How DNA "Switches" Control Evolution (*page 60*)

SCIENTIFIC AMERICAN

The Dangers of NUCLEAR RECYCLING
page 88

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The CHAOTIC BIRTH of Planets

How random collisions and gravity slingshots shape new solar systems

Science 2.0

The Risks and Rewards of Web-Based Research

Killer Worms

Winning Strategies against a Deadly Parasite

Nicotine Addiction

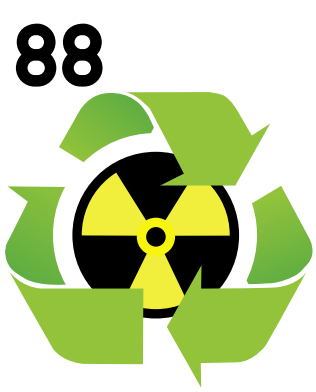
How Even One Cigarette Can Hook the Brain

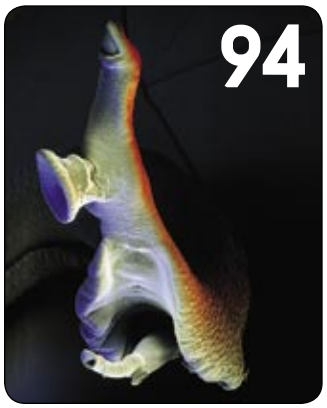
SCIENTIFIC AMERICAN May 2008 ■ Volume 298 Number 5

Image by Jean-Francois Podevin

ON THE COVER

Our early solar system was a madhouse of swirling planetesimals with haphazard orbits. Fortunately for us, some stable, rocky worlds eventually took shape. Image by Don Dixon.





Web of Science

Join the discussion about the pros and cons of Science 2.0 already in progress at **www.SciAm.com/science2point0**

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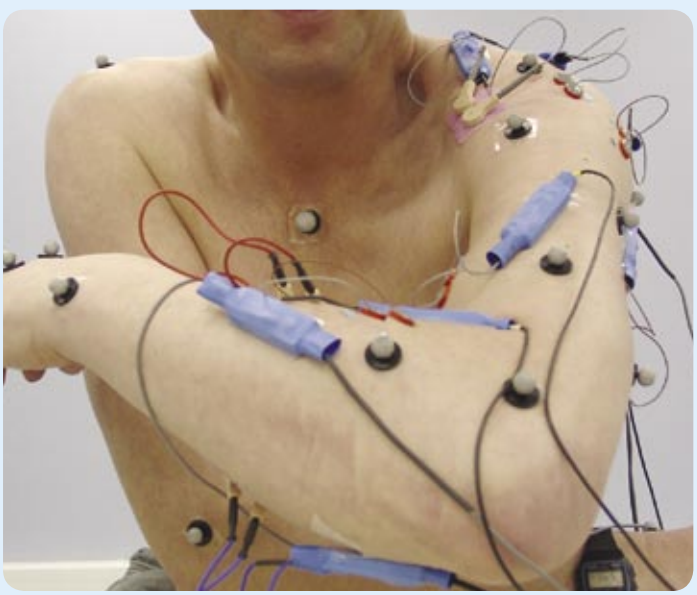
SELF-EXPERIMENTERS ▼

This month our Web site features an eight-part series on scientists who used themselves as guinea pigs. Among them is Kevin Warwick, who wired his nervous system into the Internet—and his wife.
More at **www.SciAm.com/sciammag**



COURTESY OF TODD PALMER

Strange but True
Survival in Space Unprotected Is Possible (Briefly)
But don't linger in the interstellar vacuum or hold your breath.

News
Food Containers Leach a Potentially Harmful Chemical
Is bisphenol A, a major ingredient in many plastics, healthy for children and other living things?

Podcast
A Star Is Flung
The star called HE 0437-5439 looks like it was tossed out of the Large Magellanic Cloud by a hypothesized black hole.

Video
Scientific American Hears from Climate Skeptics
We dared to visit the Heartland Institute's anti–climate change conference.

In Memoriam
Arthur C. Clarke, R.I.P.
The accomplishments of the legendary writer extend far beyond *2001.*

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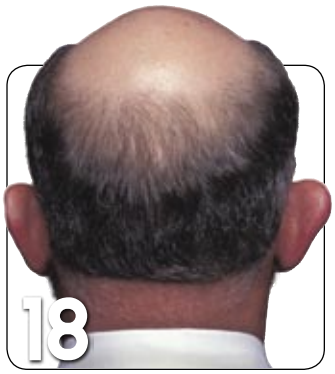
DEPARTMENTS



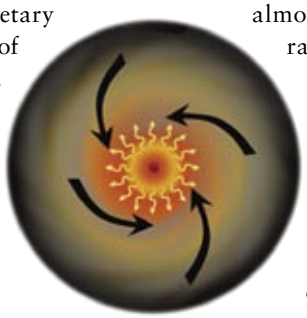
GABRIELA HASBUN

Do-It-Yourself

Have hands-on fun with astrophysics, evolution and neuroscience

Heading into the summer holidays, many people like to have a big, consuming hobby to while away the time. This issue's features lend themselves to several such do-it-yourself endeavors, if you are suitably ambitious.

Build a solar system (difficulty: 9). The great thing about this project is that although it requires considerable setup and the outcome is uncertain, it involves essentially no intervention later—just sit back and watch what happens. Take a gigantic cloud of hydrogen laced with traces of heavier elements, let a star or two coalesce in the center and stir the remainder just enough for a protoplanetary disk to form. "The Genesis of Planets," by Douglas N. C. Lin, beginning on page 50, has all the details.



SOLAR SYSTEM KIT—Some assembly required.

Astronomers used to debate whether the worlds of our solar system arose from a massive sheet of gas ripped out of our young sun during a near encounter with a passing star; that extended filament then supposedly clumped into planets. Later the favored explanation came to be that the planets were more peripheral products of the same spinning cloud that gave birth to the sun. Both those explanations involved comparatively orderly processes, with the planets taking shape in roughly the same orbits we see today.

The most recent evidence, however, reveals the heavy influence of creative chaos. When planetesimals collided, sometimes they cohered into bigger ones and sometimes they split anew; newly formed planets that were not lucky enough to find stable orbits cycled down into the sun or were flung deep into interstellar space. These discoveries might help explain some of the strange globes circling other stars that astronomers have located over the past decade, such as some super-size "hot Jupiters" that are unexpectedly close to their suns.

Invent a complex organism (difficulty: 4). Take an existing animal, then experiment with altering the genetic program that controls its embryonic development to achieve the new body plan you desire.

Hobbyists daunted by the technical complexity of that challenge should feel encouraged that nature accomplishes it routinely. Indeed, that mechanism seems to generate much of the physical variation that defines and gives rise to new species. Genomic science has found that many of the genes that build a developing body are almost identical across a wide range of highly diverse animals. What makes a horse different from a tiger, a mouse and a walrus is the set of regulatory switches in the DNA that dictate where, when and for how long those genes are active. The modern synthesis of evolutionary biology with reproductive biology is flourishing under the snappy name of "evo-devo," as Sean B. Carroll, Benjamin Prud'homme and Nicolas Gompel explain in "Regulating Evolution," starting on page 60.

Rewire your nervous system (difficulty: 0.5). This one's easy. Light a cigarette, take a few drags and voilà! For some people, that one brief exposure is all it takes to alter the brain's systems for controlling cravings and to set up a lifelong weakness for nicotine. Joseph R. DiFranza describes how that might be possible in "Hooked from the First Cigarette," beginning on page 82. Of course, too many people, particularly children, are already doing this to themselves all the time. ■

JOHN RENNIE
editor in chief

FLYNN LARSEN (*Rennie*); DON DIXON (*illustration*)

Among Our Contributors

VOJO DERETIC
holds joint professorships in molecular genetics and cell biology at the University of New Mexico Health Sciences Center, where he studies the phenomenon of autophagy.

JOSEPH R. DIFRANZA
practices medicine at the University of Massachusetts Medical School in Worcester. He has a long (and successful) history of antismoking activism.

DANIEL J. KLIONSKY
is a distinguished scholar and professor at the University of Michigan Life Sciences Institute. He also serves as editor in chief of the journal *Autophagy.*

PATRICK SKELLY
is an assistant professor at the Cummings School of Veterinary Medicine at Tufts University and president of the New England Association of Parasitologists.

FRANK N. VON HIPPEL
is a physicist by training and a professor of public affairs at Princeton University. During the Clinton administration he served in the Office of Science and Technology Policy.

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recently joined the staff of the journal *Nature.* He last wrote for *Scientific American* about mobile computing centers (August 2007).

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Fluoridation ▪ Solar Power ▪ Congress and Science

JANUARY 2008

"The National Research Council notes that its report was not initiated because of concerns about the low levels of fluoride used in community water fluoridation, nor did it examine that issue."

—*Mark Feldman* AMERICAN DENTAL ASSOCIATION

Fluoride Findings

A report by the National Research Council (NRC) is cited as suggesting negative effects of fluoride in "Second Thoughts about Fluoride," by Dan Fagin. But the NRC notes that its report was not initiated because of concerns about the low levels of fluoride used in community water fluoridation, nor did it examine that issue. Instead the report is part of a routine review by the Environmental Protection Agency to address whether the higher levels of *naturally* occurring fluoride currently allowed in drinking water pose a health risk. The EPA is evaluating the report.

The article rightly points out that enamel fluorosis only has a health impact in the severest cases, yet Fagin incorrectly refers to it as a "disease." It is rather a disruption in enamel formation that affects the way teeth look. The American Dental Association (ADA) offers information on reducing the risk of fluorosis at www.ada.org.

The ADA's support for fluoridation is based on more than six decades of research, thousands of studies, and the experience of more than 170 million Americans. We welcome additional peer-reviewed scientific studies that will add to the body of knowledge on the use of fluoride.

Mark Feldman
President, American Dental Association

Cosmic Growth Spurt

In "Making Space for Time" [News Scan], Scott Dodd explains that cosmic microwave background radiation shows that 380,000 years after its birth, the universe was filled with hot gas. He then writes, "Eventually the early cosmos underwent inflation…." This statement is misleading. It implies that the exponential expansion of the universe called inflation occurred hundreds of thousands of years after the big bang. According to inflationary cosmology, inflation occurred around 10^{-35} second after the big bang.

Mark Egdall
Hollywood, Fla.

Sunlit Path?

"A Solar Grand Plan," by Ken Zweibel, James Mason and Vasilis Fthenakis, calls for the conversion of 30,000 square miles of pristine desert into photovoltaic farms. A better alternative exists: utilize rooftops. Although this strategy will not take advantage of the concentrated sunshine of the Southwest and will not be as efficient, it will distribute power generation across all time zones and weather conditions, without paving over additional land.

Mathieu Federspiel
via e-mail

Has anyone looked into the effects of installing 30,000 square miles of low-albedo surface material? Solar panels, by design, have a much lower albedo than most flat ground in the Southwest. How would their greater heat absorption affect the local environment?

Talon Swanson
Seattle

THE AUTHORS REPLY: *In regard to the first letter, a common and valid criticism of our solar plan is that we undermodeled distributed energy systems, such as rooftop photovoltaics (PVs) and solar hot-water systems. If the price of residential systems is drastically reduced and local storage is provided, dispersed installations can play a much larger role than our article describes.*

As to the second letter, locally we would experience differences in temperature and air movements because of albedo change. Although studies on this effect have not yet been conducted for large PV plants, observations and global models suggest some tentative conclusions. Tom Hansen, manager of Tucson Electric Power Company's PV plant in Springerville, Ariz., has measured a two- to three-degree-Fahrenheit increase at the center of the PV field and a wind vortex from its periphery toward its center. An area of 50,000 square kilometers would receive about 3×10^{14} *watt-hours of solar energy daily. With a 20 percent albedo differential between desert and PV surfaces, this would amount to a net excess of* 6×10^{13} *watt-hours per day. Similar albedo changes have also been caused by the major cities of the Southwest with no apparent effects. One should also consider that albedo heating will, nationally, be counterbalanced by avoidance of the heating caused by thermoelectric plants. Greg Nemet of the University of Wisconsin–Madison has studied global net radiative forcing by supplying 50 percent of the world's energy with PVs, taking into account the albedo effect, and concludes that they are one of the most effective solutions to anthropogenic global warming.*

PROPOSED PLAN for solar power includes photovoltaic farms that would resemble Tucson Electric Power Company's solar plant in Springerville, Ariz.

Nevertheless, the potential for local effects deserves detailed studies, and it is conceivable that buffer, nonsolar zones around large arrays may be advised. Such arrays would not be built near large populations, so local heating would likely be inconsequential.

Political Science

In "Congress Fails Science" [Perspectives], the editors propose that Congress is habitually inattentive to science and that this irresoluteness has persisted despite the shift of legislative power in 2007 to the Democrats. But like college students, Congress usually concludes most of its work in the last week or two of each session. Had the editors waited one month, they might have noticed that the moribund energy bill they cite has actually passed, as has the increase in fuel economy standards. Although Congress can be slow and indecisive, it was designed that way to minimize precipitous action. Do the editors really expect it, in less than a year and facing a dead-certain presidential veto, to pass a bill that would result in historically sweeping changes to our energy and environmental policies, to our economy and probably to our lifestyles? If nothing has happened in three to four years, they can get on their high horse. But now I would be concerned about the soundness of any major proposal that passed in a few months.

Bob Palmer
Gainesville, Fla.

ERRATA "X Prize Foundation," by Kaspar Mossman [SciAm 50], incorrectly states that the space plane whose development won Mojave Aerospace the Venture Ansari X Prize in 2004 reached low-Earth orbit. The plane is a suborbital craft.

"Fueling Alternatives," by Steven Ashley [SciAm 50], refers to sugar as a hydrocarbon. Sugar is not a hydrocarbon, because it contains oxygen atoms.

Read more discussion on "A Solar Grand Plan," including replies from the authors, at **www.SciAm.com/sciammag**

Letters to the Editor

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Letters may be edited for length and clarity. We regret that we cannot answer all correspondence.

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TUCSON ELECTRIC POWER COMPANY

Veiled Self ▪ Wright Secrecy ▪ Cotton Revolt

Compiled by Daniel C. Schlenoff

MAY 1958

SELF—"Most of us live behind a wall or smoke-screen which in some degree hides our true thoughts, feelings, beliefs, desires, likes and dislikes. But the question of self-disclosure goes deeper than mere willingness or reluctance. People often cannot disclose themselves, even if they would, because they do not know their real selves—what they really want, feel or believe. Karen Horney has called this phenomenon of being a stranger to oneself 'self-alienation,' and she finds it characteristic of neurotics. It may be significant of modern society that so many people have taken to the psychoanalyst's couch to try to know themselves."

DYNAMO EARTH—"The greatest difficulty in all attempts to explain the earth's magnetic field has been the problem of introducing the driving force that produces the general symmetry of the over-all field. We have to assume that the field is generated by circular electric currents closed upon themselves. In such a setup there is no apparent place where we can insert a driving force—either a battery or any other. But the dynamo theory allows the earth's rotation to act as a driving force. The rotation causes the closed currents of the eddies to flow in the same direction. —Walter M. Elsasser"

MAY 1908

MAGAZINE FOR THE BLIND—"Undoubtedly the whitest printing plant in the world is that in which the *Ziegler Magazine for the Blind* is published. The reason is obvious. No type is used, and no ink of any description is to be found except, of course, in the editorial room. The monthly magazine is circulated without charge to any person in the United States or Canada who can read the point alphabet. In the composing room of the plant there are two machines, one of which makes the plates for the New York point edition, while the other serves for the American Braille edition. Very unfortunately, both of these point alphabets are in general use in the country."

TRACKED TRACTOR for hauling loads over rough terrain, 1908

"CATERPILLAR" TRACTOR—"For some months past the British military authorities have been experimenting with a new type of tractor for the haulage of heavy vehicles over rough and unstable ground. Briefly, its object is to crawl over the ground, there being a series of feet disposed along the periphery of two heavy side chains passing over fore and aft wheels. Because of its peculiar movement, the soldiers at the Aldershot military center, where it is in operation, promptly christened it the 'caterpillar.' The engine is the invention of Mr. David Roberts."

[NOTE: Patents for this invention were later sold to Benjamin Holt, co-founder of Caterpillar Tractor Co.]

FURTIVE FLIGHT—"Soon after the first reports were received regarding the flights being made by the Wright brothers in testing their aeroplane, a considerable number of newspaper correspondents visited the scene of the trials among the high and pointed sand dunes of the North Carolina coast south of Norfolk, Virginia. The brothers refused to make any flights, however, when the reporters were near at hand, and so the gentlemen of the press were obliged to keep in hiding nearly a mile away from the scene of operations, and to merely watch the machine from afar through spyglasses when it was flying."

➥ The drawing prepared from descriptions is available at **www.SciAm.com/sciammag**

MAY 1858

COTTON IS KING—"Just previous to the late monetary panic, cotton had attained to such a high price that British manufacturers of coarse goods found themselves compelled to curtail their operations, and as a consequence, they were greatly incited to devise some other means for securing a large supply at lower prices. Being dependent on the United States for four-fifths of that which they use, they felt that American cotton was their king, hence they looked to other regions for relief. The late expedition, fitted out with the famous Dr. Livingstone as its chief, has for one of its main objects the encouragement of cotton cultivation in Africa."

SCIENTIFIC AMERICAN, VOL. XCVIII, NO. 20, MAY 16, 1908

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More Pioneer Anomalies ▪ Black Hole Labs ▪ Hair-Raising Work ▪ Tuna Triumph

Edited by Philip Yam

Mystery Cruise Control

The velocities of Pioneer 10 and 11, now speeding out of the solar system, are mysteriously changing, as if an extra force from the sun were tugging at them. Explanations have ranged from gas leaks and observational error to modified theories of gravity [see "A Force to Reckon With"; SciAm, October 2005].

Now Jet Propulsion Laboratory astronomer John Anderson and his colleagues, who helped to uncover the Pioneer anomaly, have found similar unexpected changes with four spacecraft that have flown by Earth—namely, Galileo, the Near-Earth Asteroid Rendezvous (NEAR) mission, Cassini and Rosetta. They sped up or slowed down by amounts up to one part per million as they passed the planet.

The exception was MESSENGER, which approached Earth at a latitude of roughly 31 degrees north and left Earth at a latitude of about 32 degrees south—relatively equal distances from the equator. In comparison, the anomalous flybys were lopsided in how the craft approached and left Earth. For example, the NEAR mission came in at a latitude of roughly 20 degrees south and receded at about 72 degrees south (and then seemed to fly some 13 millimeters per second faster than expected). The greater the asymmetry, the greater the effect on velocity.

Although variations in Earth's magnetic or gravitational fields might seem to explain the anomalies, satellites that orbit Earth seem unperturbed, Anderson says. Also, although gas in space can slow craft, it would not explain why some probes apparently sped up. He notes that one feature seemingly links the flyby and Pioneer anomalies: all the craft are on hyperbolic trajectories—orbits where they are not bound to their central bodies (the sun for the Pioneer craft, Earth for the others). "Maybe there's something with hyperbolic trajectories we haven't taken into account yet," Anderson conjectures. —*Charles Q. Choi*

SPEED SHIFT: Jupiter-visiting Galileo spacecraft had an unexplainable velocity change after it swung by Earth.

Fiber-Optic Black Holes

To study black holes, physicists have looked for laboratory analogues [see "An Echo of Black Holes"; SciAm, December 2005]. Fiber optics may make that possible. The key to making artificial event horizons is to force a fluidlike medium to slosh faster than waves can ripple through it. Researchers sent a red pulse through an optical fiber, which altered the fiber's refractive index, and then beamed in longer-wavelength light crafted to chase down the pulse. The infrared beam blue-shifted, indicating that its wave fronts had piled up behind the pulse. Technically, blue-shifting is a feature of the event horizon of a *white* hole—an inside-out black hole. Still, the leading edge of the pulse would mimic the horizon of a black hole, writes the team in the March 7 *Science*. —*JR Minkel*

Hair Today, Hair Tomorrow

Hair grows, falls out and may take time to come back—too long for many older adults [see "Hair: Why It Grows, Why It Stops;" SciAm, June 2001]. Elaine Fuchs of the Rockefeller University and her colleagues have shown that blocking a protein called NFATc1 results in shorter rest phases for the stem cells in the hair follicles. The hair in Fuchs's study grew normally, suggesting that the resting phase, long thought to be a way to protect against mutation or the loss of the cells, is

not as necessary as once thought. The work, in the January 25 *Cell*, helps to explain stem cell activity and could lead to new treatments that are able to reverse thinning hair.

Spawning Success

Aquaculturists have tried—and failed—to get captive bluefin tuna to breed, as a means to save these overeaten animals [see "The Bluefin in Peril"; SciAm, March 2008]. After a three-year effort, Australian company Clean Seas Tuna Limited reported in March that it induced captive southern bluefin tuna to spawn. Bluefin larvae grow

one millimeter a day, so years will pass before any young fish reach marketable size; hence, farmed tuna may not arrive in time to save some bluefin populations.

NASA/JPL (*Galileo and Jupiter*); CHUCK PEFLEY *Aurora Photos* (*man's head*); BRIAN J. SKERRY *National Geographic Image Collection* (*bluefin tuna*)

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GENETIC TESTING

Taking Genomes Personally

Doubts about whether commercial DNA scans improve health BY SALLY LEHRMAN

For $1,000 and up, several new companies will scan an individual's entire genome for clues about ancestry, potential health limitations and the inheritance of traits such as lactose intolerance. Clients can compare their DNA with a celebrity's or invite friends and family members to share genetic profiles. Despite the comprehensive reports and background data these Web-based services deliver, some observers believe the information is more recreational than relevant.

Direct-to-consumer genetic tests have existed for at least a decade, and in recent years the number of choices has exploded. Whereas most of these offerings probe for only a small number of gene variants, advances in genome chips now allow a quick, inexpensive search for a wide range of targets all at once. Navigenics in Redwood Shores, Calif., 23andMe in Mountain View, Calif., and deCODE Genetics in Reykjavik, Iceland, recently began scanning for markers associated with as many as two dozen conditions and traits. And for upward of $350,000, Knome in Cambridge, Mass., enables customers to join J. Craig Venter and James D. Watson in the elite cadre of humans who have had their entire genome sequenced, analyzed and interpreted.

With new tools, reference sequences and big study populations in hand, geneticists have found increasingly robust associations between DNA variations and disease susceptibility. But the data are still incomplete and sometimes conflicting, cautions Muin Khoury, director of the Centers for Disease Control and Prevention's public health genomics office. For now, he says, sequencing one's genome or scanning for susceptibility markers offers "no useful information."

GENOMIC BROADSIDE: Gene chips, such as this one made by Affymetrix, can quickly scan a person's DNA for many variations. They have helped usher in personal genetic testing.

RICH PEDRONCELLI *AP Photo*

Except in the case of rare disorders caused by a single gene variant, having a genetic susceptibility is far from a guarantee of falling ill. Multiple genes interact within a complex biological system that includes many other important players, among them RNA and chemicals in the environment. Complex conditions such as diabetes or heart disease have myriad behavioral and environmental components working in concert with an unknown number of genes.

With so much still to learn, it is too early to use results from gene association studies for health-planning purposes, according to Khoury. Besides, he points out, it is unclear in the medical literature whether news about genetic susceptibility to particular conditions has any power to change people's habits. Moreover, physicians are unsure how to apply the drug metabolism information from pharmacogenomics tests in their prescribing decisions. And in some cases, the tests offered online seem altogether disconnected from genetic medicine. A July 2006 U.S. Government Accountability Office study of services provided by nutrigenetics companies questioned whether, in some cases, any DNA was analyzed at all. The agency concluded that the firms "mislead consumers by making predictions that are medically unproven."

The new genotyping companies claim to cut through the confusion by delivering high-quality, responsible science. They stop short of offering medical services and instead promote their scans as an innovative means to provide health information and empower consumers to act on it.

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While genetics research moves forward, the companies say, people can start working now with their doctors or take steps to change their diet or other behaviors. "It's better to start than to wait an indefinite period of time until the science is perfect," insists Mari Baker, chief executive of Navigenics. Not all of the 1.8 million points her company scans on the genome are informative today, she says, but customers will be able to access ongoing findings as they come in. Eventually Navigenics plans to incorporate other health data, such as family history and medication use.

Some experts worry that the rollout strategy could backfire. Because the relevance of whole-genome scans is so limited, warns Sharon Terry, president and chief executive of the advocacy group Genetic Alliance, "the average person may lose interest before there is enough information to have utility." Along with creating tools such as an online guide to family health history and a WikiGenetics Web site, Genetic Alliance is pressing for regulations that would protect against discrimination, safeguard privacy, and require quality and validity testing. So far efforts to extend laws into these areas have failed.

Navigenics, 23andMe and deCODE specify that customers own their personal data. But executives keep the door open to use their growing databases for research with commercial or nonprofit partners. Such studies should take place under research protocols, not as an outgrowth of consumer marketing, the CDC's Khoury argues. For now, he says, the best tool available to personalize medicine is low tech and low cost: family health history. It captures the effects of multiple genes, shared environment and common behavior. But less than one third of the population has actively collected such information. Genotyping is a wonderful research technology, Khoury remarks, but "it's going to take a long time to translate gene discovery into action."

Sally Lehrman is a freelance writer based in the San Francisco Bay Area.

PUBLIC HEALTH

When I'm Sixty-Four

For many baby boomers, recreational drugs continue as a way of life BY PETER BROWN

It's the kind of tongue-in-cheek concept that might have percolated out of the subversive imagination of R. Crumb, underground cartoon chronicler of the 1960s. Grandma and Grandpa are passing the time in their rockers—and passing a joint back and forth as they recall their youthful marijuana-smoking days in Haight-Ashbury. In fact, according to three investigators at the National Institute on Drug Abuse, the image is no joke.

Writing in the journal *Neuropsychopharmacology,* Gayathri J. Dowling, Susan R. B. Weiss and Timothy P. Condon warn that many aging baby boomers, long accustomed to using illicit drugs for recreation and medicinals of all kinds for treating whatever ails them, will carry their love affair with drugs into old age. Medicine is only beginning to appreciate the consequences.

The baby boomers, the generation born between 1946 and 1964, make up 29 percent of the U.S. population today. By 2030 this "pig in the python" of the nation's age-distribution profile will swell the number of people aged 65 and older to 71 million. The baby boomers, of course, became well known in the 1960s for their significantly higher use of illicit drugs than that of preceding generations. At one time, investigators were convinced that as people aged, they would "grow out of" the use of recreational drugs. There is little evidence that any such thing has taken place today.

RON WURZER *Getty Images*

TOKE THAT: Marijuana use (here at a Seattle Hempfest) and other drug indulgences continue well past the age of 30.

Dowling and his colleagues cite hospital data that record the number of people aged 55 and older who sought emergency-room treatment and mentioned using various drugs. The number of cocaine mentions rose from 1,400 in 1995 to almost 5,000 in 2002, an increase of 240 percent. Similarly, mentions of heroin increased from 1,300 to 3,400 (160 percent), marijuana from 300 to 1,700 (467 percent) and amphetamine from 70 to 560 (700 percent).

Data from the National Survey on Drug Use and Health corroborate those trends. In 2002 some 2.7 percent of adults between 50 and 59 admitted to illicit drug use at least once in the preceding year. By 2005 that number had increased significantly, to 4.4 percent. The investigators attribute the rise to the aging baby boomers, as well as to enhanced longevity coupled with people's tendency to retain their long-held

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patterns of drug use as they grow older. Those numbers will put substantial new strains on the medical system: by one estimate, the number of adults aged 50 and older treated for drug abuse will rise from 1.7 million in 2000 and 2001 to 4.4 million in 2020.

Of most concern to Dowling and his colleagues are the effects of drug abuse on the brain. The systems most affected are the ones involving the neurotransmitters dopamine, serotonin and glutamate, and all three systems change with age. The ability of receptors to bind dopamine, for instance, declines with age, and those declines often lead to some loss of motor and cognitive functioning. Cocaine users and the elderly exhibit similar brain changes, so seniors who use cocaine could be compounding the damage.

Intriguingly, the so-called cannabinoid system, which mediates the effects of marijuana in the brain, reduces addictive behavior in aging mice that have been genetically altered to crave alcohol. As the mice age, the cannabinoid receptor binds less frequently to a specific protein, which seems to diminish the animals' taste for alcohol. No one knows how aging may alter the cannabinoid system in people, but the system has wide-ranging effects on appetite, memory, addiction, and the perception of pain and pleasure.

Aging also leads to changes in metabolic rates and, in particular, in the processes whereby a drug is absorbed, distributed, metabolized and eliminated. The changes can lead to what Dowling and his colleagues call "devastating consequences" from the use of alcohol as well as from the abuse of medicines and illicit drugs. As older bodies become lean, water content is reduced and kidneys become less efficient; the concentration of a drug in the blood can remain high for a much longer time than it does in a younger person. That, in turn, poses the additional risk of adverse drug interaction, as high concentrations of various substances overlap in the blood.

The increased health risks become particularly hard to assess in connection with abused drugs because of the ethical bind it imposes on physicians. If a patient reports drug use, a doctor should include that fact in the patient's notes because of its potential effects on future treatment. But despite privacy protections under the law, many physicians hesitate to do so for fear of insurance and legal complications. For those reasons (and perhaps others), medical personnel are reluctant to question their patients' drug use, according to Dowling and his colleagues. Consequently, serious problems may go untreated.

In spite of what can be inferred about the effects of drugs on the aged, relatively little has been studied systematically. That lack of attention traces directly to the traditional—and now demonstrably false—assumption that the elderly do not abuse drugs, particularly illicit drugs. But the nation may soon discover that the pig will move more painfully through the python than anyone could have imagined.

GENETICS

Copy That

Identical twins are not genetically identical BY CHARLES Q. CHOI

Identical twins may look alike, but their DNA is not the same as long thought, a new study finds. Moreover, each twin grows more genetically distinct over time. Aside from maybe giving forensic investigators a way to tell which twin committed a crime, these recent findings highlight just how changeable human genomes might really be, twins or not.

Identical, or monozygotic, twins result when a fertilized egg, or zygote, splits in two. Because they derive from the same cell, such twins are generally assumed to be physically identical except for features shaped by environmental factors, such as fingerprints, and by womb conditions.

At times the physical differences between monozygotic twins can be profound: one may manifest a disease such as diabetes and the other not. To see if genetic changes might underlie these disparities, molecular geneticists Jan Dumanski and Carl Bruder, both at the University of Alabama at Birmingham, and their colleagues investigated nine pairs of monozygotic twins, of which each set had one twin with Parkinson's disease or a similar neurological disorder. The researchers found that all nine pairs showed genetic dissimilarities. Specifically, they discovered variations in the number of copies of genes. For instance, one twin might be missing a copy of a gene or have extra copies.

Proceeding further, the investigators then looked at 10 pairs of healthy monozygotic twins with no significant visible differences between them. Unexpectedly, in one pair they confirmed that one twin was missing a gene-laden section of chromosome 2 that the other twin had, and preliminary findings suggested eight other

IMPERFECT MATCH: **Though from the same DNA, identical twins have different numbers of gene copies.**

JULIAN WINSLOW *Corbis*

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pairs had copy number variations as well. "I can't tell you what a shock that was," Bruder recalls of their data in the March *American Journal of Human Genetics*.

Furthermore, Bruder notes the genome analysis methods they used could find only relatively large changes, those that were roughly 150,000 DNA bases in size. He suspects that higher-resolution techniques will reveal that all monozygotic twins have copy number changes. These variations generally occur when double-stranded DNA breaks—the repair process may leave out genes or insert extra copies.

In the twin with the loss in chromosome 2, only about 75 percent of blood cells had this deletion. The fractional aspect suggests that this copy number change happened relatively late in life, because alterations early in embryonic development would be expected to affect entire tissues. It remains uncertain, however, when and how often these changes occur.

Although monozygotic twins may not be perfectly genetically identical, they still are nearly so, Bruder emphasizes. Hence, twin studies—in which identical twins are compared to look for differences arising from environmental influences—should continue to have their uses. So hunting down genetic differences between twins could greatly help in identifying genes linked to diseases. "When you look between people who aren't twins who have a disease or don't, there are so many other differences you have to sort through," Bruder explains. "But with twins, it's much easier to find what's different." If anything, twin studies might now find use in discovering how environmental factors can alter one's genome, suggests Charles Lee, director of cytogenetics at the Dana-Farber/Harvard Cancer Center.

The fact that even monozygotic twins diverge genetically over their lives "shows us how much more dynamic the genome is than we thought—it's changing all the time, for good or for not," Bruder says. He and his colleagues are now investigating whether all of an individual's cells are genetically identical or whether, like twins, they diverge, making each of us mosaics of slightly different genomes.

Charles Q. Choi is a frequent contributor based in New York City.

Copy Number Variation: Genes, More or Less

People may have a shortage or extra copies of genes compared with others, and increasingly, scientists are recognizing how important such copy number variations are in human evolution. A 2006 study found that at least 12 percent of the human genome consists of copy number variable regions, and a 2007 paper found that cultures that eat a lot of starch tend to have more copies of starch-digesting amylase in saliva, suggesting that natural selection can drive copy number changes on a massive scale. These and other findings indicate that such changes may be so common "that you can find them as genetic differences between monozygotic twins," remarks Charles Lee, Dana-Farber/Harvard Cancer Center's director of cytogenetics. Copy number variation could be at least as relevant to disease development as mutations known as single-nucleotide polymorphisms (SNPs).

ECOLOGY

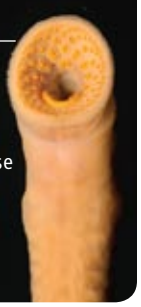
Following the Money

To find new homes, invasive fish look for a good GDP BY ADAM HINTERTHUER

Thanks to global shipping and trade, species of exotic fish are fording into new waterways worldwide, shoving native species toward extinction and costing countries billions of dollars each year as fisheries collapse and governments fight to stem the tide of aquatic interlopers. According to a new study, however, the success of these invaders depends less on ecology and more on economies.

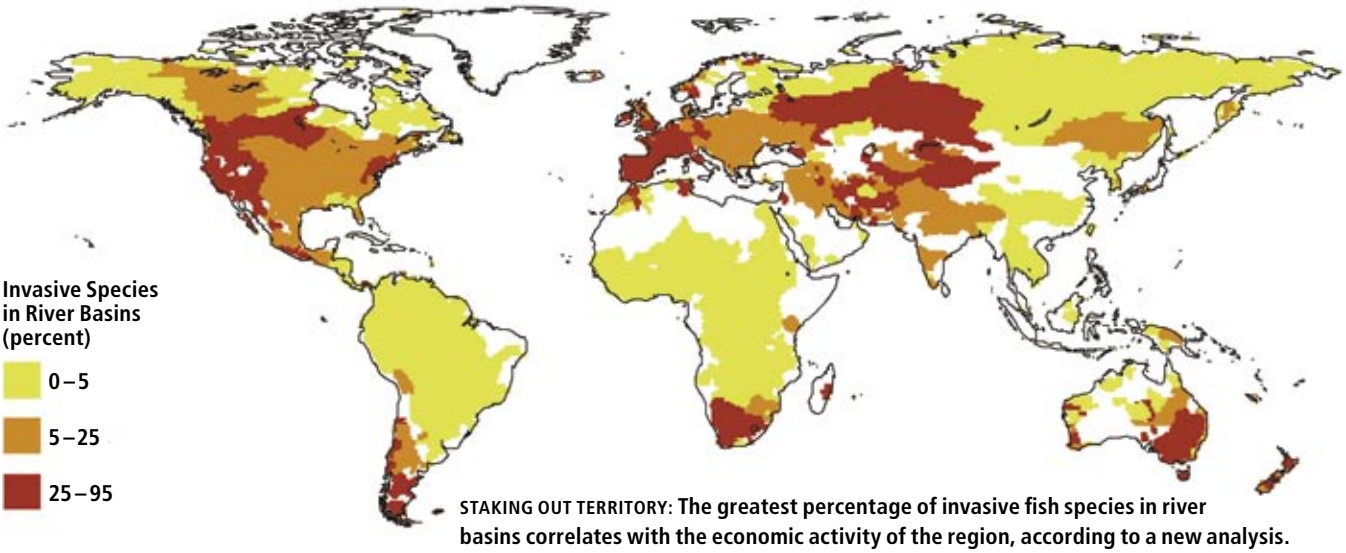
The news has come as a surprise to ecologists, who have long debated the conditions that make a habitat vulnerable to invasion. One hypothesis, popularized 50 years ago by British ecologist Charles Elton, is called biotic resistance. Elton believed that robust ecosystems had too many native occupants to make room for anything else. Essentially, invading species seeking a niche were met with a "no vacancy" sign. But in recent years, a counterhypothesis of "biotic acceptance" has emerged, contending that healthy habitats are equally alluring to both native and invasive species. As Jonathan Levine, an ecologist at the University of California, Santa Barbara, explains, "it's just as you

Minority Damage



The vast majority of introduced species cause no problems, remarks Rochelle Sturtevant, a NOAA ecologist who studies the Great Lakes. "Of the 185 nonindigenous species in the Great Lakes, probably only 10 percent have caused significant lasting economic and environmental impacts," she explains. Yet those effects can be severe. The flesh-burrowing sea lamprey (*right*), for example, gained access to the Great Lakes through shipping canals and drove lake trout to near extinction in the late 1950s. Today at least 25 exotic fish ply the lakes' waters. As a result, several native species are declining in numbers.

NORBERT WU *Minden Pictures*



STAKING OUT TERRITORY: The greatest percentage of invasive fish species in river basins correlates with the economic activity of the region, according to a new analysis.

might go to a restaurant because there are a lot of customers there, thinking it's indicative of high-quality food."

A team of researchers has muddied the long-standing debate in the February issue of *PLoS Biology*. The investigators looked at data from 1,055 river basins covering 80 percent of the earth's land and found six "global invasion hotspots," where more than 25 percent of freshwater fish are nonnative migrants. The six hotspots encompass large networks of river basins in western Europe, North and Central America's Pacific coast, southern South America, Australia and New Zealand, South Africa, and Central Eurasia. The high number of invasive species, says Fabien Leprieur of the Paul Sabatier University in Toulouse, France, and lead author of the report, coincides with maps of the world's largest gross domestic products, greatest amount of urban development and highest population densities. Perhaps most troubling, the hotspots also boast the greatest number of threatened native fish species.

At least on the scale of entire river basins, Leprieur's findings support neither biological hypothesis, says Levine, who researches how international trade spreads exotic plants. Evidently, human activity enables invasive species to get established in *any* kind of ecosystem.

Leprieur also expresses amazement "that natural processes are blurred by human activities in controlling the richness of nonnative freshwater fish species." But, he says, it is not hard to see how humans help invasive fish get a fin up—the more economically active a nation is, the more likely it is to engage in international shipping, which transports stowaways in ballast water, and to have large aquaculture and pet industries, where escaped fish are common. What is more, booming economies often come with dams, bridges and other environmental disturbances that could facilitate the spread of exotics.

Rochelle Sturtevant, an ecologist who studies the Great Lakes for the National Oceanic and Atmospheric Administration, hopes Leprieur's study can serve as a cautionary tale as developing nations join the global market and undertake activities that threaten to introduce exotic species into their relatively pristine ecosystems. Unfortunately, she points out, the conclusions drawn in the paper are too broad to help conservationists create concrete solutions. She thinks that more specific investigations may find evidence that biological processes actually do play a role in invasive dispersal. And, Sturtevant adds, terms such as "GDP" and "urbanization" should be fleshed out to include the specific human activities that drive exotic species invasions in a given region. Once conservationists uncover such details, perhaps they will be able to head off the next invasion.

Adam Hinterthuer is a freelance writer based in Madison, Wis.

SOURCE: "FISH INVASIONS IN THE WORLD'S RIVER SYSTEMS: WHEN NATURAL PROCESSES ARE BLURRED BY HUMAN ACTIVITIES," BY FABIEN LEPRIEUR ET AL., IN *PLoS BIOLOGY*, VOL. 6, NO. 2; FEBRUARY 5, 2008

PALEOANTHROPOLOGY

Finding Fossils Faster

Good-bye, field seasons? A push to year-round collecting BY FREDRIC HEEREN

East Turkana, Kenya—What unnerves Louise Leakey is not so much the banditry on the only supply road or the gun battles among herders who sometimes mistake researchers for their enemies—it's the goats. When a fossil in the Lake Turkana region in northern Kenya makes its way back to the eroding surface after several million years, it's just a matter of time before, as Leakey puts it, "a herd of 200 to 600 goats with those little hooves, four apiece, goes straight over it." To lose this race against time is to lose specimens forever—including remains of our ancestors.

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For millions of years, the Turkana basin has collected water and drawn life to it. Sediments have buried animal bones; erupting volcanoes along the Rift Valley have left tuffs with easy-to-date strata. Today the basin affords 1,200 square miles of covetable fossil exposure and 40 years of carefully worked-out geology. The east side contains hominid-bearing traces of the past four million years, where the famed Leakey family of paleoanthropologists has made ancestral-tree-shaking discoveries belonging to the genera *Australopithecus, Kenyanthropus* and *Homo*. The west side of the lake offers much older fossils from the Miocene, Oligocene and Cretaceous eras (including dinosaur remains).

Occasional rains expose the fossils not only to the light of day but also to the damage done by livestock led by herders searching for grazing. Researchers now claim to have found a way to collect fossils quickly while motivating the people to protect their heritage, a plan that involves a shift from 10-week field seasons to 50 weeks of fossil collecting annually.

The activity will fall under the aegis of the newly formed Turkana Basin Institute (TBI). Guided by Richard Leakey, his wife Meave and daughter Louise, it has raised $2.1 million to build a permanent field station at Ileret, east of Lake Turkana. Since April 2007, this camp has been transformed from a few tents into a field worker's wish list: a stone lab with plenty of curatorial space, staffed kitchens, metal prefab buildings and a garage with a full-time mechanic. The directors hope that year-round work will accelerate fossil recovery fivefold. Next year a second station is to be built on the lake's west side.

"What we're proposing is revolutionary," says Lawrence Martin, Stony Brook University paleoprimatologist and TBI director. "The Turkana Basin Institute will enable us to move away from a sort of Victorian model of fossil collecting where, typically, gentlemen and their lady scientists go out and set up a tented camp for a few months and collect fossils." The institute is offering its permanent facilities to outside researchers at a fraction of what it would cost them to bring their own support to this remote region, a four-day drive from Nairobi.

SAVING HISTORY: Paleoanthropologists Meave Leakey (*left*) and daughter, Louise (*right*), examine a fossil found near Ileret, east of Lake Turkana in northern Kenya. The Leakeys hope that a new institute, designed to support researchers who come to this region, will speed the retrieval of specimens from the fossil-rich area before they are damaged.

PETER LOURIE

So far Kenya's recent turmoil—which began after December's troubled election that resulted in deadly violence, split along ethnic lines—has not affected the institute. In fact, life goes on as usual in the north, where the people of Ileret have long led a marginalized existence with scarce food and water. The Turkana scientists will continue their tradition of employing local people, but they now hope to add many more community jobs in labs, museums, dining facilities—and a new field school to train both African and overseas students. Working with the National Museums of Kenya as an official repository for the government's local collection, the TBI also intends to attract tourists to the spot producing so many major discoveries. The scientists hope to help the region's people recognize the significance of their heritage while also channeling benefits from the research to sustainable livelihoods for the community. Moreover, the institute is partnering with two African and three foreign universities to develop career paths to help keep Kenyan Ph.D.s in the country.

Not everyone seems enamored of the institute, however. Rutgers University paleoanthropologist Jack Harris says he is content using the humbler Koobi Fora field station run by the National Museums, south of Ileret. Harris has expressed concern that the TBI might be encroaching on the government's authority in the region.

Martin argues that the institute is not trying to control the Turkana basin—"we're just trying to support science and support Kenya." He acknowledges that all are welcome to come and seek excavation permits from the National Museums of Kenya. "We just think that it's a tough area to do work, and if we have the infrastructure to help—to provide vehicles and food and well-trained staff—a lot of people will want to avail themselves of those," he adds. By inviting all researchers in the region to an August workshop at the new Ileret field station, TBI leaders hope to allay suspicions, facilitate working together and radically increase our understanding of human evolution.

Fredric Heeren is a freelance writer based near Kansas City, Kan.

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SLEEP

Naps for Better Recall

Even a six-minute snooze boosts memory BY JOHN WHITFIELD

If during that soporific hour after lunch, you succumb to the temptation of a quick nap, you are liable to earn your boss's displeasure. But judging by the latest results from sleep research, you should be getting a pat on the back.

Mountains of evidence reveal that sleep enhances memory. Now Olaf Lahl of the University of Düsseldorf in Germany and his colleagues have struck a blow for power-napping by showing that falling asleep for only six minutes is enough to significantly enhance memory. This is the shortest period of sleep found to affect mental functioning. It suggests, Lahl says, that something happens at the point of losing consciousness that solidifies memories.

YOU SNOOZE, YOU DON'T LOSE: In fact, you stand to gain, in terms of an improved short-term memory.

The subjects in Lahl's study reported to the university's sleep lab at 1 P.M. They were given two minutes to memorize a list of 30 words and tested on their recall an hour later. In the interim, they either stayed awake, took a six-minute nap or a longer snooze averaging 35 minutes. On no sleep, subjects recalled an average of just under seven words. A short nap raised performance to more than eight. A longer nap, including some time in deeper sleep, boosted recall to more than nine words.

Lahl previously thought the benefits of sleep for memory were mainly passive—that unconsciousness slows the rate at which new experience erodes old memories but that the sleeping brain does nothing special to help store waking experience. But this latest finding, appearing in the *Journal of Sleep Research*, has changed his mind, because six minutes does not seem long enough to forget much.

But sleep researcher Jim Horne of Loughborough University in England suspects that you need deep sleep to get a memory benefit and that the nappers might just have been a bit fresher than their continuously awake counterparts. In Lahl's study, he says, "it's more likely sleepiness is impairing memory than sleep enhancing it."

Robert Stickgold, who studies sleep at Harvard Medical School, disagrees. "It's hard to believe that six minutes' sleep could make you less sleepy," he says. Instead Stickgold suspects that the experiment reveals a process of memory consolidation that begins even before sleep and that could continue after waking from a very brief sleep. "In the last couple of minutes of waking, the brain could be putting stickers on topics for later processing," he speculates.

A sleeping brain is not merely on standby; it runs through a suite of complex and orderly activities. One of these is a flow of neural activity from the hippocampus, where short-term memories are formed, to the cortex, where they are stored in more durable forms—a possible reason people can remember things better on awakening. Nor is this process simply a matter of scribing data into neural tissue. Several recent studies of sleep and sleeplessness show that slumber is especially important for doing clever stuff with information, such as extracting the gist of what has been learned, combining facts in interesting ways and dealing with the day's emotions.

"Executive thinking is particularly impaired by sleep loss," Horne says. "You become much more blinkered in your thinking, less able to deal with novelty and less able to evaluate risk." This is bad news for medics, shift workers and military commanders, he observes, and perhaps explains why casinos stay open all night.

"The most important processing of information during sleep is to add meaning to information and fit it into a larger context," Stickgold explains, adding that such processing seems most likely to have driven sleep's evolution. "Of all the functions of sleep, memory is the only one that explains why you'd have to go through the dangerous phenomenon of losing consciousness, as opposed to having quiet rest."

Lahl, in contrast, thinks that sleep is primarily about repairing and detoxifying the brain—he points out that there is no correlation between how much you learn in a day and how much you need to sleep at night. Nevertheless, he is now looking for an effect of two-minute naps. "We're trying to put it at the extreme, to find the critical period of time where memory enhancement might happen. But in such short periods it's difficult to decide if the subject is asleep."

John Whitfield is based in London.

Napping Is Natural

Until recently, sleep researchers overlooked naps, perhaps because their societies frown on afternoon snoozes. But short sleeps are the norm in animals, says psychologist Olaf Lahl of the University of Düsseldorf in Germany. "Getting all your sleep in a monolithic block is quite unusual," he adds. And people with looser schedules—infants and the elderly—are much more likely to nap, he notes.

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AUDIO ENGINEERING

Down to the Wire

A Grammy Award for restoring music through electrical hum BY WENDY M. GROSSMAN

Music can be about physics and math as well as art. This year's Grammy Award for Best Historical Album went to a team that included University of New Hampshire mathematician Kevin M. Short and sound engineer Jamie R. Howarth for restoring a fragile, live 1949 wire recording of legendary folksinger Woody Guthrie. The technique developed for the restoration cleverly exploits background noise present in a recording.

The story began with two rolls of steel wire—a bootleg recording sent to the Woody Guthrie Archives in 2001. Like tape, steel wire can be run through a magnetic recorder to capture electrical signals transmitted by a microphone. Such recordings are especially susceptible to mechanical degradation. The wire (or tape) stretches, slips, breaks and kinks; rollers and bearings get worn spots; and motors develop subtle imperfections. The result is timing variations that cause artifacts known as wow and flutter.

The Guthrie recording was a particularly damaged example. "One section was so bad when I first heard it," Short says, "that it sounded like Charlie Brown's teacher." Yet now that same audio is intelligible and of listenable quality.

Aside from the custom-built, converted tape machine needed to play the Guthrie recording, the secret to its restoration lay in a key insight of Howarth's. Alongside the music being recorded, analog tape recorders lay down a "bias signal," a pure tone at 40 kilohertz or above (well outside the range of human hearing). Such a bias signal makes a tape more effective at capturing audio. Howarth's idea: if properly extracted, the bias signal could serve as a reference to identify and correct those timing variations and restore the audio to its original quality. In 2003 he took this idea to Patrick J. Wolfe, an electrical engineer at Harvard University, and asked him if he thought it would work. "It struck me as a nice idea," recalls Wolfe, who shares the resulting patent with Howarth.

But poring over the Guthrie recording, Howarth found no bias signal—wire recorders may not have used them. What he did find was a faint but usable hum at 60 hertz, a cross-feed from an electrical power line. Any steady tone, Howarth realized, could be used as a reference.

Howarth had other details to smooth out, such as the best way to digitize the analog signals. The process involves sampling audio signals tens of thousands of times per

TIME & LIFE PICTURES/GETTY IMAGES

"TO THE NEW YORK ISLAND" for a shoe shine, Woody Guthrie enthralled a crowd in 1943.

second (for CD-quality sound), but it also introduces additional timing variations. Howarth then turned to Wolfe, who "came up with a rather interesting approach using irregularly spaced sampling theory," Howarth says—a contrast to the standard method of sampling at regular intervals. Specifically, Wolfe identified ideal points at which the damaged analog signal should be sampled, and these points turned out to be irregularly spaced over time. For the Guthrie project, Short used his expertise in music compression and chaos theory to adapt Wolfe's code and to fix the time orientation. Chaos theory, Short says, enabled the team to see structures in what appeared to be random signal variations, thus allowing them to reconstruct the actual music.

Most of Howarth's work through his company, Plangent Processes in Nantucket, Mass., is on far less damaged audio—chiefly commercial film and audio from the analog era. The restoration of the Guthrie recording has, Short remarks, inspired many new ideas for approaches that may prove promising in the future. For now, it has given folk music fans a chance to hear a great American legend like never before.

Wendy M. Grossman is based in London. Before-and-after samples of the Guthrie recording can be heard at www.plangentprocesses.com

Data Points

Preparing for Doomsday

Built into permafrost on Norway's Spitsbergen Island in the Arctic Circle, the Svalbard Global Seed Vault officially opened on February 26. Funded by the Norwegian government, the secure facility intends to house a library of seeds from all food crops from all countries as a hedge against wars, poverty and environmental disasters, including climate change. The vault sits at an altitude of 130 meters, so even if the ice caps melt, the seeds will not be inundated. Each sample, stored in four-ply foil packets, may contain hundreds of seeds.

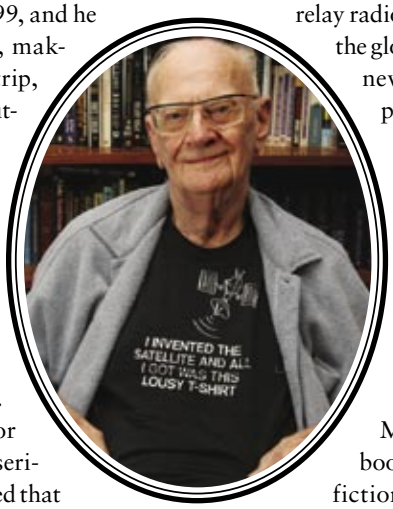
Current number of stored seed samples:	268,000
Weight in tons:	10
Maximum sample capacity:	4.5 million
Number of seeds:	2.25 billion
Storage temperature, degrees Celsius:	–18
Number of years seeds will stay frozen if power is lost:	200
Number of armored and air-locked doors protecting the seeds:	4
Estimated survival time in years of seeds from:	
Barley:	2,000
Wheat:	1,700
Sorghum:	20,000

SOURCES: Ministry of Agriculture and Food, Norway; "Seeds of Future Agriculture Enter Doomsday Deep Freeze," at www.SciAm.com, February 26

IN MEMORIAM

Sir Arthur C. Clarke, 1917–2008

He wore pajamas and a bathrobe, and a swollen bare foot was propped up on an ottoman. That was the figure cut by the revered science-fiction author Arthur C. Clarke the one time that I, along with a few other *Scientific American* editors, met him. It was October 1999, and he was in New York City, making an extremely rare trip, for medical reasons, outside of his adopted home country of Sri Lanka.



Clarke had invited us to his room at the historic Hotel Chelsea, where in the mid-1960s he worked on his best-known piece, *2001: A Space Odyssey*. There he berated us for not taking cold fusion seriously enough. He believed that a revolutionary discovery could still come from the experiments of the small scattering of remaining devotees to the idea. Clarke's optimism about the possibilities of future technology is embodied in his three famous "laws," one of which states that a sufficiently advanced technology is indistinguishable from magic.

In 1945 he wrote in the magazine *Wireless World* of how a satellite in an equatorial orbit with a radius of 42,000 kilometers would remain over the same location of the earth and how three of them could relay radio signals to anywhere on the globe. The concept was not new with Clarke, but he popularized the idea. In 1964 the first such geostationary communications satellite was launched.

Clarke, who suffered from post-polio syndrome and reportedly had trouble breathing before his death on March 18, wrote scores of books, both fiction and nonfiction, and won numerous awards. An asteroid, an orbit, a species of dinosaur and several prizes have been named after him. Many scientists, astronauts and writers have credited him with inspiring them in starting their careers. His impact, you might say, was indistinguishable from magic. —*Graham P. Collins*

MATERIALS SCIENCE

Self-Healing Rubber

A new stretchy material can be cut and rejoined at the same spot just by pressing the broken ends together for a few minutes. The self-healing rubber stays stretchy even after being severed five or six times or cut and left alone overnight, French researchers say. A chemical manufacturer is already working to create batches of the material for hypothetical applications, such as sealants. The material's secret is a molecular structure that resembles a plate of spaghetti, says physicist Ludwik Leibler of the National Center for Scientific Research (CNRS) in Paris, who led the research team. The self-mending occurs because each strand consists of molecules of vegetable fat linked to one another via relatively weak hydrogen bonds, the same chemical bonds that give water molecules their cohesiveness. The result is a rubber that can stretch to six times its resting length, the group extends in the February 21 *Nature*.

—*JR Minkel*

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MARI TEFRE *Svalbard Global Seed Vault (left)*; ANDREW HOLBROOKE *Corbis (right)*

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In Brief

RISING SEAS BE DAMMED

Melting ice caps have released far more water than previously thought. The missing water's hiding place? Artificial reservoirs. Scientists at the National Central University in Chung-Li, Taiwan, estimate that nearly 29,500 reservoirs around the globe now hold about 10,800 cubic kilometers of water, or roughly twice the volume of Lake Michigan. Although global sea level has climbed steadily during the past 80 years, reservoir construction has artificially kept sea levels from rising another 30 millimeters in the past 50 years, the researchers estimate in findings published online March 13 in *Science.* By 2100, sea levels may rise by 100 to 900 millimeters because of global warming. —*Charles Q. Choi*

CLOUDS OF ENTANGLEMENT

Researchers at the California Institute of Technology have combined quantum entanglement—the faster-than-light communication among particles—with the technique of halting light dead in its tracks. Physicists used a beam splitter to cleave a single photon into an entangled pair and stored the two states one millimeter apart in a cloud of cesium atoms chilled to near absolute zero. When they recombined the pair back into light, 20 percent of the original entanglement remained—better than prior entanglement experiments.

The demonstration opens the door for entangling two distinct atomic clouds and using quantum teleportation to flash the quantum state of a particle from one cloud to the other, a kind of quantum telecom network. —*JR Minkel*

MINI SOLAR SYSTEM

Astronomers have discovered a pair of planets around a star 5,000 light-years away that resembles smaller versions of Jupiter and Saturn. Scott Gaudi, an astronomer at Ohio State University and lead author of the study published in the February 15 *Science,* discovered the planets with his colleagues over a two-week period in 2006, when their stellar parent crossed in front of a more distant star, causing the nearer star to magnify the light from the more distant one. The finding suggests that solar systems like ours, with rocky inner planets and outer gas giants, may be common. —*JR Minkel*

ADAPTATION

Split Defense

TWO IS BETTER THAN ONE: **Larva of the sand dollar begins cloning itself.**

If you hear that a sea creature splits after sensing a foe, that may not be just a figure of speech for it swimming away—it may literally split in two. That is the case for the sand dollar (*Dendraster excentricus*), a spiny critter related to starfish. When the larvae detect mucus from nearby predatory fish, they start cloning themselves, asexually reproducing within 24 hours. Although cloning is slow compared with a fish attack, if the larvae get enough of a head start, it may boost their chances of evading detection. That is because the clones are about two-thirds the typical length of the original. Many animals clone themselves, but scientists thought that the process was generally driven solely by growth and reproduction, not by a need to defend against carnivores. The scientists, who published their findings in the March 14 *Science,* speculate that cloning in response to predators may be found where small size confers a safety advantage. —*Charles Q. Choi*

CLIMATE CHANGE

Smokestack Soak-Up

Researchers have been searching for an ideal substance that can soak up carbon dioxide (CO_2) in smokestacks before the greenhouse gas enters the atmosphere. Existing CO_2 sponges have drawbacks: they may be too expensive, take too much energy to operate, do not capture much carbon or are unstable over long periods. Now chemical engineer Christopher Jones of the Georgia Institute of Technology and his colleagues have developed a solid adsorbent that is both strong and long-lasting.

The material contains nitrogen-rich compounds called amines grown on porous silica. The amines are bases that neutralize the acidic carbon dioxide gas. Heating the substance releases trapped CO_2 for later storage. The low-cost material has a hyperbranching structure, which helps it hold many amines, Jones explains, and the strong chemical bonds holding it together allow it to be reused often. The absorbing findings appear in the March 19 *Journal of the American Chemical Society.*

—*Charles Q. Choi*

BRAIN IMAGING

Do You See What I See?

Scientists at the University of California, Berkeley, have developed a method capable of decoding the patterns in visual areas of the brain to determine what someone has seen. Specifically, they used functional magnetic resonance imaging to record activity in the visual cortices of volunteers while they viewed a series of images. The researchers could then infer what image a person was seeing by monitoring activity in different sections of the brain and deciphering what information would most likely be found in the corresponding part of the visual field. The method, however, is limited to deciphering information that can be clearly represented mathematically, such as pictures, sounds and movements. The work showed up March 5 in *Nature* online.

MIND READING isn't this easy, but functional MRI might permit a form of it.

—*Nikhil Swaminathan*

COURTESY OF DAWN VAUGHN; SOURCE: "PREDATORS INDUCE CLONING IN ECHINODERM LARVAE," BY DAWN VAUGHN AND RICHARD R. STRATHMANN, IN *SCIENCE*, VOL. 319; MARCH 14, 2008. REPRINTED WITH PERMISSION FROM AAAS *(top)*; JOHN-FRANCIS BOURKE *zefa/Corbis (bottom)*

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SciAm Perspectives

Taking Heed

The next U.S. president needs to elevate the role of the White House science adviser

BY THE EDITORS

In the wake of the near panic over the launch of Sputnik in 1957, President Dwight D. Eisenhower appointed James Killian, the president of the Massachusetts Institute of Technology, to become the first special assistant to the president for science and technology. Ever since, the relationship between the nation's chief executive and the White House's resident authority on nuclear fission, the workings of DNA and the greenhouse effect, among an array of topics, has had its highs and lows.

To be sure, advice has flowed freely at times. Eisenhower consulted frequently with Killian and other scientists, and in the Kennedy years Jerome Wiesner, another M.I.T. president, helped to coordinate the government's response to the publication of Rachel Carson's *Silent Spring*, a book that spurred a national grassroots environmental movement by pointing out the dangers of pesticides.

Just as often the adviser's position has tilted toward irrelevance. Richard M. Nixon went so far as to abolish the job altogether, along with the President's Science Advisory Committee, which had recommended against going ahead with a supersonic transport program, advice that the ill-fated 37th president did not want to hear. (The U.S. Congress restored the position in 1976.)

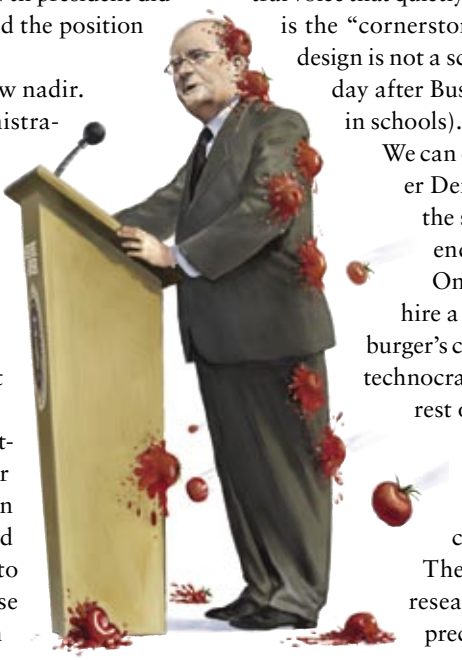
The tenure of George W. Bush marks a new nadir. On the few science-related issues the administration has cared about—stem cells and climate change were on the short list—it had largely set its course before the arrival of its new science adviser John H. Marburger III some nine months after Bush first took office. The administration, moreover, stripped the job of the title "special assistant to the president," a reminder that the adviser would never be part of the inner circle.

Nevertheless, hopes rose with the appointment of the well-regarded physicist and former head of Stony Brook University and Brookhaven National Laboratory. "As both scientist and administrator, John H. Marburger III tries to bring needed perspective into a White House not thought to be particularly interested in science," read a headline for a profile published in *Scientific American* in June 2002.

In the ensuing years, Marburger has disappointed. Much of his public persona has been as an apologist for the Bush team, trying to rebut charges from scientists, Congress and the media that the administration has engaged in a "war on science" by systematically distorting or suppressing science-related reports and politicizing federal advisory committees.

Bush's first appointed EPA administrator, former New Jersey Republican governor Christine Todd Whitman, resigned in 2003, amid this politically charged atmosphere. Mystifyingly, the ever dutiful Marburger, a registered Democrat, has spent more time as science adviser than any of the dozen or so men who have served before him.

Marburger continues to plow ahead with elaborate rationales that acknowledge in one breath the reality of global warming and in the next explain why "adaptation" to rising temperatures (think pineapple farming in North Dakota) needs to receive more attention. He has also assumed the role of the disembodied, neutral voice that quietly corrects the boss's gaffes. Yes, evolution is the "cornerstone of modern biology." No, intelligent design is not a scientific concept (comments he made the day after Bush twice said that both should be taught in schools).



We can only hope that the next president, whether Democrat or Republican, will not relegate the science adviser—and the entire scientific endeavor—to the status of afterthought. Once elected, the new chief executive should hire a leading scientist, perhaps one with Marburger's credentials though not with his compliant, technocratic demeanor. In collaboration with the rest of the community, the official should be allowed to assume a prominent, unimpeded role in helping to influence the crafting of policies that address climate change, missile defense and stem cells. The war on cancer—and a host of other research initiatives—should once again take precedence over the war on science. ■

MATT COLLINS

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Sustainable Developments

The African Green Revolution

The continent is overdue for an agricultural boon like the one that lifted Asia's prospects

BY JEFFREY D. SACHS

Africa needs a green revolution. Food yields on the continent are roughly one metric ton of grain per hectare of cultivated land, a figure little changed from 50 years ago and roughly one third of the yields achieved on other continents. In low-income regions elsewhere in the world, the introduction of high-yield seeds, fertilizer and small-scale irrigation boosted food productivity beginning in the mid-1960s and opened the escape route from extreme poverty for huge populations. A similar takeoff in sub-Saharan Africa is both an urgent priority and a real possibility.

Until this change happens, Africa's vast rural areas, which are home to two thirds of its population, will remain mired in poverty, hunger and high child mortality and will stay isolated from the world market economy. Proven technologies—high-yield seeds, new water-management techniques and ways to replenish soil nutrients—are already achieving three to five tons per hectare in many parts of Africa but too often only in small demonstration projects.

Currently tens of millions of African farmers, with hundreds of millions of dependents, are stuck living in subsistence conditions. They lack the savings or creditworthiness needed to buy better seed, fertilizer and water technology. They lack even minimal community infrastructure (roads, storage capacity and power) to participate profitably in the market economy, and so they cannot better their situations.

Until recently, donors sent only food aid in response to Africa's deepening agricultural crisis. Now they are waking up to the one real solution: increased agricultural production through a homegrown African green revolution. It would require four kinds of temporary help: financing for better farming inputs, extension services to advise farmers on the new technologies, community nurseries to diversify production, and investments in infrastructure. Market-based techniques of financial management can also offer weather-risk insurance to the farm communities.

The time for action is ripe for several reasons. Most important among them is that African leaders themselves are prioritizing agriculture and often getting major increases in harvests and farm incomes as a result. Malawi has more than doubled its food output in just three years, following a bold government program to ensure that all farm households have subsidized access to fertilizers and high-yield seeds. Others are following that lead.

International institutions such as the World Bank have returned to leadership on agriculture after years of waiting in vain for the markets alone to solve the problem. An internal review last year called on the World Bank and donors to "help design efficient mechanisms, including public-private partnerships, to provide farmers with critical inputs."

New international donors have also stepped forward. The Alliance for a Green Revolution in Africa, sponsored by the Gates and Rockefeller foundations, has given a massive boost to the agenda. Aid to Africa from the governments of wealthy countries has been promised to double between 2004 and 2010, and much of that should go to agriculture.

An additional reason speaks to the urgency for change: Africa's vulnerability to food insecurity has skyrocketed. The population has outstripped the food supply. Climate change is already wreaking havoc on crop yields. Depletion of soil nutrients has reached crisis proportions. Soaring world food prices have put a crippling burden on Africa as a net food importer. This way lies disaster.

Here are bold but realistic goals that Africa and its donor partners can adopt: to double grain yields in Africa by 2012, to graduate at least three quarters of African smallholder farm households from subsistence to commercial farming within a decade, and to expand nutrition programs alongside increased food production to cut the ranks of the hungry by at least half by 2015.

We should establish a special fund for the green revolution in Africa akin to the highly successful Global Fund to Fight AIDS, Tuberculosis and Malaria. An annual flow of $10 billion from the rich countries, half through the fund, would finance the needed breakthroughs. It would amount to roughly $10 per person in the donor countries, a modest sum that would give Africa the historic opportunity to banish extreme poverty and chronic hunger for hundreds of millions of its people. ■

Jeffrey D. Sachs is director of the Earth Institute at Columbia University (www.earth.columbia.edu).

SCI AM An extended version of this essay is available at **www.SciAm.com/sciammag**

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Forum

The Mad Scientist Myth

Readers need more novels about real science

BY MARK ALPERT

In novels and films, the most common scientist by far is the mad one. From H. G. Wells's Dr. Moreau to Ian Fleming's Dr. No to Stanley Kubrick's Dr. Strangelove, scientists are portrayed as evil geniuses unrestrained by ethics and usually bent on world domination. Over the past two years, as I struggled to write my own novel about physicists and their quest for the Theory of Everything, I often worried that I was falling prey to this stereotype myself. It is incredibly difficult to create fictional scientists who are neither insane villains nor cardboard heroes. To faithfully depict the life and work of a researcher, you need to immerse yourself in the details of his or her research, and very few writers have done this task well.

One of the earliest attempts to draw a realistic picture of science was Sinclair Lewis's *Arrowsmith,* which won the Pulitzer Prize in 1926. The book tells the story of Martin Arrowsmith, a callow Midwestern youth who after long travails throws off the temptations of money, power and fame to pursue a life of solitary medical research. Martin isn't a very likable character—he's peevish, disdainful and annoyingly self-important. One gets the sense that even the author doesn't care for him much. The true hero of the tale is Martin's mentor, Max Gottlieb, a long-suffering German-American bacteriologist. Dr. Gottlieb provides the novel's wisest insights: "To be a scientist—it is not just a different job … it is a tangle of very obscure emotions, like mysticism, or wanting to write poetry." *Arrowsmith* also gives readers a fascinating glimpse of microbiology in the early 20th century. To get his facts right, Lewis relied on Paul de Kruif, a bacteriologist and science writer who received 25 percent of the book's royalties in return for his help.

John Updike's 1986 novel *Roger's Version* features a very different kind of scientist hero: Dale Kohler, a research assistant at a computer lab whose specialty is devising graphics that simulate reality. Dale is a religious young man who becomes convinced that his simulation programs can prove the existence of God. His search for divine signals ends fruitlessly, of course, but Updike's description of Dale's late-night vigils at the computer terminal will ring true to anyone who has ever wrestled with software code. Perhaps the best parts of *Roger's Version* are the entertaining arguments about science and religion, which are peppered with ideas from cosmology and particle physics. And the book abounds with the gorgeous sentences that make Updike such a joy to read: "His necktie, purple violently interrupted by green, struck the gauche note we expect from scientists. He carried a small paper cone of zinnias, the sort of bouquet young drug addicts sell now from traffic islands."

A standout among the science novels published in the past few years is *Intuition,* by Allegra Goodman. The book delves into the hothouse atmosphere of a research institute that is investigating potential cancer treatments. One of the institute's postdocs devises a genetically modified virus that appears to shrink tumors in mice, but a colleague accuses him of fudging his results. The story's clever trick is that nobody at the lab is entirely in the wrong; the missteps of the researchers seem to be the result of sloppiness and wishful thinking rather than outright fraud. Instead of presenting a simple morality lesson, *Intuition* reveals the ambiguous, groping nature of biomedical experimentation: "Science was all about failure, and bench work consisted primarily of setbacks."

A good work of fiction can convey the smells of a laboratory, the colors of a dissected heart, the anxieties of a chemist and the joys of an astronomer—all the illuminating particulars that you won't find in a peer-reviewed article in *Science* or *Nature*. Novels such as *Intuition,* with their fully fleshed out characters and messy conflicts, can erase the ridiculously sinister Dr. No cartoons. And most important, these books can inspire readers to become scientists themselves. ■

Scientific American *staff editor Mark Alpert is author of* Final Theory, *a thriller about high-energy physics that will be published by Touchstone in June.*

PHOTOGRAPH BY DON POLLARD; ILLUSTRATION BY MATT COLLINS

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Skeptic

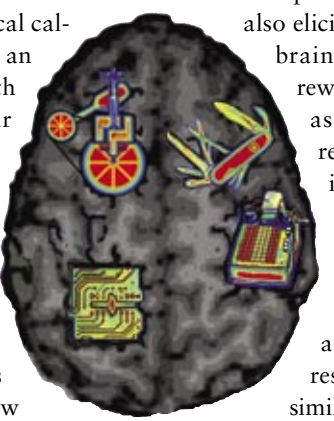
A New Phrenology?

Metaphors, modules and brain-scan pseudoscience

BY MICHAEL SHERMER

The atom is like a solar system, with electrons whirling around the nucleus like planets orbiting a star. No, actually, it isn't. But as a first approximation to help us visualize something that is so invisible, that image works as a metaphor.

Science traffics in metaphors because our brains evolved to grasp intuitively a world far simpler than the counterintuitive world that science has only recently revealed. The functional activity of the brain, for example, is nearly as invisible to us as the atom, and so we employ metaphors. Over the centuries the brain has been compared to a hydraulic machine (18th century), a mechanical calculator (19th century) and an electronic computer (20th century). Today a popular metaphor is that the brain is like a Swiss Army knife, with specialized modules for vision, language, facial recognition, cheating detection, risk taking, spirituality and even God.



Modularity metaphors have been fueled by a new brain-scanning technology called functional magnetic resonance imaging (fMRI). We have all seen scans with highlighted (usually in red) areas where your brain "lights up" when thinking about *X* (money, sex, God, and so on). This new modularity metaphor is so seductive that I have employed it myself in several books on the evolution of religion (belief modules), morality (moral modules) and economics (money modules). There is a skeptical movement afoot to curtail abuses of the metaphor, however, and it is being driven by neuroscientists themselves. The November 11, 2007, edition of the *New York Times,* for example, published an opinion piece entitled "This Is Your Brain on Politics," by neuroscientist Marco Iacoboni of the University of California, Los Angeles, and his colleagues. The writers presented the results of their brain scans on swing voters. "When we showed subjects the words 'Democrat,' 'Republican' and 'independent,' they exhibited high levels of activity in the part of the brain called the amygdala, indicating anxiety," the authors note. "The two areas in the brain associated with anxiety and disgust—the amygdala and the insula—were especially active when men viewed 'Republican.' But all three labels also elicited some activity in the brain area associated with reward, the ventral striatum, as well as other regions related to desire and feeling connected." So the word "Republican" elicits anxiety and disgust, except for when it triggers feelings of desire and connectedness. The rest of the conclusions are similarly obfuscating.

In a response befitting the self-correcting nature of science, Iacoboni's U.C.L.A. colleague Russell Poldrack and 16 other neuroscientists from labs around the world published a response three days later in the *Times,* explaining: "As cognitive neuroscientists who use the same brain imaging technology, we know that it is not possible to definitively determine whether a person is anxious or feeling connected simply by looking at activity in a particular brain region. This is so because brain regions are typically engaged by

PHOTOGRAPH BY BRAD SWONETZ; ILLUSTRATION BY MATT COLLINS

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many mental states, and thus a one-to-one mapping between a brain region and a mental state is not possible." For example, the amygdala is activated by arousal and positive emotions as well, so the key to interpreting such scans is careful experimental design that allows comparison between brain states.

Additional skepticism arises from knowing that fMRI measures blood-flow change, not neuronal activity, that the colors are artificially added in order to see the blood-flow differences and that those images are not any one person's brain but are instead a statistical compilation of many subjects' brains in the experiment. "Some of the claims made by neuroscientists sound like astrology," Poldrack told me in an interview. "It's not the science itself that is the problem. It's taking a little bit of science and going way beyond it." For example, there is the problem of reversing the causal inference, "where people see some activity in a brain area and then conclude that this part of the brain is where *X* happens. We can show that if I put you into a state of fear, your amygdala lights up, but that doesn't mean that every time your amygdala lights up you are experiencing fear. Every brain area lights up under lots of different states. We just don't have the data to tell us how selectively active an area is."

University of California, San Diego, philosopher of the mind Patricia S. Churchland told me with unabashed skepticism: "Mental modules are complete nonsense. There are no modules that are encapsulated and just send information into a central processor. There are areas of specialization, yes, and networks maybe, but these are not always dedicated to a particular task." Instead of mental module metaphors, let us use neural networks.

The brain is not random kludge, of course, so the search for neural networks associated with psychological concepts is a worthy one, as long as we do not succumb to the siren song of phrenology. ■

Michael Shermer is publisher of Skeptic *(www.skeptic.com). His new book is* The Mind of the Market.

Anti Gravity

Are You Buying This?

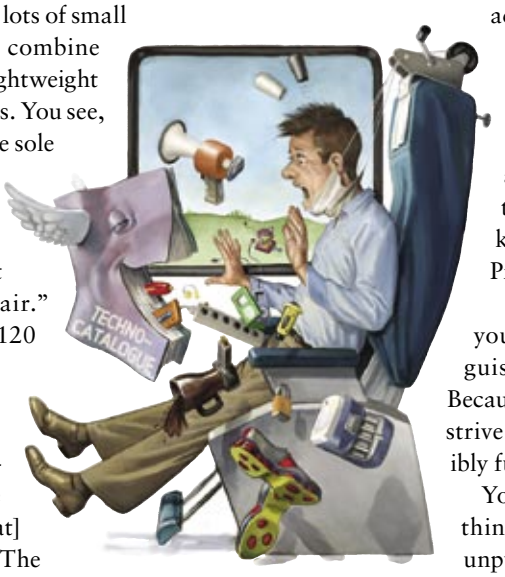
Catalogues provide the weary traveler with hi-tech gizmos galore

BY STEVE MIRSKY

I was on the train going north from New York City recently, heading to Boston for the annual conference of the American Association for the Advancement of Science (AAAS). But there was already science and technology galore right in front of me: a copy of one of those catalogues that hawks fancy, state-of-the-art goodies. I picked it up and lost myself in today's fabulous world of tomorrow.

For example, there was a product that could "instantly eliminate the appearance of baldness and thinning hair" with "keratin protein fibers." You just shake the fibers onto your head, like salt. Or pepper, if your thinning hair's not gray yet. The little fibers allegedly stick to your remaining shafts for some undisclosed period, making your hair seem thicker, fuller and more metastatic. Price: a hair-raising $23 for a third of an ounce.

Then there was the full-page ad, with lots of small type, for shock-absorbing shoes that combine inflatable tire technology with actual "lightweight energy reciprocating" springs in the heels. You see, the springs act as "the main engine of the sole using your body's weight as fuel for lift." As the ad explained, "It's almost as if Aeolus, the Greek god of wind, himself has taken his powerful wind out of his bottles and put it into each pair." Almost. Prices: ranging from a breezy $120 to a lofty $220.



A few pages down, sound waves met water waves in the ultimate beachfront and poolside iPod accessory, the waterproof stereo system. Your iPod fits inside a "shatterproof polycarbonate case [that] tightly seals against water and sand." The entire unit floats on the water's surface, finally enabling your musical taste to uplift all within earshot in an aqueous environment. What really sold me, though, was: "Includes shoulder straps." When the resulting backpack carries a video iPod, the wearer-watcher turns, literally, into a perpetual-motion machine. Price: cresting at $149.

The following page featured an automatic coin sorter that can "drop 312 coins a minute into the appropriate wrappers." Price: 17,900 pennies, with a set of assorted coin wrappers going for an additional 1,900 cents.

Next I found an ingenious piece of equipment for getting rid of love handles. This low-to-the-ground device includes handlebars up front and kneepads in back. You mount the thing and twist side to side parallel to the ground. With its low profile, however, this unit takes a backseat to the typical exercise bike as a practical place to drip-dry clothes. Price: a contorted $199.95.

Want to gauge your ability to drive before leaving the local watering hole? Try the personal alcohol breath analyzer with an "advanced semiconductor sensor." This digital alcohol monitor has an "upgraded foolproof design." But no design can protect against technology's greatest challenge: a sufficiently inebriated operator. Price: close enough to try driving it at $139.95.

Then there was the "six-way power station" that can melt all your personal electronic devices simultaneously using only one wall outlet. Price: a shocking $99.95.

Past the pages of automatic watch winders, alarm clocks that actually launch rotors into the air and a gun that shoots marshmallows, I arrived at the solar-powered mole repeller. As opposed to the solar-powered mole creator, a.k.a. skin. This stake comes with a photovoltaic panel that powers a penetrating pulse guaranteed to drive the pesky critters over to your neighbor's garden. Price: gopher it at $39.99.

How to get amplified sound *and* a more youthful appearance? A hearing aid disguised as a cell-phone Bluetooth receiver. Because all the most happening youthful playas strive to look like Borg drones. Price: a resistibly futile $39.99.

Your laptop can finally be good for something at Starbucks other than storing your unpublished novel, when you attach the USB-powered "tech-savvy travel mug" that keeps coffee hot. Price: a tall $19.99.

Finally, there was one where a picture here would really have helped, but what the heck: a do-it-yourself cervical traction device. Just sling the thing up on a door, put your head in the harness and pull the cord to stretch out your neck. Price: a numbing $54.95. Inevitable Darwin Award included. Eventually. ■

For actual coverage of the AAAS conference Steve was headed to, check out numerous podcasts he filed in February and March at **www.SciAm.com/podcast**

PHOTOGRAPH BY FLYNN LARSEN; ILLUSTRATION BY MATT COLLINS

The Genesis

Long viewed as a stately procession to a foregone conclusion, planetary formation turns out to be startlingly chaotic

KEY CONCEPTS

- Barely a decade ago scientists who study how planets form had to base their theory on a single example—our solar system. Now they have dozens of mature systems and dozens more in birth throes. No two are alike.
- The basic idea behind the leading theory of planetary formation—tiny grains stick together and swoop up gas—conceals many levels of intricacy. A chaotic interplay among competing mechanisms leads to a huge diversity of outcomes.

—The Editors

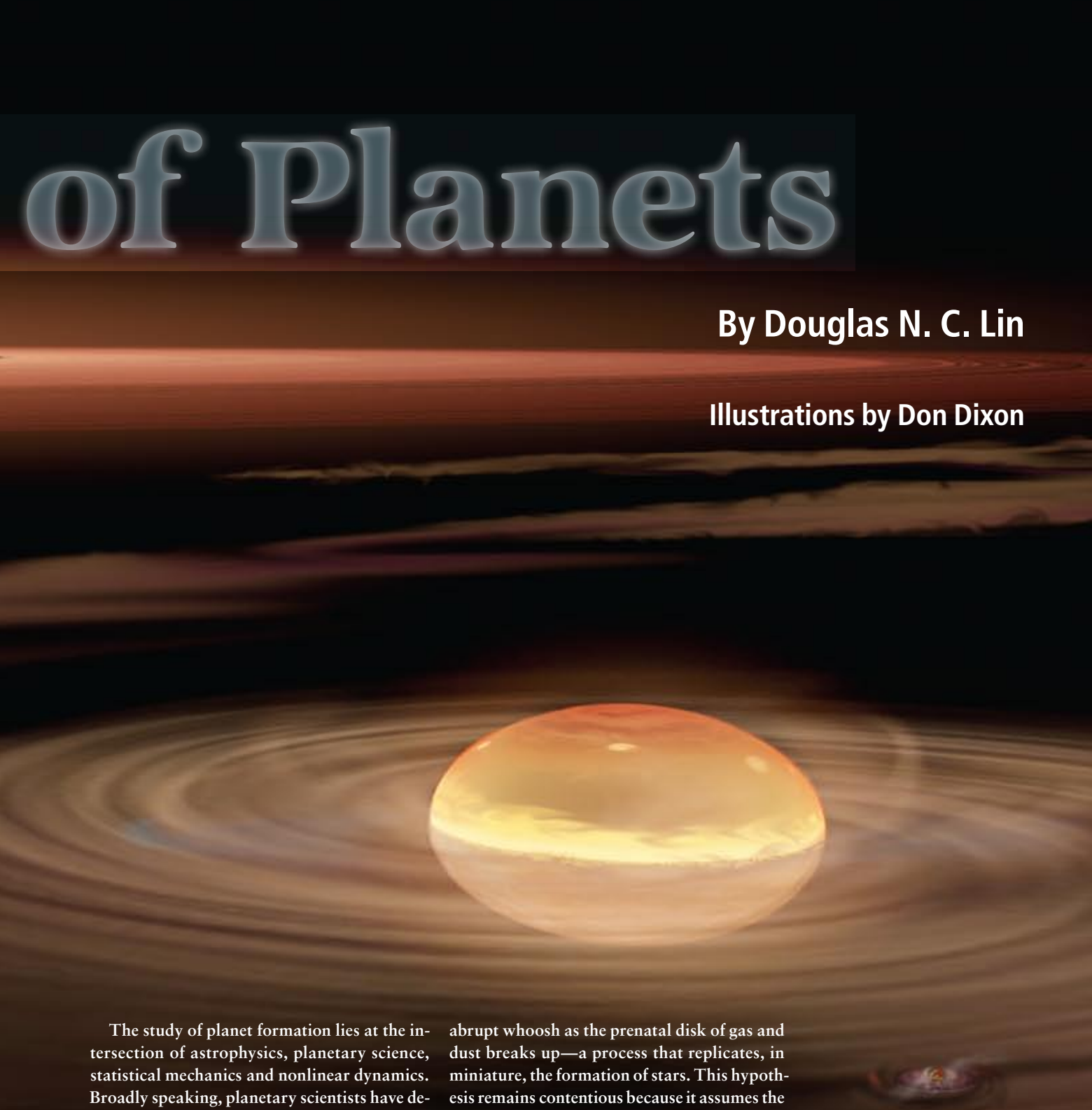
Although they are, in cosmic terms, mere scraps—insignificant to the grand narrative of heavenly expansion—planets are the most diverse and intricate class of object in the universe. No other celestial bodies support such a complex interplay of astronomical, geologic, and chemical and biological processes. No other places in the cosmos could support life as we know it. The worlds of our solar system come in a tremendous variety, and even they hardly prepared us for the discoveries of the past decade, during which astronomers have found more than 200 planets.

The sheer diversity of these bodies' masses, sizes, compositions and orbits challenges those of us trying to fathom their origins. When I was in graduate school in the 1970s, we tended to think of planet formation as a well-ordered, deterministic process—an assembly line that turns amorphous disks of gas and dust into copies of our solar system. Now we are realizing that the process is chaotic, with distinct outcomes for each system. The worlds that emerge are the survivors of a hurly-burly of competing mechanisms of creation and destruction. Many are blasted apart, fed into the fires of their system's newborn star or ejected into interstellar space. Our own Earth may have long-lost siblings that wander through the lightless void.

# of Planets

By Douglas N. C. Lin

Illustrations by Don Dixon



BABY GIANT PLANET swoops up gas from the disk around a newborn star.

The study of planet formation lies at the intersection of astrophysics, planetary science, statistical mechanics and nonlinear dynamics. Broadly speaking, planetary scientists have developed two leading theories. The sequential-accretion scenario holds that tiny grains of dust clump together to create solid nuggets of rock, which either draw in huge amounts of gas, becoming gas giants such as Jupiter, or do not, becoming rocky planets such as Earth. The main drawback of this scenario is that it is a slow process and that gas may disperse before it can run to completion.

The alternative, gravitational-instability scenario holds that gas giants take shape in an abrupt whoosh as the prenatal disk of gas and dust breaks up—a process that replicates, in miniature, the formation of stars. This hypothesis remains contentious because it assumes the existence of highly unstable conditions, which may not be attainable. Moreover, astronomers have found that the heaviest planets and the lightest stars are separated by a "desert"—a scarcity of intermediate bodies. The disjunction implies that planets are not simply little stars but have an entirely different origin.

Although researchers have not settled this controversy, most consider the sequential-accretion scenario the most plausible of the two. I will focus on it here.

1. An Interstellar Cloud Collapses

Time: 0 (starting point of planet formation sequence)

Our solar system belongs to a galaxy of some 100 billion stars threaded with clouds of gas and dust, much of it the debris of previous generations of stars. "Dust" in this context simply means microscopic bits of water ice, iron and other solid substances that condensed in the cool outer layers of stars and were blown out into interstellar space. When clouds are sufficiently cold and dense, they can collapse under the force of gravity to form clusters of stars, a process that takes 100,000 to a few million years [see "Fountains of Youth: Early Days in the Life of a Star," by Thomas P. Ray; SCIENTIFIC AMERICAN, August 2000].

Surrounding each star is a rotating disk of leftover material, the wherewithal for making planets. Newly formed disks contain mostly hydrogen and helium gas. In their hot and dense inner regions, dust grains are vaporized; in the cool and tenuous outer parts, the dust particles survive and grow as vapor condenses onto them.

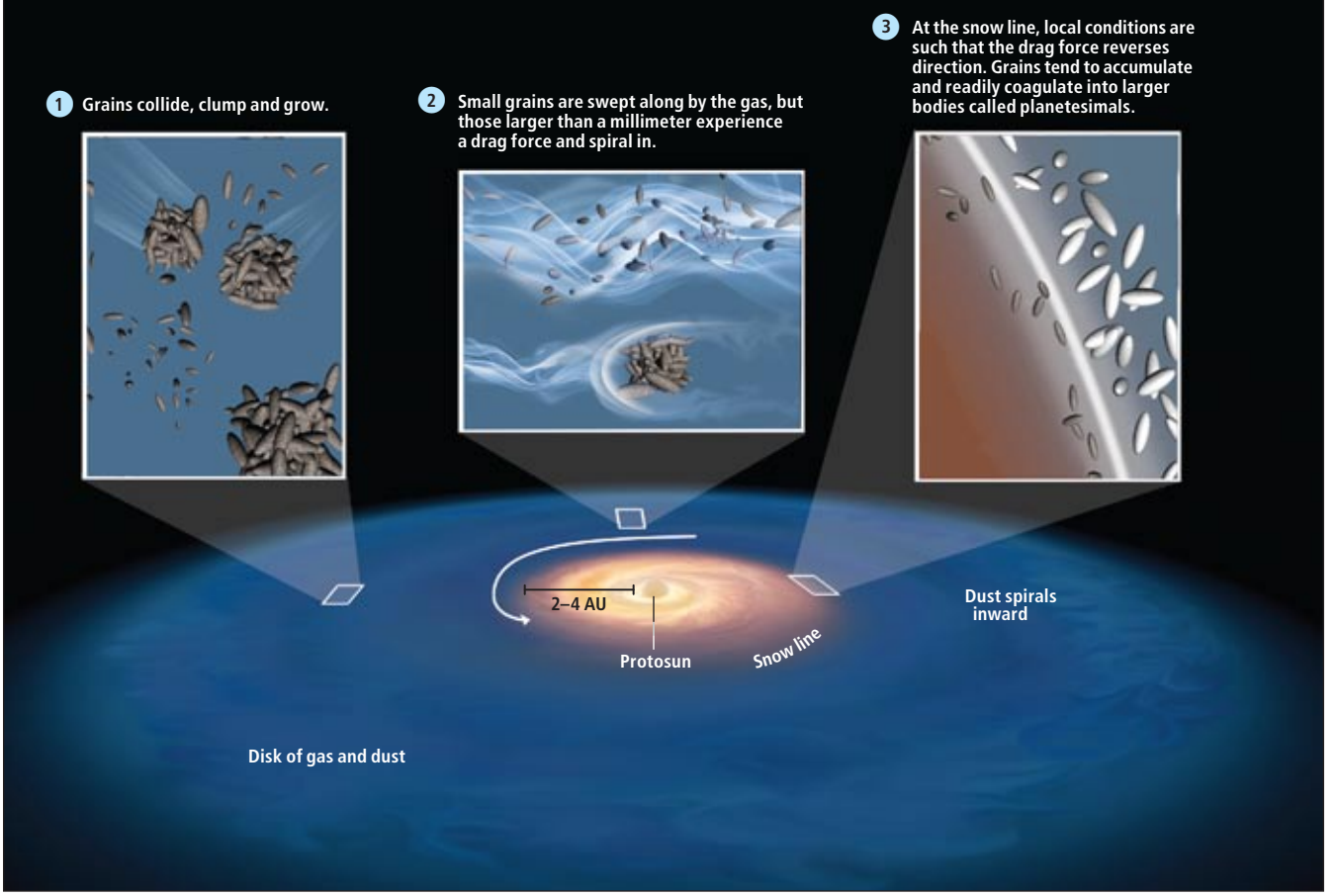
Astronomers have discovered many young stars that are surrounded by such disks. Stars between one million and three million years old have gas-rich disks, whereas those older than 10 million years have meager, gas-poor disks, the gas having been blown away by the newborn star or by bright neighboring stars. This span of time delineates the epoch of planet formation. The mass of heavy elements in these disks is roughly comparable to the mass of heavy elements in the planets of the solar system, providing a strong clue that the planets indeed arose from such disks.

Ending point: Newborn star surrounded by gas and micron-size dust grains

[STAGE 2]

COSMIC DUST BUNNIES

Even the mightiest planets have humble roots: as micron-size dust grains (the ashes of long-dead stars) embedded in a swirling disk of gas. The disk's temperature falls with distance from the newborn star, defining a "snow line" beyond which water stays frozen. In our solar system, the snow line marks the boundary between the inner rocky planets and outer gas giants.



2. The Disk Sorts Itself Out
Time: About 1 million years

Dust grains in the protoplanetary disk are stirred by nearby gas and collide with one another, sometimes sticking together, sometimes breaking apart. The grains intercept starlight and reemit lower-wavelength infrared light, ensuring that heat reaches even the darkest regions of the disk's interior. The temperature, density and pressure of gas generally decrease with distance from the star. Because of the balance of pressure, rotation and gravity, gas orbits the star slightly slower than an independent body at the same distance would.

Consequently, dust grains larger than a few millimeters in size tend to outpace the gas, thereby running into a headwind that slows them down and causes them to spiral inward, toward the star. The bigger the grains grow, the faster they spiral. Chunks a meter in size can halve their distance from the star within 1,000 years.

As they approach the star, the grains warm up, and eventually water and other low-boiling-point substances, known as volatiles, boil off. The distance at which this happens, the "snow line," lies between 2 and 4 AU (astronomical units) from the star, which in our solar system falls between the orbits of Mars and Jupiter. (The radius of Earth's orbit is 1 AU.) The snow line divides the planetary system into an inner, volatile-poor region filled with rocky bodies and an outer, volatile-rich region filled with icy ones.

At the snow line itself, water molecules tend to accumulate as they boil off grains. This build-up of water triggers a cascade of effects. It produces a discontinuity in gas properties at the snow line, which leads to a pressure drop there. The balance of forces causes the gas to speed up its revolution around the central star. Consequently, grains in the vicinity feel not a headwind but a tailwind, which boosts their velocity and halts their inward migration. As grains continue to arrive from the outer parts of the disk, they pile up at the snow line. In effect, the snow line becomes a snowbank.

Crammed together, the grains collide and grow. Some break through the snow line and continue to migrate inward, but in the process they become coated with slush and complex molecules, which makes them stickier. Some regions are so thick with dust that the grains' collective gravitational attraction also accelerates their growth.

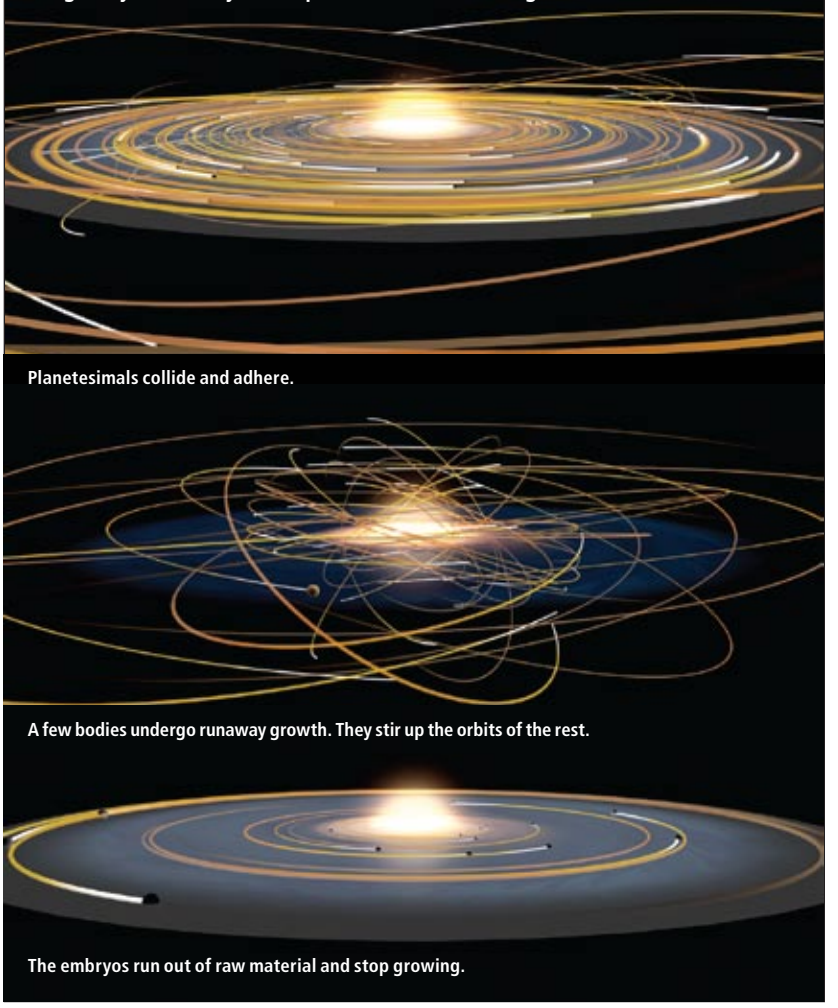
In these ways, the dust grains pack themselves into kilometer-size bodies called planetesimals. By the end of the stage of planet formation, planetesimals have swept up almost all the original dust. Planetesimals are hard to see directly, but astronomers can infer their presence from the debris of their collisions [see "The Hidden Members of Planetary Systems," by David Ardila; Scientific American, April 2004].

Ending point: Swarms of kilometer-size building blocks known as planetesimals

[STAGE 3]

THE RISE OF THE OLIGARCHS

Billions of kilometer-size planetesimals, built up during stage 2, then agglomerate into moon- to Earth-size bodies known as embryos. Relatively few in number, embryos dominate their respective orbital zones; this "oligarchy" of embryos competes for the remaining material.



Planetesimals collide and adhere.

A few bodies undergo runaway growth. They stir up the orbits of the rest.

The embryos run out of raw material and stop growing.

3. Planetary Embryos Germinate
Time: 1 million to 10 million years

The cratered landscapes on Mercury, the moon and the asteroids leave little doubt that nascent planetary systems are shooting galleries. Collisions between planetesimals either build them up or break them apart. A balance between coagulation and fragmentation leads to a distri-

bution of sizes in which small bodies account for most of the surface area in the emerging system and large bodies account for most of its mass. The orbits may initially be elliptical, but over time, gas drag and collisions tend to make the paths around the star circular.

In the beginning the growth of a body is self-reinforcing. The larger a planetesimal becomes, the stronger the gravity it exerts, and the faster it sweeps up its less massive partners. When they attain masses comparable to our moon, however, bodies exert such strong gravity that they stir up surrounding solid material and divert most of it before they can collide with it. In this way, they limit their own growth. Thus, an "oligarchy" arises—that is, a population of planetary embryos with similar masses that compete with one another for the residual planetesimals.

Each embryo's feeding zone is a narrow band centered on its orbit. Its growth stalls once it acquires most of the residual planetesimals in the zone. By simple geometry, the size of the zone and the duration of feeding grow with distance from the star. At a distance of 1 AU, embryos plateau at about 0.1 Earth mass within 100,000 years. Out at 5 AU, they reach four Earth masses over a few million years. Embryos can grow even bigger near the snow line or on the edges of gaps in the disk, where planetesimals also tend to accumulate.

Oligarchic growth fills the system with a surplus of aspiring planets, only some of which will make it. The planets in our solar system may seem widely spaced, but they are as close together as they can be. Inserting another Earth-mass planet in the present-day space between the terrestrial planets would destabilize them all. The same is true of other known systems. If you come across a cup of coffee that is filled to the very rim, you can reasonably conclude that someone actually overfilled it and spilled some coffee; filling it exactly, without wasting a drop, seems unlikely. Similarly, planetary systems probably start with more material than they end up with. Bodies are ejected until the system reaches an equilibrium configuration. Astronomers have observed freely floating planets in young stellar clusters.

Ending point: "Oligarchy" of moon- to Earth-mass planetary embryos

4 A Gas Giant Is Born

Time: 1 million to 10 million years

Jupiter probably began as a seed comparable in size to Earth that then accumulated some 300 Earth masses of gas. Such spectacular growth hinges on various competing effects. An

DOES JUPITER MAKE SENSE?

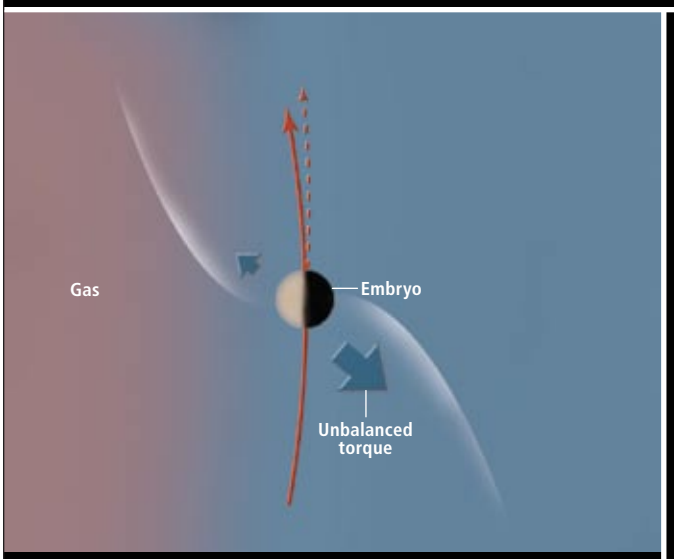
Of all the stages of planet formation, the birth of the first gas giant remains in some ways the least understood. One mystery is that Jupiter's core is small to nonexistent—far lower than the critical mass that researchers thought was needed to allow infalling gas to cool and settle. Some other cooling mechanism, such as heat dissipation in a miniature disk around the proto-Jupiter, may have operated. Alternatively, internal gas flow may have eroded Jupiter's original core.

Another problem is that, according to theoretical calculations, the proto-Jupiter should have migrated inward faster than it was able to accumulate gas. Something must have slowed down its movement, such as gas-pressure differentials, gas flows, turbulence or gravitational interactions among embryos.

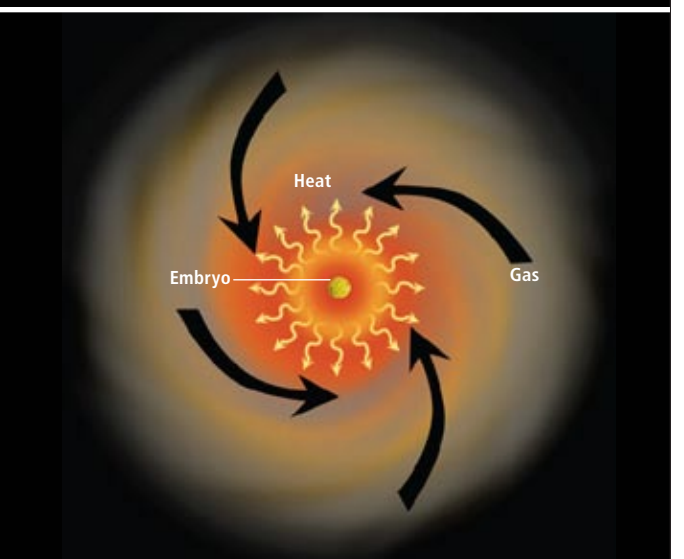
[STAGE 4]

ONE GIANT LEAP FOR PLANETKIND

The formation of a gas giant such as Jupiter is the defining moment in the history of a planetary system; if such a planet forms, it shapes the rest of the system. But for that to happen, an embryo must accumulate gas faster than it spirals inward.



Working against the formation of the giant planet are the waves that it triggers in the surrounding gas. These waves exert unbalanced torques on the planet, slowing it down and causing its orbit to shrink.



The planet's gravity draws in gas, but the gas cannot settle down until it cools off. The planet may well spiral toward the star before that happens. Giant planet formation may succeed in a minority of systems.

embryo's gravity pulls in gas from the disk, but the infalling gas releases energy and must cool off if it is to settle down. Consequently, the growth rate is limited by the cooling efficiency. If it is too slow, the star may blow away the gas in the disk before the embryo has a chance to develop a thick atmosphere. The main heat-transfer bottleneck is the flux of radiation through the outer layers of the emerging atmosphere, which is determined by the opacity of the gas (determined mainly by its composition) and the temperature gradient (determined largely by the embryo's initial mass).

Early models indicated that embryos need to have a critical mass, about 10 times that of Earth, to allow for sufficiently fast heat transfer. Such large embryos can arise near the snow line, where material will have accumulated earlier. That may be why Jupiter is located just beyond the snow line. They can arise elsewhere if the disk contains more raw material than planetary scientists used to assume it would. In fact, astronomers have now observed many stars whose disks are a few times denser than the traditional estimate, in which case heat transfer poses no insurmountable problem.

Another factor working against gas giants is that the embryo tends to spiral inward toward the star. In a process known as type I migration, the embryo triggers a wave in the gaseous disk, which, in return, pulls on the embryo's orbit gravitationally. The wave pattern follows the planet like the wake of a boat. The gas on the side that is farther from the star revolves more sluggishly than the embryo and acts to hold the embryo back, slowing it down. Meanwhile the gas interior to the orbit revolves more quickly and acts to pull the embryo forward, speeding it up. The exterior region, being larger, wins the tug-of-war and causes the embryo to lose energy and fall inward by several astronomical units over one million years. This migration tends to stall near the snow line, where the gas headwind turns into a tailwind and provides an extra boost to the embryo's orbit. That may be yet another reason why Jupiter is where it is.

Embryo growth, embryo migration and gas depletion all occur at roughly the same rate. Which wins depends on the luck of the draw. In fact, several generations of embryos may start the process only to migrate away before they can complete it. In their wake, fresh batches of planetesimals from the outer regions of the disk move in and repeat the process, until eventually a gas giant forms successfully or the gas is lost and no gas giant is ever able to take root. Astronomers have detected Jupiter-mass planets around only about 10 percent of the sunlike stars they have examined. The cores of these planets may be the rare survivors of many generations of embryos—the last of the Mohicans.

The balance among the processes depends on the system's original endowment of material. Nearly a third of stars that are rich in heavy elements are orbited by Jupiter-mass planets. Presumably these stars had denser disks that gave rise to larger embryos, which could evade the heat-transfer bottleneck. Conversely, fewer planets form around stars that are smaller or poorer in heavy elements.

Once growth takes off, it accelerates to a startlingly fast pace. Within 1,000 years, a Jupiter-mass planet can acquire half of its final mass. In the process, it dissipates so much heat that it can briefly outshine the sun. The planet stabilizes when it becomes massive enough to turn type I migration on its head. Instead of the disk shifting the orbit of the planet, the planet shifts the orbit of gas in the disk. Gas interior to the planet's orbit revolves faster than the planet, so the planet's gravity tends to hold it back, causing it to fall toward the star—that is, away from the planet. Gas exterior to the planet's orbit revolves slower, so the planet tends to speed it up, causing it to move outward—again, away from the planet. Thus, the planet opens up a gap in the disk and cuts off its supply of raw material. The gas tries to repopulate the gap, but computer simulations indicate that the planet wins the struggle if its mass exceeds about one Jupiter mass at 5 AU.

This critical mass depends on the timing. The earlier a planet forms, the bigger it can grow, because plenty of gas remains. Saturn may have acquired a lower mass than Jupiter simply because it formed a few million years later. Astronomers have noticed a shortage of planets in the range of 20 Earth masses (Neptune's mass) to 100 Earth masses (Saturn's mass), which may be a clue to the precise timing.

Ending point: Jupiter-size planet (or not)

5. The Gas Giant Gets Restless

Time: 1 million to 3 million years

Oddly, many of the extrasolar planets discovered over the past decade orbit very close to their star, much closer than Mercury orbits the sun. These so-called hot Jupiters could not have formed in their current positions, if only because the orbital feeding zones are too small

[THE AUTHOR]

Douglas N.C. Lin, like many scientists of his generation, traces his passion for astronomy to the launch of Sputnik in 1957. He was born in New York City, grew up in Beijing, attended McGill University in Montreal, received his Ph.D. from the University of Cambridge, became a postdoc at Cambridge and Harvard University and finally joined the faculty at the University of California, Santa Cruz. He is the founding director of the Kavli Institute for Astronomy and Astrophysics at Peking University. He has direct empirical knowledge of ice grains and snow lines—as an avid skier.

MARIA SLIWINSKI (*Lin*)

TIMELINE FOR WORLD-MAKING

Based on radiometric dating of meteorites and telescope observations of disks around other stars, planetary scientists have pieced together a rough timetable for planet formation.

0 to 100,000 years—star forms at center of disk and begins to undergo nuclear fusion

100,000 to 2 million years (Myr)—dust grains assemble into moon- to Earth-mass planetary embryos

2 Myr—first gas giant forms and clears out first-generation asteroids

10 Myr—gas giant triggers formation of other giant planets as well as terrestrial planets; most gas is lost by now

800 Myr—rearrangement of planets continues as late as a billion years after the process started

to provide enough material. Their presence appears to require a three-part sequence of events that for some reason did not occur in our own solar system.

First, a gas giant must form within the inner part of the planetary system, near the snow line, while the disk still has a considerable amount of gas. That requires a dense concentration of solid material in the disk.

Second, the giant planet must move to its present position. Type I migration cannot bring that about because it operates on embryos before they build up much gas. Instead type II migration must take place. The emerging giant planet opens a gap in the disk and suppresses the flow of gas across its orbit. In so doing, it must fight the tendency of turbulent gas in adjacent regions of the disk to spread. Gas never stops oozing into the gap, and its diffusion toward the central star forces the planet to lose orbital energy. This process is relatively slow, taking a few million years to shift a planet a few astronomical units, which is why the planet must start in the inner solar system if it is to end up hugging the star. As it and other planets migrate inward, they push along any residual planetesimals and embryos ahead of their paths, perhaps creating "hot Earths" in tight orbits.

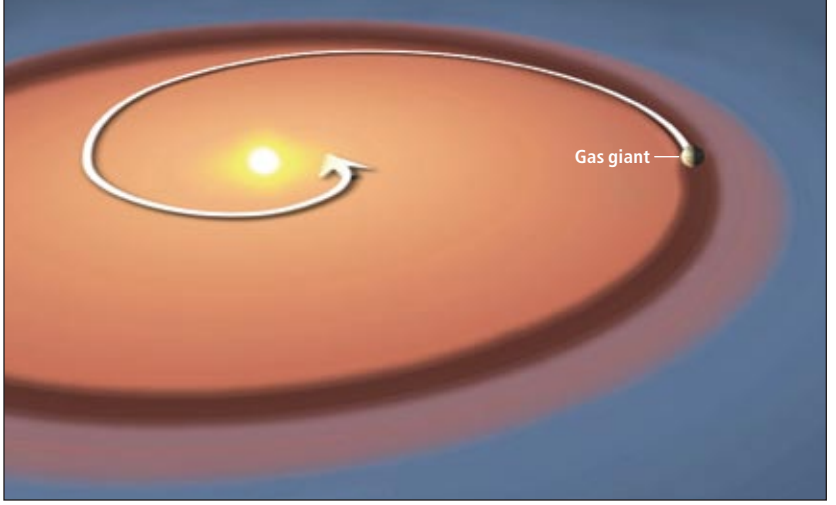
Third, something must halt migration before the planet falls all the way into the star. The stellar magnetic field might clear gas from a cavity immediately around the star; without gas, migration ceases. Alternatively, perhaps the planet raises tides on the star, and the star, in turn, torques the planet's orbit. These safeguards may not operate in all systems, and many planets may well fall all the way in.

Ending point: Tightly orbiting giant planet ("hot Jupiter")

[STAGE 5]

HOW TO HUG A STAR

In many systems, a giant planet forms and then spirals almost all the way into the star. The reason is that gas in the disk loses energy to internal friction and falls in, dragging the planet with it. Eventually the planet gets so close that the star exerts a torque on its orbit, stabilizing it.



6. Other Giant Planets Join the Family

Time: 2 million to 10 million years

If one gas giant manages to arise, it facilitates the formation of subsequent gas giants. Many, perhaps most, known giant planets have siblings of comparable mass. In our solar system, Jupiter helped Saturn to emerge much faster than it would have by itself. It also lent a helping hand to Uranus and Neptune, without which they might never have grown to their present sizes; at their distance from the sun, the unaided formation process is so slow that the disk would have dissipated long before it could finish, leaving stunted worlds.

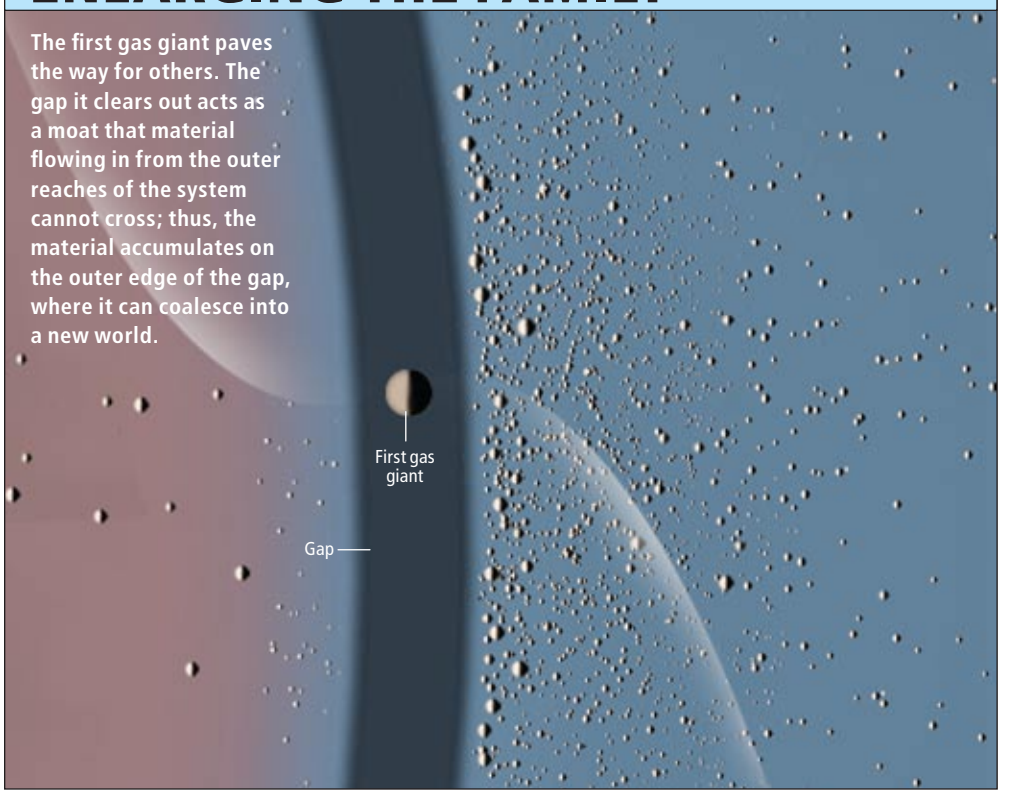
The pioneering gas giant has several helpful effects. At the outer edge of the gap that it opens up, material accumulates for much the same reasons it did at the snow line—namely, a pressure differential causes gas to speed up and act as a tailwind on grains and planetesimals, stopping their migration from more distant regions of the disk. Another effect of the first gas giant is that its gravity tends to fling nearby planetesimals to the outer reaches of the system, where they can form new planets.

The second-generation planets form out of the material that the first gas giant collects for them. The timing is critical, and fairly modest differences in timescales could lead to large differences in the outcome. In the case of Uranus and Neptune, the accumulation of planetesimals was too much of a good thing. The embryos became extra large, some 10 to 20 Earth masses, which delayed the onset of gas accretion—by which point little gas remained to be accreted. These bodies ended up with only about two Earth masses of gas. They are not gas giants but ice giants, which may in fact prove to be the more common type of giant.

The gravitational fields of the second-generation planets introduce an additional complication into the system. If the bodies form too close together, their interactions with one another and with the gaseous disk can catapult them into new, highly elliptical orbits. In our solar

[STAGE 6]

ENLARGING THE FAMILY



system, the planets all have nearly circular orbits and are spaced far enough apart to offer some immunity to one another's influence. In other planetary systems, however, elliptical orbits are the norm. In some, the orbits are resonant—that is, the orbital periods are related by a ratio of small whole numbers. Being born into this condition is highly improbable, but it can naturally arise when planets migrate and eventually lock onto one another gravitationally. The difference between these systems and our own may simply be the initial allotment of gas.

Most stars form in clusters, and more than half have binary companions. The planets may take shape in a plane that is not the same as the plane of the stellar orbit. In that case, the companion's gravity quickly realigns and distorts the planets' orbits, creating systems that are not planar, like our solar system, but spherical, like bees buzzing around a hive.

Ending point: Coterie of giant planets

7. Earth-like Planets Assemble

Time: 10 million to 100 million years

Planetary scientists expect Earth-like planets to be more prevalent than gas giants. Whereas the gestation of a gas giant involves a fine balance of competing effects, formation of rocky planets should be fairly robust. Until we discover extrasolar Earths, however, we will have to rely on the solar system as our only case study.

The four terrestrial planets—Mercury, Venus, Earth and Mars—consist mostly of high-boiling-point material such as iron and silicate rocks, indicating that they formed inside the snow line and did not migrate significantly. At this range of distances, planetary embryos in a gaseous disk could grow to about 0.1 Earth mass, not much bigger than Mercury. Further growth required the embryos' orbits to cross so that they could collide and merge. That is easy enough to explain. After the gas evaporated, embryos gradually destabilized one another's orbits and, over a few million years, made them elliptical enough to intersect.

What is harder to explain is how the system stabilized itself again and what set the terrestrial planets on their present-day nearly circular orbits. A little bit of leftover gas could do the trick, but if gas were present, it would have prevented the orbits from becoming unstable to begin with. One idea is that after the planets nearly formed, a substantial swarm of planetesimals still remained. Over the next 100 million years, the planets swept up some of these planetesimals and deflected the rest into the sun. The

BIGGEST AND BADDEST

Here are the record holders in extrasolar planetary systems as of March 2008. The planet masses are approximate because of measurement ambiguities.

Heaviest host star: HD 13189 (4.5 solar masses)

Lightest host star: GJ 317 (0.24 solar mass)

Tightest planet orbit: OGLE-TR-56b (0.0225 AU)

Widest planet orbit: PSR B 1620-26b (23 AU)

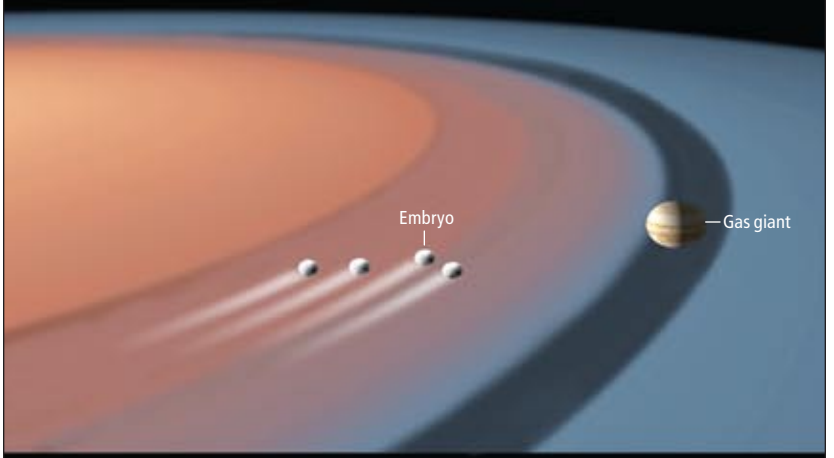
Heaviest planet: NGC 4349 No 127b (19.8 Jupiter masses)

Lightest planet: PSR 1257+12b (0.02 Earth mass)

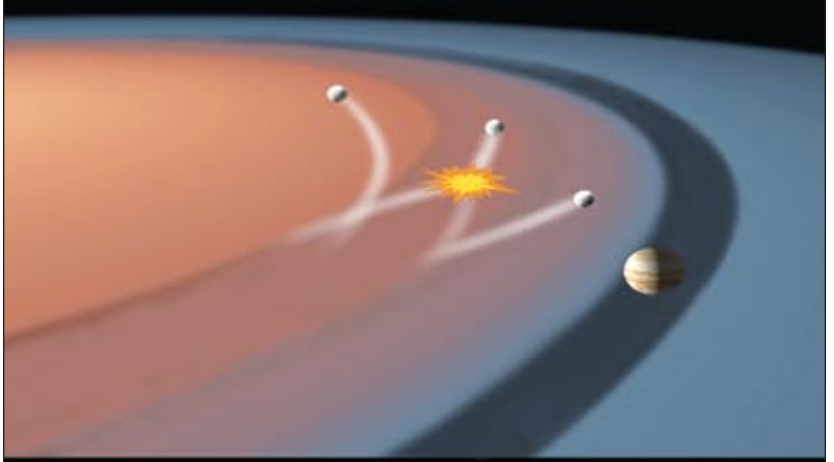
[STAGE 7]

NONCIRCULAR REASONING

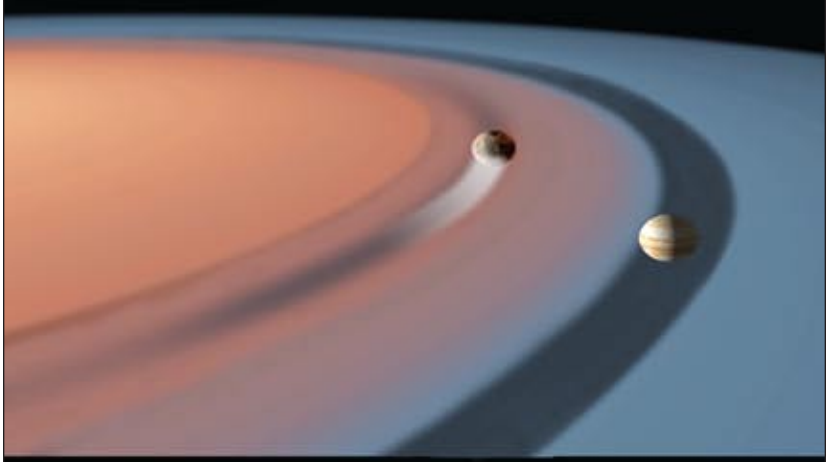
In the inner solar system, planetary embryos cannot grow by swooping up gas but must collide with one another. To do so, their orbits must intersect, and to intersect, something must disturb them from their original circular orbits.



When embryos form, they have circular or nearly circular orbits, which do not intersect.



Gravitational interactions among the embryos or with a giant planet disturb the orbits.



The embryos agglomerate into an Earth-size planet. The planet then returns to a circular orbit by stirring up the remaining gas and scattering leftover planetesimals.

planets transferred their random motion to the doomed planetesimals and entered into circular or almost circular orbits.

Another idea is that the long-range influence of Jupiter's gravity caused the emerging terrestrial planets to migrate, bringing them into contact with fresh material. This influence would have been strongest at special resonant locations, which moved inward with time as Jupiter's orbit settled into its final shape. Radiometric dating indicates that the asteroids formed early (four million years after the sun did), followed by the formation of Mars (10 million years after), then Earth (50 million years after)—as if a wave instigated by Jupiter was sweeping through the solar system. If unchecked, its influence would have pushed all the terrestrial planets to the orbit of Mercury. How did they avoid this unhappy outcome? Maybe they grew too massive for Jupiter to move them significantly, or maybe they were knocked out of Jupiter's range of influence by giant impacts.

That said, most planetary scientists do not think Jupiter's role was decisive in the formation of rocky planets. Most sunlike stars lack Jupiter-like planets, yet they still have dusty debris, indicating the presence of planetesimals and planetary embryos that could assemble into Earth-like worlds. A major question that observers need to answer over the coming decade is how many systems have Earths but not Jupiters.

For our planet, a defining moment occurred 30 million to 100 million years after the formation of the sun, when a Mars-size embryo knocked into the proto-Earth and threw out huge amounts of debris that coagulated into the moon. Such a giant impact is unsurprising given the amount of material careening around the early solar system, and Earth-like planets in other systems may have moons, too. Giant impacts also had the effect of ejecting the tenuous primitive atmosphere. The present-day atmosphere of Earth mostly came from gas that was trapped in the planetesimals that formed it and was later vented by volcanoes.

Ending point: Terrestrial planets

8. Mop-Up Operations Commence

Time: 50 million to 1 billion years

By this point, the planetary system is almost done. A few effects continue to fine-tune it: the disintegration of the wider star cluster, which may destabilize the planets' orbits gravitationally; internal instabilities that develop after the star clears out the last of its gaseous disk; and

[METEORITES]

Emissaries from the Past

Meteorites are not just space rocks but space fossils—planetary scientists' only tangible record of the origin of the solar system. Planetary scientists think that they come from asteroids, which are fragments of planetesimals that never went on to form planets and have remained in deep freeze ever since. The composition of meteorites reflects what must have happened on their parent bodies. Intriguingly, they bear the scars of Jupiter's early gravitational effects.

Iron and stony meteorites evidently originated in planetesimals that had melted, thereby allowing their iron and rocky silicate material to separate from each other, the heavy iron sinking to the core and the lighter silicates becoming concentrated in the outer layers. Researchers believe that this heating was brought about by the radioactive isotope aluminum 26, which has a half-life of 700,000 years. A supernova explosion or nearby star probably seeded the protosolar cloud with this isotope, in which case the first generation of planetesimals in our solar system contained plenty of it.

Yet iron and stony meteorites are very rare. Most meteorites consist instead of chondrules, which are millimeter-size pebbles that predate the formation of planetesimals and cannot survive melting. It therefore seems that most asteroids are not left over from the first generation of planetesimals. That generation must have been cleared out, presumably by Jupiter. Planetary scientists estimate that the region now occupied by the main asteroid belt used to have 1,000 times as much material as it does now. The few grains that eluded Jupiter's clutches, or later drifted into the region of the belt, collected into new planetesimals, but little radioactive aluminum 26 was left by then, so these bodies never fully melted. The isotopic composition of chondrules in meteorites dates them to about two million years after the solar system started forming.

The glassy texture of the chondrules suggests that before being incorporated into planetesimals, they were abruptly heated, turned to molten rock and allowed to cool. The waves that drove Jupiter's early orbital migration should have evolved into shock fronts, which could account for this flash heating. —*D.N.C.L.*

the continued scattering of leftover planetesimals by the giant planets. In our solar system, Uranus and Neptune hurled planetesimals out into the Kuiper belt or in toward the sun. Jupiter, with its greater gravity, sent them off to the Oort cloud at the very edge of the sun's gravitational domain. The Oort cloud could contain the equivalent of as much as 100 Earths of material. Every now and then, a planetesimal from the Kuiper belt or the Oort cloud drops inward toward the sun, creating a comet.

In scattering planetesimals, the planets themselves migrate somewhat, which would explain the synchrony between the orbits of Neptune and Pluto [see "Migrating Planets," by Renu Malhotra; Scientific American, September 1999]. Saturn, for example, may once have orbited closer to Jupiter and then moved outward, a process that could account for the so-called late heavy bombardment—an especially intense period of impacts on the moon (and presumably on Earth) that occurred about 800 million years after the formation of the sun. In some systems, epic collisions of full-fledged planets could occur late in the development game.

Ending point: The final configuration of planets and comets

No Grand Design

Before the age of discovery of extrasolar planets, our solar system was the only case study we had. Although it provided a wealth of information on the microphysics of important processes, it also narrowed our vision of how other systems could develop. The surprising planetary diversity discovered in the past decade has enormously expanded our theoretical horizons. We have come to realize that extrasolar planets are the last-generation survivors of a sequence of protoplanetary formation, migration, disruption and ongoing dynamic evolution. The relative orderliness of our solar system does not reflect any grand design.

Theorists have shifted their focus from providing scenarios to account for the relics of solar system formation to the construction of theories with some predictive power to be tested by forthcoming observations. Up to now, observers have seen only Jupiter-mass planets around sunlike stars. With a new generation of detectors, they will search for Earth-size planets, which the sequential-accretion scenario suggests are common. Planetary scientists may have only begun to see the full diversity of worlds in this universe. ■

MORE TO EXPLORE

Towards a Deterministic Model of Planetary Formation. S. Ida and D.N.C. Lin in *Astrophysical Journal,* Vol. 604, No. 1, pages 388–413; March 2004. **http://arxiv.org/abs/astro-ph/0312144v1**

Planet Formation, Theory, Observation, and Experiments. Edited by Hubert Klahr and Wolfgang Brandner. Cambridge University Press, 2006.

For the most up-to-date list of planet discoveries, go to **http://exoplanet.eu**

JIM STROPE (*meteorite*); NASA/JPL (*photoimage of asteroid belt*)

Switches within DNA that govern when and where genes are turned on enable genomes to generate the great diversity of animal forms from very similar sets of genes

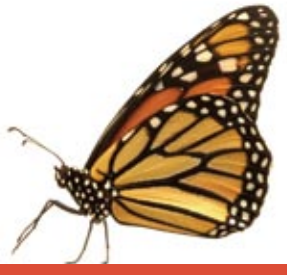
At first glance, the list of animals could suggest any zoo. There's an elephant, an armadillo, an opossum, a dolphin, a sloth, a hedgehog, big and small bats, a couple of shrews, some fish, a macaque, an orangutan, a chimpanzee and a gorilla—to name a few of the more familiar creatures. But this menagerie is not at all like any zoo that has been constructed before. There are no cages, no concession stands and, in fact, no animals. It is a "virtual" zoo that contains only the DNA sequences of those animals—the hundreds of millions to billions of letters of DNA code that make up the genetic recipe for each species.

The most excited visitors to this new molecular zoo are evolutionary biologists, because within it lies a massive and detailed record of evolution. For many decades, scientists have longed to understand how the great diversity of species has arisen. We have known for half a century that changes in physical traits, from body color to brain size, stem from changes in DNA. Determining precisely what changes to the vast expanse of DNA sequences are responsible for giving animals their unique appearance was out of reach until recently, however.

Biologists are now deciphering the DNA record to locate the instructions that make assorted species of flies, fish or finches look different from one another and that make us humans dif-

TOM DRAPER DESIGN; M. JOHNSON *Wellcome Images (cell)*; NICK PARFITT *Getty Images (zebra)*; DON FARRALL *Getty Images (fish)*; DARLYNE A. MURAWSKI *National Geographic/Getty Images (fly)*; DARRIN KLIMEK *Getty Images (frog)*; MATTHEW WARD *Getty Images (tiger)*; DAVE KING *Getty Images (elephant)*; GEOFF DANN *Getty Images (chimpanzee)*; JOSE LUIS PELAEZ *(human)*

Regulating Evolution



By Sean B. Carroll, Benjamin Prud'homme and Nicolas Gompel

ferent from chimpanzees. This quest has led to a profound change in our perspective. For most of the past 40 years or so, researchers have focused most of their attention on genes—the nucleotide sequences in DNA that encode the amino acid chains that form proteins. But to our surprise, it has turned out that differences in appearance are deceiving: very different animals have very similar sets of genes. By following the trail of evolution, devices are being found within DNA—genetic "switches"—that do not encode any proteins but that regulate *when* and *where* genes are used. Changes in these switches are crucial to the evolution of anatomy and provide new insights into how the seemingly endless forms of the animal kingdom have evolved.

Anatomy Genes and the Coding Paradox

For a long time, scientists certainly expected the anatomical differences among animals to be reflected in clear differences among the contents of their genomes. When we compare mammalian genomes such as those of the mouse, rat, dog, human and chimpanzee, however, we see that their respective gene catalogues are remarkably similar. The approximate number of genes in each animal's genome (about 20,000 or so) and the relative positions of many genes have been fairly well maintained over 100 million years of evolution. That is not to say there are no differences in gene number and location. But at first glance, nothing in these gene inventories shouts out "mouse" or "dog" or "human." When comparing mouse and human genomes, for example, biologists are able to identify a mouse counterpart for at least 99 percent of all our genes.

In other words, we humans do not, as some once assumed, have more genes than our pets, pests, livestock or even a puffer fish. Disappointing, perhaps, but we'll have to get over it.

When biologists look at individual genes in detail, similarity among species is also the rule. The DNA sequences of any two versions of a gene, as well as the proteins they encode, are generally alike to a degree that simply reflects the relative amount of time that has elapsed since the two species diverged from a common ancestor. This preservation of coding sequences over evolutionary time is especially puzzling when one considers the genes involved in body building and body patterning.

Only a small fraction of all genes—fewer than 10 percent—are devoted to the construction and patterning of animal bodies during their development from fertilized egg to adult. The rest are involved in the everyday tasks of cells within various organs and tissues. Anatomical differences among animals—differences in the number, size, shape or color of body parts—must

KEY CONCEPTS

- Because genes encode instructions for building animal bodies, biologists once expected to find significant genetic differences among animals, reflecting their great diversity of forms. Instead very dissimilar animals have turned out to have very similar genes.
- Mutations in DNA "switches" that control body-shaping genes, rather than in the genes themselves, have been a significant source of evolving differences among animals.
- If humans want to understand what distinguishes animals, including ourselves, from one another, we have to look beyond genes.

—The Editors

DON FARRALL Getty Images

somehow involve the genes for body building. Indeed, the study of the pivotal role played in evolution by genes and processes associated with the development of anatomy has even earned its own nickname: evo-devo. For specialists, like ourselves, in that area of research, the discovery that body-building proteins are even more alike on average than other proteins was especially intriguing because of the paradox it seemed to pose: animals as different as a mouse and an elephant are shaped by a common set of very similar, functionally indistinguishable body-building proteins. The same applies to humans and our closest living relatives—most of our proteins differ from those of the chimpanzee by only one or two of the several hundred amino acids that comprise each protein, and 29 percent of our proteins are exactly identical in sequence. How do we explain this disparity between evolution at the two levels of proteins and anatomy? Somewhere in all of that genomic DNA there must be meaningful differences that have evolved. The trick is to find them, and the trick to doing that has been deciding where to look. It turns out that those places are much harder to locate than are genes themselves.

Study of the pivotal role played in evolution by genes and processes associated with the development of anatomy has earned its own nickname: evo-devo.

Genetic Switches

In humans, the protein-coding stretches of DNA make up only about 1.5 percent of our genome, so genes are really like little islands of information in a vast sea of DNA sequence. Much of the remaining noncoding DNA does nothing that we know of, but some of those sequences participate in the very important task of regulating gene expression. And these regulatory sequences are key to evolution.

The expression of a gene entails the transcription of the DNA sequence into a messenger RNA (mRNA) version and the translation of that mRNA into a protein sequence. The expression of most genes is regulated at the transcriptional level—cells do not waste energy making mRNAs and proteins they do not need. Many genes are therefore expressed only in an organ-, tissue- or cell type–specific manner. Certain noncoding DNA sequences play a critical part in directing when and where that happens. They are components of "genetic switches" that turn genes on or off at the right time and place in the body. Sequence-specific DNA-binding proteins called transcription factors, which are the other components of the switch, recognize those DNA sequences, often called enhancers. The binding of the transcription factors to the enhancer within a cell nucleus determines whether the switch and the gene are on or off in that cell.

Every gene has at least one enhancer. Unlike the genes themselves, whose coding regions are readily identified because of the genetic code's fairly simple grammar, enhancers cannot be recognized solely on the basis of their DNA sequences and must be identified experimentally. Enhancers are usually hundreds of base pairs in length and may be located on either side of a gene or even within a noncoding stretch inside a gene. They can also be thousands of nucleotides away from the gene itself.

Most important to our discussion here is the fact that some genes have many separate enhancers. This is particularly true for genes that encode proteins that shape anatomy. Each enhancer independently regulates the expression of the gene in different parts of the body and at different times in the animal's life cycle, such that the complete expression of a gene is a patchwork of multiple, independently controlled sites of expression. These enhancers enable the same gene to be used many times in different contexts and thus greatly expand the functional versatility of individual genes.

A gene involved in coloring the body parts of the fruit fly illustrates the modular logic of this gene regulation system. The somewhat confusingly named *Yellow* gene encodes a protein that promotes the formation of black pigmentation (mutant flies without this protein are yellow). The *Yellow* gene has separate enhancers that activate it during the development of a variety of fly body parts, including the wings and abdomen.

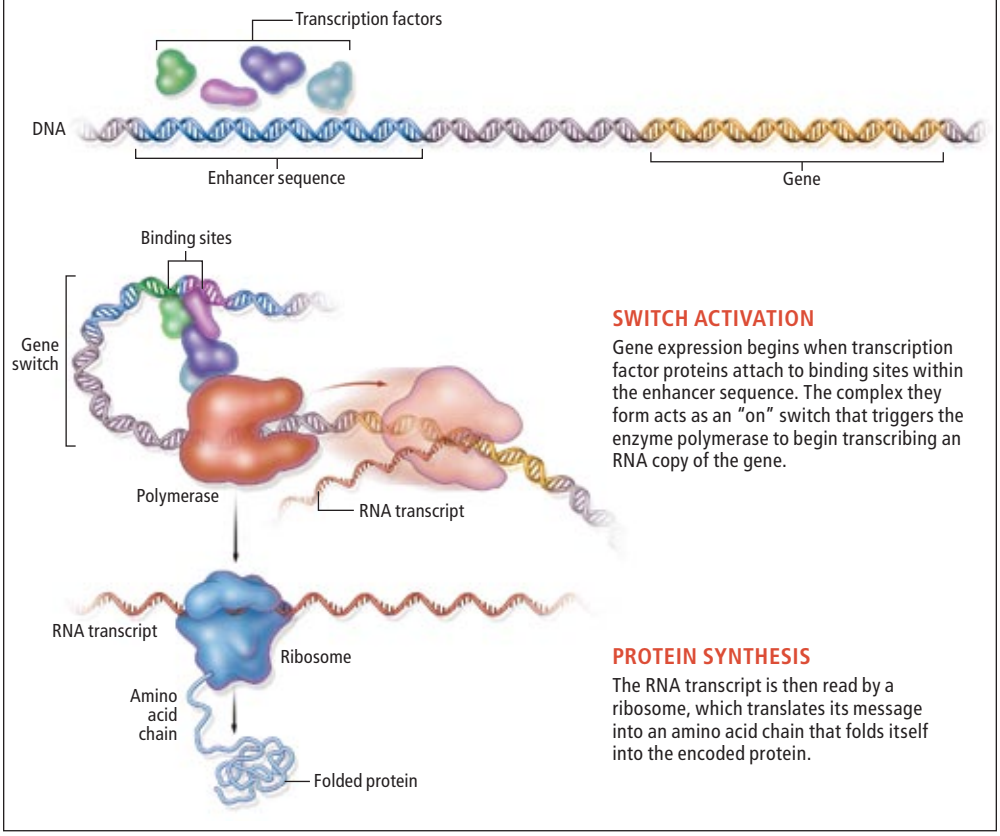
Because the *Yellow* gene plays a role during the development of so many tissues, mutations in the gene itself could be disastrous if they alter or disable the function of the protein; they would affect the function of the Yellow pigmentation protein throughout the organism. In contrast, changes in just one of the gene's enhancers will affect only the function of that enhancer and only the *Yellow* gene expression governed by that enhancer, leaving the expression and function of the protein in other tissues unchanged.

The evolutionary implications of the modular regulation of body-patterning genes are profound. In theory, mutations in enhancers would allow individual body traits to be selectively modified without changing genes or proteins themselves. And in the past few years, direct evidence has emerged that this is frequently how the evolution of various body parts and patterns has occurred.

[THE BASICS]

GENE SWITCHES IN ACTION

DNA segments called enhancers, usually found in the vicinity of genes, are key components of the switches that control gene "expression"—a cell's manufacture of the protein encoded by a gene. Enhancers are proving to be central players in the evolution of anatomy.



SWITCH ACTIVATION

Gene expression begins when transcription factor proteins attach to binding sites within the enhancer sequence. The complex they form acts as an "on" switch that triggers the enzyme polymerase to begin transcribing an RNA copy of the gene.

PROTEIN SYNTHESIS

The RNA transcript is then read by a ribosome, which translates its message into an amino acid chain that folds itself into the encoded protein.

Evolving Switches

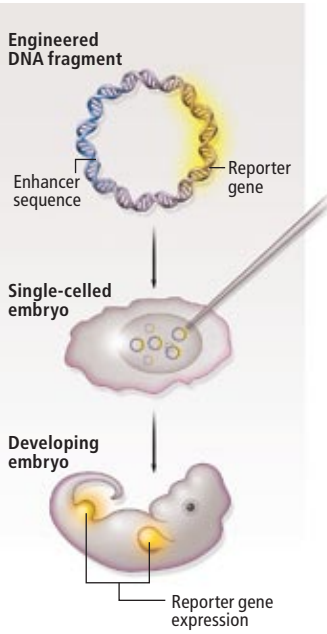
One of the most important strategies in biology is to identify the simplest experimental models of the phenomenon one wishes to understand. With respect to the evolution of body pattern, coloration fits the bill. It is one of the most obvious features of animals and plays a major role in how animals interact with their environment and with one another. Body-color patterns in fruit flies have diversified rapidly among closely related species, and analyses of how fruit flies got their spots and stripes illustrate how and why the evolution of genetic switches shapes the evolution of anatomy.

In some species, the males have intense black spots on the edges of their wings, whereas other species lack these spots. In some of these same species, males have a very dark abdomen (which is how the most famous fruit fly, *Drosophila melanogaster,* got its name: *melanogaster* means "black belly"), whereas males of other species lack this black band. In wing-spotted species, the male displays his spots to the female as he courts her with a dance. We have found that in spotted species, the Yellow protein is produced at very high levels in the cells that will make the spot and at low levels in the rest of the wing cells. In unspotted species, Yellow is made only at low levels throughout the wing, generating just a light dusting of black pigment.

To figure out how Yellow is produced in a wing spot in some species and not others, we searched the DNA sequences around the *Yellow* gene for the enhancers that control its expression in various body parts. In unspotted species, there is an enhancer that drives *Yellow* expression in a low uniform pattern in the wing. This wing-enhancer activity generates the fly wings' light-gray color. When the corresponding piece of DNA was analyzed from a spotted species, we found that it drives both this low-level pattern and the intense spot pattern of gene expression. What has happened in the course of evolution of spotted species is that new binding sites for tran-

DETECTING A SWITCH

To understand when and where an enhancer regulates a gene's expression, scientists engineer a DNA fragment containing the enhancer sequence and a reporter gene that will produce a visible signal when it is active. After this DNA construct is injected into a single-celled embryo, it will integrate into the animal's genome and be present in every cell of the developing body. The reporter gene's activation reveals the enhancer's role in body-building processes during development.



TAMI TOLPA

[CASE STUDY]

MODULAR SPOTS AND STRIPES

When multiple enhancers control the expression of a gene in different parts of the body, a change to one enhancer can alter the gene's activity in a specific place without affecting it elsewhere. A fruit fly gene called *Yellow,* for example, produces black pigment in a fly's developing body and wings, but various species have evolved distinct pigmentation patterns through changes to their enhancer sequences.

ANCESTRAL PATTERN

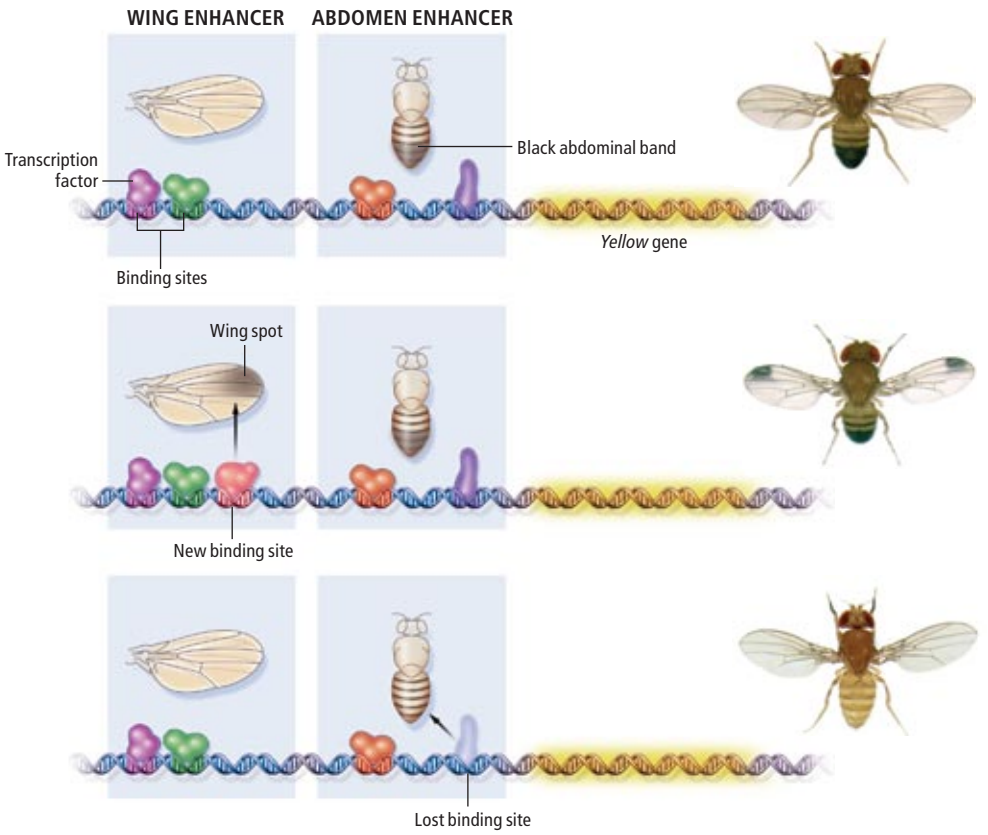
In a species representing an ancestral version of fruit flies, the enhancer that controls *Yellow* activity in the wings drives low gene expression, yielding a light-gray coloring, but in the abdomen a different enhancer drives high gene expression, producing a dark-black band.

FEATURE GAIN

Some species have evolved black wing spots by gaining a new transcription factor binding site in the wing enhancer sequence, which drives high expression of the *Yellow* gene in certain cells during wing development.

FEATURE LOSS

Other species have lost the abdominal band by losing a binding site in the corresponding enhancer sequence.



scription factors made in the wing evolved in the *Yellow* wing-enhancer DNA sequence. These changes created an expression pattern—wing spots—without altering where the Yellow protein is made or how it functions elsewhere in the body [*see box above*].

A similar story applies to the evolution of the black band in the abdomen, but with a twist. Whereas we are naturally inclined to think that the presence of a feature in one species and its absence in another related species is the result of a gain by the first, that is often not the case. A flip side to evolution, the loss of features, is very common, though much less appreciated. The loss of body characters perhaps best illustrates why the evolution of enhancers is the more likely path for the evolution of anatomy.

One enhancer of the *Yellow* gene governs its expression in the abdomen. In males of species with the black band, this enhancer drives the expression of the *Yellow* gene at high levels in cells at the rear of the abdomen. But some species, such as *Drosophila kikkawai,* lost this band of pigmentation in the course of evolution. In *D. kikkawai,* the enhancer can no longer drive high levels of *Yellow* expression in the rear of the abdomen because a few mutations have disrupted some of its transcription factor binding sites.

It is important to emphasize that the *Yellow* gene remains active elsewhere in the body and that its biochemical function is intact. Although one path to losing the black band could have been through mutations that inactivate the *Yellow* gene and its protein, this path is not permitted by natural selection, because the loss of Yellow function elsewhere in the body would have additional, detrimental consequences.

Losses of features may or may not be beneficial for survival or greater reproductive success, but some losses are adaptive because they facilitate some change in lifestyle. Hind limbs, for example, have been lost many times in verte-

TAMI TOLPA; NICOLAS GOMPEL AND BENJAMIN PRUD'HOMME (*three flies*)

brates—by snakes, lizards, whales and manatees—and those losses are associated with adaptation to different habitats and means of locomotion. The evolutionary forerunners of the hind limbs of four-legged vertebrates are the pelvic fins of fish. Dramatic differences in pelvic fin anatomy have also evolved in closely related fish populations. The three-spined stickleback fish occurs in two forms in many lakes in North America—an open-water form that has a full spiny pelvis, and a shallow-water, bottom-dwelling form with a dramatically reduced pelvis and shrunken spines. In open water, the long spines help to protect the fish from being swallowed by larger predators. But on the lake bottom, those spines are a liability because dragonfly larvae that feed on the young fish can grasp them.

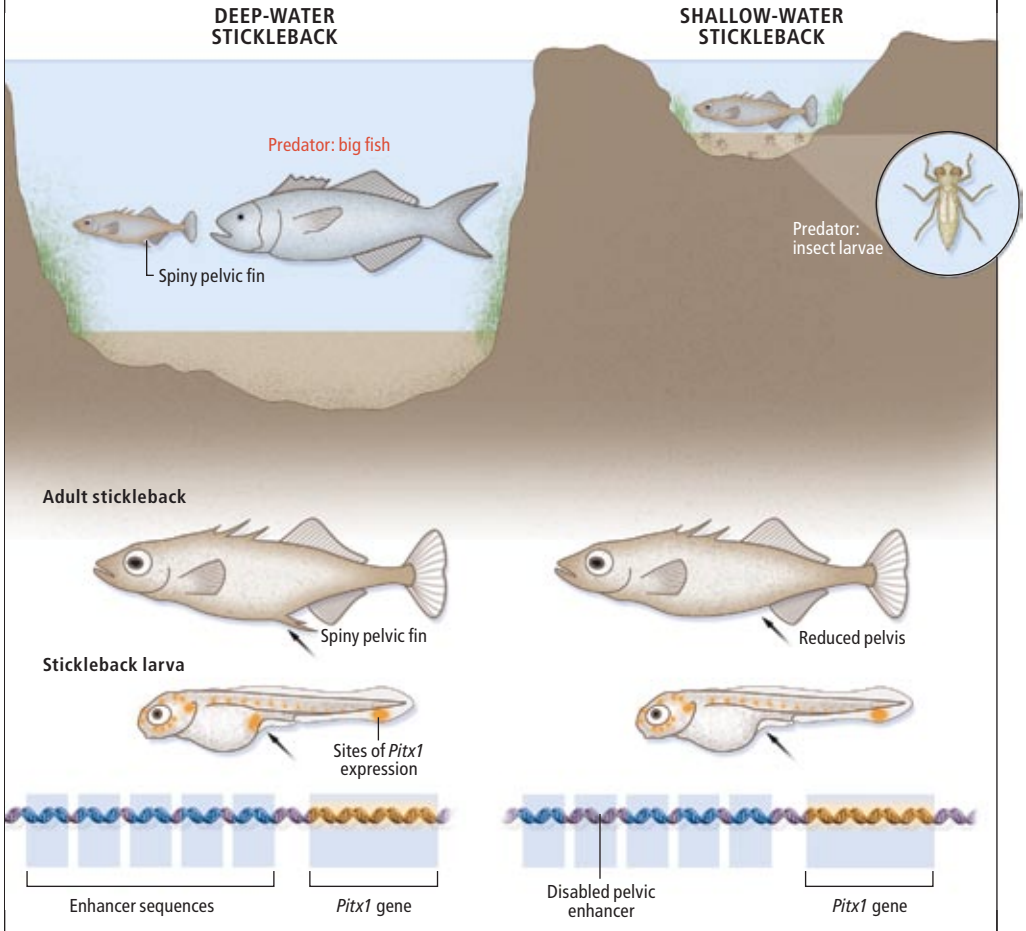
The differences in pelvic morphology among these fish have evolved repeatedly in just 10,000 years since the last Ice Age. Long-spined oceanic sticklebacks colonized many separate lakes, and the reduced form evolved independently several times. Because the fish are so closely related and interbreed in the laboratory, geneticists can

Mutations in regulatory sequences are not the exclusive mode of evolution—they are just the more likely path when a gene has multiple roles and only one of them is modified.

[CASE STUDY]

A BENEFICIAL LOSS

The three-spined stickleback offers another vivid example of adaptation through the evolution of a gene-regulating enhancer sequence. These fish take one of two forms, depending on where they live and therefore which predator threatens them most: deep-water sticklebacks have a prominent spiny pelvic fin on their underside, which makes them more difficult for larger fish to swallow; shallow-water sticklebacks have lost the pelvic fin, making it harder for bottom-dwelling insect larvae that feed on the young fish to attach themselves.



The gene that regulates pelvic-fin development, called *Pitx1,* also contributes to the development of many other major structures in the fish, each of which is regulated by a separate enhancer. In the shallow-water sticklebacks (*right*), a mutation has disabled only the enhancer responsible for pelvic-fin development, leaving *Pitx1* and its other functions intact.

TAMI TOLPA

[THE AUTHORS]

Sean B. Carroll, Benjamin Prud'homme and Nicolas Gompel have worked together for several years to decipher how the evolution of regulatory DNA sequences shapes animal morphology. Carroll is a Howard Hughes Medical Institute investigator and professor of molecular biology and genetics at the University of Wisconsin–Madison, as well as the author of two popular books about evolution. Prud'homme and Gompel, both former postdoctoral fellows in Carroll's laboratory, now investigate the evolution of animal forms and behavior in their own laboratory in France, at the Developmental Biology Institute of Marseille Luminy.

map the genes involved in the reduction of the stickleback pelvis. David M. Kingsley of Stanford University, along with Dolph Schluter of the University of British Columbia and colleagues, has shown that changes in the expression of a gene involved in the building of the pelvic skeleton are associated with the pelvic reduction. Like most other body-building genes, the *Pitx1* gene has multiple jobs in the development of the fish. But its expression is selectively lost in the area of the fish that will give rise to the pelvic-fin bud and spines. Once again, evolutionary changes in an enhancer are responsible. There are no coding changes in the Pitx1 protein between different forms of the stickleback.

Yellow, *Pitx1* and most other body-building and body-patterning genes are said to be pleiotropic, in that they influence the formation or appearance of multiple traits. Mutations in the coding sequence of a pleiotropic gene have multiple effects on all the traits controlled by this gene, and that drastic amount of change is unlikely to be tolerated by natural selection. The key lesson from the evolution of spots, stripes and skeletons is that mutations in regulatory sequences circumvent the pleiotropic effects of mutations in coding sequences and allow for the selective modification of individual body parts. Mutations in regulatory sequences are not the exclusive mode of evolution—they are just the more likely path when a gene has multiple roles and one of those roles is selectively modified.

Common Genes, Endless Variety

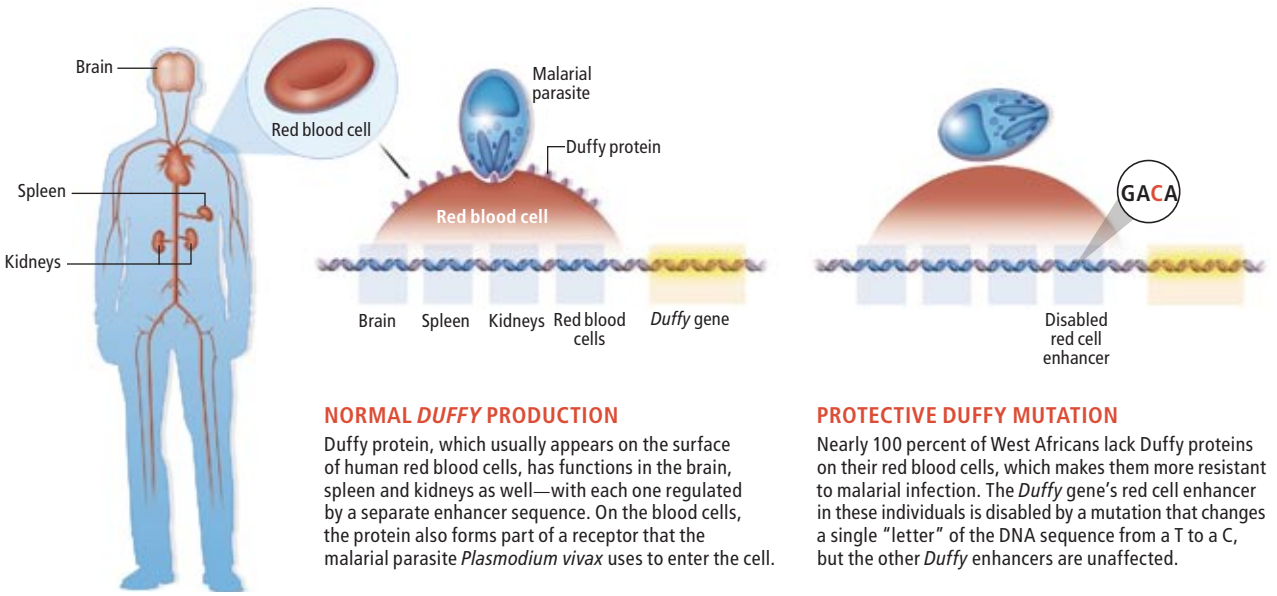
The evolution of enhancers is not at all limited to genes affecting body form nor just to fruit flies and weird fish. Quite a few examples of evolutionary changes in regulatory sequences that alter gene expression have been demonstrated for human traits as well.

One of the more striking cases in recent human evolution represents an adaptation, through selective loss of gene expression, to an environment where malaria is endemic. In addition to the familiar A, B and O blood types, other so-called minor blood types have been well studied. The status of a protein called Duffy, present on the surface of red blood cells, defines one of these types. The Duffy protein constitutes part of the receptor that is used by a malaria-causing parasite, *Plasmodium vivax*, to infect red cells, but in West Africa the protein is absent from the blood cells of almost 100 percent of the population, making individuals resistant to infection. The *Duffy* gene is also expressed in several other body tissues, including cells of the spleen, the kidneys and the brain. In the African population, *Duffy* expression in

[CASE STUDY]

HUMAN DIVERSITY

The human genome, like those of flies and fish, also displays evidence of evolution through changes to enhancer DNA. One example is the adaptive loss of a protein called Duffy on red blood cells in a West African population living in areas where malaria is endemic.



NORMAL *DUFFY* PRODUCTION

Duffy protein, which usually appears on the surface of human red blood cells, has functions in the brain, spleen and kidneys as well—with each one regulated by a separate enhancer sequence. On the blood cells, the protein also forms part of a receptor that the malarial parasite *Plasmodium vivax* uses to enter the cell.

PROTECTIVE DUFFY MUTATION

Nearly 100 percent of West Africans lack Duffy proteins on their red blood cells, which makes them more resistant to malarial infection. The *Duffy* gene's red cell enhancer in these individuals is disabled by a mutation that changes a single "letter" of the DNA sequence from a T to a C, but the other *Duffy* enhancers are unaffected.

TAMI TOLPA

Scanning for Switches

One of the main limits on the pace of discovery of human enhancers has been the difficulty of identifying where they reside in the human genome's vast noncoding regions. Biologists are now using the preservative power of natural selection to sniff out stretches of noncoding DNA that have been unusually well conserved over long stretches of evolutionary time in the hope of detecting enhancers.

In this article we have been emphasizing changes in enhancers that account for differences among organisms. But it should be easy to appreciate that some enhancers carry out functions that have not changed. While the steady pace of mutation erodes the overall similarity of DNA sequences among species as they diverge, natural selection will maintain the sequences of enhancers that maintain their function, sometimes to an extraordinary degree.

It is common knowledge that lawyers and sharks have a lot of similarities. But who would have guessed that extends to the level of DNA? Yet that is essentially what researchers at the Institute of Molecular and Cell Biology in Singapore and the J. Craig Venter Institute in Rockville, Md., have demonstrated. The team found that despite more than 500 million years of evolution separating sharks and people, we share nearly 5,000 elements in noncoding regions near genes that appear to be enhancers. Remarkably, most of these highly preserved elements are located in the vicinity of body-building genes, reflecting the shared overall body architecture of vertebrates.

Every vertebrate has anatomical features—organs, tissues, cell types, and so forth—that have been preserved throughout their diversification. Over shorter evolutionary distances, the number of shared elements and degree of similarity increases.

The genome-comparison approach is thus rapidly expanding the catalogue of known human, mammalian and vertebrate enhancers and could lead to the identification of sequences involved in the divergence of body forms. ***—S.B.C., B.P. and N.G.***

those other tissues is preserved. Not surprisingly, these Duffy-negative individuals carry a mutation in an enhancer of the *Duffy* gene that knocks out the binding site for a transcription factor that activates *Duffy* expression in red blood cell precursors but that has no effect on Duffy production elsewhere in the body.

Gregory A. Wray of Duke University and his collaborators have identified other aspects of human biology that have evolved through mutations in enhancers in different human genes. One of the most intriguing associations revealed thus far involves divergence in the great ape and human regulatory sequences controlling the *Prodynorphin* gene, which encodes a set of small opioid proteins produced in the brain and involved in perception, behavior and memory. The human gene is more highly expressed in response to stimuli than is the chimpanzee version, and strong evidence suggests that the human regulatory sequence evolved under natural selection—that is, it was retained because it was advantageous.

As these examples illustrate, mutations in regulatory DNA have undoubtedly played a role in human evolution and regulatory variation may be an important source of physical and health differences among individuals as well. Because scientists cannot tinker with the DNA of living humans the way we can with flies and fish, it is somewhat harder to study certain examples of regulatory DNA changes responsible for our divergence from other species, although some new methods for analyzing genomes are producing encouraging leads [*see box above*].

These are still early days for research into the evolution of gene-regulating DNA sequences. And hundreds of thousands of genetic switches in the virtual zoo of genomes have yet to be discovered or investigated. Biologists are already learning new principles, however, that have predictive value for future studies: evolutionary changes to anatomy, particularly those involving pleiotropic genes, are more likely to happen via changes to gene enhancers than to the genes themselves.

This phenomenon also reveals how very diverse groups of animals can share most, if not all, the genes involved in body building and body patterning—contrary to scientists' early expectations, it is mostly a matter of how and when those genes are used that shapes the different forms of the animal kingdom. If we really want to understand what makes the human form different from that of other apes or what makes an elephant distinct from a mouse, for that matter, much of that information lies not in our respective genes and proteins but in an entirely different realm of our genomes that remains to be explored. ■

MORE TO EXPLORE

Evolution at Two Levels: On Genes and Form. Sean B. Carroll in *PLoS Biology,* Vol. 3, Issue 7, pages 1159–1166; July 2005.

Endless Forms Most Beautiful: The New Science of Evo Devo and the Making of the Animal Kingdom. Sean B. Carroll. W. W. Norton, 2005.

The Making of the Fittest: DNA and the Ultimate Forensic Record of Evolution. Sean B. Carroll. W. W. Norton, 2006.

The Evolutionary Significance of cis-Regulatory Mutations. Gregory A. Wray in *Nature Reviews Genetics,* Vol. 8, pages 206–216; March 2007.

Emerging Principles of Regulatory Evolution. Benjamin Prud'homme, Nicolas Gompel and Sean B. Carroll in *Proceedings of the National Academy of Sciences USA,* Vol. 104, Supplement 1, pages 8605–8612; May 15, 2007.

For links to teaching resources, see **www.seanbcarroll.com**

SCIENCE 2.0

BY M. MITCHELL WALDROP

JON KRAUSE

Is posting raw results online, for all to see, a great tool or a great risk?

The first generation of World Wide Web capabilities rapidly transformed retailing and information search. More recent attributes such as blogging, tagging and social networking, dubbed Web 2.0, have just as quickly expanded people's ability not just to consume online information but to publish it, edit it and collaborate about it—forcing such old-line institutions as journalism, marketing and even politicking to adopt whole new ways of thinking and operating.

Science could be next. A small but growing number of researchers (and not just the younger ones) have begun to carry out their work via the wide-open tools of Web 2.0. And although their efforts are still too scattered to be called a movement—yet—their experiences to date suggest that this kind of Web-based "Science 2.0" is not only more collegial than traditional science but considerably more productive.

"Science happens not just because of people doing experiments but because they're discussing those experiments," explains Christopher Surridge, managing editor of the Web-based journal Public Library of Science On-Line Edition (www.plosone.org). Critiquing, suggesting, sharing ideas and data—this communication is the heart of science, the most powerful tool ever invented for correcting errors, building on colleagues' work and fashioning new knowledge. Although the classic peer-reviewed paper is important, says Surridge, who publishes a lot of them, "they're effectively just snapshots of what the authors have done and thought at this moment in time. They are not collaborative beyond that, except for rudimentary mechanisms such as citations and letters to the editor."

Web 2.0 technologies open up a much richer dialogue, says Bill Hooker, a postdoctoral cancer researcher at the Shriners Hospital for Children in Portland, Ore., and author of a three-part survey on open-science efforts that appeared at 3 Quarks Daily (www.3quarksdaily.com), where a group of bloggers write about science and culture. "To me, opening up my lab notebook means giving people a window into what I'm doing every day," Hooker says. "That's an immense leap forward in clarity. In a paper, I can see

KEY CONCEPTS

- Science 2.0 generally refers to new practices of scientists who post raw experimental results, nascent theories, claims of discovery and draft papers on the Web for others to see and comment on.
- Proponents say these "open access" practices make scientific progress more collaborative and therefore more productive.
- Critics say scientists who put preliminary findings online risk having others copy or exploit the work to gain credit or even patents.
- Despite pros and cons, Science 2.0 sites are beginning to proliferate; one notable example is the OpenWetWare project started by biological engineers at the Massachusetts Institute of Technology.

—The Editors

READERS SPEAK OUT

In the spirit of what might be called Journalism 2.0, *Scientific American* posted a draft of this article on its Web site and asked readers to discuss their excitement and wariness about Science 2.0. Their insights helped to broaden the final result; particularly salient comments are excerpted in green boxes (writers' screen names appear in italics).

Tell us your opinion at www.SciAm.com/science2point0

what you've done. But I don't know how many things you tried that didn't work. It's those little details that become clear with an open [online] notebook but are obscured by every other communication mechanism we have. It makes science more efficient." That jump in efficiency, in turn, could greatly benefit society, in everything from faster drug development to greater national competitiveness.

Of course, many scientists remain wary of such openness—especially in the hypercompetitive biomedical fields, where patents, promotion and tenure can hinge on being the first to publish a new discovery. For these practitioners, Science 2.0 seems dangerous: putting your serious work out on blogs and social networks feels like an open invitation to have your lab notebooks vandalized—or, worse, your best ideas stolen and published by a rival.

To advocates, however, an atmosphere of openness makes science more productive. "When you do your work online, out in the open," Hooker says, "you quickly find that you're not competing with other scientists anymore but cooperating with them."

Rousing Success

In principle, Surridge says, scientists should find a transition to Web 2.0 perfectly natural. After all, since the time of Galileo and Newton, scientists have built up their knowledge about the world by "crowdsourcing" the contributions of many researchers and then refining that knowledge through open debate. "Web 2.0 fits so perfectly with the way science works. It's not whether the transition will happen but how fast," Surridge says.

One early success is the OpenWetWare project at the Massachusetts Institute of Technology (www.openwetware.org). Launched in 2005 by graduate students working in the laboratories of M.I.T. biological engineers Drew Endy and Thomas Knight, the project was originally seen as just a better way to keep the two lab Web sites up-to-date. OpenWetWare is a wiki—a collaborative Web site that can be edited by anyone who has access. It uses the same software that underlies the online encyclopedia Wikipedia. The students happily started posting pages introducing themselves and their work.

Soon, however, they discovered that the wiki was also a convenient place to post what they were learning about lab techniques: manipulating DNA, getting cell cultures to grow. "A lot of the how-to gets passed around as lore in biology labs and never makes it into the protocol manuals," says Jason Kelly, a graduate student who now sits on the OpenWetWare steering committee. "But we didn't have that." Most of the students came from engineering backgrounds; theirs were young labs with almost no mentors. So whenever a student or postdoc managed to stumble through a new protocol, he or she would write down what was learned on a wiki page. Others would then add whatever tricks they had gleaned. The information was very useful to the labs' members, notes M.I.T. grad student and steering-committee member Reshma Shetty, but "that information also became available around the world."

Indeed, Kelly points out, "most of our users came to us because they'd been searching Google for information on a protocol, found it on our site, and said, 'Hey!' " As more and more people got on, it became apparent that the collaboration could benefit other endeavors, such as classes. Instead of making do with a static Web page posted by a professor, students began to create dynamically evolving class sites where they could post lab results, ask questions, discuss the answers and even write collaborative essays. "And it all stayed on the site, where it made the class better for next year," says Shetty, who has built an OpenWetWare template for creating such class sites.

Laboratory management benefited too. "I didn't even know what a wiki was," recalls Maureen Hoatlin of the Oregon Health & Science University, where she runs a lab studying the genetic disorder Fanconi anemia. But she did know that the frenetic pace of research in her field was making it hard to keep up with what her own team members were doing, much less Fanconi researchers elsewhere. "I was looking for a tool that would help me organize all that information," Hoatlin says. "I wanted it to be Web-based, because I travel a lot and need to access it from wherever I am. And I wanted something my collaborators and group members could add to dynamically, so that whatever I saw on that Web page would be the most recently updated version."

OpenWetWare fit the bill. "I came to love the interaction," she says, "the fact that people in other labs could comment on what we do, and vice versa. When I see how fast that is, and its power to move science forward—there is nothing like it."

A wide cross section of biological researchers now work through OpenWetWare's growing

[THE AUTHOR]

BEN ZWEIG (*Waldrop*)

M. Mitchell Waldrop prepared this article as a freelance science writer in Washington, D.C. He recently joined *Nature* as its editor for editorials.

JON KRAUSE

number of sites, such as SyntheticBiology.org, which includes postings about jobs, meetings, ethics discussions, and much more. OpenWetWare currently encompasses laboratories on five continents, dozens of courses and interest groups, and hundreds of protocol discussions—more than 6,100 Web pages edited by 3,000 registered users. A May 2007 National Science Foundation grant launched the OpenWetWare team on a five-year effort to transform the platform into a self-sustaining community independent of its current base at M.I.T. The grant will also support creation of a generic version of OpenWetWare that other research communities can use.

Skepticism Persists

For all the participants' enthusiasm, however, this wide-open approach to science does create fear for some. Even Hoatlin found the openness unnerving at first. "Now I'm converted to open wikis for everything possible," she says, "but when I originally joined I wanted to keep everything private"—in part to keep her lab pages from being trashed by some random hacker. She did not relax until she began to understand the system's built-in safeguards.

First and foremost, Kelly says, "you can't hide behind anonymity." By default, OpenWetWare pages are visible to anyone (although researchers have the option to make pages private). Unlike the oft-defaced Wikipedia, the system will let users make changes only after they have registered and established that they belong to a legitimate research organization. "We've never yet had a case of vandalism," Kelly says. Even if damage were done, it could be rolled back with the click of a mouse: the wiki automatically maintains a copy of every version of every page posted. Unfortunately, this kind of technical safeguard does little to address a second concern: getting scooped and losing the credit. "That's the first argument people bring to the table," says Drexel University chemist Jean-Claude Bradley, who created his independent laboratory wiki, UsefulChem (www.usefulchem.wikispaces.com), in December 2005. Even if incidents are rare, Bradley says, everyone has heard a story, which is enough to keep most scientists from even discussing their unpublished work too freely, much less posting it on the Internet.

Ironically, though, the Web provides better protection than the traditional journal system,

RISK OF BEING SCOOPED

Dr. Monica: My first thought was, no way am I making my scientific ruminations public property. I've learned over the years that this is a sure way to have those ideas appear in someone else's work! However, many practical and useful applications come to mind.

Funklord: The issue is not that someone is just going to replicate your work and claim credit. The issue is, What if they are able to reach the eureka moment faster than you are?

NO PROXY FOR PEER REVIEW

Darren: One of the big positives of the current journal system is peer review: Science 2.0 needs a reputation-management system, a central database responsible for tracking the reputation of those participating in the online community.

wilbanks: Blogs and wikis are the digital equivalents of the hallway conversations at a conference or a lab meeting, but they are a long way from replacing journals. You don't get points for making a statement first in science unless you can prove that statement.

Bradley maintains. Every change on a wiki gets a time stamp, "so if someone actually did try to scoop you, it would be very easy to prove your priority—and to embarrass them. I think that's really what is going to drive open science: the fear factor. If you wait for the journals, your work won't appear for another six to nine months. But with open science, your claim to priority is out there right away."

Under Bradley's radically transparent "open notebook" approach, everything goes online: experimental protocols, successful outcomes, failed attempts, even discussions of papers being prepared for publication. "A simple wiki makes an almost perfect lab notebook," Bradley declares. The time stamps on every entry not only establish priority but allow anyone to track the contributions of every person, even in a large collaboration.

Bradley concedes that researchers may sometimes have legitimate reasons to think twice about being so open. If work involves patients or other human subjects, for example, privacy is a concern. If a scientist is planning to publish in a journal that insists on copyrighting text and visuals, prepublishing online could pose a problem. And if work might lead to a patent, it is still not clear whether the patent office will accept a wiki posting as proof of priority. Until that is sorted out, he says, "the typical legal advice is: do not disclose your ideas before you file."

Still, Bradley states, the more open scientists are, the better. When he started UsefulChem, his lab was investigating the synthesis of drugs to fight diseases such as malaria. But because search engines could index what his team was doing without needing a bunch of passwords, "we suddenly found people discovering us on Google and wanting to work together. The National Cancer Institute contacted me, wanting to test our compounds as antitumor agents. Rajarshi Guha at Indiana University offered to help us do calculations about docking—figuring out which molecules will be reactive. Now we're not just one lab doing research but a network of labs collaborating."

Blogophobia

Although wikis are gaining, scientists have been strikingly slow to embrace one of the most popular Web 2.0 applications: Web logging, or blogging.

JON KRAUSE

WATCH OUT FOR LINK ROT

ScienceEditor: Internet citations are often frowned upon by authors and editors. "Link rot" almost guarantees that any cited Web address goes 404 [error: page not found] after a few years or decades. Authors, editors and publishers should support a system such as WebCite (www.webcitation.org) to archive non-journal Internet material, ensuring long-term accessibility of the scholarly record.

EXPANDED OPENNESS

Deadlyvices: Web 2.0 has fantastic potential to open up science to everyone, not just tenured academics. Perhaps if intelligent laypeople had a greater opportunity to contribute, there would be less public disaffection with science.

Richaa: One reason I left science after my Ph.D. was the isolationist culture. One scientist told me I had too many interests to be successful in physics research. I decided to take that as a compliment. I hope that the opening of science through Web 2.0 technologies will remove that culture and bring in valuable interdisciplinary thinking and collaboration.

"It's so antithetical to the way scientists are trained," Duke University geneticist Huntington F. Willard said at the January 2007 North Carolina Science Blogging Conference, one of the first big gatherings devoted to this topic. The whole point of blogging is getting ideas out there quickly, even at the risk of being wrong or incomplete. "But to a scientist, that's a tough jump to make," Willard says. "When we publish things, by and large, we've gone through a very long process of drafting a paper and getting it peer-reviewed. Every word is carefully chosen, because it's going to stay there for all time. No one wants to read, 'Contrary to the result of Willard and his colleagues. . . .'"

Nevertheless, Willard favors blogging. As a frequent author of newspaper op-ed pieces, he feels that scientists should make their voices heard in every responsible way. Because most blogs allow outsiders to comment on the individual posts, they have proved to be a good medium for brainstorming and discussions. Bradley's UsefulChem blog is one example. Chembark (www.blog.chembark.com) is another. "Chembark has morphed into the water cooler of chemistry," says Paul Bracher, who is pursuing his Ph.D. in that field at Harvard University. "The conversations are: What should the research agencies be funding? What is the proper way to manage a lab? What types of behavior do you admire in a boss? But instead of having five people around a single water cooler, you have hundreds of people around the world."

Of course, for many members of Bracher's primary audience—young scientists still struggling to get tenure—those discussions can look like a minefield. A fair number of the participants use pseudonyms out of fear that a comment might offend some professor's sensibilities, hurting a student's chances of getting a job later. Other potential participants never get involved because they feel that time spent with the online community is time not spent on cranking out that next publication. "The peer-reviewed paper is the cornerstone of jobs and promotion," PLoS ONE's Surridge says. "Scientists don't blog because they get no credit" for that.

The credit problem is one of the biggest barriers to many aspects of Science 2.0, agrees Timo Hannay, head of Web publishing at the Nature Publishing Group in London. (That group's parent company, Macmillan, also owns *Scientific American*.) Once again, however, the technology itself may help. "Nobody believes that a scientist's only contribution is from the papers he or she publishes," Hannay says. "People understand that a good scientist also gives talks at conferences, shares ideas, takes a leadership role in the community. It's just that publications were always the one thing you could measure. Now, however, as more of this informal communication goes online, that will get easier to measure, too."

The Payoff of Collaboration

Acceptance of such measures would require a big change in academic culture. But for Science 2.0 advocates, the real significance is the technologies' potential to move researchers away from an obsessive focus on priority and publication toward the kind of openness and community that were the supposed hallmarks of science in the first place. "I don't see the disappearance of the formal research paper anytime soon," Surridge says. "But I do see the growth of lots more collaborative activity building up to publication." And afterward as well: PLoS ONE allows users not only to annotate and comment on the papers it publishes online but to rate the papers' quality on a scale of 1 to 5.

Some universities may be coming around, too. In a landmark vote in February, the faculty at Harvard's College of Arts and Sciences approved a system in which the college would post finished papers in an online repository, available free to all. Authors would still hold copyright and could still publish the papers in traditional journals.

Meanwhile Hannay has been taking the Nature group into the Web 2.0 world aggressively. "Our real mission isn't to publish journals but to facilitate scientific communication," he says. Among the efforts are Nature Network, a social network for scientists; Connotea, a social bookmarking site for research references patterned on the popular site del.icio.us; and Nature Precedings, a Web site where researchers can comment on unpublished manuscripts, presentations and other documents.

Indeed, says Bora Zivkovic, a circadian rhythm expert who is the online community manager for PLoS ONE, the various experiments in Science 2.0 are now proliferating so rapidly that it is almost impossible to keep track of them. "It's a Darwinian process," he says. "About 99 percent of these ideas are going to die. But some will emerge and spread."

"I wouldn't like to predict where all this is going," Hooker adds. "But I'd be happy to bet that we're going to like it when we get there." ■

GEMS WITHIN THE RUBBLE

Matthewdsmith: It may be that by making so much information available (imagine millions of notebook pages with all the associated flotsam and jetsam), information that is actually valuable and useful will become harder to find.

jasonkelly: There are lots of resources (for example, Google) going after the problem of searching huge, diverse information sets, so we get to ride that wave for free.

Cameron Neylon: The promise of 2.0 is automated and community filtering: Facebook and Amazon do a surprisingly good job of identifying people I know or books I am interested in. The challenge lies in building big enough scientific networks that we start to see these benefits.

MORE TO EXPLORE

Computer Science: Science 2.0. Ben Schneiderman in *Science,* Vol. 319, pages 1349–1350; March 7, 2008.

The Future of Science Is Open. Bill Hooker. A three-part review of open-access science: **www.3quarksdaily.blogs.com/3quarksdaily/2006/10/the_future_of_s_1.html**

Nature Network, an online network for scientists to discuss scientific news and events: **http://network.nature.com**

Science Commons, an online project to aid open-access science on the Web: **www.sciencecommons.org**

How Cells

Worn-out proteins, malfunctioning organelles, invading microorganisms: all are swept up by tiny internal "vacuum cleaners" that keep a living cell healthy. If the process, called autophagy, can be kept in good working order, aging itself might be delayed

By Vojo Deretic and Daniel J. Klionsky

KEY CONCEPTS

- Inside the cytoplasm of a living cell, organelles called autophagosomes continually engulf bits of cytoplasm, along with damaged cell parts and invading bacteria and viruses. The "sweepings" are carried to digestive organelles for breakup and recycling. The process is called autophagy.
- Cell biologists are learning about autophagy in great detail by tracing the protein signals that drive and control the process.
- A fuller understanding of autophagy is opening up new options for treating cancer, infectious disease, immune disorders and dementia, and it may one day even help to slow down aging.

—The Editors

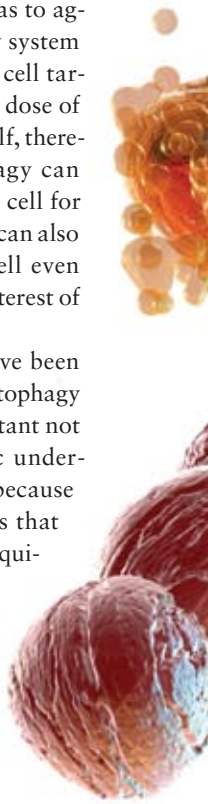
Every once in a while biologists come to realize that what was at one time regarded as a minor and relatively obscure cellular process is, in fact, of central importance. Not only is the process ubiquitous, but by virtue of that ubiquity it also plays a role in a broad range of normal and disease states. So it was with the discovery of the role of nitric oxide in the circulatory system, a discovery that led to a Nobel Prize, as well as to many beneficial drugs. Now another formerly obscure process known as autophagy is suddenly claiming extraordinary scientific attention.

In basic outline, autophagy (from the Greek, meaning "self-eating") is simple enough. Within every cell but outside the nucleus lies the cytoplasm, a kind of formless jelly supported by a skeletal matrix, in which a vast and intricate population of large molecules, or macromolecules, and specialized functional subunits called organelles is suspended. The workings of the cytoplasm are so complex—rather like some of today's computer systems—that it is constantly becoming gummed up with the detritus of its ongoing operations. Autophagy is, in part, a cleanup process: the trash hauling that enables a cell whose cytoplasm is clotted with old bits of protein and other unwanted sludge to be cleaned out.

Refurbishing the cytoplasm can give new life to any cell, but it is particularly important to cells such as neurons that do not get replaced. A neuron that must live as long as the organism that hosts it has virtually no other way to renew and maintain its operations. Cell biologists have also determined that autophagy acts as a defense against harmful viruses and bacteria. Any foreign object or organism that evades the extracellular immune system and makes its way through the cell membrane into the cytoplasm becomes a potential target for the autophagy system.

By the same token, when autophagy runs too slow, runs too fast or otherwise malfunctions, the consequences can be dire indeed. Many of the millions of people who suffer from Crohn's disease, a form of inflammatory bowel disease, may have defective autophagy systems that cannot keep the microbial flora in the gut from growing uncontrollably. A breakdown in the autophagy system in brain neurons has been linked to Alzheimer's disease, as well as to aging itself. Even a well-oiled autophagy system can be detrimental, enabling a cancer cell targeted by a blast of radiation or a toxic dose of chemotherapy to survive and repair itself, thereby perpetuating the cancer. Autophagy can sometimes act to eliminate a diseased cell for the greater good of the organism, but it can also become overzealous, consuming a cell even when the loss of that cell is not in the interest of the organism.

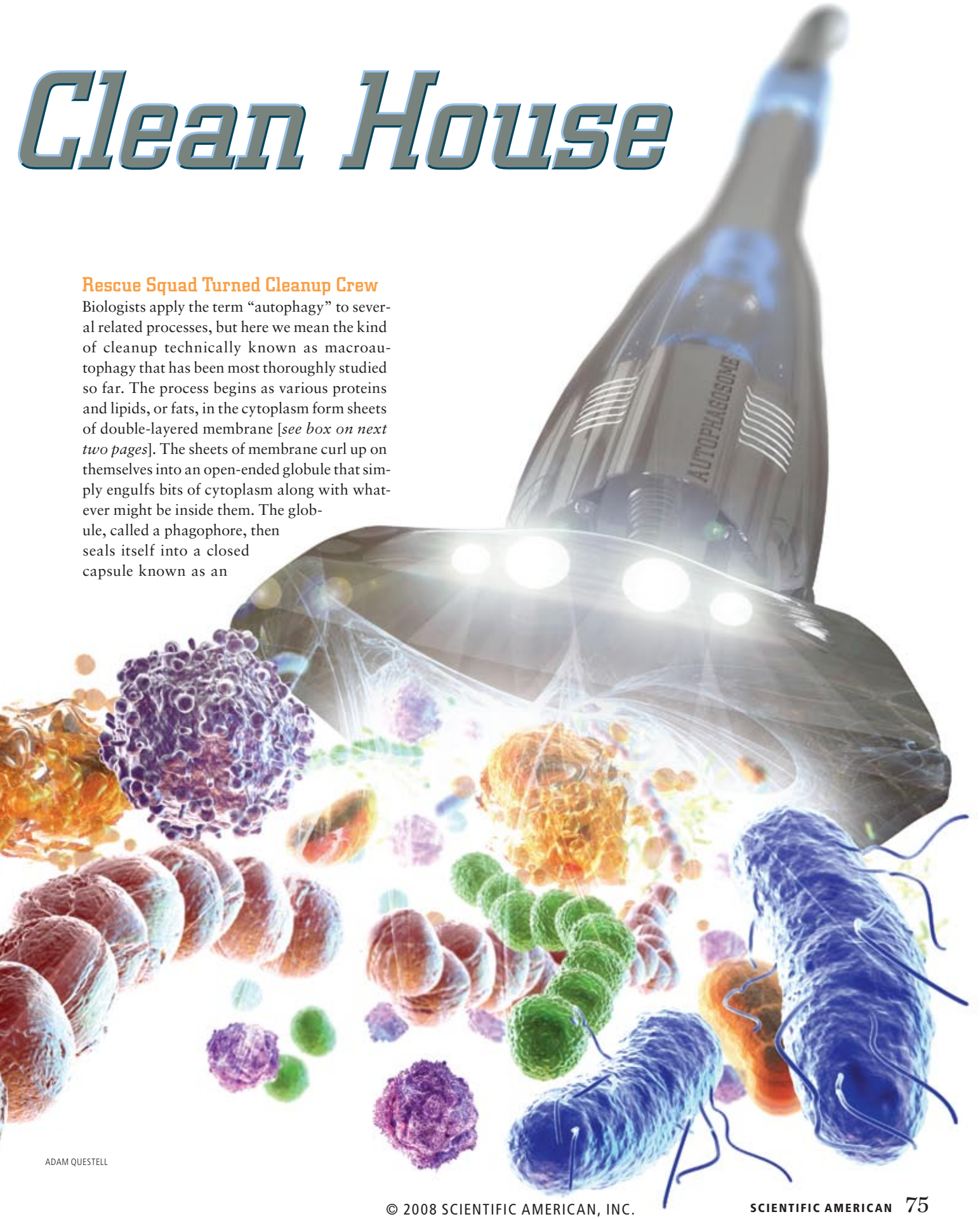
In the past decade investigators have been able to learn in great detail how the autophagy system works. Such insights are important not only because they enhance the basic understanding of how cells work, but also because they could lead to the design of drugs that might induce the system to ramp up or quiet down as needed. Controlling the rates of the process as well as the specific targets of its activities could have enormous therapeutic benefits and might even alleviate some of the decline in brain functioning people experience as they age.



Clean House

Rescue Squad Turned Cleanup Crew

Biologists apply the term "autophagy" to several related processes, but here we mean the kind of cleanup technically known as macroautophagy that has been most thoroughly studied so far. The process begins as various proteins and lipids, or fats, in the cytoplasm form sheets of double-layered membrane [*see box on next two pages*]. The sheets of membrane curl up on themselves into an open-ended globule that simply engulfs bits of cytoplasm along with whatever might be inside them. The globule, called a phagophore, then seals itself into a closed capsule known as an



ADAM QUESTELL

autophagosome. The autophagosome generally ferries its cargo to a lysosome, a kind of disposal plant, elsewhere within the cytoplasm. Typically the two organelles fuse into an "autolysosome," where the autophagosome gives up its cargo to the "digestive juices" of the lysosome. The useful molecular pieces that remain after digestion are recycled back into the cytoplasm.

In a general way, the process as an ongoing cellular activity has been recognized at least since the 1960s, when Christian de Duve of the Rockefeller University and others studied it under the electron microscope. Ten years ago one of us (Klionsky) and others (particularly Yoshinori Ohsumi of the National Institute for Basic Biology in Okazaki, Japan, and his co-workers) began to study its molecular biology in yeast, which is far simpler than studying the same function in higher animals. That strategy has exposed many of the otherwise elusive details of the autophagic machinery because many of the proteins that take part in autophagy or regulate it are virtually identical to their counterparts in people, having remained little changed throughout evolution.

Autophagy itself may have evolved as a response to cell starvation or as a primitive immune defense, or both. To appreciate the need for a starvation response, think about what happens when an entire organism is deprived of food. If a person restricts food intake, the body does not immediately cease functioning and die; instead it starts to break down its own nutritional reserves. Fat cells can go first, but ultimately even muscle cells are broken up and fed to the metabolic fires to keep essential processes running.

Similarly, when cells starve they, too, break down parts of themselves to maintain their essential activities. Autophagosomes are active continuously, whether a cell is starving or not, engulfing bits of cytoplasm and so repeatedly renewing much of the cytoplasmic content. But several kinds of stress—starvation, the absence of growth factors or lack of oxygen, to name a few—signal the cell to speed up its assembly of autophagosomes. Hence, when nutrients are scarce, autophagy intensifies; autophagosomes scavenge the cytoplasm for proteins and organelles (regardless, it seems, of their functional status) that can be digested into nutrients and energy the cell can use.

If autophagy evolved, in part, as a response to starvation, its housekeeping function—even when nutrients abound—has long since become just as vital to the cell. Autophagosomes help to rid the cell of various kinds of unwanted denizens of the cytoplasm. Proteins, for instance, which carry out all the work of the cell, are sometimes put together incorrectly, and they can "wear out" with time. As a result, they may not function or, worse, may malfunction. If so, they must be culled before they cause a problem. Continuous autophagy keeps their concentrations at a low level.

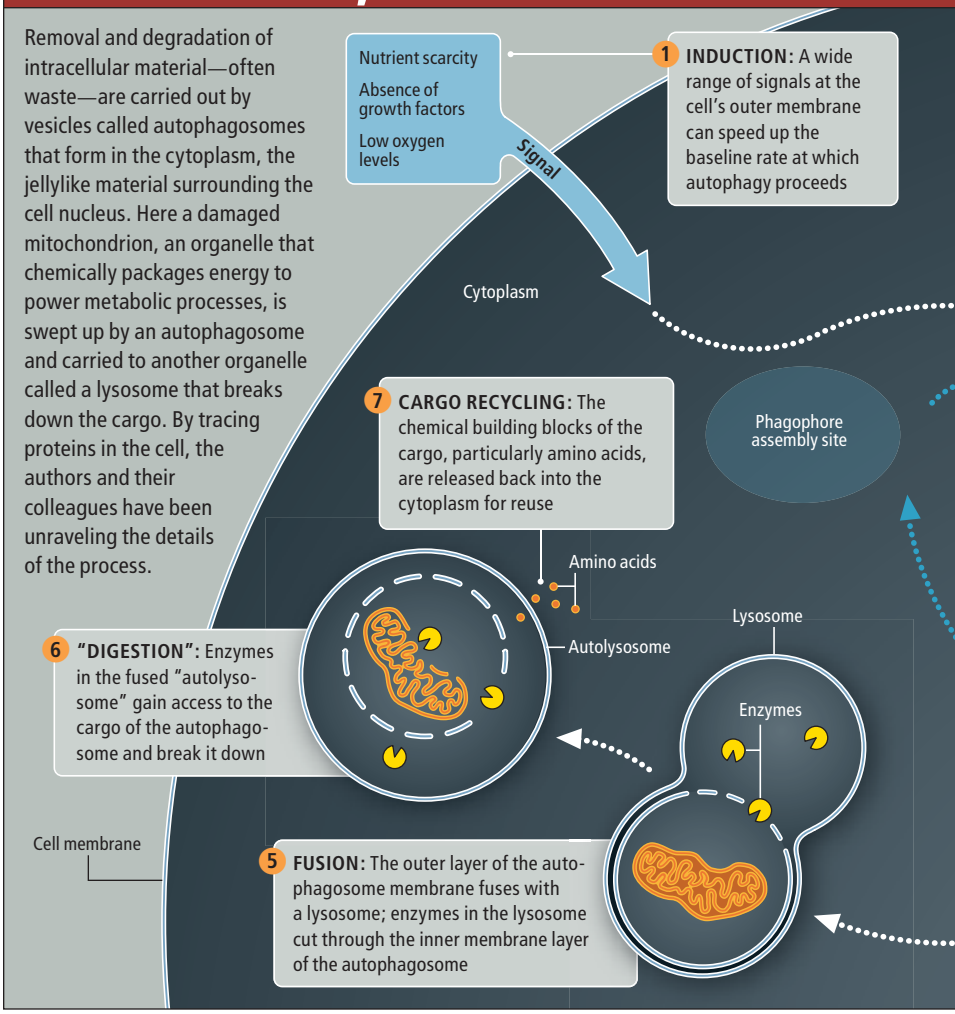
Autophagosomes not only remove damaged proteins, but they also seek out and sequester damaged organelles many times the size of a protein. Mitochondria, for instance, are the organelles primarily responsible for generating energy within a cell, and they can send signals to other parts of the cell that initiate apoptosis, or cellular suicide.

Cells induce apoptosis for a variety of reasons, all more or less for the greater good of the organism. For example, the body continu-

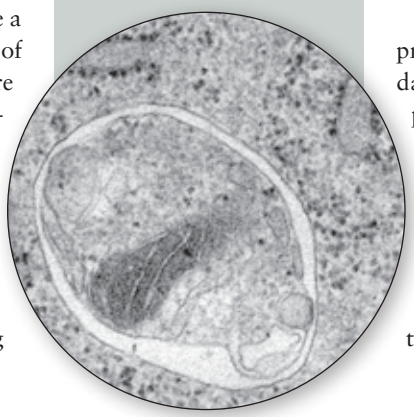
[HOW IT WORKS]

AUTOPHAGY, STEP BY STEP

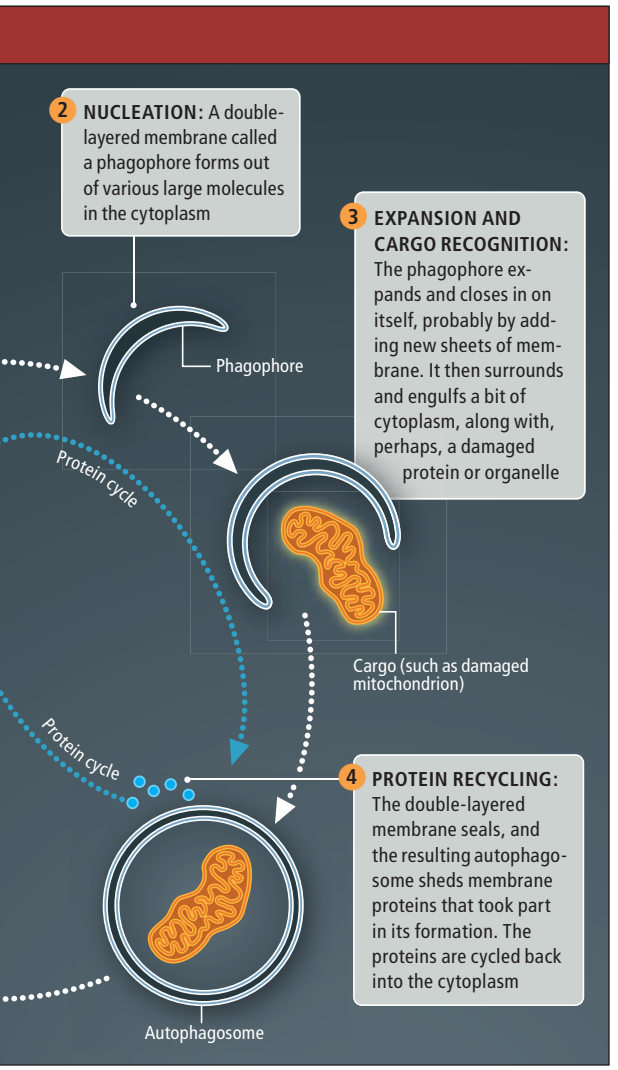
Removal and degradation of intracellular material—often waste—are carried out by vesicles called autophagosomes that form in the cytoplasm, the jellylike material surrounding the cell nucleus. Here a damaged mitochondrion, an organelle that chemically packages energy to power metabolic processes, is swept up by an autophagosome and carried to another organelle called a lysosome that breaks down the cargo. By tracing proteins in the cell, the authors and their colleagues have been unraveling the details of the process.



AUTOPHAGOSOME bounded by a double membrane has engulfed a mitochondrion, visible as the dark region inside the autophagosome. The image is magnified 35,000×.



EEVA-LIISA ESKELINEN (*electron micrograph*)



ally generates more cells than it needs, and they must be eliminated. An aging cell that has ceased functioning efficiently may kill itself to make room for younger, more robust cells. A cell that switches from normal growth to cancerous proliferation can also be induced to commit suicide, making apoptosis one of the most important built-in barriers against cancer. Apoptosis depends on a complex series of cellular events, rigorously orchestrated by numerous protein signals, and so the death of the cell by apoptosis is considered to be a programmed event.

But a faulty mitochondrion can wreak havoc if it sets off apoptosis at the wrong time [*see box on next page*]. Among the by-products of a functioning mitochondrion are reactive oxygen species (ROS)—oxygen ions and other oxygen-based molecular fragments. Working with such volatile chemicals often causes mitochondria to leak some of their contents, including the signaling proteins that initiate apoptosis. In other words, a minor flaw in a small part of the cell can lead, inadvertently, to the death of the entire cell. The accidental cellular demise of a few skin cells might not be a big deal, but such a loss of memory neurons in the brain would definitely spell trouble.

Autophagy is a fail-safe against such a destructive mistake. Autophagosomes can remove damaged mitochondria and other kinds of organelles from the cytoplasm and ensure that they are destroyed by lysosomal enzymes in an autolysosome before they can induce an unscheduled programmed cell death—or, worse, the disorganized cellular demise known as necrosis.

Mitochondria can also release ROS into the cytoplasm, which, as the name "reactive oxygen species" implies, tend to react with many other molecules. In a healthy cell ROS levels are kept under control by antioxidant molecules that scavenge ROS. According to Shengkan V. Jin of the University of Medicine and Dentistry of New Jersey, however, when mitochondria become damaged, they can flood the cell with 10 times the usual release of ROS, much more than normal cellular detoxification systems can handle. The escape of such large amounts of ROS poses a cancer threat, because ROS that reach the nucleus may induce malignant changes in genes. Once again, autophagy can come to the rescue, removing the dysfunctional mitochondria from the cell. Eileen White of Rutgers University believes that autophagy also mitigates genome damage in cancer cells, thereby helping to prevent new tumors from forming.

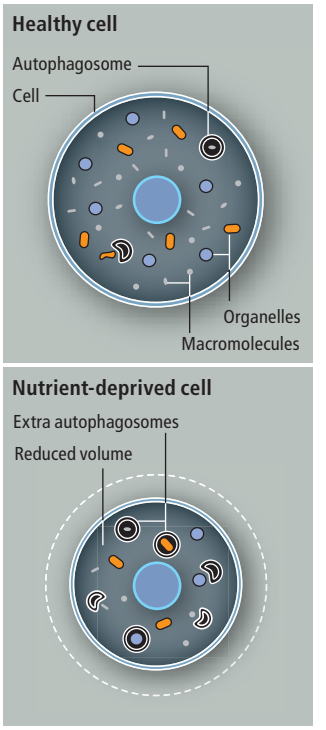
Double-Edged Sword

Soon after cell biologists unraveled the intricate molecular pathways of apoptosis, they recognized that cells can kill themselves by other means as well. Autophagy became a prime suspect. Current nomenclature reflects that history: apoptosis is also known as programmed cell death type I; autophagy is sometimes referred to as programmed cell death type II—although that designation remains controversial.

Autophagy could lead to cell death in two ways: the process might simply continue digesting the contents of the cytoplasm until the cell dies, or it may stimulate apoptosis. But why would a process that often prevents untimely cell death from accidental apoptosis sometimes be invoked to cause cell death itself? The puzzle may turn out to have a fascinating resolution. Apoptosis and autophagy may be closely interrelated and carefully balanced. For

SURVIVING STARVATION

Autophagosomes are constantly consuming parts of the cytoplasm, but nutrient scarcity boosts their baseline number. That increase speeds up the rate at which intracellular components, including intact proteins and other macromolecules, are digested by autolysosomes into basic biochemical building blocks that are delivered to the cytoplasm as nutrients. The nutrient scarcity also signals the cell to reduce its functioning volume (schematically portrayed here as shrinkage). Without such literal "self-eating," the essential activities of the cell could not continue and the cell would die.



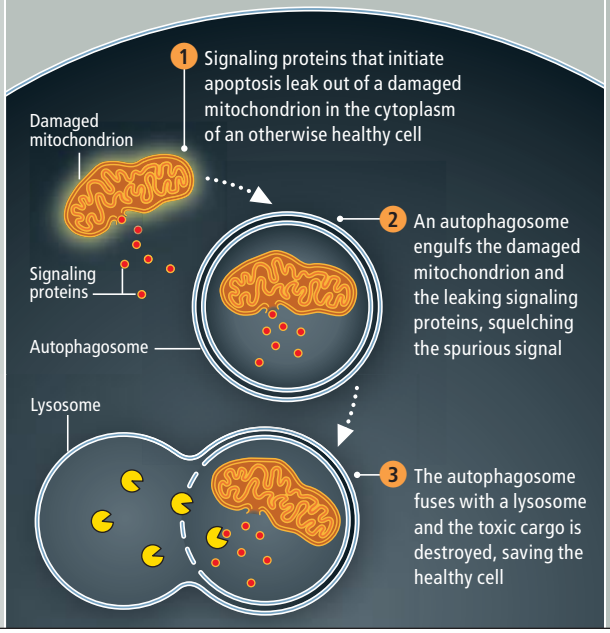
JEN CHRISTIANSEN

[LIVE OR LET DIE?]

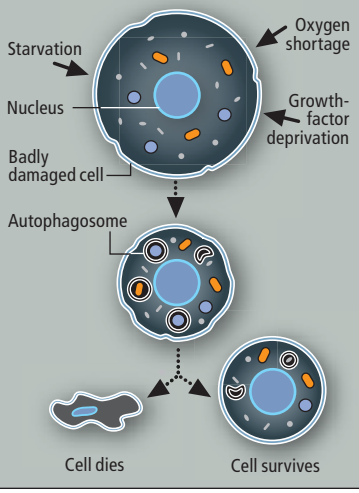
MAKING THE ULTIMATE DECISION

The last act of a badly damaged cell can be to trigger its own death for the greater good of the organism. One suicidal pathway called apoptosis begins when mitochondria in the cytoplasm release signaling proteins. Some investigators have proposed that autophagy can act to save the cell from unnecessary apoptosis (*center panel*). Paradoxically, autophagy may also act as a second suicidal pathway when cell death is needed but apoptosis fails (*right panel*). Moreover, apoptosis and autophagy share certain kinds of signaling proteins, suggesting that the two processes engage in cross talk and may best be regarded as parts of a more comprehensive system within the cell.

AUTOPHAGY AS SAFETY NET: A damaged mitochondrion can send a spurious signal for the cell to begin apoptosis, even though the cellular damage is minimal. Autophagy can prevent the signal from causing unnecessary cell suicide.



AUTOPHAGY AS "DECIDER": In a badly damaged cell the system for triggering cell suicide responds dynamically to signals of stress. In the end, autophagy may throttle down, enabling the cell to survive; continue devouring the cell from the inside until it dies; signal for cell suicide by apoptosis (*not shown*); or, if apoptosis fails, serve as a suicidal backup to prevent the disorganized cell demise known as necrosis (*not shown*).



example, if organelle damage is too extensive for autophagy to bring under control, the cell must die for the sake of the entire organism. The cell may then rely on either of its suicide programs: it may allow autophagy to continue to the end, or it can signal for apoptosis, holding autophagy as a backup system if apoptosis is compromised. Two of the most intense and somewhat controversial areas of current investigation are how autophagy and apoptosis interconnect and whether autophagy on its own should be considered a pathway for cell death.

Work at the molecular level may help resolve whether autophagy is primarily a pathway for cell survival or whether it can, in addition, act as an "angel of death." Recent studies by Beth Levine of the University of Texas Southwestern Medical Center at Dallas and Guido Kroemer of the French National Scientific Research Center (CNRS) have shown how the two processes can be coordinated. One of the proteins that signals for autophagy to begin, known as Beclin 1, binds with a protein that prevents apoptosis from starting, Bcl-2. Life-and-death decisions are made as bonds between the two kinds of proteins are enhanced or broken. Levine's findings of that connection between autophagy and apoptosis have been further supported by the discovery that a fragment of a protein known as Atg5, which plays a leading role in the formation of autophagosomes, can make its way to mitochondria. Once there Atg5 can switch what was initially a purely autophagic response to an apoptotic one.

Every benefit seems to have its flaws, and autophagy is no exception. We noted earlier that cancer cells can sometimes invoke autophagy to save themselves. Anticancer treatments are often aimed at inducing malignant cells to commit suicide. Yet some cancer cells can defend against the treatments because autophagy jumps in to remove damaged mitochondria before they can trigger apoptosis. In fact, radiation and chemotherapy can actually induce higher-than-usual levels of autophagy.

Cancer cells can also take advantage of autophagy to avoid being starved. Few nutrients can reach the inside of a tumor, but as we mentioned earlier, a shortage of nutrients can trigger autophagy, prolonging the life of a cancer cell by enabling it to break down its own macromolecules for food. A straightforward treatment strategy might therefore be to suppress autophagy within a tumor or during radiation therapy or chemotherapy. Drugs for that purpose are in clinical trials. Unfortunately, as White points out, suppressing autophagy could boost the number of genetic mutations in can-

Does autophagy contribute mainly to cell survival—or does it also act as an "angel of death"?

JEN CHRISTIANSEN

cer cells and so increase the chances of a relapse. It may take some fine-tuning to get the treatments right.

Preventing Neuron Breakdown

Given the role of autophagy in keeping the cytoplasm clear of detritus and malfunctioning parts, it is hardly surprising that the process turns out to be particularly important to the well-being of long-lived cells such as neurons. Inefficient autophagy plays a pivotal role in neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. All three cause slow but inexorable changes in the brain, but Alzheimer's, a form of dementia that afflicts 4.5 million people in the U.S. alone, is the most common.

One of the most frequent effects of normal aging is the accumulation of a brownish material called lipofuscin, a mix of lipids and proteins, in the bodies of brain cells. Superficially, the stuff can be likened to liver spots on aging skin. The accumulation of such material, according to Ralph A. Nixon of the Nathan S. Kline Institute for Psychiatric Research, is a sign that aging brain cells can no longer remove abnormally modified or damaged proteins fast enough to keep pace with their buildup. In Alzheimer's patients, a yellowish or brownish pigment called ceroid also builds up inside neurites, or projections from nerve cell bodies. The neurites swell where ceroid collects, and amyloid, or senile, plaques characteristic of the disease form on the outside of the swollen neurites.

So far investigators have not fully deciphered the exact ways senile plaques or their precursors lead to neuron damage. But the latest research shows, tellingly, that enzymes that help to deposit the plaques in certain early-onset forms of Alzheimer's are present on the membranes of autophagosomes. According to Nixon, such plaques may stem in part from incomplete autophagy and the consequent failure of the neurons to digest substances that would normally be swept up from their cytoplasm, broken down and recycled for parts [*see box at right*]. Supporting Nixon's conclusion, electron micrographs of senile plaques in the brains of Alzheimer's patients show massive numbers of immature autophagosomes accumulating inside the parts of the neurons nearest the plaques. Precisely how the plaque material may collect on the outside of nerve cells has not been conclusively traced.

Given those results, it would seem that any means of promoting autophagy might slow the onset of the debilitating symptoms of Alzheimer's. Regretfully, however, no one yet knows whether activating autophagy in Alzheimer's patients would have any benefit, if the treatment cannot also ensure that autophagosomes fuse with lysosomes. But the good news is that such a treatment might be effective for Huntington's patients. A drug known as rapamycin, or sirolimus, which suppresses immunity and is used to block the rejection of organ transplants, particularly kidney transplants, turns out to induce autophagy as well. Rapamycin is now being tested for its effectiveness in stimulating autophagy to remove a kind of protein aggregate seen in Huntington's patients.

Getting Bugs Out of the System

If an autophagosome can capture and destroy a leaky, cell-endangering mitochondrion, couldn't it do the same to unwanted parasites that invade the cellular interior—bacteria, protozoa and viruses that manage to get through the cell membrane? In fact, that hypothesis was recently verified experimentally. Taken together, studies by one of us (Deretic) and, nearly simultaneously, by two groups in Japan, one led by Tamotsu Yoshimori of Osaka University, the other by Chihiro Sasakawa of the University of Tokyo, have shown that autophagy can eliminate a diverse range of pathogens. The list includes

[THE AUTHORS]

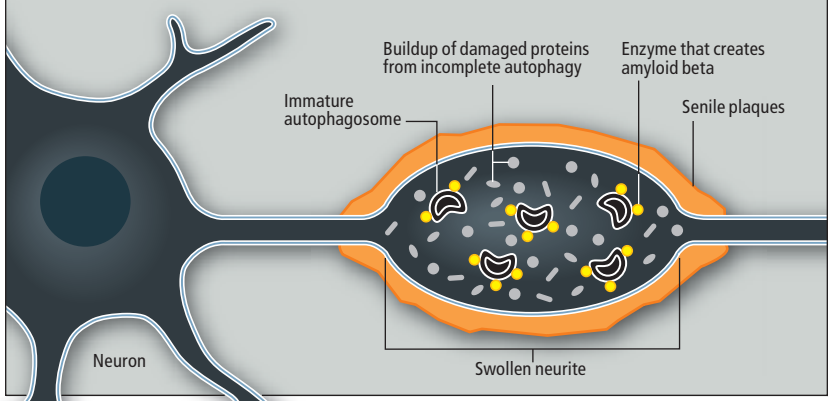
Vojo Deretic (*left*) **is a professor and chair of the molecular genetics and microbiology department at the University of New Mexico Health Sciences Center; he also holds a joint appointment there as a professor of cell biology and physiology. He was educated in Belgrade, Paris and Chicago. Deretic is fascinated with autophagy both as a fundamental biological process and as an effector of innate and adaptive immunity.**

Daniel J. Klionsky (*right*) **is Alexander G. Ruthven Professor of Life Sciences at the University of Michigan Life Sciences Institute. He is a former fellow of the John Simon Guggenheim Memorial Foundation, a National Science Foundation Distinguished Teaching Scholar and editor in chief of the journal *Autophagy*.**

[AUTOPHAGY IN ALZHEIMER'S?]

WHEN THE CLEANING STOPS

In an aging brain neuron, autophagosomes can fail to complete their development, leading to a buildup of damaged proteins and consequent swelling in a neurite, or projection from the cell body of the neuron. The immature autophagosomes collect at the same site. Enzymes (*yellow*) that create protein fragments called amyloid beta seem to concentrate on the immature autophagosomes, and those fragments collect on the outer neurite surface (*orange*). Aggregates of amyloid beta are the so-called senile plaques characteristic of neurons in the brains of Alzheimer's patients. Together those findings suggest that a breakdown in autophagy may contribute to Alzheimer's disease.



JEN CHRISTIANSEN; COURTESY OF VOJO DERETIC (*Deretic*); COURTESY OF DANIEL J. KLIONSKY (*Klionsky*)

Mycobacterium tuberculosis, the tuberculosis bacterium annually responsible for two million deaths worldwide; gut pathogens such as *Shigella* and *Salmonella;* group A streptococci; *Listeria*, which occurs in raw-milk cheeses; *Francisella tularensis*, which the Centers for Disease Control and Prevention has listed as a bioterrorism agent; and parasites such as *Toxoplasma gondii*, which is a major cause of illness in people with AIDS.

Yet just as cancer cells can exploit autophagy for their own survival, some microorganisms have evolved ways to subvert the process. For example, *Legionella pneumophila*, which causes Legionnaires' disease, is a bacterium that readily gets inside a cell. But if *L. pneumophila* bacteria are engulfed by an autophagosome, they can delay or even prevent the autophagosome from fusing with a lysosome. Thus instead of serving as a vehicle that helps to rid the cell of a pathogen, the infected organelle becomes a niche where the bacteria can replicate, using the sequestered cytoplasm as a nutrient supply.

The very existence of such clever evolutionary tactics is good evidence that autophagy has long functioned as a major barrier to invasion by pathogens and their replication in human cells—a barrier that disease-causing agents must overcome to survive. Not surprisingly, HIV is another good example of a pathogen that can harness autophagy for its own purposes. Two groups in France, one led by Martine Biard-Piechaczyk of the Center for Studies of Pathogenic Agents and Biotechnologies for Health and the other by Patrice Codogno of INSERM, have jointly shown that HIV, which infects immune system cells known as CD4+ T cells, can increase cell death in uninfected "bystander" cells of the same kind. As HIV enters a cell, it sheds its outer envelope, and the protein that makes up the envelope induces uncontrolled, excess autophagy and then apoptosis in cells that surround the HIV-infected cell. Thus by activating autophagy in "innocent" bystander cells, HIV further reduces the number of healthy CD4+ T cells in the body. Eventually the catastrophic loss of immune system cells brings about full-blown AIDS.

Some microorganisms have learned to subvert autophagy. HIV can even accelerate the process in neighboring immune system cells, causing them to commit suicide.

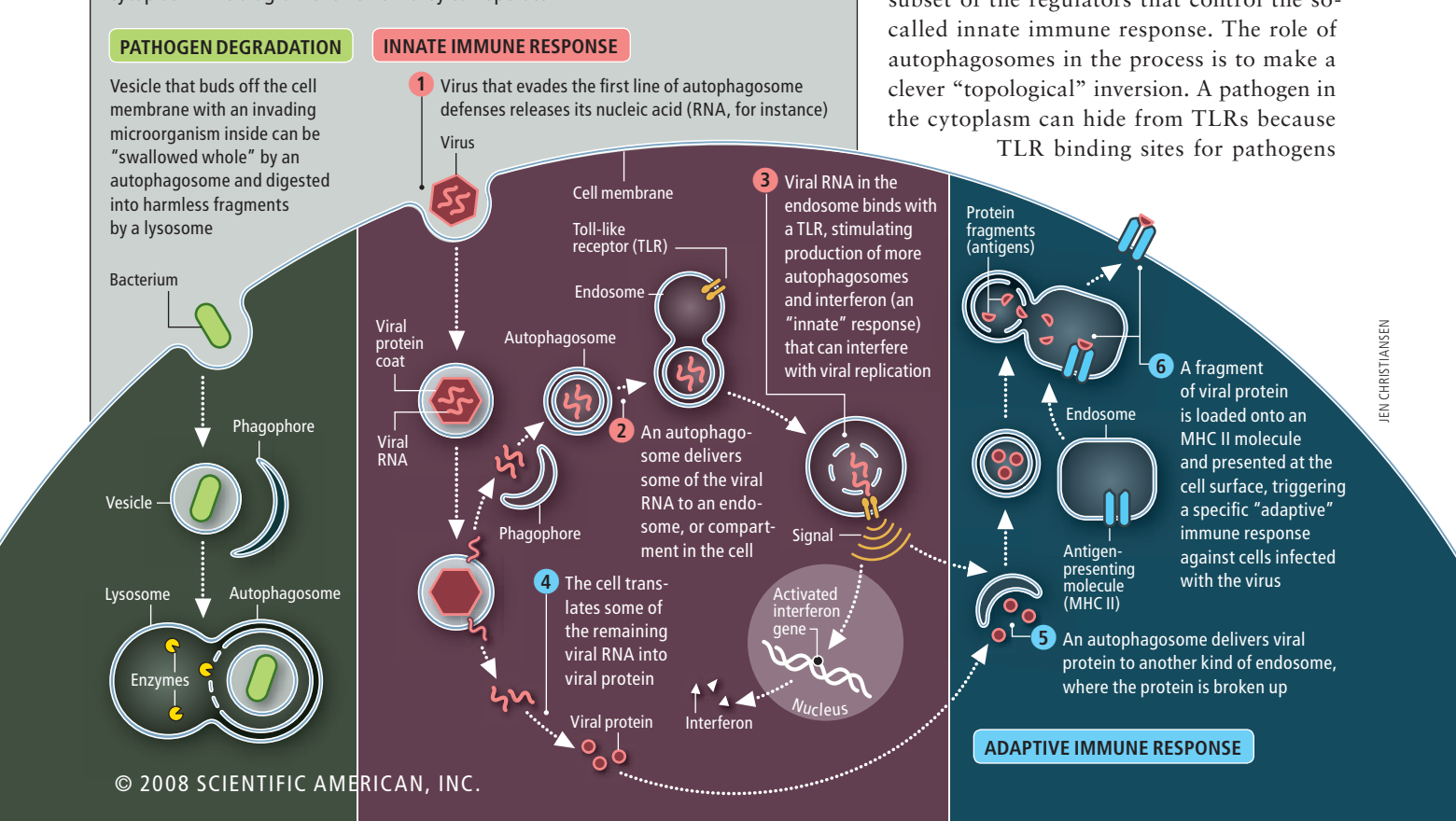
The Immune Connection

Autophagy not only eliminates pathogens directly; investigators have also found that it takes part in immune responses [*see box below*]. For example, autophagosomes help to deliver pathogens or pathogen products to membrane molecules called toll-like receptors (TLRs), a subset of the regulators that control the so-called innate immune response. The role of autophagosomes in the process is to make a clever "topological" inversion. A pathogen in the cytoplasm can hide from TLRs because TLR binding sites for pathogens

[CELL DEFENSE]

REPELLING INVADERS

Autophagy can mount several kinds of defenses against pathogens that enter the cytoplasm. The diagram shows how they can operate.



JEN CHRISTIANSEN

face away from the cytoplasm. The binding sites point either toward the space outside the cell or toward the inside of an endosome, or intracellular compartment. But autophagosomes can fix this topological problem by scooping up pathogens or their parts from the cytoplasm and delivering them to an endosome that embeds TLRs in its membrane. There the pathogen molecules meet TLRs at last. Their encounter signals the cell to produce chemicals called interferons, which act, for instance, to suppress the replication of the pathogen. This innate immune response is generated to combat infection as soon as it starts—no time is needed for the cell to build a highly specific response to the pathogen.

But autophagosomes can also help build that highly specific immune response, known as adaptive immunity. For example, when a virus invades the cytoplasm and tricks the cell into making viral protein, an autophagosome engulfs some of the viral protein and ushers it into another kind of endosome that embeds so-called MHC class II molecules in its membrane. Once inside that endosome, the viral protein is partly broken up, and a piece of it is loaded onto a part of an MHC class II molecule that faces the inside of the endosome. (Just as with the TLR, the MHC class II molecule would not meet properly with the pathogen molecule if the autophagosome did not bring the pathogen molecule inside the endosome.) Once the MHC class II molecule is bound to the pathogen fragment and the assemblage is transported to the surface of the cell, the immune system begins mounting an adaptive immune response, a slower but far more specific and more efficient response than innate immunity can muster.

Long Life?

Remarkably, autophagy may also play a role in determining the human life span. Most people take it for granted that many diseases become more frequent with age, including cancer and the degeneration of neurons. The reason, in part, may be a decline in the efficiency of autophagy. According to Ana Maria Cuervo of the Albert Einstein College of Medicine, the current thinking is that cellular systems, including autophagy, undergo a steady loss of function with age. In particular, the systems that remove aberrant or dysfunctional proteins and organelles begin to work less efficiently, and the resulting buildup of damaged cellular components leads to disease.

[AUTOPHAGY IN MEDICINE]

NEW WEAPONS AGAINST DISEASE

Intensifying, suppressing or otherwise manipulating autophagy in specific kinds of cells could become a powerful part of the medical arsenal. Here are just a few examples of the potential treatment options.

DISEASE	STRATEGY	GOALS
Cancer	Inhibit autophagy in cells of cancerous tumors	Help to prevent tumor cells from consuming the contents of their own cytoplasm, thereby surviving in oxygen- or nutrient-starved environments
Cancer	Enhance autophagy in cells at risk of cancer	Lower the chances that mutations and secondary tumors will arise when too little autophagy enables DNA-damaging molecules to accumulate in the cell
Huntington's disease	Enhance autophagy with drug rapamycin (sirolimus)	Help to remove toxic microaggregates of proteins that accumulate in nerve cells
Tuberculosis	Enhance autophagy	Kill disease-causing agents that hide in the cytoplasm, both in people who are sick and in carriers who are symptom-free

If inefficient autophagy is to blame, Cuervo says, that could help explain why caloric restriction has been found to extend average life spans in several kinds of experimental animals. The less food such animals eat (provided they get an adequate supply of essential nutrients), the longer they live, and the same may be the case for people. Recall that a restricted food supply—incipient starvation—speeds up autophagy. Hence, caloric restriction as one ages might offset the natural age-related decline of autophagy and so prolong the essential housekeeping function of the process in cells. Furthermore, Cuervo adds, recent research shows that if you can prevent the decline of autophagy in experimental animals, you can often avoid the usual age-related buildup of proteins damaged by reactions with oxygen compounds.

What was once seen primarily as a hedge against cellular starvation has come to be recognized as central to a broad range of factors affecting human health and disease. Research into autophagy is expanding in new and unexpected directions, generating an exponentially increasing body of scientific knowledge. But we have only begun. Learning to promote or inhibit autophagy at will holds great promise for the treatment of disease and perhaps even for slowing down the natural process of aging. But whether autophagy can be harnessed to benefit health, much less to become the elusive fountain of youth, will depend on gaining a fuller understanding of its mechanisms and of the intricate biochemical signals on which it depends. ■

MORE TO EXPLORE

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HOOKED FROM THE FIRST CIGARETTE

New findings reveal that cigarette addiction can arise astonishingly fast. But the research could lead to therapies that make quitting easier By Joseph R. DiFranza

KEY CONCEPTS

- New research has overturned the dogma that cigarette addiction takes years to develop. Studies of adolescent smokers show that symptoms of addiction, such as withdrawal, craving for cigarettes and failed attempts at quitting, can appear within the first weeks of smoking.
- To account for these findings, scientists have developed a new theory positing that the brain quickly develops adaptations that counter the effects of nicotine. These adaptations lead to withdrawal symptoms when the effects of nicotine wear off.
- The results highlight the importance of boosting government funding for antismoking campaigns, particularly those aimed at youngsters.

—The Editors

While I was training to become a family doctor, I learned the conventional wisdom about nicotine addiction. Physicians have long believed that people smoke primarily for pleasure and become psychologically dependent on that pleasure. Tolerance to the effects of nicotine prompts more frequent smoking; when the habit reaches a critical frequency—about five cigarettes per day—and nicotine is constantly present in the blood, physical dependence may begin, usually after thousands of cigarettes and years of smoking. Within hours of the last cigarette, the addicted smoker experiences the symptoms of nicotine withdrawal: restlessness, irritability, inability to concentrate, and so on. According to this understanding, those who smoke fewer than five cigarettes per day are not addicted.

I was armed with this knowledge when I encountered the proverbial patient who had not read the textbook. During a routine physical, an adolescent girl told me she was unable to quit smoking despite having started only two months before. I thought this patient must be an outlier, a rare exception to the rule that addiction takes years to develop. But my curiosity was piqued, so I went to the local high school to interview students about their smoking. There a 14-year-old girl told me that she had made two serious attempts to quit, failing both times. This was eye-opening because she had smoked only a few cigarettes a week for two months. When she described her withdrawal symptoms, her story sounded like the lament of one of my two-pack-a-day patients. The rapid onset of these symptoms in the absence of daily smoking contradicted most of what I thought I knew about nicotine addiction. And when I tracked that received wisdom back to its source, I found that everything I had learned was just a poor educated guess.

With funding from the National Cancer Institute and the National Institute on Drug Abuse (NIDA), I have spent the past decade exploring how nicotine addiction develops in novice smokers. I now know that the model of addiction described in the opening paragraph is fiction. My research supports a new hypothesis asserting that limited exposure to nicotine—as little as one cigarette—can change the brain, modifying its neurons in a way that stimulates the craving to smoke. This understanding, if proved correct, may someday provide researchers with promising avenues for developing new drugs and other therapies that could help people kick the habit.

A Loss of Autonomy

When I started this investigation in 1997 with my colleagues at the University of Massachusetts Medical School in Worcester, our first challenge was to develop a reliable tool to detect the first symptoms of addiction as they emerged. In my view, the defining feature of addiction is

the loss of autonomy, when the smoker finds that quitting cigarettes requires an effort or involves discomfort. To detect this loss, I devised the Hooked on Nicotine Checklist (HONC); an answer of "yes" to any of the questions on the list indicates that addiction has begun [*see side bar on page 86*]. Now in use in 13 languages, the HONC is the most thoroughly validated measure of nicotine addiction. (And the checklist could easily be adapted to the study of other drugs.)

We administered the HONC to hundreds of adolescents repeatedly over three years. It turned out that the rapid onset of addiction was quite common. The month after the first cigarette was by far the most likely time for addiction to begin; any of the HONC symptoms, including cravings for cigarettes and failed attempts at quitting, could appear within the first weeks of smoking. On average, the adolescents were smoking only two cigarettes a week when the first symptoms appeared. The data shattered the conventional wisdom and provided a wealth of insight into how addiction starts. But when I presented these

ADOLESCENTS can become addicted to cigarettes just weeks after beginning to smoke. One study showed that, on average, the youngsters were smoking only two cigarettes a week when the first symptoms of addiction appeared.

DAVID EMMITE

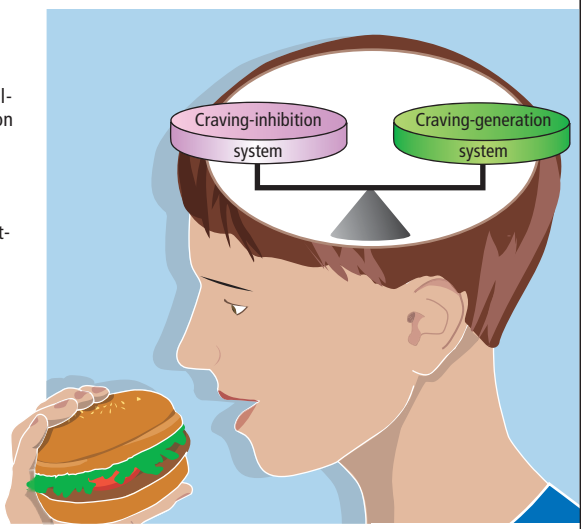
[A NEW HYPOTHESIS]

QUICK ADDICTION

Researchers have proposed a new theory to explain how withdrawal symptoms can develop so quickly in novice smokers. Although this model is controversial, it may someday lead to a better understanding of cigarette addiction.

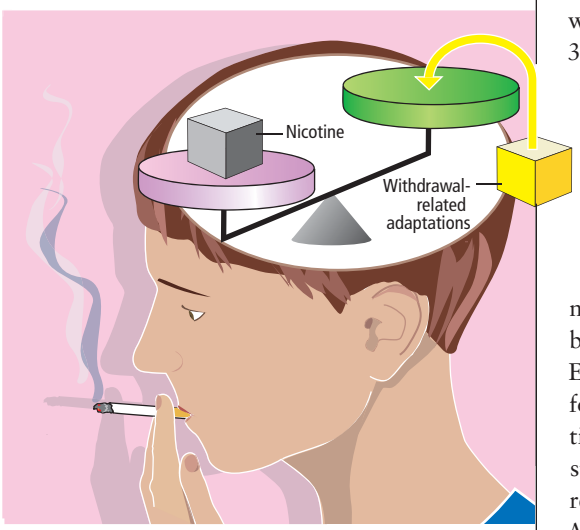
A HEALTHY BALANCE

In nonsmokers, the brain's systems for generating and inhibiting cravings are in balance. The craving-generation system triggers appetitive behavior (such as eating), and the craving-inhibition system stops the behavior when the individual is satiated (at the end of the meal).



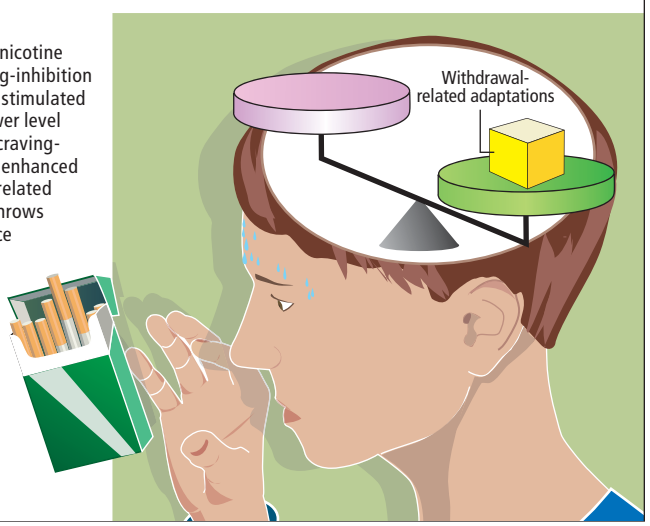
THE FIRST CIGARETTE

Nicotine stimulates the craving-inhibition system until its activity far exceeds that of the craving-generation system. The brain attempts to restore its balance by rapidly developing adaptations that boost the activity of the craving-generation system. (These changes are called withdrawal-related adaptations.)



WITHDRAWAL

Once the effects of nicotine wear off, the craving-inhibition system is no longer stimulated and returns to a lower level of activity. But the craving-generation system, enhanced by the withdrawal-related adaptations, now throws the brain off-balance again, producing an intense desire for the one thing that can inhibit the craving—another cigarette.



findings in February 2000 and proclaimed that some youths had symptoms of addiction after smoking just one or two cigarettes, I was widely regarded as the professor who had not read his textbook correctly.

Many laypeople told me that they knew from experience that I was on the right track. But if any scientists believed me, they were not willing to risk their reputations by admitting it publicly. Skepticism was widespread. How could addiction start so quickly? How could withdrawal symptoms be present in smokers who do not maintain constant blood levels of nicotine?

Vindication has come with time as teams of investigators led by Jennifer O'Loughlin of McGill University, Denise Kandel of Columbia University and Robert Scragg of the University of Auckland in New Zealand replicated all of my discoveries. A dozen studies have now established that nicotine withdrawal is common among novice smokers. Of those who experience symptoms of addiction, 10 percent do so within two days of their first cigarette and 25 to 35 percent do so within a month. In a very large study of New Zealand youths, 25 percent had symptoms after smoking one to four cigarettes. And the early appearance of HONC symptoms increased the odds that the youths would progress to daily smoking by nearly 200-fold.

These results raise the question of how the nicotine from a single cigarette could alter the brain enough to trigger the onset of addiction. Earlier research with laboratory animals has found that chronic high-dose exposure to nicotine—the equivalent of one to three packs a day—stimulates an increase in the number of neuron receptors that have a high affinity for nicotine. Autopsies of human smokers reveal 50 to 100 percent increases in the brain's frontal lobe, hippocampus and cerebellum.

I persuaded Theodore Slotkin of Duke University to determine the minimum nicotine exposure needed to provoke this so-called up-regulation of receptors. On consecutive days his team administered small amounts of nicotine (equivalent to one to two cigarettes) to rats and found up-regulation in the hippocampus—which is involved in long-term memory—by the second day. Subsequently, Arthur Brody and his colleagues at the University of California, Los Angeles, discovered that the nicotine from one cigarette was sufficient to occupy 88 percent of the brain's nicotinic receptors. Although the role of receptor up-regulation in addiction

LISA APFELBACHER

is unknown, these studies make it physiologically plausible that adolescents could have withdrawal symptoms just two days after their first cigarette.

According to addiction researchers, withdrawal symptoms result from drug-induced homeostatic adaptations—the body's attempts to keep its functions and chemicals in balance. For example, certain addictive drugs increase the production of neurotransmitters—chemicals that transmit signals among neurons—and in response the body develops adaptations that inhibit these chemicals. When the user stops taking the drug, however, the inhibition becomes excessive and withdrawal symptoms appear. We know that these withdrawal-related adaptations could develop rapidly after the first cigarette, because other addictive drugs such as morphine produce similar changes very quickly. But most longtime smokers find they can forgo cigarettes for only an hour or two before craving another, whereas novice smokers can go weeks without lighting up. Amazingly, in the early stages of addiction a single cigarette can suppress withdrawal symptoms for weeks, even though the nicotine is gone from the body within a day.

The explanation for this remarkable fact is that the consequences of flooding the brain with nicotine linger long after the event itself. Nicotine triggers brain circuits involving biochemical compounds such as acetylcholine, dopamine, GABA, glutamate, noradrenaline, opioid peptides and serotonin. In rats, a single dose of nicotine increases noradrenaline synthesis in the hippocampus for at least one month, and nicotine's effects on certain neurological and cognitive functions also persist for weeks. Although it is not known if any of these phenomena are related to withdrawal, they establish that the impact of nicotine far outlasts its presence in the brain.

The symptom-free interval between the last cigarette and the onset of withdrawal is called the latency to withdrawal (LTW). For novice smokers the LTW is long, and a cigarette every few weeks keeps withdrawal in check. With repeated use, however, tolerance develops and the impact of each cigarette diminishes; the LTW shortens, and cigarettes must be spaced at ever closer intervals to stave off withdrawal. This phenomenon of diminishing LTW is called dependence-related tolerance. Compared with the withdrawal-related adaptations that may appear overnight, dependence-related tolerance typically develops at a glacial pace. It may take years for the LTW to shrink enough to require someone to smoke five cigarettes a day. In reality, then, withdrawal symptoms are the cause of long-term heavy use, not the other way around as we had previously thought.

A NICOTINE GLOSSARY

Nicotine withdrawal: A cluster of symptoms that include craving, restlessness, nervousness, irritability, difficulty concentrating and difficulty sleeping.

Latency to withdrawal: The symptom-free interval between the last cigarette and the onset of withdrawal symptoms. It can shrink from weeks to minutes over many years of tobacco use.

Dependence-related tolerance: The mechanism that causes the latency to withdrawal to shrink gradually over time.

Abstinence-related adaptations: A mechanism that mimics the action of nicotine by inhibiting craving. It develops in ex-smokers to counter the enduring effects of dependence-related tolerance.

[THE AUTHOR]

Joseph R. DiFranza is a family physician practicing out of the University of Massachusetts Medical School in Worcester. A perennial thorn in the side of the tobacco industry for 25 years, DiFranza has been an advocate for efforts to prevent the tobacco industry from selling its products to children, and it was his research and complaint to the Federal Trade Commission that resulted in the demise of the notorious Joe Camel advertisements for Camel cigarettes. DiFranza has received a grant from Pfizer to determine whether his theory of cigarette addiction explains the effectiveness of smoking-cessation medications.

Time for a New Theory

I had always been skeptical of the notion that smokers were addicted to the pleasure of smoking, because some of my most addicted patients hated the habit. If the conventional thinking were correct, shouldn't the most addicted smokers enjoy it the most? Eric Moolchan of the NIDA demonstrated that although adolescents showed increasing levels of addiction over time, they reported decreasing pleasure from smoking. A new theory was needed to explain these discoveries.

While struggling to understand the rapid onset of nicotine addiction, a paradox occurred to me. The only action of nicotine that is obvious to the casual observer is that it provides a temporary suppression of craving for itself, yet only people previously exposed to nicotine crave it. How can one drug both create craving and suppress it? I began to speculate that the direct immediate action of nicotine is to suppress craving and that this action could become magnified to an extreme because subsequent doses of nicotine provoke greater responses than the first dose. (This phenomenon, common to all addictive drugs, is known as sensitization.) The brain might then quickly develop withdrawal-related adaptations to counter the action of nicotine, thereby restoring the homeostatic balance. But when the action of nicotine wore off, these adaptations would stimulate craving for another cigarette.

Under this sensitization-homeostasis theory, nicotine is addictive not because it produces pleasure but simply because it suppresses craving. Because nicotine stimulates neurons, I envisioned it activating the nerve cells in a craving-inhibition system in the brain. Activation of this hypothesized system would then suppress the activity in a complementary system for generating cravings. The natural role of the craving-generation system would be to receive sensory cues (such as sights and smells), compare them with memories of rewarding objects (such as food), and produce craving to motivate and direct appetitive behavior (such as eating). The role of the craving-inhibition system would be to signal satisfaction so that the animal would

COURTESY OF JOSEPH R. DIFRANZA (*DiFranza*)

stop the appetitive behavior when it became appropriate to do so.

Because the body would try to keep these two systems in balance, the nicotine-induced suppression of the craving-generation system would trigger the development of withdrawal-related adaptations that would boost the system's activity. During the withdrawal period, when the inhibitory effect of nicotine has worn off, the craving-generation system would be left in a state of excitement that would result in the excessive desire for another cigarette [*see box on page 84*]. These shifts in brain activity would come about through rapid changes in the configurations of neuron receptors, which would explain why adolescents could start to crave cigarettes after smoking just once.

The first support for this model has come from the many functional magnetic resonance imaging (fMRI) studies of humans showing that cue-induced craving for nicotine, alcohol, cocaine, opiates and chocolate increases metabolic activity in the anterior cingulate gyrus and other frontal-lobe areas of the brain. This finding suggests the existence of a craving-generation system. And Hyun-Kook Lim and his colleagues at the Korea College of Medicine recently found evidence that nicotine suppresses this system. The researchers demonstrated that prior administration of the drug can block the pattern of regional brain activation that accompanies cue-induced craving in humans.

The sensitization-homeostasis model can also explain dependence-related tolerance. Repeated suppression of activity in the craving-generation system triggers another homeostatic adaptation that stimulates craving by shortening the duration of nicotine's inhibitory effects. As mentioned earlier, tolerance develops much more slowly than the withdrawal-related adaptations, but once it emerges tolerance becomes firmly entrenched. Although it usually takes two years or more before adolescents need to smoke five cigarettes a day, I noticed that when my patients quit smoking and then relapsed, it took them only a few days to return to their old frequency, even after a lengthy abstinence.

Along with Robert Wellman of Fitchburg State College, I investigated this phenomenon in a study that asked 2,000 smokers how much they smoked before quitting, how long they had remained abstinent and how much they smoked immediately after relapsing. Smokers who relapsed after an abstinence of three months resumed smoking at about 40 percent of their previous rate, indicating that their LTW had lengthened. We believe the craving-free interval between cigarettes increases because the withdrawal-related adaptations disappear during the first few weeks of abstinence. With the resumption of smoking, however, the withdrawal-related adaptations quickly redevelop, and over the next few weeks relapsed smokers find they must smoke just as often as they used to.

We also discovered, however, that abstinences greater than three months had almost no additional impact on the length of the LTW. Even after years of abstinence, smoking resumed at about 40 percent of the prior rate, typically six or seven cigarettes a day. This finding suggests that increases in tolerance are permanent; a relapsing smoker will never get as much suppression of craving from a single cigarette as a novice smoker will. In other words, the brain of a smoker is never restored to its original state.

But if dependence-related tolerance stimulates the craving-generation system and never completely goes away, why don't former smokers continue hungering for cigarettes forever? Our research subjects could not tell us why their craving for nicotine eventually lessened, so I looked at what the sensitization-homeostasis theory would predict. I reasoned that former smokers must develop abstinence-related adaptations that mimic the action of nicotine, inhibiting the craving-generation system and restoring homeostasis. Smoking cessation would not result in a quiet return to normal brain function; rather it would trigger a dynamic period of neuroplasticity during which new adaptations would appear in the former smoker's brain. Because of these adaptations, the ex-smoker's brain would resemble neither that of the smoker nor of the nonsmoker.

To test this prediction, Slotkin and his colleagues examined the brains of rats before nicotine exposure, during exposure, during withdrawal and long after withdrawal. They found clear-cut evidence of changes in the functioning of neurons in the brain's cortex that employ acetylcholine and serotonin to transmit signals—changes that appeared only after the acute withdrawal period. As predicted, the brains of the "ex-smoker" rats showed unique adaptations that were not present in the "smokers" or "nonsmokers." And at the College of Medicine at the Catholic University of Korea, HeeJin Lim and colleagues found evidence of brain remodeling in humans who quit smoking by studying brain-derived neurotrophic factor, a stimulant of neuroplasticity. Levels of this factor in ex-

THE HOOKED ON NICOTINE CHECKLIST

Researchers use the following questions to determine whether adolescent smokers are addicted. An answer of "yes" to any one of the questions indicates that addiction has begun:

Have you ever tried to quit smoking, but couldn't?

Do you smoke now because it is really hard to quit?

Have you ever felt like you were addicted to tobacco?

Do you ever have strong cravings to smoke?

Have you ever felt like you really needed a cigarette?

Is it hard to keep from smoking in places where you are not supposed to, like school?

When you tried to stop smoking (or, when you haven't used tobacco for a while):

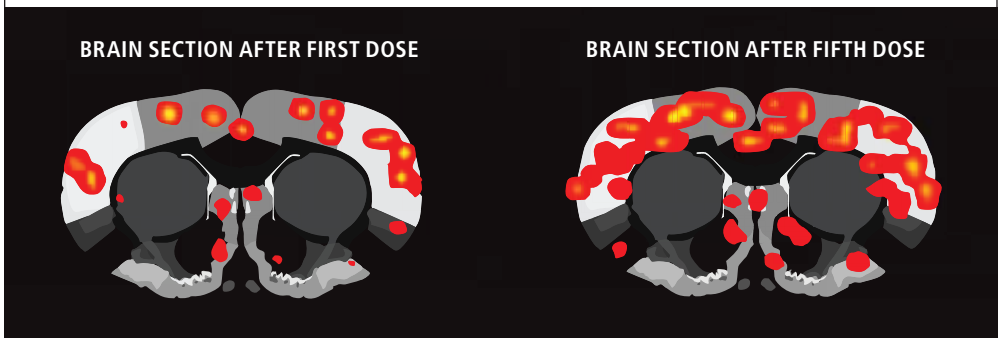
- Did you find it hard to concentrate because you couldn't smoke?
- Did you feel more irritable because you couldn't smoke?
- Did you feel a strong need or urge to smoke?
- Did you feel nervous, restless or anxious because you couldn't smoke?

SCOTT GIBSON *Corbis*

[A CLOSER LOOK]

NICOTINE ON THE BRAIN

Recent studies have confirmed that nicotine evokes rapid changes in brain physiology. The author and Jean A. King of the Center for Comparative NeuroImaging at the University of Massachusetts Medical School used functional magnetic resonance imaging (fMRI) to measure levels of metabolic activity in the brains of rats given a dose of nicotine on five consecutive days. The response to the first dose was relatively limited (*red areas in image on left*), but brain activity was much more intense (*yellow*) and widespread after the fifth dose (*image on right*). These findings indicate that the brain quickly becomes sensitized to nicotine, enabling addiction to appear after just a few doses.



WEI HUANG Center for Comparative Neuroimaging, UMMS/WPI

smokers tripled after two months of abstinence.

Thus, abstinence-related adaptations seem to counter the tolerance-related adaptations by inhibiting the craving-generation system so that it eventually stops compelling the former smoker to light up. Smoking cues in the environment might still provoke craving, however, and if the long-abstinent smoker were to surrender to an urge to smoke just once, nicotine would again produce a profound suppression of activity in the craving-generation system. The abstinence-related adaptations would then make a bad situation worse. Because these adaptations mimic the effect of nicotine, they would need to be removed to restore homeostasis; when the effect of nicotine wears off, the tolerance-related adaptations would be left unopposed in stimulating the craving-generation system. Struck with a strong craving, the relapsing smoker would need to puff six or seven cigarettes a day to keep it under control.

New Hope for Smokers

This model of addiction by no means represents the prevailing opinion. In my view, addiction is an accident of physiology. Because so many careers have been built on the assumption that the roots of addiction lie in psychology rather than physiology, I did not expect my ideas to receive a warm welcome.

Whether or not the sensitization-homeostasis theory is correct, it is clear that the nicotine from the first cigarette is sufficient to trigger a remodeling of the brain. Although some may argue about what criteria should be used to render a proper diagnosis of addiction, it is now well established that adolescents have many symptoms of addiction very soon after they smoke their first cigarette. This finding underlines the importance of bolstering government funding for antismoking campaigns, which has fallen in recent years.

To fully test my theory, which has been simplified here, researchers need a reliable method to detect sensitization in humans. I have worked with Jean A. King and her colleagues at the Center for Comparative NeuroImaging to demonstrate nicotine sensitization in rats using fMRI. Images comparing brain responses to the first dose of nicotine and to the fifth dose given four days later illustrate the dramatic changes in brain function in areas such as the anterior cingulate gyrus and hippocampus. We have just received funding from the NIDA to use fMRI to visualize sensitization in smokers, with future plans to determine which brain regions are involved in the craving-inhibition and craving-generation systems.

Our long-term goal is to identify drugs that can manipulate these systems to treat or cure addiction. Although nicotine-replacement therapies may double the success rate for smoking cessation, failed attempts still far outnumber the successes. The sensitization-homeostasis theory suggests that what is needed is a therapy that will suppress craving without stimulating compensatory responses that only make the craving worse in the long run. A better understanding of the addiction process may help researchers develop new treatments that can safely liberate smokers from nicotine's deadly pull. ■

MORE TO EXPLORE

Measuring the Loss of Autonomy over Nicotine Use in Adolescents: The DANDY (Development and Assessment of Nicotine Dependence in Youths) Study. Joseph R. DiFranza, Judith A. Savageau, Kenneth Fletcher, Judith K. Ockene, Nancy A. Rigotti, Ann D. McNeill, Mardia Coleman and Constance Wood in *Archives of Pediatrics & Adolescent Medicine,* Vol. 156, No. 4, pages 397–403; April 2002.

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A Sensitization-Homeostasis Model of Nicotine Craving, Withdrawal, and Tolerance: Integrating the Clinical and Basic Science Literature. Joseph R. DiFranza, Robert J. Wellman in *Nicotine & Tobacco Research,* Vol. 7, No. 1, pages 9–26; February 2005.

By Frank N. von Hippel

RETHINKING Nuclear Fuel Recycling

Plans are afoot to reuse spent reactor fuel in the U.S. But the advantages of the scheme pale in comparison with its dangers

KEY CONCEPTS

- Spent nuclear fuel contains plutonium, which can be extracted and used in new fuel.
- To reduce the amount of long-lived radioactive waste, the U.S. Department of Energy has proposed reprocessing spent fuel in this way and then "burning" the plutonium in special reactors.
- But reprocessing is very expensive. Also, spent fuel emits lethal radiation, whereas separated plutonium can be handled easily. So reprocessing invites the possibility that terrorists might steal plutonium and construct an atom bomb.
- The author argues against reprocessing and for storing the waste in casks until an underground repository is ready.

—The Editors

Although a dozen years have elapsed since any new nuclear power reactor has come online in the U.S., there are now stirrings of a nuclear renaissance. The incentives are certainly in place: the costs of natural gas and oil have skyrocketed; the public increasingly objects to the greenhouse gas emissions from burning fossil fuels; and the federal government has offered up to $8 billion in subsidies and insurance against delays in licensing (with new laws to streamline the process) and $18.5 billion in loan guarantees. What more could the moribund nuclear power industry possibly want?

Just one thing: a place to ship its used reactor fuel. Indeed, the lack of a disposal site remains a dark cloud hanging over the entire enterprise. The projected opening of a federal waste storage repository in Yucca Mountain in Nevada (now anticipated for 2017 at the earliest) has already slipped by two decades, and the cooling pools holding spent fuel at the nation's nuclear power plants are running out of space.

Most nuclear utilities are therefore beginning to store older spent fuel on dry ground in huge casks, each typically containing 10 tons of waste. Every year a 1,000-megawatt reactor discharges enough fuel to fill two of these casks, each costing about $1 million. But that is not all the industry is doing. U.S. nuclear utilities are suing the federal government, because they would not have incurred such expenses had the U.S. Department of Energy opened the Yucca Mountain repository in 1998 as originally planned. As a result, the government is paying for the casks and associated infrastructure and operations—a bill that is running about $300 million a year.

Under pressure to start moving the fuel off the sites, the DOE has returned to an idea that it abandoned in the 1970s—to "reprocess" the spent fuel chemically, separating the different elements so that some can be reused. Vast reprocessing plants have been running in France and the U.K. for more than a decade, and Japan began to operate its own $20-billion facility in 2006. So this strategy is not without precedent. But, as I discuss below, reprocessing is an expensive and dangerous road to take.

The Element from Hell

Grasping my reasons for rejecting nuclear fuel reprocessing requires nothing more than a rudimentary understanding of the nuclear fuel cycle and a dollop of common sense. Power reactors generate heat—which makes steam to turn electricity-generating turbines—by maintaining a nuclear chain reaction that splits (or "fissions") atoms. Most of the time the fuel is uranium, artificially enriched so that 4 to 5 percent is the chain-reacting isotope uranium 235; virtually all the rest is uranium 238. At an enrichment of only 5 percent, stolen reactor fuel cannot be used to construct an illicit atom bomb.

LISA APFELBACHER (*logo*)

▲ LA HAGUE, on France's Normandy coast, hosts a large complex that reprocesses spent fuel from nuclear power plants, extracting its plutonium for fabrication into new fuel. The U.S. Department of Energy has recently proposed building a similar facility.

MARTIN BOND *Photo Researchers, Inc.*

In the reactor, some of the uranium 238 absorbs a neutron and becomes plutonium 239, which is also chain-reacting and can in principle be partially "burned" if it is extracted and properly prepared. This approach has various drawbacks, however. One is that extraction and processing cost much more than the new fuel is worth. Another is that recycling the plutonium reduces the waste problem only minimally. Most important, the separated plutonium can readily serve to make nuclear bombs if it gets into the wrong hands; as a result, much effort has to be expended to keep it secure until it is once more a part of spent fuel.

These drawbacks become strikingly clear when one examines the experiences of the nations that have embarked on reprocessing programs. In France, the world leader in reprocessing technology, the separated plutonium (chemically combined with oxygen to form plutonium dioxide) is mixed with uranium 238 (also as an oxide) to make a "mixed oxide," or MOX, fuel. After being used to generate more power, the spent MOX fuel still contains about 70 percent as much plutonium as when it was manufactured; however, the addition of highly radioactive fission products created inside a reactor makes this plutonium difficult to access and make into a bomb. The used MOX fuel is shipped back to the reprocessing facility for indefinite storage. Thus, France is, in effect, using reprocessing to move its problem with spent fuel from the reactor sites to the reprocessing plant.

Japan is following France's example. The U.K. and Russia simply store their separated civilian plutonium—about 120 tons between them as of the end of 2005, enough to make 15,000 atom bombs.

Until recently, France, Russia and the U.K. earned money by reprocessing the spent fuel of other nations, such as Japan and Germany, where domestic antinuclear activists demanded that the government either show it had a solution for dealing with spent fuel or shut down its reactors. Authorities in these nations found that sending their spent fuel abroad for reprocessing was a convenient, if costly, way to deal with their nuclear wastes—at least temporarily.

With such contracts in hand, France and the U.K. were easily able to finance new plants for carrying out reprocessing. Those agreements specified, however, that the separated plutonium and any highly radioactive waste would later go back to the country of origin. Russia has recently adopted a similar policy. Hence, governments that send spent fuel abroad need eventually to arrange storage sites for the returning radioactive waste. That reality took a while to sink in, but it has now convinced almost all nations that bought foreign reprocessing services that they might as well store their spent fuel and save the reprocessing fee of about $1 million

A NUCLEAR RENAISSANCE?

After decades of declining interest, nuclear energy is poised for a comeback, driven by:

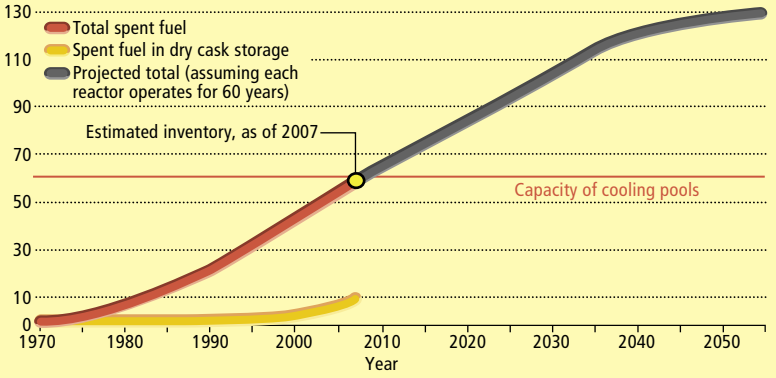
- **Rising costs of fossil fuels**
- **Nuclear power's lack of carbon emissions**
- **Generous government subsidies**

[A GROWING PROBLEM]

Too Much Waste, Too Little Storage

ACCUMULATED SPENT FUEL FROM ALL U.S. NUCLEAR POWER REACTORS

(1,000 metric tons of uranium and associated reactor products)



The amount of spent fuel will rise substantially in coming decades even if no new reactors are built. Managers at nuclear power plants increasingly are forced to transfer the oldest spent fuel in their cooling pools to dry casks situated close by. Not surprisingly, the industry is pressuring the U.S. government to help find a solution to the problem.

CRITICAL POINT

The quantity of spent fuel so far accumulated by the U.S. nuclear industry (about 58,000 metric tons) now very nearly equals the capacity of the cooling pools used to hold such material at the reactor sites. By midcentury, the amount will roughly double.

per ton (10 times the cost of dry storage casks).

So France, Russia and the U.K. have lost virtually all their foreign customers. One result is that the U.K. plans to shut down its reprocessing plants within the next few years, a move that comes with a $92-billion price tag for cleaning up the site of these facilities. In 2000 France considered the option of ending reprocessing in 2010 and concluded that doing so would reduce the cost of nuclear electricity. Making such a change, though, might also engender acrimonious debates about nuclear waste—the last thing the French nuclear establishment wants in a country that has seen relatively little antinuclear activism.

Japan is even more politically locked into reprocessing: its nuclear utilities, unlike those of the U.S., have been unable to obtain permission to expand their on-site storage. Russia today has just a single reprocessing plant, with the ability to handle the spent fuel from only 15 percent of that country's nuclear reactors. The Soviets had intended to expand their reprocessing capabilities but abandoned those plans when their economy collapsed in the 1980s.

During the cold war, the U.S. operated reprocessing plants in Washington State and South Carolina to recover plutonium for nuclear weapons. More than half of the approximately 100 tons of plutonium that was separated in those efforts has been declared to be in excess of our national needs, and the DOE currently projects that disposing of it will cost more than $15 billion. The people who were working at the sites where this reprocessing took place are now primarily occupied with cleaning up the resulting mess, which is expected to cost around $100 billion.

In addition to those military operations, a small commercial reprocessing facility operated in upstate New York from 1966 to 1972. It separated 1.5 tons of plutonium before going bankrupt and becoming a joint federal-state cleanup venture, one projected to require about $5 billion of taxpayers' money.

With all the problems reprocessing entailed, one might rightly ask why it was pursued at all. Part of the answer is that for years after civilian nuclear power plants were first introduced, the U.S. Atomic Energy Commission (AEC) promoted reprocessing both domestically and abroad as essential to the future of nuclear power, because the industry was worried about running out of uranium (a concern that has since abated).

But that was before the security risks of plutonium production went from theoretical to real. In 1974 India, one of the countries that the U.S. assisted in acquiring reprocessing capabilities, used its first separated plutonium to build a nuclear weapon. At about this time, the late Theodore B. Taylor, a former U.S. nuclear weapons designer, was raising an alarm about the possibility that the planned separation and recycling of thousands of tons of plutonium every year would allow terrorists to steal enough of this material to make one or more nuclear bombs.

Separated plutonium, being only weakly radioactive, is easily carried off—whereas the plutonium in spent fuel is mixed with fission products that emit lethal gamma rays. Because of its great radioactivity, spent fuel can be transported only inside casks weighing tens of tons, and its plutonium can only be recovered with great difficulty, typically behind thick shielding using sophisticated, remotely operated equipment. So unseparated plutonium in spent fuel poses a far smaller risk of ending up in the wrong hands.

Having been awakened by India to the danger of nuclear weapons proliferation through reprocessing, the Ford administration (and later the Carter administration) reexamined the AEC's position and concluded that reprocessing was both unnecessary and uneconomic. The U.S. government therefore abandoned its plans to reprocess the spent fuel from civilian reactors and urged France and Germany to cancel contracts under which they were exporting reprocessing technology to Pakistan, South Korea and Brazil.

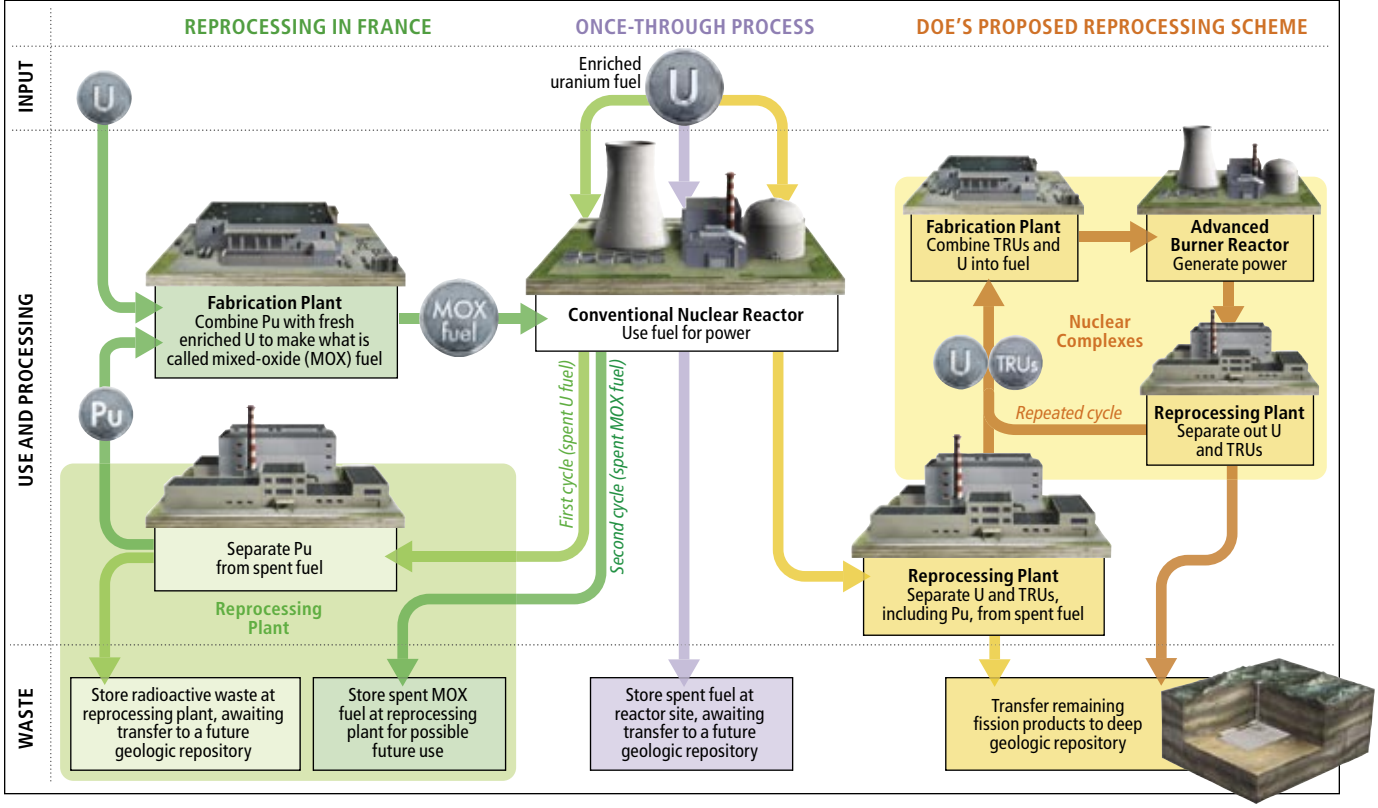
The Reagan administration later reversed the Ford-Carter position on domestic reprocessing, but the U.S. nuclear industry was no longer interested. It, too, had concluded that reprocessing

LUCY READING-IKKANDA

[BASICS]

FUEL-HANDLING OPTIONS

The nuclear power industry has a few options for managing spent reactor fuel. It can simply store the waste after fuel is used once, as the U.S. does now (*center*). Or it can reprocess the spent fuel, separating out components that can be reused. In France, plutonium (Pu) is prepared for an additional run in a reactor (*left*). Another idea, favored by the DOE, would repeatedly recycle plutonium and other elements heavier than uranium (transuranics, or TRUs) in a new kind of reactor (*right*). Reusing spent fuel seems appealing at first because it can shrink the amount of waste needing indefinite storage—but, the author notes (*box at bottom right*), the approach has serious drawbacks.



to make use of the recovered plutonium would not be economically competitive with the existing "once-through" fueling system. Reprocessing, at least in the U.S., had reached a dead end, or so it seemed.

Rising from Nuclear Ashes

The current Bush administration has recently breathed life back into the idea of reprocessing spent nuclear fuel as part of its proposal to deploy a new generation of nuclear reactors. According to this vision, transuranics (plutonium and other similarly heavy elements extracted from conventional reactor fuel) would be recycled not once but repeatedly in the new reactors to break them down through fission into lighter elements, most of which have shorter half-lives. Consequently, the amount of nuclear waste needing to be safely stored for many millennia would be reduced [see "Smarter Use of Nuclear Waste," by William H. Hannum, Gerald E. Marsh and George S. Stanford; SCIENTIFIC AMERICAN, December 2005].

Some scientists view this new scheme as "technically sweet," to borrow a phrase J. Robert Oppenheimer once used to describe the design for the hydrogen bomb. But is it really so wise?

The proposal to recycle U.S. spent fuel in this way is not new. Indeed, in the mid-1990s the DOE asked the U.S. National Academy of Sciences (NAS) to carry out a study of this approach to reducing the amount of long-lived radioactive waste. The resulting massive report, *Nuclear Wastes: Technologies for Separation and Transmutation*, was very negative. The NAS panel concluded that recycling the transuranics in the first 62,000 tons of spent fuel (the amount that otherwise would have been stored in Yucca Mountain) would require "no less than $50 billion and easily could be over $100 billion"—in other words, it could well cost something like $500 for every person in the U.S. These numbers would have to be doubled to deal with the entire amount of spent fuel that existing U.S. reactors are expected to discharge during their lifetimes.

PROS & CONS

In theory, reprocessing spent fuel and recycling it in reactors reduces the quantity of uranium mined and leaves more of the waste in forms that remain radioactive for only a few centuries rather than many millennia. But in practice, this approach is problematic because it is expensive, reduces waste only marginally (unless an extremely costly and complex recycling infrastructure is built), and increases the risk that the plutonium in the spent fuel will be used to make nuclear weapons.

—F.N.v.H.

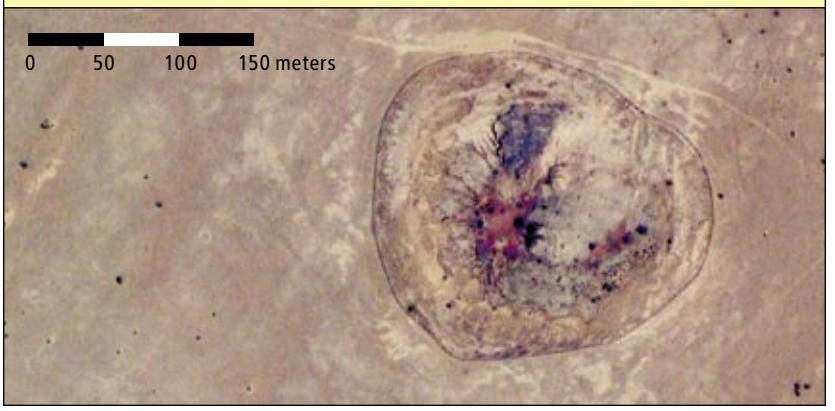
KEVIN HAND

[A MAJOR DANGER]

Mass Destruction for the Masses?

The chief concern about reprocessing spent nuclear fuel is that by producing stores of plutonium, it might allow rogue nations or even terrorist groups to acquire atomic bombs. Because separated plutonium is only mildly radioactive, if a small amount were stolen, it could be easily handled (*above*) and carried off surreptitiously. And only a few kilograms are required for a nuclear weapon.

Before this danger was fully appreciated, the U.S. shared technology for reprocessing spent nuclear fuel with other countries but ceased doing so after India detonated a nuclear weapon built using some of its separated plutonium. Satellite imagery (*below*) reveals the crater created by India's first underground nuclear test in May 1974.



Why so expensive? Because conventional reactors could not be employed. Those use water both for cooling and for slowing down the neutrons given off when the uranium nuclei in the fuel break apart; this slowing allows the neutrons to induce other uranium 235 atoms to split, thereby sustaining a nuclear chain reaction. Feeding recycled fuel into such a reactor causes the heavier transuranics (plutonium 242, americium and curium) to accumulate. The proposed solution is a completely different type of nuclear reactor, one in which the neutrons get slowed less and are therefore able to break down these hard-to-crack atoms.

During the 1960s and 1970s the leading industrial countries, including the U.S., put the equivalent of more than 50 billion of today's dollars into efforts to commercialize such fast-neutron reactors, which are cooled by molten sodium rather than water. These devices were also called breeder reactors, because they were designed to generate more plutonium than they consumed and therefore could be much more efficient in using the energy in uranium. The expectation was that breeders would quickly replace conventional water-cooled reactors. But sodium-cooled reactors proved to be much more costly to build and troublesome to operate than expected, and most countries abandoned their efforts to commercialize them.

It is exactly this failed reactor type that the DOE now proposes to develop and deploy—but with its core reconfigured to be a net plutonium burner rather than a breeder. The U.S. would have to build between 40 and 75 1,000-megawatt reactors of this type to be able to break down transuranics at the rate they are being generated in the nation's 104 conventional reactors. If each of the new sodium-cooled reactors cost $1 billion to $2 billion more than one of its water-cooled cousins of the same capacity, the federal subsidy necessary would be anywhere from $40 billion to $150 billion, in addition to the $100 billion to $200 billion required for building and operating the recycling infrastructure. Given the U.S. budget deficit, it seems unlikely that such a program would actually be carried through.

If a full-scale reprocessing plant were constructed (as the DOE until recently was proposing to do by 2020) but the sodium-cooled reactors did not get built, virtually all the separated transuranics would simply go into indefinite storage. This awkward situation is exactly what befell the U.K., where the reprocessing program, started in the 1960s, has produced about 80 tons of separated plutonium, a legacy that will cost tens of billions of dollars to dispose of safely.

Reprocessing spent fuel and then storing the separated plutonium and radioactive waste indefinitely at the reprocessing plant is not a disposal strategy. Rather it is a strategy for disaster, because it makes the separated plutonium much more vulnerable to theft. In a 1998 report the U.K.'s Royal Society (the equivalent of the NAS), commenting on the growing stockpile of civilian plutonium in that country, warned that "the chance that the stocks of plutonium might, at some stage, be accessed for illicit weapons production is of extreme concern." In 2007 a second Royal Society report reiterated that "the status quo of continuing to stockpile a very dangerous material is not an acceptable long-term option."

Clearly, prudence demands that plutonium should not be stored at a reprocessing facility in a form that could readily be stolen. Indeed, common sense dictates that it should not be separated at all. Until a long-term repository is available, spent reactor fuel can remain at the sites of the nuclear power plants that generated it.

Would such storage be dangerous? I would argue that keeping older fuel produced by the once-through system in dry storage casks represents a

[THE AUTHOR]

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U.S. DEPARTMENT OF ENERGY (*top*); 2008 DIGITALGLOBE/GOOGLE IMAGERY (*middle*); COURTESY OF FRANK N. VON HIPPEL (*bottom*)

negligible addition to the existing nuclear hazard to the surrounding population. The 10 kilowatts of radioactive heat generated by the 10 tons of 20-year-old fuel packed in a dry storage cask is carried off convectively as it warms the air around it. Terrorists intent on doing harm might attempt to puncture such a cask using, say, an antitank weapon or the engine of a crashing aircraft, but under most circumstances only a small mass of radioactive fuel fragments would be scattered about a limited area. In contrast, if the coolant in the nearby reactor were cut off, its fuel would overheat and begin releasing huge quantities of vaporized fission products within minutes. And if the water were lost in a storage pool containing spent fuel, the zirconium cladding of the fuel rods would be heated up to ignition temperature within hours. Seen in this light, dry storage casks look pretty benign.

Is there enough physical room to keep them? Yes, there is plenty of space for more casks at U.S. nuclear power plants. Even the oldest operating U.S. reactors are having their licenses extended for another 20 years, and new reactors will likely be built on the same sites. So there is no reason to think that these storage areas are about to disappear. Eventually, of course, it will be necessary to remove the spent fuel and put it elsewhere, but there is no need to panic and adopt a policy of reprocessing, which would only make the situation much more dangerous and costly than it is today.

Fear and Loathing in Nevada

The long-term fate of radioactive waste in the U.S. hinges on how the current impasse over Yucca Mountain is resolved. Opinion on the site is divided. The regulatory requirements are tough: the DOE has to show that the mountain will contain the waste well enough to prevent significant off-site doses for a million years.

Demonstrating safety that far into the future is not easy, but the risks from even a badly designed repository are negligible in comparison with those from a policy that would make nuclear weapons materials more accessible. From this perspective, it is difficult to understand why the danger of local radioactive pollution 100,000 or a million years hence has generated so much more political passion in the U.S. than the continuing imminent danger from nuclear weapons.

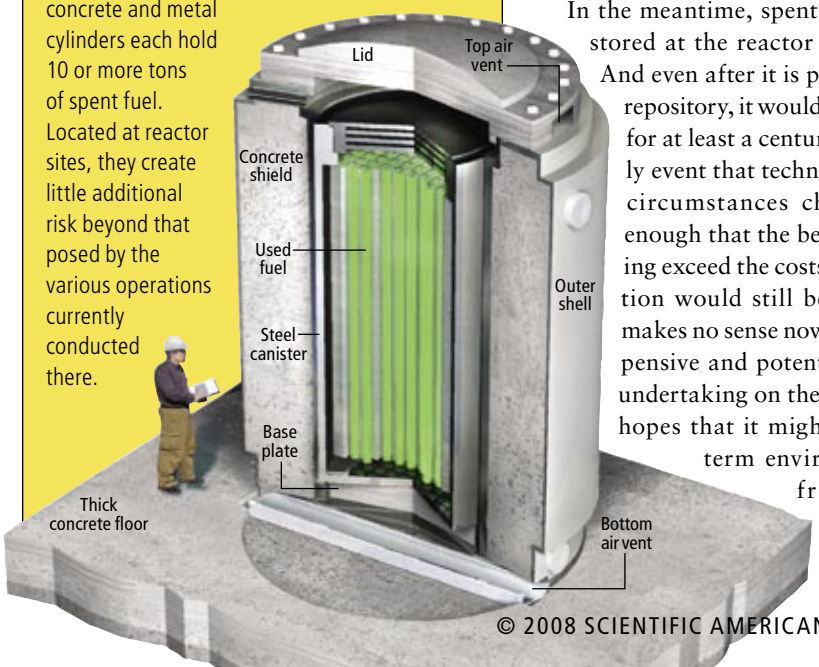
Part of the problem is the view in Nevada that the Reagan administration and Congress acted unfairly in 1987 when they cut short an objective evaluation of other candidate sites and designated Yucca Mountain as the location for the future nuclear waste repository. To overcome this perception, it may be necessary to reopen deliberations for choosing an additional site. Such a move should not be difficult. Indeed, the Nuclear Waste Policy Act of 1987 requires the secretary of energy to report to Congress by 2010 on the need for a second storage facility. Given the disastrous record of the DOE in dealing with radioactive waste, however, consideration should also be given to establishing a more specialized and less politicized agency for this purpose.

In the meantime, spent fuel can be safely stored at the reactor sites in dry casks. And even after it is placed in a geologic repository, it would remain retrievable for at least a century. So in the unlikely event that technology or economic circumstances change drastically enough that the benefits of reprocessing exceed the costs and risks, that option would still be available. But it makes no sense now to rush into an expensive and potentially catastrophic undertaking on the basis of uncertain hopes that it might reduce the long-term environmental burden from the nuclear power industry. ■

[WHAT TO DO]

A Vote for Dry Casks

Until a deep geologic repository for spent nuclear fuel opens, the author argues, the U.S. nuclear industry has a very good alternative for storing the spent fuel now accumulating in cooling pools: dry casks. These 150-ton concrete and metal cylinders each hold 10 or more tons of spent fuel. Located at reactor sites, they create little additional risk beyond that posed by the various operations currently conducted there.



KEVIN HAND

YUCCA UPDATE

Progress on the proposed U.S. nuclear repository at Yucca Mountain in Nevada remains slow. At best, its construction will not be authorized until 2011, and the project will not be completed until 2016. The U.S. nuclear industry thus will not begin storing spent fuel there until 2017—or even later, if work is delayed by scientific controversies, legal challenges or funding shortfalls.

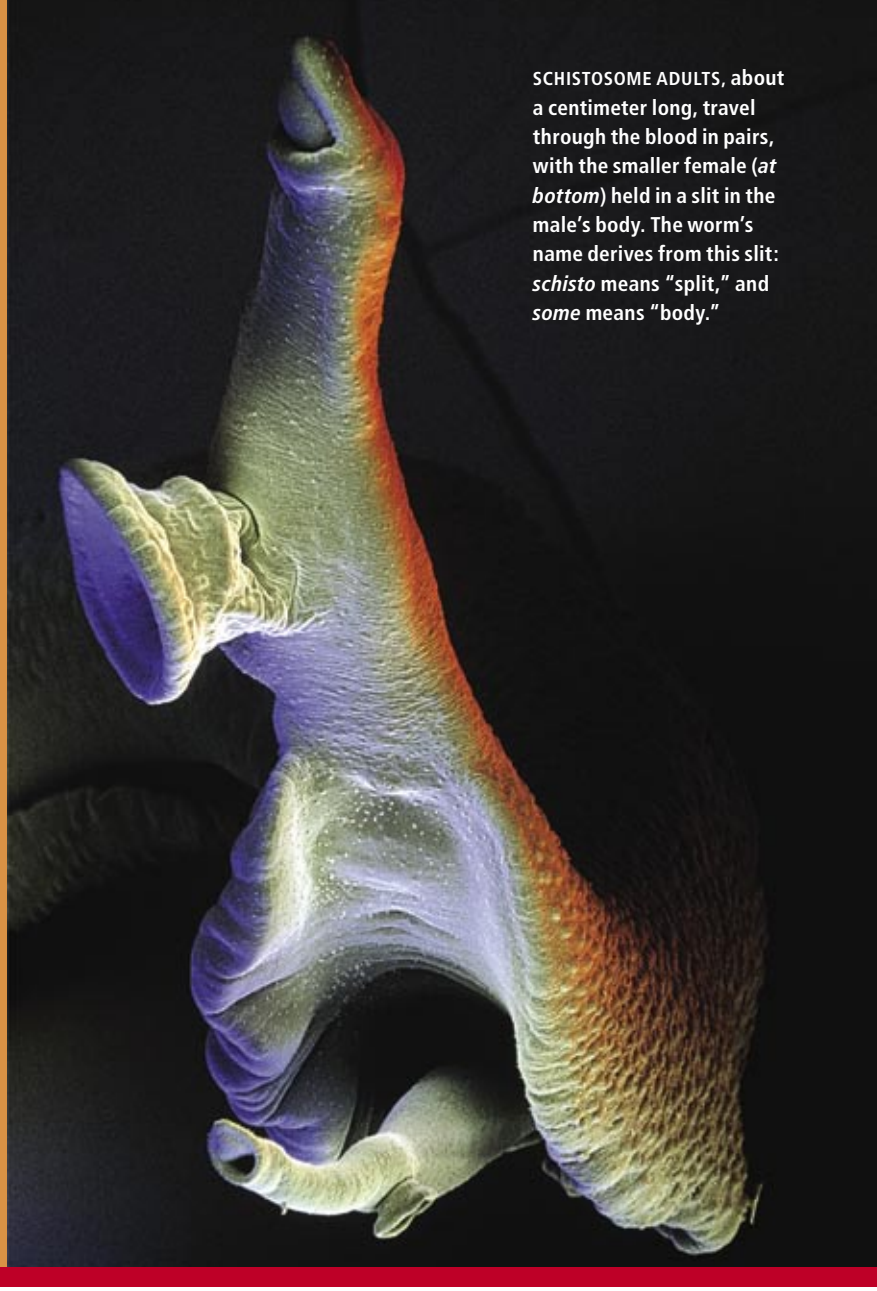
MORE TO EXPLORE

Nuclear Wastes: Technologies for Separation and Transmutation. National Academies Press, 1996.

The Future of Nuclear Power. An Interdisciplinary MIT Study, 2003. **http://web.mit.edu/nuclearpower**

Managing Spent Fuel in the United States: The Illogic of Reprocessing. Frank von Hippel in a research report of the International Panel on Fissile Materials, January 2007. **www.fissilematerials.org/ipfm/site_down/ipfmresearchreport03.pdf**

FIGHTING KILLER WORMS



SCHISTOSOME ADULTS, about a centimeter long, travel through the blood in pairs, with the smaller female (*at bottom*) held in a slit in the male's body. The worm's name derives from this slit: *schisto* means "split," and *some* means "body."

Bloodsucking worms called schistosomes are among the world's most worrisome human parasites. A new genome sequence and powerful genetic tools promise to help crack their secrets >> By Patrick Skelly

KEY CONCEPTS

- Parasitic worms known as schistosomes are a major cause of disability and death in many parts of the world, especially sub-Saharan Africa.
- Although a treatment exists, reinfection is the rule.
- A vaccine would make a world of difference, but none has yet proved effective. Genetic and other tools hold promise for generating new candidates.

—The Editors

Legend has it that vampires create no shadows, cast no reflection and—in more modern versions of the tale—cannot be captured on photographs, film or video. Of course, vampires are only myths. Unfortunately, schistosomes, which behave in some similar ways, are not. These infectious worms dwell in human veins and eat our blood. Among parasitic illnesses, the World Health Organization ranks schistosomiasis, the disease caused by the worms, second only to malaria in terms of the number of people it kills and chronically disables and the drag it imposes on the social and economic development of nations. And, in their own way, schistosomes have achieved invisibility. Cameras can capture these creatures, but our immune system does not.

Investigators have struggled for years against the schistosome's evasiveness. They have been trying to create vaccines able to rally a defense that would pounce on the parasite quickly, thereby preventing disease, or that would help the body to clear existing infections. Vaccines are a necessary and missing component of a global effort to eradicate this illness. So far the results have been disappointing. But schistosome researchers like myself feel we may be at the start of a great leap forward. Genome projects are laying bare the DNA sequence of the parasite, and scientists are beginning to develop powerful new tools to probe its molecular secrets. These

DAVID SCHARF *Photo Researchers, Inc.*

weapons may help make it possible to enhance immunity and accelerate vaccine efforts.

Preying on Humans

A vaccine would help avoid an enormous amount of suffering. Some 200 million people, mostly in tropical and subtropical countries, have schistosomiasis, meaning they harbor schistosomes in their blood. In children, persistent infection can retard growth and cause cognitive deficits. And in anyone, it can lead to anemia as well as damage to the intestines, bladder, spleen and liver, resulting in symptoms ranging from bloody diarrhea and cramping to life-threatening internal bleeding and kidney failure. Schistosomiasis can drastically reduce someone's ability to work, crippling both individuals and the economy.

People become infected when they encounter water infested by immature schistosome forms, which, though toothless, easily degrade and penetrate human skin and then enter blood vessels. There the immature parasites develop into adult bloodsucking worms and mate, after which the females begin laying eggs.

Then the eggs make matters worse. As many as half of the hundreds laid daily by each female will lodge in a variety of organs. Unrestrained, they would secrete toxins at a lethal level. The immune system, though usually unable to eliminate the worms, blocks the acute lethality, albeit at the cost of doing damage of its own: it provokes the formation of scar tissue, a major cause of the organ impairment seen in the disease. The immune response to the eggs also apparently helps them to puncture blood vessels, which in the intestinal tract allows them to make their way into feces and thus out of the body to continue development. Eggs that invade the bladder may, alternatively, escape in urine. In water the eggs hatch; then larvae emerge and infect snails. Inside snails the schistosomes replicate asexually before pouring into the water to infect, or reinfect, new human victims. [*For more on the worm's complex life cycle, see box on page 97.*]

Good sanitation and snail control have limited the disease in many countries. But in poverty-stricken regions, where clean water is still not available, it thrives. A safe antischistosome drug, praziquantel, was developed in the 1970s. It has few side effects and is now relatively cheap; plus, a single treatment can clear the infection. Reinfection, however, occurs frequently, and the worry looms that schistosomes will gain resistance to this drug. Already cases of schistosomiasis have surfaced that require higher than normal levels of the drug to clear—a possible sign of incipient resistance.

It is because of concern over drug resistance and because prevention is always the best medicine that health officials are eager to add a vaccine to the fight against the parasite—if a practical and effective one can be created. Typical vaccines deliver dead or inactive pathogens or distinctive segments of molecules (often proteins) made by those organisms in a way that induces the immune system to behave as if a true infection has occurred. The system produces cells that specifically recognize molecules present in the vaccine; thereafter some of these cells remain on the alert for the pathogen, ambushing it with antibody molecules directed to the recognized targets with other weapons before the menace can cause illness.

Investigators did not initially expect development of a vaccine against schistosomiasis to be as difficult as it has been. The worms' life cycle suggested the parasites would be a soft target for our mighty immune system. Yet they turn out to be anything but simple to handle.

Swimming with the Enemy

One reason schistosomes initially seemed like they should be an easy target is that they are relatively large and make no effort to find hiding places in the body. The first sight of an adult worm always surprises my graduate students. These biologists are familiar with the microscopic bacteria and viruses that can live in our bodies and that often evade immune attack by hiding inside cells or by outcompeting immune cells through high-speed reproduction: one virus or bacterium can beget millions, indeed billions, of others during the course of an infection.

Schistosomes, on the other hand, are big enough to be viewed by the naked eye. An adult is a centimeter long. Furthermore, the worms that start an infection on day one are the same ones present days, years or even decades later; inside the human body their numbers do not grow, except, of course, by new infections.

And evolution has chosen a hostile home for schistosomes. Lying exposed in the bloodstream would not appear to be an ideal habitat for a parasite. Blood, though nutritious, is a major conduit for all the forces of immunity, which, somehow, the worms avoid.

Beyond being big and brazen, schistosomes possess other features that suggest the immune system could be induced to recognize them if conditions were right. The body's strong reac-

[THE AUTHOR]

Patrick Skelly, who earned his Ph.D. at the Australian National University in Canberra, is assistant professor of biomedical sciences at the Cummings School of Veterinary Medicine at Tufts University and president of the New England Association of Parasitologists. He is occasionally a little happier than this photograph suggests.

FORMIDABLE FOE

Globally, an estimated 200 million people are infected (20 million severely) and 200,000 die annually.

The schistosome species that cause human disease do not multiply in people but can survive in their blood for 30 to 40 years.

The worms, also known as flukes, once brought down an army. They spread in water, and in 1948 they incapacitated large numbers of soldiers from the People's Republic of China who were preparing for an amphibious assault on Taiwan (formerly Formosa). One historian thus dubbed the worm "the fluke that saved Formosa."

ASHWIN SKELLY (*Skelly*)

FAST FACTS

Schistosomes probably originated in Asia and then dispersed to India and Africa. They jumped to the Americas in the blood of African slaves.

The worms lack an anus, so they vomit wastes out the mouth, for the host's bloodstream to whisk away.

Females do not mature unless they have contact with males; removed from a male's slit, a female will physically regress.

Schistosomes that sicken humans replicate in aquatic snails. Governments could help limit the worms' spread by eradicating snails from freshwater and by preventing them from colonizing new bodies of water, such as lakes formed when dams are built. Many fear, for example, that construction of the Three Gorges Dam in China will foster new schistosome infections.

In snails, schistosome larvae often compete with other parasites, some of which like to munch on the larvae. Researchers are considering trying to reduce schistosome populations by seeding ponds with these competitors.

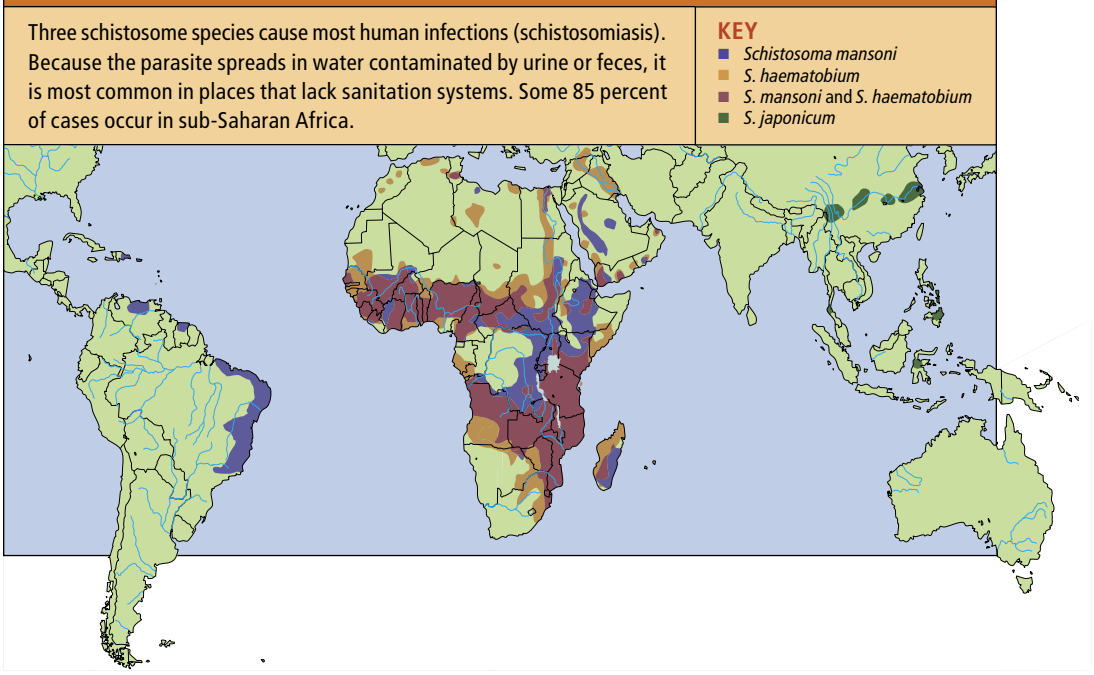
Schisotosome species that mainly infect water birds can cause a rash known as swimmer's itch in the U.S. and elsewhere. Parasitologist William W. Cort discovered the worm link in 1927, by placing larvae from contaminated water on his own skin and observing the symptoms.

THREE GORGES DAM

[THE GLOBAL PICTURE]

WHERE TROUBLE LIES

Three schistosome species cause most human infections (schistosomiasis). Because the parasite spreads in water contaminated by urine or feces, it is most common in places that lack sanitation systems. Some 85 percent of cases occur in sub-Saharan Africa.



tion to their eggs is one sign of this possibility. What is more, there is nothing intrinsically immunologically invisible about the molecules that make up the worms. R. Alan Wilson and his colleagues at the University of York in England, among other research groups, have shown that if schistosomes are lethally wounded with high doses of radiation and then introduced into experimental animals, the dying parasites do induce strong immunity. Indeed, they serve as effective vaccines, protecting the animal against later challenge by hundreds of healthy schistosomes. Unfortunately, using similarly prepared worms to vaccinate people is impractical.

This animal work has, however, encouraged hope that vaccines can be created inexpensively and in abundance using a single schistosome molecule or a mixture of selected ones as their basis. Three separate species of schistosomes account for the vast majority of human disease—*Schistosoma mansoni, S. haematobium* and *S. japonicum*—and so the ideal vaccine would work against all three. For now, however, researchers are focusing on finding a vaccine that can ward off infection by one species before trying to knock all of them down in one fell swoop.

To date, several schistosome molecules have been explored as vaccines but none has proved strongly effective. One, though, has performed well enough to enter large, phase III clinical trials—the final stage of human testing before a product can be released. This vaccine, developed at the Pasteur Institute of Lille in France, contains the *S. haematobium* version of a protein discovered in 1987: glutathione *S*-transferase. All researchers in the field hope this preparation will succeed, but in the meantime the hunt goes on for other promising vaccine candidates.

Wormy Tactics

Certainly, knowing how schistosomes typically escape immune detection is important if we are to develop vaccines that can overcome that propensity. The parasites have several tricks at their disposal that may explain their seeming invisibility to our defenses. One is that they come armed with a variety of molecules that may allow them to disable or "blind" the immune system. Kalyanasundaram Ramaswamy and his colleagues at the University of Illinois have shown, for instance, that some schistosome molecules can, at least in a test tube, inhibit proliferation of immune cells or induce the cells' death.

In addition, some newly identified schistosome genes look like human ones that are switched on in immune cells. Other genes encode receptors, or docking sites, that are closely related to human receptors that bind small molecules called cytokines (which control the activity of immune cells) or hormones (which convey messages between cells over longer distances). It stands to reason that the parasites would benefit

LISA APFELBACHER; SOURCES: CARLO DENEGRI FOUNDATION AND WHO (*map*); DU HUAJU *AP Photo/Xinhua* (*Three Gorges Dam*)

from intercepting signaling molecules that help our bodies to react to infection. The worms presumably use their receptors to essentially spy on intercellular chatter, to gain information about the state of their environment and to prepare counteractive measures before immune cells have a chance to strike.

Schistosomes also possess what seems to be a cloak of invisibility: an unusual covering known as the tegument. Most parasites are covered by a single oily membrane. In addition to that membrane, the outer part of the tegument sports a second, external one that contributes to the parasite's ability to hide. The tegument provides ample protection to the worm as it migrates through our blood, but in the hands of scientists, it is extraordinarily fragile and nebulous. This fragility has made it difficult to answer even basic questions about the tegument's biology, such as which proteins reside in it and whether any protrude from its surface. This last question is of keen interest to vaccine designers, because the targets of most successful vaccines are proteins or other molecules that appear on the outside of a pathogen.

We do know, though, that this outer coat can actually acquire *human* molecules from the blood. It is possible to detect, for instance, our own blood-group molecules (which establish the familiar blood types A, B, and so on) attached to the worm's surface. One controversial idea is that these stolen human molecules could act as a disguise, covering the parasite's own molecules and making them invisible to immune surveillance.

Tricks of Our Own

For decades, researchers have tried to pierce this impressive armor of disappearing tricks using the classic tools of molecular biology: isolating schistosome proteins and their genes one by one, then trying to discern the proteins' functions and turn those molecules into effective vaccines. Now this slow and meticulous process may be thrown into higher gear by new technologies and the approaches they make possible.

Overcoming the known and yet undiscovered schistosome evasions would be vastly accelerated by having a catalogue of all the worm's proteins. For that reason, schistosome researchers have been eager to decipher the organism's genome, the complete sequence of DNA codes it uses as a blueprint for constructing every protein it contains.

But like so much else about these creatures, this goal initially proved elusive. For one thing, the schistosome genome—with more than 300 million nucleotide base pairs (the units of DNA)—is the largest parasitic genome that biologists

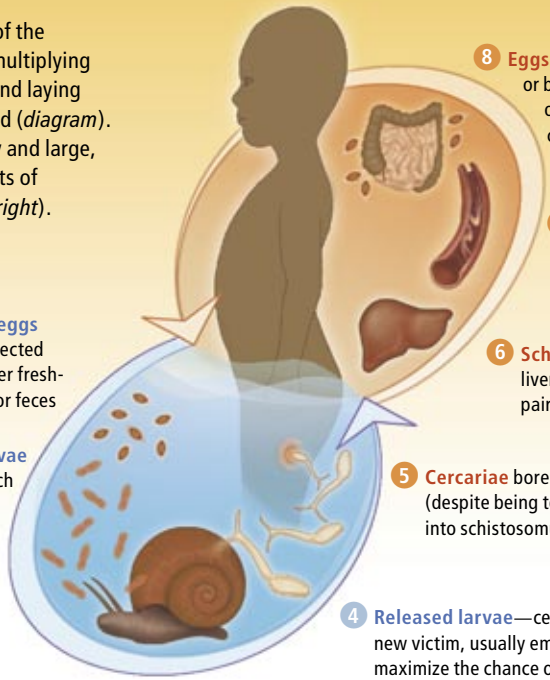
INFECTED AGAIN

Reinfection by schistosomes is common even after successful treatment because few individuals develop protective immunity and because in many areas, such as Morogoro, Tanzania, people have little choice but to wash clothes, bathe or cool off in infested water. The high rate of reinfection underscores the urgent need for a preventive vaccine.

[BIOLOGY BASICS]

A COMPLEX LIFE CYCLE

The intricate life cycle of the schistosome includes multiplying prodigiously in snails and laying eggs in a person's blood (*diagram*). Those eggs account, by and large, for the long-term effects of infection (*panel at far right*).



1 **Schistosome eggs** produced in infected individuals enter freshwater in urine or feces

2 **Snail-invading larvae** called miricadia hatch from the eggs

3 **Larvae in snails** reproduce and morph repeatedly, ultimately into a human-infecting form

4 **Released larvae**—cercariae—swim to a new victim, usually emerging in midday to maximize the chance of finding a host

5 **Cercariae** bore through the skin (despite being toothless), transform into schistosomula and enter veins

6 **Schistosomula** float to the liver circulation, where they pair up and mature into adults

7 **Worm pairs** migrate (against the flow of blood) to distant sites to lay eggs

8 **Eggs** lodge in the intestines or bladder and enter feces or urine, starting the cycle anew

How Worm Eggs Cause Chronic Disease

Schistosome eggs do harm by working their way into tissues and eliciting destructive immune reactions.

Responses to *S. mansoni* and *S. japonicum* eggs often compromise the liver and intestines and can also lead to bloody diarrhea, lethal internal bleeding and, possibly, colon cancer.

Responses to *S. haematobium* eggs can damage the urinary tract and kidneys and may induce bladder cancer.

SCHISTOSOME EGG

DANIELA NAOMI MOLNAR; NIBSC/PHOTO RESEARCHERS, INC. (*egg*); ANDY CRUMP *TDR, WHO/Photo Researchers, Inc.* (*washing clothes*)

A BRIGHT SIDE?

In experimental animals, schistosomes can prevent or ameliorate a range of debilitating autoimmune disorders, such as Crohn's disease, which causes chronic intestinal inflammation (colitis) in humans. Studies conducted by Joel Weinstock, now at the Tufts University School of Medicine, and his colleagues showed that after mice with colitis were injected with schistosome eggs, they suffered less intestinal swelling and were better protected from lethal inflammation than other mice were.

It turns out that the eggs and Crohn's disease invoke diametrically opposite immune responses. In this immunological tug-of-war, the response elicited by the eggs has the upper hand. Investigators are now hunting for the molecules that elicit these responses, because some might be valuable as therapies for autoimmune diseases. —***P.S.***

have yet attempted to sequence. (For comparison, the genome sequence of the malarial parasite *Plasmodium* is more than 10 times as small.) Just as daunting was the discovery that almost half the genome is composed of repeated DNA sequences that perform no known function. For researchers, such "junk" DNA makes deriving a completed sequence much more difficult.

Nevertheless, in an international effort spearheaded by Philip T. LoVerde, now at the Southwest Foundation for Biomedical Research, the genome of *S. mansoni* has recently been sequenced, and the sequence is available online for all to analyze. And the Chinese National Human Genome Center in Shanghai is closing in on a listing of all of *S. japonicum*'s active genes.

One great advantage of revealing the full schistosome genome is that every gene can now be seen in context of this organism's entire genetic background. We have learned, for instance, that the parasite has more than one version of some proteins that vaccines could potentially target; this variety might allow schistosomes to function in spite of vaccine-induced immune activity—by using the nontargeted version. Genomic analysis can now identify common structural features shared by such proteins so that those features might be incorporated in a vaccine and thus prevent the worms from escaping immune attack.

Alex Loukas and his colleagues at the Queensland Institute of Medical Research in Australia have taken advantage of the full genome sequence in another way. They screened it for genes whose features suggested the encoded proteins probably protruded from the tegument. The so-called tetraspanin molecules that emerged from the screen have long domains made of greasy amino acids that would be expected to span the oily surface of the outer membrane, leaving two protein loops exposed on the surface. Recently Loukas's team reported that two of these newly identified proteins, TSP-1 and TSP-2, when used to vaccinate mice, resulted in a substantial reduction in the number of adult worms and eggs in animals; in the case of TSP-2, the reduction was by more than half. The group then showed that in rare cases, people who are putatively resistant to schistosomes—who have avoided infection with the parasite despite years of known exposure—have antibodies against TSP-2 in their blood. In contrast, those who are chronically infected have no detectable level of these antibodies. This finding suggests that recognition of TSP-2 is a component of rare, natural immunity to schistosomes and that the protein might be useful for eliciting protective immunity in a vaccine as well.

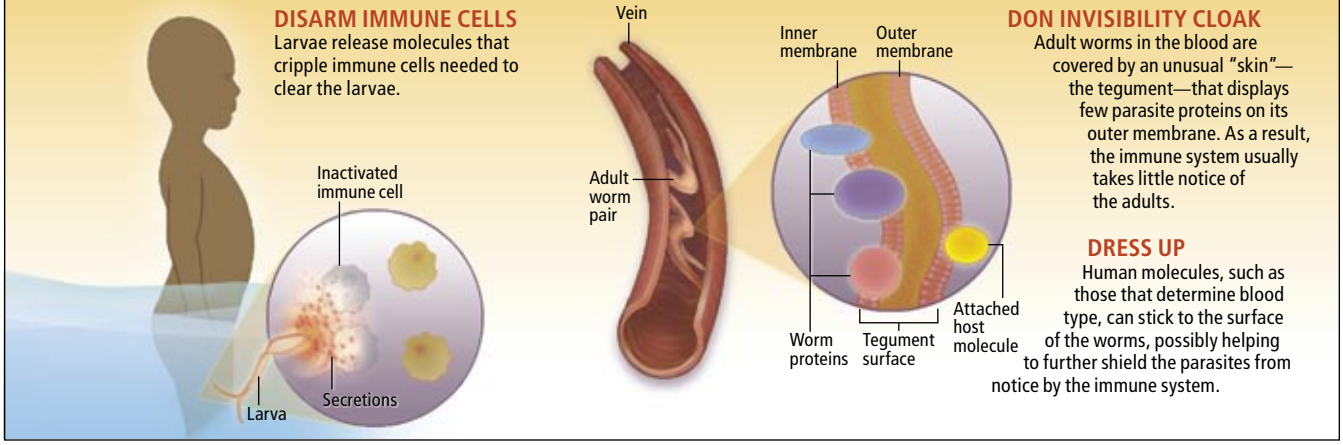
The Australian group's work is encouraging for another reason. One might reasonably wonder whether molecules that fail to evoke an immune response in the human body during an infection would be able to do so when delivered as a vaccine. Loukas's team and others, however, have demonstrated in mice that if these molecules are presented to the immune system in the right way, they can indeed, at times, elicit a strong protective response.

In parallel with examining the schistosome genome, researchers are working to understand the functions of the proteins made by the para-

[SCHISTOSOME STRATEGIES]

HOW WORMS HIDE IN PLAIN SIGHT

Schistosomes have many ways of evading the immune system, some of which are depicted below. To make successful vaccines, investigators will need to find worm molecules that when delivered to humans will elicit immune responses not defeated by such subterfuges.



DANIELA NAOMI MOLNAR

sites. Such information can help pinpoint which proteins might be the most reasonable to pursue as vaccine candidates. For instance, molecules that the worm always requires to survive or to make eggs in the human body could be useful, because an immune response targeted to them should in principle be deadly to the parasite or limit the destructive egg production.

Playing the Function Card

Several years ago knowledge of protein function led Charles Shoemaker of the Tufts Cummings School of Veterinary Medicine and me to proteins that look promising as vaccine components. These proteins are involved in importing nutrients, such as sugars and amino acids. Schistosomes, as they bathe in blood, not only gobble food through their mouth but also take in many nutrients directly through their tegument, and they require nutrient-importing proteins for this purpose. We also know that to work properly, these proteins must be in direct contact with the host's blood. These molecules are potentially very attractive as vaccine targets because prompting immunity against them could both direct a damaging attack against the parasite (because these proteins are on its surface) and impede its ability to absorb food from the blood.

A focus on function has also raised the possibility of making a vaccine from proteins that the parasites secrete. At first blush, that idea might seem silly: an immune response directed to such molecules would literally miss the target, because these molecules float away from the worm body. But if immune system components bind to these factors and thereby keep the secretions from doing jobs important to the parasite, the vaccine might reduce the worm's survival or its ability to cause disease. An obvious next step would be to shut off secreted genes one at a time, to see which ones are needed the most and would therefore be the best candidate for this approach.

Until recently, standard tools for shutting off genes did not work in schistosomes. But my laboratory and that of Tim Yoshino of the University of Wisconsin–Madison have taken a leaf from the book of 2006 Nobel Prize winners Andrew Z. Fire of Stanford University and Craig C. Mello of the University of Massachusetts Medical School and developed methods for silencing specific schistosome genes using a technique called RNA interference [see "Censors of the Genome," by Nelson C. Lau and David P. Bartel; Scientific American, August 2003]. So it is now possible to silence the genes of secreted proteins and other schistosome proteins to probe their function.

Going forward, vaccine researchers will have other new tools for uncovering the function of schistosome proteins, where they reside and when in the parasite's life cycle they are made. Notably, Paul Brindley of George Washington University, Christoph Grevelding of the University of Düsseldorf in Germany and Edward Pearce of the University of Pennsylvania are developing methods for genetically engineering worms, making it possible to add distinctive tags to a selected parasite protein; such tags will allow scientists to easily track the protein's production and location. Among other advantages, this technique could put to rest the question of which proteins normally reside in the tegument and protrude from its surface. Taking another tack, various groups, including that led by Karl Hoffman of the University of Wales, have created devices called DNA microarrays (commonly called gene chips) that can reveal which mixtures of schistosome genes are switched on at each stage of development.

The many fresh approaches to studying the parasite may yield benefits beyond ideas for vaccines. Knowing this organism's complete genetic makeup, for example, should help pinpoint proteins that are unique to schistosomes and crucial for their survival; novel drugs might then be found that act on those proteins to defeat the worm. Of course, the path from all this new knowledge and know-how to an effective vaccine or treatment is not straightforward or certain. Success will depend on researchers' intellect, intuition, dumb luck, and the level of funding governments and foundations provide. But it is exciting to know that schistosome researchers are moving in directions that were not on the map even a few years ago. ■

Vaccine Leads

The vaccine candidate in the most advanced stage of human testing relies on the schistosome protein glutathione *S*-transferase (Sm28GST) to awaken an immune attack targeted to schistosomes. In some trials of this vaccine in animals, fewer worms than usual survived, and those that did produced fewer eggs.

Recent work has identified other schistosome proteins having promise as vaccines. Those called tetraspanins, for instance, peek through the outer surface of adult worms and so can provide clear targets for immune defenses. Tetraspanin vaccines have provided some protection from infection in animal trials.

Other leads include nutrient transporters (which have to contact the host's blood directly to access nutrients and thus should be accessible to the immune system), as well as molecules secreted by the parasites to maintain infection—such as proteins that degrade host molecules or dampen antiparasite immunity. —***P.S.***

SCHISTOSOME PAIR

NIBSC/PHOTO RESEARCHERS, INC.

MORE TO EXPLORE

The Immunobiology of Schistosomiasis. Edward J. Pearce and Andrew S. MacDonald in *Nature Reviews Immunology,* Vol. 2, No. 7, pages 499–511; July 2002.

Making Sense of the Schistosome Surface. P. J. Skelly and R. A. Wilson in *Advances in Parasitology,* Vol. 63, pages 185–284; 2006.

Current Status of Vaccines for Schistosomiasis. D. P. McManus and A. Loukas in *Clinical Microbiology Reviews,* Vol. 21, No. 1, pages 225–242; January 2008.

Schistosome life cycle animation: **www.wellcome.ac.uk/en/labnotes5/animation_popups/schisto.html**

Other informative Web sites: **www.cdc.gov/ncidod/dpd/parasites/schistosomiasis** and **www.who.int/topics/schistosomiasis/en**

Dark Forces at Work

Ten years ago two teams discovered that the universe will expand forever at an ever faster rate, thanks to an unseen energy. The leader of one of the groups, Saul Perlmutter, expects that new observations will soon illuminate the universe's dark side BY DAVID APPELL

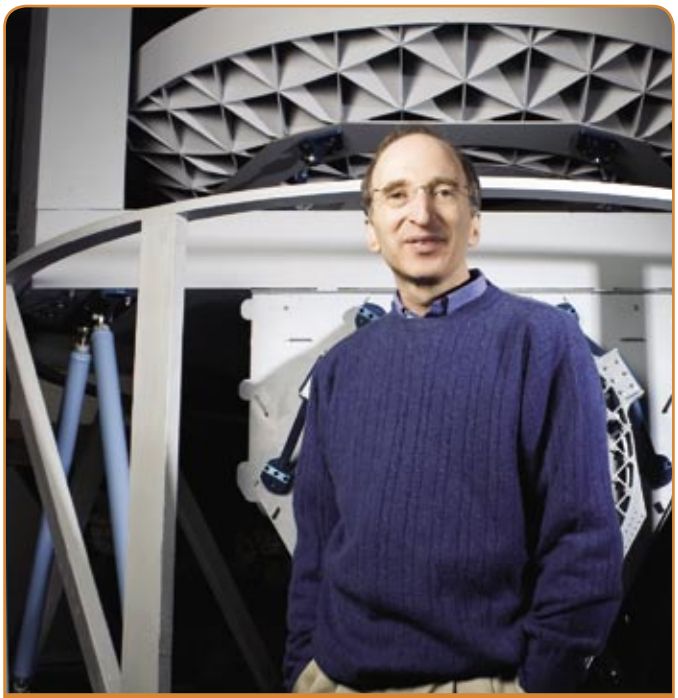
One of the chief astrophysicists behind the discovery of the acceleration of the expansion of the universe, among the most startling revelations in the history of cosmology, delights in the confusion about the observation. In fact, he wonders if the acceleration will end up being the most important feature in the ultimate explanation. "It might be something unexpected that looks like acceleration," says Saul Perlmutter, leader of the Supernova Cosmology Project (SCP), which first announced the astonishing fact in 1998. Ever the experimentalist, the 48-year-old Perlmutter is waiting, and planning, for more observations: "Until we go for a long run of more data, this just isn't a mature field."

Perlmutter philosophizes about the strangeness of the cosmos from his office at Lawrence Berkeley National Laboratory, high in the western hills of the San Francisco Bay Area. The room is the scientist's amalgam of too many computer screens, too many piles of papers and an equation-filled whiteboard that would have done Einstein proud. The spectacular view of the Golden Gate Bridge in the distance cannot help but promote lofty thinking.

It has been a decade since the science community learned of the shocking discovery made by Perlmutter's group and, independently, by the High-Z Supernova Search Team led by Brian Schmidt of the Australian National University (with analyses pioneered by Adam Riess of the Space Telescope Science Institute). The cosmos, the researchers found, is not just expanding; for unknown reasons, it is speeding up in its expansion.

The discovery took years of innovation and problem solving. The key was supernovae—specifically, those called type Ia. Such events are surprisingly invariable—the explosions have an intrinsic brightness that predictably fades over time, enabling astronomers to use them as "standard candles" and thus determine their distances from Earth. Perlmutter worked with Carl Pennypacker of the University of California, Berkeley, in the 1980s to robotically search for supernovae at relatively nearby distances. The field was then so young that their main competition came from Robert Evans, an amateur astronomer in Australia who identified supernovae with a backyard telescope.

In the beginning, the difficulty for Perlmutter's group lay in obtaining telescope time, always precious in the astronomical community. How would the researchers convince allocators to give them the chance to look for something—a supernova explosion—that had not yet taken place? So they worked out methods to predict and automatically detect supernovae in a given patch of the sky. But their goal of determining the universe's dynamics—then thought to be a decelerating expansion dominated by matter—still required additional observation to plot supernovae's brightness peaks and declines, which take place over a few weeks. Perlmutter twisted arms and begged colleagues for an hour or two on short notice, calling frantically



GABRIELA HASBUN

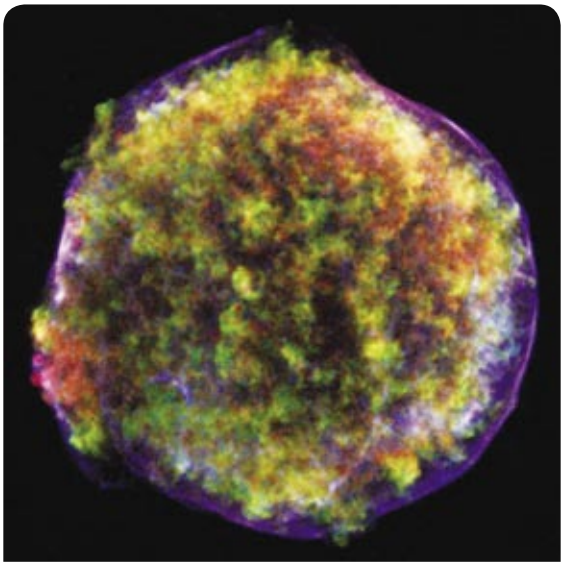
SAUL PERLMUTTER

THE NEW COSMOS: His Supernova Cosmology Project revealed that the universe's expansion is accelerating, a result that is still upending theories. About the same time, another group came to the same conclusion. (Perlmutter is standing in front of a model of the proposed SuperNova Acceleration Probe, or SNAP, for which he is lead scientist.)

DARK TIMES: Data gathered so far suggest that just 5 percent of the universe is made up of ordinary matter; the rest is dark matter (23 percent) and the negative gravity force called dark energy (72 percent).

around the world at all times of the day. Everyone knew him, he says, as half-annoying. "I was always worried about something that had to happen in the next 24 hours or sometimes the next two hours. It was a terrible way to lead an ordinary life," he recalls.

But persistence paid off. Observations of distant type Ia supernovae found them to be dimmer than expected. After eliminating the possibility of intergalactic dust and after years of painstaking data gathering and analysis at telescopes around the world (and in orbit), Perlmutter's team came to the conclusion that, incredibly, the universe is not only expanding, as Edwin Hubble discovered in 1929, but that its expansion rate is increasing. Some unknown force with negative pressure seems to be pushing the universe apart.



TYPE IA SUPERNOVA, which in 1572 produced this remnant, can elucidate cosmic expansion if the initial blast is seen.

Subsequent balloon-borne observations of the cosmic microwave background made two years later showed that the universe is spatially flat—it was stretched out by an exponential expansion, called inflation, right after the big bang. The equations behind these experiments complemented those of the supernova teams taken a few years earlier, and together the results enabled scientists to calculate separately the density of dark energy in the universe and the density of matter.

But on the other hand, the discovery opened a mystery the size of, well, the universe. The simplest explanation is that dark energy is Einstein's famed "cosmological constant," an energy that permeates space but does not interact with any type of matter. Today astronomers have homed in on the details of this scenario; if true, then the universe consists of 72 percent antigravity dark energy, 23 percent dark matter (unseen and uncharacterized, but susceptible to gravity), and 5 percent normal matter (protons, neutrons, electrons). We would be just a small part of totality, surrounded by perplexity.

"It could well be that there's some big piece of reality that we don't fully understand," says astronomer Christopher Stubbs of Harvard University, who in a paper likened the new universe to "living in a bad episode of *Star Trek*." Physicist Steven Weinberg of the University of Texas at Austin calls it simply "a bone in the throat of theoretical physics."

Magic has not yet been proposed to explain the accelerating universe, but almost everything else has. In the past few years, physicists have widened their search beyond vacuum energy to include possible modifications to general relativity, spinless energy fields that vary with time and space, massive gravitons, brane worlds and extra dimensions. "All of them are so exciting, and any is going to rewrite the textbooks," says Eric Linder, a cosmologist at Lawrence Berkeley and U.C. Berkeley. The hypothetical repulsive dark energy field may well not survive in the final explanation.

"It's true the theorists right now are stuck," Perlmutter says. "But from an experimentalist's point of view, this is great: we have a mystery, and we have ways to get at it"—namely, in the form of new telescopes and satellites to look even farther across the universe (and, hence, farther back in time).

Ground-based projects are already gathering more data, looking for hundreds of type Ia events (instead of Perlmutter's and Schmidt's five dozen) to determine the relation between the pressure and density of the universe, akin to the ideal gas law. A galaxy like our Milky Way exhibits about one type Ia supernova every few hundred years, and its brightness fades in weeks, making the search for them quite a challenge. By observing the cosmic background radiation, the soon-to-launch Planck satellite will contribute more details about the universe's expansion.

Dark energy aficionados look especially to the Joint Dark Energy Mission, now in the planning stages in the U.S. for a possible launch in 2014. The probe will host a device that could find thousands of supernovae a year and provide far smaller error bars than anything done so far. One candidate is the SuperNova Acceleration Probe (SNAP), for which Perlmutter is the lead scientist and Linder the head theorist. It would host a telescope about two meters wide and have a gigapixel camera.

The discovery of cosmic acceleration will assuredly win a Nobel Prize, and over the years there has been some dispute over which team deserves priority. Perlmutter's SCP team announced the discovery first, but Schmidt's High-Z team beat the SCP group in publishing the finding. Both Perlmutter and Schmidt shared one fourth of the 2007 Gruber Cosmology Prize, with the remaining fraction going to their two teams collectively.

Gregarious and talkative, Perlmutter attributes his success to being able to convey his excitement and convince other researchers to join his team. An amateur violinist who also teaches an undergraduate physics and music course, he draws an orchestral analogy. "As a violinist, I always love the moments when a group of people are creatively tuned in together." ■

David Appell is based in Portland, Ore. A Q&A version of his interview is at **www.SciAm.com/sciammag**

NASA/CXC/RUTGERS/J. WARREN AND J. HUGHES ET AL.

Living Cover

By Mark Fischetti

Cities worldwide are promoting environmentally "green" roofs to mitigate several urban problems. Ground cover, shrubs and other flora planted across a building's roof can reduce storm water runoff, easing the burden on local sewers and water treatment systems. And the vegetation can keep the roof cooler in summer, lowering interior air-conditioning costs and therefore peak demand on area power plants.

Green roofs have been blossoming in Europe for more than a decade, and Tokyo now requires that at least 20 percent of any new roof on medium and large buildings be cultivated. Chicago is the U.S. leader. Most installations are made on newly constructed buildings, but retrofits are rising.

In either case, the formations are built up in a series of layers that span all or part of a roof [*see main illustration*]. So-called extensive roofs have fairly thin cross sections, including perhaps three inches of soil-like growing material; they weigh from 15 to 25 pounds per square foot when saturated and support low-lying plants. Intensive roofs are thicker, heavier and more costly to erect and maintain but are capable of supporting flowerbeds, shrubs, even trees. "As the plants get more demanding, the layers must become more robust, with better drainage and aeration," says Jeff Stillman, executive vice president of ZinCo USA in Newton, Mass., a division of ZinCo, Inc., the world's largest supplier of green roof components.

Prefabricated modules of a few feet square that contain similar layers can also be assembled like puzzle pieces; this approach can be easier to install, although it can be expensive and also results in seams.

The main drawback of all the approaches is cost. Some roofs—typically older ones—may not be strong enough to handle the weight. Standard insurance policies may construe a green roof as a structure that can create "standing water" damage, which a policy probably will not cover unless it is amended. Extensive roofs typically require minimal maintenance and an occasional dose of slow-release fertilizer; intensive roofs require more ongoing attention. Both styles, however, can turn a hot, bald roof into a pleasant space for coffee breaks, lunch, sunbathing or a simple breath of fresh air.

DID YOU KNOW ...

NOT DIRT: Installers rarely use soil for the growing medium because it is heavy and because it packs tight after repeated rains, reducing water retention and aeration for plant roots. They instead use manufactured materials. For example, granulated clay or shale may be heated until it forms air pockets; it is then cooled. Organic compost and fertilizer are added as nutrients.

COOLER CONDITIONING: On a sunny, 80-degree-Fahrenheit day, a tar or black-painted roof can reach 180 degrees F; a white roof 120 degrees; and a plant-covered roof 85 degrees. Even if the building has ample roof insulation to retard interior heating, the intake vents for air-conditioning units are often located on the roof. Cooler incoming air lessens the system's burden, notes Jeff Stillman of ZinCo USA.

HEAT ISLAND EFFECT: If installed widely, green roofs could lower a city's cooling load, especially at night when bare rooftops radiate heat absorbed during the day. Since 1900 Tokyo's average temperature increase has been five times that of global warming, according to Tokyo Metropolitan University—one big reason the city is pushing such construction.

***SEDUM* PREFERRED:** Plants most recommended for green roofs belong to the genus *Sedum.* They grow low, store plentiful water in their leaves, and are bred to withstand temperature and moisture extremes. Common varieties include cape blanco, coral carpet and dragon's blood.

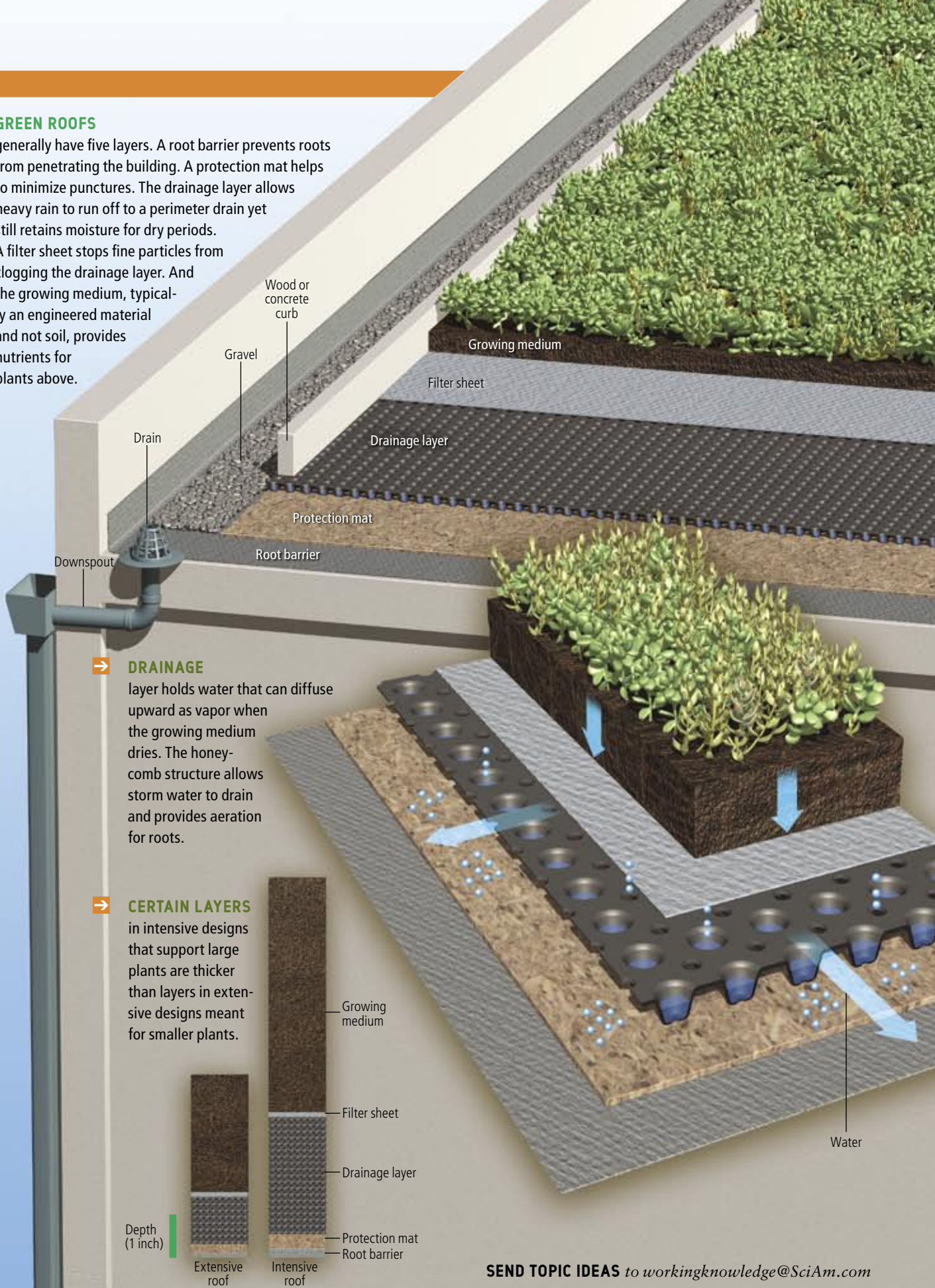
U.S. GREEN ROOFS COMPLETED IN 2006 (square feet)

ROOFTOP GARDEN overlooks residential Tokyo.

GEORGE RETSECK (*opposite page*); DANIELA NAOMI MOLNAR (*this page*); REUTERS/CORBIS (*photograph*); SOURCE FOR ROOF DATA: GREEN ROOFS FOR HEALTHY CITIES

GREEN ROOFS

generally have five layers. A root barrier prevents roots from penetrating the building. A protection mat helps to minimize punctures. The drainage layer allows heavy rain to run off to a perimeter drain yet still retains moisture for dry periods. A filter sheet stops fine particles from clogging the drainage layer. And the growing medium, typically an engineered material and not soil, provides nutrients for plants above.



DRAINAGE

layer holds water that can diffuse upward as vapor when the growing medium dries. The honeycomb structure allows storm water to drain and provides aeration for roots.

CERTAIN LAYERS

in intensive designs that support large plants are thicker than layers in extensive designs meant for smaller plants.

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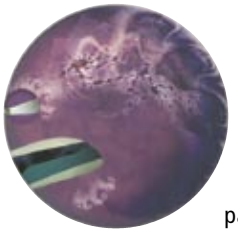
BY MICHELLE PRESS

FLATLAND: THE MOVIE

by Seth Caplan, Jeffrey Travis and Dano Johnson. Includes DVD, original novel by Edwin A. Abbott, essays on making the movie and an introduction by Thomas Banchoff. Princeton University Press, 2008 ($29.95)

Edwin Abbott Abbott wrote the mathematical allegory *Flatland* in 1884. Enmeshed in his two-dimensional world, the hero, A. Square, has an epiphany: there is an existence beyond his plane, a three-dimensional universe. By laying out how two dimensions relate to our three, Abbott entices the reader to imagine how our own world would relate to a fourth spatial dimension. And by showing the tendency to take refuge in dogma, the book satirizes Victorian class consciousness and attitudes toward women; the females of Flatland, for example, are lines, who present a danger to males, especially to the priestly circles, whom they might fatally pierce.



The filmmakers have animated the story—not the first such attempt—to make it more accessible to 21st-century readers. Their essays on the aesthetic choices they faced make fascinating reading: How do you depict a two-dimensional creature turning around and moving in the opposite direction, for instance? (See the DVD for their successful solution.) I asked Peter White, an eight-year-old friend unfamiliar with the novel, what he thought of the movie. He liked the graphics and the length (about 30 minutes), and he said he understood the "larger concept": that you can believe in things you can't see, such as other dimensions. But he had a lot of questions about motivation: Why did the priestly circles care about whether others knew about the third dimension? Why was that particular square chosen to receive this knowledge? and so on. It is true, the movie (necessarily) oversimplifies the story. It provides inspiration to read the novel rather than replacement for it—and delight for *Flatland* fans of all ages.

EXCERPT

AGAINST HAPPINESS: IN PRAISE OF MELANCHOLY

by Eric G. Wilson. Farrar, Straus and Giroux, 2008 ($20)

Wilson, a professor of English at Wake Forest University and the author of five books on the relation between literature and psychology, is careful to draw a line between clinical depression and ordinary melancholy. He then argues against relentlessly seeking happiness:

"A recent poll conducted by the Pew Research Center shows that almost 85 percent of Americans believe that they are very happy or at least happy. The psychological world is now abuzz with a new field, positive psychology, devoted to finding ways to enhance happiness through pleasure, engagement, and meaning.... Surely all this happiness can't be for real. How can so many people be happy in the midst of all the problems that beset our globe?...

"I for one am afraid that our American culture's overemphasis on happiness at the expense of sadness might be dangerous, a wanton forgetting of an essential part of a full life. I further am wary in the face of this possibility: to desire only happiness in a world undoubtedly tragic is to become inauthentic, to settle for unrealistic abstractions that ignore concrete situations. I am finally fearful over our society's efforts to expunge melancholia from the system. Without the agitations of the soul, would all of our magnificently yearning towers topple? Would our heart-torn symphonies cease?"

NEW AND NOTABLE BOOKS ABOUT NUMBERS

1 **One to Nine: The Inner Life of Numbers**
by Andrew Hodges. W. W. Norton, 2008 ($23.95)
Beginning with the puzzle of unity and ending with the recurring nines of infinite decimals, Hodges tackles mathematical conundrums in elegant, witty prose.

2 **Guesstimation: Solving the World's Problems on the Back of a Cocktail Napkin**
by Lawrence Weinstein and John A. Adam. Princeton University Press, 2008 (paperbound, $19.95)
Through a series of puzzles, the book shows how to make numerical estimates.

3 **The Jinn from Hyperspace: And Other Scribblings—Both Serious and Whimsical**
by Martin Gardner. Prometheus Books, 2007 ($25.95)
A collection of published, and a few unpublished, writings with new introductions.

4 **Group Theory in the Bedroom, and Other Mathematical Diversions**
by Brian Hayes. Hill & Wang, 2008 ($25)
Twelve essays, each built on a mystery, that explore the surprising mathematics of everyday life.

5 **The Book of Numbers: The Secret of Numbers and How They Changed the World**
by Peter J. Bentley. 350 illustrations in color and black-and-white. Firefly Books, 2008 (paperbound, $29.95)
"Numbers rule our lives," says Bentley, who then tells us how and why this is so.

FROM *FLATLAND: THE MOVIE* (geometric characters); FROM *THE BOOK OF NUMBERS* (head)

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Q *Why does my* ***cell phone screech*** *when it is near my computer?*

David Grier, chair of the physics department at New York University, dials up some possible answers to this mystery:

It sounds like a case of electromagnetic interference, or EMI: radio waves emitted by one device causing undesirable behavior in another. Virtually every piece of electrically powered equipment acts as a radio transmitter, whether it is supposed to or not; the changing electric currents running through these devices naturally radiate electromagnetic waves. This radiation is an inevitable by-product of harnessing electricity to do useful things, analogous to the clanking and clattering of traditional mechanical devices. Computers are particularly "noisy" because they rely on rapidly changing currents to act as clock signals that coordinate their calculations.

One possible explanation is that your computer unintentionally emits radio waves in the range of frequencies reserved for cell phone communications, typically around 800 megahertz (millions of cycles per second). If the signal coming from your computer were strong enough, your phone could mistake it for a cell phone transmission—albeit an indecipherable one.

Another possibility involves a deeper connection between your two devices. Just as changing currents generate radio waves, radio waves induce electric currents in conducting materials—which is how a metallic antenna allows a radio to detect signals transmitted by radio stations. The radio waves emitted by your computer may induce currents in the amplifier that drives your cell phone's speaker, which would cause it to produce random squeaks and squawks. (In 1975 computer pioneer Steve Dompier cleverly commandeered this effect, with more tuneful results: he programmed his PC, a MITS Altair 8800, so that its EMI would play the Beatles' "The Fool on the Hill" through a nearby AM radio.)

There is no way to stop electrical devices from generating radio waves, but keeping spurious waves under wraps will curb EMI. Most electronic devices are housed in cases—either made of metal or coated with a conductor—that trap these electromagnetic waves, but holes in the cases and thin spots in the coating allow some waves to escape. Usually the leakage is so small that it just affects objects very near the source, which is why your cell phone only acts up right next to your computer.

Q *How does the* ***weight of CO_2*** *released in combustion exceed the weight of the fuel burned? And by how much?*

—B. Easley, Jackson, Miss.

Susan Trumbore, chair of the earth system science department at the University of California, Irvine, replies:

Carbon fuels generally exist in reduced form—that is, the carbon atoms are attached mostly to hydrogen atoms. During combustion, the carbon becomes oxidized (combined with oxygen from the air) to make carbon dioxide (CO_2). Because oxygen is far heavier than hydrogen, the product is heavier than what is burned.

Take gasoline, for example. One of its primary components, octane, is a molecule made up of eight carbon atoms and 18 hydrogen atoms. The weight of one mole (6.02×10^{23} units) of octane molecules is equal to the weights of eight carbon atoms (at 12 grams per mole each) plus 18 hydrogen atoms (at one gram per mole each). Octane therefore weighs 114 ($8 \times 12 + 1 \times 18$) grams per mole.

The weight of CO_2 is 44 grams per mole (1×12 grams per mole for the carbon and 2×16 grams per mole for the oxygen). If all the octane combusts to carbon dioxide, each of its eight carbon atoms becomes part of a CO_2 molecule, yielding eight CO_2 molecules per octane molecule burned—or eight moles of CO_2 per mole of octane burned. Combusting one mole of octane, therefore, would produce 352 (8×44) grams of CO_2.

Thus, the weight ratio of CO_2 produced to octane burned is 352 to 114, or roughly 3 to 1. Actual ratios will vary, however, because gasoline is not purely octane. ■

HAVE A QUESTION?... *Send it to experts@SciAm.com or go to* **www.SciAm.com/asktheexperts**

ELKE VAN DE VELDE *zefa/Corbis (top);* TIM RIDLEY *Getty Images (bottom)*