES**

**In anticipating** the next pandemic, flu specialists think the H5N1 avian flu strain, which has jumped from birds to dozens of people in Asia, will inevitably adapt to spreading from person to person. The first local outbreaks could then quickly fan out across the globe. If the disease follows the pattern of previous pandemics, a third of the world's population could be infected and perhaps 1 percent of those people might die. That is, unless the inevitable could be delayed long enough for countries to ramp up production of vaccines and antiviral drugs.

WARNING SIGNS: A 13-year-old boy infected with the H5N1 avian flu virus goes into hospital quarantine north of Bangkok in October 2004. Among 71 known cases in Vietnam, Cambodia and Thailand, one instance of transmission between people has already been identified.

EPA

A bold idea circulating among flu experts offers a way to create that delay. The concept is simple: detect the first clusters quickly and then slow or squelch the emerging virus by blanketing the outbreak area with antivirals. In the past, "no one even considered this thought of containment on the agenda," says Emory University biostatistician Ira M. Longini, Jr. "Now we have a control tool, and we know a lot more about how these things emerge."

Longini is one of several researchers using computer models to test the strategy. At a conference in February, he described some of his findings for possible scenarios in a hypothetical Southeast Asian rural community of about 500,000 people. Density, demographics, travel habits, household sizes, work sites and schools are all based on Thai government data, but Longini thinks they can also be extrapolated to neighboring countries.

By simulating each person's susceptibility and daily contacts, Longini's model projects how the adapted flu strain might spread. In epidemiology, an all-important variable is the disease's "reproductive number"—the average number of new infections that one infected person will cause. This figure, abbreviated $R_0$ (R-"naught"), is typically low for flu—the 1918 pandemic strain's $R_0$ was around 2, according to Longini. Flu moves notoriously fast, however, because its incubation period is brief: within a day of infection a person may begin transmitting the virus, unwittingly, because symptoms appear only on the second day.

By plugging these parameters into the model and running each of several scenarios 100 times, Longini produces probabilities for different outcomes. A single villager could initiate a chain of human transmissions of a virus with an $R_0$ of 1.4, for example. If health officials detected the outbreak 14 days later and then began targeting victims and their contacts for treatment and prophylaxis with the antiviral drug Tamiflu, the outbreak would be contained 98 percent of the time. Just 2 percent of the time more than 500 people would become infected, but the outbreak would rarely escape the region. In all scenarios, odds of containment became better still if everyone in the geographic area received prophylactic Tamiflu when outbreaks were first detected. "Draconian quarantine" also helped, Longini adds.

The higher the $R_0$, however, the lower the likelihood of containing the virus. When the $R_0$ is set at 2.4, for example, the outbreak quickly grows uncontrollably large in 75 percent of the simulations—with the exception of scenarios in which the population has been vaccinated in advance, even if the vaccine is not a perfect match to the adapted H5N1 strain. "With prevaccination, you can contain even a large $R_0$ with antivirals," Longini explains. "It basically buys you time; it effectively lowers the reproductive number."

Such modeling enables officials "to get a handle on how much antiviral would actually be required to control an outbreak," says Nancy J. Cox, chief of the Influenza Branch at the U.S. Centers for Disease Control and Prevention. In reality, successful containment would depend on variables that cannot be predicted, Cox cautions, such as whether an infected person carried the new flu to a large city, where contacts in crowded public spaces would be harder to trace.

As of late March, no country or agency had formally declared its intent to employ the containment strategy in Asia, but the World Health Organization has a stockpile of Tamiflu in the region. If models show that intervention has a good chance of success, says WHO spokesman Dick Thompson, the agency will convene experts to talk about implementing a concrete plan.

Longini, who expected to have his full results published in April, thinks that in the real event, an emerging H5N1 virus can be contained with antivirals, provided its $R_0$ is less than 1.4 and the intervention begins within two or three weeks of the outbreak's start. He is already at work on new models to determine how the avian virus is likely to evolve as it gets better at spreading between people. "I really strongly believe that the $R_0$ will start out low, probably a little above 1," Longini says, "and then with each generation of transmission it will increase as [the virus] adapts to the human population. It gives us a strong window of opportunity to intervene before the $R_0$ evolves to a high enough level where it's basically unstoppable."

### THE LINCHPIN IN CONTAINMENT

**The crucial tool that did not exist in past pandemics is a class of antivirals called neuraminidase inhibitors, including oseltamivir, sold in pill form under the name Tamiflu. The H5N1 avian flu strain is vulnerable to the drug, which hampers the virus's ability to spread inside its host. Hence, a flu victim who takes it within 48 hours of infection has milder illness and is less infectious to others. Tamiflu is also partially effective at preventing flu infections. The drug has never been tried prophylactically on a regional scale, however, nor when a virus is so novel that no one in the population has immunity. Modeling offers health officials the only means to assess whether containment might work.**

ASTRONOMY

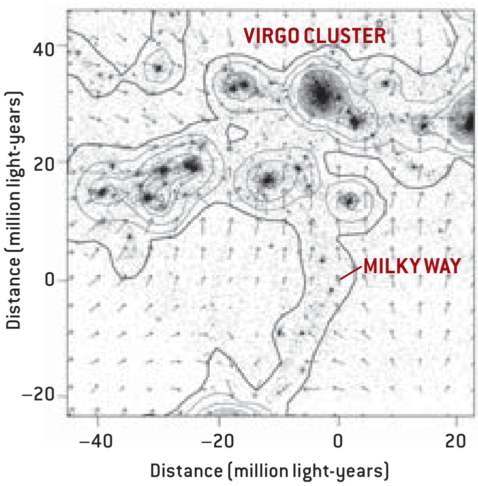
# Too Cold for Comfort

DARK ENERGY CHILLS OUR GALACTIC NEIGHBORHOOD **BY GEORGE MUSSER**

**When you first meet** dark energy, it seems so charming. An alluring stranger, outsider to the Standard Model of particle physics, it entered astronomers' lives a decade ago and won their hearts by fixing all kinds of problems, such as discrepancies in the age of the universe and the cosmic census of matter. Cosmic expansion has got its groove back: once thought to be winding down, it is actually speeding up. But astronomers have come to realize that dark energy has a dark side. The cold grip of its repulsive gravity is strangling the formation of large cosmic structures.

And now observers see it prowling the neighborhood of our own Milky Way. "You don't need to go so far to find dark energy," says Andrea Macciò of the University of Zurich. "Dark energy is also around us."

Up until recently, those seeking the exotica of the universe—dark matter as well as dark energy—focused on the very largest scales (galaxy clusters and up) and on comparatively small ones (a single galaxy). But




SIMULATED MILKY WAY AND ITS NEIGHBORS are moving (*arrows*) toward the Virgo Cluster of galaxies. But they are hardly moving relative to one another—maybe because of dark energy or gravitational tides.

in between is a poorly studied cosmic mesoscale. The Milky Way is part of the Local Group of galaxies, which in turn is part of the Local Volume, about 30 million light-years in radius. We and the rest of our gaggle are flocking en masse at 600 kilometers per second, lured by the Virgo Cluster of galaxies and other outside masses. Tracking relative motions within the volume, though, is tough; it requires distance and velocity measurements of high precision.

Early efforts by Allan R. Sandage of the Carnegie Observatories in Pasadena, Calif., and others in the 1970s, confirmed in recent years, hinted that stuff is moving abnormally slowly—on average, somewhere around 75 kilometers per second. Simulations predict that galaxies, pulled together by gravity, should buzz around at closer to 500 kilometers per second. By analogy with a gas of slow-moving molecules, the Local Volume is "cold."

Another way to think of the problem is in terms of cosmic expansion. Theory predicts that you'd have to go out hundreds of millions of light-years, where matter is spread randomly rather than finely structured, before the overall expansion should outgun localized motions. Yet in the Local Volume, you have to go out only about five million light-years.

One explanation, championed by Igor Karachentsev of the Russian Academy of Sciences, is that galaxies and their individual cocoons of dark matter swim in a sea of dark matter. The sea would mute the density contrasts and hence the gravitational forces that drive galactic motions. The only trouble is that matter, whether dark or visible, should not spread out into a sea. It should clod.

So others have looked to dark energy. Its gravitational repulsion would offset galaxies' gravitational attraction, thereby deadening their motion. In and near the Milky Way, attraction wins, but beyond a certain distance, repulsion does. As Arthur Chernin of Moscow University and his colleagues calculated in 2000, this distance is five million light-years—exactly where galactic motions deviate from standard predictions.

The initial calculations actually only halved the galactic velocities, which is not enough. But the new full-up simulations by Macciò's group indicate that dark energy works after all. "If and only if you include dark energy, there is a very good agreement," Macciò says. "This is why we state that we have found the signature of dark energy."

Not everyone agrees. In 1999 Rien van de Weygaert of the University of Groningen in the Netherlands and Yehuda Hoffman of Hebrew University in Jerusalem argued that the Local Volume is caught in a cosmic tug-of-war between surrounding galaxy clusters. This, too, would pull galaxies apart, offsetting their own gravity.

To decide whether this mechanism or dark energy is more important, astronomers have to compare the Local Volume with similar regions. If those not caught in a tug-of-war behave similarly, the dark energy must be to blame. Unfortunately, the teams disagree on what "similar" means, so the debate goes on. If Macciò's model proves to be right, then dark energy, once considered the most "out there" idea in science, an ethereal abstraction of little relevance, will bump a little closer down to earth.

## WRONG WAY MILKY WAY?

A new (and controversial) twist in the story of local galaxy motions comes from Alan Whiting of the Cerro Tololo Interamerican Observatory in Chile. He argues that not only are galaxies barely moving, they aren't even moving in the right direction. They should be falling toward one another, yet they seem to mill about at random. "Something is causing 75 kilometers per second's worth of motion in the Local Volume, and it's not the luminous matter that we see," Whiting says.

Many researchers find fault with his analysis. If he is right, though, one answer might be that our galactic neighborhood is home to stillborn galaxies—starless clumps of dimly glowing gas and invisible dark matter. Astronomers recently saw such a beast in the Virgo Cluster. The only trouble is that if a similar body lurks in our immediate vicinity, it should have been detected already.

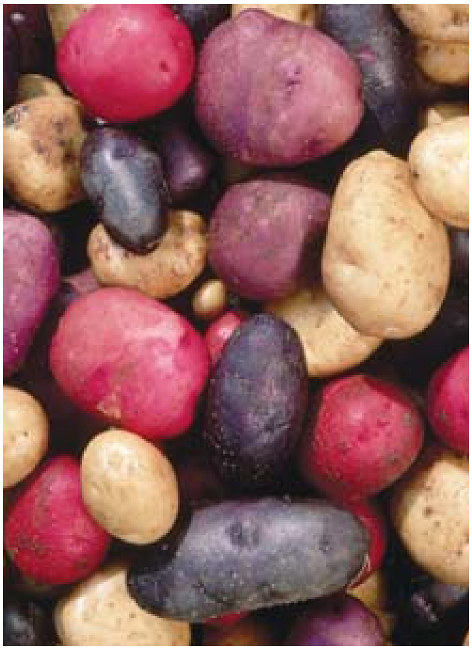
news SCAN

VACCINES

# Defensive Eating

FOOD VACCINES SHOW PROMISE—NOW FORGET ABOUT THEM **BY LUIS MIGUEL ARIZA**

**The lack of refrigeration** remains a vexing problem in vaccinating the world's poor, because drugs often lose their efficacy in the heat. One solution 200 years ago was to propagate the vaccine in orphan children [*see sidebar*]. "It was a really fascinating idea," remarks Charles Arntzen, founder of the Biodesign Institute at Arizona State University—but not one to be implemented today. Instead Arntzen has hopes for vaccines that exist inside crops and could just be eaten.



NATURAL SIZE DIFFERENCES in potatoes and other produce mean that vaccines produced in genetically modified versions could deliver variable doses.

Arntzen conceived the idea of edible vaccines in the 1990s and has since tried to realize it. He genetically engineered potatoes to produce a vaccine against the hepatitis B virus, which kills one million people every year. This past February he reported that in a trial of an edible vaccine, up to 60 percent of volunteers who ate raw chunks of the potato developed antibodies against the virus. The signs of immunity are "an excellent start," Arntzen says.

Even so, Arntzen and others in the field are abandoning food vaccines. Consumer fear that the modified fruits and vegetables could end up in grocery stores is one issue. The medical worry, though, is the dosage: as public health expert Jurrien Toonen of the Royal Tropical Institute in Amsterdam points out, a tomato or banana is never the same size, so the quantity of the vaccine could vary from one piece to the next.

Because of the dosage concern, Hilary Koprowski of Thomas Jefferson University, the discoverer of the live polio vaccine, discounts the use of raw plants for massive immunization, even for farm animals. "The edible vaccine should be given in capsules containing desiccated leaf extract," he says.

Others agree that shifting the strategy for edible vaccines from food to processed pills makes sense. Achieving uniform doses would be easier, whether the extracts come from potatoes, lettuce, corn or even tobacco leaves (if the nicotine and other alkaloids could be removed). "We can freeze and dry potato, pack it in gelatin capsules and make uniform dosages of the vaccine," Arntzen notes. And pills would be cheaper. The Biodesign Institute projects that 200 acres would produce enough hepatitis B antigen to immunize all the babies in the world, at a cost of $0.05 per dose, compared with $0.30, the lowest price of the current vaccine. Trials for edible vaccine pills will probably begin in four to five years.

"Edible vaccines offer great advantages, as they do not need cold for conservation," Toonen says. "But they are not enough to resolve the whole situation." Even if they prove their efficacy, he states, they would face the logistical problems of some countries that make it difficult to deliver even the simplest pharmaceuticals to places far from urban centers, where most children are vaccinated. And Arntzen is aware of groups that systematically oppose genetic engineering. But he is optimistic: "It is going to be hard to justify blocking genetically modified plants if we can document we are reducing infant mortality."

*Luis Miguel Ariza is a science writer and novelist in Madrid.*

## NEED TO KNOW: "ORPHAN" DRUG

**One novel solution to the lack of refrigeration for vaccines occurred 200 years ago, shortly after Edward Jenner discovered that cowpox infection acts as a vaccine against smallpox. In 1803 military doctor Francisco Xavier de Balmis embarked on an amazing expedition ordered by King Charles IV of Spain. With a small team, he sailed from Spain to bring Jenner's smallpox vaccine to the New World, where Spanish colonies were being devastated by the disease.**

**To preserve the vaccine, de Balmis harvested it from the 22 orphan children he brought along. He infected one child and waited about 10 days as pustules formed. De Balmis then took the fluid from the lesions and inoculated it into another child, continuing the cycle with successive immunizations. In this way, the vaccine reached Puerto Rico, Mexico and Venezuela. He also taught local doctors how to apply and propagate the vaccine.**

**De Balmis continued on to Spain's colonies in Asia—picking up new children along the way and finding homes for the others now vaccinated—before returning home in 1806, while an assistant, José Salvany, reached Colombia, Peru and Chile. "Four or five years after de Balmis, between 100,000 and half a million people could have been immunized," calculates Guillermo Olague, a historian of science at the University of Granada in Spain. "That marked the beginning of the end of the epidemic."**

LYNDA RICHARDSON *Corbis*

TAXONOMY

# Bending to Bar Codes

IS A ONE-GENE METHOD TO DEFINE SPECIES TRULY EFFECTIVE? BY SARA BEARDSLEY

**By the close** of the 20th century, taxonomy had reached a crossroads. Funds were declining and academic interest dwindling, even as biologists and conservationists raced to identify and quantify species. "During my long engagement in the tropics, I've been confronted with the frustration that all biologists feel, with no knowledge of the life systems around them," explains evolutionary biologist Paul D. N. Hebert, who holds the Canada Research Chair in Molecular Biodiversity. So, in 2003, Hebert proposed a new ID system, sidestepping the cumbersome taxonomic legwork: "tag" species according to a segment of a mitochondrial gene. These so-called DNA bar codes instantly won public favor, heralding a day when researchers could run simple DNA tests in the field, perhaps even with a *Star Trek*-ian "tricorder" device. But since its advent, scores of taxonomists have decried the shortcut, claiming it will undermine the purposely elaborate systems developed to ensure ID precision and accuracy.

BUTTERFLY EFFECT: Genetic bar codes and ecological data revealed that the neotropical skipper butterfly *Astraptes fulgerator* is actually a complex of 10 species. Whether bar coding by itself can define species is controversial.

Hebert's scheme focuses on a sequence fragment from the cytochrome *c* oxidase I (COI) gene, which he claims is unique to separate taxa. He and his colleagues demonstrated proof of principle last year, when DNA bar codes correctly predicted independent species in groups of previously undistinguished birds and butterflies. In a February meeting in London, the Consortium for the Barcode of Life announced plans to bar-code all birds and fish within the next five years, as well as identify all flowering plants in Costa Rica. The initiatives are stepping-stones on the way to their much grander goal: a gene tag for every living thing and a catalogue of the earth's biodiversity (only about one tenth of the world's species are formally known).

But like anything, warns entomologist Quentin D. Wheeler of the Natural History Museum in London, bar coding "can be used for good or evil." A standardized species marker is exciting, provided it corresponds to formal descriptions and classifications. To Wheeler and other critics, it is bar coders' more ambitious goal—applying the COI system backward to create "provisional" new-species definitions—that threatens to hamper taxonomic progress.

The problem, naysayers argue, is oversimplification. "Nature is messy," points out entomologist Daniel Rubinoff of the University of Hawaii at Manoa. Multiple species definitions exist today because nobody knows what qualifies as speciation; the very "science" of taxonomy involves analyzing hundreds of characters to make these distinctions—which is why the one-character data sets used by bar coders "are like returning to the Dark Ages," Rubinoff says. Biologist Brent D. Mishler of the University of California at Berkeley concurs, calling bar coding for species identification "extremely wrongheaded and damaging to the fabric of systematics," which currently relies on extensive morphological, ecological and genetic data to frame species in an evolutionary context.

Critics also raise eyebrows over bar coding's accuracy. Hebert pegs the error rate at 2 percent, small enough to validate the approach for animals. But so far only a few proofs of principle have emerged, and the tests have been easy. "Close sister species are usually the most important to identify correctly," says biologist Felix Sperling of the University of Alberta. And those are the ones scientists may have the greatest trouble resolving through COI. Recently split taxa or cases of hybridization, where independent species have produced offspring, pose particular challenges because sequences may not have evolved to reflect those events yet.

Hebert argues that the system is meant to augment current taxonomy by "heaping life into piles" that can later be revised. But with a price tag between $1 billion and

## GOING BEYOND ONE GENE

**Although DNA shortcuts may be the taxonomic tools of the future, many researchers wonder whether bar coders have pared down the process too much. The COI gene does not work for plants, for instance, because their mitochondria evolve too slowly. "Wouldn't it be smarter to focus attention on a little battery of genes from several genomes rather than one?" asks evolutionary biologist Michael J. Donoghue of Yale University. In other words, start off with multiple sequences and then narrow down species definitions from a richer stockpile of data. Donoghue cites the gene tree/species problem—in which individual genes have evolutionary histories independent of their species histories: "If you focus on only one gene, you'll get the wrong answer some percentage of the time."**

WILL COOK

$2 billion, critics worry that the initiative will only divert funds and leave "real" taxonomy to clean up the mess. "In the age of cyber-infrastructure, digital tools, and IT," Wheeler and others write in a paper in press for the journal *Systematic Biology,* "most of the weights that have held taxonomy back are gone. [But] now … it is in danger of being tossed out like rubbish for the latest parlor trick."

Experts also point out that bar codes cannot be integrated with the other major systematics enterprise—the Tree of Life, a peer-reviewed cladogram linking all known phylogenetic relationships. (Bar codes provide too little evidence to justify formal species designations on it.) At best, Hebert's database will exist alongside the tree, superimposing untested "leaves." Hebert claims that despite the obstacles "we're finally tapping into an automated, digital information stream," but others note that cut-and-dry codes seem to overlook the essential meaning of species: ever changing end points in the hands of evolution.

EXTINCTIONS

# Doubts on Dinosaurs

## YUCATÁN IMPACT CRATER MAY HAVE OCCURRED BEFORE THE DINOSAURS WENT EXTINCT BY BARRY E. DiGREGORIO

**According to** conventional paleontological wisdom, an asteroid or comet 10 to 14 kilometers wide crashed into the present-day Yucatán Peninsula 65 million years ago and wiped out the dinosaurs. Most scientists currently consider the Chicxulub impact crater, perhaps about 145 kilometers wide, to be the smoking gun of this Cretaceous-Tertiary (KT) extinction.

Not so fast, says Princeton University micropaleontologist Gerta Keller. The collision that created the Chicxulub crater, she argues, happened before the KT extinction—300,000 years too soon, to be more precise. She first made the controversial assertion last year, and the dust has yet to settle.

Keller does not dispute that a meteorite could have helped trigger the demise of the dinosaurs. But she remains confident that Chicxulub is not the crater scientists should be looking at, based on sediments she has analyzed from various Chicxulub sites. She has several lines of evidence: one in particular relates to the layer of iridium, an extremely rare element known to be abundant in many meteorites, that exists at the KT boundary at sites around the world. In theory, only massive impacts can distribute the element globally.

A big collision can also produce another kind of layer, too, by melting and vaporizing silicate rocks, which then condense into sand-grain-size glass spheres known as microtektites. Depending on the mass of the colliding meteorite, these tiny glass spheres can be thrown hundreds to thousands of kilometers from the point of impact.

Keller discovered that the original Chicxulub microtektite layers lie up to 14 meters below the KT iridium layer at the northeastern Mexico site (the crater itself extends from the northwestern tip of the Yucatán Peninsula into the Gulf of Mexico). "To date, no one has found iridium associated with Chicxulub," Keller says.

Jan Smit, a paleontologist at Vrije University in the Netherlands, doubts Keller's claims, stating that her argument about KT iridium and Chicxulub borders on tautology: "If you uncouple all the iridium-enriched ejecta layers from the Chicxulub impact, then of course there is no iridium associated with Chicxulub." In any case, Smit contends, "How and where do you hide the iridium from a large impact such as Chicxulub?"

Keller hypothesizes that the object that made Chicxulub may have been "a dirty snowball" type that did not have any iridium. Some meteorites do not. Another possibility could be that measurements may not yet have been taken from the correct rock strata.

Researchers have also raised doubts about Keller's proposed 300,000-year age difference between Chicxulub and KT, which is based on sedimentation rates extrapolated from the distance between the microtektite layer and the KT boundary layer. Geoffrey Garrison, a paleontologist from the University of Washington, wonders why the material separating the two layers could not have been just sediment that was resuspended by the impact and that had simply settled back to the seafloor.

Keller insists that she has already ruled out resuspension. She claims that sediment settling after a high-energy event, such as an impact, tsunami or storm, produces identifiable layers. Heavier grains settle out first, followed by the finest-grained muds and clays. Such a pattern does not appear in the Chicxulub crater, Keller reports.

Keller plans to bolster her case with an upcoming paper that argues that meteorite impacts that leave Chicxulub-size craters and smaller cannot by themselves cause significant species extinctions. The amount of material ejected, she finds, is insufficient to trigger long-lasting climatic or geographic changes from fire or floods. Sudden mass extinctions might require the coincidence of major volcanism and a large impact event, "but so far no one has found the source crater," Keller says in her dismissal of Chicxulub. "The history of mass extinctions seems to indicate that a single short-term shock to the environment can be survived by nearly all species." Whether conventional wisdom survives Keller's own shock to paleontology remains to be seen.

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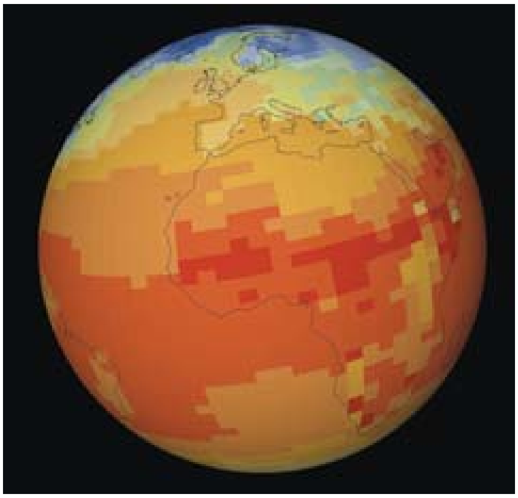
*Barry E. DiGregorio is a research associate for the Cardiff Center for Astrobiology in Wales, U.K.*

COMPUTING

# Processing for Science

"@HOME" PROJECTS BAND TOGETHER AND PROLIFERATE BY CHARLES Q. CHOI

**Fans of the spacetime continuum** can now uncover gravitational ripples at their desks thanks to the February launch of Einstein@Home. The project is one of the latest of at least 60 "@home" projects now on the Internet, in which personal-computer users can donate spare processor power to help solve scientific problems. And no need to choose one mission over another: @home software can now multitask, and enough microchip muscle exists to handle many more distributed-computing projects.



TEMPERATURE MODELING of the earth by the computing project Climateprediction.net depends on data that are divvied up in chunks and crunched by home users.

Save for computationally intense tasks such as rendering graphics, typical modern PCs that perform at least one billion floating-point operations per second (that is, most home computers built since about 2000) almost never employ their full power. Distributed computing takes advantage of this spare capacity, dividing large tasks into tinier ones and sending them over the Internet for usually idle computers to work on. The result is unparalleled processing muscle: IBM's Blue-Gene/L, now the most powerful supercomputer, cranks out about 70 trillion flops; meanwhile SETI@home conservatively runs off roughly 500,000 PCs at more than 100 trillion flops, says SETI@home director David P. Anderson.

Since the first public distributed-computing project—the Great Internet Mersenne Prime Search—was launched in 1996 to look for large prime numbers, virtual supercomputing projects have emerged for the serious (testing potential drugs with FightAIDS@home) to the sublime (the Monkey Shakespeare Simulator). Anderson expects hundreds of @home projects to emerge in the next few years and the number of participating CPUs to reach 30 million from the roughly 1.3 million of today.

A key development in the surge is the formation of distributed-computing platforms that can host multiple projects. Among the biggest is the Berkeley Open Infrastructure for Network Computing (BOINC), which hosts SETI@home and Einstein@Home as well as the formerly independent Climateprediction.net, which joined in August. In coming months BOINC partners will include FightAIDS@home, PlanetQuest and Orbit@home. Other umbrella distributed-computing software platforms include Grid.org, which is running two projects to find compounds against cancer and predict three-dimensional protein structures from amino acid sequences, and Find-a-Drug.org, which currently has nine projects looking for drugs against various ailments, such as malaria and Creutzfeldt-Jakob disease, the human relative of mad cow disease.

Such @home hosts are also time-savers for scientists. BOINC, for instance, offers open-source infrastructure code so researchers do not have to write their own. It can take several person-years to develop the software, because it must perform unobtrusively on different operating systems in up to a million computers while protecting against erroneous results and malicious attacks. "We want to make it easy for scientists to get access to millions of computers' worth of processing power," says Anderson, who also directs BOINC.

Anderson estimates that, for a typical computer, the practical upper limit for the number of @home projects is roughly 12. At that point, its processing power is parceled so thin that projects consider it useless. A service that rotates a PC automatically between projects is possible in the future, he adds. Still, umbrella platforms might interfere with one another if operating simultaneously on the same computer. But with the roughly 200 million privately owned computers in the world, notes Ed Hubbard, president of United Devices in Austin, Tex., which runs Grid.org, "there's plenty of room for everybody."

*Charles Q. Choi is a frequent contributor.*

## DISTRIBUTED BANDWAGON

**At least 60 distributed-computing projects are available today (see http://distributedcomputing.info/projects.html). Among them:**

- **SETI@home:** Analyzes radio signals to search for extraterrestrial intelligence.
- **Climateprediction.net:** Seeks to improve the accuracy of long-term global climate prediction.
- **PlanetQuest:** Analyzes telescope data to discover new extrasolar planets as they eclipse stars.
- **Orbit@home:** Tracks asteroids that might collide with Earth.
- **LHC@home:** Simulates how particle beams might travel in the Large Hadron Collider being built at CERN near Geneva.

CLIMATEPREDICTION.NET

BY THE NUMBERS

# Measuring Beauty

LIFE WITH SUN, WATER AND OTHER NATURAL AMENITIES **BY RODGER DOYLE**

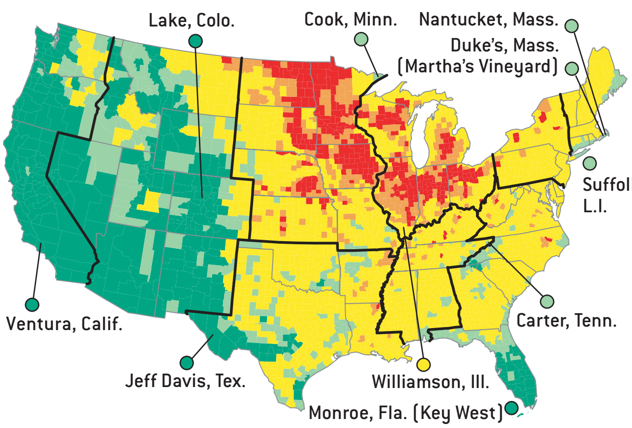
**Books such as** *Places Rated Almanac* and *America's Most Charming Towns and Villages* have long been publishing staples, but in recent years the U.S. government has joined the trend by rating each county in the contiguous 48 states in terms of its natural amenities. The ratings, made by the Economic Research Service of the U.S. Department of Agriculture, are based on six measures: January temperature, January sunshine, temperature gain between January and July (less is better), July humidity, water area, and topographic variation.

The map, which summarizes the ratings, reveals a distinct pattern, with the western states and southern Florida at the top of the scale and scoring well on most measures. In contrast, the upper Midwest, from Ohio through the Dakotas, shows a relative lack of amenities. This region, of course, tends to have cold winters. But even when January temperatures are removed from the equation, the ratings in the region do not improve significantly (the region generally lacks topographic variation). Among the few northern areas to rank high is Glacier County, Montana, which includes the eastern face of the Rocky Mountains, extensive plains area, buttes, lakes and rivers, together with diverse recreational opportunities such as fishing, skiing and big game hunting. The eastern third of the country, aside from Florida, has no top-rated counties except for several in southern Appalachia, which has a hospitable climate, many lakes and rivers, and considerable topographic diversity.

With the study, the USDA hopes to understand the factors underlying the economic viability of rural counties. It demonstrated that natural amenities correlate strongly with population change: Counties having very high amenities scores typically doubled in population during the period from 1970 to 1996, apparently because of their ability to attract retirees and recreational facilities. Those at the low end of the amenities scale lost population or barely held even. Furthermore, the degree of natural amenities helps to explain rural population shifts at least as much as economic factors, such as changing employment opportunities in farming, mining and lumbering.

Natural amenities do not play much of a role in metropolitan areas, where economic considerations such as transportation and skilled labor are vital. Of the big cities, Los Angeles and San Francisco score the highest. Manhattan (New York County) ranks only 1,689 out of 3,111 counties (but who goes there for the scenery?); Cook County, Illinois (Chicago), and Washington, D.C., rank even lower. Of the remaining major metropolitan counties, Franklin County, Ohio (Columbus), and Hennepin County, Minnesota (Minneapolis), have the lowest ratings. Most major suburban counties in the Northeast and Midwest get low ratings. Among the few exceptions are two New York City areas, Fairfield County, Connecticut, and Suffolk County, New York.

*Rodger Doyle can be reached at rdoyle2@adelphia.net*




Rating of Counties on the Natural Amenities Scale

*SOURCE: Economic Research Service, U.S. Department of Agriculture. Counties listed are those that rated highest in each of the nine U.S. Census regions (separated by dark lines). In cases where two counties have the same rating, both are shown.*

## FAST FACTS: PLACES TO LIVE

**The high and low ratings of U.S. counties are listed according to their natural amenities. The scores are scaled from 0 to 100; the national average is 37.**

**Top Five**

**Ventura (California):** 100

**Humboldt (California):** 100

**Santa Barbara (California):** 99

**Mendocino (California):** 99

**Del Norte (California):** 98

**Bottom Five**

**Mower (Minnesota):** 7

**Norman (Minnesota):** 6

**Tipton (Indiana):** 6

**Wilkin (Minnesota):** 2

**Red Lake (Minnesota):** 0

*SOURCE: Economic Research Service, U.S. Department of Agriculture*

## FURTHER READING


Natural Amenities Drive Rural Population Change. David A. McGranahan. Economic Research Service, U.S. Department of Agriculture, 1999. www.ers.usda.gov/publications/aer781/


RODGER DOYLE

## DATA POINTS: STROKE SIGNS

**Patients who suffer a major ischemic stroke—the narrowing or blocking of arteries that chokes off blood flow to the brain—often experience prior symptoms that do not result in injury. In most cases, these transient ischemic attacks preceded major strokes by no more than a week, according to a recent study of 2,416 patients. Physicians should begin preventive treatment within hours of a mini stroke rather than taking weeks to assess a patient, as some studies have found.**

Percent of strokes that are ischemic: **80**

Typical length of a mini stroke: **5 minutes**

Percent of ischemic stroke patients who experience a prior mini stroke: **15 to 30**

Annual number of strokes in the U.S.: **700,000**

Number resulting in death: **168,000**

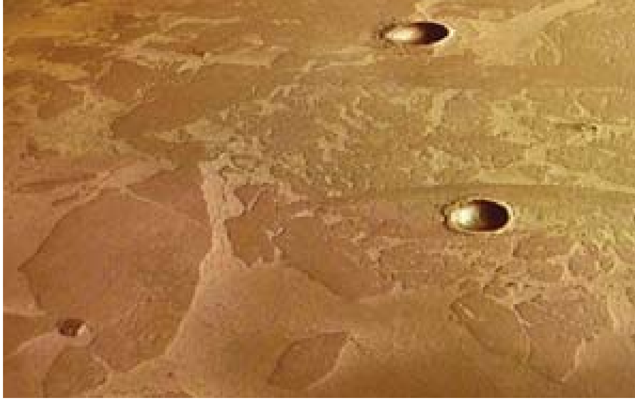
Total number of survivors: **4.7 million**

Amount spent every year on stroke-related medical costs and disability: **$51 billion**

*SOURCES:* Neurology, *March 8; Society for Neuroscience*

PLANETARY SCIENCE

# Martian Lake View



FROZEN WATER? Blocky shapes, reminiscent of fragmented sea ice, appear near the Martian equator.

**Mars seems to have** a frozen lake on its surface, according to images obtained by the European Space Agency's Mars Express satellite. One hypothesis has it that Mars sporadically belches up volcanic gases and floodwater, leaving behind huge seas, which then evaporate. Researchers have identified the apparent remnants of such an outburst: a frozen body of water the size of Earth's North Sea. Although some experts dispute the finding, believing it to be lava flow, the formation is fragmented like ice on terrestrial seas. Crater counts indicate the object is roughly five million years old—young in geologic terms—and its horizontal surface, along with several craters that seem partially filled up, suggests that the ice remains to this day. The researchers posit that an eruption from two crevasses known as Cerberus Fossae provided the water, and a layer of volcanic ash settled on the resulting glacier, preventing its sublimation into vapor, they explain in the March 17 *Nature*. *—JR Minkel*

NEUROBIOLOGY

# Discerning Intent

**So-called mirror neurons,** discovered in monkeys, fire both when a person performs an action and when a person sees someone else perform the same action. These brain cells may be enabling us to understand the intention behind other people's behavior. To test the idea, investigators from the University of California at Los Angeles showed 23 volunteers three sets of video clips. The first depicts tea and cookies either arranged neatly or haphazardly: the context for an action. The second shows someone grasping a lone teacup: the action. The third shows someone grasping the teacup amid the other objects, implying the actor's intention of either having a sip of tea or cleaning the teacup. A specific group of mirror neurons in the right inferior frontal cortex was active only during the videos depicting intention, the researchers report online in the March *PLoS Biology*. *—JR Minkel*

WILDLIFE

# Wings with a Snap

**At 80 flutters per second,** the male red-capped manakin's wings can beat faster than a hummingbird's. But rather than hovering for a drink, manakins generate finger-snap clicks to entice females. Kimberly Bostwick of Cornell University captured the frenetic beating with 1,000-frame-per-second cameras. The footage shows a surprising diversity in how wings generate sounds: the white-collared manakin claps its wings behind its back, but the red-capped manakin rubs its wing feathers against its tail. "When we think of sexual selection traits such as these, we think of mostly superficial changes such as a change in feather color," Bostwick says. Her findings instead reveal that the wing sounds of male courtship have led to extreme body diversification in manakin bones, muscles and feathers. Bostwick is one of several investigators featured in PBS's *Nature: Deep Jungle,* a three-part miniseries illustrating how researchers are relying on new technology to explore the rain forest. It airs April 17 and 24 and May 1. *—Charles Q. Choi*

Red-capped manakin

ESA/DLR/FU BERLIN (G. NEUKUM) *(top)*; MARIE P. READ *(bottom)*; ILLUSTRATION BY MATT COLLINS

IN MEMORIAM

# Hans Albrecht Bethe, 1906–2005

**I met Hans Bethe** 10 years ago, on the morning of his *festschrift,* a kind of preposthumous memorial that physicists throw for a retiring giant. It was to be an ambitious, two-day event, for Bethe's career spanned almost the entire length and breadth of nuclear physics. In his early years, he worked with Ernest Rutherford, Niels Bohr and Enrico Fermi and then soared to fame with his Nobel Prize–winning discovery in 1938 of how nuclear fires light the stars. He became head theoretician on the Manhattan Project and later helped to explain how aging stars can transform into bombs, exploding as supernovae.

As we talked in his office at Cornell University, Bethe kept steering our conversation toward the ramifications of nuclear science. Like Albert Einstein, Hans Bethe was a citizen-scientist who tried to persuade society to wield the power of atoms wisely. In articles that Bethe published in this magazine, he made the case for nuclear nonproliferation treaties (1950), cautioned against missile defense systems (1968 and 1984), and predicted the necessity of a gradual shift from fossil fuels (1976). As with his scientific discoveries, these insights have withstood the test of time. He died quietly in his Ithaca, N.Y., home on March 6 at the age of 98. —*W. Wayt Gibbs*

STAR POWER: Hans Bethe in his Cornell University office in 1996.

MICHAEL OKONIEWSKI *AP Photo*

TRANSPLANTS

## Dead Bones to Life

**Cadaver bones** can replace injured or diseased bone, but up to a third of these grafts fail because they cannot repair microscopic cracks from normal wear and tear, unlike living bone. Resurrecting dead bones could give patients an option to amputation. Molecular immunologist Edward Schwarz of the University of Rochester and his colleagues compared mice that had healthy and dead bone implants and found that living bone significantly expresses two genes involved in blood vessel growth and old bone reabsorption. The researchers incorporated these genes into a freeze-dried virus, which they coated onto dead femur bone grafts. The genes induced the body to supply blood to the dead bone, thereby revitalizing it. New bone formation did not occur uniformly on graft surfaces, but the team found other genes that might improve the approach's efficacy. The full discussion appears in the March *Nature Medicine.* —*Charles Q. Choi*

DETECTORS

## Muons for Defense

**The cosmic rays** that constantly bombard the earth could be just the thing to detect concealed nuclear materials, say Los Alamos National Laboratory physicists who have designed a detection system based on them. Security officials currently scan vehicles and containers with x-rays and gamma rays, but they are harmful to people and penetrate lead and steel poorly. Cosmic rays end up producing particles called muons, which scatter off of heavy nuclei such as those of uranium and plutonium atoms. Muons can burrow through thick steel and lead; detectors placed above and below a sample can measure the flight paths of the particles and reconstruct the shape of dense materials in-between, shielded or not. A midsize prototype for scanning sections of cars should be ready this summer, the Los Alamos team reported at the February meeting of the American Association for the Advancement of Science. —*JR Minkel*

BRIEF POINTS

- Low doses of aspirin help to prevent heart attacks in men but, for unknown reasons, not in women. The therapy lowers the risk of stroke for women, however.

*New England Journal of Medicine,* March 31

- In sonoluminescence, sound waves fired at a fluid can generate superhot flashes inside collapsing bubbles. New experiments with sulfuric acid bubbles find that the temperature hits about 20,000 degrees Celsius—four times hotter than the sun's surface.

*Nature,* March 3

- Scientists sequencing the genomes of *Drosophila* fruit flies unwittingly also sequenced three unknown species of *Wolbachia* bacteria, which had dwelled inside the flies.

*Genome Biology,* February 22

- Mutations in the complement factor H gene may boost the risk of age-related macular degeneration threefold to sevenfold. The gene helps to regulate inflammation in the immune system, suggesting that the blinding disease could be the result of a misdirected immune attack.

*Science Express,* March 10

BRAD HINES

# Turn Me On, Dead Man

**What do the Beatles, the Virgin Mary, Jesus, Patricia Arquette and Michael Keaton all have in common? By MICHAEL SHERMER**

**In September 1969,** as I began ninth grade, a rumor circulated that the Beatles' Paul McCartney was dead, killed in a 1966 automobile accident and replaced by a look-alike. The clues were there in the albums, if you knew where to look.

*Sgt. Pepper's Lonely Hearts Club Band*'s "A Day in the Life," for one, recounts the accident: *He blew his mind out in a car / He didn't notice that the lights had changed / A crowd of people stood and stared / They'd seen his face before / Nobody was really sure if he was from the House of Lords.* The cover of the *Abbey Road* album shows the Fab Four walking across a street in what looks like a funeral procession, with John in white as the preacher, Ringo in black as the pallbearer, a barefoot and out-of-step Paul as the corpse, and George in work clothes as the gravedigger. In the background is a Volkswagen Beetle (!) whose license plate reads "28IF"—Paul's supposed age "if" he had not died.

**Anecdotal thinking comes naturally; science requires training.**

Spookiest of all were the clues embedded in songs played backward. On a cheap turntable, I moved the speed switch midway between $33\frac{1}{3}$ and 45 to disengage the motor drive, then manually turned the record backward and listened in wide-eared wonder. The eeriest is "Revolution 9" from the *White Album,* in which an ominously deep voice endlessly repeats: *number nine ... number nine ... number nine....* Played backward you hear: *turn me on, dead man ... turn me on, dead man ... turn me on, dead man....*

In time, thousands of clues emerged as the rumor mill cranked up (type "Paul is dead" into Google for examples), despite John Lennon's 1970 statement to *Rolling Stone* that "the whole thing was made up." But made up by whom? Not the Beatles. Instead this was a fine example of the brain as a pattern-recognition machine that all too often finds nonexistent signals in the background noise of life.

What we have here is a signal-to-noise problem. Humans evolved brains that are pattern-recognition machines, adept at detecting signals that enhance or threaten survival amid a very noisy world. This capability is association learning—associating the causal connections between A and B—as when our ancestors associated the seasons with the migration of game animals. We are skilled enough at it to have survived and passed on the genes for the capacity of association learning.

Unfortunately, the system has flaws. Superstitions are false associations—A appears to be connected to B, but it is not (the baseball player who doesn't shave and hits a home run). Las Vegas was built on false association learning.

Consider a few cases of false pattern recognition (Google key words for visuals): the face of the Virgin Mary on a grilled cheese sandwich; the face of Jesus on an oyster shell (resembles Charles Manson, I think); the hit NBC television series *Medium,* in which Patricia Arquette plays psychic Allison Dubois, whose occasional thoughts and dreams seem connected to real-world crimes; the film *White Noise,* in which Michael Keaton's character believes he is receiving messages from his dead wife through tape recorders and other electronic devices in what is called EVP, or Electronic Voice Phenomenon. EVP is another version of what I call TMODMP, the Turn Me On, Dead Man Phenomenon—if you scan enough noise, you will eventually find a signal, whether it is there or not.

Anecdotes fuel pattern-seeking thought. Aunt Mildred's cancer went into remission after she imbibed extract of seaweed—maybe it works. But there is only one surefire method of proper pattern recognition, and that is science. Only when a group of cancer patients taking seaweed extract is compared with a control group can we draw a valid conclusion.

We evolved as a social primate species whose language ability facilitated the exchange of such association anecdotes. The problem is that although true pattern recognition helps us survive, false pattern recognition does not necessarily get us killed, and so the overall phenomenon has endured the winnowing process of natural selection. The Darwin Awards (honoring those who remove themselves from the gene pool), like this column, will never want for examples. Anecdotal thinking comes naturally; science requires training. SA

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

# When Medicine Meets Literature

**Writing and humanities studies produce better physicians, Rita Charon argues, because doctors learn to coax hidden information from patients' complaints** By MARGUERITE HOLLOWAY

**On a recent Wednesday,** 10 members of New York–Presbyterian Hospital's oncology staff gather around a long table in a windowless conference room, sharing sandwiches and fruit, discussing their work. Discussing it in terms that might well surprise their patients. A social worker reads a short essay describing nearly two decades of entering patients' rooms after the doctor has given a diagnosis of cancer as "coming into their winter, their horror," unable to keep herself warm or impervious. A physician reads a piece about how she came to understand the loss motivating one of her colleagues to treat cancer. A nurse reads what sounds like her letter of resignation: she has to get out, she says, "to dissociate my living from your dying."

## RITA CHARON: STORY LISTENER

- Director of Columbia University's program in narrative medicine, designed to train physicians to be more empathetic with patients.
- Raised in a Providence, R.I., community of transplanted French Canadians with a "densely dark" and "particularly punitive" form of Catholicism, she says. At college in New York City, "the whole world opened up."
- Before joining Columbia's medical staff in 1981, she worked as an elementary school teacher, school bus driver and peace activist.

Rita Charon responds as a literary critic to each author. The "you" changes over the course of the piece, she says to one, "we get confused in a lot of these writings about who is the 'you' and who is the 'I.'" Of another piece: "It is so very intimate, it could be written to a lover." She relates a woman's image of a tree and sharp pain to Eden's snake. For an hour or so, Charon parses point of view, prologue and metaphor; she identifies a "shimmering moment" in a piece where the writer undergoes a transformation from deep anger toward a patient to forgiveness. It is a typical meeting for the narrative oncology group, which has met voluntarily twice a month for three years. In no way is it a typical meeting for a hospital staff.

Charon is trying to change that. Besides being a general internist and a professor of clinical medicine at Columbia University's College of Physicians and Surgeons, she holds a Ph.D. in English. She and others are seeking to improve the relationship between physicians and patients using literature and writing. The goal is to make doctors more empathetic by getting them to articulate and deal with what they feel and to develop sophisticated listening skills, ears for the revelations hidden in imagery and subtext. The field—alternatively called narrative medicine, literature and medicine, or medical humanities, depending on the approach—began by most accounts about 30 years ago and is now widely reflected in medical school curricula around the country. According to the American Association of Medical Colleges, 88 of 125 surveyed U.S. medical schools offered humanities courses in 2004; at least 28 required literature or narrative study in some form.

Charon, who coined the phrase "narrative medicine," stands at the forefront of this movement. She

FLYNN LARSEN

has established voluntary groups, such as the one in narrative oncology, and designed required courses for medical students and residents in which they read literature and write to reshape how they listen and think. She is also trying to study what it is about this method that seems, anecdotally, to work.

"What Rita has done so successfully is to bring the skills we learn as literature students—point of view and how to frame a story—and she has brought those to bear in the medical interview," says Anne H. Hawkins, a professor of humanities at Penn State College of Medicine. "She can listen at a different level. For instance, your doctor might ask, 'How long have you had shortness of breath?' You say, 'Since I divorced my husband.'" The next question typically might be "How long ago was that?" Hawkins notes. In contrast, "a Rita Charon would then say, 'Tell me about that relationship.' She teaches them how to listen and what to listen for."

CREATIVE HEALING: Rita Charon leads a narrative oncology meeting. The work, one oncologist says, reduces feelings of burnout.

The 55-year-old Charon—petite, sharply blue-eyed and, as would be expected, an intense and earnest listener—says this kind of listening, which began for her more than two decades ago, has changed her relationship with patients. She spends more time with them and writes about them, often sharing what she has written. The documentation makes her more curious, more engaged, she says. "I have had very vexed, ineffective relationships with patients, and by writing about it and saying, 'Does this sound like us?,' the whole thing changes."

For instance, Charon recalled a patient who had high cholesterol and chest pain. During their first meeting, she recounts, "he started his story with the death of his father when he was a boy." By not restricting the conversation and treatment to his cholesterol and physical pain, Charon and her patient began to talk about his own challenges as a father. "It made for a very productive alliance," she says. "And his chest pains went away."

Many experts concur that such careful listening can lead to better diagnoses and approaches. Ron B. Loewe, an anthropologist and authority on narrative medicine at Mississippi State University, recalls interviewing doctors and patients at Cook County Hospital in Chicago about diabetes because few patients were complying with their doctor's orders and many were doing poorly. Loewe found that patients thought the doctors had given them diabetes when administering shots of prednisone, commonly used to treat inflammation. "What are the issues for compliance if your patient thinks you caused the disease?" asks Loewe, adding that many doctors remain uninterested in eliciting such stories. "They are under such pressure to see lots of patients in a very short period."

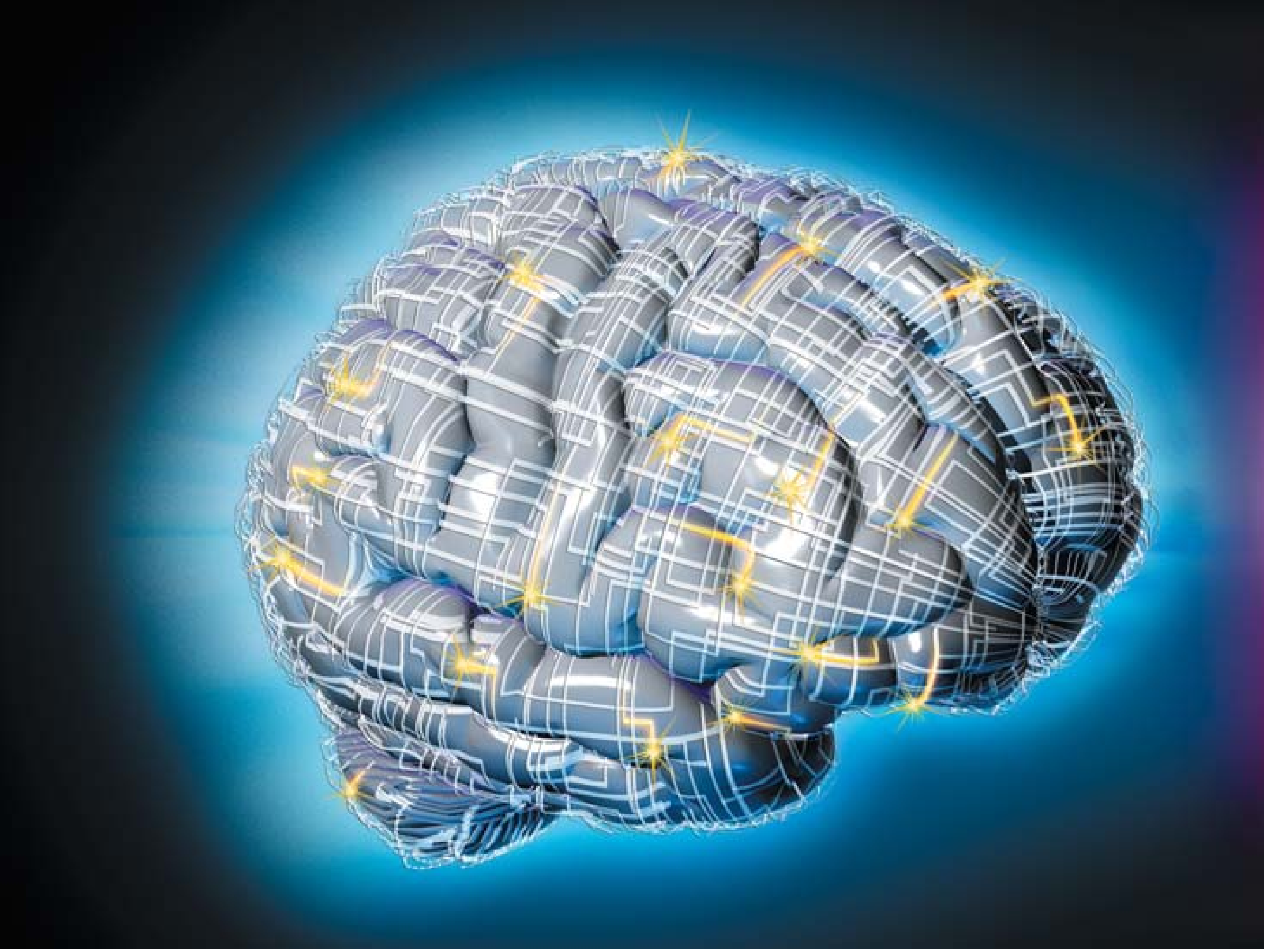
In addition, some doctors remain critical of medical school curricula that include humanities and communication skills, arguing that time is better spent on scientific subjects. "As with any change to an establishment as solid as medicine, there is skepticism," says Kelly Caverzagie of the University of Nebraska Medical Center and a member of the American Medical Association's Council on Medical Education. The old guard may harbor skepticism, but, Caverzagie points out, "the students themselves are embracing this movement."

Charon's own involvement with new movements is long-standing. In 1966 she entered Fordham University and quickly joined an experimental education project in which 30 students and six teachers designed their own curriculum. She tackled various jobs, among them teaching at a newly established progressive elementary school, before becoming a medical student at Harvard University in 1974. Her interest in narration and medicine formed during a lecture by Elliot Mishler, a Harvard social psychologist renowned for bringing narrative theory to sociology. "I was riveted," she says. She studied with Mishler, developing what she describes as a way of seeing patients as whole people, not as cases, and using her mentor's attention to the patterns of speech to hone her listening skills.

Her engagement with narrative ultimately led to a doctoral dissertation at Columbia on Henry James's late works, including *The Wings of the Dove,* in which one of the three central characters is a very ill woman; the creation of a writer-in-residence program at Columbia's medical school, in which visitors, including Susan Sontag and Michael Ondaatje, have shared their perceptions of illness with medical students and faculty; and a practice called "parallel charts," in which residents write about their patients in a nonmedical format. Charon is now designing studies to assess the impact of parallel charts and of groups such as the one in narrative oncology. Charon and oncologist Gwen L. Nichols say the readings have improved relationships among the oncology staff, prevented burnout and, therefore, led to better care.

"When a very junior nurse is in a position to give comfort and sustenance to the service chief, and when the head doctor of oncology finds himself weeping to hear what this junior nurse has written, that does something you don't do on rounds," Charon declares. "We have team meetings, we go on rounds. But *it* doesn't happen there because—well, that is what we are trying to learn." SA

FLYNN LARSEN



# HIS BRAIN,

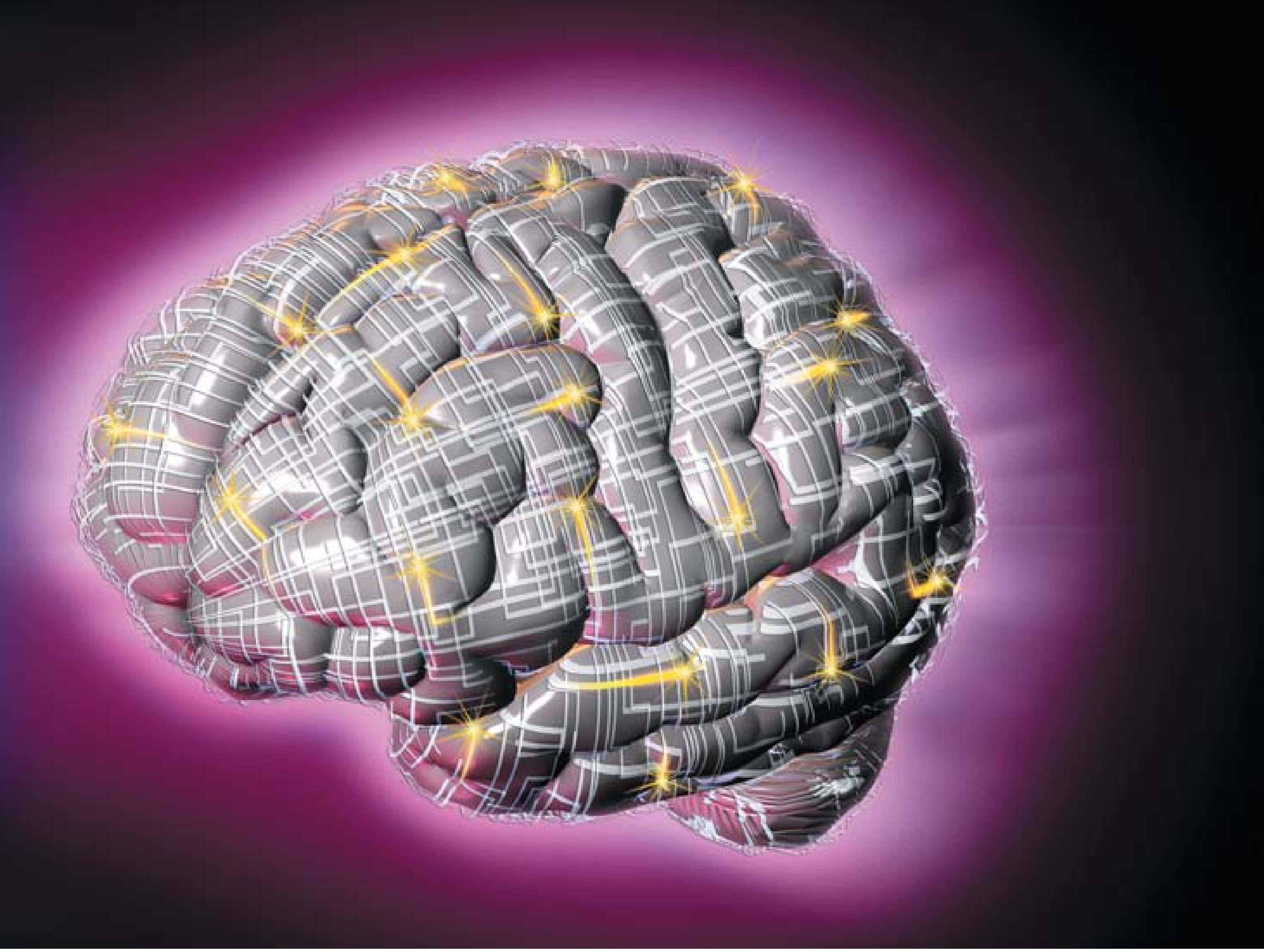
It turns out that male and female brains differ quite a bit in architecture and activity. Research into these variations could lead to sex-specific treatments for disorders such as depression and schizophrenia

## BY LARRY CAHILL

On a gray day in mid-January, Lawrence Summers, the president of Harvard University, suggested that innate differences in the build of the male and female brain might be one factor underlying the relative scarcity of women in science. His remarks reignited a debate that has been smoldering for a century, ever since some scientists sizing up the brains of both sexes began using their main finding—that female brains tend to be smaller—to bolster the view that women are intellectually inferior to men.

To date, no one has uncovered any evidence that anatomical disparities might render women incapable of achieving academic distinction in math, physics or engineering [*see box*

SLIM FILMS



# HER BRAIN

*on page 47*]. And the brains of men and women have been shown to be quite clearly similar in many ways. Nevertheless, over the past decade investigators have documented an astonishing array of structural, chemical and functional variations in the brains of males and females.

These inequities are not just interesting idiosyncrasies that might explain why more men than women enjoy the Three Stooges. They raise the possibility that we might need to develop sex-specific treatments for a host of conditions, including depression, addiction, schizophrenia and post-traumatic stress disorder (PTSD). Furthermore, the differences imply that researchers exploring the structure and function of the brain must take into account the sex of their subjects when analyzing their data—and include both women and men in future studies or risk obtaining misleading results.

## Sculpting the Brain

NOT SO LONG AGO neuroscientists believed that sex differences in the brain were limited mainly to those regions responsible for mating behavior. In a 1966 *Scientific American* article entitled "Sex Differences in the Brain," Seymour Levine of Stanford University described how sex hormones help to direct divergent reproductive behaviors in rats—with males engaging in mounting and females arching their backs and raising their rumps to attract suitors. Levine mentioned only one brain region in his review: the hypothalamus, a small structure at the base of the brain that is involved in regulating hormone production and controlling basic behaviors such as eating, drinking and sex. A generation of neuroscientists came to maturity believing that "sex differences in the brain" referred primarily to mating behaviors, sex hormones and the hypothalamus.

> Several intriguing behavioral studies add to the evidence that some sex differences in the brain arise before a baby draws its first breath.

That view, however, has now been knocked aside by a surge of findings that highlight the influence of sex on many areas of cognition and behavior, including memory, emotion, vision, hearing, the processing of faces and the brain's response to stress hormones. This progress has been accelerated in the past five to 10 years by the growing use of sophisticated noninvasive imaging techniques such as positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI), which can peer into the brains of living subjects.

These imaging experiments reveal that anatomical variations occur in an assortment of regions throughout the brain. Jill M. Goldstein of Harvard Medical School and her colleagues, for example, used MRI to measure the sizes of many cortical and subcortical areas. Among other things, these investigators found that parts of the frontal cortex, the seat of many higher cognitive functions, are bulkier in women than in men, as are parts of the limbic cortex, which is involved in emotional responses. In men, on the other hand, parts of the parietal cortex, which is involved in space perception, are bigger than in women, as is the amygdala, an almond-shaped structure that responds to emotionally arousing information—to anything that gets the heart pumping and the adrenaline flowing. These size differences, as well as others mentioned throughout the article, are relative: they refer to the overall volume of the structure relative to the overall volume of the brain.

Differences in the size of brain structures are generally thought to reflect their relative importance to the animal. For example, primates rely more on vision than olfaction; for rats, the opposite is true. As a result, primate brains maintain proportionately larger regions devoted to vision, and rats devote more space to olfaction. So the existence of widespread anatomical disparities between men and women suggests that sex does influence the way the brain works.

Other investigations are finding anatomical sex differences at the cellular level. For example, Sandra Witelson and her colleagues at McMaster University discovered that women possess a greater density of neurons in parts of the temporal lobe cortex associated with language processing and comprehension. On counting the neurons in postmortem samples, the researchers found that of the six layers present in the cortex, two show more neurons per unit volume in females than in males. Similar findings were subsequently reported for the frontal lobe. With such information in hand, neuroscientists can now explore whether sex differences in neuron number correlate with differences in cognitive abilities—examining, for example, whether the boost in density in the female auditory cortex relates to women's enhanced performance on tests of verbal fluency.

Such anatomical diversity may be caused in large part by the activity of the sex hormones that bathe the fetal brain. These steroids help to direct the organization and wiring of the brain during development and influence the structure and neuronal density of various regions. Interestingly, the brain areas that Goldstein found to differ between men and women are ones that in animals contain the highest number of sex hormone receptors during development. This correlation between brain region size in adults and sex steroid action in utero suggests that at least some sex differences in cognitive function do not result from cultural influences or the hormonal changes associated with puberty—they are there from birth.

## Overview/*Brains*

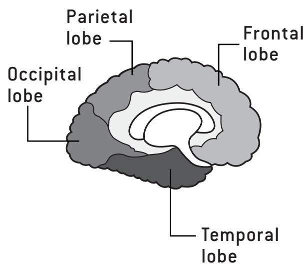
- Neuroscientists are uncovering anatomical, chemical and functional differences between the brains of men and women.
- These variations occur throughout the brain, in regions involved in language, memory, emotion, vision, hearing and navigation.
- Researchers are working to determine how these sex-based variations relate to differences in male and female cognition and behavior. Their discoveries could point the way to sex-specific therapies for men and women with neurological conditions such as schizophrenia, depression, addiction and post-traumatic stress disorder.

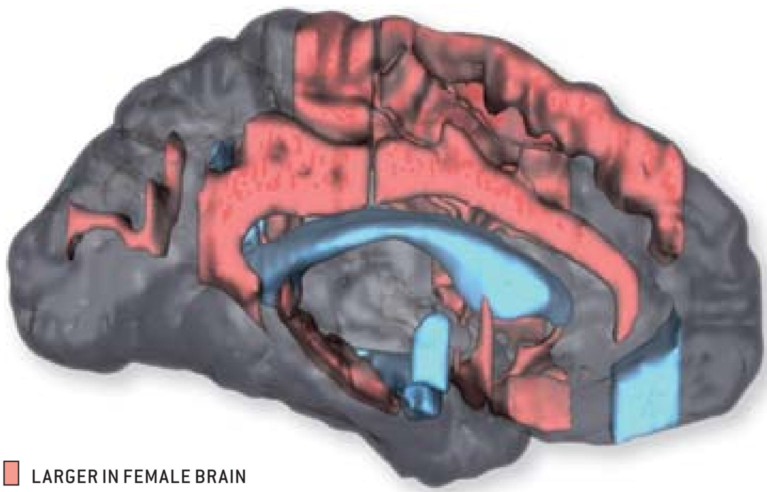
## Inborn Inclinations

SEVERAL INTRIGUING behavioral studies add to the evidence that some sex differences in the brain arise before a baby draws its first breath. Through the years, many researchers have demonstrated that when selecting toys, young boys and girls part ways. Boys tend to gravitate toward balls or toy cars, whereas girls more typically reach for a doll. But no one could really say whether those preferences are dictated

## SIZABLE BRAIN VARIATION

Anatomical differences occur in every lobe of male and female brains. For instance, when Jill M. Goldstein of Harvard Medical School and her co-workers measured the volume of selected areas of the cortex relative to the overall volume of the cerebrum, they found that many regions are proportionally larger in females than in males but that other areas are larger in males (*below*). Whether the anatomical divergence results in differences in cognitive ability is unknown.




SOURCE: JILL M. GOLDSTEIN *Harvard Medical School and Brigham and Women's Hospital, Connors Center for Women's Health and Gender Biology;* BASED ON JILL M. GOLDSTEIN ET AL. IN *CEREBRAL CORTEX,* VOL. 11, NO. 6, PAGES 490–497; JUNE 2001

by culture or by innate brain biology.

To address this question, Melissa Hines of City University London and Gerianne M. Alexander of Texas A&M University turned to monkeys, one of our closest animal cousins. The researchers presented a group of vervet monkeys with a selection of toys, including rag dolls, trucks and some gender-neutral items such as picture books. They found that male monkeys spent more time playing with the "masculine" toys than their female counterparts did, and female monkeys spent more time interacting with the playthings typically preferred by girls. Both sexes spent equal time monkeying with the picture books and other gender-neutral toys.

Because vervet monkeys are unlikely to be swayed by the social pressures of human culture, the results imply that toy preferences in children result at least in part from innate biological differences. This divergence, and indeed all the anatomical sex differences in the brain, presumably arose as a result of selective pressures during evolution. In the case of the toy study, males—both human and primate—prefer toys that can be propelled through space and that promote rough-and-tumble play. These qualities, it seems reasonable to speculate, might relate to the behaviors useful for hunting and for securing a mate. Similarly, one might also hypothesize that females, on the other hand, select toys that allow them to hone the skills they will one day need to nurture their young.

Simon Baron-Cohen and his associates at the University of Cambridge took a different but equally creative approach to addressing the influence of nature versus nurture regarding sex differences. Many researchers have described disparities in how "people-centered" male and female infants are. For example, Baron-Cohen and his student Svetlana Lutchmaya found that one-year-old girls spend more time looking at their mothers than boys of the same age do. And when these babies are presented with a choice of films to watch, the girls look longer at a film of a face, whereas boys lean toward a film featuring cars.

Of course, these preferences might be attributable to differences in the way adults handle or play with boys and girls. To eliminate this possibility, Baron-Cohen and his students went a step further. They took their video camera to a maternity ward to examine the preferences of babies that were only one day old. The infants saw either the friendly face of a live female student or a mobile that matched the color, size and shape of the student's face and included a scrambled mix of her facial features. To avoid any bias, the experimenters were unaware of each baby's sex during testing. When they watched the tapes, they found that the girls spent more time looking at the student, whereas the boys spent more time looking at the mechanical object. This difference in social interest was evident on day one of life—implying again that we come out of the womb with some cognitive sex differences built in.

### Under Stress

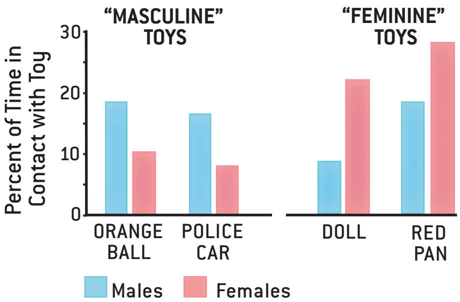
IN MANY CASES, sex differences in the brain's chemistry and construction influence how males and females respond to the environment or react to, and remember, stressful events. Take, for example, the amygdala. Goldstein and others have reported that the amygdala is larger in men than in women. And in rats, the neurons in this region make more numerous interconnections in males than in females. These anatomical variations would be expected to pro-

THE AUTHOR

*LARRY CAHILL* received his Ph.D. in neuroscience in 1990 from the University of California, Irvine. After spending two years in Germany using imaging techniques to explore learning and memory in gerbils, he returned to U.C. Irvine, where he is now an associate professor in the department of neurobiology and behavior and a Fellow of the Center for the Neurobiology of Learning and Memory.

## WIRED PREFERENCES?

Vervet monkeys observed by Gerianne M. Alexander of Texas A&M University and Melissa Hines of City University London displayed toy preferences that fit the stereotypes of human boys and girls: the males (*top photograph*) spent more time in contact with trucks, for example, whereas the females (*bottom photograph*) engaged more with dolls (*graphs*). Such patterns imply that the choices made by human children may stem in part from their neural wiring and not strictly from their upbringing.




SOURCE: GERIANNE M. ALEXANDER AND MELISSA HINES IN *EVOLUTION AND HUMAN BEHAVIOR*, VOL. 23, NO. 6, PAGES 467–479; NOVEMBER 2002. USED WITH PERMISSION FROM ELSEVIER

duce differences in the way that males and females react to stress.

To assess whether male and female amygdalae in fact respond differently to stress, Katharina Braun and her co-workers at Otto von Guericke University in Magdeburg, Germany, briefly removed a litter of Degu pups from their mother. For these social South American rodents, which live in large colonies like prairie dogs do, even temporary separation can be quite upsetting. The researchers then measured the concentration of serotonin receptors in various brain regions. Serotonin is a neurotransmitter, or signal-carrying molecule, that is key for mediating emotional behavior. (Prozac, for example, acts by increasing serotonin function.)

The workers allowed the pups to hear their mother's call during the period of separation and found that this auditory input increased the serotonin receptor concentration in the males' amygdala, yet decreased the concentration of these same receptors in females. Although it is difficult to extrapolate from this study to human behavior, the results hint that if something similar occurs in children, separation anxiety might differentially affect the emotional well-being of male and female infants. Experiments such as these are necessary if we are to understand why, for instance, anxiety disorders are far more prevalent in girls than in boys.

Another brain region now known to diverge in the sexes anatomically and in its response to stress is the hippocampus, a structure crucial for memory storage and for spatial mapping of the physical environment. Imaging consistently demonstrates that the hippocampus is larger in women than in men. These anatomical differences might well relate somehow to differences in the way males and females navigate. Many studies suggest that men are more likely to navigate by estimating distance in space and orientation ("dead reckoning"), whereas women are more likely to navigate by monitoring landmarks. Interestingly, a similar sex difference exists in rats. Male rats are more likely to navigate mazes using directional and positional information, whereas female rats are more likely to navigate the same mazes using available landmarks. (Investigators have yet to demonstrate, however, that male rats are less likely to ask for directions.)

Even the neurons in the hippocampus behave differently in males and females, at least in how they react to learning experiences. For example, Janice M. Juraska and her associates at the University of Illinois have shown that placing rats in an "enriched environment"—cages filled with toys and with fellow rodents to promote social interactions—produced dissimilar effects on the structure of hippocampal neurons in male and female rats. In females, the experience enhanced the "bushiness" of the branches in the cells' dendritic trees—the many-armed structures that receive signals from other nerve cells. This change presumably reflects an increase in neuronal connections, which in turn is thought to be involved with the laying down of memories. In males, however, the complex environment either had no effect on the dendritic trees or pruned them slightly.

But male rats sometimes learn better in the face of stress. Tracey J. Shors of Rutgers University and her collaborators have found that a brief exposure to a series of one-second tail shocks enhanced performance of a learned task and increased the density of dendritic connections to other neurons in male rats yet impaired performance and decreased connection density in female rats. Findings such as these have interesting social implications. The more we discover about how brain mechanisms of learning differ between the sexes, the more we may need to consider how optimal learning environments potentially differ for boys and girls.

Although the hippocampus of the female rat can show a decrement in response to acute stress, it appears to be more resilient than its male counterpart in the face of chronic stress. Cheryl D. Conrad and her co-workers at Arizona State University restrained rats in a mesh cage for six hours—a situation that the rodents find disturbing. The researchers then assessed how vulnerable their hippocampal neurons were to killing by a neurotoxin—a standard measure of the effect of stress on these cells. They noted that chronic restraint rendered the males' hippocampal cells more susceptible to the toxin but had no effect on the females' vulnerability. These findings, and others like them, suggest that in terms of brain damage, females may be better equipped to tolerate chronic stress than males are. Still unclear is what protects female hippocampal cells from the damaging effects of chronic stress, but sex hormones very likely play a role.

## The Big Picture

EXTENDING THE WORK on how the brain handles and remembers stressful events, my colleagues and I have found contrasts in the way men and women lay down memories of emotionally arousing incidents—a process known from animal research to involve activation of the amygdala. In one of our first experiments with human subjects, we showed volunteers a series of graphically violent films while we measured their brain activity using PET. A few weeks later we gave them a quiz to see what they remembered.

We discovered that the number of disturbing films they could recall correlated with how active their amygdala had been during the viewing. Subsequent work from our laboratory and others confirmed this general finding. But then I noticed something strange. The amygdala activation in some studies involved only the right hemisphere, and in others it involved only the left hemisphere. It was then I realized that the experiments in which the right amygdala lit up involved only men; those in which the left amygdala was fired up involved women. Since then, three subsequent studies—two from our group and one from John Gabrieli and Turhan Canli and their collaborators at Stanford—have confirmed this difference in how the brains of men and women handle emotional memories.

The realization that male and female brains were processing the same emotionally arousing material into memory differently led us to wonder what this disparity might mean. To address this question, we turned to a century-old theory stating that the right hemisphere is biased toward processing the central aspects of a situation, whereas the left hemisphere tends to process the finer details. If that conception is true, we reasoned, a drug that dampens the activity of the amygdala should impair a man's ability to recall the gist of an emotional story (by hampering the right amygdala) but should hinder a woman's ability to come up with the precise details (by hampering the left amygdala).

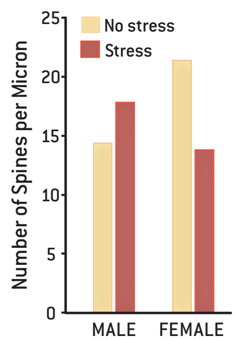
Propranolol is such a drug. This so-called beta blocker quiets the activity of adrenaline and its cousin noradrenaline and, in so doing, dampens the activation of the amygdala and weakens recall of emotionally arousing memories. We gave this drug to men and women before they viewed a short slide show about a young boy caught in a terrible accident while walking with his mother. One week later we tested their memory. The results showed that propranolol made it harder for men to remember the more holistic aspects, or gist, of the story—that the boy had been run over by a car, for example. In women, propranolol did the

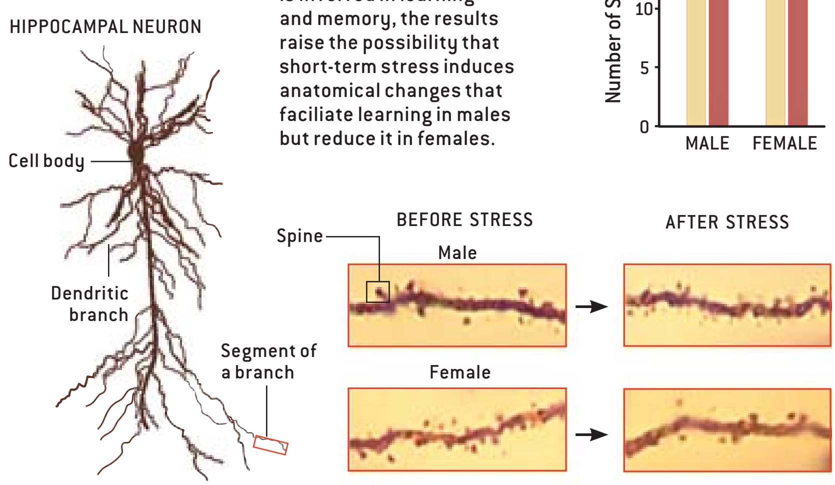
## THE STRESSED HIPPOCAMPUS

**The hippocampus in male rats reacts differently to both acute and chronic stress than does the same structure in females.**

### ACUTE STRESS

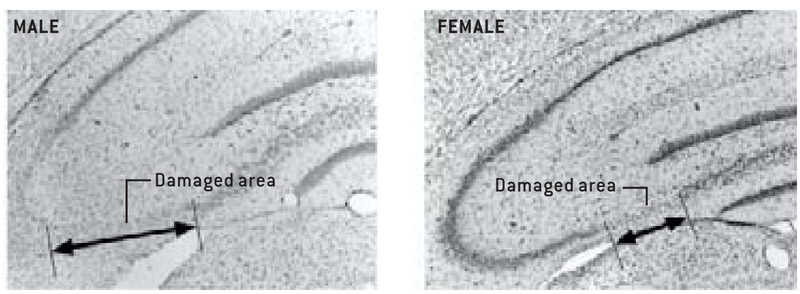
Short-term stress caused the density of dendritic "spines" in hippocampal neurons to increase in males but to decrease in females (*micrographs* and *graph*) studied by Tracey J. Shors of Rutgers University and her colleagues. The spines are the sites where dendrites receive excitatory signals from other neurons. Because the hippocampus is involved in learning and memory, the results raise the possibility that short-term stress induces anatomical changes that faciliate learning in males but reduce it in females.




### CHRONIC STRESS

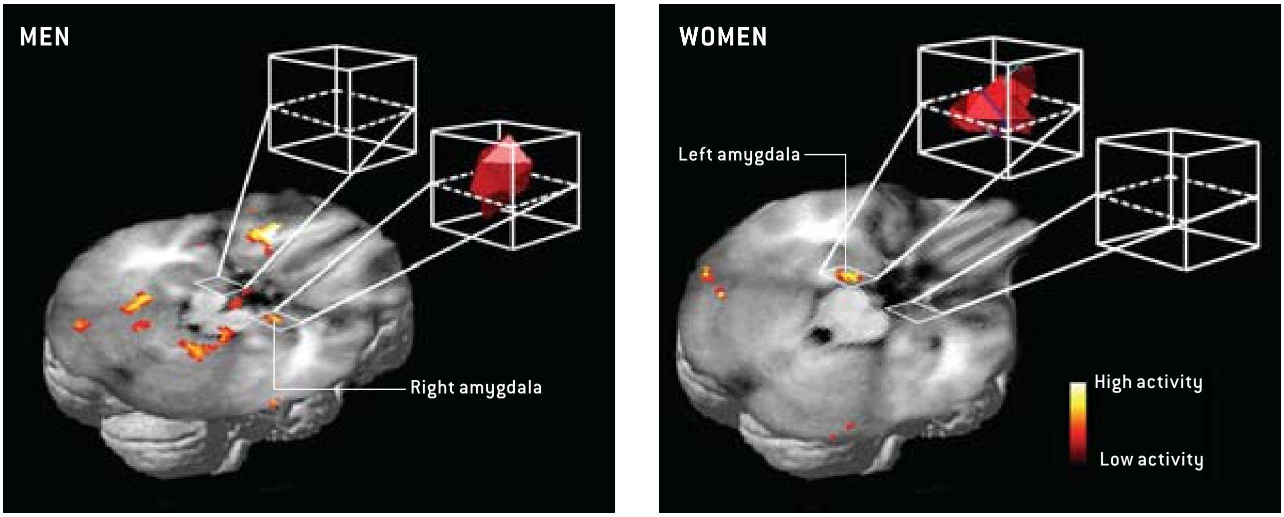
Long-lasting stress, in contrast, may leave the male hippocampus more vulnerable to harm. When Cheryl D. Conrad, J. L. Jackson and L. S. Wise of Arizona State University exposed chronically stressed rats to a nerve toxin, males, but not females, suffered more damage than same-sex controls did. The micrographs below are from stressed subjects.




SOURCE: T. J. SHORS, J. FALDUTO AND B. LEUNER IN *EUROPEAN JOURNAL OF NEUROSCIENCE*, VOL. 19, PAGES 145–150; JANUARY 2004 (*top*);
SOURCE: CHERYL D. CONRAD *Arizona State University* (*bottom*)

## THE AMYGDALA AND EMOTIONAL MEMORY

In research by the author and his collaborators, the amygdala, crucial for memory of emotional events, reacted differently in men and women who viewed emotionally arousing slides, such as of a decaying animal. Men who reported strong responses showed greatest activity in the right hemisphere amygdala (*left scan* and *schematic*) and the most accurate recall two weeks later, whereas the women who felt most worked up and showed the best recall displayed greatest activity in the left amygdala (*right panel*). Further studies by the team suggest that the hemispheric sex differences in amygdala activity cause women to be more likely to retain details of an emotional event and men more likely to remember its gist.




converse, impairing their memory for peripheral details—that the boy had been carrying a soccer ball.

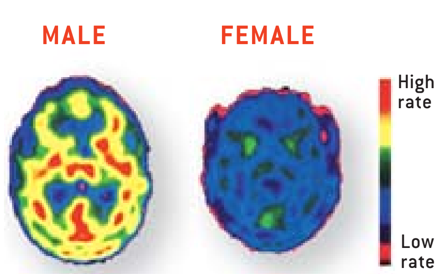
In more recent investigations, we found that we can detect a hemispheric difference between the sexes in response to emotional material almost immediately. Volunteers shown emotionally unpleasant photographs react within 300 milliseconds—a response that shows up as a spike on a recording of the brain's electrical activity. With Antonella Gasbarri and others at the University of L'Aquila in Italy, we have found that in men, this quick spike, termed a P300 response, is more exaggerated when recorded over the right hemisphere; in women, it is larger when recorded over the left. Hence, sex-related hemispheric disparities in how the brain processes emotional images begin within 300 milliseconds—long before people have had much, if any, chance to consciously interpret what they have seen.

These discoveries might have ramifications for the treatment of PTSD. Previous research by Gustav Schelling and his associates at Ludwig Maximilian University in Germany had established that drugs such as propranolol diminish memory for traumatic situations when administered as part of the usual therapies in an intensive care unit. Prompted by our findings, they found that, at least in such units, beta blockers reduce memory for traumatic events in women but not in men. Even in intensive care, then, physicians may need to consider the sex of their patients when meting out their medications.

### Sex and Mental Disorders

PTSD IS NOT the only psychological disturbance that appears to play out differently in women and men. A PET study by Mirko Diksic and his colleagues at McGill University showed that serotonin production was a remarkable 52 percent higher on average in men than in women, which might help clarify why women are more prone to depression—a disorder commonly treated with drugs that boost the concentration of serotonin.

A similar situation might prevail in addiction. In this case, the neurotransmitter in question is dopamine—a chemical involved in the feelings of pleasure associated with drugs of abuse. Studying rats, Jill B. Becker and her fellow investigators at the University of Michigan at Ann Arbor discovered that in females, estrogen boosted the release of dopamine in brain regions important for regulating drug-seeking behavior. Furthermore, the hormone had long-lasting effects, making the female rats more likely to pursue cocaine weeks after last receiving the drug. Such differences in susceptibility—particularly to stimulants such as cocaine and amphetamine—could explain why women might be more vulner-




PET SCANS, such as those above made by Mirko Diksic and his colleagues at McGill University, reveal that the brains of males produce serotonin at a faster rate than those of females. Serotonin influences mood, so the finding may help make sense of the observation that more women than men suffer depression.

able to the effects of these drugs and why they tend to progress more rapidly from initial use to dependence than men do.

Certain brain abnormalities underlying schizophrenia appear to differ in men and women as well. Ruben Gur, Raquel Gur and their colleagues at the University of Pennsylvania have spent years investigating sex-related differences in brain anatomy and function. In one project, they measured the size of the orbitofrontal cortex, a region involved in regulating emotions, and compared it with the size of the amygdala, implicated more in producing emotional reactions. The investigators found that women possess a significantly larger orbitofrontal-to-amygdala ratio (OAR) than men do. One can speculate from these findings that women might on average prove more capable of controlling their emotional reactions.

In additional experiments, the researchers discovered that this balance appears to be altered in schizophrenia, though not identically for men and women. Women with schizophrenia have a decreased OAR relative to their healthy peers, as might be expected. But men, oddly, have an increased OAR relative to healthy men. These findings remain puzzling, but, at the least, they imply that schizophrenia is a somewhat different disease in men and women and that treatment of the disorder might need to be tailored to the sex of the patient.

## A Gray Matter

Harvard University president Lawrence Summers struck a nerve in many people early this year when he raised the possibility that brain biology might help to explain why fewer women than men flourish in scientific careers. Nancy Hopkins, a biologist at the nearby Massachusetts Institute of Technology, was so offended by his musings that she walked out of the conference at which he was speaking.

What does the research say? Evidence linking inequities in anatomy to intellectual ability is hard to come by. For starters, sex differences in performance on standardized tests of general intelligence are negligible, with insignificant differences sometimes favoring women, sometimes favoring men. And although neuroscientists are discovering a multitude of sex-related differences in brain structure and function, no one can at present say whether these differences have any influence on career success in science—or, if they do, how their effect might compare with that of cultural factors.

LAWRENCE SUMMERS met a news crew this past February as he headed to a Harvard faculty meeting.

RICK FRIEDMAN *Corbis*

It is possible, however, that the brains of men and women might achieve their equivalent general intelligence in somewhat different ways. One recent study, for example, suggests that the sexes might use their brains differently when solving problems such as those found on intelligence tests. In this work, Richard Haier and his co-investigators at the University of California at Irvine and the University of New Mexico used a combination of MRI scanning and cognitive testing to develop maps that correlate gray-matter volume and white-matter volume in different parts of the brain with performance on IQ tests. Gray matter consists of the cell bodies of neurons that process information in the brain; white matter is made up of the axons through which one nerve cell relays information to another cell. The team found links between gray- or white-matter volume and test performance in both sexes, but the brain areas showing the correlations differed between men and women.

These findings have not yet been replicated. Even if they are, though, researchers will still have an unsolved question on their hands: What, if anything, might such differences have to do with how men and women reason? *—The Editors*

## Sex Matters

IN A COMPREHENSIVE 2001 report on sex differences in human health, the prestigious National Academy of Sciences asserted that "sex matters. Sex, that is, being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research."

Neuroscientists are still far from putting all the pieces together—identifying all the sex-related variations in the brain and pinpointing their influences on cognition and propensity for brain-related disorders. Nevertheless, the research conducted to date certainly demonstrates that differences extend far beyond the hypothalamus and mating behavior. Researchers and clinicians are not always clear on the best way to go forward in deciphering the full influences of sex on the brain, behavior and responses to medications. But growing numbers now agree that going back to assuming we can evaluate one sex and learn equally about both is no longer an option. SA

### MORE TO EXPLORE

**Sex Differences in the Brain.** Doreen Kimura in *Scientific American,* Vol. 267, No. 3, pages 118–125; September 1992.

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PHYSICS COULD SOON BE CREATING BLACK HOLES IN THE LABORATORY

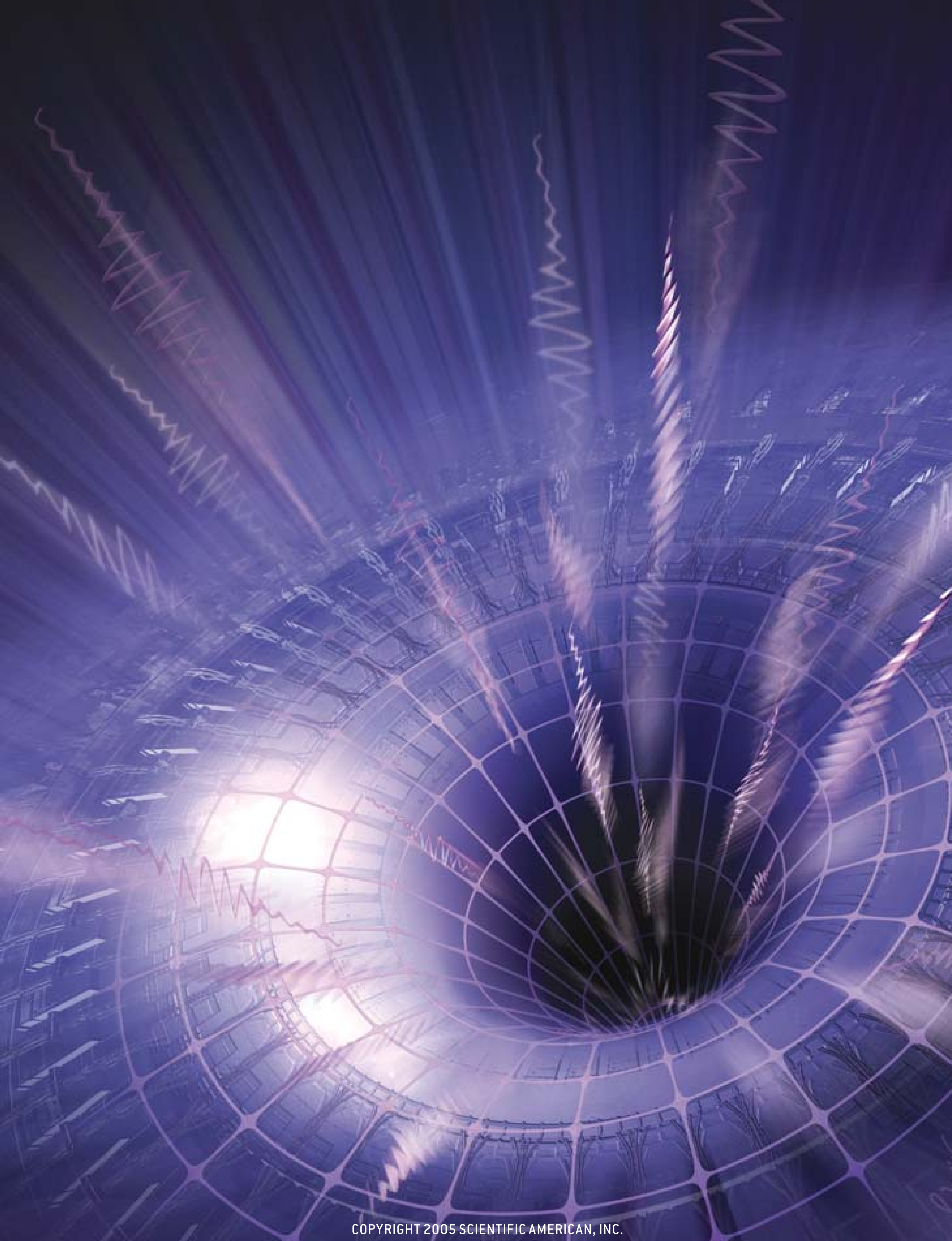
# QUANTUM BLACK HOLES

By Bernard J. Carr and Steven B. Giddings

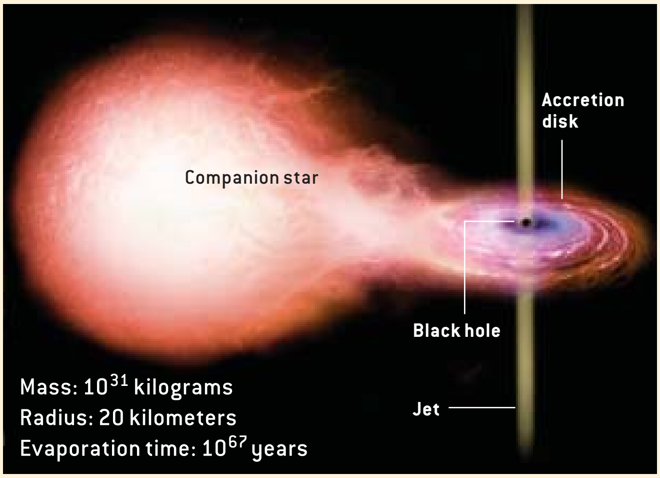
Ever since physicists invented particle accelerators, nearly 80 years ago, they have used them for such exotic tasks as splitting atoms, transmuting elements, producing antimatter and creating particles not previously observed in nature. With luck, though, they could soon undertake a challenge that will make those achievements seem almost pedestrian. Accelerators may produce the most profoundly mysterious objects in the universe: black holes.

When one thinks of black holes, one usually envisions massive monsters that can swallow spaceships, or even stars, whole. But the holes that might be produced at the highest-energy accelerators—perhaps as early as 2007, when the Large Hadron Collider (LHC) at CERN near Geneva starts up—are distant cousins of such astrophysical behemoths. They would be microscopic, comparable in size to elementary particles. They would not rip apart stars, reign over galaxies or pose a threat to our planet, but in some respects their properties should be even more dramatic. Because of quantum effects, they

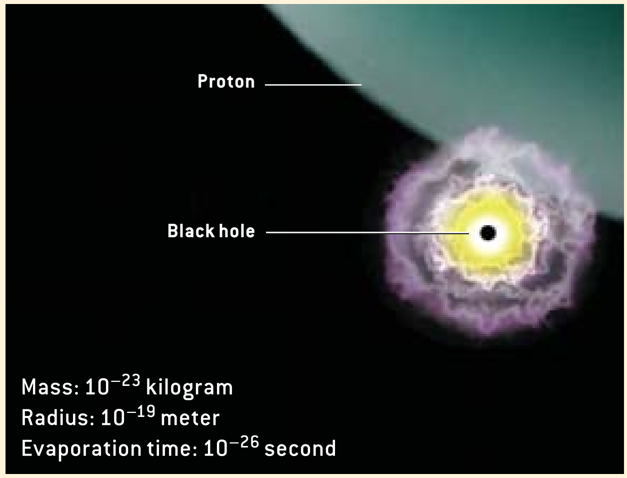
JEAN-FRANCOIS PODEVIN



## A TALE OF TWO BLACK HOLES




ASTROPHYSICAL BLACK HOLES are thought to be the corpses of massive stars that collapsed under their own weight. As matter falls into them, they act like cosmic hydroelectric plants, releasing gravitational potential energy—the only power source that can account for the intense x-rays and gaseous jets that astronomers see spurting out of celestial systems such as the x-ray binary shown here.




MICROSCOPIC BLACK HOLES have masses ranging up to that of a large asteroid. They might have been churned out by the collapse of matter early in the big bang. If space has unseen extra dimensions, they might also be created by energetic particle collisions in today's universe. Rather than swallowing matter, they would give off radiation and decay away rapidly.

DON DIXON

would evaporate shortly after they formed, lighting up the particle detectors like Christmas trees. In so doing, they could give clues about how spacetime is woven together and whether it has unseen higher dimensions.

### A Tight Squeeze

IN ITS MODERN FORM, the concept of black holes emerges from Einstein's general theory of relativity, which predicts that if matter is sufficiently compressed, its gravity becomes so strong that it carves out a region of space from which nothing can escape. The boundary of the region is the black hole's event horizon: objects can fall in, but none can come out. In the simplest case, where space has no hidden dimensions or those dimensions are smaller than the hole, its size is directly proportional to its mass. If you compressed the sun to a radius of three kilometers, about four-millionths of its present size, it would become a black hole. For Earth to meet the same fate, you would need to squeeze it into a radius of nine millimeters, about a billionth its present size.

Thus, the smaller the hole, the higher the degree of compression that is required to create it. The density to which matter must be squeezed scales as the inverse square of the mass. For a hole with the mass of the sun, the density is about $10^{19}$ kilograms per cubic meter, higher than that of an atomic nucleus. Such a density is about the highest that can be created through gravitational collapse in the present universe. A body lighter than the sun resists collapse because it gets stabilized by repulsive quantum forces between subatomic particles. Observationally, the lightest black hole candidates are about six solar masses.

Stellar collapse is not the only way that holes might form, however. In the early 1970s Stephen W. Hawking of the University of Cambridge and one of us (Carr) investigated a mechanism for generating holes in the early universe. These are termed "primordial" black holes. As space expands, the average density of matter decreases; therefore, the density was much higher in the past, in particular exceeding nuclear levels within the first microsecond of the big bang. The known laws of physics allow for a matter density up to the so-called Planck value of $10^{97}$ kilograms per cubic meter—the density at which the strength of gravity becomes so strong that quantum-mechanical fluctuations should break

## Overview/*Black Hole Factories*

- Black holes need not be gargantuan, ravenous monsters. Theory implies that they can come in a huge variety of sizes, some even smaller than subatomic particles. Tiny holes should be wracked by quantum effects, and the very smallest would explode almost as soon as they formed.
- Small black holes might be left over from the early stages of the big bang, and astronomers might be able to detect some of them exploding today.
- Theorists have recently proposed that small black holes might be created in collisions in the present universe, even on Earth. They had thought that the requisite energies were too high, but if space has extra dimensions with the right properties, then the energy threshold for black hole production is much lower. If so, holes might be produced by the Large Hadron Collider (LHC) at CERN and in cosmic-ray collisions high in the atmosphere. Physicists could use the holes to probe the extra dimensions of space.

down the fabric of spacetime. Such a density would have been enough to create black holes a mere $10^{-35}$ meter across (a dimension known as the Planck length) with a mass of $10^{-8}$ kilogram (the Planck mass).

This is the lightest possible black hole according to conventional descriptions of gravity. It is much more massive but much smaller in size than an elementary particle. Progressively heavier primordial black holes could have formed as the cosmic density fell. Any lighter than $10^{12}$ kilograms would still be smaller than a proton, but beyond this mass the holes would be as large as more familiar physical objects. Those forming during the epoch when the cosmic density matched nuclear density would have a mass comparable to the sun's and so would be macroscopic.

The high densities of the early universe were a prerequisite for the formation of primordial black holes but did not guarantee it. For a region to stop expanding and collapse to a black hole, it must have been denser than average, so density fluctuations were also necessary. Astronomers know that such fluctuations existed, at least on large scales, or else structures such as galaxies and clusters of galaxies would never have coalesced. For primordial black holes to form, these fluctuations must have been stronger on smaller scales than on large ones, which is possible though not inevitable. Even in the absence of fluctuations, holes might have formed spontaneously at various cosmological phase transitions—for example, when the universe ended its early period of accelerated expansion, known as inflation, or at the nuclear density epoch, when particles such as protons condensed out of the soup of their constituent quarks. Indeed, cosmologists can place important constraints on models of the early universe from the fact that not too much matter ended up in primordial black holes.

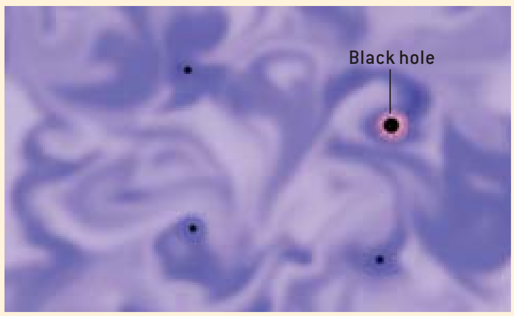
## Going, Going, Gone?

THE REALIZATION that holes could be small prompted Hawking to consider what quantum effects might come into play, and in 1974 he came to his famous conclusion that black holes do not just swallow particles but also spit them out [see "The Quantum Mechanics of Black Holes," by S. W. Hawking; SCIENTIFIC AMERICAN, January 1977]. Hawking predicted that a hole radiates thermally like a hot coal, with a temperature inversely proportional to its mass. For a solar-mass hole, the temperature is around a millionth of a kelvin, which is completely negligible in today's universe. But for a black hole of $10^{12}$ kilograms, which is about the mass of a mountain, it is $10^{12}$ kelvins—hot enough to emit both massless particles, such as photons, and massive ones, such as electrons and positrons.

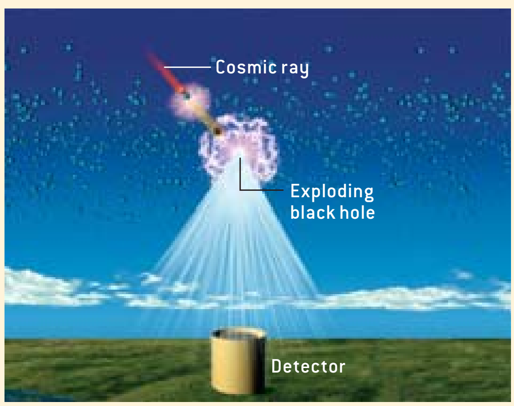
Because the emission carries off energy, the mass of the hole tends to decrease. So a black hole is highly unstable. As it shrinks, it gets steadily hotter, emitting increasingly energetic particles and shrinking faster and faster. When the hole shrivels to a mass of about $10^6$ kilograms, the game is up: within a second, it explodes with the energy of a million-megaton nuclear bomb. The total time for a black hole to evaporate away is proportional to the cube of its initial mass. For a solar-mass hole, the lifetime is an unobservably long $10^{64}$ years. For a $10^{12}$-kilogram one, it is $10^{10}$ years—about the present age of the universe. Hence, any primordial black holes of this mass would be completing their evaporation and exploding right now. Any smaller ones would have evaporated at an earlier cosmological epoch.

Hawking's work was a tremendous conceptual advance because it linked

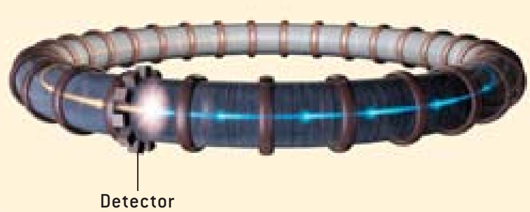
## WAYS TO MAKE A MINI BLACK HOLE




**PRIMORDIAL DENSITY FLUCTUATIONS**
Early in the history of our universe, space was filled with hot, dense plasma. The density varied from place to place, and in locations where the relative density was sufficiently high, the plasma could collapse into a black hole.



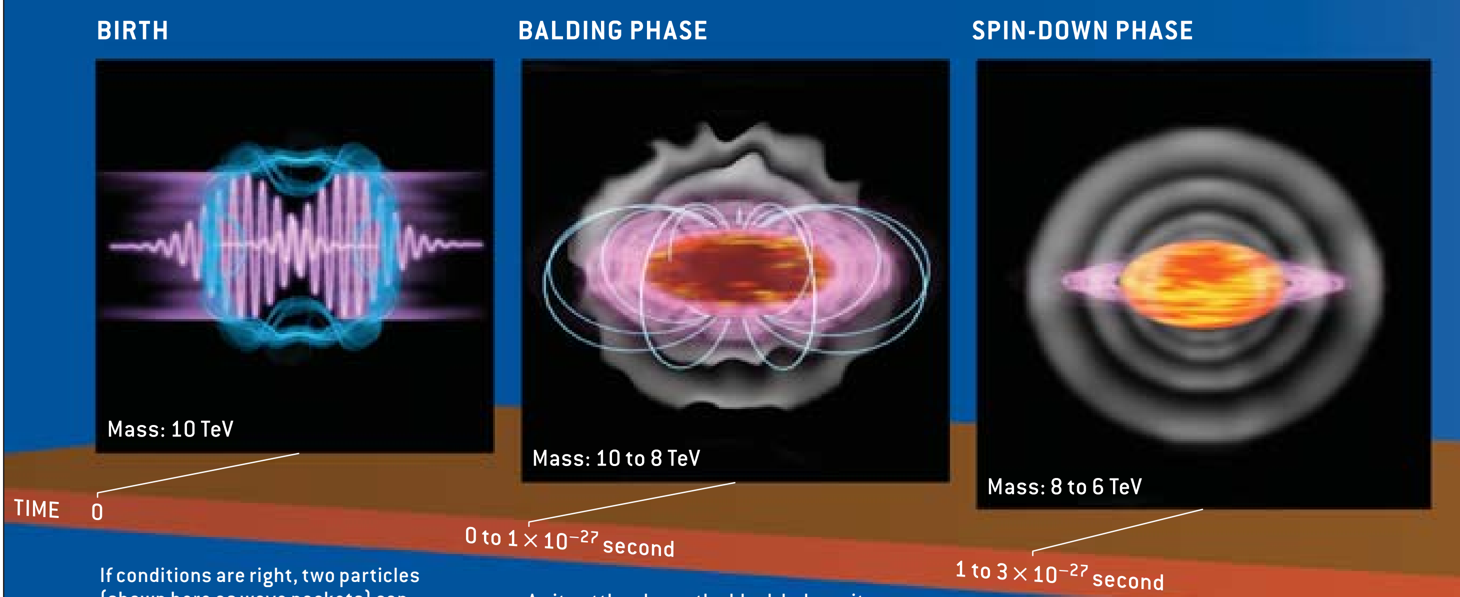

**COSMIC-RAY COLLISIONS**
Cosmic rays—highly energetic particles from celestial sources—could smack into Earth's atmosphere and form black holes. They would explode in a shower of radiation and secondary particles that could be detected on the ground.




**PARTICLE ACCELERATOR**
An accelerator such as the LHC could crash two particles together at such an energy that they would collapse into a black hole. Detectors would register the subsequent decay of the hole.

DON DIXON

## THE RISE AND DEMISE OF A QUANTUM BLACK HOLE




**BIRTH** — If conditions are right, two particles (shown here as wave packets) can collide to create a black hole. The newborn hole is asymmetrical. It can be rotating, vibrating and electrically charged. (Times and masses are approximate; 1 TeV is the energy equivalent of about $10^{-24}$ kilogram.)

**BALDING PHASE** — As it settles down, the black hole emits gravitational and electromagnetic waves. To paraphrase physicist John A. Wheeler, the hole loses its hair—it becomes an almost featureless body, characterized solely by charge, spin and mass. Even the charge quickly leaks away as the hole gives off charged particles.

**SPIN-DOWN PHASE** — The black hole is no longer black: it radiates. At first, the emission comes at the expense of spin, so the hole slows down and relaxes into a spherical shape. The radiation emerges mainly along the equatorial plane of the black hole.

DON DIXON

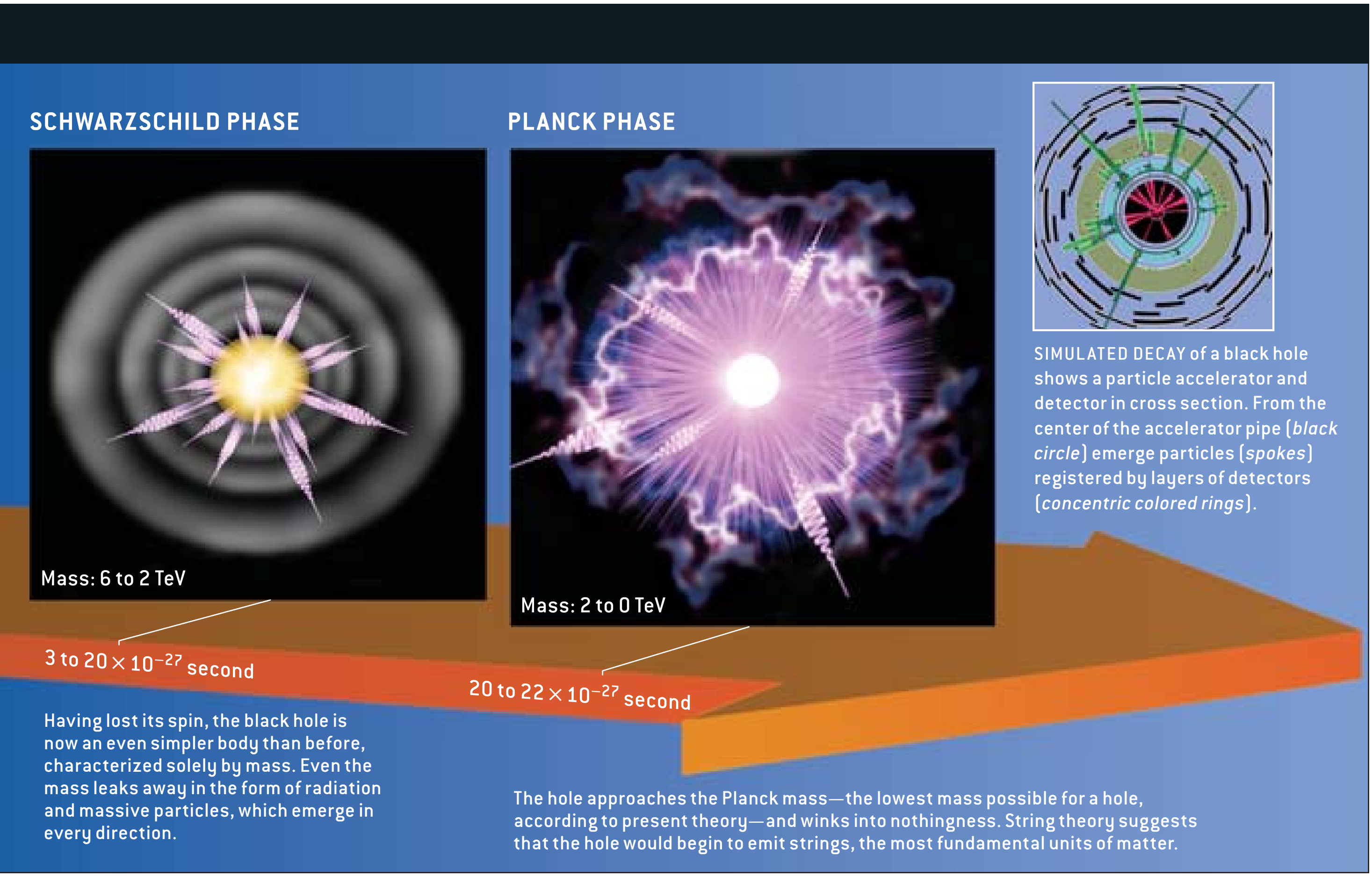
three previously disparate areas of physics: general relativity, quantum theory and thermodynamics. It was also a step toward a full quantum theory of gravity. Even if primordial black holes never actually formed, thinking about them has led to remarkable physical insights. So it can be useful to study something even if it does not exist.

In particular, the discovery opened up a profound paradox that aims at the heart of why general relativity and quantum mechanics are so hard to reconcile. According to relativity theory, information about what falls into a black hole is forever lost. If the hole evaporates, however, what happens to the information contained within? Hawking suggested that black holes completely evaporate, destroying the information—in contradiction with the tenets of quantum mechanics. Destruction of information conflicts with the law of energy conservation, making this scenario implausible.

One alternative, that black holes leave behind remnants, is equally unpalatable. For these remnants to encode all the information that could have gone into the black hole, they would have to come in an infinite variety of types. The laws of physics predict that the rate of production of a particle is proportional to the number of types of that particle. Therefore, the black hole remnants would be produced at an infinite rate; even such everyday physical processes as turning on a microwave oven would generate them. Nature would be catastrophically unstable. A third possibility is that locality—the notion that events at spatially separated points can influence one another only after light has had time to travel between them—fails. This conundrum challenges theorists to this day [see "Black Hole Computers," by Seth Lloyd and Y. Jack Ng; Scientific American, November 2004].

## Looking for Holes

PROGRESS IN PHYSICS usually requires some guidance from experiment, so the questions raised by microscopic black holes motivate an empirical search for them. One possibility is that astronomers might be able to detect primordial black holes with an initial mass of $10^{12}$ kilograms exploding in the present universe. Most of the mass of these holes would go into gamma rays. In 1976 Hawking and Don Page, then at the California Institute of Technology, realized that gamma-ray background observations place stringent upper limits on the number of such holes. They could not, for example, constitute a significant amount of the universe's dark matter, and their explosions would rarely be close enough to be detectable. In the mid-1990s, however, David Cline of the University of California at Los Angeles and his colleagues suggested that the shortest gamma-ray bursts might be primordial black holes blowing up. Although longer bursts are thought to be associated with exploding or merging stars, the short events may have another explanation. Future observations should settle this issue, but the possibility that astronomical




SIMULATED DECAY of a black hole shows a particle accelerator and detector in cross section. From the center of the accelerator pipe (*black circle*) emerge particles (*spokes*) registered by layers of detectors (*concentric colored rings*).

C. M. HARRIS *University of Cambridge* AND THE ATLAS COLLABORATION (*far right*)

observations could probe the final stages of black hole evaporation is tantalizing.

The production of black holes by particle accelerators is an even more exciting possibility. When it comes to producing high densities, no device outdoes accelerators such as the LHC and the Tevatron at the Fermi National Accelerator Laboratory near Chicago. These machines accelerate subatomic particles, such as protons, to velocities exceedingly close to the speed of light. The particles then have enormous kinetic energies. At the LHC, a proton will reach an energy of roughly seven tera-electron volts (TeV). In accord with Einstein's famous relation $E = mc^2$, this energy is equivalent to a mass of $10^{-23}$ kilogram, or 7,000 times the proton's rest mass. When two such particles collide at close range, their energy is concentrated into a tiny region of space. So one might guess that, once in a while, the colliding particles will get close enough to form a black hole.

As it stands, this argument has a problem: a mass of $10^{-23}$ kilogram is far shy of the Planck value of $10^{-8}$ kilogram, which conventional gravity theory implies is the lightest possible hole. This lower limit arises from the uncertainty principle of quantum mechanics. Because particles also behave like waves, they are smeared out over a distance that decreases with increasing energy—at LHC energies, about $10^{-19}$ meter. So this is the smallest region into which a particle's energy can be packed. It allows for a density of $10^{34}$ kilograms per cubic meter, which is high but not high enough to create a hole. For a particle to be both energetic enough and compact enough to form a black hole, it must have the Planck energy, a factor of $10^{15}$ beyond the energy of the LHC. Although accelerators might create objects mathematically related to black holes (and according to some theorists have already done so), the holes themselves appear to lie out of reach.

## Reaching into Other Dimensions

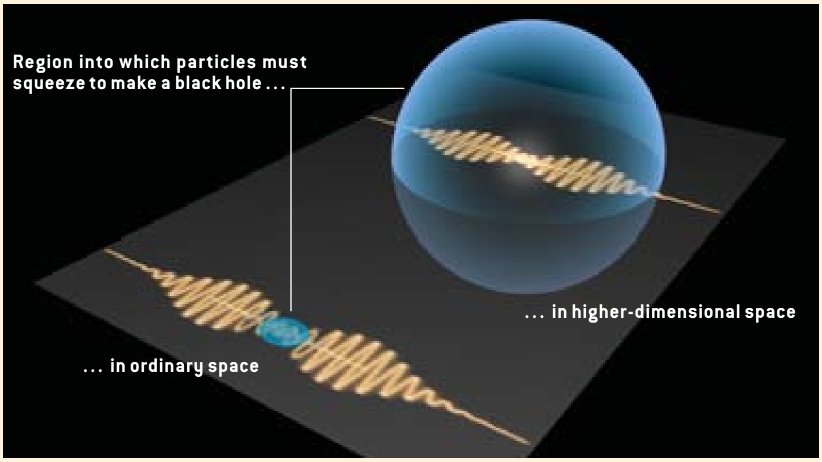
OVER THE PAST DECADE, however, physicists have realized that the standard estimate of the necessary Planckian density could be too high. String theory,

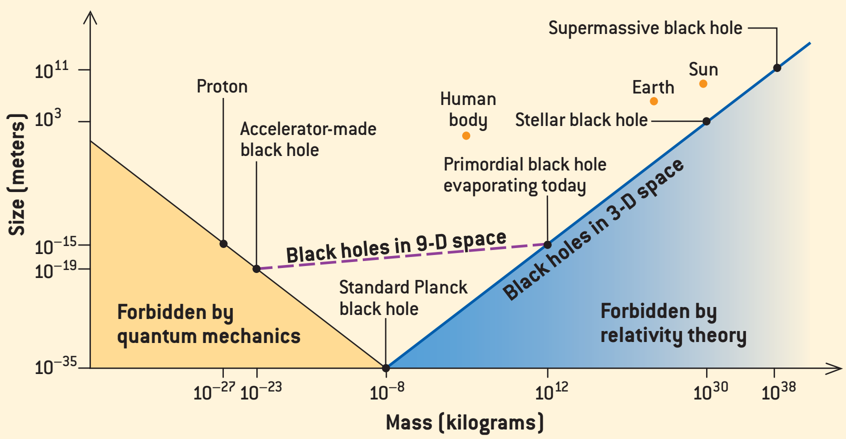
**THE AUTHORS**

*BERNARD J. CARR* and *STEVEN B. GIDDINGS* first met in person at a conference to celebrate Stephen W. Hawking's 60th birthday in 2002. Carr traces his enthusiasm for astrophysics to the famous 1969 BBC television documentary by Nigel Calder entitled "The Violent Universe." He became a graduate student of Hawking's in the 1970s, was one of the first scientists to investigate small black holes and today is a professor at Queen Mary, University of London. Giddings says he caught the physics bug when his father first told him about the weird properties of quantum mechanics. He went on to become an expert on quantum gravity and cosmology, was among the first to study the possibility of creating black holes in particle accelerators and is now a professor at the University of California, Santa Barbara. When not theorizing about gravity, he defies it by rock climbing.

## MAKING HOLES IS HARD TO DO

How much do you need to squeeze a piece of matter to turn it into a black hole? The lighter a body is, the more you must compress it before its gravity becomes strong enough to make a hole. Planets and people are farther from the brink than stars are (*graph*). The wave nature of matter resists compression; particles cannot be squeezed into a region smaller than their characteristic wavelength (*diagram*), suggesting that no hole could be smaller than $10^{-8}$ kilogram. But if space has extra dimensions, gravity would be inherently stronger over short distances and an object would not need to be squeezed as much, giving would-be hole makers hope that they might succeed in the near future.




one of the leading contenders for a quantum theory of gravity, predicts that space has dimensions beyond the usual three. Gravity, unlike other forces, should propagate into these dimensions and, as a result, grow unexpectedly stronger at short distances. In three dimensions, the force of gravity quadruples as you halve the distance between two objects. But in nine dimensions, gravity would get 256 times as strong. This effect can be quite important if the extra dimensions of space are sufficiently large, and it has been widely investigated in the past few years [see "The Universe's Unseen Dimensions," by Nima Arkani-Hamed, Savas Dimopoulos and Georgi Dvali; Scientific American, August 2000]. There are also other configurations of extra dimensions, known as warped compactifications, that have the same gravity-magnifying effect and may be even more likely to occur if string theory is correct.

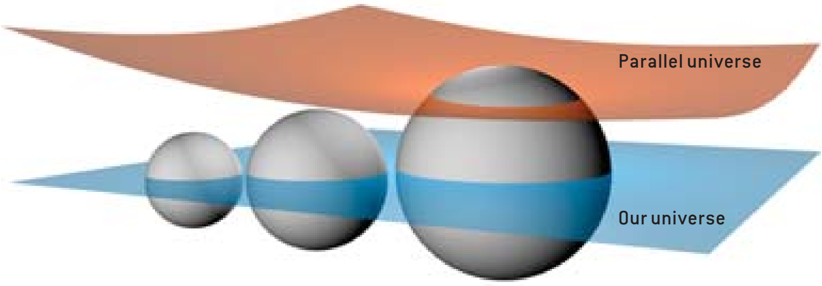
This enhanced growth of the strength of gravity means that the true energy scale at which the laws of gravity and quantum mechanics clash—and black holes can be made—could be much lower than its traditional value. Although no experimental evidence yet supports this possibility, the idea sheds light on numerous theoretical conundrums. And if it is true, the density required to create black holes could lie within the range of the LHC.

The theoretical study of black hole production in high-energy collisions goes back to the work of Roger Penrose of the University of Oxford in the mid-1970s and Peter D'Eath and Philip Norbert Payne, both then at Cambridge, in the early 1990s. The newfound possibility of large extra dimensions breathed new life into these investigations and motivated Tom Banks of the University of California at Santa Cruz and Rutgers University and Willy Fischler of the University of Texas to give a preliminary discussion in 1999.

At a 2001 workshop, two groups—one of us (Giddings) with Scott Thomas of Stanford University, and Savas Dimopoulos of Stanford with Greg Landsberg of Brown University—independently described what one would actually see at particle colliders such as the LHC. After a few calculations, we were astounded. Rough estimates indicated that under the most optimistic scenarios, corresponding to the lowest plausible value for the Planck scale, black holes could be produced at the rate of one per second. Physicists refer to an accelerator producing a particle at this rate as a "factory," so the LHC would be a black hole factory.

The evaporation of these holes would leave very distinctive imprints on the detectors. Typical collisions produce moderate numbers of high-energy particles, but a decaying black hole is different. According to Hawking's work, it radiates a large number of particles in all directions with very high energies. The decay products include all the particle species in nature. Several groups have since done increasingly detailed investigations into the remarkable signatures that black holes would produce in the detectors at the LHC.

DON DIXON; JANA BRENNING (*graph*)




BLACK HOLES OF DIFFERENT SIZES could probe extra dimensions that are otherwise inaccessible to us. Because gravity, unlike other forces, extends into those dimensions, so do black holes. Physicists would vary their size by tuning the particle accelerator to different energies. If a hole intersects a parallel universe, it will decay faster and appear to give off less energy (because some of the energy is absorbed by that other universe).

## Is it Raining Black Holes?

THE PROSPECT of producing black holes on Earth may strike some as folly. How do we know that they would safely decay, as Hawking predicted, instead of continuing to grow, eventually consuming the entire planet? At first glance, this seems like a serious concern, especially given that some details of Hawking's original argument may be incorrect—specifically the claim that information is destroyed in black holes. But it turns out that general quantum reasoning implies that microscopic black holes cannot be stable and therefore are safe. Concentrations of mass energy, such as elementary particles, are stable only if a conservation law forbids their decay; examples include the conservation of electric charge and of baryon number (which, unless it is somehow violated, assures the stability of protons). There is no such conservation law to stabilize a small black hole. In quantum theory, anything not expressly forbidden is compulsory, so small black holes will rapidly decay, in accord with the second law of thermodynamics.

Indeed, an empirical argument corroborates that black hole factories would pose no danger. High-energy collisions such as those at the LHC have already taken place—for example, in the early universe and even now, when sufficiently high energy cosmic rays hit our atmosphere. So if collisions at LHC energies can make black holes, nature has already been harmlessly producing them right over our heads. Early estimates by Giddings and Thomas indicated that the highest-energy cosmic rays—protons or heavier atomic nuclei with energies of up to $10^9$ TeV—could produce as many as 100 black holes in the atmosphere a year.

In addition, they—along with David Dorfan of U.C. Santa Cruz and Tom Rizzo of the Stanford Linear Accelerator Center and, independently, Jonathan L. Feng of the University of California at Irvine and Alfred D. Shapere of the University of Kentucky—have discovered that collisions of cosmic neutrinos might be even more productive. If so, the new Auger cosmic-ray observatory in Argentina, which is now taking data, and the upgraded Fly's Eye observatory in Utah may be able to see upward of several holes a year. These observations, however, would not obviate the need for accelerator experiments, which could generate holes more reliably, in greater numbers and under more controlled circumstances.

Producing black holes would open up a whole new frontier of physics. Their mere presence would be proof positive of the previously hidden dimensions of space, and by observing their properties, physicists might begin to explore the geographic features of those dimensions. For example, as accelerators manufacture black holes of increasing mass, the holes would poke further into the extra dimensions and could become comparable in size to one or more of them, leading to a distinctive change in the dependence of a hole's temperature on mass. Likewise, if a black hole grows large enough to intersect a parallel three-dimensional universe in the extra dimensions, its decay properties would suddenly change.

Producing black holes in accelerators would also represent the end of one of humankind's historic quests: understanding matter on ever finer scales. Over the past century, physicists have pushed back the frontier of the small—from dust motes to atoms to protons and neutrons to quarks. If they can create black holes, they will have reached the Planck scale, which is believed to be the shortest meaningful length, the limiting distance below which the very notions of space and length probably cease to exist. Any attempt to investigate the possible existence of shorter distances, by performing higher-energy collisions, would inevitably result in black hole production. Higher-energy collisions, rather than splitting matter into finer pieces, would simply produce bigger black holes. In this way, the appearance of black holes would mark the close of a frontier of science. In its place, however, would be a new frontier, that of exploring the geography of the extra dimensions of space. SA

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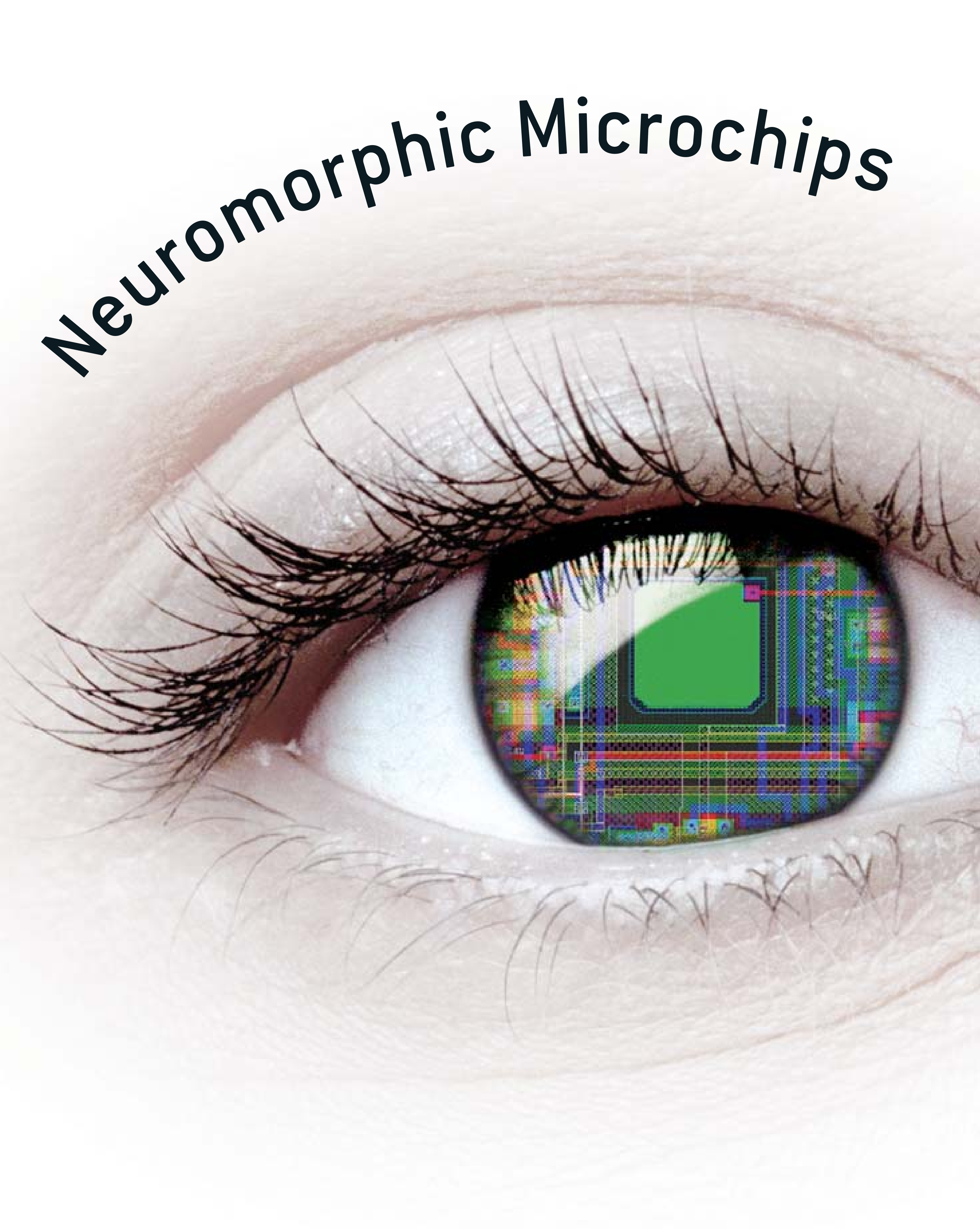
DON DIXON

# Neuromorphic Microchips



**Compact, efficient electronics based on the brain's neural system could yield implantable silicon retinas to restore vision, as well as robotic eyes and other smart sensors**

**BY KWABENA BOAHEN**

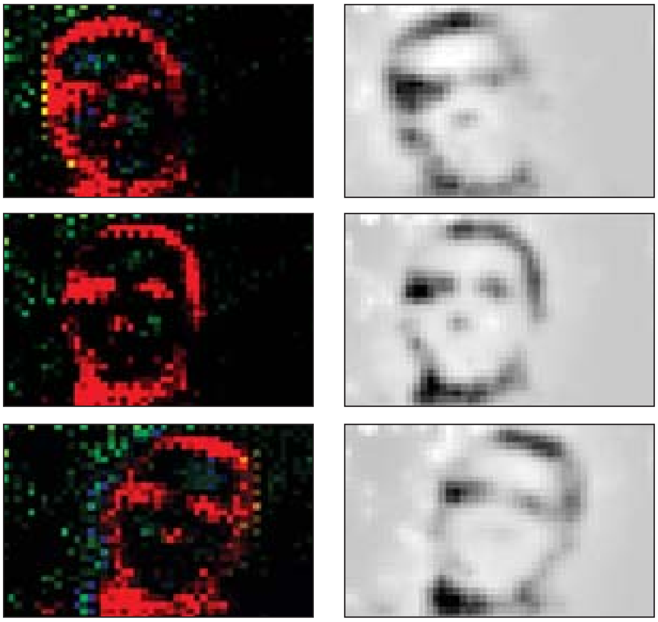
When IBM's Deep Blue supercomputer edged out world chess champion Garry Kasparov during their celebrated match in 1997, it did so by means of sheer brute force. The machine evaluated some 200 million potential board moves a second, whereas its flesh-and-blood opponent considered only three each second, at most. But despite Deep Blue's victory, computers are no real competition for the human brain in areas such as vision, hearing, pattern recognition, and learning. Computers, for instance, cannot match our ability to recognize a friend from a distance merely by the way he walks. And when it comes to operational efficiency, there is no contest at all. A typical room-size supercomputer weighs roughly 1,000 times more, occupies 10,000 times more space and consumes a millionfold more power than does the cantaloupe-size lump of neural tissue that makes up the brain.

How does the brain—which transmits chemical signals between neurons in a relatively sluggish thousandth of a second—end up performing some tasks faster and more efficiently than the most powerful digital processors? The secret appears to reside in how the brain organizes its slow-acting electrical components.

The brain does not execute coded instructions; instead it activates links, or synapses, between neurons. Each such activation is equivalent to executing a digital instruction, so one can compare how many connections a brain activates every second with the number of instructions a computer executes during the same time. Synaptic activity is staggering: 10 quadrillion ($10^{16}$) neural connections a second. It would take a million Intel Pentium-powered computers to match that rate—plus a few hundred megawatts to juice them up.

Now a small but innovative community of engineers is making significant progress in copying neuronal organization and function. Researchers speak of having "morphed" the structure of neural connections into silicon circuits, creating neuromorphic microchips. If successful, this work could lead to implantable silicon retinas for the blind and sound processors for the deaf that last for 30 years on a single nine-volt battery

IMPLANTABLE SILICON RETINA, shown in this artist's conception, could emulate the eye's natural function, restoring vision for patients with certain types of blindness.



SILICON RETINA senses the side-to-side head movements of University of Pennsylvania researcher Kareem Zaghloul. The four types of silicon ganglion cells on his Visio1 chip emulate real retinal cells' ability to preprocess visual information without huge amounts of computation. One class of cells responds to dark areas (*red*), whereas another reacts to light regions (*green*). A different set of cells tracks leading edges of objects (*yellow*) and trailing edges (*blue*). The gray-scale images, generated by decoding these messages, show what a blind person would see with neuromorphic retinal implants.

or to low-cost, highly effective visual, audio or olfactory recognition chips for robots and other smart machines [*see box on opposite page*].

Our team at the University of Pennsylvania initially focused on morphing the retina—the half-millimeter-thick sheet of tissue that lines the back of the eye. Comprising five specialized layers of neural cells, the retina "preprocesses" incoming visual images to extract useful information without the need for the brain to expend a great deal of effort. We chose the retina because that sensory system has been well documented by anatomists. We then progressed to morphing the developmental machinery that builds these biological circuits—a process we call metamorphing.

## Neuromorphing the Retina

THE NEARLY ONE MILLION ganglion cells in the retina compare visual signals received from groups of half a dozen to several hundred photoreceptors, with each group interpreting what is happening in a small portion of the visual field. As features such as light intensity change in a given sector, each ganglion cell transmits pulses of electricity (known as spikes) along the optic nerve to the brain. Each cell fires in proportion to the relative change in light intensity over time or space—not to the absolute input level. So the nerve's sensitivity wanes with growing overall light intensity to accommodate, for example, the five-decade rise in the sky's light levels observed from predawn to high noon.

Misha A. Mahowald, soon after earning her undergraduate biology degree, and Carver Mead, the renowned microelectronics technologist, pioneered efforts to reproduce the retina in silicon at the California Institute of Technology. In their groundbreaking work, Mahowald and Mead reproduced the first three of the retina's five layers electronically ["The Silicon Retina," by Misha A. Mahowald and Carver Mead; SCIENTIFIC AMERICAN, May 1991]. Other researchers, several of whom passed through Mead's Caltech laboratory (the author included), have morphed succeeding stages of the visual system as well as the auditory system. Kareem Zaghloul morphed all five layers of the retina in 2001 when he was a doctoral student in my lab, making it possible to emulate the visual messages that the ganglion cells, the retina's output neurons, send to the brain. His silicon retina chip, Visio1, replicates responses of the retina's four major types of ganglion cells, which feed into and together make up 90 percent of the optic nerve [*see illustration on this page*].

Zaghloul represented the electrical activity of each neuron in the eye's circuitry by an individual voltage output. The voltage controls the current that is conveyed by transistors connected between a given location in the circuit and other points, mimicking how the body modulates the responses of neural synapses. Light detected by electronic photosensors affects the voltage in that part of the circuit in a way that is analogous to how it affects a corresponding cell in the retina. And by tiling copies of this basic circuit on his chip, Zaghloul replicated the activity in the retina's five cell layers [*see box on page 60*].

The chip emulates the manner in which voltage-activated ion channels cause ganglion cells (and neurons in the rest of the brain) to discharge spikes. To accomplish this, Zaghloul installed transistors that send current back onto the same location in the circuit. When this feedback current arrives, it increases the voltage further, which in turn recruits more feedback current and causes additional amplification. Once a certain initial level is reached, this regenerative effect accelerates, taking the

## Overview/*Inspired by Nature*

- Today's computers can perform billions of operations per second, but they are still no match for even a young child when it comes to skills such as pattern recognition or visual processing. The human brain is also millions of times more energy-efficient and far more compact than a typical personal computer.
- Neuromorphic microchips, which take cues from neural structure, have already demonstrated impressive power reductions. Their efficiency may make it possible to develop fully implantable artificial retinas for people afflicted by certain types of blindness as well as better electronic sensors.
- Someday neuromorphic chips could even replicate the self-growing connections the brain uses to achieve its amazing functional capabilities.

STONE (*eye photograph*); KAREEM ZAGHLOUL (*retina layout*); JEN CHRISTIANSEN (*photoillustration*) (*preceding pages*); KAREEM ZAGHLOUL (*this page*)

## NEUROMORPHIC ELECTRONICS RESEARCH GROUPS

**Researchers seek to close the efficiency gap between electronic sensors and the body's neural networks with microchips that emulate the brain. This work focuses on small sensor systems that can be implanted in the body or installed in robots.**

| ORGANIZATION | INVESTIGATORS | PRINCIPAL OBJECTIVES |
|---|---|---|
| Johns Hopkins University | Andreas Andreou, Gert Cauwenberghs, Ralph Etienne-Cummings | Battery-powered speech recognizer, rhythm generator for locomotion and camera that extracts object features |
| ETH Zurich (University of Zurich) | Tobi Delbruck, Shi-Chii Liu, Giacomo Indiveri | Silicon retina and attention chip that automatically select salient regions in a scene |
| University of Edinburgh | Alan Murray, Alister Hamilton | Artificial noses and automatic odor recognition based on timing of signaling spikes |
| Georgia Institute of Technology | Steve DeWeerth, Paul Hasler | Coupled rhythm generators that coordinate a multisegmented robot |
| HKUST, Hong Kong | Bertram Shi | Binocular processor for depth perception and visual tracking |
| Massachusetts Institute of Technology | Rahul Sarpeshkar | Cochlea-based sound processor for implants for deaf patients |
| University of Maryland | Timothy Horiuchi | Sonar chip modeled on bat echolocation |
| University of Arizona | Charles Higgins | Motion-sensing chip based on fly vision |

voltage all the way to the highest level, resulting in a spike.

At 60 milliwatts, Zaghloul's neuromorphic chip uses 1,000 times less electricity than a PC. With its low power needs, this silicon retina could pave the way for a total intraocular prosthesis—with camera, processor and stimulator all implanted inside the eye of a blind person who has retinitis pigmentosa or macular degeneration, diseases that damage photoreceptors but spare the ganglion cells. Retinal prostheses currently being developed, for example at the University of Southern California, provide what is called phosphene vision—recipients perceive the world as a grid of light spots, evoked by stimulating the ganglion cells with microelectrodes implanted inside the eye—and require a wearable computer to process images captured by a video camera attached to the patient's glasses. Because the microelectrode array is so small (fewer than 10 pixels by 10 pixels), the patient experiences tunnel vision—head movements are needed to scan scenes.

Alternatively, using the eye itself as the camera would solve the rubbernecking problem, and our chip's 3,600 ganglion-cell outputs should provide near-normal vision. Biocompatible encapsulation materials and stimulation interfaces, however, need further refinement before a high-fidelity prosthesis becomes a reality, maybe by 2010. Better understanding of how various retinal cell types respond to stimulation and how they contribute to perception is also required. In the interim, such neuromorphic chips could find use as sensors in automotive or security applications or in robotic or factory automation systems.

### Metamorphing Neural Connections

THE POWER SAVINGS we attained by morphing the retina were encouraging, a result that started me thinking about how the brain actually achieves high efficiency. Mead was prescient when he recognized two decades ago that even if computing managed to continue along the path of Moore's law (which states that the number of transistors per square inch on integrated circuits doubles every 18 months), computers as we know them could not reach brainlike efficiency. But how could this be accomplished otherwise? The solution dawned on me eight years ago.

Efficient operation, I realized, comes from the degree to which the hardware is customized for the task at hand. Conventional computers do not allow such adjustments; the software is tailored instead. Today's computers use a few general-purpose tools for every job; software merely changes the order in which the tools are used. In contrast, customizing the hardware is something the brain and neuromorphic chips have in common—they are both programmed at the level of individual connections. They adapt the tool to the specific job. But how does the brain customize itself? If we could translate that mechanism into silicon—metamorphing—we could have our neuromorphic chips modify themselves in the same fashion. Thus, we would not need to painstakingly reverse-engineer the brain's circuits. I started investigating neural development, hoping to learn more about how the body produces exactly the tools it needs.

Building the brain's neural network—a trillion ($10^{12}$) neurons connected by 10 quadrillion ($10^{16}$) synapses—is a daunting task. Although human DNA contains the equivalent of a billion bits of information, that amount is not sufficient to specify where all those neurons should go and how they should connect. After employing its genetic information during early development, the brain customizes itself further through internal interactions among neurons and through external interactions with the world outside the body. In other words, sensory neurons wire themselves in response to sensory inputs. The overall rule that regulates this process is deceptively simple: neurons that fire together wire together. That is, out of all the signals that a neuron receives, it accepts those from neurons that are consistently active when it is active, and it ignores the rest.

To learn how one layer of neurons becomes wired to another, neuroscientists have studied the frog's retinotectal projection, which connects its retina to its tectum (the part of the midbrain that processes inputs from sensory organs). They have found that wiring one layer of neurons to another occurs in two stages. A newborn neuron extends projections ("arms") in a multilimbed arbor. The longest arm becomes the axon, the cell's output wire; the rest serve as dendrites, its input wires. The axon then continues to grow, towed by an amoeboid structure at its tip. This growth cone, as scientists call it, senses chemical gradients laid down by trailblazing precursors of neural communication signals, thus guiding the axon to the right street in the tectum's city of cells but not, so to speak, to the right house.

Narrowing the target down to the right house in the tectum requires a second step, but scientists do not understand this process in detail. It is well known, though, that neighboring retinal ganglion cells tend to fire together. This fact led me to speculate that an axon could find its retinal cell neighbors in the tectum by homing in on chemical scents released by active tectal neurons, because its neighbors were most likely at the source of this trail. Once the axon makes contact with the tectal neuron's dendritic arbor, a synapse forms between them and, voilà, the two neurons that fire together are wired together.

In 2001 Brian Taba, a doctoral student in my lab, built a chip modeled on this facet of the brain's developmental process. Because metal wires cannot be rerouted, he decided to reroute spikes instead. He took advantage of the fact that Zaghloul's Visio1 chip outputs a unique 13-bit address every time one of its 3,600 ganglion cells spikes. Transmitting addresses rather than spikes gets around the limited number of input/output pins that chips have. The addresses are decoded by the receiving chip, which re-creates the spike at the correct location in its silicon neuron mosaic. This technique produces a virtual bundle of axons running between corresponding locations in the two chips—a silicon optic nerve. If we substitute one address with another, we reroute a virtual axon belonging to one neuron (the original address) to another location (the substituted address). We can route these "softwires," as we call them, anywhere we want to by storing the substitutions in a database (a look-up table) and by using the original address to retrieve them [*see box on page 62*].

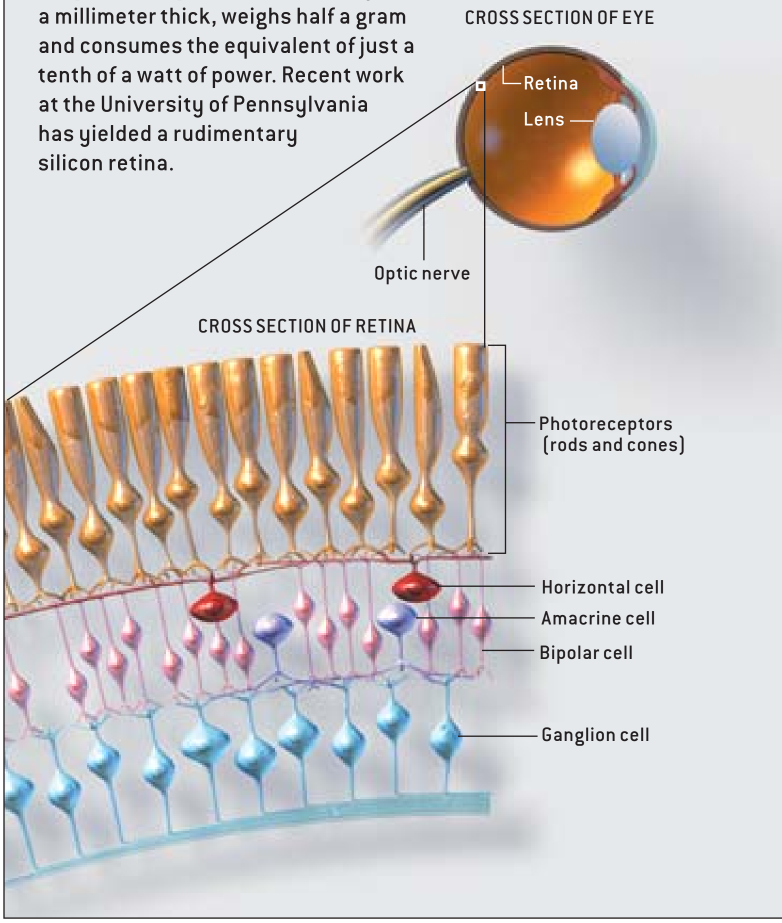
In Taba's artificial tectum chip, which he named Neurotrope1, softwires activate gradient-sensing circuits (silicon growth cones) as well as nearby silicon neurons, which are situated in the cells of a honeycomb lattice. When active, these silicon neurons release electrical charge into the lattice, which

**THE AUTHOR**

*KWABENA BOAHEN* is a neuromorphic engineer and associate professor of bioengineering at the University of Pennsylvania. He left his native Ghana to pursue undergraduate studies in electrical and computer engineering at Johns Hopkins University in 1985 and became interested in neural networks soon thereafter. Boahen sees a certain elegance in neural systems that is missing in today's computers. He seeks to capture this sophistication in his silicon designs.

## RETINAL

Biological sensory systems provide compact, energy-efficient models for neuromorphic electronic sensors. Engineers attempting to duplicate the retina in silicon face a tough challenge: the retina is only half a millimeter thick, weighs half a gram and consumes the equivalent of just a tenth of a watt of power. Recent work at the University of Pennsylvania has yielded a rudimentary silicon retina.




BRYAN CHRISTIE DESIGN; KAREEM ZAGHLOUL (*silicon retina*)

Taba designed to conduct charge like a transistor. Charge diffuses through the lattice much like the chemicals released by tectal cells do through neural tissue. The silicon growth cones sense this simulated diffusing "chemical" and drag their softwires up the gradient—toward the charge's silicon neuron source—by updating the look-up table. Because the charge must be released by the silicon neuron and sensed by the silicon growth cone simultaneously, the softwires end up connecting neurons that are active at the same time. Thus, Neurotrope1 wires together neurons that fire together, as would occur in a real growing axon.

Starting with scrambled wiring between the Visio1 chip and the Neurotrope1 chip, Taba successfully emulated the tendency of neighboring retinal ganglion cells to fire together by activating patches of silicon ganglion cells at random. After stimulating several thousand patches, he observed a dramatic change in the softwiring between the chips. Neighboring artificial ganglion cells now connected to neurons in the silicon tectum that were twice as close as the initial connections. Be-

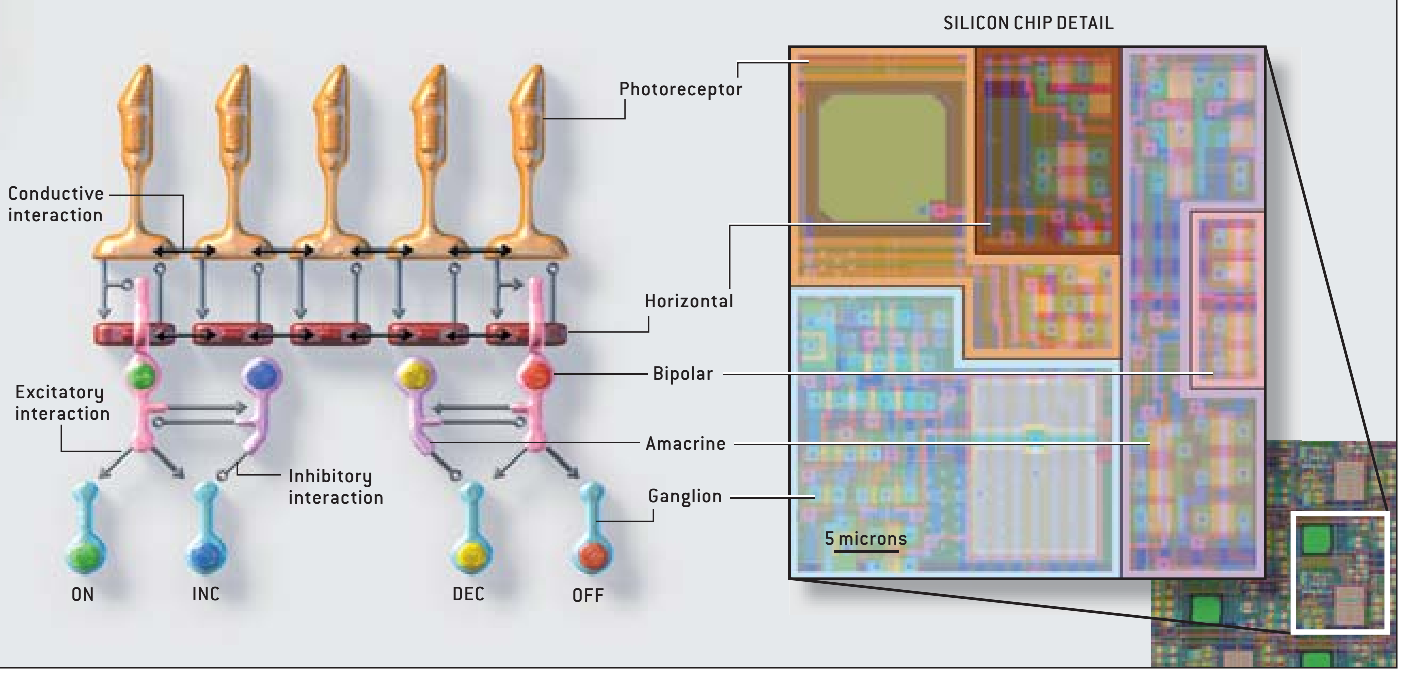
# NEURONS AND NEUROMORPHIC VISION CHIPS

### BIOLOGICAL RETINA

The cells in the retina, which are interconnected, extract information from the visual field by engaging in a complex web of excitatory (*one-way arrows*), inhibitory (*circles on a stick*), and conductive or bidirectional (*two-way arrows*) signaling. This circuitry generates the selective responses of the four types of ganglion cells (*at bottom*) that make up 90 percent of the optic nerve's fibers, which convey visual information to the brain. On (*green*) and Off (*red*) ganglion cells elevate their firing (spike) rates when the local light intensity is brighter or darker than the surrounding region. Inc (*blue*) and Dec (*yellow*) ganglion cells spike when the intensity is increasing or decreasing, respectively.

### SILICON RETINA

Neuromorphic circuits emulate the complex interactions that occur among the various retinal cell types by replacing each cell's axons and dendrites (signal pathways) with metal wires and each synapse with a transistor. Permutations of this arrangement produce excitatory and inhibitory interactions that mimic similar communications among neurons. The transistors and the wires that connect them are laid out on silicon chips. Various regions of the chip surface perform the functions of the different cell layers. The large green squares are phototransistors, which transduce light into electricity.




cause of noise and variability, however, the wiring was not perfect: terminals of neighboring cells in the silicon retina did not end up next to one another in the silicon tectum. We wondered how the elaborate wiring patterns thought to underlie biological cortical function arise—and whether we could get further tips from nature to refine our systems.

## Cortical Maps

TO FIND OUT, we had to take a closer look at what neuroscience has learned about connections in the cortex, the brain region responsible for cognition. With an area 16 inches in diameter, the cortex folds like origami paper to fit inside the skull. On this amazing canvas, "maps" of the world outside are drawn during infancy. The best-studied example is what scientists call area V1 (the primary visual cortex), where visual messages from the optic nerve first enter the cortex. Not only are the length and width dimensions of an image mapped onto V1 but also the orientation of the edges of objects therein. As a result, neurons in V1 respond best to edges oriented at a particular angle—vertical lines, horizontal lines, and so forth. The same orientation preferences repeat every millimeter or so, thereby allowing the orientations of edges in different sectors of the visual scene to be detected.

Neurobiologists David H. Hubel and Torsten N. Wiesel, who shared a Nobel Prize in medicine for discovering the V1 map in the 1960s, proposed a wiring diagram for building a visual cortex—one that we found intimidating. According to their model, each cortical cell wires up to two groups of thalamic cells, which act as relays for retinal signals bound for the cortex. One group of thalamic cells should respond to the sensing of dark areas (which we emulate with Visio1's Off cells), whereas the other should react to the sensing of light (like our Visio1's On cells). To make a cortical cell prefer vertical edges, for instance, both groups of cells should be set to lie along a vertical line but should be displaced slightly so the Off cells lie just to the left of the On cells. In that way, a vertical edge of an object in the visual field will activate all the Off cells and all the On cells when it is in the correct position. A horizontal edge, on the other hand, will activate only half the cells in each group. Thus, the cortical cell will receive twice as much input when a vertical edge is present and respond more vigorously.

At first we were daunted by the detail these wiring patterns required. We had to connect each cell according to its orientation preference and then modify these wiring patterns systematically so that orientation preferences changed smoothly, with neighboring cells having similar preferences. As in the cortex, the same orientations would have to be repeated every millimeter, with those silicon cells wired to neighboring locations in the retina. Taba's growth cones certainly could not cope with this complexity. In late 2002 we searched for a way to escape this nightmare altogether. Finally, we found an answer in a five-decade-old experiment.

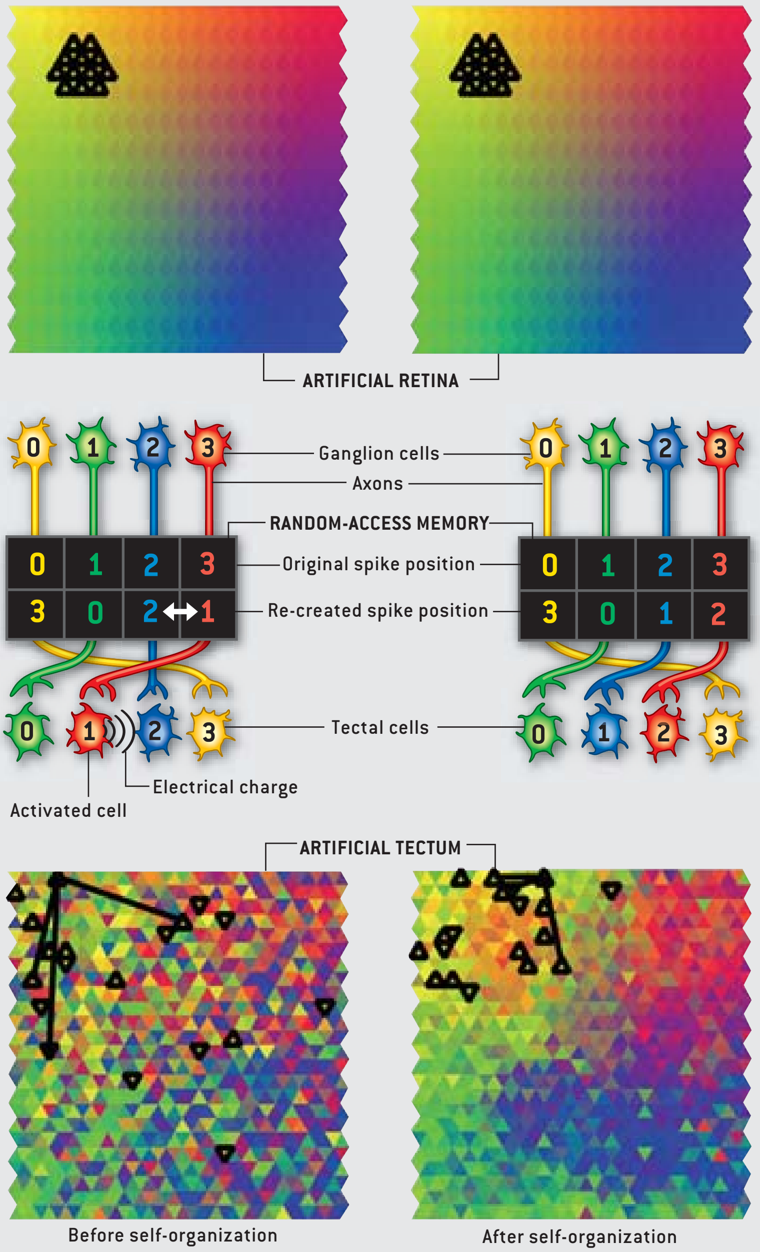
In the 1950s famed computer scientist Alan M. Turing showed how ordered patterns such as a leopard's spots or a cow's dapples could arise spontaneously from random noise. We hoped we could use a similar technique to create neighboring regions with similar orientation patterns for our chip. Turing's idea, which he tested by running simulations on one of the first electronic computers at the University of Manchester, was that modeled skin cells would secrete "black dye" or

## MAKING CONNECTIONS (BIOLOGICAL OR SILICON)

In the early stages of the eye's development, ganglion cells in the retina project axons into a sensory center of the midbrain called the tectum. The retinal axons home in on chemical trails released by neighboring tectal cells that are activated at the same time, so neurons that fire together wire together. Ultimately, a map of the retinal sensors' spatial organization forms in the midbrain.

To emulate this process, University of Pennsylvania neuromorphic engineers use "softwires" to self-organize links between cells in their silicon retina chip, Visio1 (*top*), and those in their artificial tectum chip, Neurotrope1 (*bottom*). Electrical output pulses called spikes are "routed" from the artificial ganglion cells to the tectal cells using a random-access memory (RAM) chip (*middle*). The retinal chip supplies the address of the spiking silicon neuron, and the tectal chip re-creates that pulse at the corresponding location. In this example, the artificial tectum instructs the RAM to swap address entries 1 and 2. As a result, ganglion cell 2's axon terminus moves to tectal cell 1, bumping ganglion cell 3's axon from that location. The axons "sense" the gradient of electrical charge released by an activated silicon tectal cell, which helps to guide the connections.

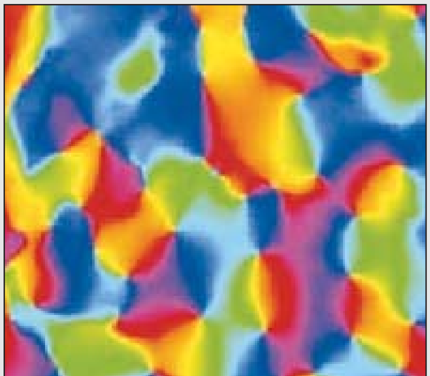
After engineers repeatedly activated patches of neighboring silicon neurons in the artificial retina (*outlined triangles, top left*), the tectal cells' axon end points—which were initially widely distributed (*outlined triangles, bottom left*)—grew closer, yielding more uniform swaths on a colorized map (*bottom right*).



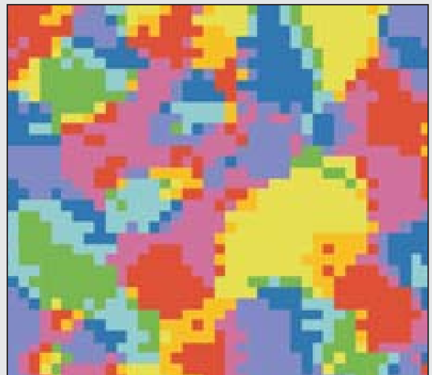

BRIAN TABA AND JEN CHRISTIANSEN

## ORIENTATION PREFERENCES IN THE BRAIN AND IN SILICON

In both the visual cortex of a ferret (*left*) and a neuromorphic cortex chip (*right*), researchers have mapped the location of cells that respond preferentially to object edges of a certain orientation (*key, below*). In both maps, neighboring cells tend to have similiar orientation preferences, which shows that the cortex chip emulates the biological system.



FERRET CORTEX



CORTEX CHIP

MARCOS FRANK (*ferret*); PAUL MEROLLA (*chip*)

"bleach" indiscriminately. By introducing variations among the cells so that they produced slightly different amounts of dye and bleach, Turing generated spots, dapples and even zebralike stripes. These slight initial differences were magnified by blotting and bleaching to create all-or-nothing patterns. We wondered if this notion would work for cortical maps.

Four years ago computational neuroscientist Misha Tsodyks and his colleagues at the Weizmann Institute of Science in Rehovot, Israel, demonstrated that, indeed, a similar process could generate cortexlike maps in software simulations. Paul Merolla, another doctoral student in my lab, took on the challenge of getting this self-organizing process to work in silicon. We knew that chemical dopants (impurities) introduced during the microfabrication process fell randomly, which introduced variations among otherwise identical transistors, so we felt this process could capture the randomness of gene expression in nature. That is putatively the source of variation of spot patterns from leopard to leopard and of orientation map patterns from person to person. Although the cells that create these patterns in nature express identical genes, they produce different amounts of the corresponding dye or ion channel proteins.

With this analogy in mind, Merolla designed a single silicon neuron and tiled it to create a mosaic with neuronlike excitatory and inhibitory connections among neighbors, which played the role of blotting and bleaching. When we fired up the chips in 2003, patterns of activity—akin to a leopard's spots—emerged. Different groups of cells became active when we presented edges with various orientations. By marking the locations of these different groups in different colors, we obtained orientation preference maps similar to those imaged in the V1 areas of ferret kits [*see box above*].

## Building Brains in Silicon

HAVING MORPHED the retina's five layers into silicon, our goal turned to doing the same to all six of the visual cortex's layers. We have taken a first step by morphing layer IV, the cortex's input layer, to obtain an orientation preference map in an immature form. At three millimeters, however, the cortex is five times thicker than the retina, and morphing all six cortical layers requires integrated circuits with many more transistors per unit area.

Chip fabricators today can cram a million transistors and 10 meters of wire onto a square millimeter of silicon. By the end of this decade, chip density will be just a factor of 10 shy of cortex tissue density; the cortex has 100 million synapses and three kilometers of axon per cubic millimeter.

Researchers will come close to matching the cortex in terms of sheer numbers of devices, but how will they handle a billion transistors on a square centimeter of silicon? Thousands of engineers would be required to design these high-density nanotechnology chips using standard methods. To date, a hundredfold rise in design engineers accompanied the 10,000-fold increase in the transistor count in Intel's processors. In comparison, a mere doubling of the number of genes in flies to that of humans enabled evolutionary forces to construct brains with 10 million times more neurons. More sophisticated developmental processes made possible the increased complexity by elaborating on a relatively simple recipe. In the same way, morphing neural development processes instead of simply morphing neural circuitry holds great promise for handling complexity in the nanoelectronic systems of the future. SA

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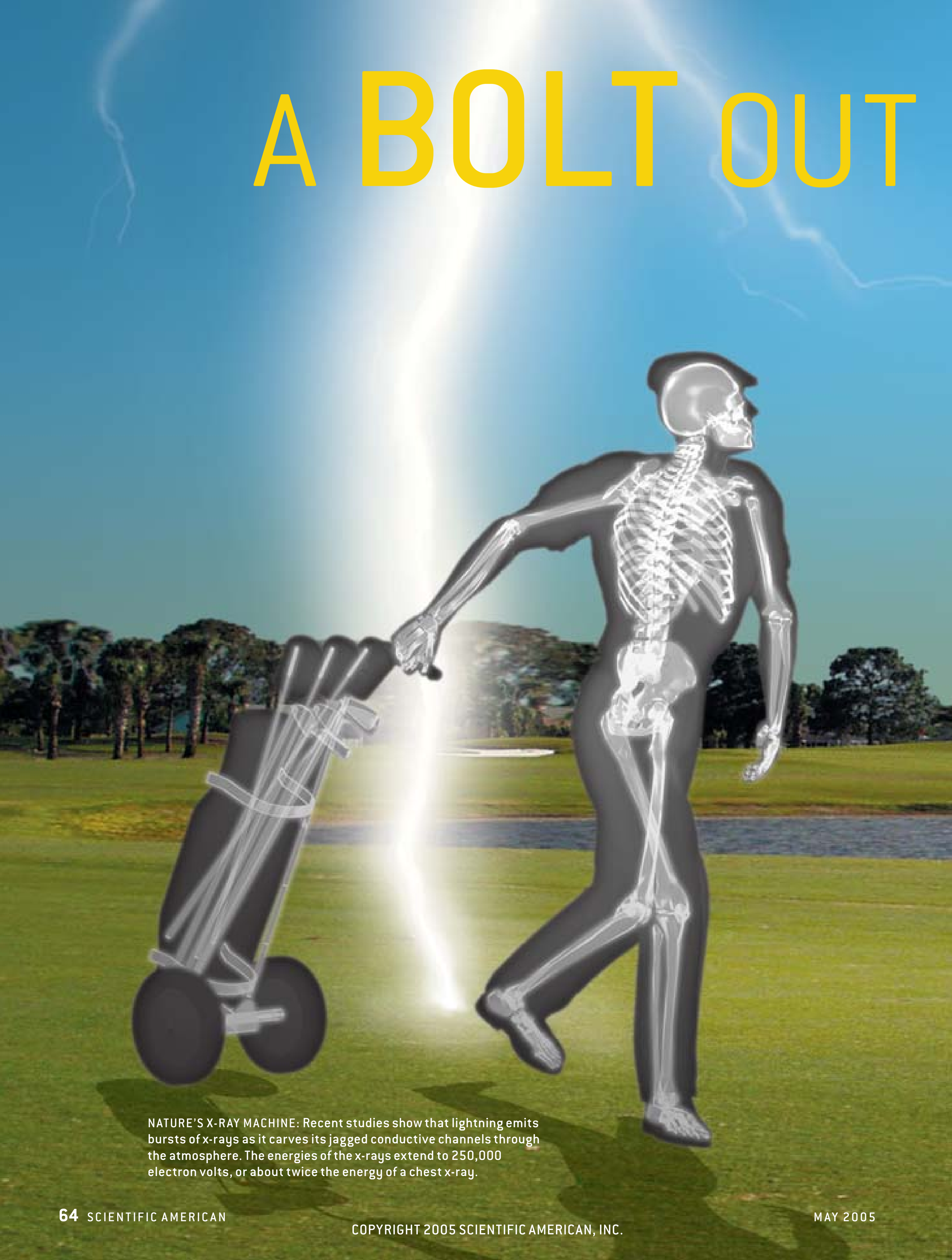
The author's Web site: **www.neuroengineering.upenn.edu/boahen**

# A BOLT OUT



NATURE'S X-RAY MACHINE: Recent studies show that lightning emits bursts of x-rays as it carves its jagged conductive channels through the atmosphere. The energies of the x-rays extend to 250,000 electron volts, or about twice the energy of a chest x-ray.

# OF THE BLUE

## New research shows that lightning is a surprisingly complex and mystifying phenomenon

By Joseph R. Dwyer

**Lightning** is a particularly unsettling product of bad weather. It causes more deaths and injuries in the U.S. than either hurricanes or tornadoes do, and it strikes without warning, sometimes with nothing but blue sky overhead. In central Florida, where I live, thunderstorms are a daily occurrence during the summer, and so, ironically, people in the Sunshine State often spend their afternoons indoors to avoid the risk of death from the sky.

Worldwide, lightning flashes about four million times a day, and bolts have even been observed on other planets. Yet despite its familiarity, we still do not know what causes lightning. It is a misconception that Benjamin Franklin solved the puzzle when he conducted his famous kite experiment in 1752.

Although Franklin demonstrated that lightning is an electrical phenomenon, scientists to this day are struggling to understand how thunderstorms generate their charge and how lightning occurs. Some physicists have hypothesized that lightning may actually have an extraterrestrial connection, with cosmic rays—high-energy particles bombarding the earth from space—triggering cascades of speedy electrons in the atmosphere.

Researchers have recently discovered a new avenue for studying lightning: examining the x-rays emitted as lightning streaks from the clouds to the ground. In the past few years, our team has measured the x-rays produced by both natural lightning and man-made bolts created by launching rockets during thunderstorms. The results suggest that lightning may carve its jagged, conductive channels by sending out blasts of high-speed electrons. But how lightning manages to accelerate these electrons is extremely perplexing. To solve the mystery, we are now building an array of x-ray detectors at a site in Florida.

## Stranger than Sparks

IN SOME WAYS, lightning resembles a big spark. Consider the conventional spark, the kind you get when you touch a doorknob after walking across a carpet. When you traverse the carpet, your shoes rub off electrons and you accumulate an electrical charge, which produces an electric field between you and other objects in the room. For small fields, air is a good insulator—electrons attach to oxygen atoms faster than they are knocked loose by collisions—and electric current cannot flow in any appreciable amount. As your finger approaches the knob, however, the electric field becomes locally enhanced. If it reaches a critical value of about three million volts per meter, called the breakdown field, the air becomes a conductor and a discharge occurs: current bridges the gap.

The electrification of thunderstorms shares some similarities with the carpet example. Inside thunderclouds, the role of the shoes on the carpet is most likely played by soft hail—snow pellets—falling through ice crystals and water droplets. (The exact mechanisms are still under debate.) When these particles bump into one another, they can rub off electrons and become charged. The positive and negative charges are then separated by updrafts and gravity, producing the electric field. But if we try to press the doorknob analogy any further, we run into a big problem: decades of balloon, aircraft and rocket measurements made directly inside the clouds rarely find fields above about 200,000 volts per meter, which is much too low to cause air to break down like it does when we touch a doorknob.

Until recently, scientists had focused on two explanations to solve this conundrum. First, it is possible that stronger electric fields do exist inside thunderstorms but only in relatively small volumes, making them difficult to measure. Although such a scenario cannot be ruled out observationally, it is not altogether satisfying, because we are merely replacing one problem with another: How do clouds produce strong electric fields in such small volumes? The second explanation comes from experiments showing that the electric field needed to produce a discharge is reduced substantially when raindrops or ice particles are present in the air, as they are inside thunderstorms. Unfortunately, the addition of rain or ice alleviates only some of the discrepancy; the fields in thunderstorms still appear to be too weak to generate a conventional discharge.

Scientists are also uncertain about how lightning propagates many kilometers through the air. The process begins with the formation of a leader, a hot channel that can ionize the air and transport charge over long distances [*see box on opposite page*]. Interestingly, the leader does not travel to the ground in a continuous fashion but instead moves along in a series of discrete steps. Exactly how all this occurs, however, is somewhat mysterious. Efforts to model these processes have not been entirely successful. These difficulties have led many researchers in the field, including me, to wonder if we have missed something important. For example, perhaps viewing lightning as an entirely conventional discharge, like a spark to a doorknob, is not correct. It turns out that another, more unusual kind of discharge exists: runaway breakdown.

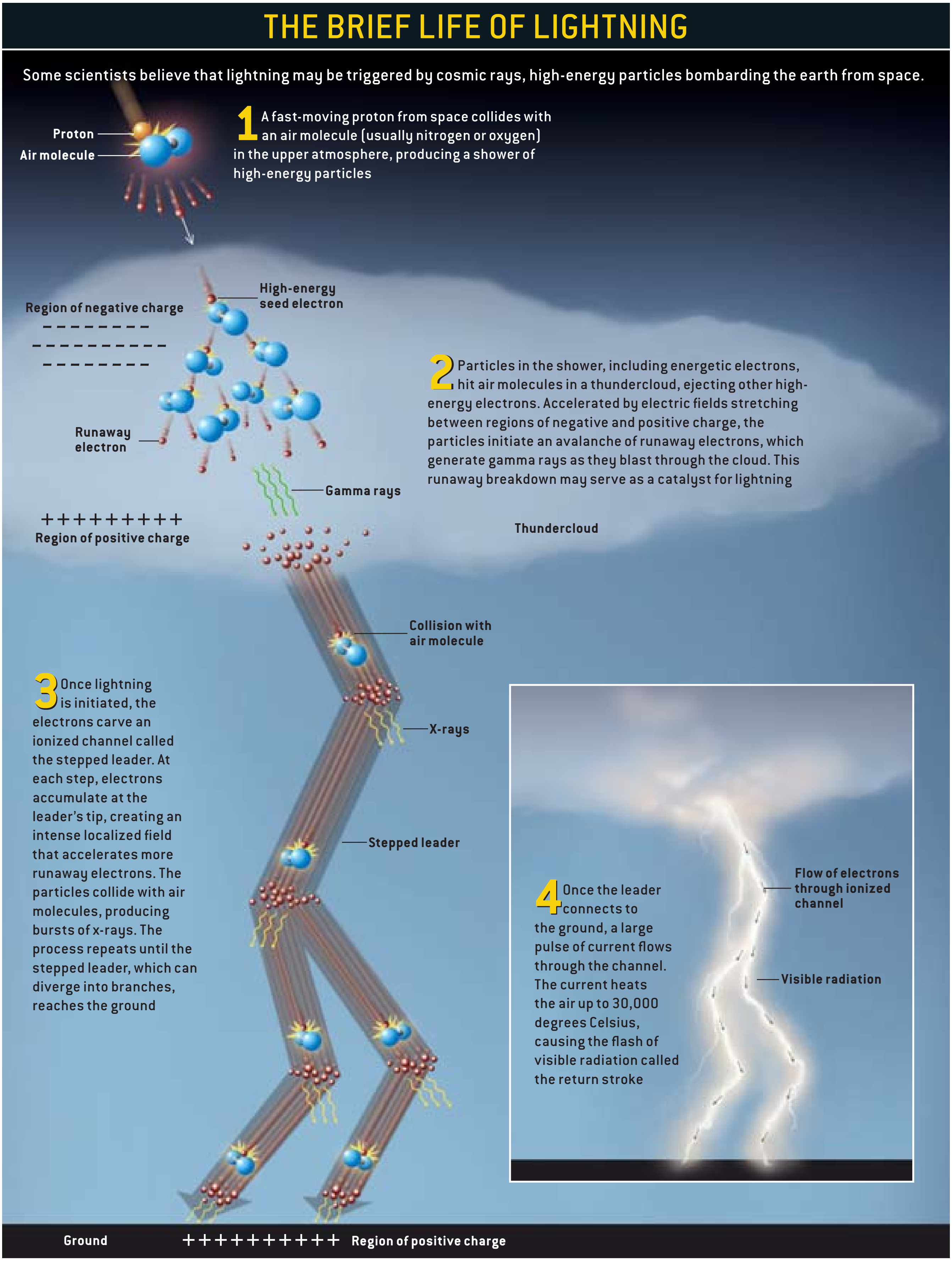
In a conventional discharge, all the electrons move relatively slowly because they are hampered by their constant collisions with air molecules. The collisions create an effective drag force that is similar to what you feel when you stick your hand out a car window: as the car goes faster the drag force increases, and as the car slows down it decreases. But if the electron velocities are high enough—at least six million meters per second, or about 2 percent of the speed of light—the drag force actually decreases the faster the electrons go [*see illustration on page 69*]. If a strong electric field accelerates a high-speed electron, the drag force becomes smaller, which allows the electron to move even faster, thereby reducing the drag force further, and so on. Such runaway electrons can accelerate to nearly the speed of light, gaining enormous amounts of energy and producing the discharge called runaway breakdown.

This process, though, requires a seed population of electrons with high initial energies. In 1925 Scottish physicist

## Overview/*The Nature of Lightning*

- Lightning has baffled physicists for decades because the electric fields inside thunderclouds do not appear to be strong enough to generate a conventional discharge of current.
- New observations of x-rays from lightning bolts support the hypothesis that lightning somehow accelerates electrons to nearly the speed of light in a phenomenon called runaway breakdown.
- Researchers are building an array of x-ray detectors in Florida to study the processes that initiate lightning and allow it to propagate.

SLIM FILMS (*preceding pages*)




ALISON KENDALL

## Lightning is not just an ordinary spark like the kind you get when you touch a doorknob.

C.T.R. Wilson first suggested that the decay of radioactive isotopes or the collisions of cosmic-ray particles with air molecules could generate energetic electrons that would run away in the electric fields inside thunderclouds. Wilson's model, however, predicted that radioactive decay and cosmic-ray collisions would produce too few runaway electrons to cause lightning.

In 1961 Alexander V. Gurevich of the Lebedev Institute of Physics in Moscow hypothesized another mechanism for making runaway electrons. Gurevich showed that in very strong electric fields, large numbers of runaway electrons could be produced by accelerating them directly out of the ubiquitous population of low-energy free electrons, thereby sidestepping Wilson's problem of a lack of energetic seed electrons. To generate such runaway electrons, Gurevich used a brute-force method in which the electric field is so incredibly strong that some of the low-energy electrons are quickly accelerated up and over the energy threshold, allowing them to run away. The difficulty with this mechanism is that it requires an electric field about 10 times larger than the conventional breakdown field, which in turn is much larger than the fields observed in thunderstorms. In short, physicists seemed to be heading in the wrong direction.

Finally, in 1992, a new idea emerged that has shown promise for explaining what happens inside thunderstorms and how lightning occurs. Gurevich, along with Gennady M. Milikh of the University of Maryland and Robert Roussel-Dupré of Los Alamos National Laboratory, proposed the Relativistic Runaway Electron Avalanche (RREA) model. According to this scenario, the runaway electrons themselves generate more energetic seed electrons by bumping forcefully into air molecules and knocking off other high-energy electrons. These knocked-off electrons then run away and collide with more air molecules, producing still more energetic seed electrons, and so on. The result is a large avalanche of high-energy electrons that grows exponentially with time and distance. Because this process can be initiated by as few as one energetic seed electron, the steady background of cosmic-ray collisions and radioactive decays would be sufficient to trigger an avalanche of runaway electrons. And as long as the avalanche remains in a region with a strong electric field, it will continue to grow almost indefinitely, resulting in a runaway breakdown.

Furthermore, unlike Gurevich's older hypothesis, this new model of runaway breakdown requires an electric field only one tenth as large as that needed for a conventional breakdown in dry air. At thunderstorm altitudes, where the air density is lower than at sea level, the electric field needed for this type of runaway breakdown is about 150,000 volts per meter—comfortably within the range of values measured inside thunderstorms. Indeed, it is probably not a coincidence that the maximum observed electric field inside thunderclouds and the field needed for runaway breakdown are about the same; my calculations have shown that runaway breakdown would efficiently discharge the electric field if it were to rise much higher.

In a normal discharge, all the electrons have low energies and travel fairly slowly, so the electromagnetic radiation emitted by the spark extends only as high as the ultraviolet range. In a runaway breakdown, though, the fast-moving electrons ionize large numbers of air molecules and produce high-energy x-rays and gamma rays. (The phenomenon is known as bremsstrahlung, German for "braking radiation.") Consequently, one way to test for runaway breakdown is to search for x-rays.

### If Superman Saw Lightning

MOTIVATED FIRST by Wilson's hypotheses and later by Gurevich's work, scientists have attempted to observe x-rays from thunderstorms and lightning since the 1930s. Such measurements are very challenging to make and until recently have produced mostly ambiguous results. One difficulty is that x-rays do not travel very far through the atmosphere and are usually absorbed within a few hundred meters of the source. Another problem is that thunderstorms are electromagnetically noisy environments. Lightning, in particular, emits large amounts of radio-frequency noise, causing the familiar crackle on AM radios many kilometers away. Detecting x-rays involves recording small electrical signals; trying to make such measurements near lightning is like trying to hear a conversation in a raucous restaurant. Because it can be hard to distinguish real electrical signals produced by x-rays from spurious ones produced by radio-frequency emissions, many of the early results were not readily accepted.

The situation got more interesting in the 1980s, when George K. Parks, Michael P. McCarthy and their collaborators at the University of Washington made aircraft observations within thunderstorms. Later, Kenneth B. Eack, now at the New Mexico Institute of Mining and Technology (NMT), and his coworkers made a series of balloon soundings inside thunderclouds. These observations provided tantalizing hints that thunderstorms occasionally produce large bursts of x-rays. The source of these x-rays could not be pinpointed, but the radiation seemed to be associated with the enhanced electric fields inside the clouds. Interestingly, the x-ray emission sometimes began right before lightning was observed and stopped once the lightning occurred, perhaps because lightning shorted out the electric fields need-

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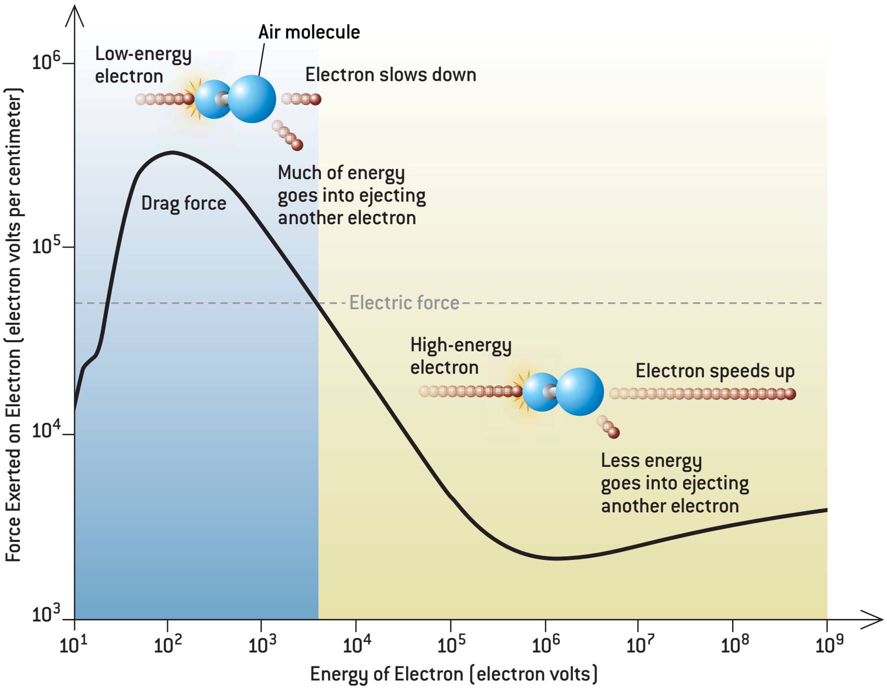


**RUNAWAY ELECTRONS** blaze the trails for lightning bolts. Low-energy electrons, which move relatively slowly, lose more energy to drag—collisions with air molecules—than they gain from an electric field, so they slow down further. But because high-energy electrons lose less energy to drag, the electric field can accelerate them to nearly the speed of light.

ed to produce runaway breakdown.

Researchers know of no mechanism besides runaway breakdown that could produce such large quantities of x-rays in our atmosphere. Other phenomena associated with lightning cannot be responsible for the emissions; although lightning can heat the air up to 30,000 degrees Celsius—five times as hot as the sun's surface—virtually no x-rays are produced at this temperature.

Scientists finally found a direct link between x-rays and lightning in 2001, when Charles B. Moore and his co-workers at NMT reported observing energetic radiation, presumably x-rays, from several natural lightning strikes on top of a tall mountain. Unlike the earlier aircraft and balloon observations, this energetic radiation seemed to be produced by the lightning itself and not by the large-scale electric fields inside the thundercloud. Furthermore, the emissions appeared to occur during the first phase of lightning, the movement of the leader from the cloud to the ground. This observation was something entirely new.

Here is where I entered the picture. As a physicist, I have always been interested in how x-rays and gamma rays are produced. Although such radiation is common in space, where the vacuum allows energetic particles to travel unimpeded, it is much rarer on the earth. Consequently, I became fascinated by Gurevich, Milikh and Roussel-Dupré's runaway breakdown model, which suggested that the same kind of x-rays produced by events such as solar flares could also be made by thunderstorms and lightning. I decided to see for myself if these purported x-rays really did exist by investigating the frequent thunderstorms in my own backyard.

In 2002, with funding from the National Science Foundation, my group at the Florida Institute of Technology, in collaboration with Martin A. Uman and his team at the University of Florida, began a systematic campaign to search for x-ray emissions from lightning. To reduce the problems of spurious signals, we placed sensitive x-ray detectors inside heavy aluminum boxes designed to keep out moisture, light and radio-frequency noise. We set up our instruments at the International Center for Lightning Research and Testing (ICLRT) in Camp Blanding, Fla. Operated by the University of Florida and Florida Tech, the ICLRT is equipped to measure, among other things, the electric and magnetic fields and optical emissions associated with lightning. Moreover, the facility is capable of artificially triggering lightning from natural thunderstorms using small rockets.

When a thunderstorm is above the ICLRT and the electric field on the ground reaches several thousand volts per meter, researchers launch a one-meter-long rocket from a wooden tower. The rocket uncoils a spool of thin Kevlar-coated copper wire, one end of which remains attached to the ground. As the rocket rises as high as 700 meters, the vertical grounded wire enhances the electric field at the rocket's tip, resulting in an upward-propagating leader that eventually snakes its way into the thundercloud. Electric current rising from the ground into the leader quickly vaporizes the wire. About half the launches trigger lightning from the clouds above, and the bolts usually strike the rocket launcher.

Both natural and man-made lightning flashes are usually composed of several strokes. For triggered lightning, each stroke starts as a downward-propagating column of charge called a dart leader that, near the ground, more or less follows the path left by the rocket and triggering wire. The dart leader brings down negative charge from the cloud and ionizes the channel as it moves. Once the dart leader connects to the ground, a short circuit is created and a large pulse of current, called the return stroke, flows through the channel. The current in the return stroke quickly heats the channel, causing the visible light that

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ALISON KENDALL

**This research may help us finally solve the puzzle tackled by Benjamin Franklin 250 years ago.**

we see, and the subsequent rapid expansion of the hot air causes the thunder that we hear. After the return stroke, another dart leader can follow, whereupon the entire process repeats. The quick succession of strokes is what causes the lightning channel to flicker.

In natural lightning the role of the rocket is played by a stepped leader, which forges the ionized path, extending in jagged steps from the cloud to the ground. The subsequent strokes of natural lightning, however, are initiated by a dart leader, making them very similar to the strokes of triggered lightning. The advantage of studying the latter is that the exact time and place of the lightning strike can be controlled. What is more, the experiment can be repeated over and over; dozens of lightning flashes are triggered at the ICLRT every summer.

To be honest, given the long history of negative and ambiguous x-ray results, I was not really expecting to measure any x-rays from lightning when we first set up our instruments at the ICLRT. For this reason, after we made our first triggered-lightning measurements I did not get around to looking at our data for more than a week. When I finally sat down with my graduate student, Maher Al-Dayeh, and plotted the data from the x-ray detectors, I nearly fell off my chair. To my surprise—and to the surprise of just about everyone else—we discovered that triggered lightning produces lots and lots of x-rays nearly every time. Indeed, the x-ray flashes were so intense that our instruments were temporarily blinded by the radiation.

Subsequent experiments over the next year showed that the x-ray emission is produced by the lightning dart leaders, possibly with some contribution from the beginning of the return strokes. The energies of the x-rays extend to around 250,000 electron volts, or about twice the energy of a chest x-ray. Furthermore, the x-ray emission is not produced continuously but happens in rapid bursts a millionth of a second apart. If humans had x-ray vision like Superman, lightning would look quite different from what we are used to: as the lightning leader propagated downward, we would see a rapid series of bright flashes descending from the clouds. The flashes would strengthen as they approached the ground, ending with a very intense burst at the instant the return stroke began. Although the pulse of current that would follow would be brilliant in visible light, it would look black in x-rays.

The observation of x-rays from lightning indicates that some form of runaway breakdown must be involved to accelerate the electrons enough to produce bremsstrahlung radiation. But it turns out that our measurements do not square well with the RREA model developed by Gurevich, Milikh and Roussel-Dupré. The x-rays we observed had much lower energies than those predicted by the avalanche model, and the intensity of the bursts was much higher than expected. In fact, the results suggest that the electric fields produced by lightning leaders are much, much larger than what was previously believed possible. Ironically, our experiments so far indicate that the mechanism at work in lightning leaders is more akin to the old model of runaway breakdown proposed by Gurevich in 1961—the one requiring such a large electric field that it was initially discounted. Exactly how lightning can generate such large electric fields remains a mystery, but further x-ray observations should provide clues.

Since the initial discovery of x-rays from triggered lightning, we have observed several natural lightning strikes at the ICLRT as well. These data showed beautiful x-ray emissions from the stepped-leader phase, confirming the earlier NMT measurements. Furthermore, the x-rays arrived in fast bursts at exactly the same times when the leader stepped downward. This result demonstrates that runaway breakdown is involved in the stepping process, determining where the lightning will go and how it branches. A similar mechanism is also at work during the dart-leader phases of the subsequent strokes.

In short, the x-ray emissions from natural lightning are very similar to those from triggered lightning. It is becoming clear that runaway breakdown is a common phenomenon in our atmosphere. Despite the fact that air molecules hinder the acceleration of fast electrons, we see evidence for runaway breakdown even near the ground, where the air is densest. (Most of the x-rays we observed came from the bottom 100 meters or so of the lightning channel.) Thus, runaway breakdown may happen even more frequently at thunderstorm altitudes.

## Back in the Thunderstorm

WHAT ABOUT LIGHTNING initiation within thunderclouds? In the past few years, researchers have constructed promising models that show how the particle showers created by cosmic-ray impacts could work together with runaway breakdown to make lightning. Because big avalanches of runaway electrons can be produced by just one energetic seed electron, the discharge triggered by a large cosmic-ray shower—which involves millions of energetic seed particles arriving simultaneously—must be truly enormous. Such a large discharge could generate a localized enhancement of the electric field at the front of the avalanche because of the great increase in the electrical charge there. This enhancement may act like a finger near a doorknob, briefly raising the electric field to the point where a conventional electrical breakdown can take place.

A fascinating piece of evidence sup-

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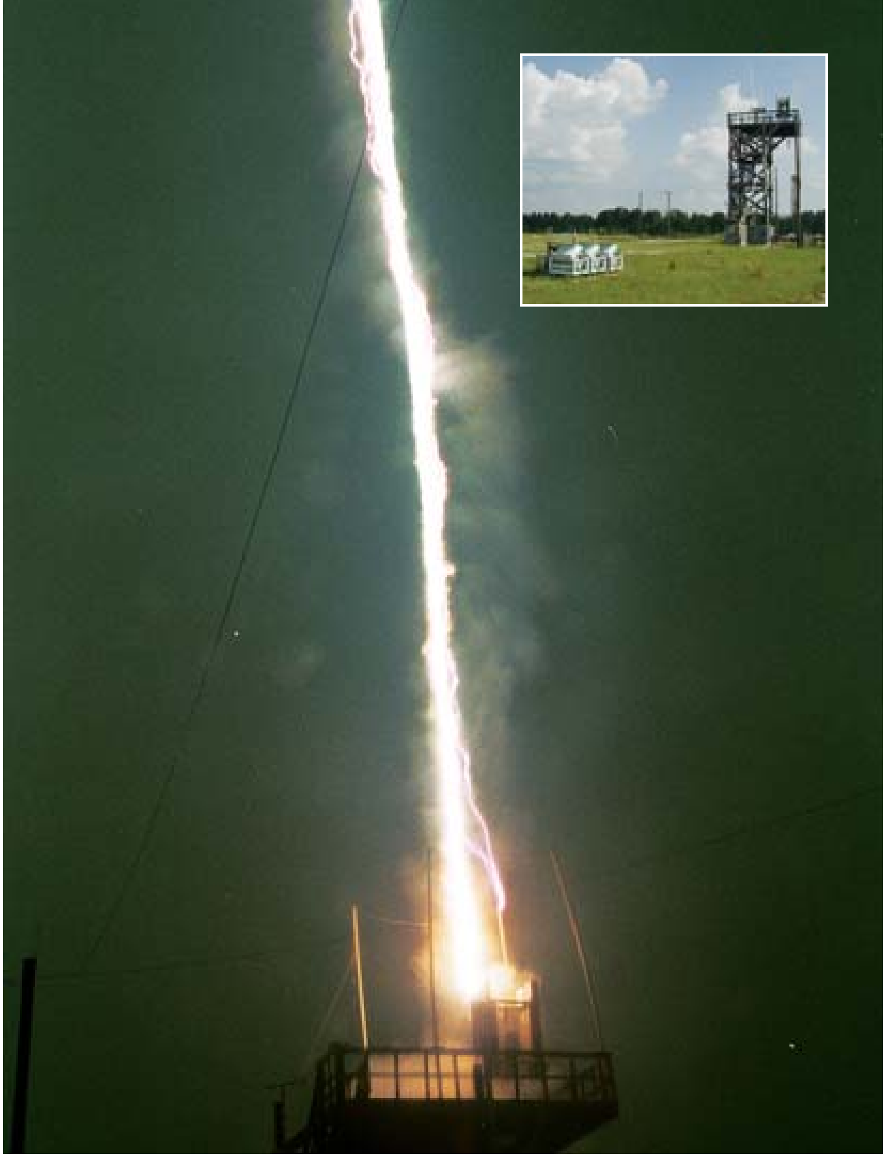

TRIGGERED LIGHTNING is produced at the International Center for Lightning Research and Testing in Florida by launching a small rocket from a wooden tower (*inset*) during a thunderstorm. The rocket trails a wire that carries current from the ground, creating a path for the lightning bolt. Nearby instruments measure the energy and intensity of the emitted x-rays.



porting runaway breakdown inside thunderclouds came from our experiments at the ICLRT last summer. During the final rocket launch of the season, we fortuitously caught a huge burst of very high energy radiation—gamma rays, not x-rays—using three detectors placed 650 meters from the lightning channel. The energies of the individual gamma-ray photons extended to more than 10 million electron volts, or about 40 times higher than the energies of the x-rays that we had previously observed from lightning leaders. Anyone who pictures scientists as calm and reserved should have seen us when the data from that gamma-ray flash appeared on our computer. One might have thought that our favorite team had just scored the winning touchdown at the Super Bowl.

Based on our measurements of the lightning channel current, the electric fields and the properties of the gamma rays, we have inferred that the source of the emission was probably many kilometers up in the thundercloud. We did not expect to see gamma rays from this altitude because the atmosphere absorbs such radiation, but apparently the intensity at the source was so great that some photons were able to make it to the ground. This finding suggests that massive runaway breakdown may have happened within the thundercloud in a process related to the initiation of the triggered lightning. Our observations demonstrate that it is possible to study this phenomenon on the ground, which is experimentally much simpler than lofting detectors onto aircraft or balloons. Furthermore, scientists recently reported that the Reuven Ramaty High Energy Solar Spectroscopic Imager (RHESSI) detected similar gamma-ray bursts associated with thunderstorms while orbiting 600 kilometers away!

With additional funding from the National Science Foundation, we are now expanding the number of x-ray instruments at the ICLRT from five to more than 36, covering one square kilometer of the Camp Blanding site. This expansion should improve our ability to study natural lightning as well as triggered lightning and should increase the odds of detecting more gamma-ray bursts from the thunderclouds. The x-ray and gamma-ray emissions can serve as probes to help determine the electric fields in regions that are otherwise very difficult to measure. The results should allow us to better understand the breakdown processes that initiate lightning and facilitate its propagation.

Using x-rays to study lightning is still new, and consequently, just about every time we conduct an experiment we discover something we did not know before. We have already learned that lightning is not just an ordinary spark like the kind you get when you touch a doorknob. It involves a more exotic type of discharge that produces runaway electrons and x-rays. Because x-rays allow us to look at lightning in a novel way, this research may help us finally solve the puzzle tackled by Benjamin Franklin two and a half centuries ago. SA

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# Can Chlamydia Be Stopped?

By David M. Ojcius, Toni Darville and Patrik M. Bavoil

**Chlamydia is a rampant sexually transmitted disease, the world's leading cause of preventable blindness and a possible contributor to heart disease. Recent discoveries are suggesting new ways to curtail its spread**

Ask the average American about chlamydia, and you will probably evoke an uneasy cringe. Most people think immediately of one of the world's most common sexually transmitted diseases (STDs). But the term actually refers to an entire genus of tiny bacteria that can ignite a variety of serious illnesses.

Ask a poor mother in Africa about chlamydia, and she may tell you that flies transmitting this infection gave her two young children the painful eye condition known as conjunctivitis. This illness—caused by a strain of *Chlamydia trachomatis* (the species that also causes STDs)—can lead to trachoma, a potentially blinding disease. In industrial countries, an airborne species, *C. pneumoniae,* causes colds, bronchitis and about 10 percent of pneumonias acquired outside of hospitals. Researchers have even drawn tentative links between *C. pneumoniae* and atherosclerosis, the artery-narrowing condition that leads to heart attacks and strokes.

Because chlamydiae are bacteria, antibiotics can thwart the infections they produce. Unfortunately, the illnesses often go undetected and untreated, for various reasons. The genital infections rarely produce symptoms early on. And in developing countries where trachoma is a concern, people often lack access to adequate treatment and hygiene. As a result, many of the estimated 600 million people infected with one or more *Chlamydia* strains will go without medical care until the consequences have become irreversible.

It is unrealistic to expect that doctors will ever identify all individuals who have the STD or that improved hygiene will soon wipe out the trachoma-causing bacteria in developing countries. For these reasons, the best hope for curtailing the spread of these ailments is to develop an effective vaccine or other preventive treatments. To discover agents able to block infections before they start, scientists need to know more about how chlamydiae replicate, incite disease and function at a molecular level. But that information has been hard to come by. These bugs are wily. Not only do they have varied strategies for evading the body's immune system, they also are notori-

MINDY JONES

SEVERAL PARTS of the body, including the eyes, lungs and reproductive tract, are vulnerable to chlamydial infection.

ously difficult to study in the laboratory. In the past five years, however, new research—including the complete sequencing of the genomes of several *Chlamydia* strains—has helped scientists begin to address these obstacles. The resulting discoveries are renewing hope for developing new prevention strategies.

## Silent Injury

ONE MAJOR IMPEDIMENT to the production of a vaccine is chlamydia's surreptitious way of wreaking havoc on the body. The microbes that cause tetanus or cholera swamp tissues with toxins that damage or kill vulnerable cells. Chlamydiae, in contrast, do not damage tissues directly. Rather they elicit an enthusiastic immune response that attempts to rein in the infection through inflammation for as long as the bacteria remain in the body—even at low levels. Ironically, this way of fighting the infection actually brings on the long-term damage. Vaccines prevent illness by priming the immune system to react strongly to specific disease-causing agents, but in this case, the inflammatory component of such a response could do more harm than good.

Whether in the genital tract, eyelids or elsewhere, inflammation begins when certain cells of the host immune system secrete factors called cytokines—small signaling proteins that attract additional defensive cells to the site of infection. The attracted cells and the cytokines try to wall off the area to prevent the bacteria's spread. In the skin, this process gives rise to familiar outward manifestations of inflammation: redness, swelling and heat. At the same time, the inflammatory cytokines help to trigger the tissue repair response called fibrosis, which can lead to scarring.

In the genital tract, the early inflammation is not obvious. Of the 3.5 million Americans infected with sexually transmitted chlamydia every year, 85 to 90 percent show no symptoms. Men, whose inflammation occurs in the penis, may experience slight pain during urination; women may feel nothing as the bacteria move up the genital tract into the fallopian tubes. Unaware of the problem, these individuals inadvertently pass the bugs along. Indeed, a woman may not learn of her infection until she tries to become pregnant and realizes she is infertile. In other cases, persistent inflammation and scarring of the fallopian tubes causes chronic pelvic pain or increases the chances of ectopic, or tubal, pregnancy—the leading cause of first-trimester pregnancy-related deaths in the U.S.

Inflammation of the eyelids is more immediately obvious. Such infections afflict an estimated 150 million people living in developing countries with hot climates; there treatments may be scarce, and flies and gnats can readily transmit the bacteria between people's infrequently washed hands and faces. (Trachoma does not occur in the U.S. or western Europe because of better public health systems.) When infections scar the inside of the upper eyelid repeatedly over many years, the eyelid may begin to turn under, pointing the eyelashes inward where they can scratch the cornea. Unchecked, the corneal damage can cause blindness decades after the initial infection.

Given that inflammation accounts for most of chlamydia's ill effects, those who are striving to develop a vaccine must find a way to control the bacteria without inducing a strong inflammatory reaction. Ideally, any intervention would fine-tune the inflammatory response—evoking it just enough to help the body's other immune defenses eliminate the bacteria.

Much research on infections caused by chlamydia and other pathogens is focusing on factors that either initiate secretion of the inflammatory cytokines or dampen the inflammatory response once the infection has been cleared. Over the past few years, investigators have discovered small molecules that normally stimulate or inhibit these responses in the body. The next step will be to develop compounds that are able to regulate the activities of these molecules. These agents might be delivered to shut down inflammation artificially after an antibiotic has been administered to control the bacteria.

## Overview/*Too Little, Too Late*

- Chlamydia has many modes of attack. Untreated infections have blinded more than six million people worldwide, leave more than 10,000 women in the U.S. sterile every year, and account for 10 percent of pneumonia cases in industrial countries.
- Most people affected by chlamydia are not treated with antibiotics until after the damage is done; either they do not notice their symptoms right away, or they do not have access to adequate hygiene or health care.
- Global sex education campaigns and improved hygiene can certainly help limit the bacterium's spread, but other preventive measures such as vaccines are probably the only way to stamp out the disease entirely.

## Hanging Around

BEYOND INDUCING INFLAMMATION, chlamydiae have other properties that impede development of an effective vaccine. For instance, once you get mumps or measles—or the vaccines against them—you are immune for life. Not so with chlamydia. The body has a hard time eliminating the bacteria completely, and natural immunity after a bout with the microbes lasts only about six months. Hence, an infection that has apparently disappeared may flare up again months or years later, and little protection remains against new outbreaks. If the body's natural response to infection cannot confer long-term protection, it seems likely that a vaccine that merely mimicked this response would fail as well. To be successful, a vaccine would have to elicit defenses that were more powerful than those occurring naturally without triggering excessive inflammation.

One way that vaccines or natural immune responses to an initial infection protect against future colonization by certain microorganisms is by inducing the body to produce so-called memory B lymphocytes targeted to those specific invaders. These immune cells patrol the body throughout its lifetime, ready to secrete antibody molecules that can in turn latch onto any new bugs and mark them for destruction before they in-

## CHLAMYDIA IS NOT JUST AN STD

| SPECIES | DISEASE | DISTRIBUTION | MODE OF TRANSMISSION | NUMBERS AFFECTED |
|---|---|---|---|---|
| *C. pneumoniae* | Pneumonia; possibly atherosclerosis | Worldwide | Inhalation of the bacterium within aerosols produced when an infected person coughs | Causes about 10 percent of pneumonia cases in developed countries, including up to 300,000 new cases in the U.S. every year |
| *C. psittaci* | Psittacosis, a flulike infection of the lungs that can cause inflammation of the liver, heart and brain | Worldwide | Inhalation of the bacterium in aerosols or dust; a bite from or handling the plumage or tissues of an infected bird | Common in wild and domestic birds; rare but potentially fatal when transmitted to humans; 50 to 100 new human cases in the U.S. every year |
| *C. trachomatis* (Different strains cause different disorders.) | Trachoma, a painful eye infection that begins as conjunctivitis and leads to scarring of the cornea and possible blindness | Southeast Asia, South America, India, Middle East, Africa; rare in the U.S. | Direct contact with bodily secretions of infected people or contact with carrier flies or clothing contaminated with such secretions | More than 500 million people worldwide have trachoma, and seven million to nine million are blind as a result of it; virtually no incidence in areas with adequate hygiene |
| *C. trachomatis* | Sexually transmitted disease (STD) of the adult genital tract; can cause conjunctivitis and pneumonia in newborns | Worldwide | Sexual contact; newborns acquire the bacterium from their infected mothers while passing through the birth canal | 50 million to 90 million new STD infections occur globally every year; in the U.S. alone, 3.5 million new infections and more than 10,000 cases of female infertility |
| *C. trachomatis* | *Lymphogranuloma venereum,* an STD of the lymph glands in the genital area | Asia, Africa, South America, Central America; rare in the U.S. | Sexual contact | Global incidence is unknown; 300 to 500 cases in the U.S. every year |

SOURCE: www.med.sc.edu:85/mayer/chlamyd.htm

vade healthy cells. The antibody system works well against a number of disease-causing agents or pathogens—especially against the many bacteria that live outside a host's cells. In theory, antibodies could attack the microbes before they entered cells or when newly minted copies traveled from one cell to another. But the B lymphocyte system is not terribly effective at these tasks when it comes to chlamydiae, which live inside the cells, where circulating antibodies cannot reach them.

To prevent chlamydiae from lying dormant in cells and then proliferating anew, a vaccine would probably need to pump up the so-called cellular arm of the immune system in addition to evoking an antibody attack. This arm, critical to eradicating viruses (which also live inside cells), relies on killer and helper T cells as well as on scavenger cells known as macrophages to eliminate invaders. Unfortunately, even this trio of immune cells does an incomplete job of eliminating chlamydiae, too often allowing infected cells to survive and become bacteria-producing factories.

**THE AUTHORS**

*DAVID M. OJCIUS, TONI DARVILLE* and *PATRIK M. BAVOIL* each bring different expertise to chlamydia research. After studying the cellular and immunological aspects of infections for 12 years in France, Ojcius joined the faculty at the University of California, Merced, in 2004. Darville, who is a pediatric infectious disease specialist at the University of Arkansas for Medical Sciences, has explored the immunology of chlamydial infection since 1994 using mice and guinea pigs. As an associate professor at the University of Maryland, Baltimore, Bavoil works on the biochemistry and molecular biology of the disease.

Developing a vaccine able to evoke a better cellular response than the body could mount on its own is a tall order. Most existing vaccines elicit a targeted antibody response, but safely activating cellular immunity against many infectious diseases remains a challenging task. The job is particularly difficult in the case of chlamydiae because these bacteria have special ways of protecting themselves from attack by the cellular branch of the immune system.

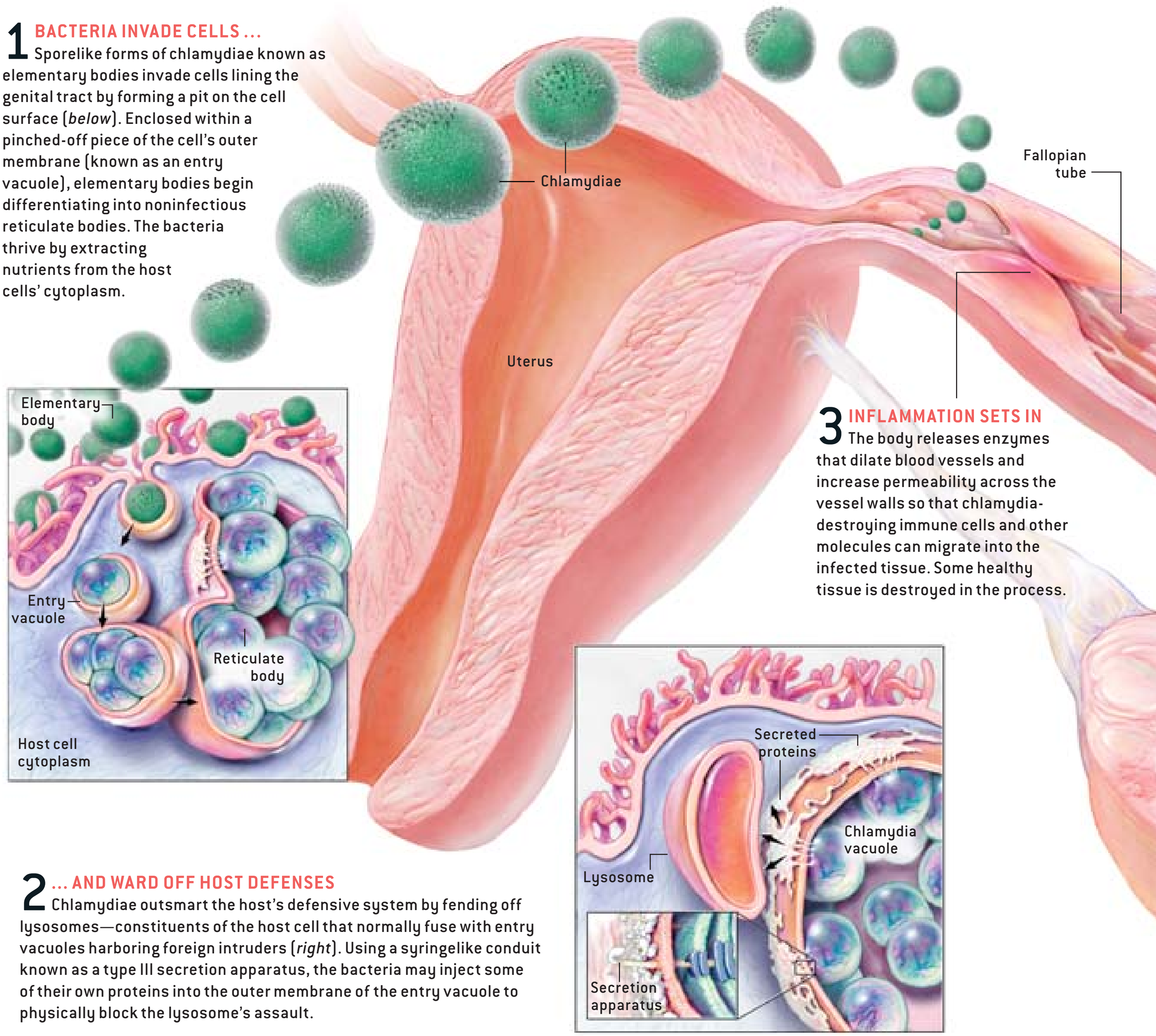
### Hidden Hijackers

LIKE CERTAIN OTHER bacterial pathogens, chlamydiae induce epithelial cells—in this case, those lining genital tracts, eyelids or lungs—to absorb them within a membrane-bound sac, or vacuole. Healthy cells typically attempt to kill internalized pathogens by having the entry vacuoles fuse with lysosomes, cellular structures containing enzymes that chop up proteins, lipids and DNA. All cells display the chopped-up pieces on proteins called major histocompatibility complex (MHC) molecules at the cell surface. Killer and helper T cells, which travel around the body continuously, will then glom on to MHC molecules that display bits of foreign proteins. If the T cells also receive other indications of trouble, they will deduce that the cells are infected and will orchestrate an attack on them.

But chlamydiae somehow compel their entry vacuoles to avoid lysosomes, enabling the bacteria to proliferate freely while separated physically from the rest of the infected cell. If the lysosomes cannot provide bits of the bacteria for display on the cell surface, patrolling T cells will not recognize that a cell harbors invaders. Understanding how the bacteria grow

## CHLAMYDIA'S STEALTHY ATTACK

Sexually transmitted chlamydia leaves most of its victims unaware of their infections until the damage is irreversible. In the worst case, infection of a woman's fallopian tubes creates scar tissue that stops a fertilized egg from reaching the uterus (*main illustration*), leading to a life-threatening tubal (ectopic) pregnancy. New revelations about the bacteria's survival tactics (*insets*) may soon make it possible to interrupt chlamydia's silent attack [*see box on page 79*].




**1 BACTERIA INVADE CELLS ...** Sporelike forms of chlamydiae known as elementary bodies invade cells lining the genital tract by forming a pit on the cell surface (*below*). Enclosed within a pinched-off piece of the cell's outer membrane (known as an entry vacuole), elementary bodies begin differentiating into noninfectious reticulate bodies. The bacteria thrive by extracting nutrients from the host cells' cytoplasm.

**2 ... AND WARD OFF HOST DEFENSES** Chlamydiae outsmart the host's defensive system by fending off lysosomes—constituents of the host cell that normally fuse with entry vacuoles harboring foreign intruders (*right*). Using a syringelike conduit known as a type III secretion apparatus, the bacteria may inject some of their own proteins into the outer membrane of the entry vacuole to physically block the lysosome's assault.

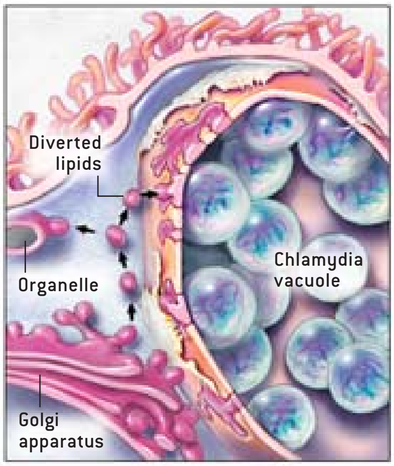
**3 INFLAMMATION SETS IN** The body releases enzymes that dilate blood vessels and increase permeability across the vessel walls so that chlamydia-destroying immune cells and other molecules can migrate into the infected tissue. Some healthy tissue is destroyed in the process.

ANDREW SWIFT

and avoid lysosomes might suggest new ways to forestall or halt the infection. Recent findings, including the newly sequenced *Chlamydia* genomes, are aiding in that effort.

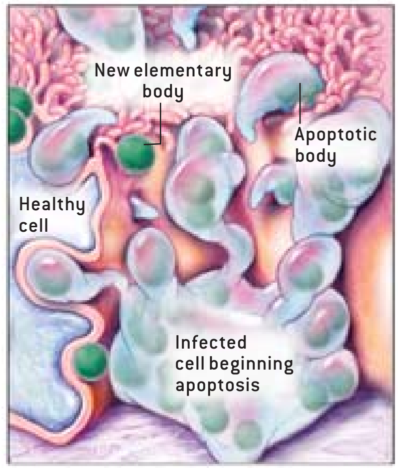
The sequence of genetic building blocks in an organism's DNA specifies the proteins that cells make; the proteins, in turn, carry out most cellular activities. Thus, the sequence of codes in a gene says a good deal about how an organism functions. Researchers, including Ru-ching Hsia and one of us (Bavoil) of the University of Maryland, discovered a particularly important element of chlamydiae by noting similarities between their genes and those of larger bacteria, such as *Salmonella typhimurium*, infamous for causing food poisoning. Scientists now generally agree that chlamydiae have everything they need to form a versatile, needlelike projection called a type III secretion apparatus. This apparatus, which spans the membrane of the entry vacuole, serves as a conduit between the bacteria and the cytoplasm of the host cell.

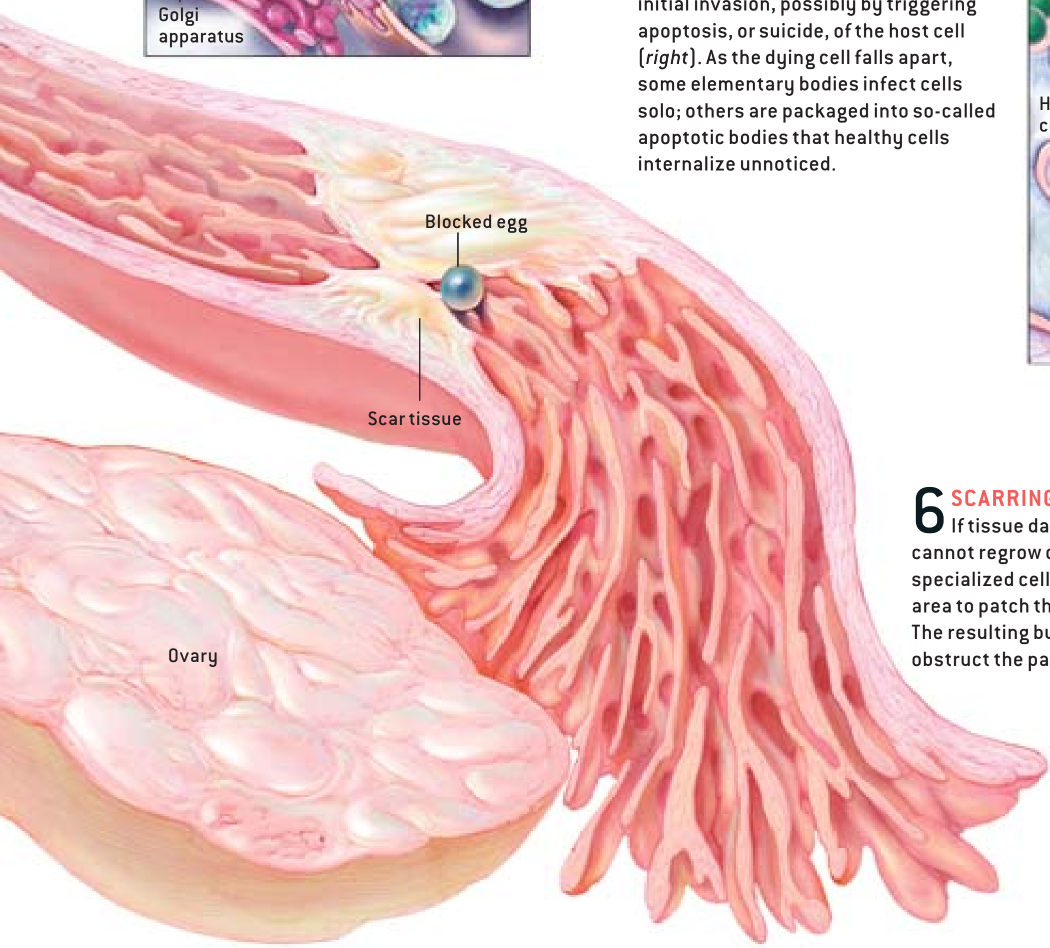
Such a connection implies that chlamydiae can inject pro-




**4 BACTERIA EVADE DETECTION ...**
Chlamydiae also hide from lysosomes, by refurbishing their entry vacuole with molecules they divert from the host cell's lipid distribution center, the Golgi apparatus (*left*). These stolen lipids make the vacuole virtually indistinguishable from the cell's own membrane-bound organelles.

**5 ... AND LAUNCH A NEW ATTACK**
New elementary bodies break out of the host cell within 72 hours after the initial invasion, possibly by triggering apoptosis, or suicide, of the host cell (*right*). As the dying cell falls apart, some elementary bodies infect cells solo; others are packaged into so-called apoptotic bodies that healthy cells internalize unnoticed.




**6 SCARRING CLOGS TUBES**
If tissue damage is so severe that normal cells cannot regrow once the inflammation subsides, specialized cells called fibroblasts move into the area to patch the defect with scar tissue.
The resulting buildup of scar tissue can eventually obstruct the passage of eggs released by the ovary.

teins into the cytoplasm of the host cell. The apparatus may thus help chlamydiae resist interaction with lysosomes, because it can secrete proteins that remodel the vacuole membrane in ways that bar lysosome function. In addition, investigators have watched the chlamydiae-bearing vacuole divert artificially fluorescing lipids from certain compartments of the host cell, including the Golgi apparatus, to the vacuole membrane. Normally, the membrane of an entry vacuole bears molecules made by the pathogen inside. In this case, a membrane enclosing a bacterium would look foreign to the host cell, which would target the bacterium for immediate destruction by lysosomes. But the lipids that chlamydiae use to rebuild the membrane of their entry vacuole come from the host cell: the vacuoles are therefore indistinguishable from the host cell's organelles and invisible to lysosomes.

If scientists identify the proteins the bacteria secrete to camouflage vacuoles, they might be able to devise two kinds of infection-preventing treatments. One potential drug could interfere with the proteins' activity in a way that would force the entry vacuole to fuse with lysosomes, triggering an immune attack right after the chlamydiae invade the cell. Another drug might incapacitate the mechanisms the bacteria use to divert lipids from the host cell to the chlamydial vacuole, halting the trespassers' ability to hide. Hypothetically, such drugs could be incorporated into a topical microbicide that would thwart sexually transmitted chlamydiae.

Some of the proteins mentioned above—and any others that are unique to the bacteria and not made by human cells—might also be useful ingredients in vaccines. Newly sequenced genomes should be helpful in identifying good candidates.

## Suicidal Tendencies

RECENT FINDINGS about the role of T cells may open other doors. Biologists have long known that killer T cells normally destroy infected cells by inducing a type of cell death known as apoptosis or "cell suicide," during which cells use their own enzymes to lyse their proteins and DNA. Also known is that immune cells—including T cells and macrophages—stimulate the production of cytokines that help to cripple bacteria and to trigger an inflammatory response that stops their spread. One cytokine known to have this dual purpose is tumor necrosis factor-alpha (TNF-alpha). Laboratory investigations have shown, however, that some infected cells survive despite treatment with TNF-alpha and other apoptosis-inducing cytokines, leading to persistent infections. The problem is that the body does not give up easily. Cytokines continue to trigger chronic inflammation in an effort to contain the infection even if they cannot eliminate it outright.

But even persistently infected cells cannot live forever. Indeed, it appears that chlamydiae have developed their own way to elicit the death of a host cell, which they must do to ensure their own longevity. (The host cell must fall apart before the bacteria can infect other cells.) And as Jean-Luc Perfettini discovered while working as a graduate student with one of us (Ojcius) at the Pasteur Institute in Paris, chlamydiae can kill and exit the infected cells in a way that minimizes the host immune system's ability to sense any danger, thereby allowing the infection to spread essentially undetected in the body.

Addressing this final stage of the bacterial life cycle will require further investigation into the proteins involved in inducing apoptosis and in protecting persistently infected cells from suicidal signals. From what biologists know so far, the

## Cardiovascular Connections

Colds, bronchitis and pneumonia may not be the sole concern for people who have inhaled the airborne species of *Chlamydia.* Recent evidence hints that *C. pneumoniae* infections may also contribute to strokes and heart attacks. Such a link may have an upside, however—doctors might eventually be able to prescribe antibiotics to fight both the infection and the heart disease.

Atherosclerosis—a narrowing of the coronary arteries that leads to most strokes and heart attacks—causes approximately half of all adult deaths in the Western world. But traditional risk factors, such as elevated cholesterol and cigarette smoking, account for only about half of that total. Scientists searching for a reason behind the other 50 percent began to consider infections once it became clear that inflammation—a generalized immune response against any perceived invader—also underlies the growth and destructive ruptures of the fat-laden deposits that constrict coronary arteries [see "Atherosclerosis: The New View," by Peter Libby; SCIENTIFIC AMERICAN, May 2002].

*C. PNEUMONIAE* (*arrow*) turned up in the atherosclerotic coronary arteries of 54 percent of the 272 patients surveyed for a study published in 2000.

*C. pneumoniae* became a prime suspect in the condition shortly after it was identified as a separate chlamydial species in 1983. It drew suspicion because of its ubiquity—more than 60 percent of adults worldwide carry antibodies against it (a sign of past or ongoing infection). Support for the hunch emerged in 1988, when physicians in Finland reported a positive correlation between the presence of these antibodies and the risk of developing coronary artery disease; other researchers identified the bacterium in clogged human arteries five years later. Since then, organizations such as the National Institutes of Health and the American Heart Association have invested millions of dollars to study the relation between *C. pneumoniae* and atherosclerosis.

Animal studies conducted within the past five years or so have provided some of the most convincing evidence for a link. One demonstrated, for example, that chlamydial bacteria can move from the lungs of mice to other parts of the body within white blood cells, the agents responsible for inflammation. Other research has shown that *C. pneumoniae* infections accelerate atherosclerosis in both mice and rabbits and that antichlamydial antibiotics can prevent that acceleration.

Experimental results such as these, though tentative, were enough to justify a handful of small clinical trials in humans. Five of these trials showed that one to three months of antibiotic treatment had a statistically significant benefit against the progression of atherosclerosis. But results were mixed as to whether the antibiotics could actually prevent serious cardiac events. The promise for longer-term treatment was also dealt a blow by the negative outcomes of two large trials completed in 2004, each involving 4,000 volunteers who received antibiotics for one to two years.

Establishing whether a clear connection exists between *C. pneumoniae* infection and atherosclerosis in humans may prove difficult simply because so many other factors participate in heart disease. Exactly how troublesome such complications will be, however, remains to be seen. *—D.M.O., T.D. and P.M.B.*

## CHLAMYDIA, INTERRUPTED

Sex education and improved hygiene cannot halt the spread of chlamydial infection on their own. That is why many scientists continue searching for an effective vaccine or other preventive treatments. Recent discoveries have suggested promising strategies, some listed below, for undermining the bacterium's survival tactics or limiting damage from an excessive immune response.

**Kill the bacterium as it enters the body.**
Develop a topical microbicide—a gel, cream or foam—that would be applied vaginally or rectally. Such products are in human trials to treat HIV, which infects the same tissues as chlamydia does.

**Interfere with the bacterium's ability to invade the host cell.** Devise a vaccine that pumps up the host's antibody response. Following a vaccine or antibiotic treatment with anti-inflammatory drugs could decrease damage but has so far failed to do so in animal trials.

**Inhibit the bacterium's growth within infected cells.**
Interfere with the activity of the proteins chlamydia uses to divert lipids and other nutrients from the host cell. Such proteins have not yet been identified; once found, they could potentially be immobilized by a specially designed vaccine.

**Promote intracellular destruction of the bacterium.**
Disable the bacterium's type III secretion apparatus, which may release proteins that ward off lysosomes, constituents of the host cell that chop up foreign invaders.

In trials, bacteria with nearly identical apparatuses have been unable to cause symptoms of infection when scientists have disabled the genes that code for each apparatus; this finding suggests that drugs able to block the proteins encoded by those genes in chlamydia could be helpful.

**Halt the bacterium's ability to spread.**
Induce "suicide" of infected cells before the bacterium has a chance to convert into the form able to invade uninfected cells. Compounds that can induce premature cell death in tumors are under development; the same drugs could theoretically work against chlamydia.

latter avenue may prove more fruitful in developing a vaccine. By rendering persistently infected cells more sensitive to apoptosis, it might be possible to eliminate the bacteria that remain dormant in the system for long periods as well as decrease the lasting consequences of chronic infection.

### Multiple Avenues of Attack

REGARDLESS OF THE DISCOVERIES that lie ahead, the ideal chlamydia vaccine will not be a simple one. It will have to activate both the antibody and cellular arms of the immune system more effectively than the body's natural response does yet somehow limit inflammation as well. For those concerned with preventing chlamydia-related STDs, an additional challenge is ensuring that memory lymphocytes remain in the genital tract poised to combat infection at all times. This tract does not contain the type of tissue that produces memory cells; such cells tend to vacate the area, leaving the person susceptible to infection after a brief period of immunity.

Recall that females bear the lasting effects of genital infection. One feasible goal of a vaccine might be to protect women from the disease rather than from infection per se. This aim might be achieved by vaccinating both men and women. In this scenario, the vaccine would have to generate only enough antibodies to reduce, rather than eliminate, the amount of bacteria men carry. Then, if a woman were exposed to a man's infection through intercourse, memory cells induced by her immunization would travel to the genital tract in numbers adequate for killing the relatively small number of organisms before they spread to her fallopian tubes.

Until researchers manage to develop such a vaccine, contraceptives that include antichlamydial drugs could pay off. These agents might take the form of compounds that either block the proteins chlamydiae use to bind to genital tract cells or target the proteins the microbes secrete to promote intracellular survival. For eye infections, the only vaccine likely to be useful is one that completely prevents infection.

While awaiting effective preventive strategies against chlamydia, it is worth remembering that current antibiotic treatment is highly successful when it is accessible. New details from genomic discoveries indicate that this efficacy will continue. Compared with free-living bacterial pathogens, which can share genes easily, the genomes of *Chlamydia* species have remained essentially the same for millions of years. This genetic stability implies that chlamydiae cannot easily acquire genes—including those for antibiotic resistance—from other bacteria.

It is also worth noting that antibiotics cannot undo the tissue damage caused by inflammation, and to be most useful, they must be given early. Therefore, more widespread screening of high-risk individuals is needed. Researchers have already proved the feasibility of employing noninvasive urine screening of sexually active young men and women, particularly in settings such as high schools, military intake centers and juvenile detention facilities. Public health officials need to pursue such strategies in parallel with the ongoing search for effective vaccines. SA

### MORE TO EXPLORE


***Chlamydiae pneumoniae*—An Infectious Risk Factor for Atherosclerosis?** Lee Ann Campbell and Cho-cho Kuo in *Nature Reviews Microbiology,* Vol. 2, No. 1, pages 23–32; January 2004.

**Chlamydia and Apoptosis: Life and Death Decisions of an Intracellular Pathogen.** Gerald I. Byrne and David M. Ojcius in *Nature Reviews Microbiology,* Vol. 2, No. 10, pages 802–808; October 2004.

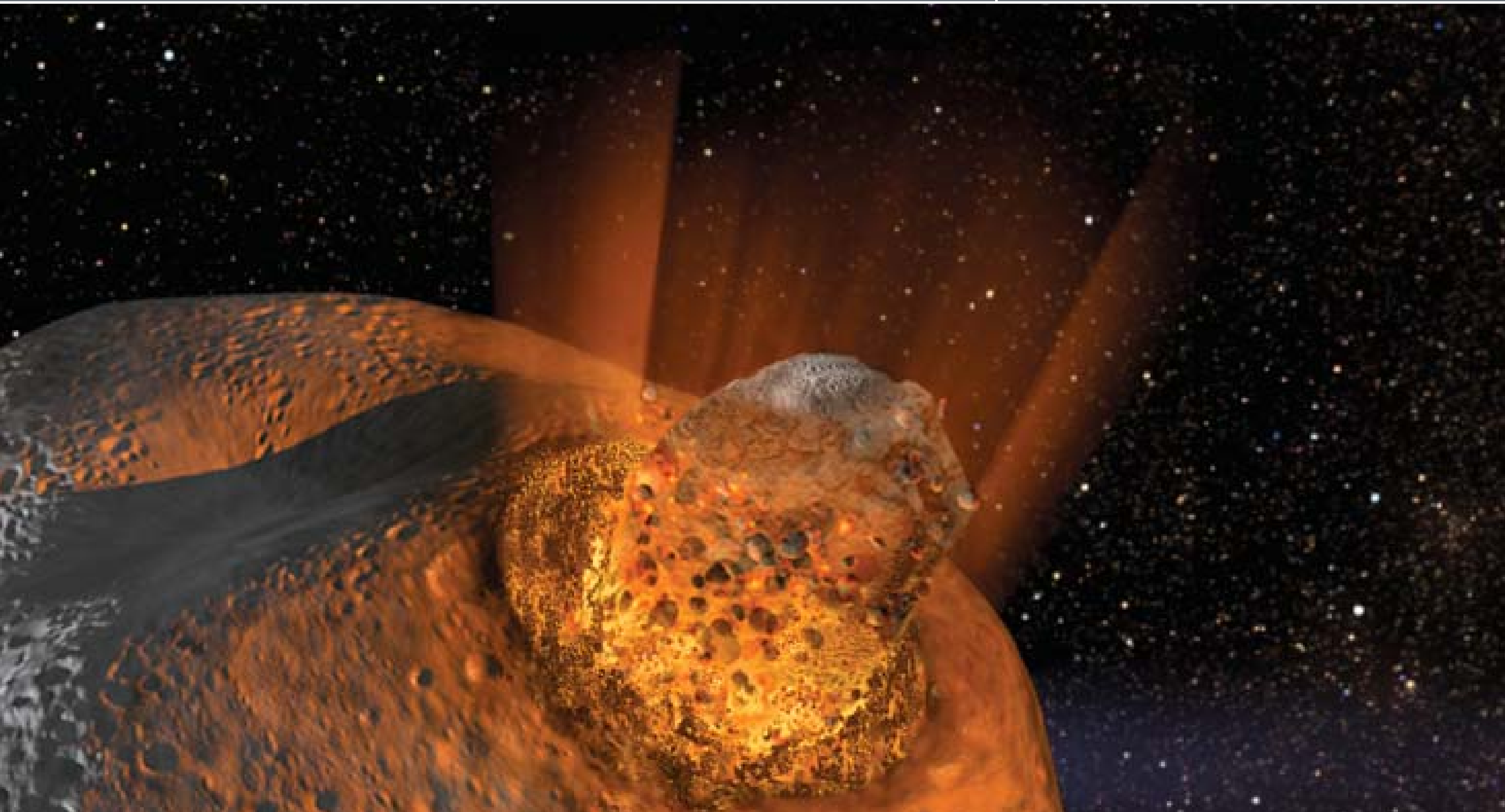
Basic information on the infections, genomes, basic biology and immunology of chlamydia can be found at **http://chlamydia-www.berkeley.edu:4231/** and **www.chlamydiae.com/chlamydiae/**

# What Heated the

Collisions among asteroids in the early history of the solar system may

# Asteroids?

By Alan E. Rubin



help explain why many of these rocky bodies reached high temperatures

## Big objects retain heat better than small objects do.

Most of Earth's internal heat is generated by four long-lived radioisotopes—potassium 40, thorium 232, uranium 235 and uranium 238—that release energy over billions of years as they decay into stable isotopes. Earth's large size (about 12,740 kilometers across) ensures that this heat is lost relatively slowly, which explains why our planet still has a molten outer core and volcanic eruptions at its surface. Smaller bodies, however, have a larger ratio of surface area to volume, allowing them to cool down faster by radiating their heat into space. Earth's moon, for example, is only about one fourth the size of Earth, so it loses heat much more quickly. As a result, major lunar eruptions of basalt, the most common volcanic rock, ceased nearly three billion years ago.

Heat loss is even faster in the small rocky asteroids that whirl through the inner solar system, mostly between the orbits of Mars and Jupiter. Vesta, the third-largest asteroid, has a diameter of 516 kilometers, giving it a surface-to-volume ratio 25 times greater than Earth's. But a paradox arises: despite its small size, Vesta shows evidence of past geologic activity. Spectroscopic observations of Vesta's surface indicate that it is covered with volcanic basalt, leading researchers to conclude that Vesta's interior once melted. The cause of the heating cannot be long-lived radioisotopes; given the primordial concentrations of the isotopes and the expected rate of heat loss, calculations show that the radioactive decay could not have melted Vesta or any other asteroid. Another heating mechanism must therefore be responsible, but what is it? This question has dogged planetary scientists for decades.

In recent years, though, a possible answer has emerged from spacecraft observations, particularly those made by the Near Earth Asteroid Rendezvous (NEAR) mission. As the NEAR spacecraft flew by the asteroid Mathilde in 1997, measurements of the gravitational pull on the craft revealed that the asteroid's mass was unexpectedly low. Scientists concluded from the low density that Mathilde is a highly porous pile of rubble with gaps and voids in its structure. This finding has challenged researchers' assumptions about the dynamics of asteroids and raised the possibility that collisions among the rocky bodies could have generated large amounts of heat (although Mathilde itself probably never melted). This hypothesis is controversial, but it is supported by new studies of meteorites, the pieces of asteroids that have landed on Earth. If proved correct, the collisional-heating theory could solve a long-standing astronomical mystery as well as revamp our understanding of the early history of our solar system.

### Toasty Meteorites

ONE OF THE KEY TOOLS for investigating asteroids is spectroscopy: astronomers compare the spectra of light reflected off the rocky bodies with the reflectance spectra determined for rocks in the laboratory. Different minerals absorb and reflect light at different wavelengths; basalt, for example, strongly absorbs light just beyond the red end of the visible spectrum. Asteroid researchers have used spectroscopy to categorize asteroids into taxonomic classes. The inner part of the asteroid belt is dominated by S-class asteroids, a mixed group that probably contains some bodies that once melted and others that never melted. In the outer part of the belt—farther than about 450 million kilometers from the sun—the predominant objects are C-, P- and D-class asteroids, all of which appear to be primitive bodies that never melted. A significant drawback to remote spectroscopy is that astronomers can examine only the uppermost surface of a body. In some cases, the dusty outermost layer of an asteroid may not be representative of the underlying crustal material.

An alternative is to inspect the meteorites that originated in the asteroid belt. Detached and ejected from their parent asteroids as a result of impacts, these rocks gradually migrated to Earth-crossing orbits and were finally captured by our planet's gravity. (The vast majority of the tens of thousands of meteorites in institutional collections came from the asteroid belt; only 60 or 70 specimens are believed to have been ejected from the moon or Mars.) The most common meteorites are the chondrites, which typically contain many small spheres called chondrules [*see box on page 84*]. Composed mainly of silicate minerals and measuring about one millimeter across or less, the chondrules formed nearly 4.6 billion years ago in the solar nebula—the cloud of gas and dust from which the solar system emerged—and later became the principal components of the asteroids as the rocky bodies began to assemble.

Scientists know that the chondrites never melted after the formation of their parent asteroids because melting would have obliterated their chondrules. Nevertheless, many of the chondrites do show signs of having been heated to temperatures below the chondrules' melting point. The chondrites are divided into six types depending on the amount of thermal metamorphism or aqueous alteration—mineralogical changes caused by heat or water—that they have undergone since their creation. Type 3 chondrites are the most primitive; the mineral grains

### Overview/*Heat from Asteroid Impacts*

- Studies of asteroids show that despite their small size they reached high temperatures in the early history of the solar system.
- Geochemists have hypothesized that the source of asteroid heating was a short-lived radioisotope of aluminum, but new calculations suggest that radioactive decay alone would not have been sufficient.
- Collisions among porous asteroids could have supplied the extra heat. Meteorite evidence indicates that high-energy impacts may have heated many asteroids in the era following their formation.

DON DIXON (*preceding pages*)

in these meteorites never recrystallized as a result of heating. These rocks also have moderately high abundances of volatile substances (including noble gases and water) and contain numerous tiny presolar grains (dust particles that formed long ago in the outer atmospheres of other stars and remained unchanged through the history of our solar system). Such characteristics indicate that the type 3 chondrites were never heated above 400 to 600 degrees Celsius.

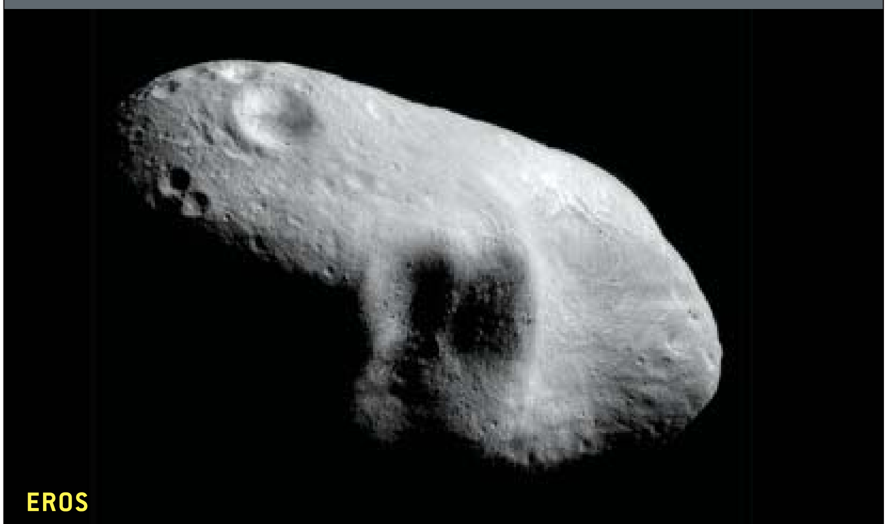
Although the type 3 chondrites never experienced high temperatures, many underwent aqueous alteration on their parent asteroids. The source of the water may have been ice crystals that melted when the rocks were heated above zero degrees C or water-bearing silicate minerals that dehydrated at a few hundred degrees C. Chondrites designated as types 1 and 2 differ from type 3 mainly in having experienced a greater amount of aqueous alteration, with the water oxidizing much of the iron and nickel in the rock. The water content (by weight) of the meteorites is about 11 percent for type 1 chondrites, about 9 percent for type 2, and 2 percent or less for type 3.

Chondrites of types 4 through 6 show increasing levels of thermal metamorphism. Extensive recrystallization has caused the chondrules and the adjacent mineral grains in the matrix—the material in which the chondrules are embedded—to coarsen and impinge on one another. In addition, heating has destroyed most of the presolar grains and greatly reduced the content of noble gases and water in the rocks. These chondrites apparently reached temperatures ranging from 600 to 950 degrees C.

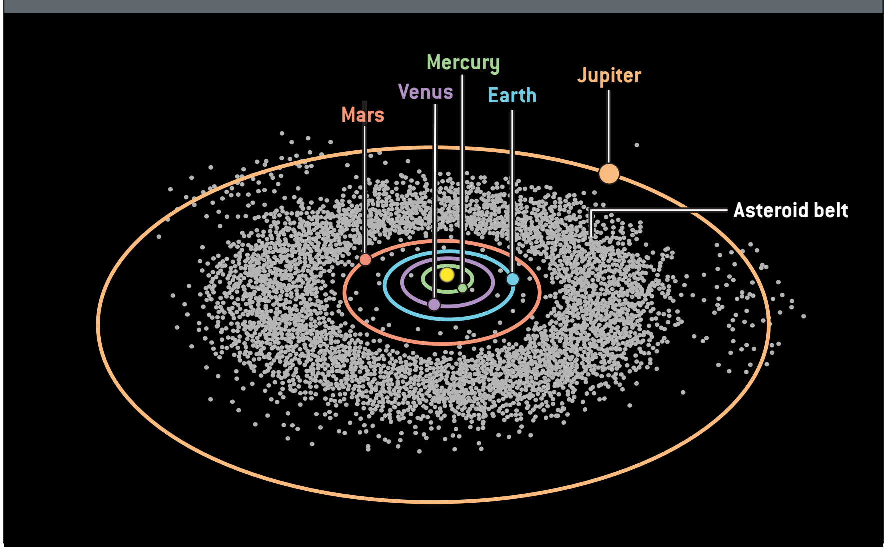
Still other classes of meteorites show signs of melting. If a chondritic asteroid melts completely, the metals and silicates will form immiscible liquids: they will separate according to density, just like oil and water. The dense liquid iron and nickel will sink to the asteroid's core and slowly crystallize as it cools. Above the core, the silicates will harden into a stony mantle; partial melting of the mantle will produce basalts that can rise to the surface and form a crust. The result is called a differentiated body, and many

## ASTEROIDS: PRIMORDIAL RELICS

The asteroids formed more than 4.5 billion years ago, when rocky bodies in the solar nebula began to coalesce. In 1997 the Near Earth Asteroid Rendezvous (NEAR) spacecraft flew by Mathilde (*right*) and found evidence that this asteroid is a porous rubble pile deformed by violent impacts. In 2000 NEAR went into orbit around Eros (*below*), a smaller, denser body pocked with craters.


▼ Most asteroids, including Mathilde, are in a belt between the orbits of Mars and Jupiter. (Eros is in an orbit closer to Earth.) Although the diagram makes the asteroid belt look crowded, the larger bodies are actually millions of kilometers apart.




NASA/NSSDC (*Mathilde and Eros*); JEN CHRISTIANSEN (*orbital diagram*) meteorites appear to have come from such asteroids. Most of the iron meteorites—the biggest of the extraterrestrial fragments found on Earth—are chunks of the cores of melted asteroids. Many of the stony-iron meteorites are believed to have come from the boundary between the core and the mantle, and yet another group of meteorites, the eucrites, apparently originated in the crust.

In all, more than 90 percent of the asteroidal meteorites that have been observed falling to Earth before they are recovered on the ground bear evidence of melting (for example, the irons, stony-irons and eucrites) or significant metamorphism (the chondrites of types 4, 5 and 6). It is thus clear that many asteroids were once quite hot. But what mechanism could have raised the temperatures of the asteroids to this extent if the rocky bodies were too small to retain the heat from long-lived radioisotopes?

## Aluminum Heating?

A POSSIBLE SOLUTION was suggested 50 years ago by Nobel Prize–winning chemist Harold Urey, who proposed that the decay of the relatively short-lived radioisotope aluminum 26 ($^{26}$Al) could have heated the asteroids. Unlike the more common aluminum 27 ($^{27}$Al), which has one more neutron, $^{26}$Al is unstable; it decays into the isotope magnesium 26 ($^{26}$Mg), releasing energy in the process. $^{26}$Al has a half-life of 730,000 years, thousands of times shorter than the half-lives of the long-lived radioisotopes. Because $^{26}$Al decays so rapidly, tiny amounts of the isotope can dramatically raise the temperature of even a small body before the heat is lost to space. But the heating does not last long; within a few million years, nearly all the $^{26}$Al transmutes into $^{26}$Mg.

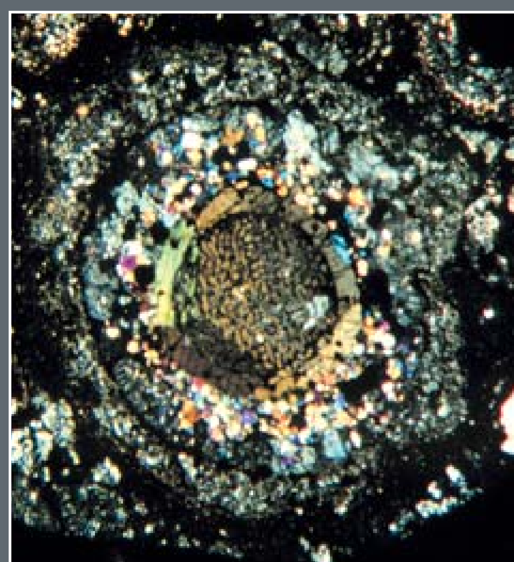
Some scientists maintain that the $^{26}$Al in our solar system was produced by nuclear reactions inside another star and then spread by a supernova explosion, which injected the isotope into the solar nebula about 4.6 billion years ago. In fact, some researchers have theorized that it was the shock wave from this same supernova that triggered the collapse of the gas cloud from which the sun and planets formed. Such an event could have spread $^{26}$Al uniformly throughout the nebula, providing a heat source to rocky bodies assembling at various distances from the sun. (Alternatively, some $^{26}$Al could have been formed by intense irradiation of particles near the early sun that were later blown outward by the turbulent winds.) If the abundance of $^{26}$Al was high enough, it could have completely melted some asteroids soon after their formation. In those that assembled later, and thus incorporated lower amounts of $^{26}$Al, the radioisotope heating would have produced an onion-shell structure; because the asteroid's interior would cool more slowly than the exterior, the rocks in the core would be the most metamorphosed (becoming, for example, type 6 chondrites). Progressively less metamorphosed rocks (types 5, 4 and 3 chondrites) would reside in concentric shells closer to the asteroid's surface.

To test this hypothesis, scientists have searched for unusually high amounts of $^{26}$Mg, the decay product of $^{26}$Al, in meteorites. In particular, geochemists look for excesses of $^{26}$Mg in meteorite minerals that contain abundant aluminum but not much magnesium. In most recent studies, researchers have analyzed aluminum-rich minerals such as anorthite and hibonite using an ion microprobe, which bombards a sample with a focused ion beam to release secondary ions from the sample's surface. The instrument directs the secondary ions to a mass spectrometer that identifies their compositions.

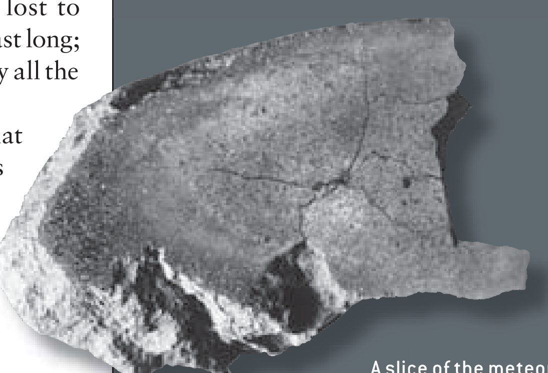
These investigations have found strong evidence for the former presence of $^{26}$Al in the so-called refractory inclusions: tiny mineral assemblages, rich in calcium and aluminum, embedded in chondritic meteorites alongside the chondrules. The minerals in these assemblages form at high temperatures, at least 1,180 degrees C, so the refractory inclusions presumably date from the very beginning of the solar system's his-

## METEORITES: BITS OF HEAVEN ON EARTH

Scientists can explore the history of the asteroids by studying meteorites, rocks detached and ejected from their parent asteroids and captured by Earth's gravity. The most common are the chondrites, which typically contain many small spheres called chondrules. By slicing the rocks into thin sections and examining their crystalline structures under a microscope, geochemists can find evidence of heating and impacts.



▲ Microscope image of a chondrule in the Allende meteorite, which fell in Mexico in 1969, shows signs of heating. The concentric rings suggest it experienced at least three melting episodes.



A slice of the meteorite known as Colony, a 3.9-kilogram carbonaceous chondrite found on an Oklahoma cotton farm in 1975.

SMITHSONIAN INSTITUTION (*Colony*); ALAN E. RUBIN (*Allende and Kernouvé*) tory, before the solar nebula cooled significantly. In most of the inclusions studied, researchers determined that the abundance of $^{26}Al$ at the time of their formation—expressed as a ratio of $^{26}Al$ to the more common $^{27}Al$—was about $4.5 \times 10^{-5}$. This value has been called the canonical ratio.

At this relatively high abundance, $^{26}Al$ could have caused substantial heating. The ratio is the same for inclusions found in most classes of chondrites. (In addition to being categorized by metamorphic type, the chondrites are divided into three main classes based on their chemical compositions: ordinary, carbonaceous and enstatite.) But refractory inclusions account for just a small fraction of the aluminum in chondrites; much more is in the chondrules, which contain 30 to 90 percent of the aluminum in most chondrite classes. Thus, the chondrules should have made a much greater contribution to radioisotope heating than the refractory inclusions did.

In 2000 Noriko Kita of the Geological Survey of Japan and her co-workers examined the chondrules in ordinary chondrites—a class that comprises the three most common chondrite groups, which are labeled H, L and LL—and found that the average $^{26}Al$ to $^{27}Al$ ratio at the time of their formation was only $7.4 \times 10^{-6}$, about one sixth of the canonical ratio. Given the decay rate of $^{26}Al$, the lower initial ratio in the chondrules implies that these objects formed between one million and two million years after the creation of the refractory inclusions (assuming that the radioisotope was indeed homogeneously distributed in the early solar system). Because the chondritic asteroids formed after the chondrules did, the initial $^{26}Al$ to $^{27}Al$ ratio in chondrules places an upper limit on the amount of $^{26}Al$ that was available to heat the rocky bodies.

▼ The Kernouvé meteorite, a 4.45-billion-year-old ordinary chondrite that fell in France in 1869, was originally believed to be unshocked because its silicate grains did not appear deformed. But the presence of veins of metal, which appear yellow in the image, indicate that a high-energy impact had heated the rock.

## The vast majority of meteorites came from the asteroid belt.

It seems unlikely that this abundance would have been sufficient to cause all the heating observed in meteorites. Thermal models show that even if the asteroids assembled immediately after the formation of the chondrules, $^{26}Al$ heating would have raised temperatures in the interiors of ordinary-chondrite bodies to a maximum of 1,100 degrees C—high enough to cause melting of metals and sulfides but too low to melt silicate minerals extensively and differentiate an asteroid. The efficacy of radioisotope heating was even lower in the parent asteroids of the carbonaceous chondrites; in a study of the chondrules in one of these meteorites (conducted by Takuya Kunihiro and his colleagues at the University of California at Los Angeles, including me), we found an average initial $^{26}Al$ to $^{27}Al$ ratio of $3.8 \times 10^{-6}$, or about half the abundance found in the ordinary-chondrite chondrules. Even after making generous assumptions, we determined that the maximum temperature reached in carbonaceous-chondrite asteroids with a diameter of 80 kilometers or more would be only 670 degrees C, too low to cause any melting at all.

To circumvent this problem, advocates of $^{26}Al$ heating hypothesize that some chondrules might have formed earlier in the solar system's history—perhaps closer to the time when the minerals in the refractory inclusions condensed from the solar nebula—and thus had much higher $^{26}Al$ to $^{27}Al$ ratios. According to this scenario, researchers could never find evidence of such early chondrules because all these objects would have been destroyed by the melting of the chondritic asteroids into which they accreted. Although this hypothesis cannot be refuted, it seems unlikely. If such $^{26}Al$-rich chondrules once existed, there should also have been some intermediate chondrules that formed somewhat later and had moderately lower initial $^{26}Al$ to $^{27}Al$ ratios, not high enough to cause the destruction of the chondrules but higher than the ratios observed so far. Although such hypothetical chondrules should have been preserved, researchers have not yet found any. (To be fair, though, scientists have only just begun to look.)

## Some Alternatives

BECAUSE THE DEGREE of $^{26}Al$ heating may not have been sufficient to melt the asteroids, it is prudent to look for other possible heat sources. One frequently discussed alternative is another short-lived radioisotope: iron 60 ($^{60}Fe$), which has a half-life of 1.5 million years. Its decay product, nickel 60 ($^{60}Ni$) was found in a few eucrites by Alexander Shukolyukov and Gunter Lugmair of the University of California at San Diego and in a few chondrites by Shogo Tachibana and Gary Huss, then at Arizona State University. Yet the inferred initial abundance of $^{60}Fe$ is low, on the order of $3 \times 10^{-7}$. Kunihiro and his colleagues calculated that the decay of $^{60}Fe$ would raise temperatures in asteroids by only about 180 degrees C. The researchers concluded that the heat generated by the joint decay of $^{26}Al$ and $^{60}Fe$ could not have caused asteroidal melting.

## The same collisions that formed the asteroids also led to Earth's creation.

Another possible heating mechanism is electromagnetic induction. The early sun could have produced an intense ionized solar wind with an embedded magnetic field that moved outward at hundreds of kilometers per second. If this wind encountered asteroids that were electrically conductive, it could have induced currents in the rocky bodies, thereby generating heat. This idea, however, has few defenders because of its uncertainties. It is not clear that the early sun ever possessed such an intense wind. In addition, nascent stars that manifest such winds tend to emit them at their poles, far from any asteroids residing in the stars' equatorial accretion disks.

### Collisional Heating

THE ONLY REMAINING viable alternative is the heat produced when asteroids collide with one another. This hypothesis has its own problems, though. Klaus Keil, director of the University of Hawaii Institute of Geophysics and Planetology at Manoa, and his colleagues have raised various objections. First, a single impact cannot raise the global temperature of an asteroid-size body by more than a few degrees. Second, the high surface-to-volume ratios of such bodies promote heat loss, so they cool quickly between successive impacts. Third, a typical impact generates minuscule amounts of melted rock relative to the volume of the impact-generated debris. And last, the low escape velocities of asteroids allow much of the most strongly heated material to escape.

Although these objections are sound, they may be largely irrelevant because they assume that the target of the impact is a cohesive body with low porosity, such as Earth or its moon. As mentioned earlier, the discovery that many asteroids have very low densities (as low as 1.2 grams per cubic centimeter) indicates that many of these bodies are highly porous piles of rubble. The inferred porosity of Mathilde, for example, is 50 percent: half of this asteroid is empty space. What is more, asteroid porosities may have been even greater immediately after they accreted from the debris of the early solar system. Accretion occurs at very low relative velocities and forms fluffy structures; energetic impacts are required to compress the porous materials into cohesive bodies.

When a large meteorite strikes Earth's surface, it creates a shallow crater; on a low-density asteroid, a similar impact would drill a deep, nearly cylindrical depression into the porous body [*see box on opposite page*]. Because shock energy attenuates rapidly in porous materials, an impact can heat the rocks bordering the deep crater very efficiently. Compared with impacts into cohesive targets, more energy goes into heating the rocks inside the asteroid and less goes into ejecting debris. Instead debris would fall back into the depression, cover the initial crater and act as a blanket, retarding heat loss. Although the global temperature of the asteroid would not increase appreciably, parts of the target would be significantly heated; some rocks would even be melted. Successive impacts would create a large number of metamorphosed regions in the vicinity of craters.

Studies of meteorites are now providing evidence for the collisional-heating hypothesis. Researchers have traditionally determined whether a meteorite is shocked—that is, whether it has ever experienced a major impact—by examining the structure of its silicate grains. Strong shocks deform crystal structures and create mosaic patterns that are easily detectable under the microscope. (The collision that detached the meteorite from its parent asteroid is usually not the cause of the shock; debris is typically ejected without its constituent minerals being significantly deformed.)

I recently examined more than 200 metamorphosed ordinary chondrites that were initially classified as unshocked or very weakly shocked because their silicate grains did not appear deformed. Yet I found that every one of these rocks in fact possessed other shock-produced features, such as veins of metal. (Because metals have lower melting points than silicate minerals, they often liquefy and form veins after an impact.) I concluded that every metamorphosed ordinary chondrite has been shocked and subsequently heated, some of them multiple times. Signs of shock were easy to miss because the heating had erased some of the shock features by annealing the deformed silicate grains.

Isotope dating of one shocked-and-heated ordinary chondrite by Eleanor Dixon (then at the NASA Johnson Space Center) and her co-workers (including me) showed that the rock underwent this trauma about 4.27 billion years ago. Short-lived radioisotopes could not have been the source of the heating because this event occurred about 300 million years—or about 400 half-lives of $^{26}$Al—after the asteroids formed. If impacts were capable of generating heat this late in the history of the solar system, they must also have been capable of heating the asteroids during earlier times when impacts were more prevalent. In fact, I identified a few highly metamorphosed ordinary chondrites that are consistent with this scenario: they date from about 4.45 billion years ago and have prominent shock features, such as melted metal and sulfide assemblages, adjacent to apparently annealed silicates.

The hypothesis that impacts were a major contributor to asteroid heating can be further tested by looking for a positive correlation between the meta-

THE AUTHOR

*ALAN E. RUBIN* is a geochemist at the University of California, Los Angeles, whose research has focused on shock effects in meteorites and the nature and origin of their chondrules. Rubin received his Ph.D. in geology from the University of New Mexico in 1982. In 2002 Asteroid 6227 was named "Alanrubin" in honor of his contributions to meteorite research. He is author of *Disturbing the Solar System: Impacts, Close Encounters and Coming Attractions* (Princeton University Press, 2002).

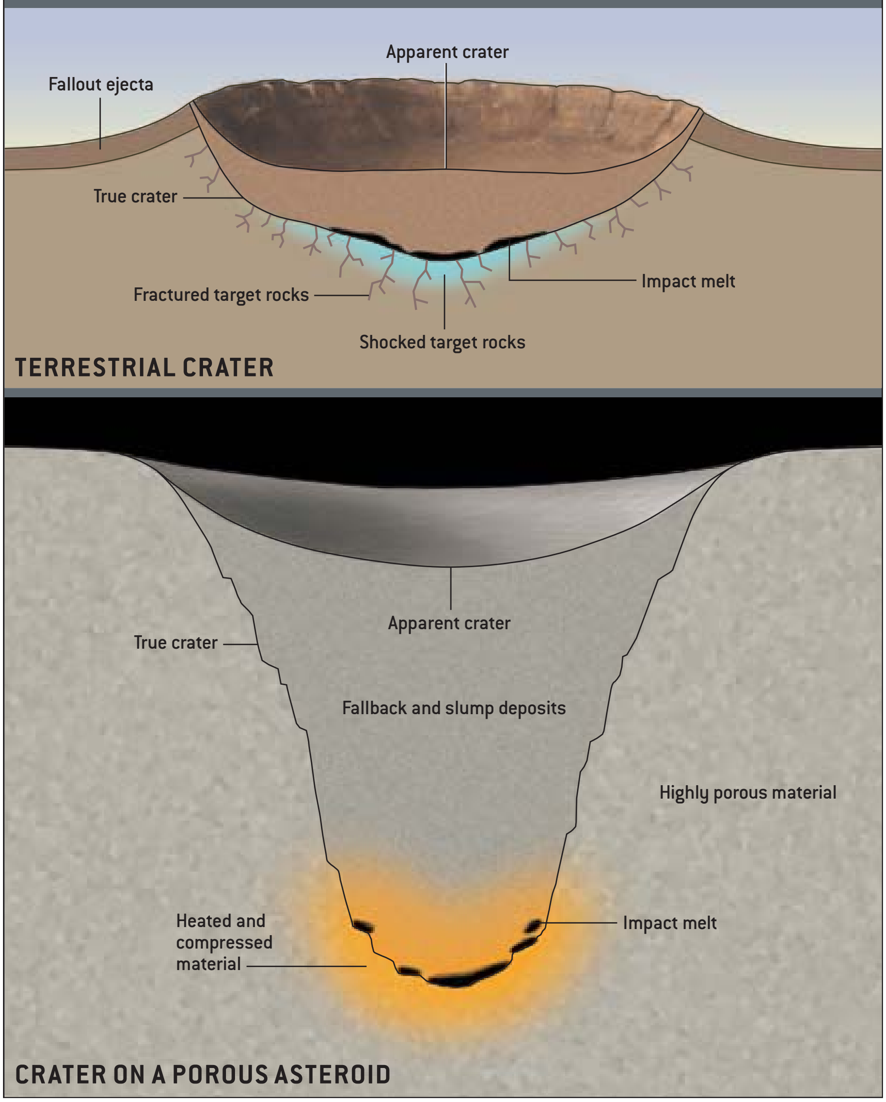
morphic grade of chondrites and their degree of shock. Rocks that were hit harder should have been heated more. Data on more than 1,650 ordinary chondrites that I culled from the *Catalogue of Meteorites* show that this is indeed the case. Collisional-heating models also predict that the chondrite groups with the greatest proportions of metamorphosed members would have the greatest proportions of shocked members. This, too, is the case for the ordinary- and carbonaceous-chondrite groups.

In summary, a fair appraisal of the evidence indicates that collisions and the decay of $^{26}$Al were both important sources of asteroidal heating. In my view, collisions were the dominant mechanism, but most cosmochemists still cast their lot solely with $^{26}$Al. If impact heating was dominant, the thermal histories of asteroids would be at odds with those predicted by the standard onion-shell model of asteroid interiors. For example, the cooling times for rocks buried underneath the floors of impact craters would be far shorter than the millions of years postulated for interior rocks heated by the decay of $^{26}$Al. Ed Scott of the University of Hawaii at Manoa recently conducted a review of data on cooling times for one group of ordinary chondrites and concluded that the preponderance of evidence was against the layered parent-body structure that would be expected from $^{26}$Al heating.

Asteroids, planets and comets share a common ancestry. The same collisions that formed and cratered the asteroids also led to the creation of Earth; the bodies in the asteroid belt would have also agglomerated into a planet if not for the disturbing influence of Jupiter's gravity. For this reason, the asteroids offer a revealing glimpse into the evolution of our own planet 4.5 billion years ago. The ancient pockmarked surfaces of most of these rocky bodies indicate that high-energy impacts remained frequent for hundreds of millions of years. The recent recognition that collisions among asteroids may have been at least partly responsible for heating these bodies demonstrates once again that the effects of cratering are not just skin-deep. SA

## CRATERS COMPARED

When an object slams into a cohesive body such as Earth, it creates a bowl-shaped crater and ejects large amounts of debris (*top*). Some of the debris settles in the crater (creating the apparent crater, which is about half as deep as the true crater), and some surrounds the crater's rim. But when an object strikes a low-density asteroid, it drills through the porous material like a bullet in Styrofoam (*bottom*). The impact energy goes into heating and compressing rocks instead of ejecting them; the debris falls back into the crater and retards heat loss. This process may explain why so many meteorites show signs of shock and heating.




JEN CHRISTIANSEN

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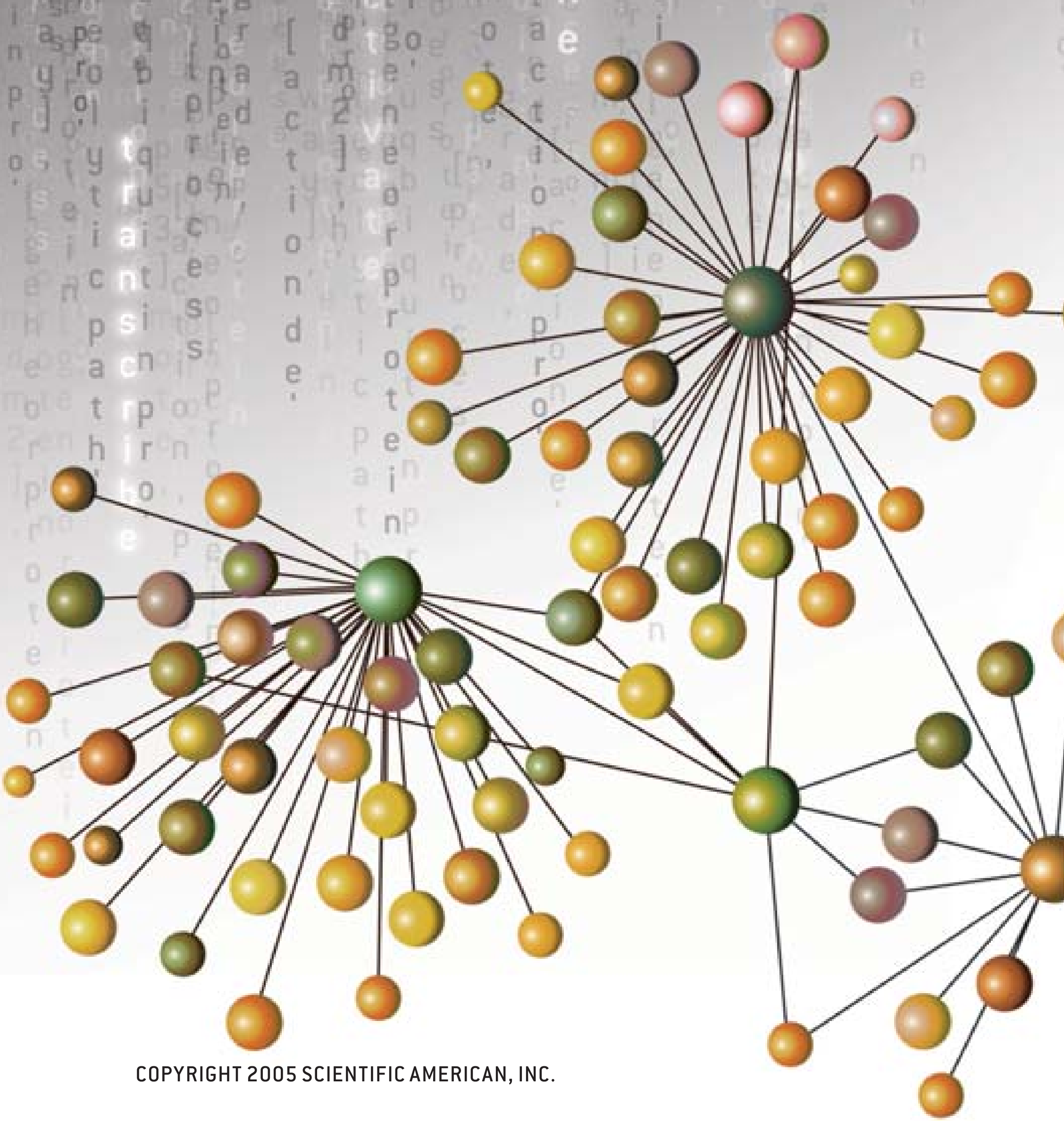
# MOLECULAR TREASURE HUNT



*A software tool elicits previously undiscovered gene or protein pathways by combing through hundreds of thousands of journal articles*

By Gary Stix

When Andrey Rzhetsky arrived at Columbia University as a research scientist in 1996, the first project he collaborated on involved a literature search to try to understand why white blood cells called lymphocytes do not die in chronic lymphocytic leukemia. The mathematician-biologist found a few hundred articles on apoptosis (programmed cell death) and the cancer. Even if he had devoted every moment to the task, it would have been impossible to perform a comprehensive scan of everything that had reached the journals. Worse, "it was just the tip of the iceberg, not nearly enough to understand the whole process," he laments.

The experience led him to an idea that would have made his job on that first project much easier: an automated search tool that could supplant the mind-numbing task of finding and reading all the literature. But it also might do much more; it could even let a machine conduct research on its own, discovering the patterns among the data much as a human would do.

Rzhetsky's outsized approach to the research endeavor had been shaped by his postdoctoral adviser, Masatoshi Nei, a renowned phylogenist from Pennsylvania State University and a major figure in population genetics. Nei had recruited Rzhetsky to Penn State in 1991 from the Institute of Cytology and Genetics, a locus of mathematical biology in Novosibirsk, Siberia. When Rzhetsky received the offer, the Soviet Union was in free fall, and restrictions on academic exchanges had eased, giving outsiders access to the wealth of mathematical talent harbored there. Rzhetsky had risen through the Soviet star system, not unlike the one for athletics, by winning several math Olympiads in his native Kazakhstan.

Nei knew of the skills of Russian mathematicians but quickly set about teaching Rzhetsky that any problem in statistics had to be one that would deepen insight into biology and not merely demonstrate that his pupil was a math whiz kid. Rzhetsky recalls Nei telling him, "It's easy to find some mathematical toy that's completely useless for biology."

When Rzhetsky left Novosibirsk, he planned to return a year later, but with the nation's collapse the Siberian institute had sunk into chaos. Nei helped him procure his permanent residency, and in 1996 he moved to Columbia. In addition to steeping him in the laboriousness of literature searching, the leukemia project made him realize that the topic of molecular networks, the patterns of how genes or proteins interconnect, was largely unstudied—making it an important area that met the Nei test of ensuring that mathematics would function in the service of biology.

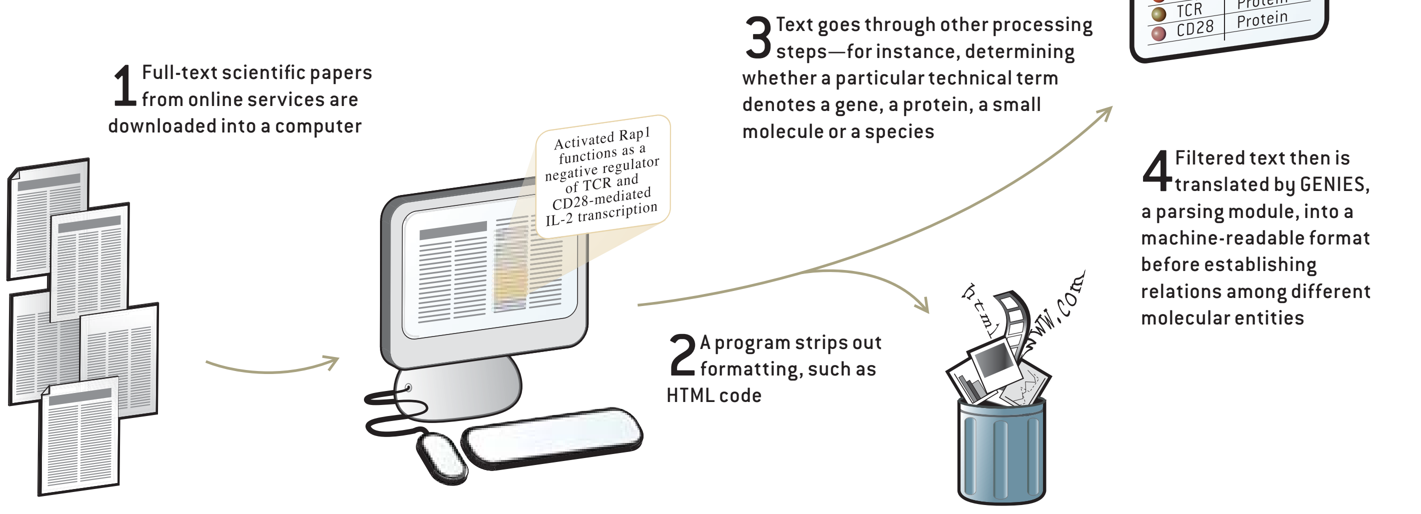
In 1997 Rzhetsky received a grant of $100,000 from the university's Center for Advanced Technology to begin development of his automated search tool. A few researchers of natural language—the artificial-intelligence subfield that deals with languages used by humans, not computers—were devising tools for biological searches and data extraction but mostly for abstracts rather than entire papers. Rzhetsky set about designing a system that would not only search entire articles but also identify networks of overlooked relations among genes and proteins—in essence, eliciting new knowledge and hypotheses by examining a large corpus of old information. "Scientists see only a small portion of what's known," he says of the rationale for building the system that became known as GeneWays. The full power of text mining might even foster the discovery of novel pathways that could then be tested in the laboratory.

To become more than just a glorified Google, GeneWays had to incorporate multiple software modules. Each module would encompass a task such as downloading papers off the Web, deducing the various pathways, and outputting graphics that delineate each gene or protein and how they tie together. After downloading an article and converting it into plain text—stripping out HTML, the document coding, can itself pose a challenge—the software must "understand" the terms invoked by the scientist. The name "p53" might refer to a

ALISON KENDALL

## DEEP SEARCH: MINING NEW KNOWLEDGE FROM OLD INFORMATION

GeneWays software "reads" tens of thousands of scientific papers and files information automatically into a database. In response to a query about a certain molecule or pathway, the database can then define how that molecule relates to others, a process that allows discovery of new molecular interactions and pathways. Text mining enables a more wide-ranging search of the literature than can be carried out by humans using manual methods.




LUCY READING-IKKANDA

gene, a protein or a messenger RNA, depending on sentence usage. Moreover, for some genes—*forever young* in the plant *Arabidopsis thaliana* or *mothers against decapentaplegic* in fruit flies—their function as utilitarian DNA is disguised by the whimsicality of their discoverers.

The best tools in statistics and AI were thrown at the problem. The most understandable part of this identification and disambiguation phase is a parts-of-speech tagging engine that helps other modules grasp noun phrases, such as "the tumor suppressor p53." The rest of this information grinder is a mathematical and computer science miasma that consists of the likes of support-vector machines, hidden Markov models, Naive Bayes classifiers and decision-tree algorithms.

Once an object is identified as gene, protein, RNA or small organic molecule, GeneWays proceeds to structure the information using a parsing module called GENIES so that a computer can "read" each sentence from an article. Rzhetsky and his group drew on Columbia's deep resources in the natural-language area.

In 1995 researcher Carol Friedman led a team at Columbia that completed a natural-language system referred to as MedLEE. It enabled the textual information in chest x-ray medical records at what is now called New York–Presbyterian Hospital (and later other records) to be extracted for use in multiple automated hospital information systems. Friedman (now a professor) and Rzhetsky took parts of MedLEE and used them as the foundation for developing a grammar specialized for molecular biology. The grammar specifies relations among distinct molecular entities.

GENIES might begin this process by lifting the following sentence from a molecular biology paper:

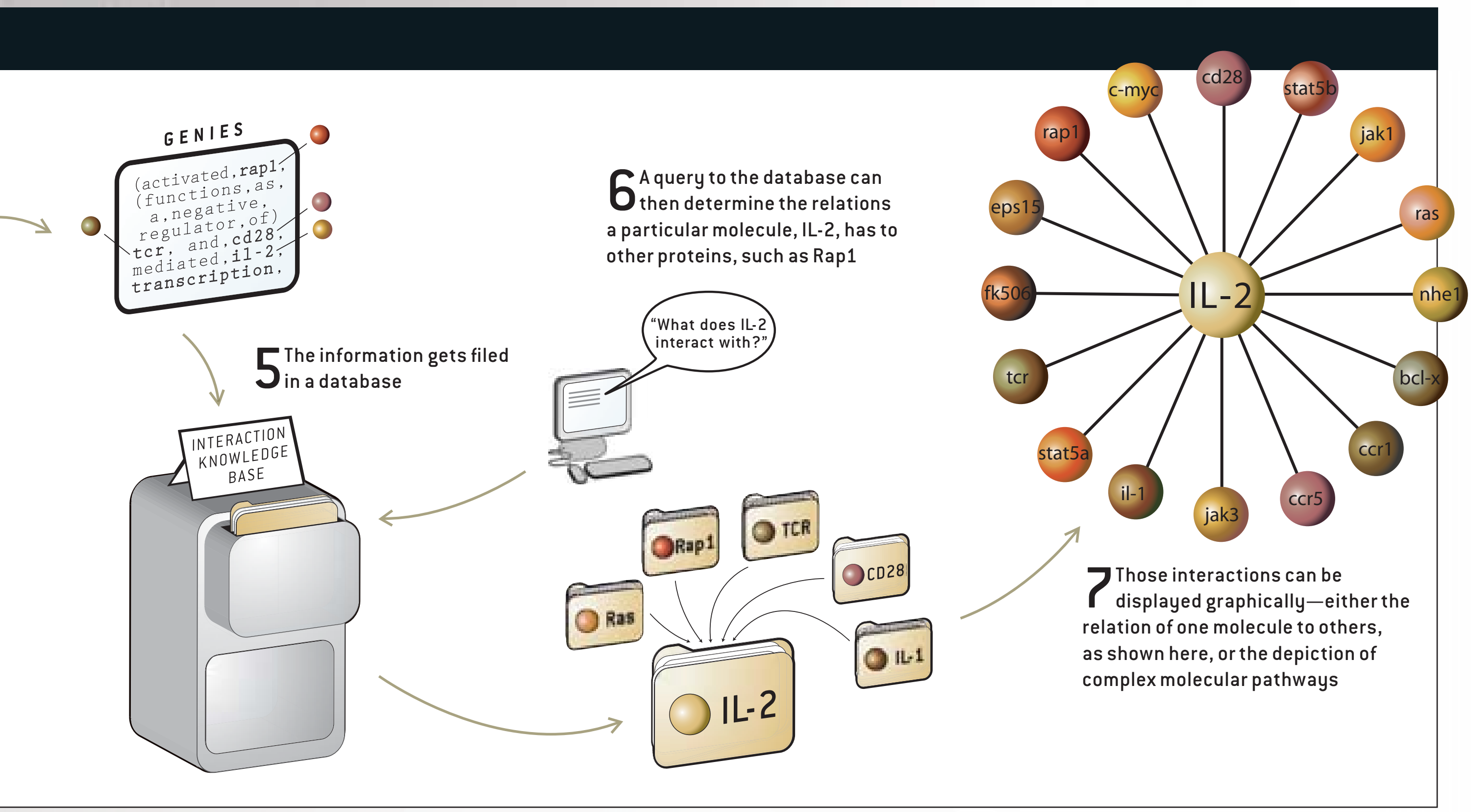
> Recent studies have reported that mdm2 promotes the rapid degradation of p53 through the ubiquitin proteolytic pathway.

It would then take the description of one protein, mdm2, promoting degradation of another, p53, through an enzyme pathway that involves a protein, ubiquitin, and translate it as:

```
[action promote,
    [geneorprotein mdm2],
    [action degrade,
            [process ubiquitin proteolytic pathway],
            [geneorprotein, p53]]]
```

A database—the Interaction Knowledge Base—can then store and access this so-called semantic tree. Its more than two million unique statements, such as "mdm2 promotes degradation of p53," can be used for searching the database, finding relations among molecules or building new networks of molecular interactions. It draws these statements from about 250,000 full-text articles from 80 journals in molecular biology. Other GeneWays modules determine the reliability of a given statement, look for additional relations and display the various pathways graphically.

The idea of modeling molecular interactions from the existing literature was slow to gain acceptance in the broader scientific community. For years, the National Institutes of Health and the National Science Foundation turned down Rzhetsky's grant applications. Reviewers at the NIH—and even big-name scientists—said they believed that GeneWays was either impossible to execute or would only rediscover the




obvious, turning up pathways that an experienced scientist had to memorize in graduate school. The flow of grant money started to thaw about five years ago for no apparent reason, although by that time the bioinformatics field had come into its own.

By 2001 Rzhetsky had begun to collaborate with Kevin White, a Yale University geneticist. White helped to broaden the scope of the Interaction Knowledge Base by incorporating raw genomics and proteomics data from the fruit fly *Drosophila melanogaster.* Graphical depictions derived from both textual and experimental data identified various new possibilities for genes involved in the fruit fly's early development, genes that could then be researched in the laboratory. "It allows us to look at several different large data sets systematically and simultaneously," White says, adding, "It's like PubMed on steroids," a reference to the ubiquitous biomedical database.

In another project, reported in an October 19, 2004, paper in *Proceedings of the National Academy of Sciences USA,* Rzhetsky worked with Columbia researchers to find new genes that might cause Alzheimer's disease. GeneWays began with four "seed" genes that had a proven role in Alzheimer's and then, based on a literature analysis, created a model of genes and proteins that interact with those four genes. It was assumed that genes with the minimum number of intermediary links to the seed genes would be the most likely Alzheimer's candidates. The genes identified matched closely those spotted by an expert using manual methods.

The accuracy of automated text mining does not replicate—and probably never will—the work of human curators who sift through the literature document by document. "GeneWays is valuable because we don't have enough people to scan the literature," says Peter Karp, a bioinformatics researcher at SRI International. "But it's not to the point that it can replace people." The development of the software, however, has progressed sufficiently so that Columbia has licensed it to a small New York City–based start-up called ExerGen Biosciences.

Even with this deal, Rzhetsky, now a tenured professor, can still continue to develop GeneWays on a noncommercial basis at Columbia. If Rzhetsky has his way, GeneWays will grow until its knowledge base encompasses all of biology and chemistry. "It's completely doable technically," he says. For now, Rzhetsky, White and their collaborators are working to expand the scope of GeneWays by using literature analyses to show how consensus is achieved among biologists.

What they have found is that, at the most fundamental level, the herd instinct prevails. A simple statement—"Protein A activates gene B"—is usually taken as gospel, a "microparadigm" that makes existing knowledge difficult to contradict, even in the face of new evidence. Documenting the process of collective reasoning demonstrates how GeneWays allows for a deeper reading of the published literature. It also shows the potential for text mining to extend bibliographic analysis to unify the full range of human knowledge. SA

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# WORKINGKNOWLEDGE

**SLIM TV**

# Thin Is In

**The narrow profile** of plasma and liquid-crystal-display (LCD) televisions has caught the public's eye, but the sets are still far more expensive than the conventional cathode-ray tubes (CRTs) that have long dominated the market. Nevertheless, CRTs have lost some luster. Manufacturers are responding by designing a much shallower picture tube.

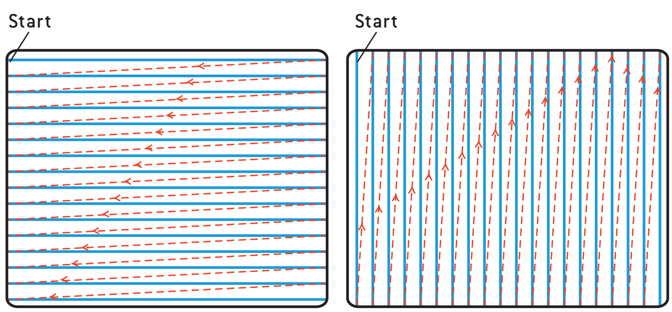
Several makers have unveiled prototype slim TVs, which could be sold in the U.S. by this summer. A 30-inch (diagonal) set will be about 16 inches deep instead of 24 inches and be priced somewhat higher. Though heftier than the eight inches or so for a plasma or LCD in the 30-inch range, slim TVs will "save considerable space and maintain their superior picture quality and cost savings," says Istvan Gorog, general manager of Thomson/RCA's R&D Center in Lancaster, Pa.

Slim TVs, in laboratories for some time, will handle the usual analog signals from broadcast and cable TV providers and may offer tuners for the digital television signals that carry so-called high-definition television. Flat-panel fronts, instead of the usual curved CRT faces, will also be available.

A shorter tube means that the three electron beams that sweep horizontally across the screen must cover a wider angle from side to side. That stretch distorts the illumination of the screen's phosphor pixels, which emit the light that viewers see. To keep the beams properly focused, the electron-emitting gun has to continually reshape the cross section of each beam. At the same time, magnets must direct each beam differently. The electronics that control these tricks require new sophisticated algorithms and faster processors, says Lancelot Braithwaite, a consultant at Samsung Electronics America in Ridgefield Park, N.J.

TV makers generally agree that conventional and thin CRTs become too big or heavy beyond a 36-inch screen. But CRTs could continue to rule below that boundary—the bulk of the TV market. Thomson and Philips are working on digital CRTs that would scan screens vertically instead of horizontally, which could slim a 30-inch TV to 14 or even 12 inches deep. —*Mark Fischetti*

**CATHODE-RAY TUBE** in a slim TV is about 33 percent shallower than a conventional design. In both models, an electron gun accelerates and focuses three electron beams toward a metallic shadow mask. Two sets of deflection coils create varying magnetic fields that steer the beams across the mask. The beams pass through a slot in the mask at slightly different angles, then hit distinct phosphor stripes on the inside face of the screen. Three phosphors fill each stripe and, when energized by the beams, emit the red, green and blue light that can combine to create any color at any point, or pixel, on the screen. Because the gun is closer to the mask in slim models, the beams must deflect 125 degrees laterally instead of 90 to 110 degrees.




**RASTER SCAN** technique paints an image on a screen line by line. On current CRTs (*left*), the electron beam (*blue*) begins at the top left corner, scans a horizontal line of pixels (points), then jumps back (*red*) to the left edge of the second line, and so on. Future slim TVs may switch to a vertical scan (*right*), which would lessen the beam's angle of incidence with respect to the phosphor stripes, allowing even slimmer designs; this method requires digital-signal-processing electronics to remap the TV picture data.

GEORGE RETSECK

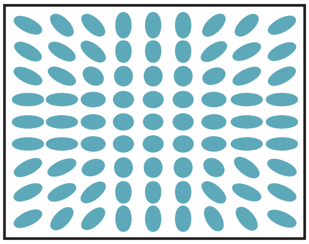
## DID YOU KNOW...

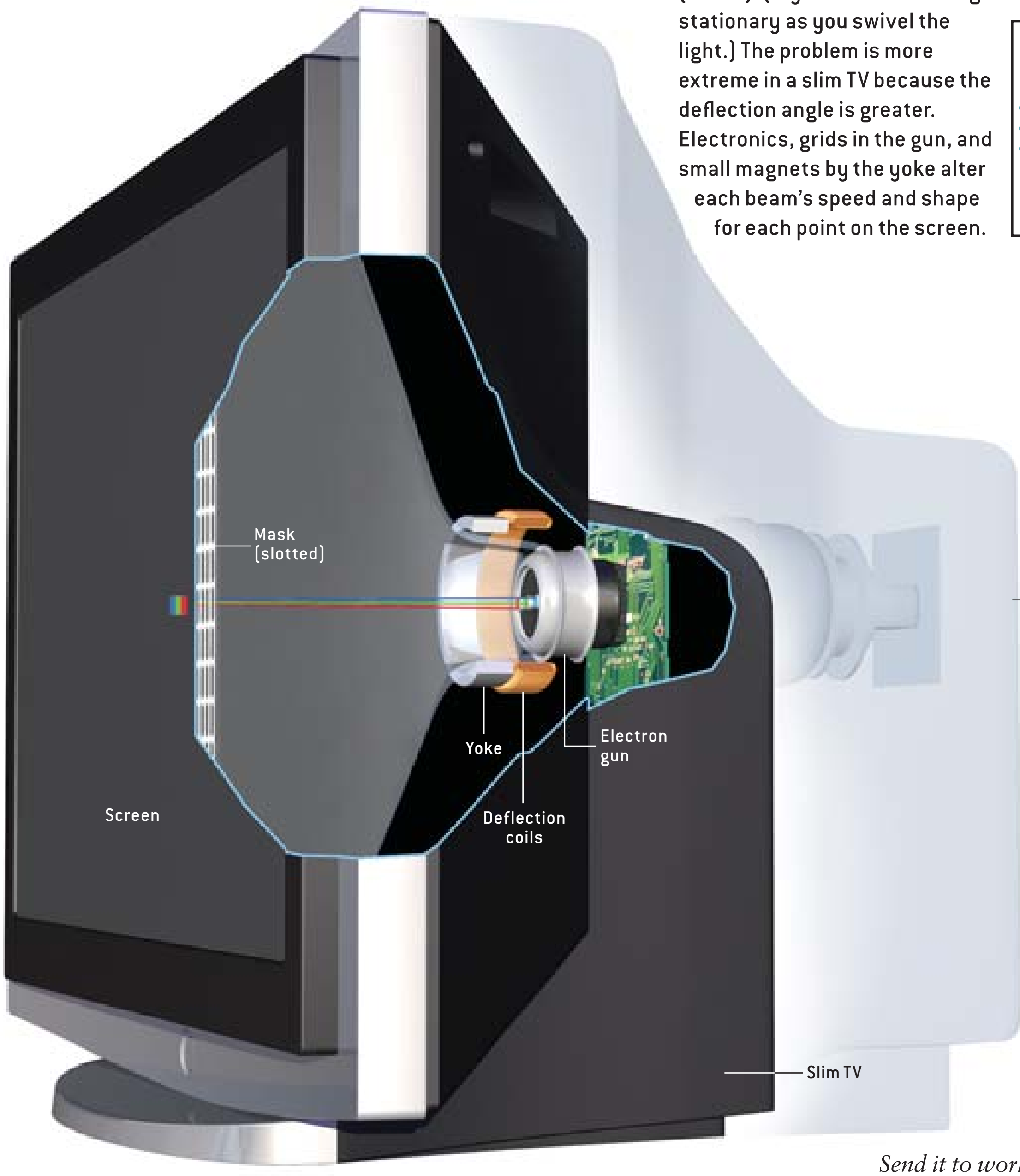
THE HOLE SECRET: The three adjacent, tightly packed phosphor stripes coating the inside of a CRT screen are together less than one millimeter wide. A thin metal mask stands about half an inch behind the screen, and the slot-shaped holes in it are about one quarter of a pixel's diameter. The three electron beams, each wider than a millimeter, reach each hole at a slight angle to one another. Because the beams are wider than a hole, only some of their electrons pass through.

LITTLE LATITUDE: The earth's magnetic field can slightly alter the trajectory of a CRT's electron beams. The field is strongest at the poles, diminishes at the equator, and differs in polarity from the Northern to the Southern Hemisphere. A TV made for Japan will display poor color in Ecuador or Australia. Manufacturers must add magnets, magnetizable rings, coils or shields and tune them for their approximate latitude of destination. In digital TVs, adjustments to magnet-control electronics can simply be programmed in.

GLASS PRESSURE: When formed, a CRT is evacuated so the cathode—the source of electrons—lasts a long time and so beam electrons can flow undisturbed. A slim TV is shaped more like a basin than a cone. The glass must be thicker across the back than in a standard CRT so atmospheric pressure does not crush it owing to the vacuum inside.

**ELECTRON BEAM** illuminates a circle at the screen's center. But the circle naturally elongates toward an edge because the beam hits the mask at an increasing angle of incidence (*below*). (Try this with a flashlight on a wall, keeping your hand stationary as you swivel the light.) The problem is more extreme in a slim TV because the deflection angle is greater. Electronics, grids in the gun, and small magnets by the yoke alter each beam's speed and shape for each point on the screen.



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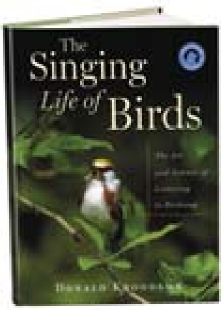
# How to Listen to Birds

AN EXPERT SHARES HIS SECRETS **BY BERND HEINRICH**




**THE SINGING LIFE OF BIRDS: THE ART AND SCIENCE OF LISTENING TO BIRDSONG**
By Donald E. Kroodsma
Houghton Mifflin, 2005 ($28, includes compact disc)

**Just as the colors** and patterns of the feathers that birds wear show tremendous variation, so, too, do the songs that they broadcast—but much more so. Songs may be absent, or they may range from a few simple genetically encoded notes endlessly repeated, to virtuosos of variety resulting from copying and learning, and even to seemingly endless improvisation. In *The Singing Life of Birds,* Donald E. Kroodsma, an emeritus professor of biology at the University of Massachusetts Amherst, celebrates the diversity through carefully chosen examples, one for each of the 30 years that he has studied birdsong.

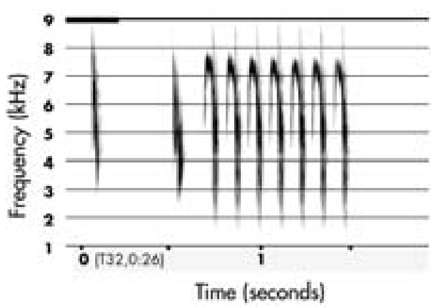
The book is best described by its subtitle, *The Art and Science of Listening to Birdsong.* Kroodsma shares his secrets—solid, practical advice on how to record bird sounds and how to "see" the sounds in sonagrams, visual representations of the recordings of songs. A compact disc that accompanies the text aids readers in this task. He concludes: "There's no longer any mystique to what I have done all these years. Anyone can do this kind of stuff. And anyone should."

His infatuation started with a single male Bewick's wren in his backyard in Oregon. Kroodsma discovered that this one wren sang 16 different songs, and in any singing bout it poured forth 40 to 50 renditions of one of them before switching to another, and then to another, and on and on. Meanwhile neighboring wrens hearing the song replied with the same one, while distant males sang other songs. Why?

The proximal answers to why birds sing and what they sing run from the trivial to the fascinating: they enjoy it, they are primed by hormones that activate neuronal pathways, they respond to neighbors. But the ultimate, evolutionary question of why they sing and what they sing can be answered only by the comparative study of many species.

Sometimes the anomalies provide a clue. For example, most individual wrens of different species learn many songs, and neighboring birds have similar songs—that is, they have dialects. The sedge wren of North America is an exception, however. Unlike other wrens and the sedge wrens of Central and South America, it has lost the ability to learn songs; it can only improvise on songs that are inscribed on its DNA. It is therefore unable to "match" the songs of its neighbors, and no dialects are found.

So what is different about the North American sedge wrens in respect to other wrens? They are nomads that live in unpredictable habitat—meadows that can quickly dry up. As a consequence, these birds can never predict who their neighbors will be from one season to the next; hence, learning songs as youngsters for later use in song matching is pointless. Contrast this to the bellbird, a long-lived tropical bird in which individuals come to know one another well. These birds listen to one another all year long and learn the changes in others' songs throughout life. The young birds learn the latest of these variations, and the dialect of the population changes from year to year.




NORTH AMERICAN SEDGE WREN: This unusual species has lost the ability to learn songs. A few general instructions in the DNA guide the male in his singing. The sonagram above shows a typical aria. "The black images of songs against the white paper," the author writes, "reveal the magic in the singing bird."

Kroodsma takes us repeatedly into the field, into the birds' world. He shares an all-night vigil with a whip-poor-will, tallying 20,898 identical repetitions of its one song for the entire night. He describes a brown thrasher that in one two-hour session sang 4,654 songs, 1,800 of them different (many borrowed from neighbors of other species). We enter the mind of the researcher as he tries to penetrate the mind of the bird.

As much as we humans may enjoy the spectacle of birds flaunting their gaudy garb to the accompaniment of vocalizations and dancelike antics, the show is meant primarily to attract females. It is about sex—about who will be the father of the female's chicks. The males presumably enjoy putting on their show, but whatever else it may do for them (such as serving as a territorial marker), it is the females who have shaped the performance by their tastes and preferences, and these are as various as the 10,000 or so species of birds.

Kroodsma emphasizes that we know little about why one or another bird has a specific repertoire. Yet despite the dazzling variety, it appears to me that all birdsongs have general requirements and constraints, and I believe that these shared characteristics may in themselves shed some light on the enigma. The primary requirement of a species' display song is that it must stand out from environmental noise—that is, it must carry—and it must be distinct from competing voices on the stage. Once females reward a specific song type with mating, then success breeds success, and whatever it is that attracts, the male that has more of it enjoys a huge advantage.

But singing is not cheap: the performers are conspicuous to predators, and the displays are so costly in time and energy that the performers may appear to handicap themselves. I doubt, however, that it is the flaunting of handicap as such that attracts the females ("I am so strong and healthy that I have energy to waste on singing"). The singer must cater to the females' taste. As in our own fashions of clothing and music, there is not necessarily rhyme or reason in the specifically chosen attribute, except


the most important one—it works.

Konrad Lorenz reputedly said that birdsong is "more beautiful than necessary." It seems to me that it is just as likely that the flamboyant displays of song and dance, of feathers and, in the bowerbirds, of decorated love shacks are indeed necessary, because females compare, and they are picky. Arbitrary though their criteria of choice may be, it is significant that we humans also find many of the same displays beautiful. SA

*Bernd Heinrich is professor emeritus at the University of Vermont and author of many popular books on science. Among the most recent are* The Geese of Beaver Bog, Winter World *and* Mind of the Raven.

## THE EDITORS RECOMMEND

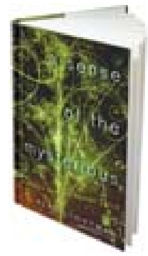
### EXUBERANCE: THE PASSION FOR LIFE

***by Kay Redfield Jamison. Alfred A. Knopf, 2004 ($24.95)***

"Exuberance," Jamison says, "is an abounding, ebullient, effervescent emotion." She celebrates a galaxy of exuberant figures. Theodore Roosevelt was "incapable of being indifferent." Wilson Bentley, a New England farmer who made himself a respected expert on the crystal structure of snowflakes, "was as exuberant in pursuit of them as they were in their numbers." The eminent physicist Richard Feynman "was an exuberant teacher in every way." Jamison also celebrates exuberant characters in literature, including Tigger, Toad and Snoopy. Professor of psychiatry at the Johns Hopkins University School of Medicine, she is concerned that exuberance "has not been a mainstay of psychological research" but sees signs that it is receiving more scholarly attention. She has produced an exuberant book.

### A SENSE OF THE MYSTERIOUS: SCIENCE AND THE HUMAN SPIRIT

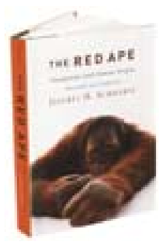
***by Alan Lightman. Pantheon Books, 2005 ($23)***



This collection of 11 finely chiseled essays begins with an autobiographical account of Lightman's journey through life with his passion divided between science and art. "I was fortunate to make a life in both, as a physicist and a novelist, and even to find creative sympathies between the two, but I have had to live with a constant tension in myself and a continual rumbling in my gut." Other essays include wonderfully perceptive pieces on Albert Einstein, Richard Feynman (with his intellectual leaps, he was "the Michael Jordan of physics"), Edward Teller and Vera Rubin. Lightman, who has taught both physics and writing at M.I.T., ends with a rumination on what the ever connected, always-turned-on technology of the 21st century has cost us.

### THE RED APE: ORANGUTANS AND HUMAN ORIGINS

***by Jeffrey H. Schwartz. Revised and updated. Westview Press, 2005 ($27.50)***




Schwartz argues that it is not chimpanzees or other African apes that are humankind's closest relatives, but Asian orangutans. His theory is controversial, to say the least, but the case he makes for it is compelling—and highly readable. Schwartz, a professor of physical anthropology at the University of Pittsburgh, has thoroughly revised this edition to give a new perspective on the latest debates about the process of evolution, raising questions about scientific reasoning and the interpretation of biological data. He also reminds us of our responsibility to protect the large red apes who may turn out to be our closest evolutionary cousins. It is a fascinating and provocative read.

# Crime Scene Instigation

TV SUPERSCIENTISTS AFFECT REAL COURTS, CAMPUSES AND CRIMINALS **BY STEVE MIRSKY**

**Television's troika** of *CSI* shows—*CSI: Crime Scene Investigation, CSI: Miami* and *CSI: NY*—arguably presents popular culture's most positive view of scientists since the Professor was engaged in his unfunded better-living-through-coconut-chemistry project on *Gilligan's Island*. In February, at the annual meeting of the American Association for the Advancement of Science in Washington, D.C., a group of real forensic scientists put the *CSI*s under the microscope.

The fictional series have inadvertently put pressure on real-life prosecutors. "'The CSI effect' is a term that came into use around 2003, when the show really started to become popular," says trace evidence analyst Max Houck, director of West Virginia University's Forensic Science Initiative. "It represents the impossibly high expectations jurors may have for physical evidence." Prosecutors worry that without having the ironclad physical evidence jurors see on TV, the reasonable-doubt line may be shifting.

Houck pointed to a case in Los Angeles last year featuring a bloody coat. "Jurors were alarmed," Houck says, "because no DNA testing had been done on the coat. Well, the wearer of the coat admitted to being at the murder scene trying to help the victim, so the lab had said there was no reason to test it—he said he was there." According to Houck, the judge made a statement along the lines that "TV has taught jurors about DNA tests but not about when to use them."

Indeed, many people still don't know the ABCs of DNA. A lab may request a sample of a missing person's clothing in order to compare DNA on that clothing to unidentified remains. Dress shirts are particularly good at grabbing skin cells at the tight collar. "We asked for the family to send in dress shirts," recalls Demris Lee of the Armed Forces DNA Identification Laboratory about one case. "And the family sent in his new shirts that were still in packaging. They couldn't believe we wanted his dirty clothes."

Criminals may be feeling *CSI*'s heat—and taking notes. "What I've heard is that it's closely watched in prisons," remarks Richard Ernest, a forensic firearms expert in Fort Worth, Tex. "And prisons become almost like a crime school for certain individuals. They'll look at a particular segment and say, 'So that's how they caught me. Well, I won't make those mistakes again.' "

Instead they'll probably make new ones. "When they try to escape detection from what they see on *CSI,* they're actually leaving more evidence," Houck contends. "A good example of that is instead of licking an envelope [for fear of providing DNA in their saliva] they'll use adhesive tape. Well, they'll probably leave fingerprints on the tape, and it'll pick up hairs and fibers from the surroundings. So the more effort you put into trying to evade detection, honestly, the more evidence you leave behind."

Another CSI effect is that college kids think it's cool. In 1999 Houck's institution graduated four students with a concentration in forensics. "We're now the largest major on campus," he declares. "If you add all four years together, we have over 400 students." Perhaps their most important lesson is that real life doesn't look like a TV show. Houck tells his students that "it's less about wearing leather pants and driving Hummers than it is about wearing Tyvek jumpsuits and crawling under people's front porches looking for body parts. Honest. I've never worn leather pants in my life."

Houck also has a tough time watching his TV counterparts use analytical tools that don't quite really exist. "We joke that we need to get one of those—that's a damn fine instrument," he says. (The amazing databases employed on some episodes prompted a friend of mine to ask, "Why don't they just ask the computer who did it?") Another show convention that annoys Houck is investigators wandering around dark indoor crime scenes. "They always use flashlights," Houck notes. "I don't know why. I usually just turn the lights on." SA

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

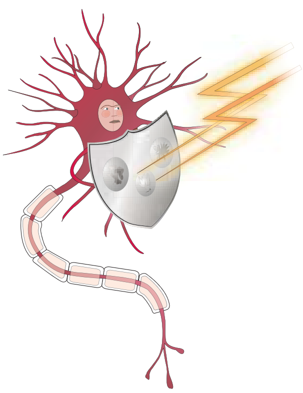
# ASK THE EXPERTS

## How does anesthesia work?

**Bill Perkins, associate professor of anesthesiology at the Mayo Clinic College of Medicine, explains:**

Local and general anesthetics work by blocking nerve transmission to pain centers in the central nervous system, although the exact mechanisms for general anesthetics are not well understood, despite use of such pharmacological agents for more than 150 years.

Local anesthetics, such as Novocain, bind to and inhibit the function of the sodium channel in the nerve cell membrane, a type of ion channel required for the propagation of nerve impulses. This action obstructs the movement of nerve impulses from tissue innervated by nerves at the site of local anesthetic injection but causes no changes in awareness and sense perception elsewhere in the body.



In contrast, general anesthetics provide overall insensibility to pain. The most commonly used such agents are inhaled, and they are structurally related to ether. Their primary site of action is in the central nervous system. Unlike local anesthetics, the general anesthetics reduce nerve transmission at the synapses, the sites at which neurotransmitters are released by neurons and adjacent nerve cells respond. General anesthetics affect the response of receptors and ion channels to neurotransmitters, thereby decreasing nerve cell activity.

General anesthetics bind only very weakly to their sites of action and interact with proteins in a lipid environment, factors that together make it difficult to determine their exact binding structure. Despite such limitations, researchers are taking advantage of various methods to better discern how anesthetics work at the molecular level.

Genetic tools, for example, enable researchers to alter specific protein function and then determine whether this protein can be linked to sensitivity or resistance to anesthetic action in lower organisms. Other approaches, including sophisticated structural modeling of anesthetic binding to protein targets, are also showing promise. The targets for different agents do not appear to be the same, so there is probably no single molecular mechanism of action for all anesthetics.

## Are one's fingerprints similar to those of his or her parents?

—Eric C., Lakeland, Fla.

**Glenn Langenburg, a certified latent print examiner at the Minnesota Bureau of Criminal Apprehension, offers this answer:**

Yes, we inherit the overall size, shape and spacing of so-called friction ridge skin (FRS)—fingerprints. The individual details that make a fingerprint unique are not genetically determined, however. Made up of a series of ridges and furrows that aid in grasping, FRS is unique and permanent. No two individuals—including identical twins—have the same arrangement, which also does not change throughout life (except in the case of significant damage that creates a permanent scar).

Why are the general patterns but not the identifying ridge features inherited? The reason is in the timing of aspects in fetal development. Fetuses acquire smooth volar pads—raised pads on the fingers, palms and feet—because of swelling mesenchymal tissue, which is a precursor of blood vessels and connective tissues. Around week 10, the fetus's volar pads stop growing, but the hand continues to enlarge. Over the next few weeks, the volar pads are absorbed back into the hand. During this stage, the first signs of ridges appear on the skin of the pads. The shape of the volar pads at the time the first ridges appear will dictate the general pattern that develops.

Once the overall pattern has begun to take shape within its confines, the exact arrangement of the identifying ridge features is dictated by random, localized stresses on the skin. The timing of these two events—volar pad regression and primary ridge appearance—is genetically linked. The precise locations of the ridges and other features, however, are random. SA

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

LUCY READING-IKKANDA