GEOENGINEERING: How to Cool the Earth—at a Price (*page 24*)

SCIENTIFIC AMERICAN

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SPECIAL REPORT

HIV 25 Years Later: IS A CURE POSSIBLE?

page 46

PLUGGING into the BRAIN

Download new memories?
Control machines by thought?
Can this be the ultimate computer interface?

Order from Chaos

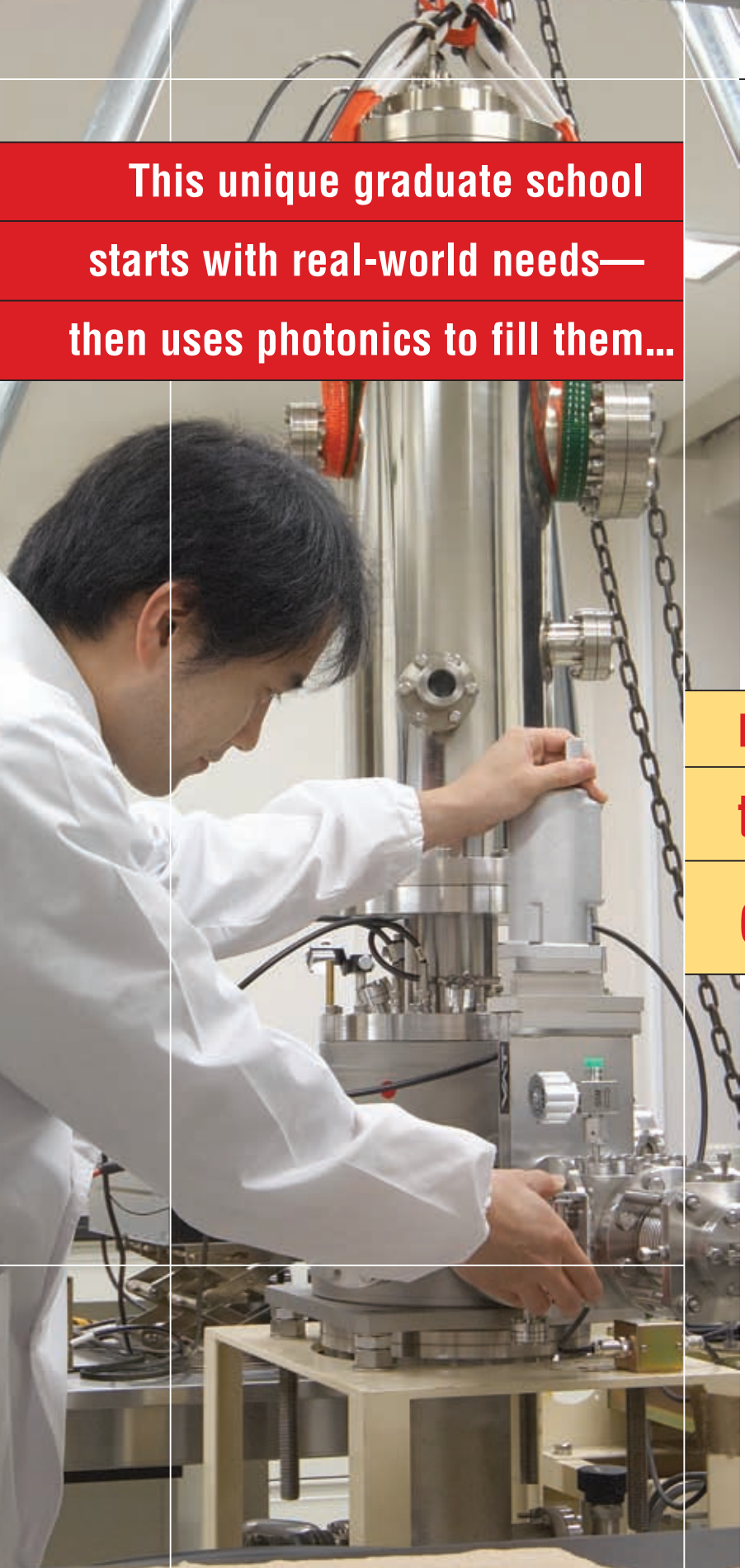
How Nature "Breaks" the Second Law of Thermodynamics

Scan Anywhere

MRI-like Machine Becomes Portable

DNA Logic

Program Molecules for Work and Play



This unique graduate school starts with real-world needs— then uses photonics to fill them...

Hamamatsu is opening the new frontiers of Light

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Another develops laser-based therapeutic instruments for treating living tissue.

Another is creating new measurement technology using colloidal crystals and UV detectors.

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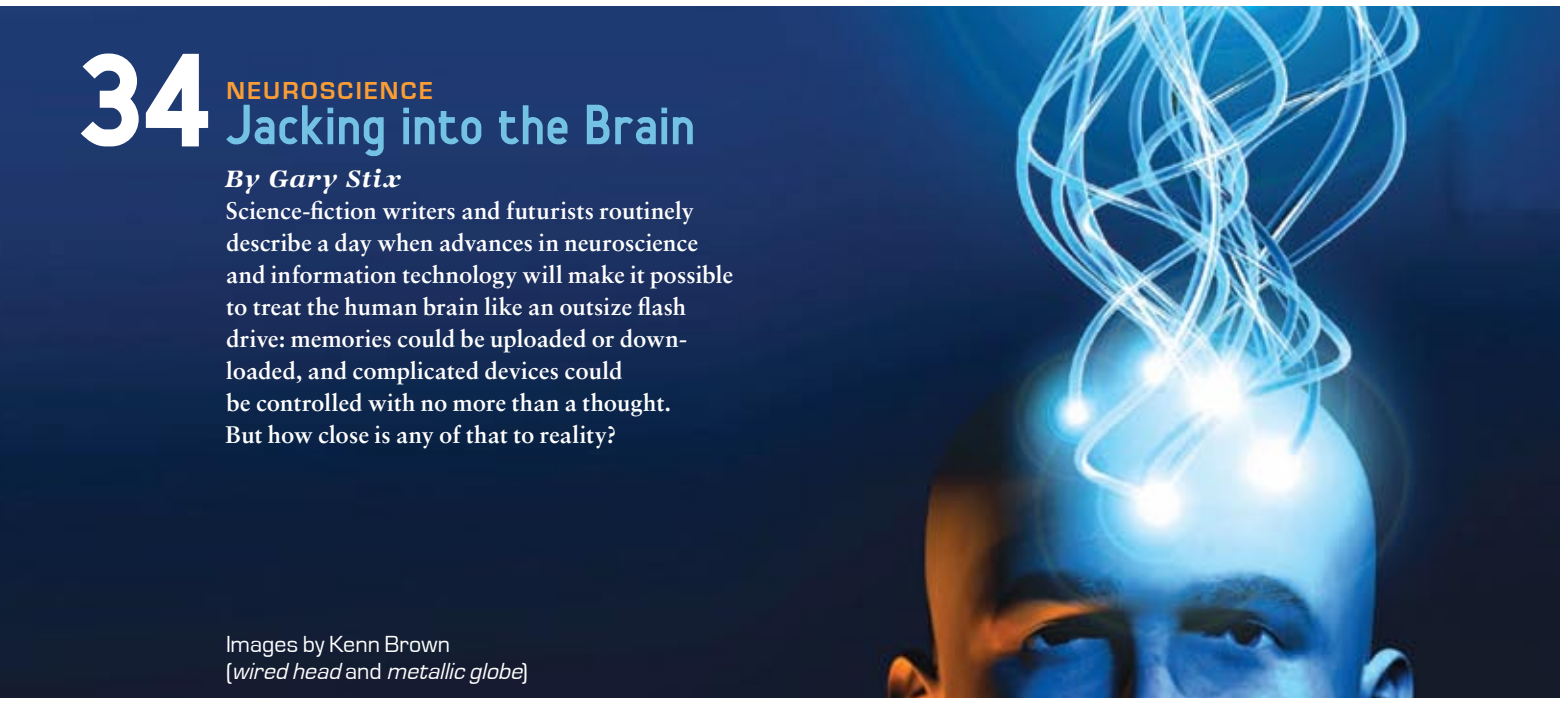
http://jp.hamamatsu.com/en/rd/publication/

HAMAMATSU

Photon is Our Business

An associate professor sets up an imaging mass spectrometer for a student project investigating ion distribution at the subcellular level—at the *Graduate School for the Creation of New Photonics Industries* in Hamamatsu City, Japan.

SCIENTIFIC AMERICAN November 2008 ■ Volume 299 Number 5



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Jacking into the Brain
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Science-fiction writers and futurists routinely describe a day when advances in neuroscience and information technology will make it possible to treat the human brain like an outsize flash drive: memories could be uploaded or downloaded, and complicated devices could be controlled with no more than a thought. But how close is any of that to reality?

Images by Kenn Brown
[*wired head* and *metallic globe*]

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Brain signals now can control a cursor or a prosthetic arm. How far will the human-machine interface go? Image by Kenn Brown.

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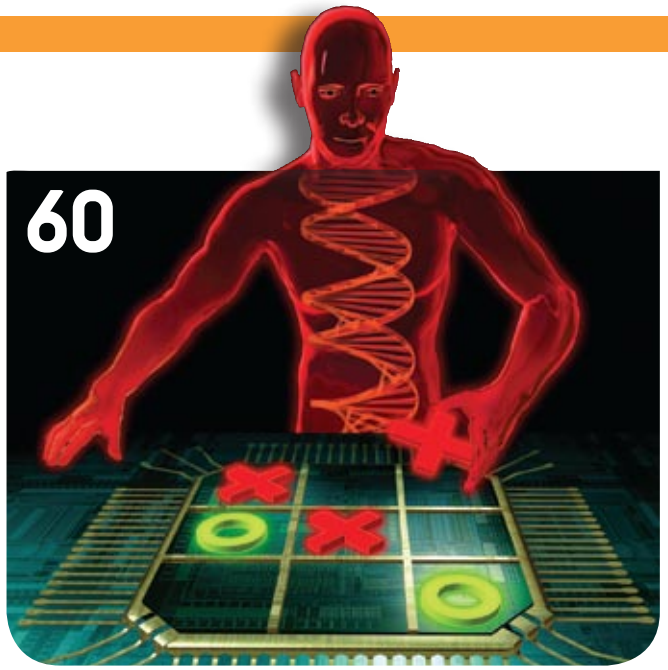

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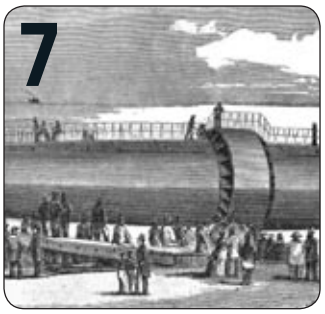

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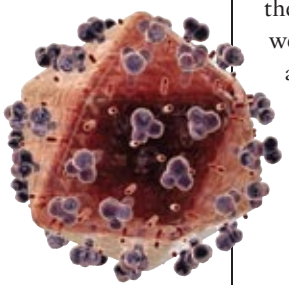
Hope and HIV

The battle must continue, even if 25 years of research have disappointed

In February, Nobel laureate David Baltimore, president of the American Association for the Advancement of Science (AAAS), could scarcely have been more depressing. "We have been trying to make an HIV vaccine since the day HIV was discovered. In 1984 we were told that as the virus had been found, a vaccine should be just around the corner," he reminded an audience at the annual AAAS meeting in Boston. "Every year since then, we have been saying it is at least 10 years away. I still think it is at least 10 years away."



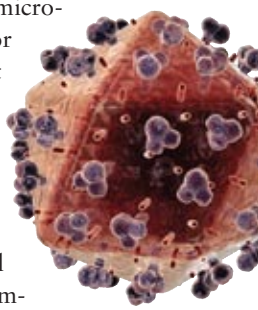
All attempts with vaccines to raise antibodies against HIV had failed, he observed. Researchers would need to go back to basics and pursue new approaches to fighting the virus. "Our lack of success may be understandable," Baltimore declared, "but it is not acceptable." It was (and remains) an admirable sentiment, but of course determination is no substitute for results for those in need.

A grim report in August from the Centers for Disease Control and Prevention drove home how numerous those in need are. The CDC concluded that it had been underestimating the number of new HIV infections in the U.S. by about 40 percent annually for the past 10 years or more. More than half of all new infections were in gay and bisexual men; African-Americans were seven times as likely to have contracted a new infection as whites, and Latinos were three times as likely. The catastrophe of HIV/AIDS in the developing world is even more horrifying.

If the past quarter of a century of vaccine research has been bleak, so has the outlook for a cure. Beyond killing certain immune cells outright, HIV can infiltrate and lie dormant in the central nervous system, the gut and other tissues, waiting for a chance to erupt and renew its assault on the body. So far the dream of curing HIV infections by eliminating the virus from the body remains elusive.

Even so, all is not lost. Our special report on the 25-year fight against HIV, beginning on page 46, looks at both the vaccine and virus-elimination efforts, reviews where they failed and identifies the best opportunities for making some progress in the future.

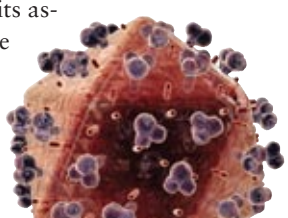
Moreover, public hygiene–based prevention efforts and aggressive treatments of infections can still do much of what elusive vaccines and cures ever would, if society is prepared to commit to them. Safe-sex education and condom-distribution programs can help prevent not only HIV infections but also other sexually transmitted diseases. Meanwhile microbicides—creams and gels for killing vaginal infections that raise the risk of HIV transmission—show tremendous promise; they deserve far more research funding than they have received to date. Strong epidemiological evidence suggests that circumcision, too, reduces the risk of transmitting HIV as much as 60 percent.



For many HIV patients, protease inhibitors and other drugs have turned their infections into long-term manageable conditions. The treatment regimen called HAART (*h*ighly *a*ctive *a*nti*r*etroviral *t*herapy) can knock viral levels in the body down so low that transmission risk is greatly reduced. Scientists are even checking whether people at risk for infection might benefit from taking antiretroviral drugs before they are exposed.

Ideas for fighting HIV are not in short supply. But well-directed funding and commitment to clear-sighted public health policies sometimes are. We can't blame the virus for that. ■

JOHN RENNIE
editor in chief



FLYNN LARSEN (*Rennie*); ZYGOTE MEDIA GROUP, INC. (*3-D computer renderings of HIV*)

Among Our Contributors

BERNHARD BLÜMICH
developed the portable NMR scanner and is a professor of macromolecular chemistry at RWTH Aachen University in Germany.

ROBERT KUNZIG
is a freelance journalist and author of two books: *Mapping the Deep,* on the history of ocean science, and *Fixing Climate* (with Wallace S. Broecker), on responding to global warming.

J. MIGUEL RUBÍ
is a professor of physics at the University of Barcelona and a past recipient of the Onsager Medal and the Alexander von Humboldt Prize for his work on nonequilibrium thermodynamics.

MARIO STEVENSON
is a professor of AIDS research at the University of Massachusetts Medical School and a fellow of the American Academy of Microbiology.

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No-Till Farming ▪ Spacetime Triangles ▪ Dancing Animals

JULY 2008

"I cannot believe that anyone other than the herbicide manufacturers is seriously proposing that flooding the earth with lethal chemicals is any solution to the problems of agriculture."
—Louise Tremblay Cole GALT, CALIF.

Justifiable Herbicide?

In "No-Till: The Quiet Revolution," David R. Huggins and John P. Reganold argue for no-till farming as a more sustainable alternative to plow-based agriculture and describe how herbicide use has enabled growers to effectively practice no-till on a commercial scale. I cannot believe that anyone other than the herbicide manufacturers is seriously proposing that flooding the earth with lethal chemicals is any solution to the problems of agriculture. Their effect on humans and other animals is known, and their effect on soil and groundwater is potentially disastrous (even if the Environmental Protection Agency gives out assurances about the latter). Producing enough food to feed the world's population without harming the earth is a hard question; this is certainly not the answer.

Louise Tremblay Cole
Galt, Calif.

THE AUTHORS REPLY: *As we have stated, reliance on herbicides is a weakness of no-till as it is currently practiced. We contend, however, that no-till is a positive step in the evolution toward more sustainable farming. In addition, we support and are actively engaged in research efforts that integrate no-till into strategies that limit or even eliminate synthetic pesticide use, as in organic production.*

Tillage exposes fertile topsoil to the ravages of water and wind, resulting in soil erosion rates that are greater than soil renewal rates in many parts of the world. Sadly, this practice imperils worldwide food security and environmental quality. The fall of past civilizations has been "written on the land," as soil erosion claimed their capacity to produce food. No-till agriculture preserves precious topsoil, bringing erosion rates into line with those of soil formation. But no-till currently comes with the trade-off of using herbicides.

We share Cole's skepticism about herbicides—not all is known about their impacts—and support science-based efforts to assess the short- and long-term effects of such chemicals as well as other agricultural tools and practices within the guiding precepts of sustainable agriculture. We also share Cole's concern of feeding the world's population while protecting the environment. We believe we will not only need appropriate emerging technologies and traditional conservation farming practices but also good government policies, smart business models and social ingenuity to accomplish this.

Universal Units?

In "The Self-Organizing Quantum Universe," Jan Ambjørn, Jerzy Jurkiewicz and Renate Loll describe how, in looking to reconcile quantum theory with Einstein's general theory of relativity, they developed a new approach to quantum gravity called causal dynamical triangulations. In this approach, on the smallest scales spacetime has only two dimensions (approximated as a series of triangles), but on larger scales it smoothly transforms to three, then four dimensions (approximated as the triangles constructing curved shapes).

Could this fact mean that quantum mechanics would apply only to particles that experience less than four dimensions and that relativity would apply only to the four-dimensional universe?

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If so, there would seem to be no point in looking for a mathematical framework that can join these two pillars of physics.

Howard Wolowitz
via e-mail

Ambjørn, Jurkiewicz and Loll state that "space keeps its overall form as time advances; it cannot break up into disconnected pieces." How, then, is the expansion of the universe explained by the geometric spacetime structures they describe? Perhaps new pieces keep getting created in between and push away the others?

Fuat Bahadir
Omaha, Neb.

THEORY of causal dynamical triangulations approximates spacetime as a mosaic of triangles. On small scales, each triangle is "flat." But on larger scales, they can create curves.

THE AUTHORS REPLY: *As to the first question, all known elementary particles—those that are in an energy range that allows us to observe them directly in particle accelerators—behave according to the rules of both quantum mechanics and four-dimensional space, so there is no contradiction here. The phenomenon of the change in the spectral dimension observed in the theory of causal dynamical triangulations happens on much shorter scales and crucially needs the input of both general relativity and quantum theory in a unified way. This unusual behavior will affect particles (matter) as well as the dynamical behavior of spacetime itself at these scales.*

Regarding the second question, when we wrote about the "overall form" of space, we were referring to the way it "hangs together" as a whole (what a mathematician would call its topology). This approach still leaves the freedom for space to grow or shrink, to bend, deform or develop bumps in places, and so on, which indeed will depend on how the microscopic pieces fit together, appear and disappear. The important point is that three-dimensional space cannot break up into several pieces or develop additional handles to change its overall connectedness.

Beat and the Beast

I disagree with Steven Brown and Lawrence M. Parsons's assertion in "The Neuroscience of Dance" that humans are the only species that can dance or display rhythm. Other species are quite capable of displaying rhythm. Horses performing dressage, for instance, are accompanied by music. And parrots and other birds move to music. (A simple Google search for "animal dancing" returns many videos of animals exhibiting rhythmic movement as well.) Although one can argue that these animals are displaying learned behaviors, they must have a predisposition for rhythmic movement.

Dennis Carrasquillo
via e-mail

THE AUTHORS REPLY: *Our point on unique human rhythm capacity was not about synchronization per se but about the ability to entrain to an isochronous (steady) beat, as is typical in group dance and music. We are not aware of any evidence that nonhuman animals naturally show coordinated group movements to an isochronous beat. Since completing our article, however, two teams of colleagues (led by Aniruddh D. Patel of the Neurosciences Institute in San Diego and by Marc D. Hauser of Harvard University) have reported studies showing evidence that parrots, cockatoos and macaws can move in synchrony to a limited range of musical beats.*

Thus, the ability of an individual to synchronize to an isochronous beat may not be limited to humans. Such a capacity in birds is latent, though, because in the wild they do not generate isochronous sounds and hence have no opportunity to entrain to beats. Research in this area is developing rapidly, so we will all need to stay tuned.

Letters to the Editor

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Letters may be edited for length and clarity. We regret that we cannot answer each one. Join the discussion of any article at www.SciAm.com/sciammag

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JEAN-FRANCOIS PODEVIN

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Ideology Trumps Science ▪ The Too Big Diamond ▪ Light Cure

Compiled by Daniel C. Schlenoff

NOVEMBER 1958

POLITICS BEFORE DATA—"The school of Soviet genetics led by Trofim D. Lysenko seems to have acquired a new lease on life. It had been expected that various non-Lysenkoist geneticists would represent the U.S.S.R. at the International Congress of Genetics in Montreal, but none arrived. Their absence, and the last-minute submission of several papers, gave the Soviet contribution to the meeting a distinctly Lysenkoist flavor. The Congress adopted a resolution condemning 'any attempts on the part of governments to interfere on political, ideological or other grounds with the free pursuit of science and free dissemination of scientific information.'"

THERE WILL BE COSTS—"In the deeper sections of a 20,000-foot well the drilling costs increase to more than $100 a foot; with crude oil at $3 a barrel, the well must be a good producer to pay for itself. When it comes to exploratory drilling, these costs look even more forbidding. The world record 25,000-foot well may be close to the economic limit of present drilling methods. Yet sedimentary rock deposits in some areas are over 40,000 feet thick, and there seems to be no geologic reason why oil should not be found at these enormous depths. If the rapidly increasing demand for oil products is to be satisfied, we must find ways of exploring and tapping these deep formations."

NOVEMBER 1908

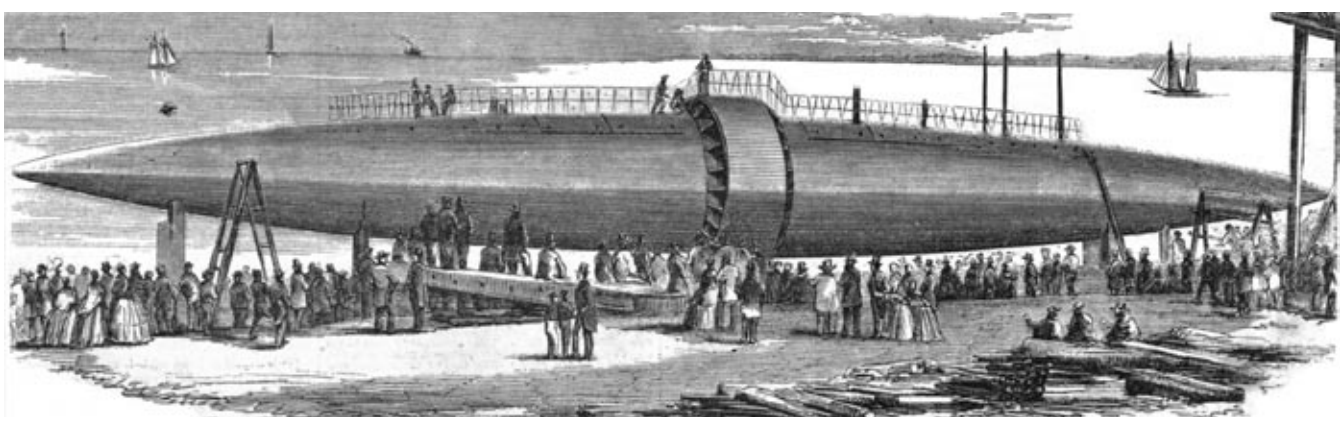
ANXIOUS WORK—"The famous Cullinan diamond has been successfully divided into eleven stones. The diamond was a white elephant in its way. Too big and too precious to find a purchaser, the problem of disposing of it perplexed the company not a little. Finally it was decided to present the stone to King Edward, who entrusted an Amsterdam firm with the splitting and polishing. The *London Times* states that in the original state the Cullinan weighed over 1.3 pounds avoirdupois. Normally a brilliant has fifty-eight facets. In view, however, of the immense size of the Cullinan it was determined to give seventy-four facets. This decision has been abundantly vindicated by the results."

NOVEMBER 1858

LET THERE BE LIGHT—"Sir James Wylie, late physician to the Emperor of Russia, attentively studied the effects of light as a curative agent in the hospitals of St. Petersburg. He discovered that the number of patients cured in rooms properly lighted was four times greater than that of those confined in darkness. This led to a complete reform in lighting the hospitals of Russia, with the most beneficial results. These results are due to the agency of light, without a full supply of which plants and animals maintain but a sickly and feeble existence. The health statistics of all civilized countries have improved greatly in the past century. This may be justly due to the superior construction of houses, by admitting more light into them."

CIGAR BOAT—"Two weeks ago we noticed the novel steamship in course of construction by Messrs. Winans, of Baltimore, Md. We now give a view of it taken from a photograph. The propellers are arranged between the two halves of the ship, protected by a sleeve or guard from being damaged by floating timber, drift, or the piers at which it may be lying. To the hull will be added ventilators, smoke stacks and pilothouse. Such is the construction in this boat, which is without sails, so that if any accident occurs to the machinery, it must lie a helpless log upon the waves. However strongly its parts may be secured, its shape is an unstable one, as any one can see for themselves by observing the motion of a barrel on waves or any rough water."

[NOTE: The ship, designed for surface travel, had some innovative ideas but despite extensive modifications was never truly seaworthy.]



WINANS STEAMSHIP under construction, 1858

SCIENTIFIC AMERICAN, VOL. XIV, NO. 9; NOVEMBER 6, 1858

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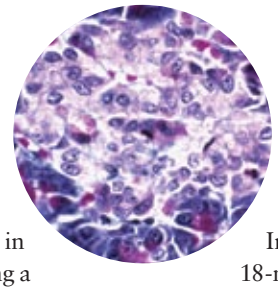
Diabetes ▪ Methane from Grass ▪ Virus-Built Battery ▪ The Skinny on Brown Fat

Edited by Philip Yam

Targeting Troublesome T Cells

In type 1 diabetes, renegade T cells of the immune system kill the insulin-making beta cells of the pancreas. New beta cells could, in theory, cure diabetes, but because the misguided autoreactive T cells would eventually destroy them as well, stopping the wayward attack is important [see "Insights: Putting Up with Self"; SciAm, December 2006]. Previously, Denise L. Faustman of Harvard Medical School had shown in mice that activating a natural compound in the body called tumor necrosis factor (TNF) could selectively kill the autoreactive T cells and permit restored beta cell function. The same process can happen with human cells, as she and her colleagues show in a paper published online August 28 by the *Proceedings of the National Academy of Sciences USA*.



BETA CELLS (*purple in white areas*) in the pancreas die in type 1 diabetes.

In March an 18-month clinical trial began in which human patients receive a generic tuberculosis drug that stimulates TNF production.

Viral Micropower

Self-assembly is a key strategy in nanotechnology, and genetically modified viruses are of great help, such as those deployed by Angela M. Belcher of the Massachusetts Institute of Technology [see "The Scientific American 50: Research Leader of the Year"; SciAm, December 2006]. She and her colleagues have now shown that virus-based construction can make the electrodes of a microbattery. First, they etched onto a rubber substrate posts a few microns wide and deposited on them polymer layers that serve as a solid electrolyte. On top of the electrolyte they added a virus modified to produce a protein coat that collects molecules of cobalt oxide. The virus builds up the cobalt oxide into a structure that acts as the negative electrode of a discharging battery. Although the team still has to make the positive end, the partial battery—described in a study published online August 27 by the *Proceedings of the National Academy of Sciences USA*—displayed full electrochemical functionality. Microbatteries might power labs-on-a-chip, implantable medical devices and other tiny tech.

Slimming Down with Brown

Obesity studies strive to reveal the biochemical pathways that create fat cells [see "What Fuels Fat"; SciAm, September 2007]. More fat could be the secret to losing weight—as long as that fat is brown. Unlike the white kind, which rings the abdomen and pockets the hips, brown adipose releases energy and promotes calorie burning. In humans, most brown fat disappears shortly after birth, when it has fulfilled its role of keeping a newborn's body temperature stable. Two studies in the August 21 *Nature* describe ways to bring back the brown. Specifically, they describe proteins that control the creation of brown fat cells from immature muscle and white fat cells. Mice given one of the proteins developed more brown fat and became leaner than those that did not receive the protein. Conceivably, a drug version could jump-start a change of white to brown fat cells. Alternatively, brown cells transplanted into an obese person's abdomen could fuel calorie burning.

—Nikhil Swaminathan

CNRI/SPL/PHOTO RESEARCHERS, INC. (*beta cells*); KAZUYOSHI NOMACHI *Corbis (Tibetan grasslands)*; TIM PLATT *Getty Images (man)*

Methane-Producing Grass

That plants can emit methane stunned researchers and sparked controversy over the role of forests in global warming [see "Methane, Plants and Climate Change"; SciAm, February 2007]. Some doubted the real-world relevance of the laboratory findings, but researchers have now demonstrated methane release by plants in a natural setting. Using large plastic chambers to capture emissions, a team finds that grasses on the Tibetan Plateau, such as those shown here, produce methane. Shrubs in the alpine meadow absorbed atmospheric methane, however—a result at odds with lab evidence showing the contrary for lowland shrub species. Study leader Xinquan Zhao of the Northwest Plateau Institute of Biology in Xining, China, says these discrepancies highlight the need to examine each species individually because plants vary in chemical composition and metabolism, which affect their capacity to produce the greenhouse gas. *Biology Letters* published the study online August 26.

—Barbara Juncosa

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BIOTERROR

After the Anthrax

Has increased biodefense spending really made us safer? BY JOHN DUDLEY MILLER

As the Federal Bureau of Investigation was about to move in, U.S. Army biodefense scientist Bruce Ivins committed suicide, thus possibly closing the chapter on the first—and so far only—fatal bioattack in U.S. history. The FBI alleges that Ivins, who worked at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Md., mailed anthrax-laden letters in September and October 2001 that killed five people. The incidents sparked a massive infusion of research funds to counter civilian bioterrorism, $41 billion spread over seven federal departments and agencies. Yet some observers argue that those funds have done little to guard against another bioterror incident, especially if the FBI is right about Ivins.

SHAWN THEW Getty Images

MAILED ANTHRAX infected workers at this Brentwood postal facility in Washington, D.C., leading to a major testing and cleanup effort in October 2001. The attacks led to a massive increase in biodefense funding, which critics claim has done more harm than good.

In an opinion that echoes those of several public health scientists, Keith Rhodes, the Government Accountability Office's chief technologist, told a congressional hearing in October 2007 that "we are at greater risk today" than before of an infectious disease epidemic because of the great increase in biolaboratories and the absence of oversight they receive. In the past six years, says Rutgers University microbiologist Richard Ebright, "the Bush administration has driven a 20- to 30-fold increase in the number of institutions and individuals with access to live, virulent bioweapons agents," to about 400 institutions and 15,000 people. Every one of them, he claims, "is a potential source of an attack like the 2001 attack." Even before the expansion, some 100 scientists had access to the anthrax strain Ivins managed. Moreover, huge growth "multiplies the chance of an accidental release," argues Hillel Cohen, an epidemiologist at the Albert Einstein College of Medicine in New York City.

The hallmark of the stepped-up biodefense spending has been the construction of dozens of new biolabs. The several being built to investigate diseases that have no known cure are called biosafety level four (BSL-4) labs, the highest level possible, and they require researchers to wear space suits and breathe piped-in air. "It's definitely the case that when you have a rapid expansion of personnel, the mean experience drops dramatically, and the training level drops dramatically," Ebright remarks.

Whether the extent of this expansion was necessary is unclear. The National Institutes of Health never assessed exactly how much new BSL-4 space it needed, according to Gigi Kwik Gronvall, a senior associate at the University of Pittsburgh Medical Center's Center for Biosecurity. By April 2004 the NIH had announced it would build 20 times as much space as it already had, and the Departments of Defense, Agriculture and Homeland Security were planning huge labs of their own. The late John La Montagne, deputy director of the National Institute of Allergy and Infectious Diseases at the time, stated that until a needs assessment was completed, "whether we need six times more, 12 times more or 100 times more, I can't tell you."

Scientists, security experts and legislators are now pondering various ideas to prevent lab-based terrorism. Some suggest 24/7 video surveillance, and the army is considering a "buddy system" so that no researcher can enter unaccompanied. A bill in Congress, the Select Agent Program and Biosafety Improvement Act of 2008, would mandate that a needs assessment for bioterror labs and manpower finally be conducted; that training for the thousands of new bioterror researchers be funded;

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and that the Select Agent Rule, the law that sets strict security requirements on bioweapons agents so they will not be lost or stolen, be reviewed and strengthened.

One security proposal that stems directly from the Ivins case is psychological screening, something no federal laws now require. (USAMRIID demands it only if researchers admit they have attempted suicide in the past.) C. J. Peters, a virologist at the University of Texas Medical Branch at Galveston and a longtime USAMRIID researcher who knew Ivins, doubts the utility of such screening. "I don't think it would have picked up Bruce," he says. He describes Ivins as "kind of a weird guy" who came across to most colleagues as simply nerdy. In the years since the anthrax attacks, the addition of thousands of biolab workers has made separating quirky personalities from murderous ones that much harder.

John Dudley Miller, based in Cleveland, described the rise in biolab accidents in the August 2007 issue.

Slow Going on Biodefense Drugs

In the fight against bioterror, bigger budgets have yet to produce significant biomedical products. In return for getting a sixfold budget boost for the National Institute of Allergy and Infectious Diseases (NIAID) between 2002 and 2003 (from $270 million up to $1.75 billion), director Anthony S. Fauci set an ambitious goal. In an October 2002 speech, he said that in 10 years, his institute would produce a vaccine, a therapeutic drug and an adjuvant drug for each of some two dozen bioweapons diseases, such as plague and hemorrhagic fever. Many experts thought the target was unrealistic, and indeed six years later not one of those products has been commercially manufactured. One scientist who requested anonymity said that Fauci told him that the Bush administration had demanded this goal and that he accepted it to prevent the Department of Defense or the Department of Homeland Security from getting the job.

BIOTERRIBLE: The Ebola virus is a target for defense work.

CDC/PHOTO RESEARCHERS, INC.

Nevertheless, Michael Kurilla, NIAID's director of extramural research, says that "we're much better off" having spent $41 billion on bioterror research since 2002. Kurilla points out that two important products are in the final stage of development. The U.S. signed a contract with Emergent BioSolutions this past September to manufacture a high-tech anthrax vaccine, after a small company named VaxGen spent years at the task but failed. By the end of 2008, the U.S. should start taking delivery on a next-generation, safer smallpox vaccine from Danish company Bavarian Nordic, he says. This vaccine might even be modifiable to prevent other infections, an approach preferable to the conventional "one bug, one drug" tactic.

CANCER

Confidence Booster

Proponents see hope in changing cancer vaccines' bad reputation BY JESSICA WAPNER

Stimulating the immune system to destroy tumor cells has long been a hope—but judging from past studies, perhaps a dashed one. Clinical trials testing various cancer vaccines have failed miserably; in one, a melanoma vaccine called Canvaxin did not improve the survival of patients, an outcome that ultimately forced the drugmaker to sell itself to another firm. But rather than writing off cancer immunotherapy, some researchers argue that the agents have been examined in the wrong way, resulting in erroneous conclusions. With the correct study design, proponents say, cancer vaccines should prove to be promising.

Such optimism arises from data that have surfaced in the wake of failed tests. After phase III trials, reported in 2006, ended in disappointment for the prostate cancer vaccine Provenge (made by Dendreon in Seattle), subsequent analyses revealed that men whose prostate cancer had spread survived a median of 4.5 months longer than those given a placebo. Patients who took the vaccine and went on to receive chemotherapy survived even longer: a median of 34.5 months, versus 25.4 months for patients who received the placebo followed by chemotherapy.

With standard clinical trials, the criteria used to confirm benefit do not apply to vaccines, points out Jeffrey Schlom, chief of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute. He explains that, unlike traditional cancer drugs, vaccines do not shrink tumors. Therefore, measuring response in those terms, as most trials do, will always show them to be ineffective. Instead, Schlom says, "what we're seeing is increases in patient survival, as opposed to tumor shrinkage."

Moreover, experimental cancer agents are usually tested in patients who have already received several prior therapies, which blunt the immune system, Schlom remarks. This dulling is irrelevant when it comes to testing new drugs, but it impairs the ability of a vaccine to elicit an immune response. Additionally, because vaccines work better with repeated dosing (booster shots), their benefit may not appear until much later than anticipated.

Armed with the knowledge of how to

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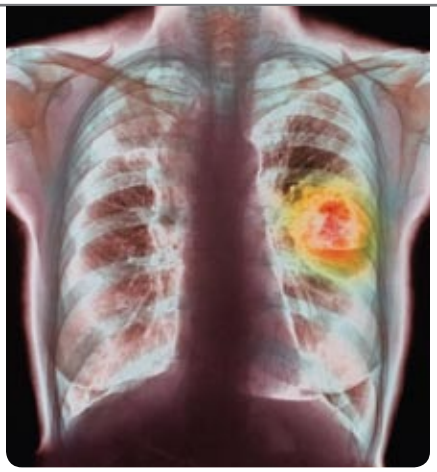
study vaccines appropriately, scientists ideally should have no trouble conducting proper trials. But in reality, problems persist. One of the major hurdles is the lack of available adjuvants, drugs that augment the activity of the vaccines. Given without an adjuvant, a vaccine is unlikely to provide any real benefit. But finding appropriate adjuvants is difficult, because the Food and Drug Administration does not approve new adjuvants alone, explains Martin "Mac" Cheever, director of solid-tumor research at the Fred Hutchinson Cancer Research Center in Seattle. As Cheever notes, the FDA only approves adjuvants for use with the vaccine with which it was tested.

Consequently, researchers cannot access approved adjuvants with experimental vaccines, because each is already locked up with a specific vaccine. Some adjuvants have been tested as therapy in and of themselves, but they have rarely proved effective and have usually been shelved. "Companies in general are not willing to develop compounds that only work as components of other people's products," Cheever comments. This situation leaves vaccine investigators stuck with inadequate study designs.

To be sure, scientists have zeroed in on some promising vaccine-adjuvant combinations, and a few well-designed trials are now under way. GlaxoSmithKline (GSK) is testing its MAGE-3 vaccine in a phase III trial with 2,300 lung cancer patients who have had their tumors surgically removed but received little or no other therapy. The study size requires screening about 10,000 patients for the presence of the MAGE-A3 antigen that the vaccine targets. "A lot of studies are underpowered and not controlled appropriately," says Vincent Brichard, who heads GSK's antigen-specific cancer immunotherapeutics program. "With this number of patients, there will be no ambiguity." Patients will receive the vaccine plus three adjuvants. The study, which will not be completed for at least five years, will evaluate whether the vaccine prevents tumor recurrence rather than causing shrinkage. Other promising vaccine trials include those for WT1 for leukemia (GSK) and Onyvax-P for prostate cancer (Onyvax in London), on top of ongoing studies of Provenge.



SIMON FRASER *Photo Researchers, Inc.*

CANCER VACCINE TESTS that look for the shrinkage of tumors (*red and yellow mass*) are unfair, proponents argue.

Some researchers remain skeptical. One concern is that some vaccines target naturally occurring proteins that the immune system would not normally attack. "We are asking the body to override these existing control mechanisms," says Mark Kelley of Vanderbilt-Ingram Cancer Center in Nashville, Tenn., who was involved with the failed Canvaxin studies. This "self" immune response could cause autoimmune disease as a side effect. Kelley also worries about the fundamental complexity of vaccines, which makes it harder to achieve full medical potential than with other cancer therapies, he feels.

Schlom, who lived through a decade of negativity over monoclonal antibodies, sees much of the nay-saying as par for the course. When it comes to new medicines, "there is always a period of skepticism," he recounts. "I have absolutely no doubt that several years from now there will be several vaccines approved for several cancer indications."

Jessica Wapner, based in New York City, writes frequently about cancer.

A Cancer Vaccine's Mystery Deaths

Proponents of cancer vaccines note that past clinical failures nonetheless have shown that the vaccines lengthened patients' survival times. But that was not the case this past August, when Cell Genesys in South San Francisco halted a clinical trial of the prostate cancer vaccine GVAX when it discovered that more patients receiving the vaccine plus chemotherapy had died (67 deaths) as compared with those receiving chemotherapy alone (47 deaths). The reasons are under investigation, but the 408 patients in the study had the most advanced prostate cancer possible, "exactly the patient population for which [one] would not use a vaccine," remarks Jeffrey Schlom, chief of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute. An ongoing companion study of GVAX in patients with less advanced prostate cancer should help clarify this issue.

SOCIOLOGY

Going beyond Fair and Balanced

Researchers aim to put more rigor into studies of media bias BY VIVIAN B. MARTIN

Nothing ratchets up the perennial debate over media bias like a presidential election. But as Tim Groeling, a political scientist at the University of California, Los Angeles, observes, public discussions about media bias are often just "food fights," with pundits and partisans throwing around anecdotes.

Groeling is hoping to advance scientific

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(and public) knowledge beyond this mush with research he used to demonstrate selection bias in television networks' decision to run or withhold the results of presidential approval polls. For an article appearing in *Presidential Studies Quarterly* this December, Groeling designed a method to deal with a problem that often besets research on the media: people can identify all the news that journalists saw fit to print, but it's more difficult to determine what they chose to ignore.

To counter the problem of the "unobserved population," Groeling collected two different data sets: in-house presidential approval polling by ABC, CBS, NBC and FOX News and the networks' broadcasts of such polls on evening news shows from January 1997 to February 2008. Groeling found that, with varying degrees of statistical significance, CBS, NBC and ABC showed what Groeling calls a pro-Democrat bias. For instance, CBS was 35 percent less likely to report a five-point drop in approval for Bill Clinton than a similar rise in approval and was 33 percent more likely to report a five-point drop than a rise for George W. Bush. Meanwhile FOX News showed a statistically significant pro-Republican bias in the most controlled of the three models Groeling tested: its *Special Report* program was 67 percent less likely to report a rise in approval for Clinton than a decrease and 36 percent more likely to report the increase rather than the decrease for Bush.

Groeling's work is one of the few studies to quantify partisan bias in the media, a subject notoriously difficult for social scientists to research and discuss. These scientists work with theories such as the so-called hostile media effect to predict that ardent supporters of a cause will view media as slanted for the other side, and they have conducted hundreds of studies that have revealed imbalances in the ways journalists frame news on topics ranging from AIDS to the war in Iraq. But there is not a cohesive literature on media bias. Maxwell McCombs of the University of Texas at Austin, who pioneered agenda-setting theory, one of the leading paradigms on news media, says that a researcher would need a few years to make sense of existing data and develop an approach to study media bias. Like many scholars, McCombs sees "bias" as a loaded term, preferring to speak of journalists' "predilections."

"Scholars hate the word 'bias' because they feel like they're entering the ideological fray," says S. Robert Lichter, head of the Center for Media and Public Affairs (CMPA) at George Mason University, who prefers the term "tone." Despite his efforts, Lichter himself got sucked into that fray. His content analysis of the transcripts of TV news broadcasts at the statement level is a respected and widely adopted methodology. This past summer, just as the view that journalists were going softer on Barack Obama than on John McCain was becoming widely accepted, CMPA issued a report showing that 72 percent of the statements in TV news reports about Obama in late spring and early summer were negative, whereas 57 percent of the statements about McCain were negative. When FOX News commentator Bill O'Reilly attacked Lichter's method during a radio interview, saying it would embolden liberal bias, Lichter responded, "You can take all my studies or none of my studies"—an allusion to past uses of his work to support conservative views.

PARTISAN POLEMICS: Despite popular accounts, researchers found that Barack Obama got more negative press coverage than John McCain did in the early summer.

In recent years disciplines not traditionally interested in media have turned their attention to them. In 2005 the *Quarterly Journal of Economics* invigorated the debate with a provocative study by Tim Groseclose, a political scientist at U.C.L.A., and Jeffrey Milyo, an economist at the University of Missouri–Columbia. Groseclose and Milyo created a scale and assigned 20 major news outlets and legislators in Washington, D.C., positions based on their citations of think tanks and policy groups labeled liberal or conservative. They also factored in the voting records of House and Senate members. Their measure determined that most of the major media were left of center of the average legislator—even the news pages of the *Wall Street Journal* were slightly left of the "average Democrat." The exceptions were the *Washington Times* and FOX News's *Special Report*.

Most media scholars do not think the issue of bias can be settled by a formula, though. For example, Groeling observes that the context of news making, including professional definitions of newsworthiness, cannot be ignored when looking at the disproportionate front-page coverage of Obama.

"What more often occurs is this tendency for everybody to start seeing the story the same way," says Elizabeth Skewes of the University of Colorado at Boulder, who analyzed journalists cover-

EMMANUEL DUNAND *Getty Images (Obama)*; ROBYN BECK *Getty Images (McCain)*

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ing presidential races in her 2007 book *Message Control: How News Is Made on the Presidential Campaign Trail*. A former journalist herself, Skewes has a view similar to other scholars who have watched journalists work. She says the interplay of campaign logistics, journalistic norms and pressures from competitive editors "make it all but impossible" for different frames of issues and candidates to break into the evening news or the front pages. Journalists may have political biases, but that might not be why the news comes out the way it does.

Vivian B. Martin, based in New Britain, Conn., is a journalism professor at Central Connecticut State University.

ENVIRONMENT

Less Wash, More Dry

For hotel towel reuse, social pressure beats green values BY MARINA KRAKOVSKY

Most travelers staying at hotels have encountered a bathroom sign asking them to help save the environment by reusing their towels. Daily laundering makes a large hotel go through several million gallons of water a year, and detergent and energy use take a hefty toll, too. New research shows, however, that appealing to people's green conscience is hardly the most effective way of convincing guests how best to dry off.

In experiments whose results ultimately confirmed what persuasion experts long believed, a team led by Noah Goldstein, now at the University of California, Los Angeles, created two types of professional-looking signs: one with the standard environmental message and the other telling guests that most of their fellow guests had reused towels. "It's one of the oldest marketing tricks in the book," says Goldstein, citing the plentiful research showing that in ambiguous situations people tend to follow the pack. Sure enough, as the investigators describe in the October *Journal of Consumer Research,* the social-norm message worked about 25 percent better than the standard environmental one. In a follow-up study that tested different tweaks to the social-norm message, Goldstein's team got even more remarkable results. Telling guests that those who had stayed in *this room* had reused towels worked better than saying that other guests at the same hotel had done so—even though all the rooms were alike.

Savvy travelers realize that hotels save on laundry bills if guests reuse their towels, so environmental appeals could appear disingenuous. After all, a hotel could decide to give back that money to guests. One problem with such financial incentives, though, is logistical: according to the American Hotel & Lodging Association, tracking the number of towels reused per room could be difficult. But there is a bigger problem. If financial incentives are not high enough, Goldstein suspects, they could backfire.

That is the idea of "motivation crowding," a theory predicting that monetary incentives push away the drive to do things for other reasons. "A good example is sex," says Uri Gneezy, an economist at the University of California, San Diego, who studies the effect of incentives. When you make a sexual overture, your partner may or may not accept, but if you offer to also throw in $10, you will strike out for sure. "When you introduce money, you completely change the meaning of the interaction," Gneezy explains. "Instead of a communal relationship, where we're just nice to each other, now it's an exchange relationship." In a frequently cited study, Gneezy found that when an Israeli day care center started fining parents 10 shekels (about $3) for picking up their children late, tardy pickups actually increased because parents saw the fine as the price for being late. Similarly, Gneezy says that offering guests, say, a $1 discount for reusing towels will make them reason, "For a dollar, I might as well get fresh towels." Of course, a sufficiently high incentive would boost towel reuse but at prohibitive cost to the hotel.

JUAN SILVA Getty Images

DAMPENED ENTHUSIASM: Guests are more likely to reuse towels if others do.

Estimates of towel reuse range from 35 to 75 percent, depending on how reuse is measured; to increase reuse, Gneezy suggests that hotels keep money out of it but signal sincerity with donations to environmental causes. Goldstein cautions, though, that there must be no strings attached to hotels' donations. His team found that promising to donate money in exchange for towel reuse did not increase reuse. But when hotels said they had already donated, towel reuse rose by 45 percent. The norm of reciprocity, Goldstein believes, obliges many guests to be more green themselves.

Marina Krakovsky is based in the San Francisco Bay Area.

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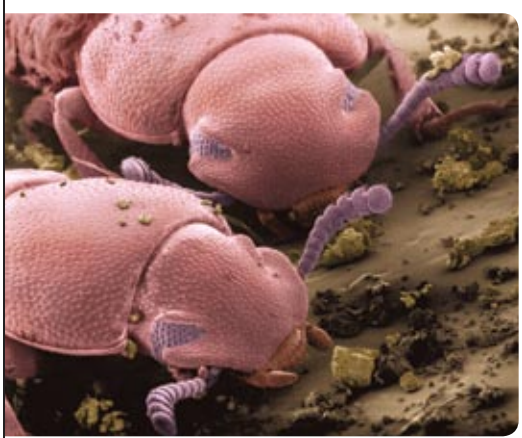
CONSERVATION

Random Challenges

Chance disaster as a bigger extinction threat than once thought BY BARBARA JUNCOSA

Researchers assess the risk of species extinction with conservation models that combine factors that drive down populations—including habitat loss, hunting and overfishing—with the probability of chance disasters affecting the group. Even if human activities greatly affect a species, "all populations that go extinct [ultimately] suffer a string of unfortunate random events, such as a fire, that wipe out the last individuals," says Brett Melbourne, a mathematical ecologist at the University of Colorado at Boulder.



RANDOM FACTORS: **Studies of flour beetles suggest that variables such as sex ratios and physical size contribute greatly to a species' risk of extinction.**

Until recently, mathematical models of extinction risk included only two types of randomness. The first—variability in the environment, such as rainfall or temperature changes—impacts birth and death rates across the entire population. The second involves random events affecting select individuals within a group. Siblings may have the same probability of dying in a given year, for example, but only one may be lost to, say, an accidental drowning or other chance event.

Ecologists have long known that other types of randomness influence population dynamics, but computational limitations in the early 20th century forced scientists to simplify traditional models. By observing groups of flour beetles in the laboratory, Melbourne and Alan Hastings, a mathematical ecologist at the University of California, Davis, demonstrated that random variations in sex ratios and physical differences, such as body size, greatly contribute to the overall threat of extinction. A large number of males born into a small group, for instance, limits the reproductive potential of the population.

As populations decrease, they become more vulnerable to chance events that precipitate extinction. "With our current understanding, we think that the population size must be very small. But when you add in these new factors, even larger populations may be at risk," Melbourne explains. Stuart Pimm, a conservation ecologist at Duke University, emphasizes that the model cannot indicate which new species may be threatened with extinction. Rather, he says, "it tells us which species in the emergency room is most at risk" and identifies those that may be in more imminent danger than previously recognized.

From the standpoint of conservation management, "their work could potentially have a big impact, but we need to explore its implications for real species," notes Sandy Andelman, a senior director at Conservation International. She has recently teamed up with Melbourne to test if his laboratory results can be generalized to the real world. They plan to apply the new model to species such as nonhuman primates and African elephants, for which a great deal of population data exists.

Ultimately, the scientists will examine a variety of populations—from threatened species to those that are critically endangered—to explore the full implications of the model. With 16,000 plant and animal species now threatened by extinction, the stakes couldn't be higher for global biodiversity.

ALBERT LLEAL *Minden Pictures*

MATERIALS

Plastic Coolers

Getting a bigger chill out of polymers that respond to electric fields BY STEVEN ASHLEY

Whether they sit in your kitchen or inside your personal computer, refrigerators and other cooling devices are typically bulky, often noisy and frequently power-hungry. A team at Pennsylvania State University recently found that certain plastics cool off a significant amount—12 degrees Celsius—when an applied electric field is removed. Should the technique become feasible, the resulting solid-state coolers could efficiently and quietly eliminate heat from, say, integrated-circuit boards, enabling smaller, faster computers.

Engineers have long known of so-called

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electrocaloric substances that drop in temperature when an external electric field is withdrawn, but the amount of chilling either was too small at practical temperatures or occurred at too high a temperature to be useful. Effective chip cooling, for instance, requires reductions of at least 10 degrees C from typical operating temperatures—about 85 degrees C, says G. Dan Hutcheson, chief executive officer at VLSI Research, a microelectronics industry market research firm in Santa Clara, Calif. Computers usually require heat sinks, radiators, fans, heat pipes or even fluid-based heat pumps to extract the surplus degrees.

If successful, the new technology should be compact and at least 10 times more energy-efficient than conventional cooling techniques, according to Penn State electrical engineer Qiming Zhang, who led the team. The group found that a micron-thick film of a polyvinylidene fluoride co-polymer—polyvinylidene fluoride trifluoroethylene—heats up a dozen degrees C when zapped with 120 volts at ambient temperatures as low as 55 degrees C. Such a rise constitutes an order of magnitude improvement over other electrocaloric materials (mostly ceramics) at that temperature range.

Zhang, who in the past worked on plastic "artificial muscles" that alter shape under electric fields, says that years ago he "started thinking about melting ice into water, which is one of the most effective ways to cool objects." That effect is based on a phase change in which an ordered system (solid ice) transforms into a disordered one (liquid water). In time, the scientists identified several promising polymers in which an applied voltage caused the atoms or molecules to align, thus creating greater order.

The electrocaloric materials, Zhang reports, consist of long molecular chains with a positive electric charge on one end and negative on the other. These dipolar chains, which can move around freely, are normally oriented randomly. But "when you apply an electric field, the dipoles tend to spin around until they align with the field," he says. Thermodynamically speaking, this molecular ordering lowers the system's entropy, so the system compensates by heating up as a consequence of energy conservation. When the field is disengaged, the chains randomize and the polymer cools off. The rigid microstructures of electrocaloric ceramics, in contrast, "can move only a little bit," Zhang notes, which accounts for their weak temperature response. The polymers can also absorb seven times as much heat as the ceramics.

MELTING ICE, a material phase change that effectively chills things down, inspired a new refrigeration technique.

TOM GRILL *Corbis*

In an ideal solid-state refrigerator, a chilling cycle starts when contact breaks between the polymer and the object that is being cooled, thermally isolating the polymer. An applied electric field causes the temperature of the polymer to rise. It is then placed into momentary thermal contact with a heat sink, which absorbs any heat and entropy that the polymer has. The polymer is next isolated from the heat sink; the electric field is then lowered, which reduces the temperature of the polymer and enables it to cool the target object once again.

A workable system could in particular prove a boon for the computer industry. Silicon chips run hotter than is desirable for optimal performance, comments Benson Inkley, a senior power/thermal engineer at Intel in Hillsboro, Ore. Cooling with electrocaloric plastics offers intriguing possibilities, Inkley states: "Imagine coating an entire circuit board with a layer of polymer, in effect, forming a cooling blanket."

But Zhang emphasizes that his polymer is not yet practical. One drawback is that it requires 120 volts, much more than the few volts available in portable devices.

He remains optimistic, though, and feels that the approach could scale up beyond microelectronics. The development of larger refrigerators based on the polymers depends on finding various other substances that exhibit the effect at adjacent temperature ranges. That way the right combination could operate as a "temperature cascade," rejecting heat progressively. Says Zhang: "This could be the first step in the development of an electric-field refrigerator"—one with no bulky coils or noisy compressors. Someday chilling a picnic cooler might mean flipping a switch rather than loading up on ice.

Chilling with Crystals

Other mobile dipolar molecules might offer solid-state cooling superior to that of polyvinylidene fluoride co-polymers, Pennsylvania State University engineer Qiming Zhang says. Especially promising are the molecules that form images on flat-panel liquid-crystal displays (LCDs). Liquid crystals contain rodlike dipoles that align with an electric field and revert to their original arrangement when the field is removed. Zhang is as yet unsure if the electric charges on the ends of the rods will respond strongly enough to applied electric fields.

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GENOMICS

Getting a (New) Leg Up

Genome-sequencing contest renews regeneration research BY CHRISTINE SOARES

Wei Zhu and Gerald Pao had questions about basic mechanisms that allow some human and animal cells to change identity, becoming more like stem cells. David M. Gardiner and S. Randal Voss had been chipping away for years at the mysteries of the salamander, a creature whose cells can repeatedly morph into an entire new body part. So when a chance at a data windfall that could help all their diverse investigations came along, these researchers, based in California and Kentucky, pooled their ideas and entered a contest.

Their bid went to Roche Biosciences in Palo Alto, Calif. Eager to demonstrate a new low-cost, high-speed DNA-sequencing technology, Roche held a competition seeking interesting projects last year, offering a first prize of a million DNA base pairs' worth of free sequencing. Pao and Zhu, both postdoctoral researchers at the Salk Institute for Biological Studies in La Jolla, Calif., sent in the winning proposal for a project that would use multiple techniques to examine what goes on at the molecular level when salamander cells start rebuilding a lost limb.

The question is relevant not just to salamanders but to understanding whether humans could ever perform the same feat, perhaps by making our own cells revert to a stemlike state. Now that the collaborators have sifted some of their data, the serendipitous sequencing project is yielding nuggets of information valuable to each of them, while potentially reviving the study of salamander regeneration.

Pao and Zhu focused on the earliest stage of healing in cells at the site of an amputated salamander limb, examining stretches of DNA that were unwinding and presumably contained genes that were about to turn on. Sequencing this material revealed that genes seemingly involved in triggering the cellular regeneration program are some of the same ones active in embryonic stem cells, suggesting that the cells had reverted to a more primitive state. "We have several very interesting candidate genes that are basically almost exclusively active in germ cells," Zhu says, "and we're trying to define their function."

"Obviously the goal is to understand which genes are turned on during regeneration and to understand more of the process," explains Zhu's boss, Tony Hunter. Figuring out which genes are important would be easier, though, if scientists knew what kinds of genes the salamander possesses. Unfortunately, Hunter remarks, "there is no complete sequence."

DISARMING WORK: Original salamander legs (*topmost part of this sequence*), after being cut off, regrow in a process thought to reprise embryonic limb development.

That is because the salamander genome is huge, "10 times the size of the human genome sequence," Hunter points out. Its size has always scared off would-be sequencers because of the cost of traditional sequencing methods, says Voss, a University of Kentucky biologist who maintains the Sal-Site repository for salamander gene data. He used some of the free sequencing prize to read large chunks of genome, in part to study its overall structure. The results revealed salamander genes to be organized much like human genes, with protein-encoding DNA stretches interrupted by noncoding sections, called introns. In salamanders, though, the introns are enormous and filled with repeated sequences, which helps to finally explain the genome's extraordinary size.

The group has also been cataloguing newfound genes that have an obvious counterpart in humans and other vertebrates, a step toward figuring out if something unique to salamanders permits them to regenerate. "What the Roche contest did was take us from a little over 1,000 axolotl [salamander] genes that were clearly orthologues of human genes to now having 10,000," says Gardiner of the University of California, Irvine. "It's not all of them, but it's a quantum leap."

The tantalizing tidbits that came out of the sequencing prize have each of the researchers craving more. Pao and Zhu think further molecular studies of salamanders could yield insights into more universal mechanisms in embryonic stem cells, for instance. And after seeing what access to cheaper sequencing technology can accomplish, Gardiner thinks that the project will jump-start a new molecular era in salamander regeneration research, which he admits had reached something of an impasse using traditional biology techniques.

"Roche came along, and it was like a fairy godmother, sprinkling some fairy dust," Gardiner remarks, "and now we can use the tools available in the bioinformatics community."

FROM "AMPHIBIAN LIMB REGENERATION: REBUILDING A COMPLEX STRUCTURE," BY JEREMY P. BROCKES ET AL., IN *SCIENCE*, VOL. 276; APRIL 4, 1997. REPRINTED WITH PERMISSION FROM AAAS

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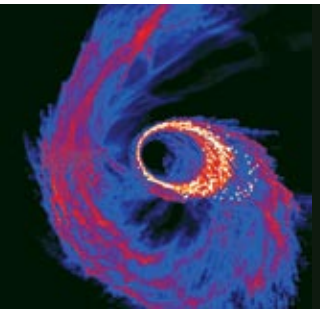
ASTROPHYSICS

Star Making around Holes

Researchers may have figured out how the 100 or so stars around the Milky Way's central supermassive black hole could have formed. Stars emerge when clouds of hydrogen molecules coalesce under their collective gravitational attraction. The gravity around a supermassive black hole, however, should have shredded such a cloud like paint dropped on an eggbeater before it got a chance to make stars. Astrophysicists simulated the fate of a hydrogen cloud as massive as 10,000 suns that suddenly wafted near a black hole. Although much of the cloud would splatter, shock waves and other turbulence would drain the angular momentum out of the inner 10 percent. That material would take up orbit around the black hole and give time for stars to form. The August 22 *Science* brought the results to light. —*JR Minkel*



LIGHTS ON: In a hydrogen cloud (*purple*) around a black hole, stars can form in portions that collapse and become dense (*red* and *yellow*).

DRUG ADDICTION

Blow Away

A ramped-up version of the body's cocaine-purging protein could lead to the world's first effective medicine for combating overdoses and addictions to the illicit drug. The body can break down and inactivate cocaine with the natural blood protein butyrylcholinesterase, but this enzyme is normally too weak and ineffective for medical use. Now, with the aid of computer simulations to test molecules virtually, scientists at the University of Kentucky and their colleagues have developed a far more active form of this protein. They created it by stabilizing its reactive structures and stripping away parts that hindered its function. In laboratory studies, the mutant form of the enzyme broke down cocaine roughly 2,000 times faster than the natural version. The scientists also found that the artificial enzyme prevented convulsions and death when injected into mice that were given otherwise lethal overdoses of cocaine. Read more in the September 24 *Journal of the American Chemical Society*. —*Charles Q. Choi*

EXTREMOPHILES

Space Suits Them

Humans can survive unprotected in space for a few minutes before the air in their lungs expands, gas bubbles out of their blood and the saliva in their mouths begins to boil. In contrast, a tiny animal, reaching 1.5 millimeters in length, can survive for days in the harsh environment. Known as tardigrades, or water bears, they are found all over the world, from the sediments on the ocean floor to the lichens on mountaintops. In an adaptation to desiccation, some tardigrades can persist for a decade without moisture. Tardigrades that went into orbit last year faced the vacuum of space for 10 days and survived.

"WATER BEARS," or tardigrades, can survive the vacuum of outer space for several days.

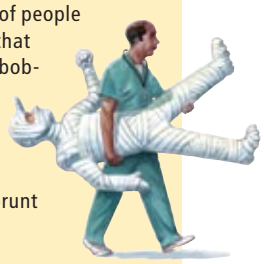
Only when they also encountered radiation did the water bears capitulate—just 10 percent made it. Much like the bacterium *Deinococcus radiodurans*, the tardigrades that survived must have some mechanism that repairs cellular damage. The researchers who describe the space-faring tardigrades in the September 9 *Current Biology* speculate that other creatures adapted to survive extreme dryness—such as rotifers, nematodes and brine shrimp—might share the tardigrades' ability to endure space. —*David Biello*

COURTESY OF *SCIENCE*/AAAS (*hydrogen cloud around black hole*); BOB GOLDSTEIN *University of North Carolina at Chapel Hill (water bear)*; ILLUSTRATION BY MATT COLLINS

Data Points

Hurts So Good

In the first study of its kind, researchers from the Centers for Disease Control and Prevention have compiled national estimates of emergency room injuries resulting from outdoor recreation. Every year in the U.S. tens of millions of people participate in activities that range from boating and bobsledding to tobogganing and water-skiing. Predictably, teenagers get hurt the most, and legs and arms bear the brunt of the punishment.



ESTIMATED ANNUAL INJURIES:	**212,708**
NUMBER INJURED PER 100,000 INDIVIDUALS WHO ARE:	
Male:	99.9
Female:	45.1
NUMBER INJURED PER 100,000 WHO ARE:	
0 to 9 years old:	31.9
10 to 14:	187.1
15 to 19:	214
20 to 24:	121.1
NUMBER INJURED PER 100,000 WHO ARE:	
Snowboarding:	18.3
Sledding:	7.7
Hiking:	4.6
NUMBER INJURED PER 100,000 WHO HURT THEIR:	
Leg:	19.4
Arm:	18
Head/neck:	16.8
Upper trunk:	12

SOURCE: Wilderness and Environmental Medicine, *June 2008*

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In Brief

NEW MEGA PRIME NUMBERS

The Great Internet Mersenne Prime Search (GIMPS), a volunteer-powered distributed-computing group, formally announced in September the discovery of the two largest known prime numbers—those divisible only by 1 and themselves. The bigger of the two, $2^{43,112,609} - 1$ in shorthand, has nearly 13 million digits and came out of the machine of Edson Smith of the University of California, Los Angeles. GIMPS is set to claim the $100,000 prize offered by the Electronic Frontier Foundation for the first 10-million-plus-digit prime. The smaller of the new primes, turned up by a German GIMPS member at 11.2 million digits, would also have qualified but was found two weeks later. —*John Matson*

FIRE BREATHING

Air must contain at least 12 percent oxygen for matter to burn, according to conventional wisdom. New experimental burns using pinewood, moss, paper, matches and a candle have convinced scientists at University College Dublin in Ireland that fires need at least 15 percent oxygen. (Air is typically about 21 percent oxygen.) Low oxygen levels, coupled with ancient charcoal evidence of wildfires, have been implicated in mass extinctions in the earth's history. The new findings, in the August 29 *Science*, suggest oxygen levels could not be as low in some eras as once thought and may help refine models of the ancient atmosphere. —*Charles Q. Choi*

STEM CELLS AGAINST STROKE

Injecting stem cells into the brains of mice that recently suffered a stroke can reduce damage to neurons by up to 60 percent, according to new research. But the stem cells do not simply replace damaged nerve cells as previously believed. Instead they affect the brain's immune cells, called microglia, which go into overdrive during stroke, attacking and destroying healthy tissues. In the mouse experiment the stem cells calmed down the microglia and got them to call off their assault. The treated mice performed better than their untreated peers on a battery of movement, cognitive and behavioral tests. —*Nikhil Swaminathan*

PALEONTOLOGY

Survival of the Luckiest

Dinosaurs might have ruled the planet out of sheer luck. The dominant status that dinosaurs enjoyed for some 135 million years had suggested there was something inherently superior about the creatures. To see why the dinosaurs rose to prominence, paleontologists investigated the first years of their existence in the late Triassic, from 230 million to 200 million years ago. The researchers discovered their main competitors at that time, the crurotarsans (ancestors to crocodiles), thrived—the fossil record shows that crurotarsans were actually twice as diverse as dinosaurs when it came to body types, diets and ways of life and that they were more abundant in many ecosystems. Hence, the scientists, from the University of Bristol in England and the American Museum of Natural History in New York City, conclude that dinosaurs did not outcompete crurotarsans, which were largely wiped out by rapid climate change at the end of the Triassic. For some reason, the change did not affect the dinosaurs; the crurotarsans might have easily inherited the earth instead. Dig up more in the September 12 *Science*. —*Charles Q. Choi*

NEUROSCIENCE

Hockey Head Trick

Sports can work out not only the body but also the mind when it comes to comprehending language. To see what effect expertise in a physical endeavor such as ice hockey might have on the brain, scientists used functional magnetic resonance imaging to scan 12 hockey players, eight fans of the sport and nine volunteers who had never watched a hockey game. Not surprisingly, the hockey players and fans were substantially better than novices at understanding sentences about hockey actions, such as shooting or making saves. But the University of Chicago researchers also discovered that, in players and fans, parts of the brain usually involved in planning and controlling physical actions are recruited to help understand language, suggesting that the brain may be more flexible into adulthood than previously thought. Take a shot at reading the findings reported online September 2 in the *Proceedings of the National Academy of Sciences USA*. —*Charles Q. Choi*

JOHN ROSS *Getty Images (paper on fire)*; CHRISTOPHER PASATIERI *Getty Images (hockey players)*

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SciAm Perspectives

Overshadowing Difficulties

Geoengineering is a seductive idea. Maybe too seductive

BY THE EDITORS

Earth is absorbing too much solar energy and heating up. Rather than fiddling with hybrid cars and funny-looking lightbulbs, why not just build a planet-size parasol to shade us? Or a forest of carbon scrubbers to cleanse heat-trapping gases from the air?

Such grand schemes for "geoengineering" our way out of the climate crisis appeal to the dreamer in us all. If technology got us into this mess, maybe technology can get us out of it [see "A Sunshade for Planet Earth," by Robert Kunzig, on page 24]. Once considered fringe science, geoengineering gained respectability with an essay two years ago by chemist Paul J. Crutzen, who is something of an environmentalist hero—it was his Nobel Prize–winning work on the ozone hole that led to the ban on Freon and other ozone-destroying chemicals.

There are just a few problems. The first is the side effects. The best-studied proposal, to pump sulfate aerosols into the upper atmosphere to block sunlight, would cause its own troubles. The sulfates would slow or reverse the recovery of the ozone layer; they might also reduce global rainfall, and the rain that did fall would be more acidic. And those are just the foreseeable effects. Aerosols are the least understood aspect of the climate system.

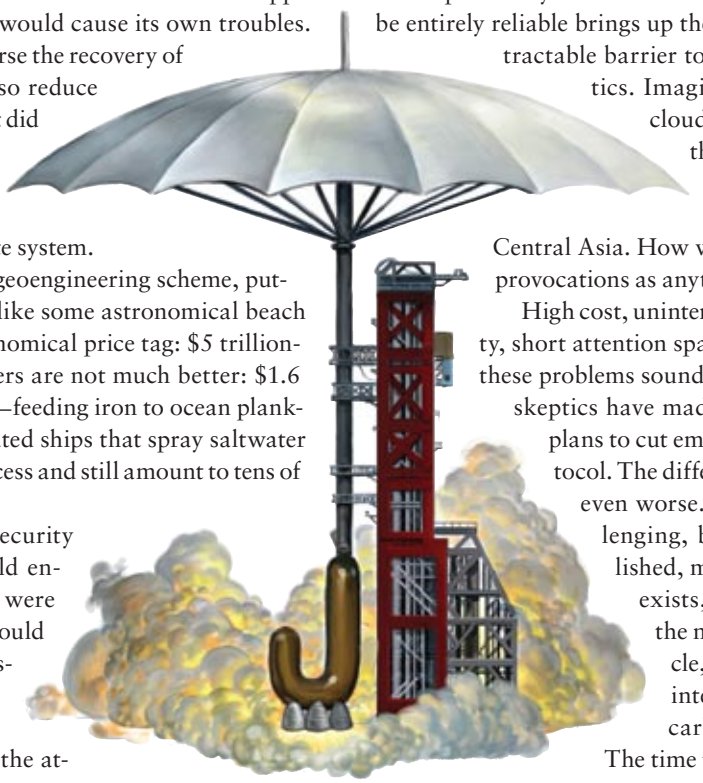
Second is cost. The priciest geoengineering scheme, putting a giant sunshade in space like some astronomical beach umbrella, comes with an astronomical price tag: $5 trillion-plus. Arrays of carbon scrubbers are not much better: $1.6 trillion-plus. Cheaper schemes—feeding iron to ocean plankton, launching fleets of automated ships that spray saltwater aerosol—are less assured of success and still amount to tens of billions of dollars a year.

Third is the false sense of security that such geoengineering could encourage. Suppose a sunshade were built and actually worked. It would take the heat off politicians; emissions reductions would seem less urgent. Yet carbon dioxide would continue to build up in the atmosphere—breaching the level of 450 parts per million by volume (ppmv) that most climatologists now recommend as an upper limit, then passing the 550 ppmv mark that is the goal of many current policy initiatives, and eventually reaching 1,000 ppmv, a level not seen on Earth since the days of the dinosaurs. If we let our maintenance of that sunshade slip even briefly—because of war, economic depression or simple apathy—the shade would lift and a century's worth of warming would hit us.

Proponents recognize this risk and see geoengineering merely as a stopgap measure to buy time for emissions reductions, which may take decades to achieve. But what is the point of buying time? Every year that we put off those reductions makes our job that much harder. The logic of compounding argues for focusing on emissions *first* and keeping geoengineering projects in reserve—rather than the other way around.

The possibility that international collective action might not be entirely reliable brings up the fourth and perhaps most intractable barrier to geoengineering: the geopolitics. Imagine if, say, Chinese-produced clouds of sulfuric acid blew across the Pacific or if American efforts to reduce flooding on our shores triggered drought in Central Asia. How would nations respond to such provocations as anything but an act of war?

High cost, unintended consequences, uncertainty, short attention spans, international bickering: if these problems sound familiar, it is because climate skeptics have made the very same criticisms of plans to cut emissions, such as the Kyoto Protocol. The difference is that geoengineering is even worse. Emissions cuts may be challenging, but the science is well established, most of the technology already exists, the costs can be spread over the natural capital-replacement cycle, public awareness is high, and international institutions such as carbon markets are taking root. The time to act is now. ■



MATT COLLINS

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Sustainable Developments

Looking after the Future

Don't pit today against tomorrow: instead focus on the public capital we will leave to the future

BY JEFFREY D. SACHS

Many of the greatest problems facing the planet will hit hardest in 50 to 100 years. Climate change, which already wreaks havoc through local droughts and heat waves, could well unleash global-scale havoc in a few decades. Higher temperatures and changing rainfall patterns could cut global food production sharply and trigger mass famine in needy parts of the world; conceivably, the great ice sheets of Greenland and Antarctica could partially collapse and raise the sea level by several meters, flooding the coasts.

Prevention of those disasters is usually seen as pitting the current generation against the future: we are advised to cut back on consumption, energy use and other resource-depleting activities now to ensure the well-being of later generations. The conflict is thereby framed in ethical terms: What does the present owe the future? How much should the current generation tighten its belt on behalf of later ones? Such questions are important, but they miss a crucial and overlooked aspect of the challenge.

Suppose we take extant consumption levels as a given, set by shortsighted politicians responding to a shortsighted electorate. We can nonetheless affect the well-being of future generations through how we manage public investment decisions that have long-term consequences. Imagine that we can head off future climate change through a more expensive energy system that costs an extra 1 percent of national income. For instance, this plan might include the research, development and deployment costs of carbon capture and storage technologies at coal-fired power plants or those for a large-scale solar-based electric grid.

These extra costs need not be borne by today's generation. Instead they can be financed through long-term government bonds to be serviced by later generations. Without changing our consumption levels, we thereby have a choice of what we offer the future: a low-carbon power grid and a stable climate, at the cost to later generations of a somewhat larger public debt, or a dirty power grid, runaway climate change and a smaller public debt.

Rather than asking how to sacrifice for the sake of the future, we can focus instead on how to leave a given amount of public capital to the future. Naturally, future generations might prefer that we pay for the cleanup through belt-tightening today. Yet if that was not to be, later generations would presumably choose a safer climate and a sustainable energy system at the cost of inheriting a somewhat larger public debt.

The challenge of effectively allocating public capital for the future involves more than climate change, of course. We can bequeath to the future more or less biodiversity (versus human-built infrastructure) or a larger or smaller global population (depending on public investments to support voluntary reductions in fertility through access to family planning). Those choices do not pit the present against the future; they represent alternatives for the kinds of public capital being left to the future.

Our political process is designed mainly to make choices about collective investments for those alive now. It is poorly equipped to deal with long-term problems, even when they are recast to make a future generation bear the costs of its own well-being. Nor are today's politicians and the general public prepared to think about such choices with any clarity.

We need to experiment with new ways to represent the future politically. We can use powerful analytical tools, such as the "generational accounts" developed by economist Laurence J. Kotlikoff of Boston University, to examine various balances of public, natural and private capital that we leave to later generations—and thereby elucidate our alternative effects on their well-being. We might introduce trained ethicists or even politicians as ombudsmen to represent future generations at the negotiating table. Such ideas might sound outlandish but are less so than would be a future beset by environmental devastation because we failed to think clearly about the consequences of our choices. ■

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/nov2008**

PHOTOGRAPH BY BRUCE GILBERT/EARTH INSTITUTE; ILLUSTRATION BY MATT COLLINS

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Skeptic

Stage Fright

From the stages of grief to the stages of moral development, stage theories have little evidentiary support

BY MICHAEL SHERMER

Denial, anger, bargaining, depression, acceptance. So annealed into pop culture are the five stages of grief—introduced in the 1960s by Swiss-born psychiatrist Elisabeth Kübler-Ross based on her studies of the emotional state of dying patients—that they are regularly referenced without explication.

There appears to be no evidence, however, that most people most of the time go through most of the stages in this or any other order. According to Russell P. Friedman, executive director of the Grief Recovery Institute in Sherman Oaks, Calif. (www.grief-recovery.com), and co-author, with John W. James, of *The Grief Recovery Handbook* (HarperCollins, 1998), "no study has ever established that stages of grief actually exist, and what are defined as such can't be called stages. Grief is the normal and natural emotional response to loss.... No matter how much people want to create simple, bullet-point guidelines for the human emotions of grief, there are no stages of grief that fit any two people or relationships."

Friedman's assessment comes from daily encounters with people experiencing grief in his practice. University of Memphis psychologist Robert A. Neimeyer confirms this analysis. He concluded in his scholarly book *Meaning Reconstruction and the Experience of Loss* (American Psychological Association, 2001): "At the most obvious level, scientific studies have failed to support any discernible sequence of emotional phases of adaptation to loss or to identify any clear end point to grieving that would designate a state of 'recovery.'"

Nevertheless, the urge to compress the complexities of life into neat and tidy stages is irresistible. Psychoanalyst Sigmund Freud insisted that we moved through five stages of psychosexual development: oral, anal, phallic, latency and genital. Developmental psychologist Erik H. Erikson countered with eight stages: trust vs. mistrust (infant); autonomy vs. doubt (toddler); initiative vs. guilt (preschooler); industry vs. inferiority (school-age period); identity vs. role confusion (adolescent); intimacy vs. isolation (young adult); generativity vs. stagnation (middle age); and integrity vs. despair (older adult). Harvard University psychologist Lawrence Kohlberg postulated that our moral development progresses through six stages: parental punishment, selfish hedonism, peer pressure, law and order, social contract and principled conscience.

Why stages? We are pattern-seeking, storytelling primates trying to make sense of an often chaotic and unpredictable world. A stage theory works in a manner similar to a species-classification heuristic or an evolutionary-sequence schema. Stages also fit well into a chronological sequence where stories have set narrative patterns. Stage theories "impose order on chaos, offer predictability over uncertainty, and optimism over despair," explained social psychologist Carol Tavris, author of *The Mismeasure of Woman* (Touchstone, 1993) and co-author, with Elliot Aronson, of *Mistakes Were Made (But Not by Me)* (Harcourt, 2007), in an interview with me. "One appeal of stage theories is that they tell a story—they give us a narrative to live by ('you feel this now, but soon ...'). In cognitive psychology and also in 'narrative psychotherapy,' there has been a lot of work on the importance of storytelling. Some therapists now make this idea explicit, helping clients change a negative, self-defeating narrative ('look at all I suffered') into a positive one ('I not only survived but triumphed')."

What's wrong with stages? First, Tavris noted, "in developmental psychology, the notion of predictable life stages is toast. Those stage theories reflected a time when most people marched through life predictably: marrying at an early age; then having children when young; then work, work, work; then maybe a midlife crisis; then retirement; then death. Those 'passages' theories evaporated with changing social and economic conditions that blew the predictability of our lives to hell."

Second, Tavris continued, "is the guilt and pressure the theories impose on people who are *not* feeling what they think they should. This is why consumers of any kind of psychotherapy or posttraumatic intervention that promulgates the notion of 'inevitable' stages should be skeptical and cautious."

Stages are stories that may be true for the storyteller, but that does not make them valid for the narrative known as science. ■

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

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Anti Gravity

Hungry for Change

Why reading this magazine might cause you to clean out the fridge—and other mysteries explained

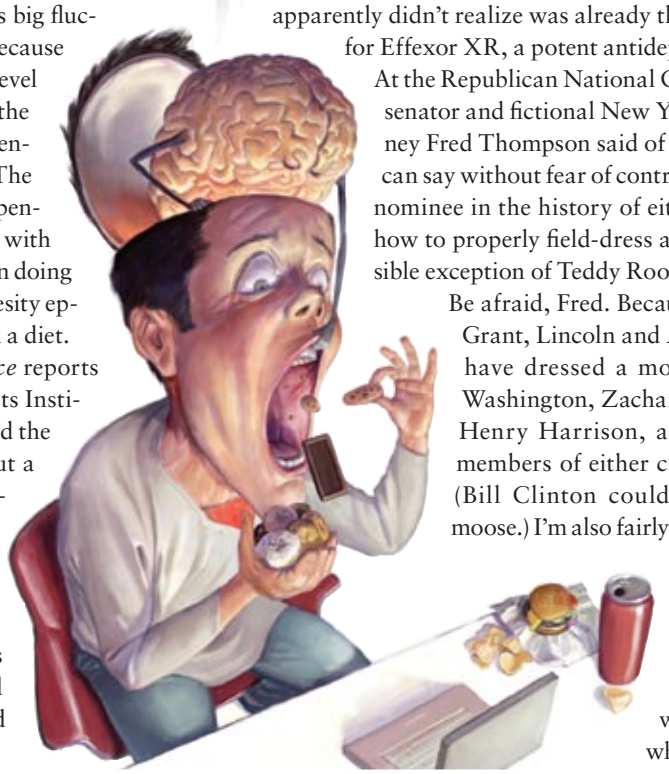
BY STEVE MIRSKY

Why am I so hungry after writing one of these columns? I have often wondered. Now comes an answer.

A study in the journal *Psychosomatic Medicine* contends that intellectual work—that's right, I'm calling writing this stuff, ya know, intellectual—induces a big increase in caloric intake. The research had 14 Canadian students do three things at different times: sit and relax; complete a series of memory and attention tests; and read and summarize a text. (It was that last activity that disqualified rodents and U.S. students as study subjects.) After 45 minutes at each task, the kids were treated to an all-you-can-eat buffet lunch. Because Canada has a truly advanced code of human-subject research ethics.

Each session of intellectual work required the burning of only three more calories than relaxing did. But when the students hit the buffet table after the text summation, they took in an additional 203 calories. And after the memory and attention tests, the subjects consumed another 253 calories. Blood samples taken before, during and after the activities found that all that thinking causes big fluctuations in glucose and insulin levels. And because glucose fuels the neurons, a transitory low level in the brain may signal the stomach to get the hands to fill up the mouth, even though the energy actually spent has gone up just a hair. The researchers note that such "caloric overcompensation following intellectual work, combined with the fact that we are less physically active when doing intellectual tasks, could contribute to the obesity epidemic." Think about that—unless you're on a diet.

Speaking of calories. The journal *Science* reports that mathematicians from the Massachusetts Institute of Technology, New York University and the Free University of Brussels have figured out a better way to wrap spherical pieces of chocolate. There's a lot of wasted material when wrapping spheres with square pieces of foil or paper. But our intrepid geometers found that by using equilateral triangles rather than squares, they could generate a savings of 0.1 percent. That's one full square saved for every 1,000 pieces of triangle-wrapped chocolate you eat.



Speaking of the munchies. Some of the chemical compounds found in marijuana show promise for fighting drug-resistant bacterial infections. That's according to the *Journal of Natural Products,* published by the American Chemical Society. (As opposed to *The Book of Mr. Natural,* published by Fantagraphics Books. Seriously.) Naturally, scientists have long known that pot contains antibacterial constituents. But lack of seed money stems research, so little has been done to investigate pot's potential.

In the new study researchers tested five cannabinoid marijuana ingredients against the superbug MRSA, methicillin-resistant *Staphylococcus aureus*. All five did a lot of damage to the bacterium. And two of the substances don't even appear to be psychoactive, meaning they could be turned into medications that don't cause a high. Because the last thing you want to administer to a patient incapacitated for weeks in a hospital bed experiencing the horrors of an out-of-control staph infection is an antibacterial drug that would also lighten his mood.

Speaking of mood-altering. Earlier this year Republicans in the House of Representatives adopted as a reelection sales pitch the phrase "The Change You Deserve." Which they apparently didn't realize was already the trademarked slogan for Effexor XR, a potent antidepressant. But I digress.

At the Republican National Convention former real senator and fictional New York City district attorney Fred Thompson said of Sarah Palin, "I think I can say without fear of contradiction she is the only nominee in the history of either party who knows how to properly field-dress a moose. With the possible exception of Teddy Roosevelt."

Be afraid, Fred. Because I'm fairly sure that Grant, Lincoln and Andrew Jackson could have dressed a moose. Not to mention Washington, Zachary Taylor and William Henry Harrison, although they weren't members of either current political party. (Bill Clinton could probably undress a moose.) I'm also fairly sure that if Teddy Roosevelt were alive today, he'd be referred to in some quarters as "that effete East Coast elitist environmentalist wacko." Speaking of which, I'm hungry. ■

PHOTOGRAPH BY FLYNN LARSEN; ILLUSTRATION BY MATT COLLINS

PHOTOGRAPH BY FLYNN LARSEN; ILLUSTRATION BY MATT COLLINS

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A Sunshade for

Global warming has become such an overriding emergency that some climate experts are willing to consider schemes for partly shielding the planet from the sun's rays. But no such scheme is a magic bullet

By Robert Kunzig

KEY CONCEPTS

- Many scientists now support serious research into "geoengineering," deliberate actions taken to slow or reverse global warming.
- Of the various geoengineering proposals, the ones that shade the earth from the sun could bring about the most immediate effects. But all of them have drawbacks and side effects that probably cannot be anticipated.
- Pumping sulfur dioxide into the stratosphere, as volcanoes do, is the most well established way to block the sun. Other proposals call for brightening clouds over the oceans by lofting sea salt into the atmosphere and building a sunscreen in space.

—The Editors

When David W. Keith, a physicist and energy expert at the University of Calgary in Alberta, gives lectures these days on geoengineering, he likes to point out how old the idea is. People have been talking about deliberately altering climate to counter global warming, he says, for as long as they have been worrying about global warming itself. As early as 1965, when Al Gore was a freshman in college, a panel of distinguished environmental scientists warned President Lyndon B. Johnson that carbon dioxide (CO_2) emissions from fossil fuels might cause "marked changes in climate" that "could be deleterious." Yet the scientists did not so much as mention the possibility of reducing emissions. Instead they considered one idea: "spreading very small reflective particles" over about five million square miles of ocean, so as to bounce about 1 percent more sunlight back to space—"a wacky geoengineering solution," Keith says, "that doesn't even work."

In the decades since, geoengineering ideas never died, but they did get pushed to the fringe—they were widely perceived by scientists and environmentalists alike as silly and even immoral attempts to avoid addressing the root of the problem of global warming. Three recent developments have brought them back into the mainstream.

First, despite years of talk and international treaties, CO_2 emissions are rising faster than the worst-case scenario envisioned as recently as 2007 by the Intergovernmental Panel on Climate Change. "The trend is upward and toward an ever increasing reliance on coal," says Ken Caldeira, a climate modeler at the Carnegie Institution for Science in Stanford, Calif.

Second, ice is melting faster than ever at the poles, suggesting that climate might be closer to the brink—or to a tipping point, in the current vernacular—than anyone had thought.

And third, Paul J. Crutzen wrote an essay. The 2006 paper in the journal *Climatic Change* by the eminent Dutch atmospheric chemist, in which with heavy heart he, too, urged serious consideration of geoengineer-

KEVIN HAND

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Planet Earth

CLOUDS OF "PARASOLS" in space, as shown in this artist's conception of a sunshade, might slow the warming of our world.

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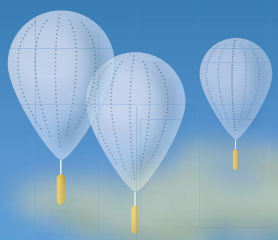
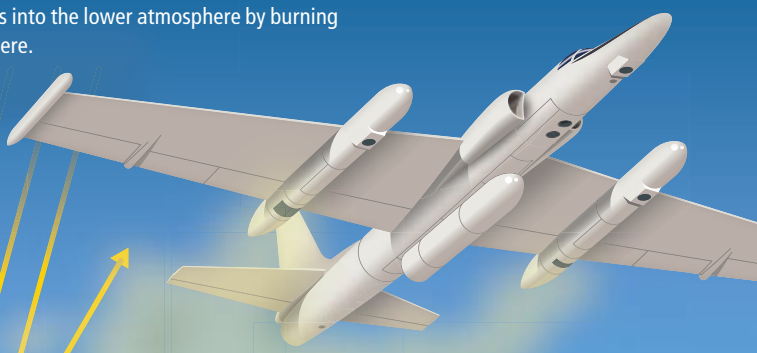
[SUNSHADE #1: THE VOLCANO EFFECT]

Sulfur in the Stratosphere

Past volcanic eruptions have cooled the earth substantially by injecting sulfur dioxide (SO_2) gas into the upper atmosphere. Atmospheric scientists have proposed that SO_2—already emitted in vast quantities into the lower atmosphere by burning fossil fuels—could have the same cooling effect if it were lofted into the stratosphere.



Light is scattered by clouds of sulfate droplets



DEPLOYMENT BY BALLOON

Lighter-than-air craft would require very little energy to raise a cargo of SO_2 at least six miles high.

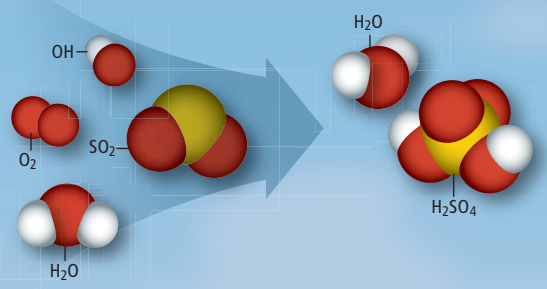
DEPLOYMENT BY PLANE

Running on "dirty," high-sulfur fuel at cruising altitudes, airplanes could add plenty of SO_2 to the stratosphere.

STRATOSPHERE

HOW IT WORKS

When SO_2 reaches the stratosphere, a series of chemical reactions that involve such molecules as the hydroxyl radical (OH), diatomic oxygen (O_2) and water, either in its vapor form or condensed into a liquid droplet, give rise to sulfate particles about a micron across. The particles—made up of sulfuric acid (H_2SO_4), water and trace amounts of impurities—deflect some of the incoming sunlight. The diagram below shows some of the molecules involved, but none of the specific chemical pathways are portrayed.



Past volcanic eruption

DEPLOYMENT BY MISSILE

Shells charged with SO_2 and fired from ships at sea could respond quickly to changing conditions in the upper atmosphere, provided atmospheric scientists gain a better understanding of the details of aerosol formation there.

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[THE AUTHOR]

Robert Kunzig is a freelance science writer who specializes in ocean science and global climate. He is author of *Mapping the Deep: The Extraordinary Story of Ocean Science,* which won the 2001 Aventis Prize for Science Books, and, more recently (with Wallace S. Broecker), *Fixing Climate: What Past Climate Changes Reveal about the Current Threat—and How to Counter It.* He divides his time between Birmingham, Ala., and Dijon, France.

THE DOWNSIDES

- **UNPREDICTABLE CHANGES** in regional wind and rainfall patterns
- **REDUCED EVAPORATION,** leading to reduction in global rainfall
- **INCREASING ACID RAIN,** possibly polluting pristine ecosystems
- **ACCELERATED DESTRUCTION** of ozone layer, causing higher incidence of skin cancer
- **CHEAP ENOUGH** to be done unilaterally, without international agreements, which could increase global tensions
- **CONTINUAL MAINTENANCE** required; the earth would warm quickly if maintenance was deferred and carbon emissions continued unabated

SAMUEL AND PEDRO VELASCO *5W Infographics;* KAREN FITZPATRICK (*Kunzig*)

ing, "let the cat out of the bag," Keith says. Crutzen had won the Nobel Prize in Chemistry for his work on the destruction of atmospheric ozone in 1995; if he was taking geoengineering seriously, it seemed, everyone needed to.

By November 2007 Keith and Harvard University geophysicist Daniel P. Schrag had no trouble convincing top climate scientists to join zealous geoengineers at a workshop in Cambridge, Mass. At the end, all agreed that more research was necessary—some because geoengineering truly excites them, some because they consider it the lesser of two evils, and some because they hope to drive a stake through its heart. But still there was a consensus: geoengineering is back.

Geoengineering schemes fall into two categories, corresponding to the two knobs you might imagine twiddling to adjust the earth's temperature. One knob controls how much sunlight—or solar energy, to be more precise—reaches the planet's surface; the other controls how much heat escapes back into space, which depends on how much CO_2 is in the atmosphere. Schemes for removing CO_2 from the atmosphere, say, by fertilizing the oceans with iron [*see box on pages 32 and 33*], would strike closer to the root of the problem. But they would inevitably take decades to have much of an effect. In contrast, a sunshade could, in principle, stop global warming immediately—albeit only for as long as it was maintained. Sunshade ideas thus address what some scientists see as the extreme urgency of the climate problem. "If the Greenland ice sheet started to collapse tomorrow, and you're president of the United States, what do you do?" Schrag asks. "You don't have a choice."

So far, however, relatively little research has been done on any of the approaches or on their potentially substantial and unpredictable side effects. "There's a lot more talk than work," Caldeira says. "Most of the research has been at the hobby level." Some ideas do not merit much more than that—scattering reflective particles over a large part of the ocean, for instance, would inevitably pollute it, and the particles would probably wash up on beaches fairly quickly. But others are harder to dismiss.

Dismissing the basic rationale behind geoengineering is harder still. Few investigators today suggest that blocking the sun is a substitute for stopping the rise of atmospheric CO_2 or that geoengineering can fix the CO_2 problem by itself. They argue instead that it might give us time for the revolution needed to convert the world to carbon-neutral energy sources. "The reason I think geoengineering should be considered," says Tom M. L. Wigley of the National Center for Atmospheric Research (NCAR), "is I don't think we are going to save the planet with the emissions-reductions approaches that are on the table. No one is taking the magnitude of the technological challenge seriously."

Particles in the Stratosphere

The geoengineering scheme Crutzen and Wigley both defend is the cheapest and most certain to work; it was proposed as long ago as 1974 by the late Russian physicist Mikhail I. Budyko, then at the Main Geophysical Observatory in Leningrad. The idea is to inject several million tons a year of sulfur dioxide (SO_2) into the stratosphere. There it would react with oxygen, water and other molecules to form minute sulfate droplets made up of water, sulfuric acid (H_2SO_4) and whatever dust, salt or other particles onto which the acid and water condense. Clouds of sulfate droplets would scatter sunlight, making sunsets redder, the sky paler and the earth's surface, on average, cooler—everyone agrees on all that. In 1991 the volcanic eruption of Mount Pinatubo in the Philippines put 20 million tons of SO_2 into the stratosphere, and it had all those effects: it cooled the earth by nearly one degree Fahrenheit for about a year. "So we basically know it works," Caldeira says. In fact, Caldeira started modeling the idea nearly a decade before Crutzen wrote about it.

By the time Crutzen picked up the thread, the world was readier for geoengineering; it had gotten a degree warmer since Budyko's paper, and a lot of ice had melted. In the 1990s Edward Teller and his colleagues at Lawrence Livermore National Laboratory had suggested that metallic particles might stay aloft longer and reflect more sunlight, but Crutzen stuck with the more well established idea of injecting SO_2. It enabled him to frame his proposal in an appealing way.

By burning fossil fuels, he pointed out, people are already putting 55 million tons of SO_2 into the lower atmosphere every year (along with eight billion tons of CO_2). According to the World Health Organization, the resulting concentration of SO_2 kills 500,000 people a year. It also cools the planet, however—although no one knows by exactly how much—and so as governments enforce antipollution laws, such as the U.S. Clean Air Act, they are making global warming worse. Wouldn't it make more sense, Crutzen suggested, to loft some of that SO_2 into

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[SUNSHADE #2: BRIGHTENING THE CLOUDS]

Sea Mist in the Troposphere

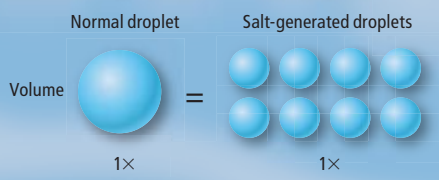
Seawater sprayed high into the air will largely evaporate as it rises, leaving little more than airborne crystals of salt by the time it reaches 1,000 feet. Those crystals could brighten the clouds that form at that altitude, reflecting more sunlight back into space.

DEPLOYMENT

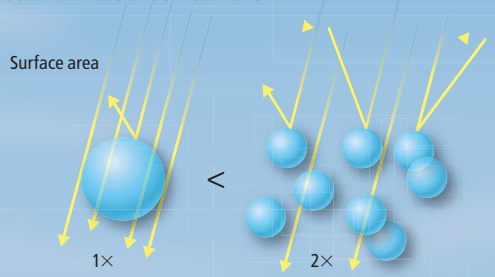
Unmanned, satellite-guided Flettner ships would crisscross the oceans, spraying seawater mist upward through vertical rotors. Turbines driven by the ship's motion through the water would generate electricity that turns the rotors. The spinning rotors would act as sails because they spin with the wind on one side and against the wind on the opposite side, generating lift.

HOW IT WORKS

Rising into cool, humid air over the ocean, the mist adds to the density of particles onto which water vapor in the atmosphere can condense, or nucleate, into cloud-forming droplets (*right*). For a given quantity of liquid condensate (which depends only on the temperature and humidity of the air), the higher the density of airborne nucleation particles, the smaller the droplets in the resulting cloud and the greater their total surface area: eight small droplets, for instance, have the same volume but twice the surface area of one large droplet with twice their diameter.



The greater surface area of the smaller droplets leads to the reflection of more incoming sunlight back into space, thereby brightening the clouds they form and cooling the ocean surface underneath them.



5 Cloud-forming water droplets remain small

4 Water vapor condenses around existing dust and added salt crystals

3 Salt crystals precipitate

2 Water evaporates from mist droplets

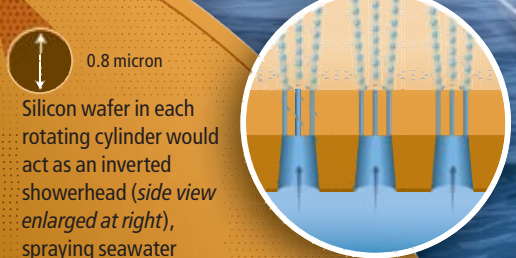
1 Droplets of seawater mist contain dissolved salt

Ship rotors

Silicon wafer nozzle

Antenna

Flettner ship



Silicon wafer in each rotating cylinder would act as an inverted showerhead (*side view enlarged at right*), spraying seawater upward in a fine mist.

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"If the **Greenland** ice sheet started to **collapse** tomorrow, and you're president of the United States, **what do you do?**"

—Daniel P. Schrag, Harvard University

THE DOWNSIDES

- **UNPREDICTABLE CHANGES** in regional temperatures, perhaps with wider swings of hot and cold
- **INCREASED LONGEVITY** of clouds made up of smaller droplets, reducing rainfall
- **MAGNITUDE** of the brightening effect not well understood
- **UNPROVED EFFECT;** no field testing of the idea yet conducted
- **CHEAP ENOUGH** to be done unilaterally, without international agreements, which could increase global tensions
- **CONTINUAL MAINTENANCE** required; the earth would warm quickly if maintenance was deferred and carbon emissions continued unabated

SAMUEL AND PEDRO VELASCO *5W Infographics*

the stratosphere? Up there it would shade us from the sun without killing us.

Budyko's original idea had been to send planes into the stratosphere burning high-sulfur fuel; Crutzen proposed delivering the SO_2 with balloons. Estimates vary of just how much SO_2 would be needed to counteract, say, a doubling of CO_2 over preindustrial levels. Wigley put the number (generally expressed as the weight of the sulfur alone) at five million tons a year; Crutzen and Philip J. Rasch of NCAR have calculated that 1.5 million tons would do the job—provided the particles were smaller, on average, than the typical volcanic ones, which are less than 0.2 micron across.

All those estimates are small compared with the amount of SO_2 we have already put in the lower atmosphere—and by the scale of the CO_2 problem, they are tiny. The annual amount of SO_2 needed, Caldeira remarks, is roughly what you could push through a fire hose. Crutzen estimated that his scheme would cost between $25 billion and $50 billion a year, which amounts to between $25 and $50 for each citizen of the developed countries. That is less than the average American spends on lottery tickets, and the return would be far more certain: a cooler planet—at least on a globally averaged basis.

All Climate Change Is Local

Yet the regional temperature pattern is what matters most. On that score, according to climate modeler David S. Battisti of the University of Washington, sun-blocking SO_2 and heat-trapping CO_2 are not well matched. CO_2 warms the planet day and night, summer and winter. As ice melts on sea and land, replacing a white and cold surface with a dark and warmer one, the CO_2 warming is amplified near the poles. In contrast, a stratospheric sulfate sunshade would block the sun only when and where the sun was shining; it would have no direct effect at all during polar winter. One would thus expect it to cool the tropics more than the poles—just the opposite of what is needed to restore climate to its preindustrial state.

Surprisingly, the few model simulations done so far suggest the effects of a sulfate sunshade are not that simple. "What we found is that it actually did a pretty good job" of reversing the warming trend in global climate, Caldeira says. By cooling the poles enough during the summer to maintain sea ice, the sunshade triggers the same powerful feedback that amplifies CO_2 warming, but in reverse.

But the sulfate sunshade could have serious drawbacks on other grounds. SO_2, like CO_2, would not just affect the planet's temperature; it would change winds and precipitation as well, in ways that are not yet foreseeable. As less sunlight reached the earth's surface, there would be less evaporation, particularly in the tropics, which would probably make rain and freshwater scarcer than they are today. The eruption of Mount Pinatubo seems to have done just that: according to an analysis by Kevin E. Trenberth and Aiguo Dai, both at NCAR, the amount of precipitation on land and the volume of river runoff dropped dramatically in the year after the eruption. At the same time, less evaporation should lead to moister soils. And Caldeira's modeling suggests that adding SO_2 to the atmosphere along with the CO_2 leads to smaller changes in precipitation than adding the CO_2 alone—in short, that geoengineering would still be an improvement over business as usual.

Whether or not there is less of it, the rain is likely to become more acidic if we put millions of tons of sulfuric acid into the stratosphere. Globally, the acid increase will probably be small—because we are already putting so much SO_2 into the lower atmosphere—but as Alan Robock of Rutgers University has pointed out in the *Bulletin of the Atomic Scientists,* some acid rain might fall in pristine areas that have been spared so far.

Return of the Ozone Hole?

A more serious worry is stratospheric ozone. Chlorine atoms that reach the upper atmosphere, the legacy of the chlorofluorocarbons long used as coolants and spray propellants, dig a hole in the Antarctic ozone layer every spring and let ultraviolet (UV) sunlight flood in. The chemical reactions that destroy ozone, however, take place only below a certain temperature threshold and only on the surfaces of stratospheric particles—including tiny droplets of sulfuric acid. As chlorofluorocarbons are phased out under the 1987 Montreal Protocol, the ozone hole is getting both smaller and shallower. But if more sulfuric acid is pumped into the stratosphere, it could act as a catalyst that could delay ozone recovery.

Sure enough, the Pinatubo "experiment" caused some ozone loss but not very much. According to Simone Tilmes of NCAR, however, the small size of the effect is misleading, because the winters following the eruption happened to be mild. In a colder winter, Tilmes says, the ozone destruction at the poles would have been

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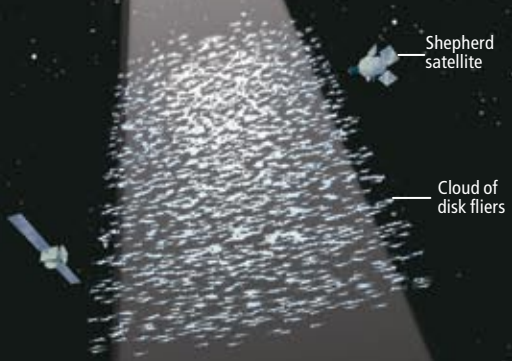
[SUNSHADE #3: VENETIAN SPACE BLINDS]

Disks by the Trillion in Space

Trillions of two-foot-wide, disk-shaped "fliers" placed in stationary solar orbit could provide enough shade to cool the earth. Constructing a sunshade in space would avoid tampering with the earth's atmosphere.

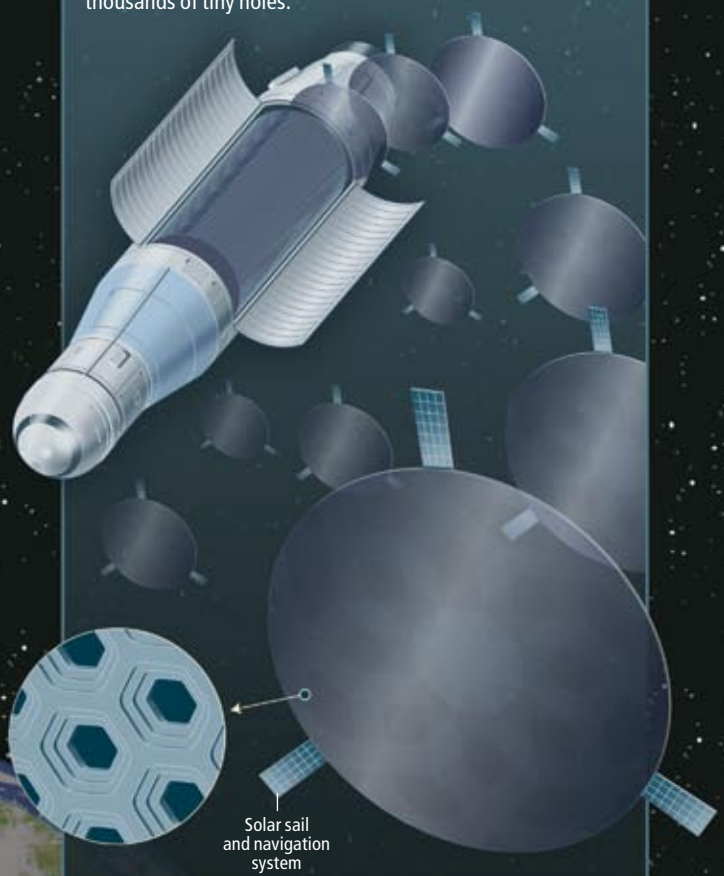


DEPLOYMENT

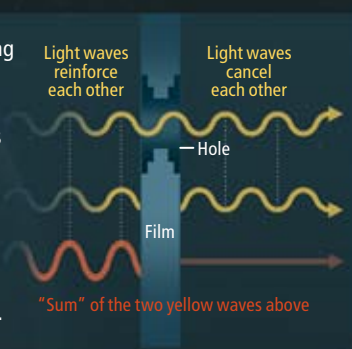
The disk fliers, each equipped with an onboard navigation system, would be stacked into cylinders a million fliers long and launched into space by electromagnetic coil guns at a rate of one cylinder a minute for 30 years. The combined launch weight of the cylinders would be kept to less than 20 million tons. The fliers would eventually separate (*right*) and form a cloud (*above*) 60,000 miles long and 4,500 miles in diameter, parked a million miles from the earth at "Lagrangian point 1" (L1), where the gravity of the sun and the earth are equal and in balance.

HOW IT WORKS

Once the fliers reached the cloud at L1, they would steer themselves, by means of mirrors acting as sails in the solar wind, to positions as directed by "shepherd" satellites. Each disk flier, one-fortieth the thickness of Saran Wrap and weighing no more than a gram, would be pricked with thousands of tiny holes.



Rays of sunlight passing through a hole in the disk would interfere destructively with rays that slow down briefly as they pass through the disk itself (*right*), thereby reducing the total solar radiation that reaches the earth.



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With a $5-trillion price tag for putting a **sunshade in space**, maybe it's easier to build **wind turbines** and **solar power plants** instead.

THE DOWNSIDES

- **COST ESTIMATED** at $5 trillion, requiring huge diversion of resources that could be spent on alternative energy
- **LENGTHY CONSTRUCTION TIME,** too long for the necessary quick fix
- **UNPREDICTABLE CHANGES** in regional wind and rainfall patterns
- **REDUCED EVAPORATION,** leading to reduction in global rainfall
- **REPLACEMENT OF "FLIERS"** needed after 50 years; the earth would warm quickly if replacement was deferred and carbon emissions continued unabated
- **DIFFICULTY** convincing people that cloud of disks could not be used as a weapon to change sunlight on various parts of the earth

SAMUEL AND PEDRO VELASCO *5W Infographics*

far more severe. Even worse for the ozone, the greenhouse gases that cause global warming actually tend to cool the stratosphere by trapping heat closer to the surface.

By Tilmes's calculations, if we were to start injecting SO_2 into the stratosphere in the next few years, the recovery of the Antarctic ozone hole would be delayed by between 30 and 70 years. In cold years an ozone hole would appear in the high northern latitudes as well, bathing cities there in cancer-causing UV radiation. As Rasch points out, however, Tilmes's results may represent a "worst-case scenario"; she combined the amount of SO_2 needed to counteract a doubling in CO_2 decades from now with the amount of chlorine that is in the stratosphere today—even though chlorine is steadily decreasing.

The effect of SO_2 on ozone thus remains uncertain, like just about every aspect of sulfate geoengineering. We could start doing it next year, but aside from cooling the planet globally we would have no real idea what we were doing—much as we did not know what we were doing to the ozone layer when the world began using chlorofluorocarbons in refrigerators and underarm deodorant. Crutzen acknowledged this iron law of unintended consequences in his essay, writing: "The chances of unexpected climate effects should not be underrated, as clearly shown by the sudden and unpredicted development of the Antarctic ozone hole."

Sea Mist in the Troposphere

In the lower atmosphere, SO_2 does not just scatter sunlight and cause respiratory disease: it creates clouds where there were none, and it brightens existing ones, the so-called aerosol indirect effect. Climate scientists think this effect already cools the planet at least as much as direct scattering by aerosol particles. Ship tracks—linear clouds of engine exhaust—illustrate the phenomenon vividly: they persist for days and extend for hundreds of miles as the ship steams along. Satellite photographs record the sunlight they reflect back to space.

John Latham's idea for cooling the planet is essentially to whiten existing marine clouds by lacing them with lots of ship tracks—but made in a cleaner way. Latham, a retired English cloud physicist, thinks spraying microscopic drops of seawater into the sky from a fleet of unmanned sailing vessels could do the trick.

The basic mechanism of the aerosol indirect effect is simple enough. The amount of sunlight reflected by a cloud depends on the surface area of the water drops that make up the cloud. "If instead of having a few big drops, you have a lot of little drops, then for the same amount of water [condensing from the vapor phase into droplets], there's more surface area," Latham explains. In principle, adding particles to the atmosphere makes for more but smaller drops, hence whiter and more reflective clouds.

Over land these days, the air is loaded with man-made particles, and as a result clouds are thought to be whiter and more reflective than they otherwise would be. But over the ocean the air is filled primarily with natural particles, including seawater droplets blown aloft by foaming waves. By the time the droplets reach 1,000 feet, most of the water has evaporated, leaving particles of salt—but at that altitude water vapor begins to condense again around the particles. The new droplets form low marine stratocumulus clouds, which cover about a quarter of the world's ocean. Latham's idea is to brighten such clouds by adding enough airborne salt spray to quadruple the number of water droplets in the clouds.

Stephen Salter, an emeritus engineering professor at the University of Edinburgh, has come up with a scheme that, on paper at least, looks ingenious. "It's basically a watering can," Latham says—but the nozzle would be a silicon wafer etched with billions of holes less than a micron across, and it would be mounted on an unmanned, satellite-guided sailing ship. More specifically, the vessel would be a Flettner ship, which has tall, spinning cylinders that resemble smokestacks but act as sails, generating lift because one side is moving with the wind and the other side against it.

In Salter's concept, turbines spun by water moving past the ship would generate the electricity to keep the cylinders spinning and also to spray seawater out the stacks in 0.8-micron droplets. Salter and Latham estimate that 1,500 ships, each spraying eight gallons a second—and each costing $2 million, for a total of $3 billion—could offset the global warming caused by a doubling of CO_2. Half the job could be done, according to modeling results from the Met Office Hadley Center for Climate Prediction and Research in Exeter, England, by deploying ships over just 4 percent of the ocean.

Still, no one has modeled how evenly the cooling would spread around the planet. "You could end up with a polka-dotted world, where there are really cold places and really hot places," Battisti says. Another concern is drought downwind

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of the spray vessels; clouds made of many small droplets last longer, which is desirable in a sunshade, but they also produce less rain.

Finally, just how much brighter the new clouds would be is not known. Existing climate models overestimate the effect: according to them, the aerosols in the atmosphere right now should be canceling global warming, which is manifestly not happening. Rasch has thus started modeling Latham's idea. "This is one of the parts of climate that we understand most poorly," he says.

Still, as geoengineering schemes go, spraying seawater into the air from wind-powered vessels sounds pretty benign. If anything went wrong, Latham says, you could shut off the spray within days or, at most, a few weeks—whereas sulfuric acid in the stratosphere would stay aloft for years. "It's definitely worth looking into," Wigley says. But only a field test could answer some of the questions about the idea—and so far the only support Latham has received has been from the Discovery Channel. In need of good visuals for a documentary series on geoengineering, television producers funded the construction of a small Flettner ship.

A Sunshade in Space

The Discovery Channel has also paid to build something for J. Roger P. Angel: a half-inch-wide disk of silicon nitride ceramic. It is transparent, pierced with many tiny holes, and about a quarter-micron thick—one-fortieth the thickness of Saran Wrap but much stiffer. Angel, director of Steward Observatory Mirror Laboratory at the University of Arizona, is well known as an innovative developer of telescope mirrors and optics, and so his idea for a disk-shaped optical device made out of the same stuff used in high-performance automotive bearings is entirely in character. A couple of years ago his wife asked him if he could do something about climate change. He responded by looking into an old geoengineering proposal that, to put it mildly, lies way outside the box.

That proposal called for placing a sunshade at L1, the inner Lagrangian point, a million miles from the earth in the direction of the sun. (At a Lagrangian point the sun exerts the same pull of gravity as the earth does.) From L1 a sunshade would cast an even shadow over the planet without polluting the atmosphere.

In Angel's scheme, the space-based sunshade would not be a single spacecraft but trillions of them—each a two-foot-wide disk of silicon nitride equipped with a computer and a navigation system and weighing no more than a gram. (Monarch butterflies, Angel points out, weigh less than a gram, and they navigate thousands of miles to their breeding grounds in Mexico.) These "fliers" would be launched in stacks of a million, one stack every minute or so for 30-odd years, by electromagnetic coil guns that would be more than a mile long and mostly underground. Thus, Angel proposes to keep the weight of the sunshade to less than 20 million tons launched from the earth. Still, for comparison, that is only slightly less than 70,000 times the current mass of the International Space Station—no trivial mass to fling into the heavens.

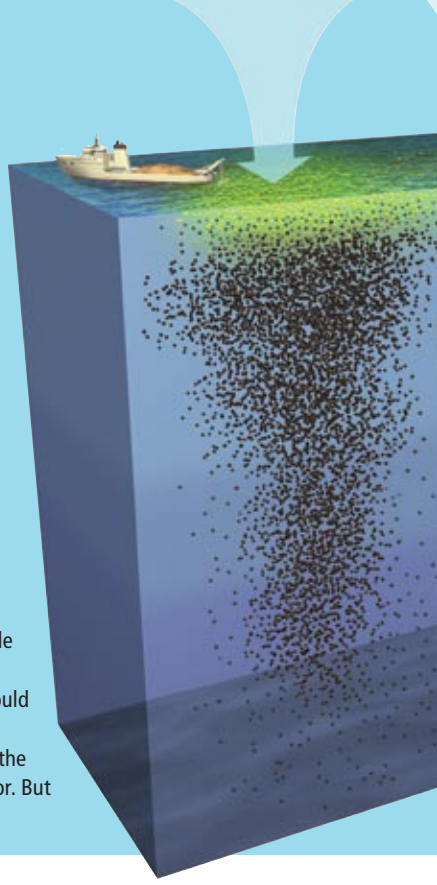
Highly efficient, ion-propulsion engines would carry each stack from earth orbit to L1, where the fliers would be dealt, like cards flung from a deck, into a cloud 60,000 miles long, pointed at the sun. "Shepherd" satellites patrolling the cloud would set up a local Global Positioning System, and each flier would keep itself from drifting out of the cloud with tiny mirrors acting as solar sails. Solar photons would pass right through the silicon nitride in each flier, but the ones passing through the holes in the flier would come out slightly ahead. The two sets would thus interfere destructively, blocking some of the sunlight that would otherwise reach the earth and scattering around 2 percent of it to either side of the planet.

It is hard to know just how serious Angel is about the idea. "It's not a quick, cheap fix," he says cheerfully. In fact, with a price tag loosely

Capturing Carbon

One way of taking carbon out of the atmosphere is to increase the growth of plankton, say, by spreading iron, a micronutrient, across iron-poor regions of the ocean. The resulting plankton bloom would draw carbon dioxide (CO_2) out of the air—that much is certain. What is not clear after a dozen field tests of iron fertilization is just how much of the carbon captured by organic matter would go deep enough to stay out of the atmosphere, as shown in the artist's conception (*right*), or what the side effects would be of such a substantial manipulation of marine ecosystems.

A second way, suggested most recently by graduate student Kurt Zenz House and his colleagues at Harvard University, is to make seawater itself more alkaline. House's idea is to split sea salt, or sodium chloride, and allow it to react with seawater to create sodium hydroxide and hydrochloric acid. The acid would then be stored on land and the sodium hydroxide left in the ocean. That would cause more CO_2 to dissolve into the water—without acidifying the ocean any further. Ultimately, House says, the carbon would end up as calcium carbonate on the seafloor. But building the seawater treatment plants would be hugely



SAMUEL ARD AND PEDRO VELASCO *SW Infographics*

If we did not reduce carbon emissions and ever allowed a **cooling sunshade to fail,** temperatures would soar so fast that one scientist labels the event "**Fall of Rome.**"

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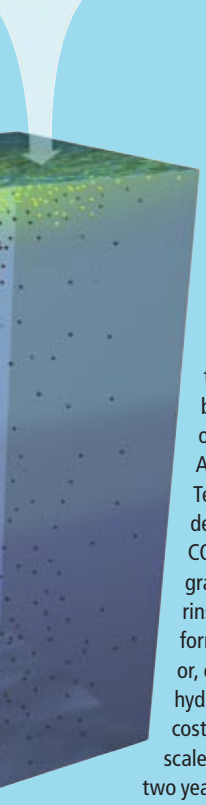

expensive—it would take 100 large ones just to absorb about a tenth of the CO_2 people add to the atmosphere every year.

Perhaps the most promising alternative, pioneered by Klaus S. Lackner of Columbia University as well as by David W. Keith of the University of Calgary in Alberta, is to build scrubbers on land that can capture CO_2 out of ambient air. Lackner and his partner, Allen B. Wright of Global Research Technologies (GRT) in Tucson, Ariz., have developed a proprietary plastic that grabs CO_2 from the atmosphere the way flypaper grabs flies. When the CO_2-enriched plastic is rinsed with water vapor, a stream of pure CO_2 forms that can be sequestered underground—or, one day perhaps, even converted back into a hydrocarbon fuel. The stumbling block again is cost, but the approach could start on a small scale: GRT is hoping to sell its first units in about two years to commercial greenhouses, which use CO_2 to enrich the atmosphere for their plants. —***R.K.***

estimated at $5 trillion, a space-based sunshade is, according to Wigley, "just completely out of the question." It would "require such a Herculean effort," Caldeira says, "that maybe it's easier to build wind turbines and solar power plants." Angel himself seems to agree; he spends most of his time these days trying to think of ways to concentrate sunlight and make photovoltaics more efficient. After all, he notes, any sunshade would waste solar power.

Smart vs. Stupid

Geoengineering cannot solve the CO_2 problem—in part because the problem is not just one of global warming. If we were to stop global warming with a sunshade, CO_2 would continue to seep into the ocean, slowly acidifying it, and in time the ecological consequences would likely be dire. Nevertheless, stopping global warming temporarily might be worthwhile. And sulfate geoengineering, Caldeira says, would be "cheap enough that single actors could do it and bear the cost themselves." The U.S. could choose to save Greenland's ice cap (and thus prevent Florida from flooding), China its Himalaya glaciers, Switzerland its ski industry, all without the fuss of negotiating a global climate treaty. Depending on your point of view, that is one of the more appealing or one of the scarier things about geoengineering.

Probably the scariest thing to think about, though, is what would happen if we did not reduce carbon emissions, built a cooling sunshade—and then allowed it to fail. Raymond T. Pierrehumbert, a climate modeler at the University of Chicago, refers to this scenario as "DamoclesWorld." The thin sulfate thread that holds up the CO_2 sword would have to be maintained, year after year, with steady injections of ever increasing amounts of SO_2. If it ever snapped, for reasons of war or civil unrest or budget crises, the accumulated CO_2 would warm the planet in one fell swoop, creating precisely the emergency the sunshade was intended to prevent, only worse. Caldeira, too, has simulated the collapsing-sunshade scenario, along with H. Damon Matthews of Concordia University in Montreal; they found that the earth might warm at a rate of between four and seven degrees F per decade, 10 times faster than it is warming today. Human history, Pierrehumbert argues, does not inspire confidence that we could forestall such a catastrophe. On a graph he uses to illustrate the result of his own simulations, the point at which geoengineering stops and temperatures soar is labeled "Fall of Rome."

No one knows today whether geoengineering could ever make sense. Most workers would agree that further research is now inevitable—but their attitudes toward such study vary. To some, such as Wigley, a sunshade could be a rational strategy to buy time for the long labor of converting to a carbon-neutral energy supply. Others fear it would remove the incentive to do that hard work. "It's extremely unfortunate that this genie has come out of the bottle just at a time when the world seems finally awakening to the seriousness of climate change," Pierrehumbert told an audience recently at the Kavli Institute for Theoretical Physics at the University of California, Santa Barbara. "There is a huge risk that if people begin to see this prematurely as a fallback position, this technology will cut off at the knees actions that are just starting to be taken that make serious reductions in emissions."

In the end the debate comes down to differing views about human nature—and the power of science to restrain it. "Scientifically it would be utterly stupid just to do geoengineering" without reducing emissions, Wigley says. "If we were to do that, we'd get to the crunch where people realize there aren't any more fish in the sea. We're not that stupid. We can be guided by good science."

Pierrehumbert, like many others, takes a darker view. A bullet point on one of his PowerPoint slides reads simply: "We are quite capable of doing stupid things." ■

MORE TO EXPLORE

Feasibility of Cooling the Earth with a Cloud of Small Spacecraft near the Inner Lagrange Point (L1). Roger Angel in *PNAS,* Vol. 103, No. 46, pages 17184–17189; November 14, 2006.

20 Reasons Why Geoengineering May Be a Bad Idea. Alan Robock in *Bulletin of the Atomic Scientists,* Vol. 64, No. 2, pages 14–18, 59; May/June 2008. Available at **www.thebulletin.org/files/064002006_0.pdf**

Alan Robock's article and the debate it triggered are available at **www.thebulletin.org/web-edition/roundtables/has-the-time-come-geoengineering**

The September 2008 issue of the *Philosophical Transactions of the Royal Society A,* devoted to geoengineering, is available at **http://publishing.royalsociety.org/index.cfm?page=1814**

Talks on geoengineering by David W. Keith, Raymond T. Pierrehumbert, Kurt Zenz House and others are available at the Web site of the Kavli Institute for Theoretical Physics: **http://online.itp.ucsb.edu/online/climate_c08**

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Jacking into the Brain

How far can science advance brain-machine interface technology? Will we one day pipe the latest blog entry or NASCAR highlights directly into the human brain as if the organ were an outsize flash drive?

By Gary Stix

KEY CONCEPTS

- Futurists and science-fiction writers speculate about a time when brain activity will merge with computers.
- Technology now exists that uses brain signals to control a cursor or prosthetic arm. How much further development of brain-machine interfaces might progress is still an imponderable.
- It is at least possible to conceive of inputting text and other high-level information into an area of the brain that helps to form new memories. But the technical hurdles to achieving this task probably require fundamental advances in understanding the way the brain functions.

—The Editors

The cyberpunk science fiction that emerged in the 1980s routinely paraded "neural implants" for hooking a computing device directly to the brain: "I had hundreds of megabytes stashed in my head," proclaimed the protagonist of "Johnny Mnemonic," a William Gibson story that later became a wholly forgettable movie starring Keanu Reeves.

The genius of the then emergent genre (back in the days when a megabyte could still wow) was its juxtaposition of low-life retro culture with technology that seemed only barely beyond the capabilities of the deftest biomedical engineer. Although the implants could not have been replicated at the Massachusetts Institute of Technology or the California Institute of Technology, the best cyberpunk authors gave the impression that these inventions might yet materialize one day, perhaps even in the reader's own lifetime.

In the past 10 years, however, more realistic approximations of technologies originally evoked in the cyberpunk literature have made their appearance. A person with electrodes implanted inside his brain has used neural signals alone to control a prosthetic arm, a prelude to allowing a human to bypass limbs immobilized by amyotrophic lateral sclerosis or stroke. Researchers are also investigating how to send electrical messages in the other direction as well, providing feedback that enables a primate to actually sense what a robotic arm is touching.

But how far can we go in fashioning replacement parts for the brain and the rest of the nervous system? Besides controlling a computer cursor or robot arm, will the technology somehow actually enable the brain's roughly 100 billion neurons to function as a clandestine repository for pilfered industrial espionage data or another plot element borrowed from Gibson?

Will Human Become Machine?

Today's Hollywood scriptwriters and futurists, less skilled heirs of the original cyberpunk tradition, have embraced these neurotechnologies. *The Singularity Is Near,* scheduled for release next year, is a film based on the ideas of computer scientist Ray Kurzweil, who has posited that humans will eventually achieve a form of immortality by transferring a digital blueprint of their brain into a computer or robot.

Yet the dream of eternity as a Max Headroom–like avatar trapped inside a television set (or as a copy-and-paste job into the latest humanoid bot) remains only slightly less distant than when René Descartes ruminated on mind-body dualism in the 17th century. The wholesale

BILL DIODATO

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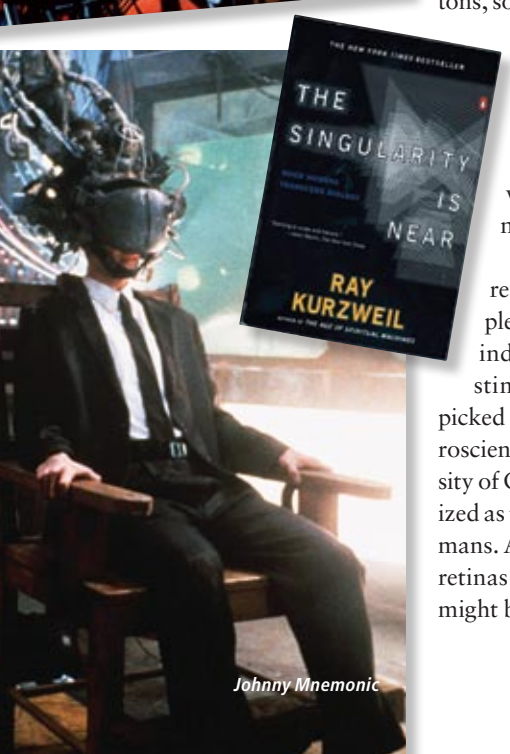
▼ NEURAL IMPLANTS—iconic props in science-fiction and futurist literature—have now made their way into the lab. But the more far-reaching uses of the technology (text input into the brain, for one) are still a literary figment.



transfer of self—a machine-based facsimile of the perception of the ruddy hues of a sunrise, the constantly shifting internal emotional palette and the rest of the mix that combines to evoke the uniquely subjective sense of the world that constitutes the essence of conscious life—is still nothing more than a prop for fiction writers.

Hoopla over thought-controlled prostheses, moreover, obscures the lack of knowledge of the underlying mechanisms of neural functioning needed to feed information into the brain to re-create a real-life cyberpunk experience. "We know very little about brain circuits for higher cognition," says Richard A. Andersen, a neuroscientist at Caltech.

What, then, might realistically be achieved by interactions between brains and machines? Do the advances from the first EEG experiment to brain-controlled arms and cursors suggest an inevitable, deterministic progression, if not toward a Kurzweilian singularity, then perhaps toward the possibility of inputting at least some high-level cognitive information into the brain? Could we perhaps download *War and Peace* or, with a nod to *The Matrix,* a manual of how to fly a helicopter? How about inscribing the sentence "See Spot run" into the memory of someone who is unconscious of the transfer? How about just the word "see"?

These questions are not entirely academic, although some wags might muse that it would be easier just to buy a pair of reading glasses and do things the old-fashioned way. Even if a pipeline to the cortex remains forever a figment of science fiction, an understanding of how photons, sound waves, scent molecules and pressure on the skin get translated into lasting memories will be more than mere cyberpunk entertainment. A neural prosthesis built from knowledge of these underlying processes could help stroke victims or Alzheimer's patients form new memories.

Primitive means of jacking in already reside inside the skulls of thousands of people. Deaf or profoundly hearing-impaired individuals carry cochlear implants that stimulate the auditory nerve with sounds picked up by a microphone—a device that neuroscientist Michael S. Gazzaniga of the University of California, Santa Barbara, has characterized as the first successful neuroprosthesis in humans. Arrays of electrodes that serve as artificial retinas are in the laboratory. If they work, they might be tweaked to give humans night vision.

The more ambitious goal of linking Amazon.com directly to the hippocampus, a neural structure involved with forming memories, requires technology that has yet to be invented. The bill of particulars would include ways of establishing reliable connections between neurons and the extracranial world—and a means to translate a digital version of *War and Peace* into the language that neurons use to communicate with one another. An inkling of how this might be done can be sought by examining leading work on brain-machine interfaces.

Your Brain on Text

Jacking text into the brain requires consideration of whether to insert electrodes directly into tissue, an impediment that might make neural implants impractical for anyone but the disabled. As has been known for nearly a century, the brain's electrical activity can be detected without cracking bone. What looks like a swimming cap studded with electrodes can transmit signals from a paralyzed patient, thereby enabling typing of letters on a screen or actual surfing of the Web. Niels Birbaumer of the University of Tübingen in Germany, a leading developer of the technology, asserts that trial-and-error stimulation of the cortex using a magnetic signal from outside the skull, along with the electrode cap to record which neurons are activated, might be able to locate the words "see" or "run." Once mapped, these areas could be fired up again to evoke those memories—at least in theory.

Some neurotechnologists think that if particular words reside in specific spots in the brain (which is debatable), finding those spots would probably require greater precision than is afforded by a wired swim cap. One of the ongoing experiments with invasive implants could possibly lead to the needed fine-level targeting. Philip R. Kennedy of Neural Signals and his colleagues designed a device that records the output of neurons. The hookup lets a stroke victim send a signal, through thought alone, to a computer that interprets it as, say, a vowel, which can then be vocalized by a speech synthesizer, a step toward forming whole words. This type of brain-machine interface might also eventually be used for activating individual neurons.

Still more precise hookups might be furnished by nanoscale fibers, measuring 100 nanometers or less in diameter, which could easily tap into single neurons because of their dimensions and their electrical and mechanical properties. Jun Li of Kansas State University and his colleagues

KOBAL COLLECTION (*poster and film stills*)

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have crafted a brushlike structure in which nanofiber bristles serve as electrodes for stimulating or receiving neural signals. Li foresees it as a way to stimulate neurons to allay Parkinson's disease or depression, to control a prosthetic arm or even to flex astronauts' muscles during long spaceflights to prevent the inevitable muscle wasting that occurs in zero gravity.

Learning the Language

Fulfilling the fantasy of inputting a calculus text—or even plugging in *Traveler's French* before going on vacation—would require far deeper insight into the brain signals that encode language and other neural representations.

Unraveling the neural code is one of the most imposing challenges in neuroscience—and, to misappropriate Freud, would likely pave a royal road to an understanding of consciousness. Theorists have advanced many differing ideas to explain how the billions of neurons and trillions of synapses that connect them can ping meaningful messages to one another. The oldest is that the code corresponds to the rate of firing of the voltage spikes generated by a neuron.

Whereas the rate code may suffice for some stimuli, it might not be enough for booting a Marcel Proust or a Richard Feynman, supplying a mental screen capture of a madeleine cake or the conceptual abstraction of a textbook of differential equations. More recent work has focused on the precise timing of the intervals between each spike (temporal codes) and the constantly changing patterns of how neurons fire together (population codes) [*see box on next two pages*].

Some help toward downloading to the brain might come from a decadelong endeavor to build an artificial hippocampus to help people with memory deficits, which may have the corollary benefit of helping researchers gain insights into the coding process. A collaboration between the University of Southern California and Wake Forest University has worked to fashion a replacement body part for this memory-forming brain structure. The hippocampus, seated deep within the brain's temporal lobe, sustains damage in stroke or Alzheimer's. An electronic bypass of a damaged hippocampus could restore the ability to create new memories. The project, funded by the National Science Foundation and the Defense Advanced Research Projects Agency, might eventually go further, enhancing normal memory or helping to deduce the particular codes needed for high-level cognition.

▲ QUADRIPLEGIC confined to a wheelchair can negotiate a virtual street using brain waves captured by an electrode cap.

▲ MONKEY SEE, MONKEY GRAB: Neural signals from a primate manipulate a robotic arm to snatch a morsel at the University of Pittsburgh.

The two groups—led by Theodore W. Berger at U.S.C. and Samuel Deadwyler at Wake Forest—are preparing a technical paper showing that an artificial hippocampus took over from the biological organ the task of consolidating a rat's memory of pressing a lever to receive a drop of water. Normally the hippocampus emits signals that are relayed to cortical areas responsible for storing the long-term memory of an experience. For the experiment, a chemical temporarily incapacitated the hippocampus. When the rat pressed the correct bar, electrical input from sensory and other areas of the cortex were channeled through a microchip, which, the scientists say, dispatched the same signals the hippocampus would have sent. A demonstration that an artificial device mimicked hippocampal output would mark a step toward deducing the underlying code that could be used to create a memory in the motor cortex—and perhaps one day to unravel ciphers for even higher-level behaviors.

If the codes for the sentence "See Spot run"—or perhaps an entire technical manual—could be ascertained, it might, in theory, be possible to input them directly to an electrode array in the hippocampus (or cortical areas), evoking the scene in *The Matrix* in which instructions for flying a helicopter are downloaded by cell phone. Artificial hippocampus research postulates a scenario only slightly more prosaic. "The kinds of examples [the U.S. Department of Defense] likes to typically use are coded information for flying an F-15," says Berger.

The seeming simplicity of the model of neural input envisaged by artificial hippocampus-related studies may raise more questions than it answers. Would such an implant overwrite existing memories? Would the code for the sentence "See Spot run" be the same for me as it is for you or, for that matter, a native Kurdish speaker? Would

ROBERT LEEB *Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology (man in wheelchair);* COURTESY OF MOTORLAB, UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE *(prosthesis experiment series)*

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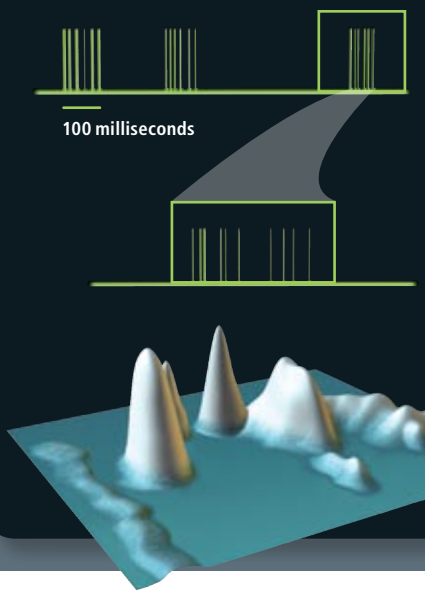
[PROGRESS AND PROSPECTS FOR NEUROTECHNOLOGY]

How to Load Text into Neurons—Maybe

A clue to how you might input *War and Peace* or other high-level information directly into the brain might be discerned by looking at some of the most advanced research in neuroscience. Scientists are studying ways to connect computers and prostheses directly to the brain and to understand the brain's neural code—how it converts electrical signals that serve as inputs into behavioral outputs, such as moving an arm or producing speech. Whether the obstacles to constructing a brain input device can be overcome is highly uncertain.

TYPES OF NEURAL CODE

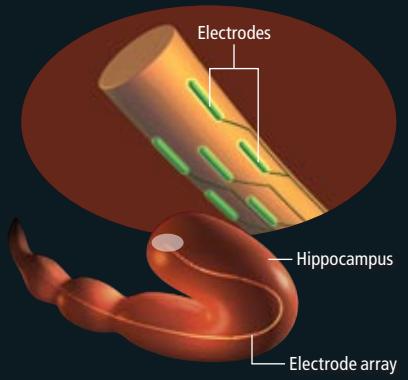


RATE CODE
The nature of the neural code is a topic of ongoing research and debate. The oldest notion is that of a rate code made up of the average number of voltage spikes when a neuron fires in a given interval of, say, 100 milliseconds.

TEMPORAL CODE
More recently, neuroscientists have focused on temporal codes that gauge how much time elapses between each individual spike within that 100-millisecond interval, allowing the coding of more information than in a simple rate code.

POPULATION CODE
The most advanced research assesses population codes: the patterns of activity that change in both space and time when groups of neurons fire. A graph of neurons firing together is at the left.

PLUGGING INTO NEURONS



Wiring brain cells presents numerous challenges: the connections can jiggle out of place, disintegrate and even cause infection. Existing designs of neural electrodes would need to achieve a higher level of spatial and temporal resolution for a task such as inputting information into the hippocampus, a brain structure that helps to form memories.

the hippocampal codes merge cleanly with other circuitry that provides the appropriate context, a semantic framework, for the sentence? Would "See Spot run" be misinterpreted as a laundry mishap instead of a trotting dog?

Some neuroscientists think the language of the brain may not be deciphered until understanding moves beyond the reading of mere voltage spikes. "Just getting a lot of signals and trying to understand what these signals mean and correlating them with particular behavior is not going to solve it," notes Henry Markram, director of neuroscience and technology at the Swiss Federal Institute of Technology in Lausanne. A given input into a neuron or groups of neurons can produce a particular output—conversion of sensory inputs to long-term memory by the hippocampus, for instance—through many different pathways. "As long as there are lots of different ways to do it, you're not even close," he says.

The Blue Brain Project, which Markram heads, is an attempt that began in 2005 to use supercomputer-based simulations to reverse-engineer the brain at the molecular and cellular levels—modeling first the simpler rat organ and then the human version to unravel the underlying function of neural processes. The latter task awaits a computer that boasts a more than 1,000-fold improvement over the processing power of current supercomputers. The actual code, when it does emerge, may be structured very differently from what appears in today's textbooks. "I think there will be a conceptual breakthrough that will have significant implications for how we think of reality," Markram says. "It will be quite a profound thing. That's probably why it's such an intractable problem."

The challenge involved in figuring out how to move information into the brain suggests a practical foreseeable limit for how far neurotechnology might be advanced. The task of forming the multitude of connections that make a memory is vastly different from magnetizing a set of bits on a hard disk. "Complex information like the contents of a book would require the interactions of a very large number of brain cells over a very large area of the nervous system," observes neuroscientist John P. Donoghue of Brown University. "Therefore, you couldn't address all of them, getting them to store in their connections the correct kind of information. So I would say based on current knowledge, it's not possible."

GEORGE RETSECK

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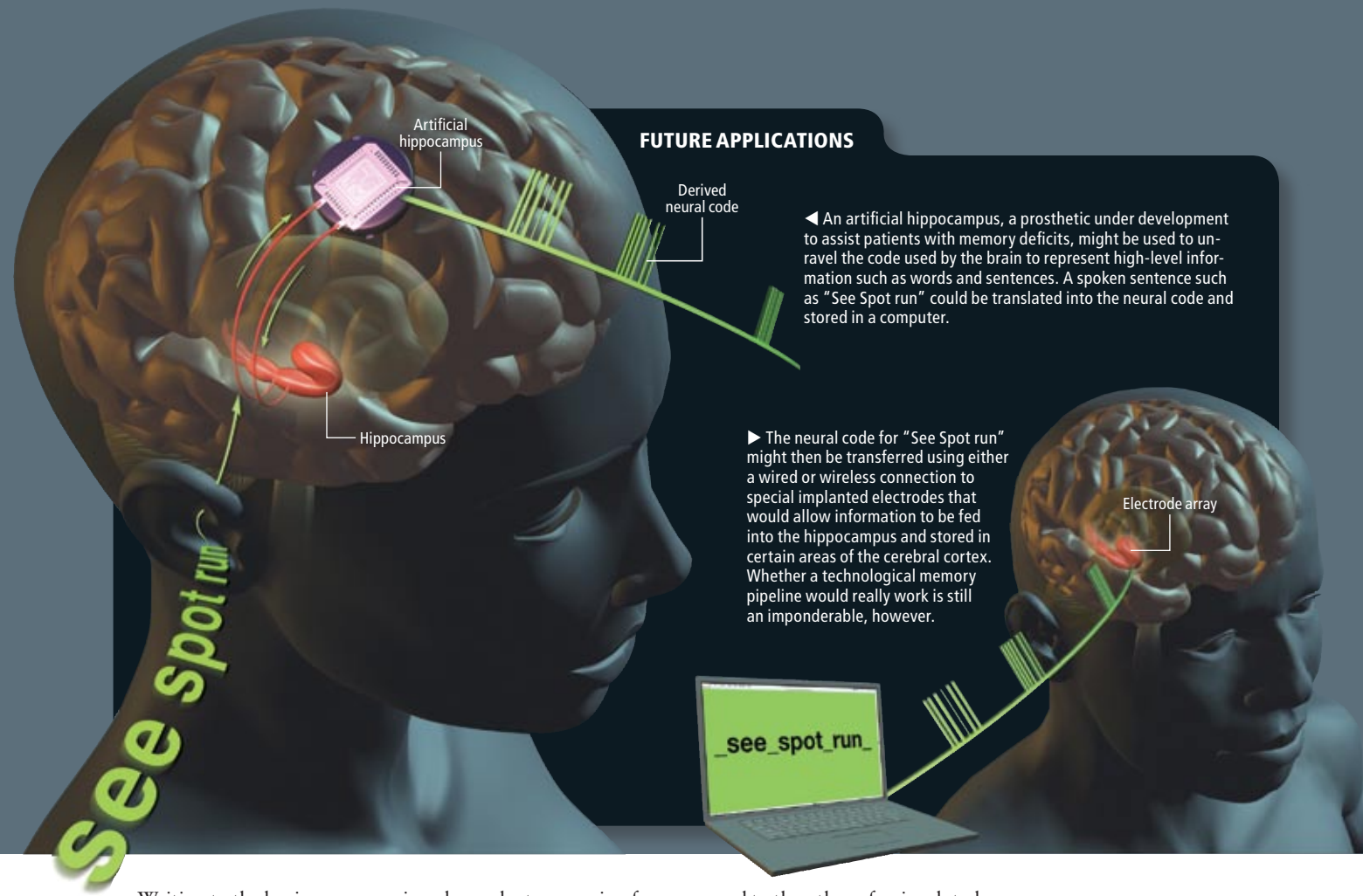

Writing to the brain may remain a dream lost in cyberspace. But the seeming impossibility does not make Donoghue less sanguine about ultimate expectations for feeding information the other way and developing brain-controlled prostheses for the severely disabled. He has been a leader in studies to implant an array of multiple electrodes into the brain that can furnish a direct line from the cortex to a prosthetic arm or even a wheelchair.

Donoghue predicts that in the next five years brain-machine interfaces will let a paralyzed person pick up a cup and take a drink of water and that, in some distant future, these systems might be further refined so that a person with an upper spinal cord injury might accomplish the unthinkable, perhaps even playing a game of basketball with prosthetics that would make a reality of *The Six Million Dollar Man,* the 1970s television series. Even without an information pipeline into the brain, disabled patients and basic researchers might still reap the benefits of lesser substitutes. Gert Pfurtscheller of the Graz University of Technology in Austria and his colleagues reported last year on a patient with a spinal cord injury who was able, merely by thinking, to traverse a virtual environment, moving from one end to the other of a simulated street. Duke University's Miguel A. L. Nicolelis, another pioneer in brain-machine interfaces, has begun to explore how monkeys connected to brain-controlled prosthetic devices begin to develop a kinesthetic awareness, a sense of movement and touch, that is completely separate from sensory inputs into their biological bodies. "There's some physiological evidence that during the experiment they feel more connected to the robots than to their own bodies," he says.

The most important consequences of these investigations may be something other than neural implants and robotic arms. An understanding of central nervous system development acquired by the Blue Brain Project or another simulation may let educators understand the best ways to teach children and determine at what point a given pedagogical technique should be applied. "You can build an educational development program that is engineered to, in the shortest possible time, allow you to acquire certain capabilities," Markram says. If he is right, research on neural implants and brain simulations will produce more meaningful practical benefits than dreams of the brain as a flash drive drawn from 20th-century science-fiction literature. ■

MORE TO EXPLORE

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THE LONG ARM OF

By J. Miguel Rubí

In seeming defiance of the second law of thermodynamics, nature is filled with examples of order emerging from chaos. A new theoretical framework resolves the apparent paradox

Science has given humanity more than its share of letdowns. It has set limits to our technology, such as the impossibility of reaching the speed of light; failed to overcome our vulnerabilities to cancer and other diseases; and confronted us with inconvenient truths, as with global climate change. But of all the comedowns, the second law of thermodynamics might well be the biggest. It says we live in a universe that is becoming ever more disordered and that there is nothing we can do about it. The mere act of living contributes to the inexorable degeneration of the world. No matter how advanced our machines become, they can never completely avoid wasting some energy and running down. Not only does the second law squash the dream of a perpetual-motion machine, it suggests that the cosmos will eventually exhaust its available energy and nod off into an eternal stasis known as heat death.

Ironically, the science of thermodynamics, of which the second law is only one part, dates to an era of technological optimism, the mid-19th century, when steam engines were transforming the world and physicists such as Rudolf Clausius, Nicolas Sadi Carnot, James Joule and Lord Kelvin developed a theory of energy and heat to understand how they work and what limited their efficiency. From these nitty-gritty beginnings, thermodynamics has become one of the most important branches of physics and engineering. It is a general theory of the collective properties of complex systems, not just steam engines but also bacterial colonies, computer memory, even black holes in the cosmos. In deep ways, all these systems be-

MICHAEL MORGENSTERN

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THE SECOND LAW

have the same. All are running down, in accordance with the second law.

But despite its empirical success, the second law often seems paradoxical. The proposition that systems steadily run down seems at odds with the many instances in nature not only of disorganization and decay but also of self-organization and growth. In addition, the original derivation of the second law has serious theoretical shortcomings. By all rights, the law should not apply as widely as it does.

Many of the scientists who founded thermodynamics were conscious of these failings and sought to formulate a more complete theory, a task taken up in the 20th century by Lars Onsager, Ilya Prigogine, Sybren de Groot, Peter Mazur and others. Yet even their more sophisticated approach had limited applicability. My colleagues and I have recently made progress in solidifying the foundations of thermodynamics and extending it into new realms. We have confirmed that the second law is universal but also found that it is not nearly as gloomy as its reputation suggests.

Out of Balance

Thermodynamics is one of the most widely misunderstood branches of physics. Laypeople and scientists alike regularly use concepts such as temperature, pressure and energy without knowing their rigorous meaning and subtleties. But those of us who plumb the theory's depths are acutely aware of the need to take care. The Achilles' heel of thermodynamics is that, strictly speaking, it applies only when the system under study is in a quiescent state called equilibrium. In this state the system's parameters, such as mass, energy and shape, have ceased to change. Putting two objects together at different temperatures makes heat flow from the hotter object to the colder. This process stops when both reach the same temperature—that is, when

KEY CONCEPTS

- Waste is unavoidable—a sad fact of life quantified by the famous second law of thermodynamics. But if the world is steadily becoming more disordered, how do you explain the self-organization that often occurs in nature? At root, the trouble is that classical thermodynamics assumes systems are in equilibrium, a placid condition seldom truly achieved in the real world.
- A new approach closes this loophole and finds that the second law holds far from equilibrium. But the evolution from order to disorder can be unsteady, allowing for pockets of self-organization.

—The Editors

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[WHERE THERMODYNAMICS FAILS]

CAUTION: CONTENTS MAY BE BOTH HOT AND COLD

Temperature seems like such a simple, universal concept. Things may be hot or cold, but they always have a temperature, right? Not quite. It is possible to assign a temperature only to systems (such as the molecules in a glass of water) that are in, or almost in, a stable condition known as equilibrium. As systems deviate from equilibrium, the temperature becomes progressively more ambiguous.

EQUILIBRIUM

A glass of water, left undisturbed, comes to room temperature. The water molecules collide with one another and reapportion their energy so that their overall pattern of velocities stabilizes. Although the glass contains billions on billions of molecules, it takes only one number—the temperature—to describe this pattern. Classical thermodynamics applies.

MODEST DISEQUILIBRIUM

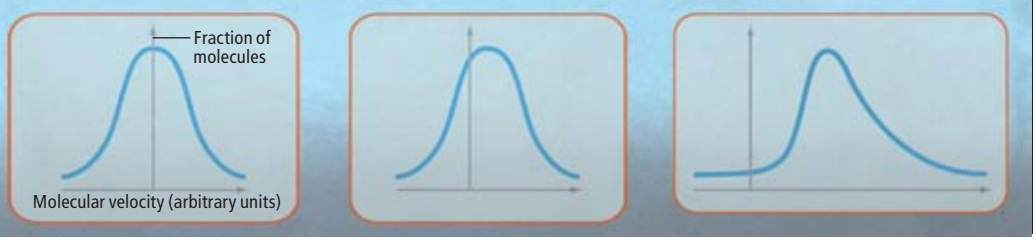
Heating the water from below disturbs the equilibrium. But if the heating is modest, individual layers of water remain approximately in equilibrium—so-called local equilibrium—and the water can be described by a temperature value that increases from top to bottom. The theory of nonequilibrium thermodynamics developed in the 20th century applies.

SEVERE DISEQUILIBRIUM

If you crank up the heat, individual layers may no longer be even approximately in equilibrium. The molecules become a chaotic jumble in which the concept of temperature ceases to apply. To describe the system, you would have to introduce a raft of new variables and, in the most extreme case, specify the molecular velocities one by one. This situation demands a new theory.

MOLECULAR VELOCITIES

Some textbooks define temperature as the average random velocity of molecules. In fact, temperature is the measure of an entire pattern of velocities. In modest departures from equilibrium, this pattern is merely shifted, but in severe departures, it is distorted, rendering temperature meaningless.



the two are in thermal equilibrium. From that point on, nothing changes.

A common example is when you put ice in a glass of water. The ice melts, and the water in the glass reaches a uniformly lower temperature. If you zoom in to the molecular level, you find an intense activity of molecules frantically moving about and endlessly bumping into one another. In equilibrium, the molecular activity organizes itself so that, statistically, the system is at rest; if some molecules speed up, others slow down, maintaining the overall distribution of velocities. Temperature describes this distribution; in fact, the very concept of temperature is meaningful only when the system is in equilibrium or sufficiently near it.

Thermodynamics therefore deals only with situations of stillness. Time plays no role in it. In reality, of course, nature never stands still, and time does matter. Everything is in a constant state of flux. The fact that classical thermodynamics is limited to equilibrium situations may come as a surprise. In introductory physics classes, students apply thermodynamics to dynamic systems such as car engines to calculate quantities such as efficiency. But these applications make an implicit assumption: that we can approximate a dynamic process as an idealized succession of equilibrium states. That is, we imagine that the system is always in equilibrium, even if the equilibrium shifts from moment to moment. Consequently, the efficiency we calculate is only an upper limit. The value that engines reach in practice is somewhat lower because they operate under nonequilibrium conditions.

The second law describes how a succession of equilibrium states can be irreversible, so that the system cannot return to its original state without exacting a price from its surroundings. A melted ice cube does not spontaneously reform; you need to put it in the freezer, at a cost in energy. To quantify this irreversibility, the

THE SECOND LAW

The second law is the best known of the four laws of thermodynamics, the study of heat and energy. Whereas the first law states that you cannot get something for nothing, the second law states that you cannot even get something for something. Almost all processes lose some energy as heat, so to get something, you have to give something more. Such processes are irreversible; to undo them exacts a toll in energy. Consequently:

- Engines are inherently limited in their energy efficiency.
- Heat pumps tend to be more efficient than furnaces, because they move rather than generate heat.
- Erasing computer memory is an irreversible act, so it produces heat.

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second law introduces a key quantity: entropy. Entropy is popularly described as the degree of disorder in the system, but as I will discuss later, this description can be misleading. Quantitatively, entropy is the amount of heat exchanged in a process divided by the temperature. In an isolated system, entropy always stays the same or increases.

For instance, a typical engine works by exploiting the flow of heat from a hot to a cold reservoir, which are two large masses exterior to the engine mechanism. If the reservoirs maintain a constant temperature and the engine parts are frictionless, the engine goes through its cycle in a completely reversible way; the total entropy remains constant. In a real engine, these idealizations do not apply, so the cycle is irreversible and the total entropy increases. Eventually the engine runs out of available energy, heat ceases to flow and entropy reaches a maximum value. At that point, the reservoirs and engine are in equilibrium with one another and will remain that way, unchanged, from then on.

The fact that classical thermodynamics presumes equilibrium situations limits the applicability of the second law. Entropy and temperature cannot even be defined unless the system is in equilibrium. Moreover, many systems cannot be modeled as a heat engine. The cosmos is one: if space is expanding, entropy can increase without limit, so that the universe approaches but never reaches equilibrium [see "The Cosmic Origins of Time's Arrow," by Sean M. Carroll; Scientific American, June]. What these systems have in common is that they are not in equilibrium or even close to it.

Order from Chaos

Nonequilibrium systems behave in some fascinating ways that the classical theory of thermodynamics does not capture and that belie the idea that nature tends to become steadily more disordered. For instance, consider a familiar appliance, the electric toaster. The wire inside it heats up because the wire material offers resistance to the flow of electric current. The second law stipulates that this process is irreversible: you cannot use a toaster to untoast a piece of bread and thereby generate electricity.

You can, however, do something similar. You can impose a temperature difference between the tips of the toaster wire, thereby ensuring the system remains out of equilibrium. Then it will indeed generate electricity. This reversal is the basis of the thermocouple, a device used to measure temperature or produce power.

A related phenomenon is reverse osmosis for seawater desalination. In standard osmosis, the difference in salt concentration across a membrane creates a difference in pressure, ensuring that water flows to the saltier side and dilutes it. The system thereby approaches equilibrium. In reverse osmosis, an external pressure keeps the system out of equilibrium, forcing water to flow over to the less salty side and become potable.

The toaster and thermocouple, and forward and reverse osmosis, are mirror-image processes. They are connected by the so-called reciprocity relation, the formulation of which won Onsager the 1968 Nobel Prize in Chemistry. The symmetry between these processes reflects the reversibility of the laws governing the motion of the particles of the system. Those laws work equally well backward or forward in time. The irreversibility we observe at a macroscopic level arises only when we consider particles en masse.

The discovery of the reciprocity relation changed how physicists think of equilibrium. They used to think of it as the most highly ordered state. Although the molecules may be maximally disordered, the system overall is placid, symmetrical and orderly. Yet the reciprocity relation exemplifies how a nonequilibrium system, too, can be highly ordered. Regularities, symmetries and islands of tranquility may come up in situations far from equilibrium.

Another classic example is a thin fluid layer heated from below. Heat flows from the bottom to the top, and a temperature gradient develops across the layer. By increasing the gradient, one can increase the departure from equilibrium. For modest gradients, the fluid remains at rest. For larger gradients, however, it begins to move. Its convective motion, far from being chaotic, is orderly. Small hexagonal cells form as if the fluid were a crystal. For even larger gradients, the motion becomes turbulent. This phenomenon, known as the Bénard problem, demonstrates that order can shade into chaos and back to order as a system deviates from equilibrium.

In yet another example, an experimenter begins with a fluid at rest. The fluid is isotropic: it looks the same in every direction. The experimenter then forces the fluid to pass through a metal grid at a certain speed. Although the fluid becomes turbulent on the downstream side, its motion still takes place in one direction. Thus, the fluid is no longer isotropic. As the experimenter increases the speed of the fluid, the tur-

APPLICATIONS

Many important physical and biochemical processes operate far from equilibrium, where the standard theory of thermodynamics dare not tread. The author and his colleagues have fixed this shortcoming.

Microfluidics. Fluids flowing through microscopic channels are prone to effects that are negligible in larger channels, such as diffusion of molecules. The standard equations describing the fluids' behavior are often intractable. But the new nonequilibrium theory of thermodynamics circumvents these complications and can readily calculate the basic flow properties.

Chemical reactions. Chemical reactions and other processes such as crystallization are inherently nonlinear: they occur only when the energy exceeds a certain threshold. They become still more complex when they occur in a medium whose density and other properties vary. The nonequilibrium theory is nonetheless able to predict the reaction rates.

Molecular folding and unfolding. Strings of amino acids pack themselves into three-dimensional proteins whose shape helps to determine their biological function. The process is notoriously poorly understood. The nonequilibrium theory has recently had some success on the related problem of how RNA molecules unfold.

Cell membranes. Molecules weasel their way through cell membranes aided by various biochemical contraptions, such as ion channels and proteins that act as ratchets. Yet the speed of this process has long puzzled theorists. The nonequilibrium theory shows that features once seen as complications—large and sustained departures from equilibrium, as well as nonlinearities and fluctuations of density—are actually what enable the process.

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[THE AUTHOR]

J. Miguel Rubí describes his introduction to physics as almost accidental. As a student, he nearly decided to study Latin instead, but an inspiring physics teacher, he says, "opened my eyes to a fascinating world full of principles and laws that surprisingly could explain what was observed." Today Rubí is a physics professor at the University of Barcelona, the city of his birth. In 2003 he received the Onsager Medal (awarded by the Norwegian University of Science and Technology) and the Alexander von Humboldt Prize (awarded by the eponymous foundation) for his contributions to nonequilibrium thermodynamics and the theory of stochastic processes.

bulence increases and eventually becomes so great that the fluid no longer flows one way. At this point, the fluid is again isotropic. The fluid has gone from isotropic to anisotropic and back to isotropic—a type of progression from order to disorder to order.

Standard thermodynamics does not capture such phenomena, a limitation that has become all the more pressing in recent years. Researchers in molecular biology and the nascent field of nanotechnology have discovered a great diversity of organized but ever changing structures in physical, chemical and biological systems. To explain them requires a theory of nonequilibrium thermodynamics.

Breaking It Down

Earlier efforts to develop such a theory started from the concept of local equilibrium states. Although a system may not be in equilibrium, individual pieces of it can be. For instance, imagine stirring a cocktail with a swizzle stick. The equilibrium is disturbed by the motion of the stick but can still be found if you look closely at small pockets of fluid, which retain their internal coherence. These small regions are able to reach equilibrium if the forces acting on the system are not too large and if its properties do not change by large amounts over small distances. Concepts such as temperature and entropy apply to these islands of equilibrium, although the numerical values of these quantities may vary from island to island.

For instance, when one heats up one of the ends of a metal bar, heat flows through the bar toward the other end. The temperature difference between the ends of the bar acts as a force driving the heat flow, or flux, along the bar. A similar phenomenon occurs with a drop of ink in water. The difference in ink concentration is the driving force that makes the ink invade the host liquid until it becomes uniformly colored. These forces are linear: the heat flux is proportional to the temperature difference and the particle flux to the concentration difference, a proportionality that holds even when the forces acting on the system are strong. Even in many turbulent flows, the internal stresses in the fluid are proportional to the velocity gradients. For these cases, Onsager and others formulated a theory of nonequilibrium thermodynamics and showed that the second law continues to hold.

But when those conditions are not met, this theory breaks down. When a chemical reaction takes place, one substance suddenly changes into another—an abrupt change described by a nonlinear equation. Another type of failure occurs when the system is so small that the chaotic jumble of molecular motions dictates its behavior and causes the system's properties to vary wildly over short distances. Processes taking place in small systems, such as the condensation of water vapor and the transport of ions through a protein channel in a cell membrane, are dominated by such fluctuations. In them, temperature and entropy cease to be well-defined quantities. Does the failure of the theory in these instances imply the failure of the second law, too?

In the past several years David Reguera of the University of Barcelona, José M. G. Vilar of the Sloan-Kettering Institute and I have extended thermodynamics into these realms. We have shown that many of the problems go away with a change of perspective. Our perception of abruptness depends on the timescale we use to observe these processes. If we analyzed one of the seemingly instantaneous chemical processes in slow motion, we would see a gradual transformation as if we were watching a pat of butter melting in the sun. When the process is viewed frame by frame, the changes are not abrupt.

The trick is to track the intermediate stages of the reaction using a new set of variables beyond those of classical thermodynamics. Within this expanded framework, the system remains in local thermodynamic equilibrium throughout the process. These additional variables enrich the behavior of the system. They define a landscape of energy that the system rambles through like a backpacker in the mountains. Valleys correspond to a dip in energy, sometimes involving molecular chaos, other times molecular order. The system can settle into one valley and then be kicked into another by external forces. If it is in the grasp of chaos, it can break away from disorder and find order, or vice versa.

Next, consider the problem of fluctuations. Does thermodynamics fail when systems are excessively small? A simple example shows that the answer is no. If we toss a coin only a few times, it could happen, by chance, that we would get a series of heads. But if we flip the coin many times, the result reliably approaches an average. Nature flips coins quite often. A few particles moving around in a container collide only occasionally and can maintain large velocity differences among themselves.

But even in a seemingly "small" system, the number of particles is much larger, so collisions are much more frequent and the speed of the

COURTESY OF J. MIGUEL RUBÍ (*author*); MICHAEL MORGENSTERN (*hand pouring water*)

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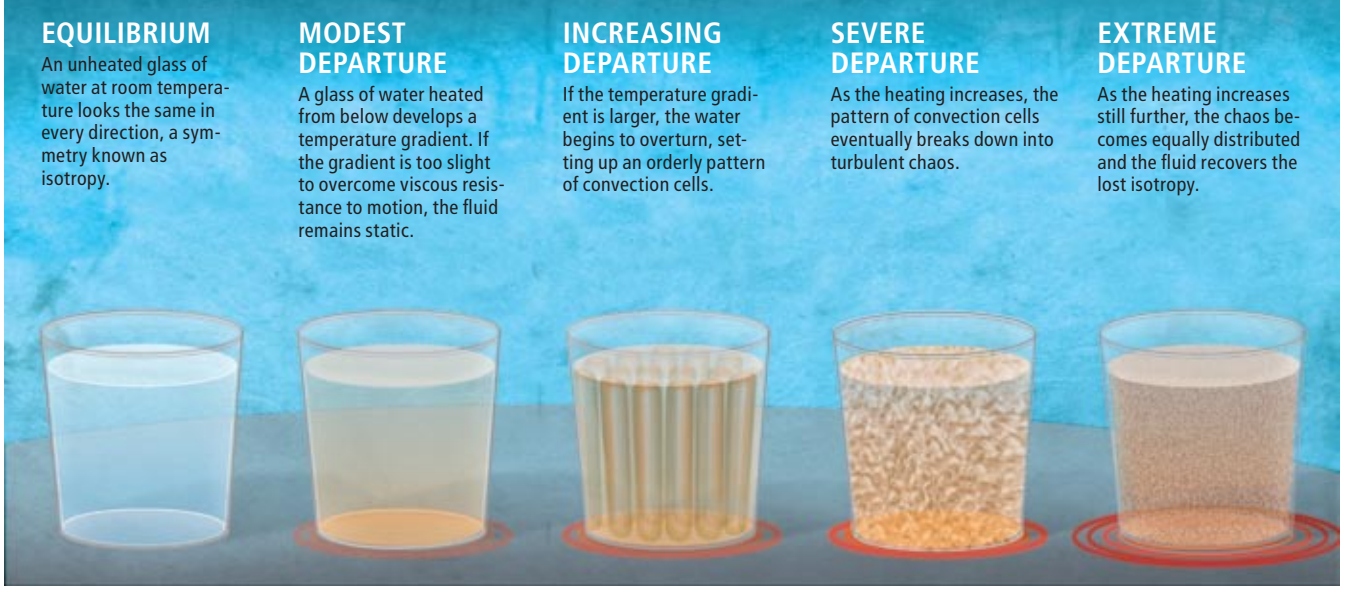
[WHY A NONEQUILIBRIUM THEORY IS NEEDED]

ORDER FROM DISORDER

Although the molecules in a system out of equilibrium may be hopelessly jumbled, the system can become ordered in other ways. Classical thermodynamics, based as it is on equilibrium, cannot account for that, but the newly developed nonequilibrium theory can.



particles is brought down to an average (if slightly fluctuating) value. Although a few isolated events may show completely unpredictable behavior, a multitude of events shows a certain regularity. Therefore, quantities such as density can fluctuate but remain predictable overall. For this reason, the second law continues to rule over the world of the small.

From Steam Engines to Molecular Motors

The original development of thermodynamics found its inspiration in the steam engine. Nowadays the field is driven by the tiny molecular engines within living cells. Though of vastly differing scales, these engines share a common function: they transform energy into motion. For instance, ATP molecules provide the fuel for myosin molecules in muscle tissue to move along actin filaments, pulling the muscle fibers to which they are attached. Other motors are powered by light, by differences in proton concentrations or by differences in temperature [see "Making Molecules into Motors," by R. Dean Astumian; Scientific American, July 2001]. Chemical energy can drive ions through channels in a cell membrane from a region of low concentration to one of high concentration—precisely the opposite direction that they would move in the absence of an active transport mechanism.

The analogy between large and small machines is very deep. Fluctuations of the chemical energy affect a molecular motor in the same way that a random and variable amount of fuel affects the piston of a car motor. Therefore, the long tradition of applying thermodynamics to large motors can be extended to small ones. Although physicists have other mathematical tools for analyzing such systems, those tools can be tricky to apply. The equations of fluid flow, for example, require researchers to specify the conditions at the boundary of a system precisely—a Herculean task when the boundary is extremely irregular. Thermodynamics provides a computational shortcut, and it has already yielded fresh insights. Signe Kjelstrup and Dick Bedeaux, both at the Norwegian University of Science and Technology, and I have found that heat plays an underappreciated role in the function of ion channels.

In short, my colleagues and I have shown that the development of order from chaos, far from contradicting the second law, fits nicely into a broader framework of thermodynamics. We are just at the threshold of using this new understanding for practical applications. Perpetual-motion machines remain impossible, and we will still ultimately lose the battle against degeneration. But the second law does not mandate a steady degeneration. It quite happily coexists with the spontaneous development of order and complexity. ■

MORE TO EXPLORE

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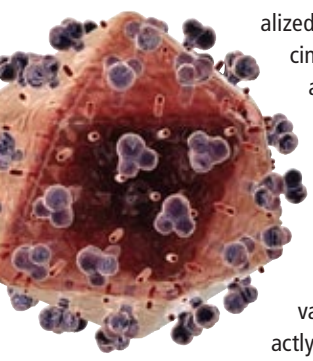
HIV 25 YEARS LATER

THE BIG CHALLENGES

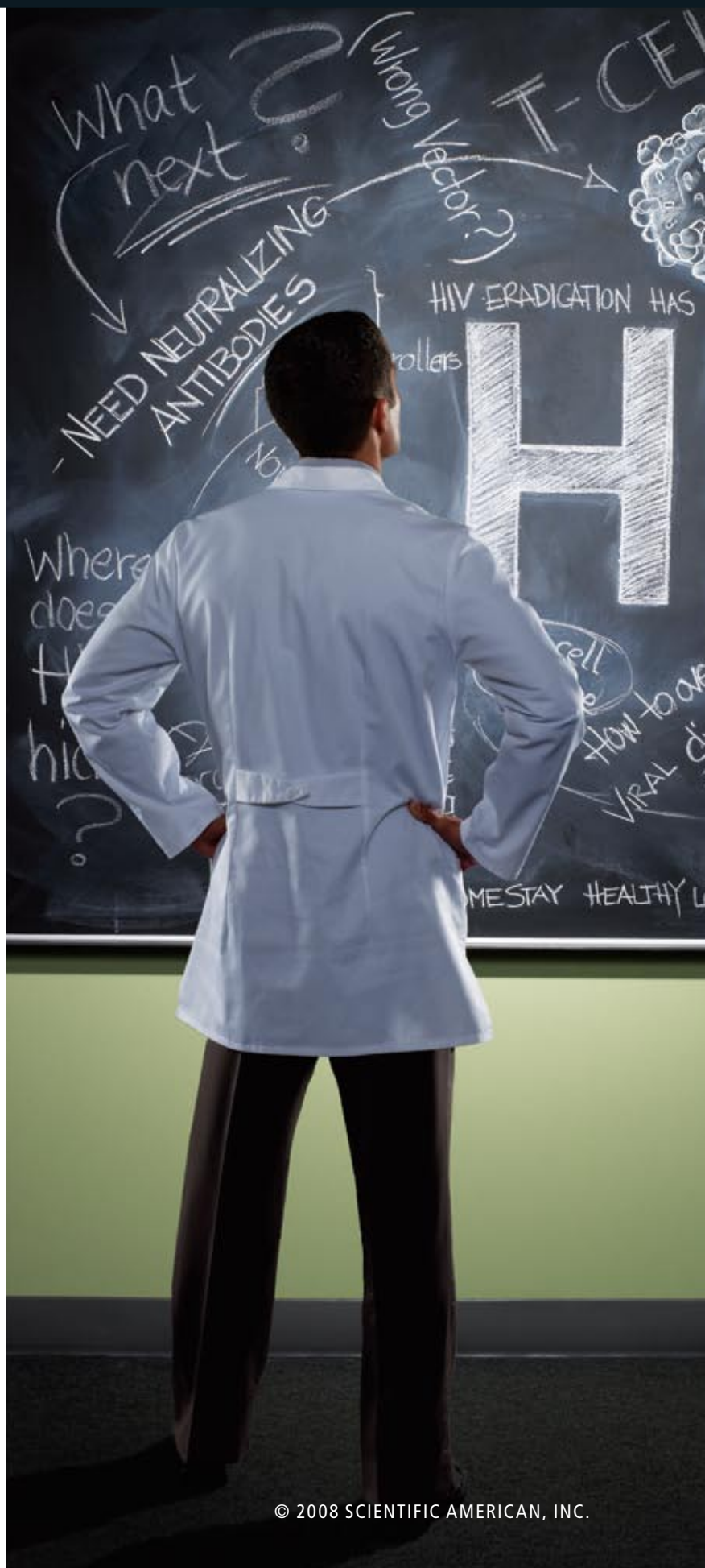
EDITORS' INTRODUCTION

In 1983 and 1984 scientists established that HIV (the human immunodeficiency virus) causes AIDS, which had recently begun cropping up in gay men in California and New York. The discovery quickly led to predictions that a preventive vaccine would soon be on tap. Similarly, in 1996, after powerful drug combinations began forcing HIV down to undetectable levels in the blood, prominent HIV researcher David D. Ho of the Rockefeller University voiced optimism that attacking the virus early and hard could prove curative.



Yet neither a vaccine nor a cure has materialized. Indeed, the most promising vaccine prospects have failed. And when aggressive treatment stops, the wily virus comes roaring back.

Where do we go from here? SCIENTIFIC AMERICAN asked two leading HIV researchers to address the biggest scientific challenges facing the field today: Is finding a vaccine even possible? And what, exactly, would it take to rid a person's body of HIV and thus effect a cure? Their frank, thought-provoking answers follow.



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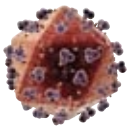
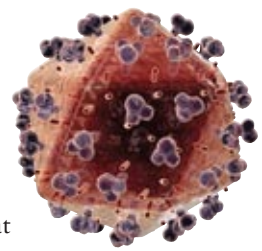
MARK HOOPER (*man at blackboard*); ZYGOTE MEDIA GROUP, INC. (*all 3-D computer renderings of HIV*)



THE VACCINE SEARCH GOES ON

Repeated failures in the quest for an AIDS vaccine have sent investigators back to the drawing board

By David I. Watkins



Not long after the virus that causes AIDS was identified, Margaret Heckler, then the U.S. secretary of health and human services, told a group of reporters that the discovery would enable scientists to develop a vaccine to prevent AIDS. "We hope to have such a vaccine ready for testing in approximately two years," she declared proudly. It was 1984.

Government officials have certainly been spectacularly wrong on other occasions but rarely has a large portion of the scientific community been so overly optimistic as well. Twenty-five years after isolating HIV, we still have no effective vaccine. One year ago a major clinical trial of a candidate made by Merck was shut down because it became obvious that the vaccine was not working and might even be doing harm. This past summer another vaccine hopeful was shelved and its trial canceled before it could begin because there was no reason to believe its results would be any better.

After decades of struggle to make a vaccine against HIV, these events plunged the effort into disarray. We in the field have realized that if none of the classical methods of making vaccines

KEY CONCEPTS

- HIV has so far defeated the best efforts of vaccine scientists because the virus evades and undermines the immune system.
- If HIV infection cannot currently be prevented, a second goal of vaccine makers is to reduce the virus's spread and the severity of illness it causes.
- Researchers are already returning to basic science to follow new leads, and are far from giving up.

—The Editors

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works against this virus, then we need a new one—some unusual creative approach that has yet to be imagined or some new insight into the virus itself that might reveal a vulnerability. We have to go back to basics, but that is not to say we have learned nothing of value over the past 25 years. Indeed, every failure has revealed tricks this virus uses, suggesting new ways to go after it. Those lessons are already spawning fresh ideas and bringing scientists together to attack remaining unanswered questions about this unique virus.

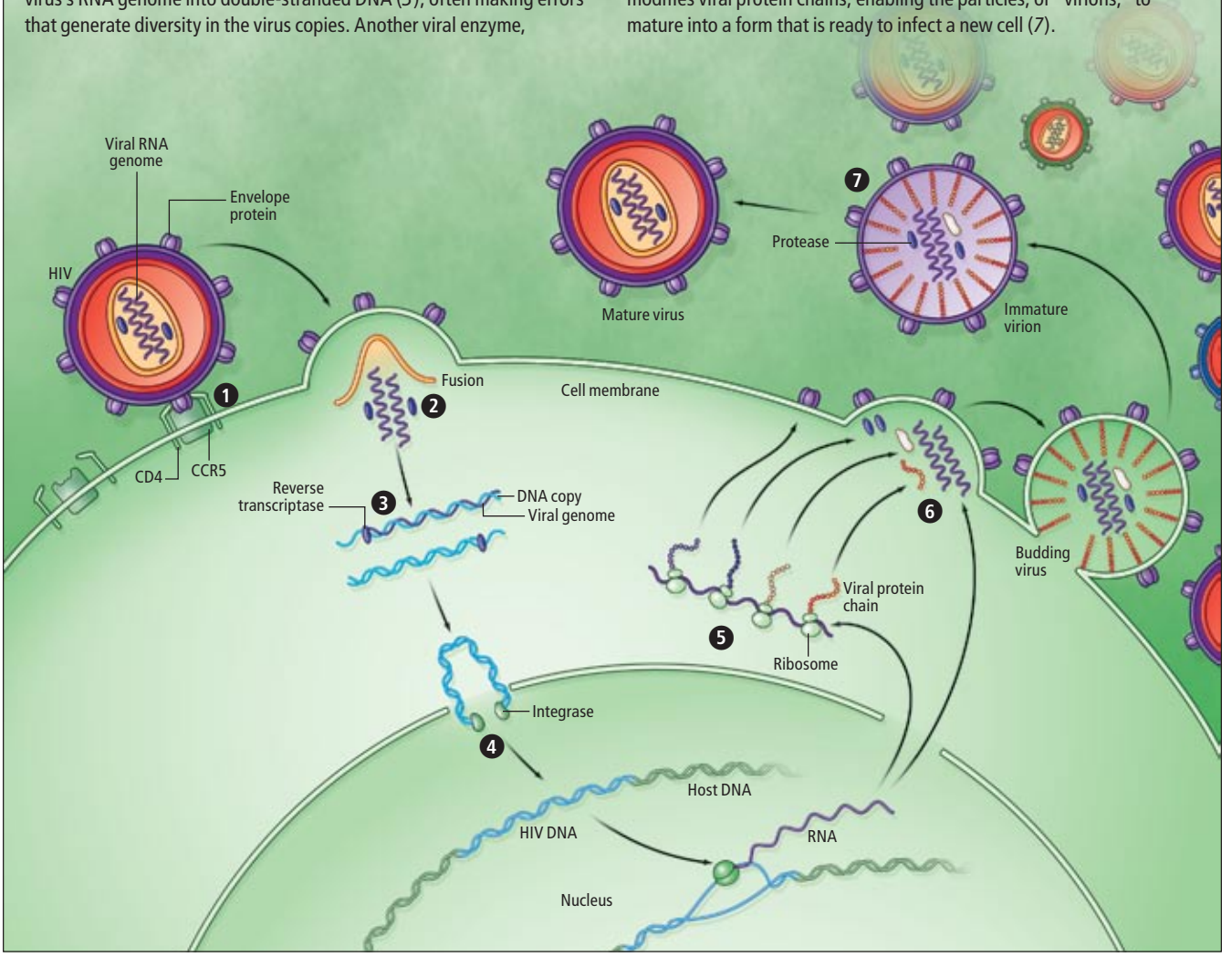
Why Vaccines Work—but Not against HIV

Understanding how to approach the problem of making a vaccine against HIV first requires an understanding of how vaccines normally function. Several different methods for manufacturing vaccines exist, but in each case a vaccine's effectiveness depends on the human body's natural immune responses. The annual influenza vaccine, for example, is made by inactivating that year's strains of influenza virus and administering the killed viruses to people through a

[HIV LIFE-CYCLE BASICS]

A SELF-COPYING COMMANDO

Efforts to devise vaccines and new treatments for HIV depend on knowledge of the virus's life cycle. HIV invades host cells and commandeers their machinery to make more copies of itself. First, a protein called Envelope on the virus must bind to CD4 and CCR5 proteins on the cell surface (*1*). As the virus fuses with the cell, it empties its contents into the cytoplasm (*2*). A viral enzyme, reverse transcriptase, then copies the virus's RNA genome into double-stranded DNA (*3*), often making errors that generate diversity in the virus copies. Another viral enzyme, integrase, inserts the copy into the host DNA (*4*). Cell machinery transcribes the viral genes back into RNA (including RNA that can serve as templates for proteins) that travels to the cytoplasm, where ribosomes produce the encoded proteins (*5*). Viral RNA and proteins then move toward the cell membrane, where they gather into a budding virus particle (*6*). In the immature new virus copy, the HIV protease enzyme modifies viral protein chains, enabling the particles, or "virions," to mature into a form that is ready to infect a new cell (*7*).



TAMI TOLPA

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shot in the arm. Immune cells in the deep layers of the skin recognize the viral proteins as foreign and within a few weeks cause the body to manufacture tiny molecules called antibodies tailored to that virus strain. If the same virus enters the body again during flu season, the antibodies will "neutralize" the virus by attaching themselves to it, blocking its ability to infect the cells of the host.

In 1962 Albert Sabin licensed a successful vaccine made from live but attenuated (disabled) polioviruses. Because this live vaccine is able to infect cells to a limited degree, it induces not only antibodies but also a so-called cellular immune response from specialized cells known as T lymphocytes. Should someone vaccinated this way be exposed to polio, the T cells would quickly respond, destroying any host cells infected by viruses that eluded the antibodies.

These two examples represent the basic principles underlying vaccines that have been the mainstay of defense against infectious agents over the past 50 years. Unfortunately, the standard methods of inducing antibodies and T cells have failed to protect against HIV. In essence, all vaccines imitate aspects of a natural infection, allowing the immune system to create a "memory" of the event and respond more aggressively the next time. Yet everything about HIV seems almost perfectly adapted to evading or disabling that very system of natural immune responses.

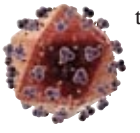
When HIV first infects a new host, the virus starts rapidly reproducing itself inside the host's cells, and the new viruses move on to commandeer additional cells [*see box on opposite page*]. Viral replication is so intensive that sometimes infected individuals can have 100 million viral copies per milliliter of blood plasma within a month after infection. Normally the first line of natural immune defense is the innate, or "nonspecific," immune system, made up of cells that patrol the body for invaders. Some of these will destroy any virus-infected cell they encounter on the spot, although in most people this system is probably overwhelmed by the initial onslaught of replicating HIV. Innate immune cells known as antigen-presenting cells, however, are also busy engulfing some of the viral proteins so that they can later show them to more specialized immune system components with the aim of inciting a response.

Among these are the aforementioned T cells, which have two important types: "helper" and "killer." The helper T cells play a critical role in sounding an alarm to engage the cellular immune system and in orchestrating its attack. Antigen-presenting cells first display the foreign proteins—antigens—they have sampled to the helper and killer T cells, using major histocompatibility complex (MHC) molecules to present the fragments. The T cells, in turn, use their T cell receptors to recognize the antigen-MHC complexes [*see box on next two pages*]. Once the killer cells have a description of the intruder and receive a chemical signal from helper cells, they multiply, then fan out on a seek-and-destroy mission. This killer T cell response kicks in approximately three weeks after infection, and it destroys most virus-infected cells, driving virus levels down. But the response is usually too little and too late, and lifelong chronic infection has been established.

The helper T cells may represent the body's most important regulator of responses to infectious agents because of their pivotal role in directing the activities of other immune cells. Unfortunately, from the start, HIV targets helper T cells themselves, replicating inside them and destroying them in the process. In particular, HIV goes after so-called memory helper T cells, which serve as the immune system's memory of past exposures to pathogens. Within a few weeks of the initial infection, the body's supply of these memory helper T cells is so depleted that the entire immune system's command-and-control system is crippled and never fully recovers.

At the same time, the virus gets better at evading the killer T cells. After entering a cell, HIV copies its RNA genetic material into DNA in a sloppy procedure prone to errors that result in mutations in the viral copy. These changes get passed along and added to every time the progeny viruses copy themselves. Moreover, if two virus copies infect the same cell, they can swap genetic material in a process called recombination, creating another virus variant.

As a result of this growing diversity, viral proteins displayed by infected cells become increasingly unrecognizable to immune cells primed to remember the original version of the virus. As the killer T cells destroy all the cells displaying recognizable antigens, the virus-infected cells carrying mutant proteins take over. For much the same reason, antibodies produced by the immune system three to four weeks after the initial infection cannot recognize many of the virus particles in the host later in the infection.



This problem of immune defenses being unable to recognize variant versions of HIV is per-

[THE AUTHOR]

BRYCE RICHTER *University of Wisconsin–Madison*

David I. Watkins investigates the biology of immunity at the University of Wisconsin–Madison, where he also directs a molecular diagnostics laboratory for the university's hospital and clinics. Having long specialized in HIV and AIDS research, he has been an Elizabeth Glaser Scientist and served on the National Institutes of Health AIDS Vaccine Research Subcommittee. In his Wisconsin laboratory, he has created a program to study simian immunodeficiency virus, a close relative of HIV, in the hope of better understanding human immune responses to HIV and how to develop an effective vaccine.

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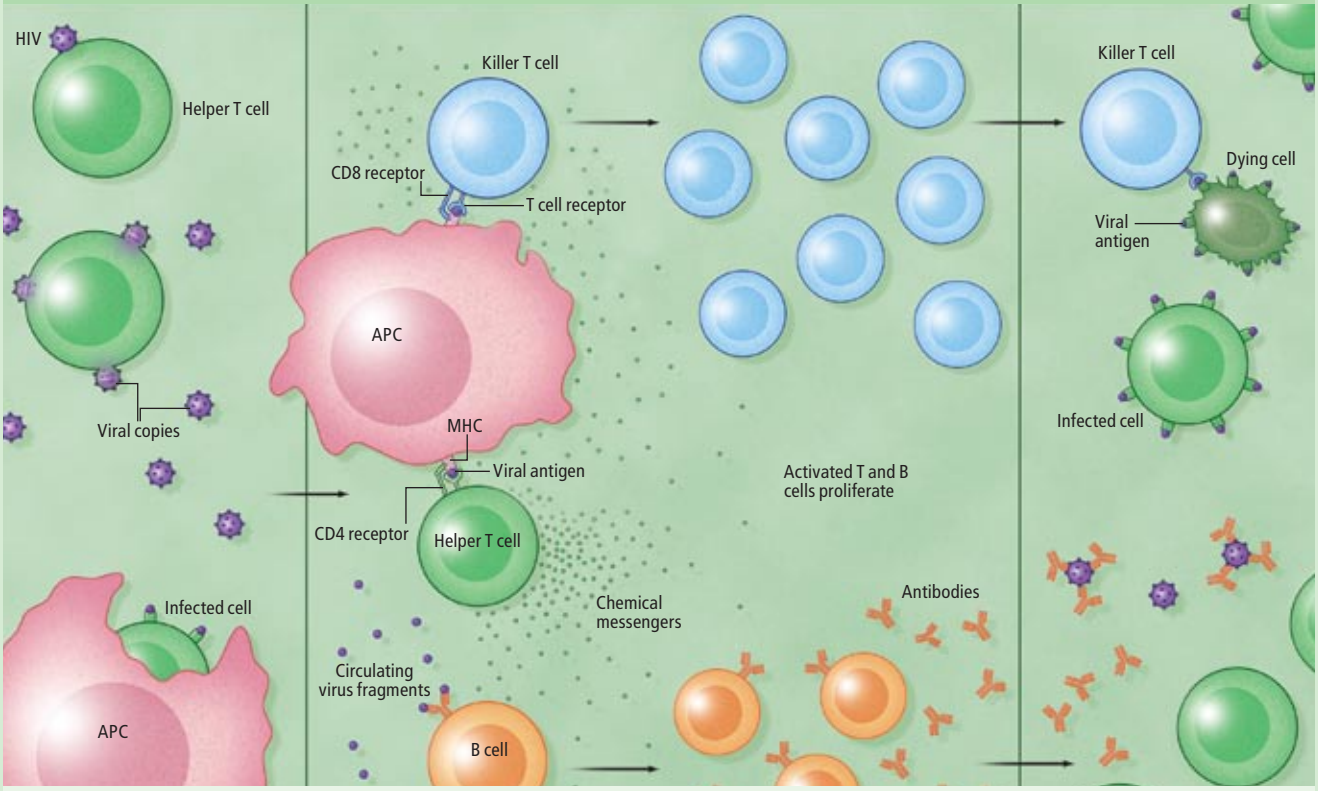
[THE GOAL]

EARLY IMMUNE RESPONSE

An ideal vaccine would prime the body's immune defenses to prevent HIV from infecting cells. A second-best solution would allow infection but prevent the virus from reproducing to high levels in the critical early stages of infection. Toward those ends, vaccines typically depend on stimulating some of the same immune responses provoked by natural infection to create a "memory" of the virus; however, HIV's tremendous mutability often thwarts this approach because immune memory is not broad enough. The trick to making an effective vaccine is generating antibodies and killer T cells able to recognize HIV particles that may be as much as 20 percent different from the version used to make the vaccine.

NATURAL INFECTION



Within hours of entering the body, HIV starts infecting helper T cells. Antigen-presenting cells (APCs) patrolling for invaders engulf any infected cells or viruses they encounter.

Within days, APCs display small pieces of virus (antigens) on major histocompatibility complex (MHC) molecules to uninfected helper T cells and killer T cells. In response, helper T cells release chemical messengers to activate B cells and the killer T cells. These, in turn, begin proliferating. Some of the resulting "memory" B and T cells are retained by the immune system to respond to future infections.

Within weeks, the trained killer T cells seek out infected cells displaying viral antigens to destroy them, while the antibodies block viruses from infecting new cells.

haps the greatest source of frustration for vaccine developers because it is equally true of antibodies and killer T cells generated by a vaccine. Even a strong vaccine-evoked memory response against one strain of HIV might be ineffective against the strain that later enters the body or might become useless as the virus mutates.

To get a sense of the scale of the challenge presented by the enormous diversity of HIV, note that manufacturers change the flu vaccine every year because the flu viruses in circulation around the world are continuously evolving, slightly changing their outer proteins just enough so that last year's antibodies will not recognize and protect against this year's flu strains. HIV mutates so rapidly that the diversity of proteins on the surface of HIV particles in a single person after six years of infection is estimated to be greater than the diversity of all the human flu virus strains worldwide in a given year. In effect, a vaccine that uses traditional methods to produce antibodies and other immune responses to HIV would have to be a vaccine against thousands, and perhaps hundreds of thousands, of different viruses, not just one.

Shifting Goals, Litany of Failures

The best long-term solution to the HIV pandemic would be a vaccine that prevents infection completely, providing "sterilizing immunity." At

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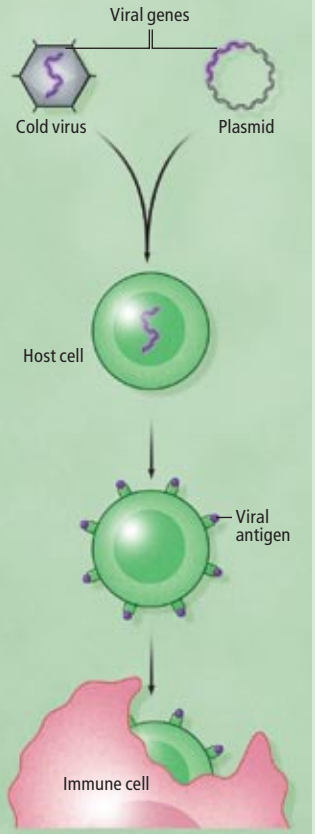
VACCINE OBJECTIVES

To induce production of memory B and T cells ready to respond to HIV, vaccines try to simulate HIV infection of host cells.



Candidate vaccines usually package HIV genes inside a live but harmless virus or bacterium or within a DNA ring called a plasmid that host cells will take in. When the cells manufacture the viral proteins encoded by the genes and display them, they appear to immune cells to be infected.

a minimum, that would probably require a vaccine able to induce broadly reactive neutralizing antibodies that can recognize HIV in all its forms and prevent it from infecting cells.

Once scientists discovered that to enter helper T cells HIV must attach to a CD4 receptor and usually to a co-receptor called CCR5 on the cells' surface, blocking the ability of the virus to bind to those receptors became a major objective of vaccine research. One of the primary targets of that work is a glycoprotein on the virus's outer shell that makes contact with the two receptors before the virus fuses with a cell. Known simply as Envelope, that protein is even more variable than the rest of the virus, however.

One of the first HIV vaccines to be tried in humans, called AIDSVAX, was designed to induce antibody responses against Envelope. After a five-year trial beginning in 1998, the vaccine was deemed a failure. Antibodies engendered by the vaccine did not prevent HIV from entering CD4+ T cells and thus did not prevent HIV infection in the people who received it.

To date, no HIV vaccine tried in humans has induced the kind of broadly neutralizing antibodies required to prevent HIV from entering cells. Because this neutralizing antibody problem remains the primary obstacle to a safe and effective vaccine, researchers are also now exploring the less desirable but still acceptable option of a vaccine that does not prevent infection but rather lowers the likelihood of getting sick or transmitting the disease.

Such a vaccine would aim to keep virus levels very low by inducing killer T cells that are primed and ready to destroy infected cells, thereby preventing viral levels from soaring in the early phase of infection. Suppressing HIV replication at this acute infection stage could help spare the body's population of helper T cells. It could also reduce the risk of virus transmission to others. After the initial surge of viral replication, the virus levels in untreated HIV-positive subjects settle at a median of about 30,000 virus copies per milliliter of plasma, but in observational studies, those whose viral loads are less than 1,700 copies per milliliter had a substantially reduced risk of transmitting the virus to their HIV-negative partners. Any HIV vaccine that cannot provide sterilizing immunity should therefore aim to limit peak viral levels and to reduce chronic viral loads to 1,700 or less.

This approach has also been encouraged by data from studies of human HIV infections and of monkeys experimentally infected with a similar simian immunodeficiency virus (SIV), showing that killer T cells are important in controlling viral load. Furthermore, rare cases exist of both humans and monkeys whose bodies control replication of the AIDS virus with neither vaccines nor drugs. Most of these individuals possess particular variations in their genes encoding certain MHC molecules, which act as important intermediaries in priming killer T cells to respond to foreign antigens.

Such evidence formed a rationale to proceed with T cell-inducing vaccines, and researchers had high hopes for a recent trial of an HIV vaccine developed by Merck and aimed at inducing anti-HIV killer cells. The company had invested heavily in HIV vaccine research and tested many different methods for inducing the killer T cells. Ultimately, it settled on using a common cold virus known as adenovirus type 5 (Ad5) to carry three HIV genes into cells, expecting the cells to manufacture the HIV proteins. The immune system would then be tricked into thinking the body was infected with HIV and would mount a protective response. The proteins used, called Gag, Pol and Nef, are relatively conserved—meaning they tend not to vary much—across diverse HIV variants.

Unfortunately, this most promising approach for inducing killer T cell responses tested in humans failed in the trial. On average, individual volunteer subjects mounted relatively weak T cell responses to the vaccine—between 10 and 20 percent of what is seen in HIV-infected individuals whose immune systems are controlling viral replication. Moreover, the cellular responses were specific to only three regions of the viral proteins. In contrast, HIV-infected patients who exhibit some measure of control over viral replication normally make between three and six specific responses against the Gag protein alone.

The Merck vaccine's failure to suppress HIV replication may have been caused by the Ad5 vector or the choice of HIV genes it carried, or a combination of those factors. It is possible that Ad5 is inherently unable to stimulate cellular immune responses that are sufficiently potent or broad to control HIV infection. Many of us have been infected by this common cold virus and have already made immune responses to it. Preexisting cold virus–specific antibodies will restrict the number of Ad5 particles that can infect target cells, weakening the vaccine's effect. Similarly, preexisting adenovirus-specific killer T cells might have dominated the initial immune response to the vaccine, potentially reducing the

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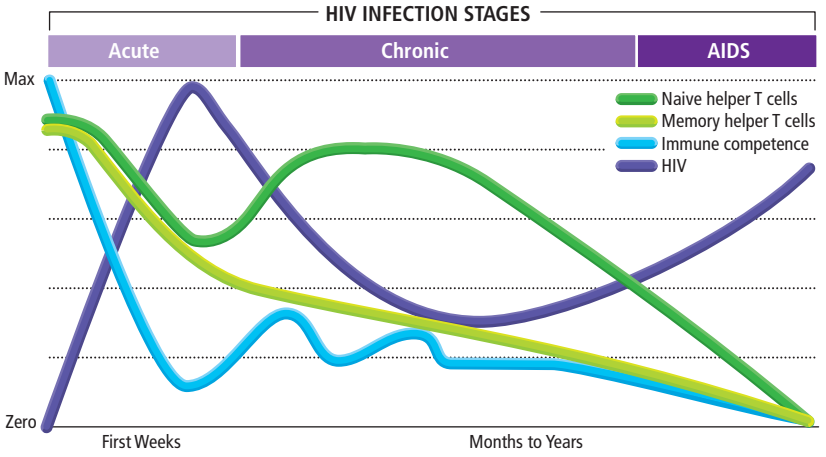
[VACCINE PLAN B]

Altering the Course of Infection

In the first 21 days after infection, HIV wipes out significant numbers of helper T cells, and memory helper T cells are the hardest hit. This cell population never fully recovers from the onslaught. Any vaccine that cannot prevent infection should aim to keep viral levels low early on. Sparing the memory helper T cells could prevent the sharp decline in overall immune competence that eventually leads to AIDS, the highly symptomatic end stage of HIV infection.



CRITICAL CLUES

Rhesus macaques provide a valuable model for AIDS research because they are susceptible to simian immunodeficiency virus (SIV), which is very similar to HIV.

Vaccines made from a disabled version of SIV completely protect the monkeys from SIV infection for years. Unfortunately, the weakened strain eventually repairs itself and the monkeys ultimately succumb to AIDS caused by the vaccine.

Understanding why the monkeys are protected for so long could reveal what immune responses need to be induced by an effective vaccine.

potency and breadth of HIV-specific T cell responses. Finally, the trio of HIV genes selected may be insufficient for viral control.

In contrast with the limited number of HIV proteins generated by the Ad5 vaccine, a live, attenuated SIV vaccine produces every viral antigen except parts of the Nef protein. Like the polio vaccine, this live virus can replicate in immunized monkeys, though more weakly than a natural virus, and it does protect the animals against later infection with versions of SIV that are significantly different from the vaccine virus. This vaccine's ability to protect a host against infection, even when the immune system is challenged by diverse versions of the virus, is, of course, the goal of HIV vaccine researchers. But the experiments also show that the disabled vaccine virus eventually repairs itself and goes on to create a full-fledged SIV infection that kills the monkeys. Furthermore, the vaccine and experimental challenge viruses can combine, producing a deadly new strain. For safety reasons, therefore, a live, attenuated HIV is unlikely to ever be used as a vaccine in humans.

The Road Ahead

The Merck vaccine failure was a huge blow to the field, prompting open discussions about whether an effective vaccine against HIV will ever be possible. It has also led to a careful rethinking of current vaccine candidates. At present, a vaccine trial being conducted in Thailand and due to wrap up later this year is the only large-scale human test of a vaccine candidate under way, and none are expected to begin in the near future. A big international trial of a DNA plasmid vaccine developed at the National Institutes of Health had been scheduled to start this fall. In July, however, Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, canceled the trial, stating that the evidence did not support such a large test.

At the same time, Fauci announced that his agency would redirect its funding for HIV vaccine research efforts toward basic science to address fundamental questions about HIV and its behavior in the body that could reveal a new approach to disarming the virus. Developing the next generation of improved vaccine candidates will require that scientists tackle a number of important issues.

HIV diversity remains the great barrier to vaccine-induced antibodies or killer T cell responses able to mount an effective defense early in infection. As a result of mutation and recombination within each infected person, an individual vaccinee is likely to be exposed to a virus that differs by more than 10 percent from the virus used to make a vaccine. For instance, accumulated changes within the highly mutable *env* gene that encodes the viral Envelope glycoprotein are important in classifying HIV into different groups (labeled M, N and O) and then into subtypes, or clades. Analyses of the amino acid sequences that make up Envelope show that they can vary by up to 35 percent from one clade to another. Even within a clade, Envelope sequence diversity can reach 20 percent.

For this reason, many T cell–based HIV vaccine designs have abandoned the idea of using Envelope to induce a response by the immune system, focusing instead on more conserved regions of the virus, such as the Pol and Gag proteins. Relatively minor variations in those proteins may still have grave implications for vaccine efficacy, however. Single amino acid differences in a viral protein can impair or even eliminate the ability of vaccine-induced antibodies or killer T cells to recognize the virus. Figuring out how to make a broadly neutralizing antibody remains the most important goal of the HIV vaccine field.

A related question has to do with host killer T cell responses to HIV during natural infection: Should we be seeking to emulate or boost all of them, or should we focus on just certain kinds? Killer T cells select various parts of HIV to re-

PETE OXFORD *Minden Pictures*

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Vaccine Timeline

Only a handful of vaccine candidates made it to large-scale human trials in the past decade. So far traditional vaccine-making methods for inducing antibodies or mobilizing immune T cells have failed to produce a vaccine that protects against AIDS. In light of these disappointments, the National Institute of Allergy and Infectious Diseases (NIAID) announced in August it would refocus on fundamental HIV research.

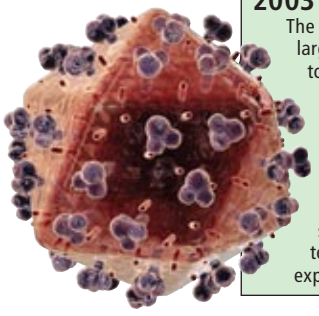
1984

April 23: Margaret Heckler, U.S. secretary of health and human services, and Robert Gallo of the National Cancer Institute announced the discovery of a virus believed to be the cause of AIDS. With the infectious agent known, Heckler said that a vaccine could be ready for trials in two years.

New HIV particles bud from the surface of an infected helper T cell

1998

VaxGen's AIDSVAX was the first vaccine to enter phase III testing. After international trials, the vaccine—designed to stimulate antibodies to HIV's outer envelope—was declared a failure in 2003. It provided no greater protection against infection than a placebo.



2003

The U.S. and Thailand launched a large trial of a vaccine designed to elicit T cell responses to the Envelope glycoprotein by first priming the immune system with canarypox virus. Many scientists publicly opposed the trial at its outset because smaller studies showed only weak responses to the vaccine. Final results are expected in 2009.

2004

Merck's STEP trial tested a vaccine comprising three HIV genes within the Ad5 cold virus. Also designed to induce T cells, the vaccine generated robust immune responses in recipients. Nevertheless, the trial was cut short in 2007 when monitoring showed that more vaccinees than placebo recipients had become infected with HIV. Analyses of the vaccine failure are ongoing.

2008

An international trial set to start in September of a vaccine that delivered HIV genes packaged in naked DNA, followed by Ad5, was canceled in July by NIAID director Anthony S. Fauci. The PAVE 100 trial would have included 2,400 men. Immune responses produced by the vaccine in smaller tests were not substantially different from those produced by the Merck vaccine, and Fauci called the trial's size unwarranted.

spond against, depending on the amino acid sequences of those viral pieces, and some viral regions provoke responses more frequently than others do. It is also becoming increasingly apparent that not all killer T cell responses are functionally equivalent—some are more efficient than others at controlling viral replication. New laboratory assays developed very recently should help us determine, for the first time, which of the many cell responses can actually control HIV replication in the laboratory. If it turns out that some of the rarest responses seen in natural infections are the most efficient at controlling the virus, then the best vaccine approach might be to boost those by altering the natural frequency patterns of HIV-specific killer T cell responses.

Similarly, understanding how certain rare individuals known as elite controllers are naturally able to suppress HIV or SIV replication should help inform vaccine design. A limited number of people and monkeys spontaneously control viral replication after infection, much as an effective killer T cell–inducing vaccine would aim to do. In these cases, the suppression of viral replication occurs after the initial acute infection subsides, so studying that transition phase should yield clues to how the virus is first brought under control. We already know that certain of these individuals have genetic variations that boost the number or functioning of their immune cells or that reduce the virus's ability to access CCR5 receptors on cells. A large group of human controllers is currently being assembled for study, and extensive genetic, immunological and virological analyses will likely yield important clues as to why these individuals are able to suppress virus replication. These discoveries, in turn, will give rise to new vaccine concepts that can be directly tested in monkeys.

Further studies of monkey responses to attenuated, live SIV vaccines will also be valuable because these potent vaccines enable the monkeys to fend off highly pathogenic viruses, even those that differ significantly from the vaccine strain, for considerable amounts of time. Although safety concerns mean the attenuated virus approach will never be used in humans, understanding exactly why it is so effective could yield new insights.

Finally, scientists' ability to find a new approach to creating an HIV vaccine will also benefit from our taking a new approach in our work. For the first time, groups of researchers have assembled in consortia to address these key issues, and funding for these collaborative efforts is coming from the Bill & Melinda Gates Foundation, the International AIDS Vaccine Initiative and the NIH. Working together, these consortia have a stronger chance than ever before of finding the all-important clues that facilitate the discovery of an HIV vaccine.

Far from giving up, HIV vaccine researchers are gearing up for a renewed fight. We could never have imagined in Margaret Heckler's day how stubbornly this virus would resist traditional vaccine techniques, but we are a stubborn bunch, too, and given time, science will find a way to defend against HIV. ■

MORE TO EXPLORE

HIV Pathogenesis: The First Cut Is the Deepest. Louis J. Picker and David I. Watkins in *Nature Immunology,* Vol. 6, No. 5, pages 430–432; May 2005.

Basic HIV Vaccine Development. David I. Watkins in *Topics in HIV Medicine,* Vol. 16, No. 1, pages 7–8; March/April 2008.

HIV Vaccine Research: The Way Forward. Anthony S. Fauci et al. in *Science,* Vol. 321, pages 530–532; July 25, 2008.

Reflecting on a Quarter Century of HIV Research. Andrew E. Armitage, Andrew J. McMichael and Hal Drakesmith in *Nature Immunology,* Vol. 9, No. 8, pages 823–826; August 2008.

PAULA BRONSTEIN *Getty Images (AIDSVAX vial)*; BETTMANN/CORBIS *(Heckler and Gallo)*; R. DOURMASHKIN *Wellcome Images (HIV micrograph)*; PAULA BRONSTEIN *Getty Images (injection)*; ZYGOTE MEDIA GROUP, INC. *(3-D computer rendering of HIV)*; RAMON ESPINOSA *AP Photo (gloved hands holding syringe)*

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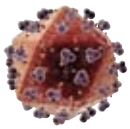
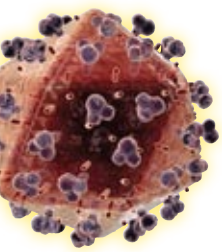


CAN HIV BE CURED?



Eliminating HIV from the body would require flushing the virus out of its hiding places and preventing those reservoirs from being refilled. A tall order but perhaps not impossible

By Mario Stevenson

KEY CONCEPTS

- Current drug regimens can dramatically suppress HIV in patients, but none of these agents can completely eliminate the virus.
- To eradicate HIV from infected individuals, researchers must figure out where the virus hides and how to hit it in those places.
- Recent findings have exposed some of HIV's refuges, suggesting new therapeutic targets.

—The Editors

In contrast to the failed attempts at developing a vaccine against HIV, efforts to provide drug therapies stand as a great success. More than 25 agents have been approved thus far, and the right combinations can suppress replication of the virus, often keeping blood levels so low as to be undetectable by standard tests. These powerful drug cocktails, collectively termed highly active antiretroviral therapy, or HAART, have prolonged life and health in countless infected individuals. Yet vexingly, today's treatments cannot actually cure the infection. If for any reason therapy is interrupted, the virus rapidly rebounds.

Figuring out how HIV manages to hang around in the company of these potent drugs is one of the most important tasks currently facing researchers. Over the past decade investigators have gleaned key insights into this mystery. The answers, we hope, will ultimately reveal whether complete eradication of the virus in a patient is feasible.

Understanding the nature of HIV's hiding places, or reservoirs, and what it will take to eradicate them requires some insight into how HIV typically behaves in the body. Like all viruses, HIV needs to get into the body's cells to replicate. There the invader exploits the cells' machinery to make copies of its own genome and to translate viral genes into proteins. It thus generates new viral copies, called virions, which spread to other cells. But unlike most human viruses, HIV actually inserts its genome into that of the cell. Every time the cell reproduces, the viral genes get copied and passed down to the daughter cells, thereby ensuring that the virus persists for as long as the cell and its progeny survive in the body.

The immune system typically manages to eliminate viruses by knocking out infected cells. It identifies such cells readily by the bits of viral proteins, or antigens, they display on their surface to flag the presence of interlopers within. In the case of HIV, the immune system has a hard time eradicating infected cells on its own in part because the virus attacks components of the immune system itself. The body does manage for a while to counterattack, generating healthy new immune cells able to recognize the virus and other infectious agents. In untreated individuals, however, the virus gains the upper hand over time, leading to AIDS.

Today's powerful drug combinations protect the immune system because they suppress HIV replication and limit the spread of virus to new cells. In theory, these treatments should permit

ZYGOTE MEDIA GROUP, INC. *(all 3-D computer renderings of HIV)*

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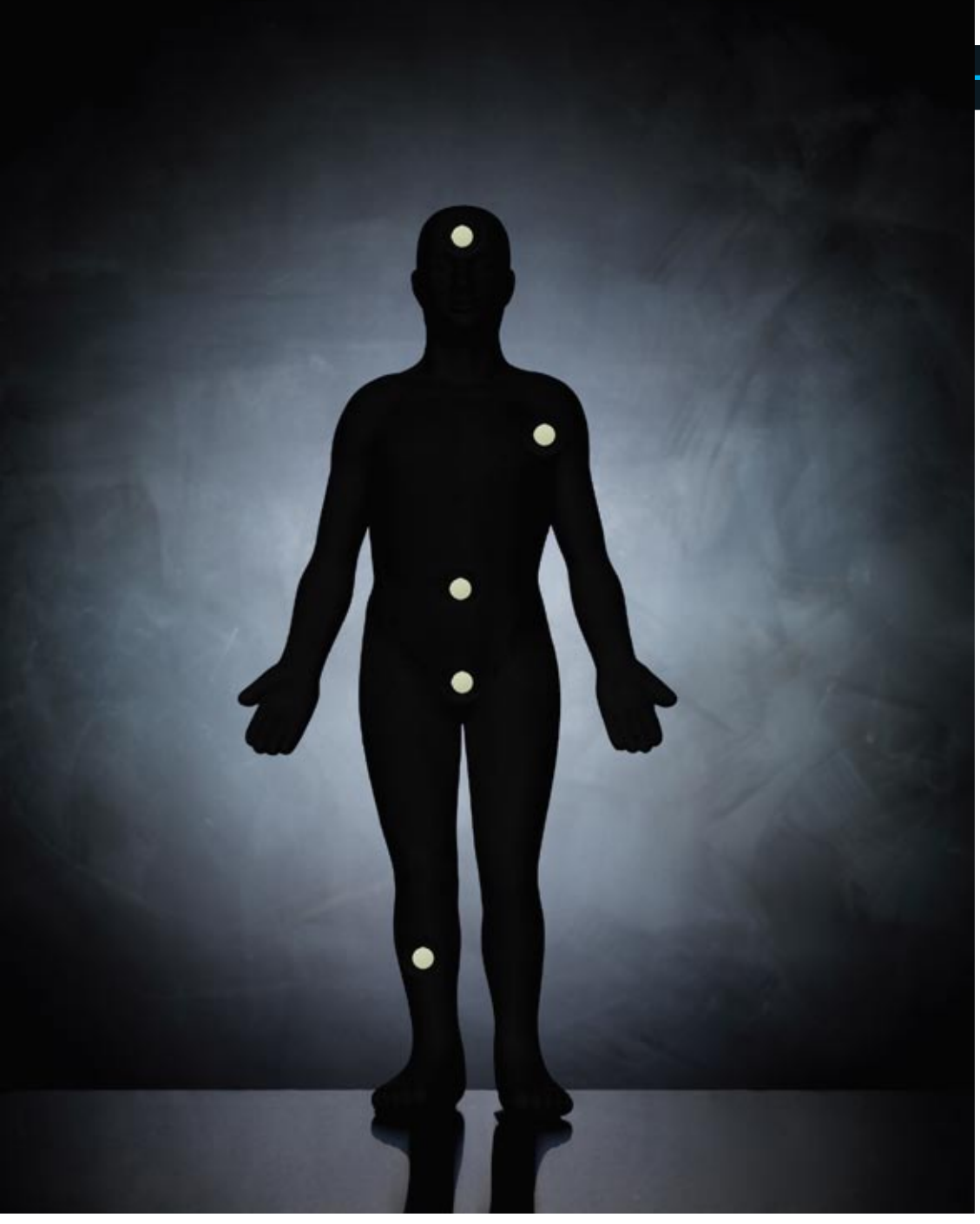


LYING IN WAIT: Even after therapy forces HIV in the blood down to undetectable levels, the virus still lurks elsewhere—ready to storm back if given the chance.

MARK HOOPER (*human silhouette*); COURTESY OF MARIO STEVENSON (*author*)

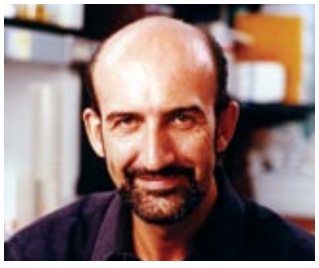
the still healthy parts of the immune system to clear out any remaining infected cells and cure the disease. So why is the drug-protected immune system failing to do that job?

Keeping a Low Profile

A big component of the answer appears to be the persistence of cells that are genetically able to make new virions but that do not produce any and thus do not inform the immune system of their presence. As David I. Watkins notes in "The Vaccine Search Goes On," starting on page 47, HIV preferentially infects immune cells called helper T lymphocytes, which mostly reside in the lymph nodes and connective tissue of the gastrointestinal tract but also occupy other lymph nodes and circulate in the blood.

In the course of fighting most kinds of viral infections, the bulk of helper T cells involved in the fight die off when they are no longer needed. A subset, however, survives as long-lived memory T cells, ready to multiply and call in the reserves when they encounter signs of reinfection. It is these memory T cells that appear to produce the most virus in HIV-infected patients. As they prepare to divide to fight remembered pathogens, they both duplicate their own DNA and proteins and churn out new HIV virions. Most of the infected memory cells die from the virus itself or the immune attack against them, but some return to a dormant state. At that point, HIV exists only as viral DNA sitting quietly in

[THE AUTHOR]



Mario Stevenson is David Freelander Professor of AIDS Research in the Program in Molecular Medicine at the University of Massachusetts Medical School. He earned his Ph.D. from the University of Strathclyde in Glasgow, where he studied liposomal drug uptake in macrophages. He is a recipient of Harvard Medical School's Shipley Lectureship, chair of the research committee of the American Foundation for AIDS Research, and director of the Center for AIDS Research at the UMASS Medical Center. He has also been a consultant to Merck. In his spare time he dabbles in piano and in-line speed skating.

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the cells' genome. This viral DNA does not get copied and does not give rise to viral proteins, so no protein bits get displayed on the surface. Consequently, anti-HIV drugs have no effect on the cells, and the immune system remains blind to them.

This understanding has been informed by studies published in 1997. Teams led independently by Robert F. Siliciano of Johns Hopkins University, Anthony S. Fauci of the National Institutes of Health and Douglas D. Richman of the University of California, San Diego, found that inactive T lymphocytes isolated from HIV-infected individuals do not manufacture HIV. When those cells were roused, however, the previously dormant virus began replicating anew. HIV is not the only virus to exhibit such latency. An array of viruses can enter into similarly quiet states. In fact, some, such as the herpesviruses, make proteins that actually encourage the virus to become latent. Estimates based on the life span of memory T cells suggest it would take in excess of five decades for the reservoir of cells infected with latent HIV to naturally die out.

Researchers are also beginning to comprehend that it is not only latent helper T cells that bring HIV back after therapy stops. It seems that despite the absence of virus in the blood, some helper T cells and other cells keep on making new virus at a low level even when therapy seems to be working beautifully. This activity falls under the radar of tests, because the virus either hides successfully in the cells or, when released, stays trapped in tissues and does not find its way into the blood. In the past year, for instance, research has revealed that helper T lymphocytes in the gut get depleted within weeks of the individual contracting HIV and even before the virus is detected in the blood. It is therefore possible that during treatment the virus can continue to replicate in tissues such as those of the gut—activity that could go unnoticed for quite some time until the virus spills over into the blood.

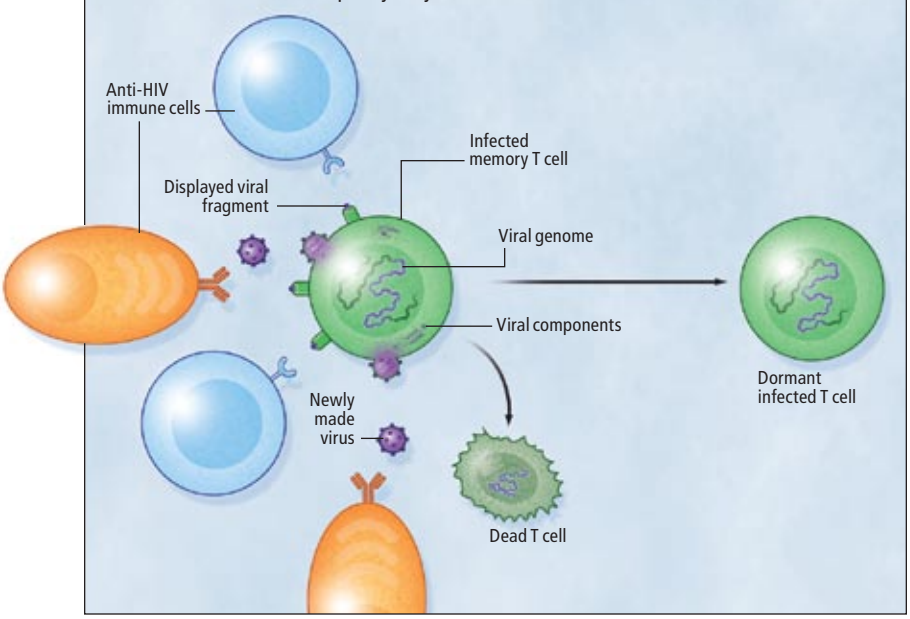
FAST FACTS

- In 2007 an estimated **33 million** people worldwide were living with HIV.
- Every day some **6,000** people die from HIV and another **6,800** contract the virus.
- **Less than a third** of people who need HIV treatment have access to it.
- Highly active antiretroviral therapy (HAART) increases patient survival by **13.3 years** on average.

[OBSTACLE TO A CURE]

THE MAKING OF A HIDEOUT

Most HIV in the blood appears to come from immune cells known as memory T lymphocytes that have been infected by the virus. These cells, which display bits of HIV on their surface, usually die from the infection itself or from an immune attack targeted to the displayed bits. But some survive and enter a dormant state (*far right*). In this condition they harbor the HIV genome in their DNA and can make new copies of the virus if reactivated but tend to sit quietly for years.



Another Unwitting Accomplice

Most AIDS research has focused on helper T cells because they circulate in the blood, which can easily be drawn for study. Recently, however, investigators have come to realize that other immune cells infected by HIV—macrophages and dendritic cells—may also contribute to resurgence of the virus after HIV therapy is halted or after the virus becomes resistant to it. Less is known about macrophages and dendritic cells because they are located strictly in tissues, but recent findings suggest that drug therapy may not totally stop HIV reproduction in these cells. The level may be too low to result in the virus reaching the blood in detectable amounts. It may, however, be high enough to reach nearby T lymphocytes and to continually restock the reservoir of dormant infected memory T cells. Also, some infected macrophages seem to evade being killed by the virus inside them or by other components of the immune system. Macrophages, then, may sit ready to pump up replication when drug therapy stops.

In 2001, for instance, Malcolm A. Martin of the NIH and his colleagues reported that although monkeys infected with simian immunodeficiency virus (SIV)—a close relative of HIV—lost most of their helper T lymphocytes within a few weeks of being infected, copious quantities of virus were still being produced. Macrophages, it turned out, were generating the virus. Subsequent treatment of the monkeys with a drug that inhibits viral replication—and thus prevents infection of new cells—failed to significantly lower the amount of virus in the animals' blood. This finding meant that the mac-

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rophages were not dying in the process of spewing out new copies of the virus.

HIV also seems to replicate somewhat differently in macrophages as compared with T cells—in a way that may be additionally advantageous to the virus. Whereas in T cells the virus components assemble close to, and subsequently detach from, the cell surface, in macrophages some viral particles appear to be deposited into compartments within the cells called vacuoles. Eventually the vacuoles may migrate up to the cell surface to release the stored virus particles. The packing of the virus into walled-off compartments might help HIV dodge immune detection by preventing the display of antigens on the cell surface that tip the immune system off to the presence of an intruder.

Finally, studies suggest that higher drug concentrations are needed to suppress viral replication in macrophages than in T cells. Exactly why this should be the case is uncertain. Yet we do know that some cellular proteins whose normal function is to excrete biological substances from the cell can interfere with drug therapy by hindering the uptake and retention of drugs. Perhaps, then, in macrophages these cellular proteins are particularly active and so prevent the drugs from being efficiently retained inside the cells. The same thing may occur in dendritic cells, although so far very little is known about how these cells respond to HIV.

Anatomical Refuges

It is not only the inherent properties of helper T cells and macrophages that allow HIV to persist in the face of intensive therapy. Certain of these cells also sit in anatomical compartments that may shelter them from various drugs or immune defenses, or both. Ridding the body of HIV would necessitate reaching it in those places.

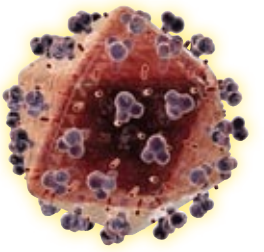
The central nervous system (CNS) is one such compartment. Researchers have long known that the CNS is susceptible to HIV infection. The neurological problems that arise in late-stage AIDS stem largely from the production of neurotoxins released from infected macrophages in the brain. To enter the brain, any molecule or cell must cross the blood-brain barrier, essentially a selectively permeable membrane that regulates the traffic of cells and other substances from the blood to the CNS. Macrophages that become infected with HIV in the tissues outside the CNS can apparently cross the blood-brain barrier and settle down in the CNS, where the virus may go on to infect specialized macrophages known as microglia, which reside permanently within the CNS.

Evidence suggests that infection of cells in the CNS would afford the virus some degree of protection from drugs because certain of them—notably protease inhibitors important to the proper processing of new viral proteins—do not efficiently cross the blood-brain barrier. Further, most other circulating immune cells stay out of the brain. No one knows whether infected cells in the brain can send HIV out to other parts of the body, but if the virus-infected macrophages can cross the blood-brain barrier into the CNS, they can probably filter back out as well.

Other sites that seem difficult for some drugs to penetrate include the walls of the gastrointestinal tract and the genital tract. Semen often contains HIV RNA even in people whose blood seems to be clear of the virus.

New Plans of Attack

At a minimum, thoroughly clearing HIV from an infected individual would require removal of all latently infected T cells. One way that researchers are currently exploring to address

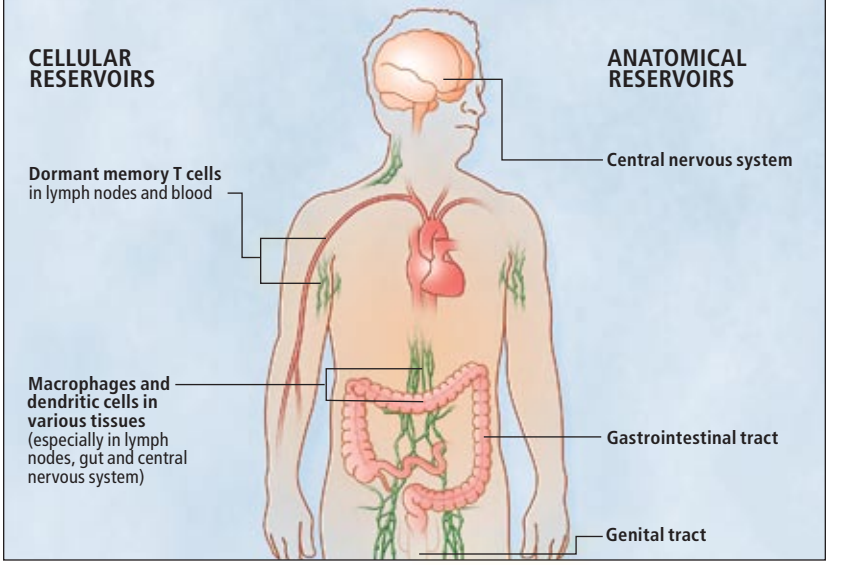


At a minimum, thoroughly clearing HIV from an infected individual would require removal of all latently infected T cells.

[WHERE THE VIRUS HIDES]

HIV'S MANY RESERVOIRS

Beyond lying in wait in dormant memory T cells, HIV may reproduce at a low rate in certain other immune system cells—particularly macrophages and dendritic cells that seem inherently able to ward off immune defenses and anti-HIV drugs to some extent. Further, HIV-infected cells in a few parts of the body may be physically shielded to a degree from the immune system and certain drugs. HIV made in cellular and anatomical reservoirs does not reach the blood readily in aggressively treated patients but might generate a vigorous infection if treatment stops.



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the latent reservoirs is treating patients with compounds that stimulate dormant infected T lymphocytes to divide, in the hopes that the cells will make virus and thus become vulnerable to antiretroviral therapy. A couple of limited human trials have tested this approach using drugs previously approved to treat other conditions. They have yielded mixed results, however.

The ideal agents would tickle the T cells enough to rekindle the production of the viral proteins that get displayed on the cell surface but not so much as to trigger the cells to make new copies of the virus. To that end, researchers are currently exploring the potential of drugs that would induce the synthesis of HIV proteins by altering the organization of chromatin (complexes of DNA and protein that compose chromosomes) in dormant infected T cells. Yet even these so-called chromatin remodelers would be of limited use if they worked only in T cells and the virus were also present in macrophages.

A second prong of attack for clearing HIV from the body would involve blocking all viral replication, so that HIV disappears not only from the blood but from all tissues and from all cell types that harbor it. Drugs currently in use typically interfere with one of two enzymes: reverse transcriptase, which converts the virus's genetic material from RNA to DNA for insertion into the cellular genome, or protease, which helps nascent viral particles to mature. Within weeks after a person starts standard therapy, the level of virus in the individual's blood drops

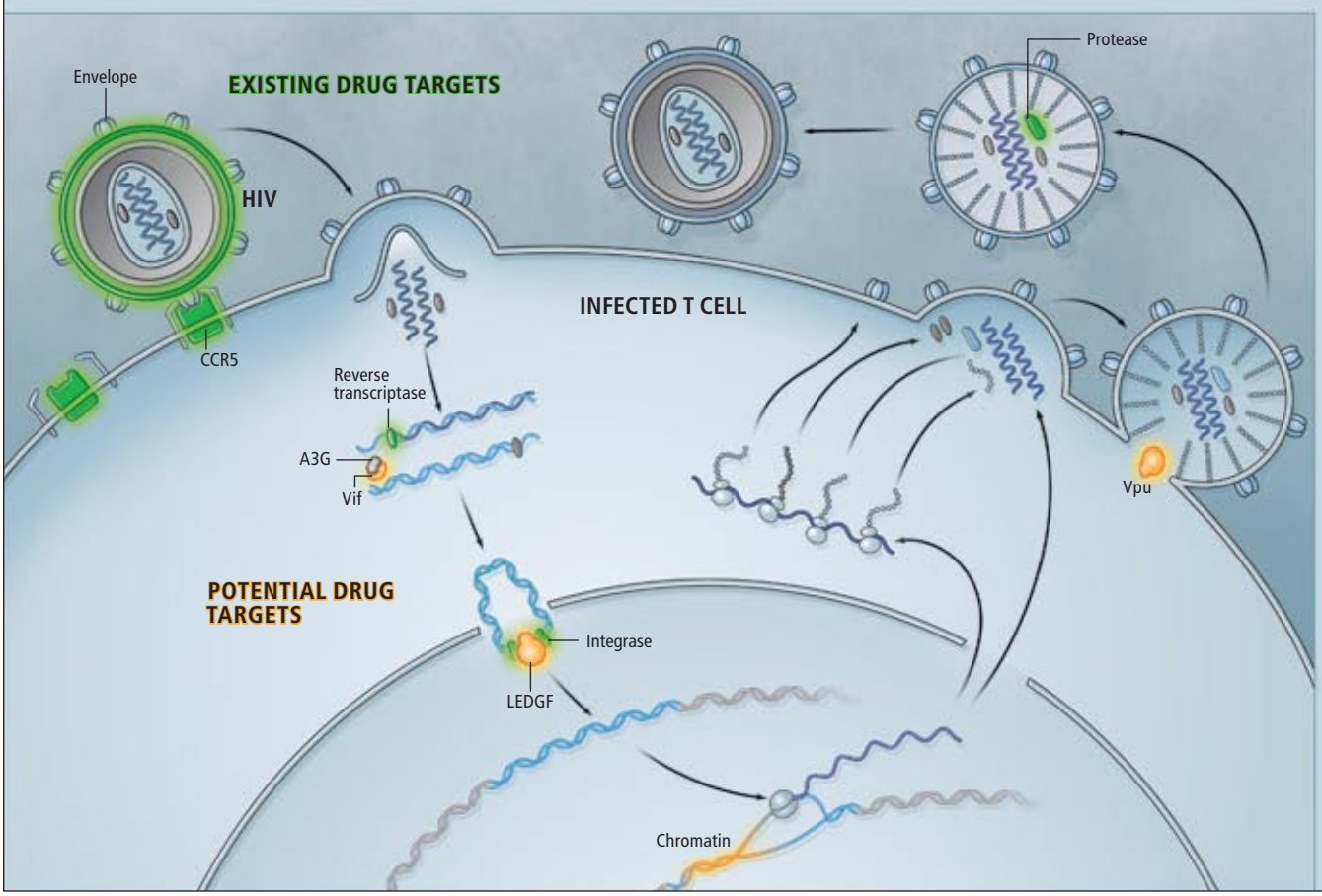
TAMI TOLPA

[NEW IDEAS]

PROMISING TREATMENT APPROACHES

At a minimum, erasing HIV from the body would require inducing infected dormant T cells to make new virus or viral proteins—actions that would invite attack by drugs or the immune system. Such treatments would be given together with standard drugs that block cell-to-cell spread of the virus. New evidence suggests that intensifying control of HIV replication—by hitting new viral or cellular targets—could be helpful as well.

Some potential therapeutic targets for achieving these aims (*orange*) are described at the right. Drugs already on the market take aim at the virus's envelope protein and the T cell's CCR5 receptor (to block viral entry into cells) and try to inhibit HIV's reverse transcriptase, integrase and protease enzymes (to halt, respectively, the copying of HIV's genome, its insertion into the cells' DNA and the maturation of HIV proteins).



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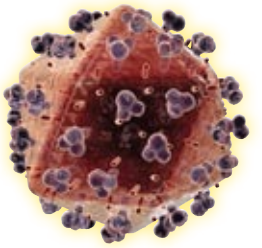
to undetectable levels. The slope of decay is fairly consistent from patient to patient, which researchers have taken to mean that the therapies thoroughly forestall viral replication. Yet recent studies have shown that intensifying existing drug regimens with raltegravir, a new drug that targets a viral enzyme not hit by earlier agents (the viral integrase enzyme, which stitches HIV DNA into the cells' own DNA), actually accelerates the viral decay. This success suggests that infected cells can probably be hit faster and more effectively than is now the case. If that surmise is correct, the work also implies that intensifying HIV therapy even further might limit the size of the original latent reservoir, block its later restocking and—dare we hope—lower replication so much that the immune system really can wipe out any virus-making reservoirs left over when latent infected memory cells are eliminated.

In the past year several new drugs that interfere with previously untargeted steps in viral replication have entered into clinical trials. In addition to the integrase inhibitor, another drug blocks infection by interfering with the ability of the virus to attach to a molecular receptor known as CCR5 that sits on the cell surface. Research also suggests that certain cellular proteins may be good therapeutic targets. Whereas HIV commandeers some of these proteins to aid its replication (CCR5, for example), it is now apparent that other cellular proteins—or cellular restrictions, as they are termed—actually antagonize viral replication.

Six years ago Michael H. Malim of King's College London and his research group identified the first of these cellular restrictions, called A3G. This protein is abundant in macrophages and in lymphocytes. Unfortunately, the virus has evolved a countermeasure to A3G: it makes a protein called Vif that induces the degradation of A3G. The good news is that both A3G and the viral Vif protein represent promising targets for therapy. Drugs that inhibit Vif or otherwise protect A3G from degradation would theoretically render human cells resistant to HIV infection.

Just this year Paul D. Bieniasz of the Aaron Diamond AIDS Research Center in New York City and John C. Guatelli of U.C.S.D. and their teams independently identified a second cellular restriction, named tetherin, that prevents the release of new copies of the virus from infected cells. The virus has evolved a defense against tetherin, too—in this case, the viral Vpu protein. Drugs that stymie Vpu could prevent HIV from spreading to new cells.

Basic research will probably continue to reveal novel therapeutic targets, which could lead to the development of new antiviral agents that hit HIV in multiple ways. If we can design drugs that complement and intensify the effects of existing therapies, we may finally be able to deplete the all-important latent reservoir and eradicate the virus. To that end, larger studies exploring the impact of long-term therapy intensification on the virus are currently under way, with results expected within the next two years. Those findings should tell us whether the eradication of HIV from an infected individual is a realistic goal. We wait with great anticipation. ■



Infected cells can probably be hit faster and more effectively than is now the case.

POTENTIAL DRUG TARGETS

Vif (viral infectivity factor)
A cellular protein called A3G undercuts HIV's viability by dramatically mutating its genes. But HIV's Vif protein interferes. Inhibition of Vif or some other way of shielding A3G should allow A3G to carry out its antiviral tasks.

LEDGF (lens epithelium-derived growth factor)
In HIV-infected cells, LEDGF, a cellular protein, helps integrase to splice HIV DNA into the cell's genome. Some findings indicate that LEDGF inhibition reduces HIV replication.

CHROMATIN (complexed DNA and protein that composes chromosomes)
Drugs called chromatin remodelers would alter the organization of chromatin in dormant infected T cells in a way that activates synthesis of HIV proteins—a step that would render the cells visible to the immune system and susceptible to attack.

Vpu (viral protein U)
HIV-infected cells tether newly made virus to the surface, but HIV's Vpu protein sets it free. A Vpu inhibitor should keep the virus from spreading to other cells.

MORE TO EXPLORE

Macrophages Are the Principal Reservoir and Sustain High Virus Loads in Rhesus Macaques after the Depletion of CD4+ T Cells by a Highly Pathogenic Simian Immunodeficiency Virus/HIV Type 1 Chimera (SHIV): Implications for HIV-1 Infections of Humans. T. Igarashi et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 98, No. 2, pages 658–663; January 16, 2001.

Isolation of a Human Gene That Inhibits HIV-1 Infection and Is Suppressed by the Viral Vif Protein. A. M. Sheehy et al. in *Nature*, Vol. 418, pages 646–650; August 8, 2002.

Antiretroviral Therapy with the Integrase Inhibitor Raltegravir Alters Decay Kinetics of HIV, Significantly Reducing the Second Phase. J. M. Murray et al. in *AIDS*, Vol. 21, No. 17, pages 2315–2321; November 12, 2007.

Tetherin Inhibits Retrovirus Release and Is Antagonized by HIV-1 Vpu. S.J.D. Neil et al. in *Nature*, Vol. 451, pages 425–430; January 24, 2008.

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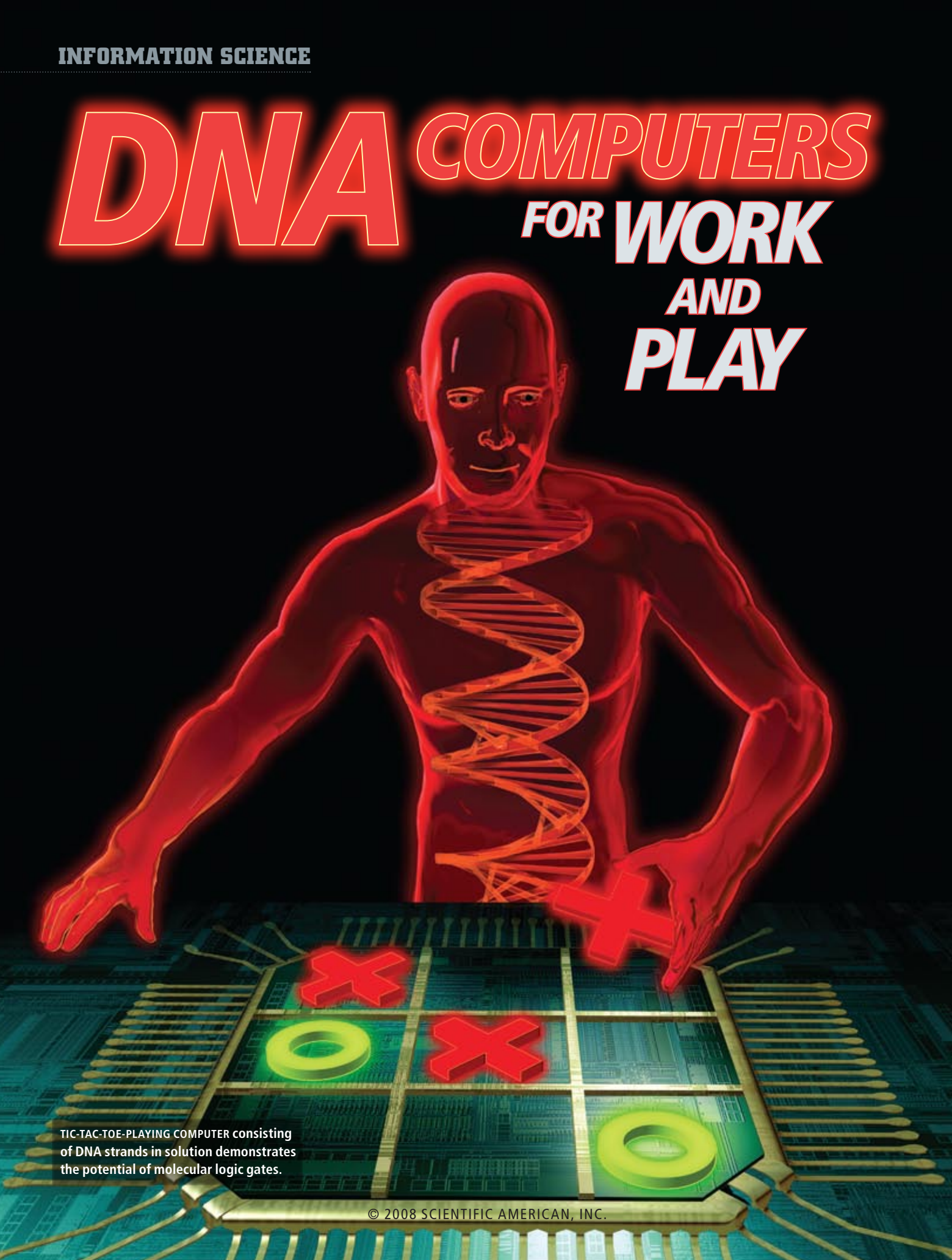
DNA COMPUTERS FOR WORK AND PLAY



TIC-TAC-TOE-PLAYING COMPUTER consisting of DNA strands in solution demonstrates the potential of molecular logic gates.

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Logic gates made of DNA could one day operate in your bloodstream, collectively making medical decisions and taking action. For now, they play a mean game of in vitro tic-tac-toe

By Joanne Macdonald, Darko Stefanovic and Milan N. Stojanovic

From a modern chemist's perspective, the structure of DNA in our genes is rather mundane. The molecule has a well-known importance for life, but chemists often see only a uniform double helix with almost no functional behavior on its own. It may come as a surprise, then, to learn that this molecule is the basis of a truly rich and strange research area that bridges synthetic chemistry, enzymology, structural nanotechnology and computer science.

Using this new science, we have constructed molecular versions of logic gates that can operate in water solution. Our goal in building these DNA-based computing modules is to develop nanoscopic machines that could exist in living organisms, sensing conditions and making decisions based on what they sense, then responding with actions such as releasing medicine or killing specific cells.

We have demonstrated some of the abilities of our DNA gates by building automata that play perfect games of tic-tac-toe. The human player adds solutions of DNA strands to signal his or her moves, and the DNA computer responds by lighting up the square it has chosen to take next. Any mistake by the human player will be punished with defeat. Although game playing is a long way from our ultimate goals, it is a good test of how readily the elementary molecular computing modules can be combined in plug-and-play fashion to perform complicated functions, just as the silicon-based gates in modern computers can be wired up to form the complex logic circuits that carry out everything that computers do for us today.

Dissolved Doctors

Near the end of 1997 two of us (Stojanovic and Stefanovic) decided to combine our individual skills in chemistry and computer science and work on a project together. As friends from elementary school in Belgrade, Serbia, we happened to be having dinner, and, encouraged by some wine, we considered several topics, including bioinformatics and various existing ways of using DNA to perform computations. We decided to develop a new method to employ molecules to compute and make decisions on their own.

We planned to borrow an approach from electrical engineering and create a set of molecular modules, or primitives, that would perform elementary computing operations. In electrical engineering the computing primitives are called logic gates, with intuitive names such as AND, OR and NOT. These gates receive incoming electrical signals that represent the 0s and 1s of binary code and perform logic operations to produce outgoing electrical signals. For instance, an AND gate produces an output 1 only if its two incoming inputs are both 1. Modern-day computers have hundreds of millions of such logic gates connected into very complex circuits, like elaborate structures built out of just a few kinds of Lego blocks. Similarly, we hoped that our molecular modules could be mixed together into increasingly complex computing devices.

We did not aim, however, to compete with silicon-based computers. Instead, because Stojanovic had just finished a brief stint with a pharmaceutical company, we settled on developing a system that could be useful for making "smart" therapeutic agents, such as drugs that could sense and analyze conditions in a patient and respond appropriately with no human intervention after being injected. For example, one such smart agent might monitor glucose levels in the blood and decide when to release insulin. Thus, our molecular logic gates had to be biocompatible.

Such molecular modules could have innumerable functions. For instance, in diseases such as leukemia, numerous subpopulations of white blood cells in the immune system display char-

KEY CONCEPTS

- DNA molecules can act as elementary logic gates analogous to the silicon-based gates of ordinary computers. Short strands of DNA serve as the gates' inputs and outputs.
- Ultimately, such gates could serve as dissolved "doctors"—sensing molecules such as markers on cells and jointly choosing how to respond.
- Automata built from these DNA gates demonstrate the system's computational abilities by playing an unbeatable game of tic-tac-toe.

—The Editors

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acteristic markers on their cell surfaces, depending on the cells' lineage and their stage of development. Present-day therapies using antibodies eliminate large numbers of these subpopulations at once, because they target only one of the surface markers. Such indiscriminate attacks can suppress the patient's immune system by wiping out too many healthy cells, leading to serious complications and even death. Molecular modules capable of working together to sense and analyze multiple markers—including performing logical operations such as "markers A and either B or C are present, but D is absent"—might be able to select the specific subpopulations of cells that are diseased and growing out of control and then eliminate only those cells.

Another application of our modules could be in the analysis of DNA, looking for a large array of possible genetic mutations or identifying one of a wide variety of microbiological pathogens. Our most advanced tic-tac-toe-playing automaton combines 32 different short DNA sequences (oligonucleotides). That many logic gate inputs could analyze four billion possible combinations of oligonucleotides and partition them into thousands of patterns, each pattern being characteristic of certain pathogens or genotypes.

Molecular Logic

Researchers reported logic gates based on synthetic molecules as long ago as the early 1990s. In 1993, for instance, A. Prasanna de Silva and his collaborators at Queen's University Belfast made AND gates out of small organic molecules that would fluoresce only if both hydrogen ions (from acid) and sodium ions were bound to them. In 1997 J. Fraser Stoddart, now at Northwestern University, and his co-workers made "exclusive OR" (XOR) gates, in which the molecules fluoresced in the presence of either, but not both, of the inputs (in this case, hydrogen ions and molecules called amines). These examples, however, were not biocompatible, because they required concentrations of acid and other compounds that would harm living cells.

In the mid-1990s other researchers exploited DNA's ability to store information in its sequence of bases—the molecules conventionally abbreviated as A, T, G and C, which pair up to form the rungs connecting the two strands of the famous double-helix structure. Their techniques, however, were very different from the kind of system we envisaged, namely, one in which molecular logic gates floating in solution would process inputs and outputs in a fashion very analogous to the workings of silicon logic gates. Nevertheless, DNA clearly had a lot of potential for biocompatible computation, and a couple of other advances gave us the tools to invent our own brand of DNA logic gates.

First, in 1995 Gerald F. Joyce of the Scripps Research Institute in La Jolla, Calif., developed a method for producing enzymes made out of single strands of DNA that cut other pieces of single-stranded DNA into two segments. These so-called deoxyribozymes have two short arms that will bind only to another stretch of DNA that has the correct complementary sequence of bases, so they are very specific about which substrate DNA strands they will cleave [*see box on page 64*].

Special dye molecules attached to each end of the substrate strands enable laboratory workers to monitor the cleaving process. At one end of the substrate, the dye molecule is a "quencher," which prevents the fluorescent marker dye at the other end from fluorescing as long as the strand remains intact, keeping the quencher close enough to be effective. After the strand is cut, its two pieces move apart and the marker dye molecule can fluoresce unhindered. As the work of the DNA enzymes progresses, cutting more and more strands, the solution gradually lights up with the marker dye's fluorescent color.

The other key advance came soon after our initial planning, when Ronald R. Breaker of Yale University reported a way to integrate a deoxyribozyme with molecular groups acting as recognition modules. These modules work like sensors that either activate or inhibit their attached DNA enzyme when the correct input molecule is bound to them. Breaker even combined two such modules in a construct that could serve as an AND gate with two small input molecules. Very intriguingly, his group has found that such two-sensor constructs have been used by natural riboswitches—molecules made of RNA used by bacteria to control which of their genes actively produce proteins [see "The Power of Riboswitches," by Jeffrey E. Barrick and Ronald R. Breaker; Scientific American, January 2007].

We saw that we could build our logic gates out of DNA enzymes integrated with controlling sensor modules designed to recognize short DNA strands having specific base sequences. The DNA strands would thus act as inputs to the logic gates (an input of 1 if the strand is present; 0 if it is absent), and the gates' enzymes would output "1" by cleaving other DNA strands in the solution. With DNA serving as both inputs and outputs, our gates could in principle be chained together

OTHER DNA COMPUTERS

Researchers over the years have devised several ways to perform computations by exploiting DNA's ability to store information in its sequence of bases.

1994: Leonard M. Adleman of the University of Southern California solved a puzzle known as the Hamiltonian path problem by encoding all the possible solutions (both correct and incorrect) on a large number of DNA molecules and carrying out a series of steps to isolate the molecules with the correct solution [see "Computing with DNA," by Leonard M. Adleman; Scientific American, August 1998].

1995: Erik Winfree, now at the California Institute of Technology, proposed that tiles made of DNA could be designed to perform computations by self-assembling into two-dimensional structures [see "Nanotechnology and the Double Helix," by Nadrian C. Seeman; Scientific American, June 2004].

2004: Ehud Shapiro of the Weizmann Institute of Science in Rehovot, Israel, and Yaakov Benenson of Harvard University, building on a proposal by Paul W. K. Rothemund of Caltech, developed a "doctor in a cell." Enzymes operating on DNA analyzed whether a combination of RNA molecules indicative of a disease was present in the solution and responded by releasing another molecule as a model for a drug [see "Bringing DNA Computers to Life," by Ehud Shapiro and Yaakov Benenson; Scientific American, May 2006].

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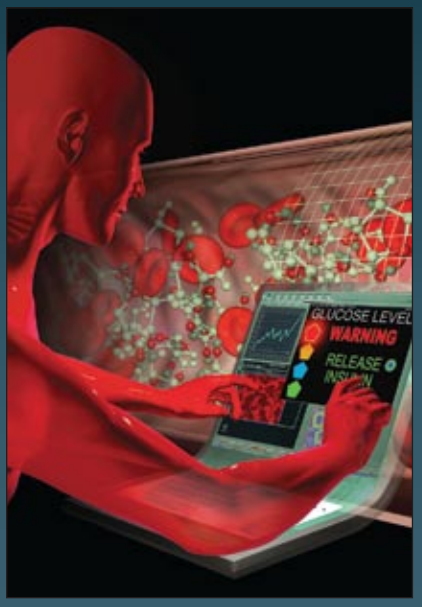
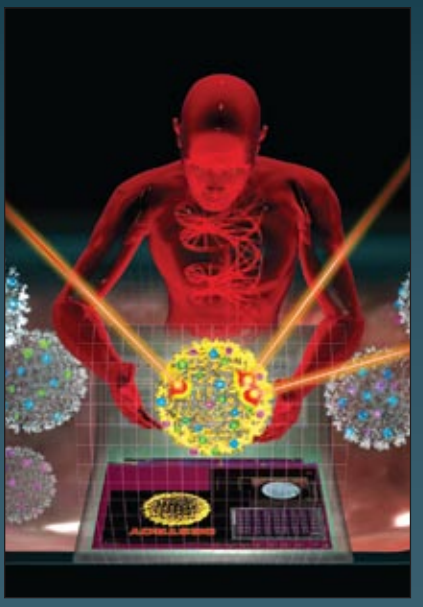
[APPLICATIONS]

JOBS FOR INTELLIGENT DNA

DNA logic gates could have many applications, ranging from medical treatments to counterterrorism.



INJECTABLE PANCREAS
Logic gates operating in the bloodstream of a diabetic patient could monitor glucose levels and release insulin when appropriate.



TARGETED TREATMENT
Gates that sense different markers on white blood cells and combine their data could target leukemia cells for destruction while sparing healthy cells that may have some but not all the same markers.

COUNTERTERRORISM
DNA-based chemical sensors, along with DNA logic gates, could sniff out previously unknown nerve agents such as Soviet-made "novichok" chemicals as well as more familiar ones such as sarin.

to form complex circuits. Like wires in electrical circuits, the base sequences of the sensors and the enzymes would control which gates' outputs "connected" to which inputs, even as all the gates sloshed around independently in a test tube.

After some less than successful attempts using other designs, we settled on DNA structures known as stem-loops for our recognition modules. Sanjay Tyagi and Fred Kramer, both at the Public Health Research Institute in Newark, N.J., had reported that stem-loops switch between two shapes, or conformations. In the closed conformation the DNA strand making up the stem-loop folds onto itself, and the two ends zip together, forming a stem along with a loop of unzipped DNA, like the outline of a lollipop. An input DNA strand consisting of the sequence of bases complementary to the loop will bind to it, but in forming a stretch of the familiar double helix it pries the stem apart—the double-helical DNA cannot form a tight enough curve to maintain the closed loop.

Depending on how we attach a stem-loop to a DNA enzyme, opening the loop may either activate or inhibit the enzyme's activity. If one of the enzyme's two substrate-matching arms serves as one side of the stem, then the closed stem will block the enzyme's activity. We call this structure a sensor or a YES gate because adding the input strand (say, "input X") for the stem-loop controller opens the stem, exposing the enzyme's substrate-matching region and allowing it to function. The enzyme's output (specific cleaved strands of DNA) in essence says, "YES, input X is present."

Adding a second stem-loop with a different loop sequence (Y) on the other of the enzyme's two arms yields an AND gate. Only if input X AND input Y bind to it can the enzyme function and cleave DNA [*see box on page 65*].

We make an inhibitory controller—one that will deactivate the enzyme when the correct input binds to the loop—by plugging a stem-loop sequence into the "back" of the enzyme. Now when the stem is closed, the enzyme is intact and produces output. The relevant input strand will open the stem-loop and deform the enzyme enough to inactivate it. Of course, this inactivation will not remove output strands already produced by the gate, so in isolation this NOT gate does not function as conveniently as an electronic NOT gate. But the NOT unit comes into its own when combined with the AND gate structure. The resulting gate, which we call AND-

[THE AUTHORS]

Joanne Macdonald, Darko Stefanovic and Milan N. Stojanovic bring very different backgrounds to the task of programming DNA to compute. Macdonald is an associate research scientist at Columbia University. She conducts biology-related research within the division of clinical pharmacology and experimental therapeutics and pursues practical applications of DNA computing for viral detection. Stefanovic is an associate professor of computer science at the University of New Mexico working on algorithms for memory management in computers. He is the recipient of a U.S. National Science Foundation (NSF) CAREER award. Stojanovic is associate director of the division of clinical pharmacology and experimental therapeutics at Columbia and director of the NSF Center for Molecular Cybernetics. He is a Leukemia & Lymphoma Society Fellow. MAYA is named after his daughter.

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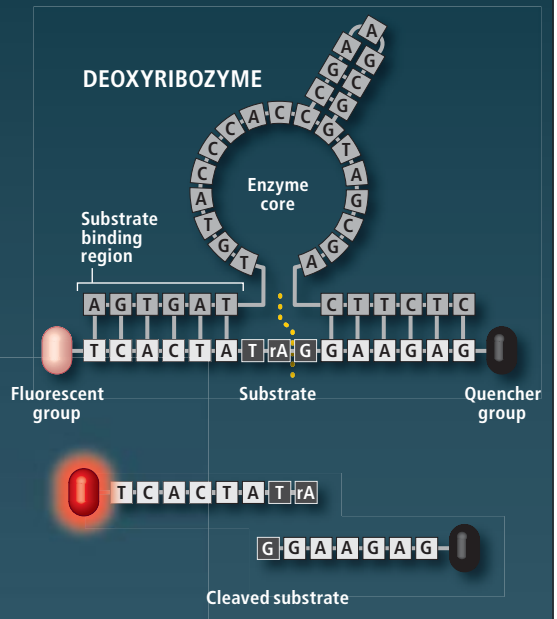
[WORKING PARTS]

MOLECULAR MODULES

To perform as logic gates analogous to silicon ones, a technology must produce specific outputs in response to a variety of inputs. DNA enzymes and recognition modules provide these output and input functions for a system based on DNA in solution.

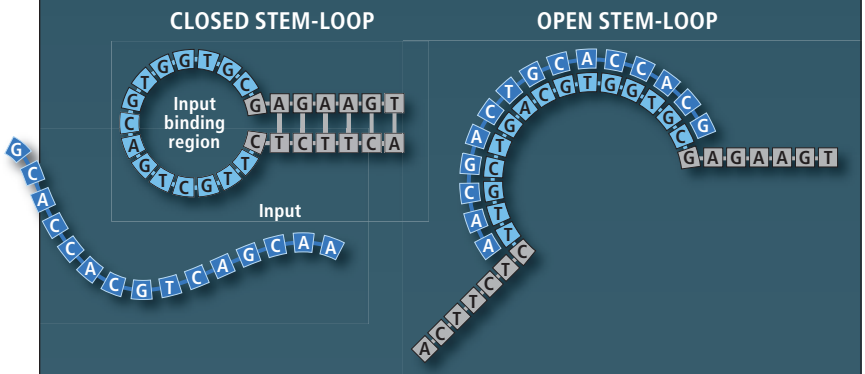
OUTPUT ENZYME

A DNA enzyme called a deoxyribozyme (*top*) consists of single-stranded DNA folded into a "core" structure with arms at each end that can bind to a substrate DNA strand that has the complementary sequences of bases separated by a specific sequence of three other bases (*dark gray*). The enzyme cleaves the strand into two pieces (*bottom*). The process can be monitored by attaching a fluorescent molecule at one end of the substrate strands and a quencher molecule at the other end. The quencher molecule blocks fluorescence until the cleaving of the strand takes it out of range.



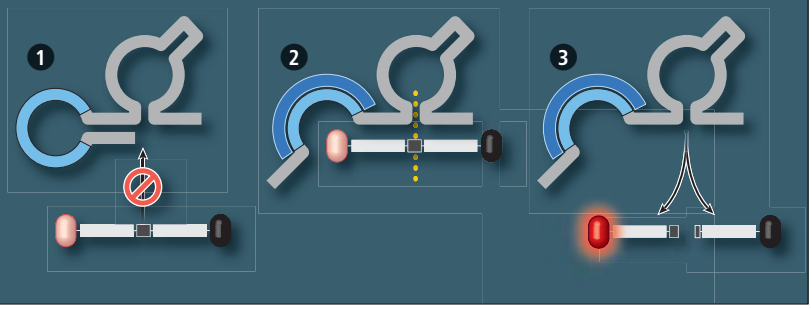
INPUT SENSOR

In a DNA structure called a stem-loop, the DNA folds onto itself and zips together to form a double-stranded stem with a single-stranded loop (*left*). When a matching input strand binds to the loop, it pries the stem apart (*right*).



SENSOR GATE

A stem-loop attached to the arm of an enzyme blocks the enzyme's function (*1*) until an input DNA strand opens the controller and exposes the arm (*2*), enabling the enzyme to bind and cleave substrates (*3*). This structure is also called a YES gate because it signals, "Yes, the input is present."



AND-NOT, produces output only if inputs X AND Y AND NOT Z are present. That function, also known as an INHIBIT gate, turned out to be very useful for our tic-tac-toe automata.

The most important aspect of our system is that it is highly modular. We can use hundreds and theoretically millions of different base sequences for the inputs, and we can also change the sequences of the output strands. We could even switch the underlying enzyme to be a ligase, one that joins together short strands to produce longer ones. Indeed, Andrew D. Ellington's group at the University of Texas at Austin has studied ligase-based switches extensively.

The functioning of the gates is also autonomous. That is, once we trigger a computation by adding the input to the solution, no more human intervention is required. In essence, DNA molecules make the decisions on their own, based on whatever inputs they receive.

Our gates do have some significant differences, however, from the silicon-based logic in electrical circuits. First, we cannot reset our gates. Once an input strand is bound to a stem-loop controller, it tends to remain there for the rest of the computation. Nor can the cleaved oligonucleotide output strands be reassembled. Our ultimate biomedical goals do not require a gate-reset function, but it would be useful for potential molecular robotics applications (involving moving parts). We are exploring the use of ligase enzymes to reassemble output strands.

Second, electronic gates have a threshold voltage at which their switching happens, and their outputs are tied to specific voltages so that they cannot linger at an intermediate voltage. Thus, the 0s and 1s are well defined, and the logic is truly digital. Solutions of our gates, in contrast, change in continuous fashion between the inactive and the fully active forms depending on how many inputs we add to the fluid. This behavior would be important if we were attempting to build the molecular equivalent of a personal computer, but it does not matter for many biomedical applications.

DNA Plays Tic-Tac-Toe

With a general approach to constructing molecular logic gates in our hands, we looked for an objective test of their ability to compute. We wanted to apply our logic gates in a situation in which everyone would immediately see that the molecules were making decisions. A traditional test for a new computer system is to make it play a game of strategy. The rules of a game provide

TOMMY MOORMAN

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a challenge with a straightforward measure of success: the system will either be able to play the game or not. Game-playing ability is intimately connected with general computational ability.

We chose the classic children's game of tic-tac-toe for our demonstration. In this game, played on a 3 × 3 grid, two players try to put three marks in a row while blocking the opponent from doing the same. Tic-tac-toe is one of the simplest two-player games of perfect information, meaning that a player knows everything that there is to know about the state of the game at each move (unlike, for instance, most card games, in which rivals' cards are unknown). Tic-tac-toe will always end in a draw if both parties play well, but our device will exploit any mistake the opponent makes.

The game is simple enough that we can encode all decision making into logic operations that examine only the opponent's moves. That is, when you are using a fixed strategy, even if you remember only what your opponent's moves have been, you can work out what your own past moves must have been and therefore what the current board position is and what your strategy dictates as your next move. We condensed that chain of reasoning down to a network of logic gates that takes the opponent's moves as inputs and produces your next move as the output. In 2002 we set out to build just such a network out of DNA logic gates, a tic-tac-toe-playing automaton that we christened MAYA (*m*olecular *a*rray of YES and *A*ND-AND-NOT gates).

MAYA consists of nine wells corresponding to the squares of the tic-tac-toe grid. Each well contains its own precisely defined set of DNA logic gates in solution [*see box on next page*]. The enzymes of these gates are all designed to cleave the same substrate DNA strand, which is also in all the wells, but they require magnesium ions to function. Thus, adding magnesium ions stirs MAYA into action. Because the enzymes in the central well have no stem-loop controllers on them, they start cleaving the substrate immediately. The fluorescence from the central well increases, signaling that MAYA has taken the central square as the opening move.

The human (let's call him Harry) has eight input strands (one for each of the eight remaining squares) for inputting his moves. The base sequences of these strands are complementary to the sequences on the stem-loops that control MAYA's DNA gates. To move in square 4, for instance, Harry adds input 4 to all nine of MAYA's wells. MAYA signals its move in re-

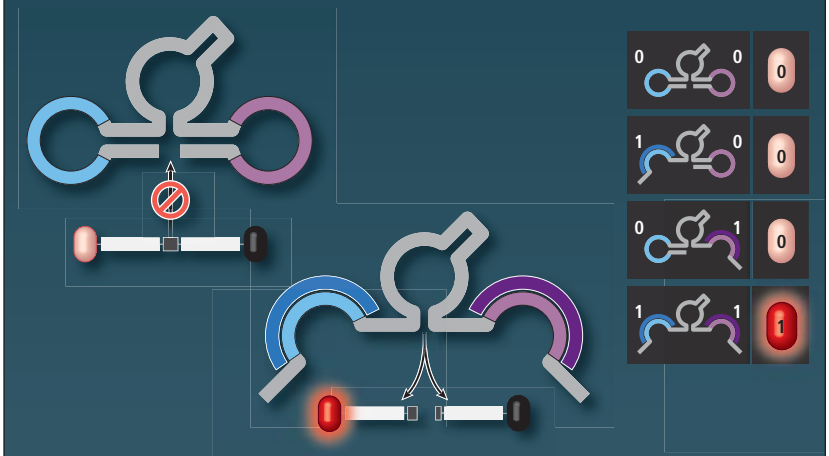
[LOGIC GATES]

HOW DNA COMPUTES

Combining DNA enzymes with stem-loop controllers yields a variety of fundamental logic gates that use short strands of DNA as both inputs and outputs. The cleaving action of the enzyme produces the strands that serve as the gate's output of 1. No cleaving is an output of 0.

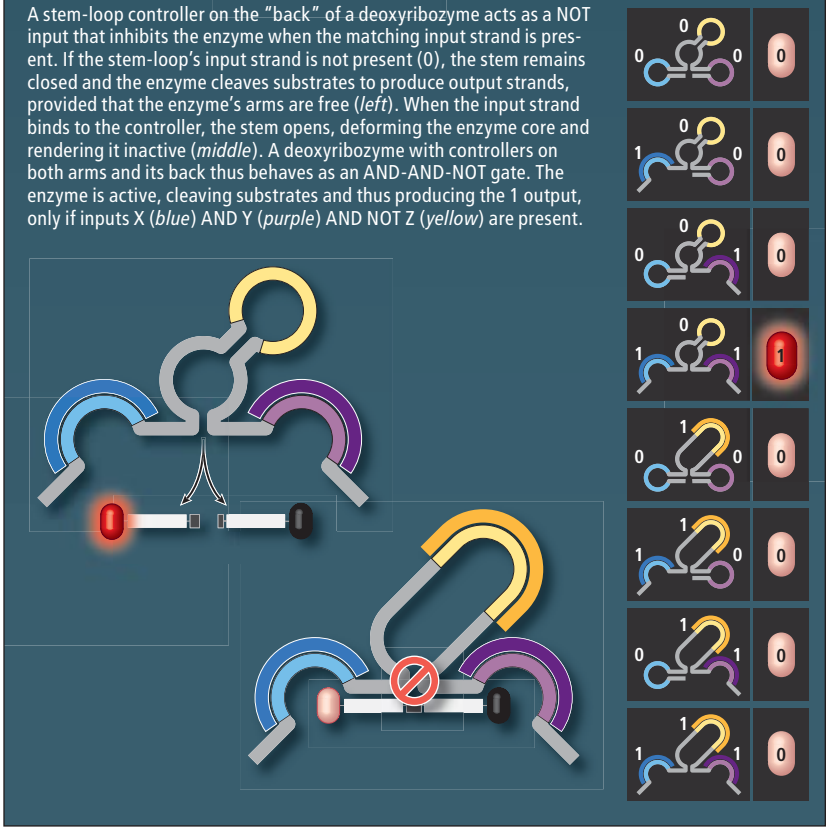
AND GATE

A logical AND gate has two inputs and produces an output of 1 only if both inputs are 1. A deoxyribozyme with a stem-loop on each of its arms acts as an AND gate. The closed stems disable the enzyme (*left*), and only when both loops' matching input strands are added can the enzyme cleave substrates (*middle*). Truth table (*right*) summarizes the gate's function.



AND-AND-NOT GATE

A stem-loop controller on the "back" of a deoxyribozyme acts as a NOT input that inhibits the enzyme when the matching input strand is present. If the stem-loop's input strand is not present (0), the stem remains closed and the enzyme cleaves substrates to produce output strands, provided that the enzyme's arms are free (*left*). When the input strand binds to the controller, the stem opens, deforming the enzyme core and rendering it inactive (*middle*). A deoxyribozyme with controllers on both arms and its back thus behaves as an AND-AND-NOT gate. The enzyme is active, cleaving substrates and thus producing the 1 output, only if inputs X (*blue*) AND Y (*purple*) AND NOT Z (*yellow*) are present.



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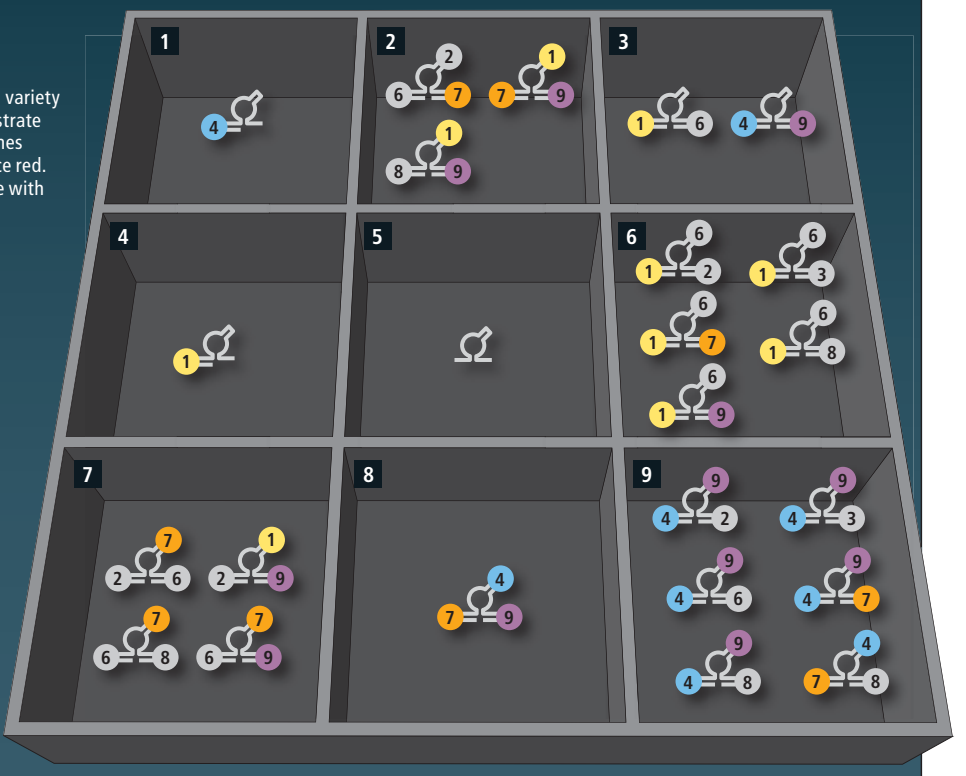
[PROOF OF PRINCIPLE]

PLAYING TIC-TAC-TOE WITH DNA

The first-generation automaton, MAYA-I, proves the potential of DNA logic gates by playing a perfect game of tic-tac-toe, albeit with some restrictions to simplify its programming. MAYA plays first, selecting the central square (*5*), and the human player's first move must be in either the upper left corner (square 1) or the left side (square 4).

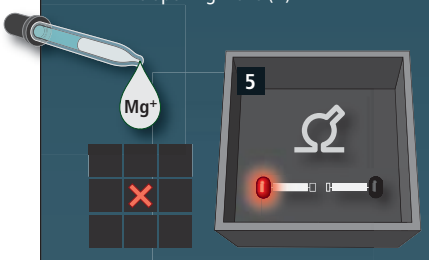
MAYA-I'S STRUCTURE

The computer's 3 × 3 array of wells contains a variety of molecular gates in solution, along with substrate strands (*not shown*). In wells where any enzymes become active, the cleaved substrates fluoresce red. The "gate" in the central well is a DNA enzyme with no stem-loop controllers.

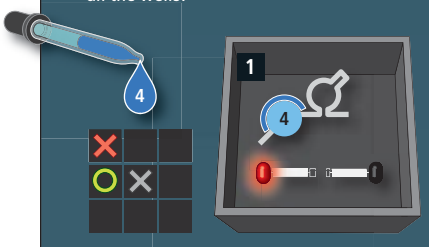


EXAMPLE GAME

The human, "Harry," adds magnesium ions to all nine wells to switch MAYA on. The enzymes in well 5 cleave substrate strands, and the well lights up, signaling MAYA's opening move (X).

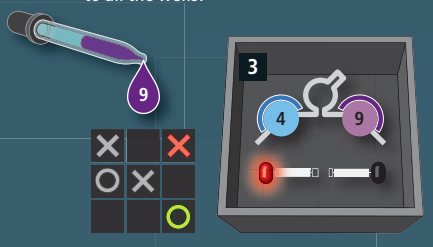


For his first move, Harry takes square 4. He tells MAYA by adding input strand 4 to all the wells.



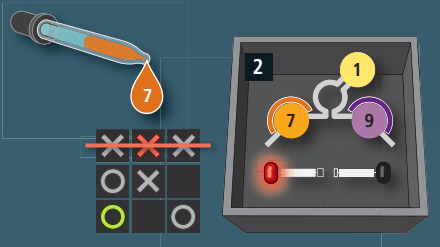
Input strand 4 activates the YES-4 gates in well 1, which lights up; MAYA has taken square 1 for its second move.

To block MAYA from taking the diagonal, Harry takes square 9 by inputting strand 9 to all the wells.



His two inputs activate the 4-AND-9 gates in well 3; MAYA takes that square.

Harry desperately tries blocking MAYA by taking square 7.



Unfortunately for Harry, his inputs now activate the 7-AND-9-AND-NOT-1 gate in well 2 (he has not added strand 1), and MAYA takes that square to win.

sponse by turning on the fluorescence in another of the wells.

As the game progresses, each well contains input strands representing all Harry's moves, and the combination of gates in each well processes those inputs. After every move, one of the wells contains a gate that the last input triggers in combination with the previous inputs. That well lights up to indicate a move by MAYA.

To simplify MAYA's programming, we restricted Harry's first move to be either the upper left corner (square 1) or the left side (square 4). Those two moves are representative of all the moves that Harry might make in response to MAYA's opening move in the center because the board is symmetric. If he moved somewhere else, the board could be rotated to make it a move in either square 1 or 4. With that restriction, the strategy we chose for MAYA allows 19 different possible games to be played. In one of the games,

TOMMY MOORMAN

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Harry plays perfectly and the game ends in a draw. In the remaining 18 games, MAYA exploits his mistakes and wins.

To work out all the required gates for the automaton, we considered every move in all 19 games and determined which gates would produce the desired move. The hardest part was matching the strategy requirements with our logic-gate technology. Although our gates are designed to output DNA strands that could in principle serve as inputs to other gates, for MAYA we chose to avoid relying on that feature and the extra complications it might engender. Altogether we took less than three months to design and develop MAYA and fully test all 19 games in the laboratory.

MAYA-II

Not content with MAYA's limitations, we built an unrestricted version, MAYA-II. We also made MAYA-II more user-friendly, displaying both players' moves in two different fluorescent colors. The automaton still goes first and claims the middle square, but Harry the human can then take any of the remaining eight squares. MAYA-II plays four times as many possible games as MAYA, winning 72 of them and drawing four.

We wrote a computer program (for a standard silicon-based computer) to determine an appropriate arrangement of logic gates. The resulting design calls for 128 different logic gates, 96 for deciding and signaling the automaton's moves using red fluorescence and 32 to highlight Harry's moves in green fluorescence.

The sheer size of this automaton made building and testing MAYA-II an enormous challenge. One of us (Macdonald) led the project and trained several high school students to test automata, mostly during summers and on Saturdays. The students checked all 76 games multiple times. They had to make changes in MAYA-II's design to deal with several problems (and then recheck all the games after each tweak).

Our chief concern going into the project was that some sequences might bind in unintended places. Our computer-modeling tools were not advanced enough to be able to predict such difficulties. In fact, spurious binding was relatively rare. Instead the more serious problem turned out to be individual gates cleaving their substrates at different rates. We (or, rather, our students) had to adjust concentrations and structures to correct for this variability. We also quickly discovered that some gates acted differently within a mixture than they did on their own, necessitating other redesigns. Finally, after three consecutive summers and many Saturdays, through some changes of inputs and many small adjustments of gate sequences and concentrations, our team had a system in which we could clearly distinguish active and inactive gates in all wells, for all the games, reproducibly.

Implications

Integrating more than 100 molecular logic components in a single system represented a substantial milestone. In the jargon of electronics, MAYA-II is the first "medium-scale integrated molecular circuit." Our work on a device of such complexity let us refine our deoxyribozyme logic gates as plug-and-play computing primitives. New efforts in our laboratories now proceed more smoothly with existing components, and we can design gates that usually work immediately without needing any fine-tuning.

We could integrate our method with other molecular computing approaches developed recently. For example, Erik Winfree's group at the California Institute of Technology came up with impressive "strand displacement cascades," which could be used to analyze mixtures of oligonucleotides in a similar fashion. In this scheme, strands of DNA combine, joining and displacing one another mostly without the need for any catalysts analogous to the DNA enzymes of our gates. Winfree's system has been demonstrated with a cascade of five units. In comparison, our present system suffers from becoming prohibitively slow if three layers of gates are combined. MAYA-II, for all its complexity, functions as a single layer of gates and takes around 15 minutes to carry out a move.

For our decision-making molecules, we are now very confident about putting many gates together, and tasks representing fresh challenges beckon. We hope one day to report a mixture of molecules that can be taught a strategy by playing example games with them or by introducing some selection to eliminate the gates that encode losing strategies. We might then develop automata that we can train to recognize cancer cells.

But perhaps the most important next step of our program is to incorporate new primitives to carry out more functions, such as sensing and moving (or "actuating"). These are automata that would take action based on the presence of a given input. Our plug-and-play system would then be moving well beyond "play" and would be ready for some real work. ■

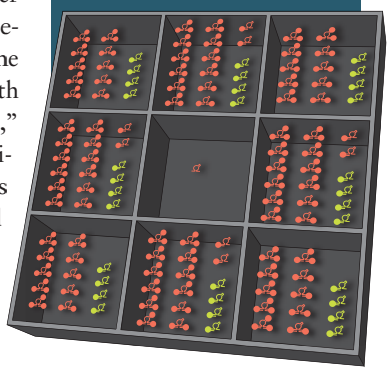
MAYA-II

The second generation of the authors' tic-tac-toe-playing DNA computer, MAYA-II, goes beyond MAYA-I in several respects.

The human player may make any legal move in response to MAYA-II's opening move, increasing the number of possible games to 76. MAYA-II wins 72 of them and draws 4.

32 logic gates cleave green-fluorescing substrates to highlight the human's squares.

96 logic gates compute MAYA-II's moves and indicate them with red fluorescence. A computer program designed the arrangement of gates.



TOMMY MOORMAN

MORE TO EXPLORE

A Deoxyribozyme-Based Molecular Automaton. Milan N. Stojanovic and Darko Stefanovic in *Nature Biotechnology,* Vol. 21, No. 9, pages 1069–1075; September 2003.

Medium Scale Integration of Molecular Logic Gates in an Automaton. Joanne Macdonald et al. in *Nano Letters,* Vol. 6, No. 11, pages 2598–2603; November 2006.

MAYA II, a Second-Generation Tic-Tac-Toe Playing Automaton. Online at **http://tinyurl.com/4mvbnm**

Eric Winfree's home page: **www.dna.caltech.edu/~winfree**

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The Incredible Shrinking Scanner

A portable version of a room-size nuclear magnetic resonance machine can probe the chemistry and structure of objects ranging from mummies to tires

By Bernhard Blümich

KEY CONCEPTS

- Scientists have for decades used nuclear magnetic resonance (NMR) systems to investigate the chemical composition of materials without damaging them. And physicians have employed essentially the same technique, using magnetic resonance imaging (MRI) machines to view inside the human body.
- NMR and MRI machines are large. But researchers have now developed portable versions. A good example is the NMR-MOUSE, which has found applications in the control of manufacturing processes, the nondestructive testing of materials, archaeology and art conservation.
- Ongoing research could lead to improved, specialized versions, including perhaps a football-helmet-like brain scanner that could operate in a speeding ambulance.

—The Editors

You or someone you know has probably had an internal malady examined with a magnetic resonance imaging (MRI) machine. Lying in the claustrophobic confines of the room-size magnetic doughnuts that make MRI possible can be stressful, but the diagnostic value of the resulting high-contrast pictures of the various soft tissues inside the body makes up for any angst. A more generalized version of the technique, nuclear magnetic resonance (NMR), also offers enormous benefits, enabling scientists to characterize the chemical compositions of materials as well as the structures of proteins and other important biomolecules without having to penetrate the objects under study physically.

But doctors and scientists have long yearned for portable NMR devices that could be used outside the laboratory. They have envisioned, for example, paramedics using a helmetlike MRI scanner to pinpoint blood clots in the brain of a stroke victim while still inside a speeding ambulance. And they have imagined a handheld NMR spectroscope that could discern the chemical makeup of pigments, thus permitting art experts to distinguish old-master paintings hanging in museums and galleries from modern fakes.

Researchers are nowhere near producing the all-purpose "tricorder" of television's *Star Trek* fame, but Peter Blümler—a former doctoral student of mine—and I took some of the first baby steps toward a portable NMR device in 1993, when we were both at the Max Planck Institute for Polymer Research in Mainz, Germany. Our effort eventually resulted in a small materials-testing tool that provides useful findings to investigators out in the field. Since then, other workers in the now budding discipline of "mobile NMR" have been building on our initial approach and those of others to develop a wide range of related technologies that pack increasingly powerful analytical and imaging capabilities.

The Simplest NMR

Fifteen years ago, when Blümler and I first began to speculate half-jokingly on the simplest setup that could produce a practical NMR signal, the entire notion was indeed rather laughable. Most researchers were moving in the opposite direction—designing ever more complex NMR measurement protocols to provide ever finer details about the structure of objects and matter. But our earlier efforts to develop MRI techniques for polymer materials had taught us that the costly and bulky magnets—and the uniform, or homogeneous, fields they create—are not always needed for successful imaging.

▶ **EXAMINING A PAINTING with the NMR-MOUSE, a portable materials analyzer (*inside a positioning frame*), allows Eleonora Del Federico of Pratt Institute to discriminate among the layers of varnishes, paints, gesso and the canvas backing to determine the work's state of conservation.**

GRANT DELIN (*photograph*); *NEW DOMESTIC DAYDREAMING*, BY KENNETH BROWNE, 2007 (*painting*)

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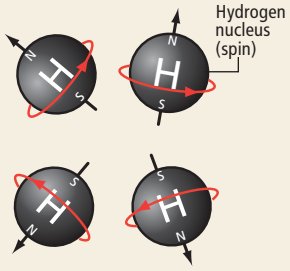
[BASICS]

How Nuclear Magnetic Resonance Works

Nuclear magnetic resonance (NMR) technology exposes objects to a magnetic field and pulses of radio-frequency (RF) energy. Analysis of a material's response to those inputs can reveal both the constituent molecules and such properties as the substance's strength or hardness. Huge magnetic resonance imaging (MRI) machines common in hospitals (*right*) are a form of NMR device.

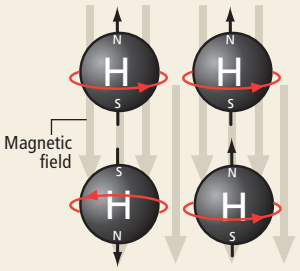
Creation of Nuclear Magnetization

1 RANDOM ORIENTATION



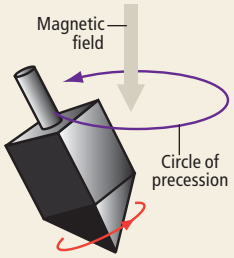
Single, unpaired protons (here, hydrogen nuclei) spin on their axes along random orientations. The motion of the positively charged protons (known as spins) makes them act as if they are tiny bar magnets.

2 MAGNETIZED SPINS ALIGN…



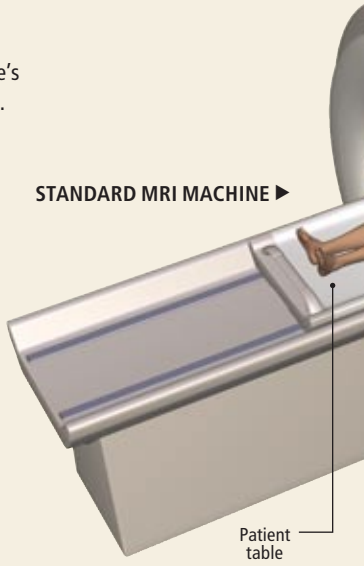
When the NMR machine applies a strong magnetic field to the sample, the spins (on average) tend to align their axes along the field lines.

3 … AND PRECESS LIKE TOPS



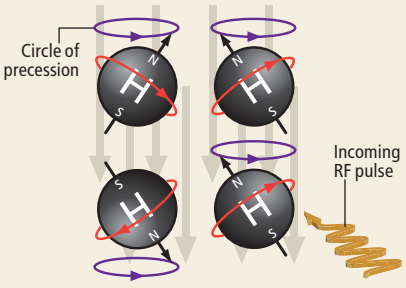
The alignment is inexact, though, resulting in precession—the axes rotate around the field lines—at a frequency that is unique for each type of nucleus and chemical group in a molecule.

STANDARD MRI MACHINE ▶



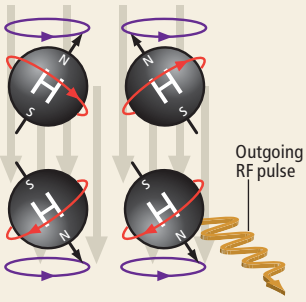
RF Energy Absorption and Release

1 MAGNETIZED SPIN GROUP



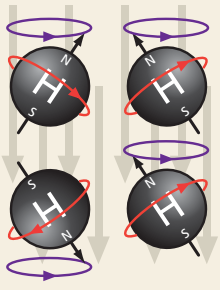
Magnetized spins precess along random orientations in the magnetic field. When a coil in the NMR machine sends an RF pulse toward the group, only a spin that precesses at a rate and phase that matches the pulse's frequency can absorb its energy.

2 SPIN HAS ABSORBED RF ENERGY



Absorption causes the spin to flip 180 degrees. All nuclei that interact with the RF pulse in the same way absorb its energy and flip 180 degrees. The machine's coil picks up the signal induced by the magnetization caused by these changes in spin precession and feeds it to a computer.

3 SPIN HAS RELEASED RF ENERGY



At random intervals, flipped spins release the absorbed RF energy and return to their original (prepulse) orientations.

Results ▶

The computer registers the time it takes for each type of spin to release the absorbed radio energy (T_1 *graph*). The system can also monitor the precessing spins as they fall randomly out of sync (T_2 *graph*). At the same time, it records the precession frequency of the spins of different chemical groups, which are summarized by a value called the chemical shift. The shift forms the basis of NMR spectra plots that identify constituent chemical groups in a sample, such as those in the hydrocarbon molecule toluene (*chemical analysis graph*). MRI machines combine all these NMR data to produce views of internal body tissues, including images of the human brain (*above right*).

We realized that the weaker and nonuniform, or inhomogeneous, magnetic fields of cheap permanent magnets (though some 20 to 50 times stronger than those that adorn refrigerators) could likewise produce data that could clearly distinguish among regions of different varieties of soft matter. Blümler soon came up with a design for a device that would yield the basic information contained in a single pixel of a conventional magnetic resonance image. Thinking that we could shift it around like a computer mouse to scan sizable objects, we named it NMR-MOUSE, for *n*uclear *m*agnetic *r*esonance *mo*bile *u*niversal *s*urface *e*xplorer.

The most intriguing aspect of our invention was that it promised to be potentially as small as a coffee cup, which would make it easy to move around. And unlike conventional NMR, which limits the maximum size of samples to something smaller than the big bore diameters of the toroidal magnets it uses, our system could be positioned on the surface of arbitrarily large objects to look inside them.

But the NMR-MOUSE's highly inhomogeneous magnetic field was a problem. According to the textbook knowledge of the time, it would eliminate the possibility that the tool would be able to provide chemical analyses of materials.

LUCY READING-IKKANDA (*nuclei illustrations and graphs*); GEORGE RETSECK (*cutaway MRI machine*)

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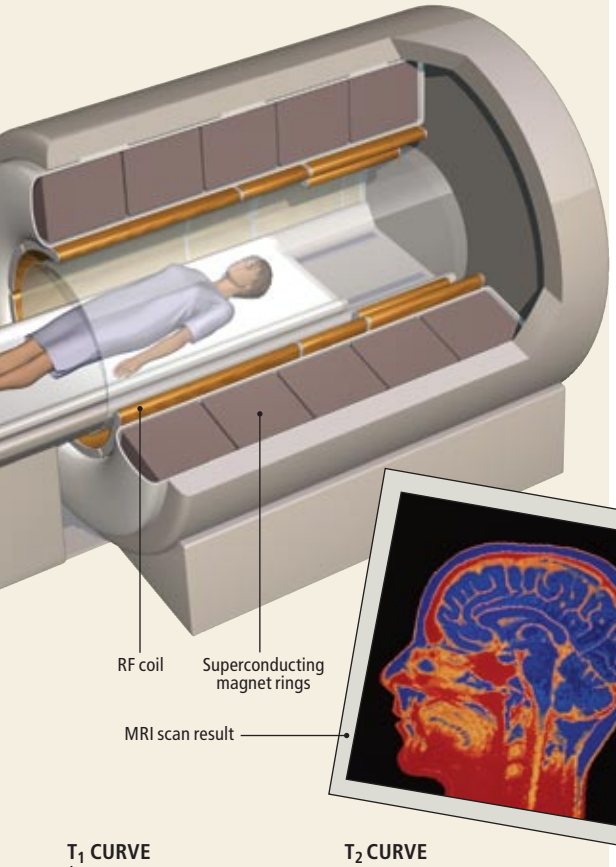
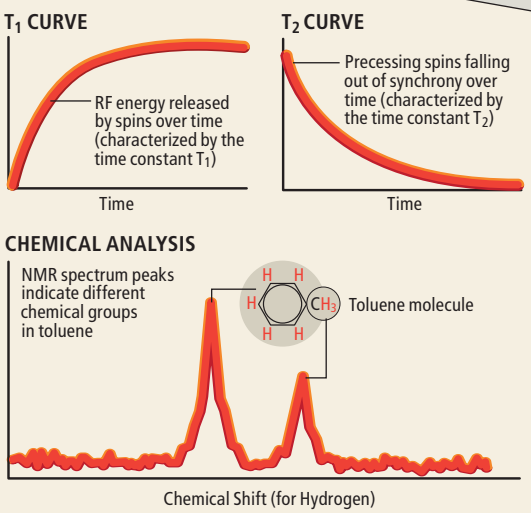




MEHAU KULYK/SPL/Photo Researchers, Inc. (*MRI image*); COURTESY OF PAUL CALLAGHAN (*researchers*)

Conventional NMR

We overcame that roadblock by taking advantage of a specific metric used in standard NMR procedures known as the T_2 time constant. Classic, high-resolution NMR spectroscopy is typically conducted today by placing a sample inside a huge, stationary magnet that produces a powerful, homogeneous magnetic field. The technique exploits the fact that the atomic nuclei (bundles of positively charged protons and neutral neutrons) in certain atoms spin on their axes like miniature tops, which makes them behave like tiny bar magnets with north and south poles [*see box above*]. In a strong magnetic field these spinning "bar magnets" try to line up with the magnetic field lines. Their alignment is not exact, however, and so the spinning nuclei, or spins, wobble (precess) about the field force lines in a way that resembles the dancing motion of a spinning top when a sideways force is applied to it.

If these nuclei are then hit with a pulse of radio-frequency (RF) energy, they will absorb and later reemit energy at specific frequencies according to their individual rates of rotation. These frequencies give rise to an NMR spectrum as distinct peaks of varying height that, like a set of fingerprints, can be used to identify the sample's constituent chemical groups. The data can also be manipulated to yield images that distinguish different materials.

More specifically, NMR spectroscopy relies on measuring the precession frequencies of the spins when they respond to the applied magnetic field and RF pulses. When a nonmagnetized sample is first exposed to a magnetic field, the spins roughly align with the field. After the sample is subjected to an RF pulse (from an RF coil), the spins first precess in synchrony, eventually fall out of sync, then return to their original states. Their return to equilibrium takes a characteristic time T_1 during which they release the energy they absorbed from the RF pulse. (A characteristic time or time constant is something like a radioactive half-life, which is the time it takes for the level of nuclear-decay emissions from a sample to drop by half.)

The synchronous precession of magnetic spins induces an oscillating voltage in the coil that decays with a characteristic T_2 time constant for each spin type as the spins fall out of synchrony. To create NMR spectra that indicate the chemistry of a substance and to produce images, the T_1, T_2 and precession data results are massaged with various complex mathematical formulas that, for example, derive the density of the spins in a volume of a sample, from which the contrast of an image of an object can be derived.

Riding the Echo Train

The key to our device was the realization that T_2 could be measured in nonuniform magnetic fields. Back in 1949, Erwin L. Hahn, a noted physicist then at the University of Illinois, had shown that responses to NMR stimuli can be detected even when one employs inhomogeneous magnetic fields because of certain signals called echoes that arise. In these nonuniform

PIONEERS OF PORTABLE NMR

The budding technical field of "mobile NMR" has been advanced by many distinguished researchers worldwide. Here are a few of the leaders:

PAUL CALLAGHAN

Victoria University
Wellington, New Zealand
Produced innovations in NMR microscopy, developed NMR methods for the molecular study of soft and porous materials, and invented novel portable NMR spectrometry devices (*see photograph below*).

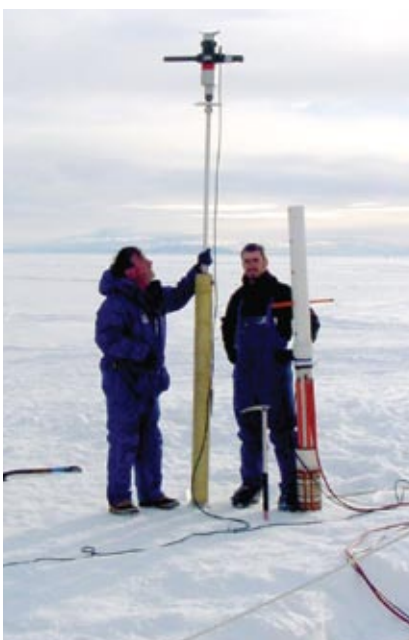
EIICHI FUKUSHIMA

New Mexico Resonance
Albuquerque, N.M.
Created NMR methods to analyze technical processes and developed new mobile NMR technologies.

ALEXANDER PINES

University of California, Berkeley
Responsible for multiple advances in NMR methodology, including solid-state NMR and NMR techniques that boost signals using hyperpolarization effects.

▼ MOBILE NMR PROBE (*right*) developed by Paul Callaghan (*holding drill at left*), Mark Hunter and other researchers was dropped into a drill hole to assess the physical properties of Antarctic sea ice.



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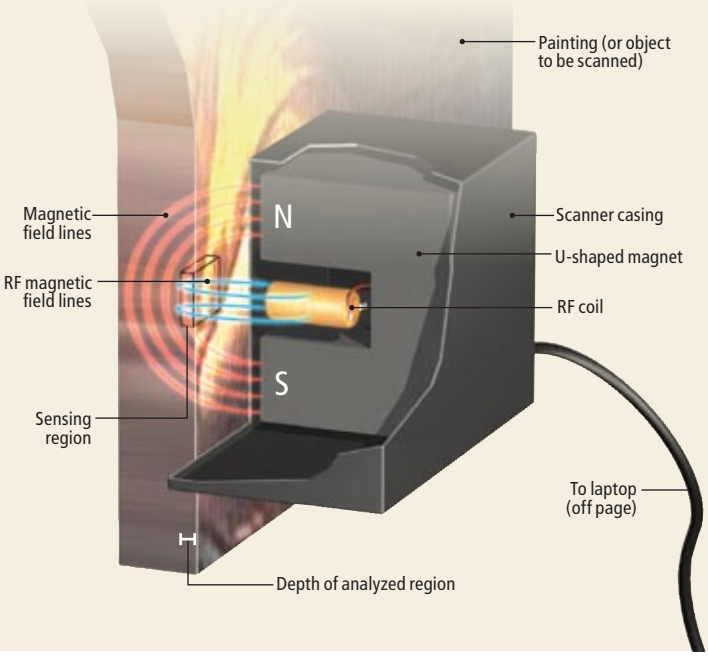
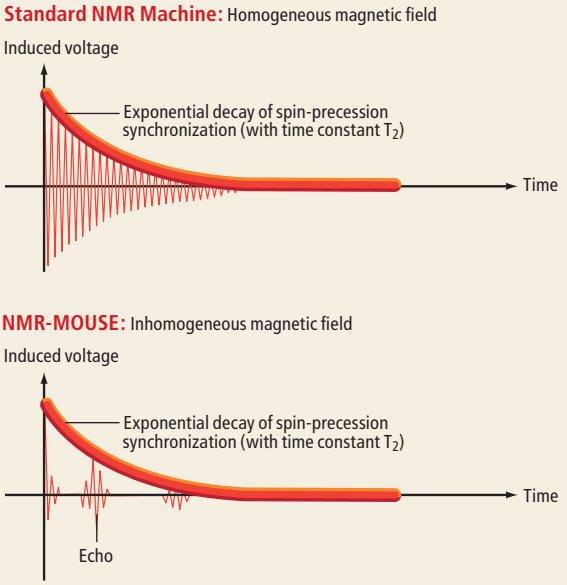
[MOBILE MATERIALS PROBE]

The First Miniaturized NMR Machine

The author's portable materials analyzer, the NMR-MOUSE (*shown in cutaway view*), consists of a U-shaped magnet that has an RF coil in its gap. The device senses the composition of matter where the magnetic field lines of the magnet and of the RF coil cross each other. Operators place the device at different distances from the surface to analyze slices at different depths.





▲ **HOW STANDARD AND MOBILE NMR DIFFER**

A standard NMR machine produces a homogeneous magnetic field and thus can generate a T_2 signal with a single RF pulse. But the NMR-MOUSE cannot do the same because it uses an inhomogeneous magnetic field. It can, however, generate a T_2 signal response by exciting samples with multiple RF pulses that create signals known as echoes. The amplitudes of the echoes can then be assembled into a useful T_2 signal.

[THE AUTHOR]

Bernhard Blümich, a professor of macromolecular chemistry at RWTH Aachen University in Germany, studies the methodology and use of NMR spectroscopy and imaging in materials science and chemical engineering. He received his doctoral degree from the Technical University of Berlin in 1981. More information on his chief development, the mobile NMR-MOUSE materials probe, can be found at www.nmr-mouse.de

fields the coil voltage caused by the excitation of an RF pulse rapidly decays to zero, but it can be recovered some time later by applying a second pulse. Adding further pulses generates a series of echoes that form what scientists call an echo train [*see box above*]. The amplitudes of the echoes in a train decay with the T_2 relaxation time that varies characteristically for different materials.

The T_2 value reflects the mobility of the molecules under investigation: soft matter (in which molecules can move easily) has a long T_2, whereas hard matter (in which there is less molecular mobility) has a short T_2. Whenever a chemical reaction or a phase transition occurs, the molecular mobility of the constituents also changes. The different T_2 values thus provide information about the physics and chemistry of a material as well as contrast data that can be used to help differentiate regions of dissimilar tissues in medical images.

When Blümler and I moved to RWTH Aachen University in Germany in 1994, we started to build the first version of the NMR-MOUSE. Two years later we observed the first signal from the device and were amazed to find that our invention was capable of producing responses from nearly any proton-containing material, including wood, rubber and chocolate. For some materials, the echo trains were long; for others, they were short. We then began to systematically investigate how the associated T_2 values correlate with the properties of the materials we probed.

After several years of refinement and with key contributions from Federico Casanova and Juan Perlo, researchers who had since joined the RWTH group, we ended up with the purse-size configuration of the NMR-MOUSE that we currently use. It has a single-sided design, in which the magnetic field extends outward away from the magnet, and it consumes little power, about the same amount needed to run an incandescent lightbulb. Some 40 to 50 such units are now operating worldwide.

Using the NMR-MOUSE

Rubber was one of the first materials we studied because it is commercially important for products such as tires and is soft like the body tissues

COURTESY OF BERNHARD BLÜMICH (*author*); GEORGE RETSECK (*illustration*)

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for which MRI works so well. Rubber consists of long, spaghettilike polymer molecules that are tied together into a three-dimensional network by random cross-links. For many applications, the density of the cross-links is the most important characteristic in determining overall stiffness. The performance of a tire, which is composed of multiple layers of rubber compounds with different chemistries and cross-link densities, depends on the interplay of all these components. Tests on the track are typically needed to determine how a new design will perform. It turned out, however, that the NMR-MOUSE could analyze the cross-link density of the layers in the finished product individually without having to destroy the tire. This capability also eliminated the need for some tests on the racetrack.

The NMR-MOUSE can access layers at different depths—up to a few centimeters deep. Its magnetic field generates an NMR signal only at a certain distance from the device, so investigators shift this sensitive region through the different layers of a tire to obtain T_2 readings (and thus cross-link densities) for each layer. Other similar uses for the NMR-MOUSE include analysis of the degree of environmental degradation inflicted on polymers (including rubber and polyethylene) and of the chemical makeup of tempera paint binders in old-master paintings.

Another key application revolves around the production of internal profiles of materials under the surface of, say, human skin or the layers of dirt, varnish and touch-up paints on old paintings. A few years ago, for instance, we applied our probe technology to Ötzi the Iceman, the well-preserved Neolithic mummy that climbers found in 1991 when the glaciers at the border between Austria and Italy melted enough to reveal the body. The device successfully produced a clear-cut depth profile that shows a layer of ice, a layer corresponding to Ötzi's freeze-dried skin and subcutaneous tissue, and a layer corresponding to the underlying bone structure of dense and spongy material. Such a nondestructive visualization of bones could prove to be of great value to archaeologists searching for intact but buried caches of prehistoric DNA.

The uses for portable NMR machines are meanwhile starting to expand elsewhere as the principles of the technique become more widely known. One notable example is the work by Magritek, a Wellington, New Zealand–based firm co-founded by Paul Callaghan, a pioneering NMR researcher. Among other endeavors, Magritek is using a technology that is related to ours to analyze how the mechanical properties of Antarctic ice cores change as the glaciers there encounter the effects of global warming.

Progress in Mobile NMR

Casanova and Perlo have recently increased the homogeneity of the magnetic field generated by the system's permanent magnet to improve its resolution. As a result, the improved NMR-MOUSE can now reveal the chemistry of a solution in a beaker that has been placed on top of the device. This surprising capability has opened the door to chemists to use the NMR-MOUSE for molecular analysis. Today researchers are studying various arrangements of magnets that could allow for coffee cup–size NMR systems that could perform chemical assays.

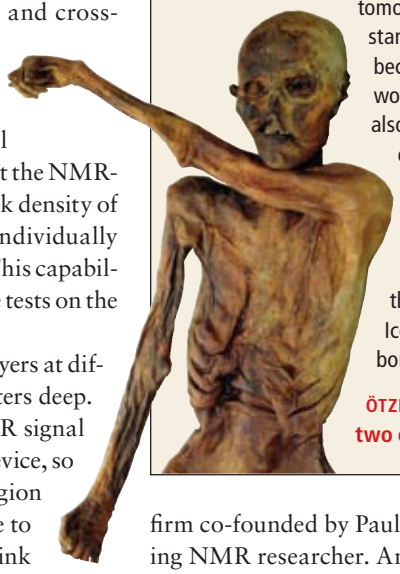
And because the current hardware is essentially that of a cell phone combined with a small magnet, the cost of the device should drop as demand grows. At some point in the future, portable NMR machines may even be sold in department stores for personal use. Someone suffering from a skin condition, for example, may one day monitor a problem with a home NMR device and then adjust a skin care program according its findings. Perhaps something like the *Star Trek* tricorder is not so far off after all. ■

[MOBILE NMR APPLICATIONS]

Other Uses for the NMR-MOUSE

Beyond analyzing paintings, the NMR-MOUSE has also found applications in industry and science. Manufacturers of automotive tires, for instance, use the device to image and determine the chemical compositions of the many individual layers of different rubber compounds that make up a tire (in some cases, a competitor's product). A conventional NMR tomography machine would not work on a standard steel-belted tire, for example, because the strong magnetic field it creates would attract the belt, whose ferrous nature would also disrupt the results. Other users employ the technology to evaluate the environmental damage done to aging polymer materials such as polyethylene.

Scientists have also applied the NMR-MOUSE to the study of Ötzi the Iceman, the ancient, partially thawed-out mummy discovered in 1991 by climbers in the Alps. In 2006 the sensor probe successfully mapped a cross section of the Iceman's well-preserved skin, subcutaneous tissue and skull bone at the Museum of Archaeology in Bolzano, Italy. —***B.B.***



ÖTZI THE ICEMAN (*left*) and car tires (*above*) are only two of the many study subjects for the NMR-MOUSE.

MORE TO EXPLORE

The NMR-MOUSE, a Mobile Universal Surface Explorer. G. Eidmann, R. Savelsberg, Peter Blümler and Bernhard Blümich in *Journal of Magnetic Resonance, Series A,* Vol. 122, No. 1, pages 104–109; September 1996.

Well Logging. R. L. Kleinberg in *Encyclopedia of Nuclear Magnetic Resonance,* Vol. 8. Edited by David M. Grant and R. K. Harris. Wiley, 1996.

NMR Logging Principles and Applications. George R. Coates, Lizhi Xiao and Manfred G. Prammer. Halliburton Energy Services, 1999.

Essential NMR. Bernhard Blümich. Springer, 2005.

Mobile Single-Sided NMR. Bernhard Blümich, Federico Casanova and Juan Perlo in *Progress in Nuclear Magnetic Resonance Spectroscopy,* Vol. 52, No. 4, pages 197–269; April 14, 2008.

Virtual Institute for Portable NMR: **www.portable-nmr.eu**

THE BRIDGEMAN ART LIBRARY/GETTY IMAGES (*iceman*); RYAN McVAY *Getty Images (tire)*

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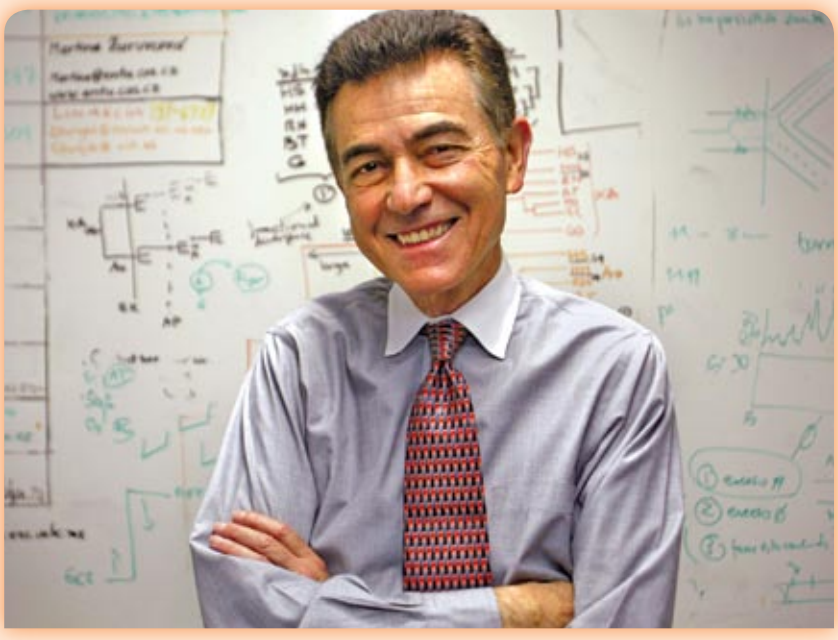
The Christian Man's Evolution

A geneticist ordained as a Dominican priest, Francisco J. Ayala sees no conflict between Darwinism and faith. Convincing most of the American public of that remains the challenge BY SALLY LEHRMAN

Francisco J. Ayala pulls open the top drawer of a black cabinet and flips through nearly a dozen files, all neatly titled by publication and due date. These are the essays on evolution he has been churning out over the past six to eight weeks for popular books and magazines. "Hack jobs," he calls them with a smile, bragging that each one takes only a day or two to complete.

After some 30 years of proselytizing about evolution to Christian believers, the esteemed evolutionary biologist at the University of California, Irvine, has honed his arguments to a fine point. He has stories and examples at the ready, even a shock tactic or two at his fingertips. One out of five pregnancies ends in spontaneous miscarriage, he often reminds audiences. Next he will pointedly ask, as in an interview with *U.S. Catholic* magazine last year, "If God explicitly designed the human reproductive system, is God the biggest abortionist of them all?" Through such examples, he explains, "I want to turn around their arguments."



UNIVERSITY COMMUNICATIONS, UNIVERSITY OF CALIFORNIA, IRVINE

FRANCISCO J. AYALA

COMPATIBLE CONCEPTS: Studied at a Spanish monastery and never saw evolution as an enemy, arguing instead that Darwinism resolves the paradox in Christianity of how a loving creator can allow suffering and evil.

PROLIFIC PEN: Has published some 900 articles, written or edited 32 books, and won several awards, including the National Medal of Science in 2001.

BRANCHING OUT: Applies his genetics knowledge and maverick tendencies to raise 30 varieties of wine grapes in vineyards near Lodi, Calif.

The 74-year-old Ayala is preparing for an exceptionally busy 2009. The year marks the bicentennial of Charles Darwin's birthday and the sesquicentennial of the publication of *On the Origin of Species,* and the battle over the teaching of evolution is sure to heat up. Ayala says the need is especially great for scientists to engage religious people in dialogue. As evidence, he lugs over the 11-by-17-inch, 12-pound *Atlas of Creation* mailed out by Muslim creationist Adnan Oktar in Turkey to scientists and museums across the U.S. and France. This richly illustrated tome not only attacks evolution but also links Darwin's theory to horrors, including fascism and even Satan himself.

In the U.S. the intelligent design–promoting Discovery Institute in Seattle has published biology textbooks questioning evolution and has promoted the 2008 film *Expelled: No Intelligence Allowed* to make the case that anti-Darwinist scientists are persecuted. (For a rebuttal, see "Ben Stein's *Expelled:* No Integrity Displayed," by John Rennie, and related articles at www.SciAm.com.) Republican vice presidential candidate Sarah Palin has said she believes that creationism should be taught alongside evolution in schools. One in eight high school biology teachers already treat creationism as a valid alternative, according to a Pennsylvania State University poll.

Despite outreach efforts by scientists and constitutional rulings against them, creationists and intelligent design advocates "are not getting weaker," Ayala says. "If anything, they're more visible."

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But Ayala thinks that scientists who attack religion and ridicule the faithful—most notably, Richard Dawkins of the University of Oxford—are making a mistake. It is destructive and gives fodder to the preachers who insist followers must choose either Darwin or God. Often students in Ayala's introductory biology class tell him that they will answer test questions as he wishes, but in truth they reject evolution because of their Christian beliefs. Then, a couple of years later, when they have learned more science, they decide to abandon their religion. The two, students seem to think, are incompatible.

That saddens him, Ayala says. Instead he would like believers to reconcile their faith with science. Drawing on five years of study in preparation for ordination as a Dominican priest, Ayala uses evolution to help answer a central paradox of Christianity—namely, how can a loving, all-knowing God allow evil and suffering?

Nature is poorly designed—with oddities such as blind spots built into the human eye and an excess of teeth jammed into our jaws. Parasites are sadists. Predators are cruel. Natural selection can explain the ruthlessness of nature, Ayala argues, and remove the "evil"—requiring an intentional act of free will—from the living world. "Darwin solved the problem," Ayala concludes. He refers to science-savvy Christian theologians who present a God that is continuously engaged in the creative process through undirected natural selection. By addressing religious people on their own terms, Ayala aims to offer a better answer than intelligent design or creationism.

Ayala straddles science and religion by speaking both languages extremely well (and with a Castilian accent). Despite his prolific—and time-consuming—activity in the public arena, he keeps his molecular genetics at the cutting edge. As in his theological debates, he enjoys challenging accepted scientific ideas. Ayala's early work was the first to demonstrate the extensive nature of genetic variation and the action of natural selection at the protein level. His measures led to important modifications to the theory of the uniform "molecular clock," which is used to time when species diverged from a common ancestor, based on differences in either protein structure or DNA. He no longer maintains a wet lab but collaborates extensively.

Ayala graduated in physics at the University of Madrid, then worked in a geneticist's lab while studying theology at the Pontifical Faculty of San Esteban in Salamanca, Spain. By his ordination in 1960 he had already decided to pursue science instead of a ministerial role. At the monastery Darwinism had never been perceived as an enemy of Christian faith. So a year later, when Ayala moved to New York City to pursue a doctorate in genetics, the prevailing U.S. view of a natural hostility between evolution and religion was a shock.

Smart people are being told their faith is not compatible with science. Ayala wants believers to see evolution as an ally.

Ever since, Ayala has attempted to address religious skepticism about Darwin's theory. At first, he recalls, his scientific colleagues were wary and took the position that researchers should not engage in religious discussions. By 1981, when the Arkansas legislature voted to give creationism equal time in schools, the mood began to change. The National Academy of Sciences prepared an *amicus curiae* brief for a Supreme Court case on the Louisiana "Creation Act" and asked Ayala to lead the effort. The booklet became the 1984 *Science and Creationism: A View from the National Academy of Sciences*.

For the second edition in 1999 Ayala presented the idea of incorporating the words of some theologians but recalls, "I was almost eaten alive." In the third edition, published this year, one section features statements by four religious denominations and three scientists on the compatibility of evolution with religious beliefs.

Ayala is again giving his colleagues pause by sitting on the advisory board of the John Templeton Foundation, which paid out $70 million in grants last year alone for research and scholarly programs "engaging life's biggest questions." Some scientists complain that the organization's main mission is to inject religion into science. But Ayala defends Templeton's interest in connecting science to religious life. The foundation has "started to do very good things in recent years," he explains.

Even so, some philosophers of science, such as Philip Kitcher of Columbia University, have come to believe that evolution and belief in a providential creator cannot coincide. Kitcher admires Ayala but complains that "he has residual supernaturalist tendencies." For others, Ayala's approach of debating theological questions and clearly explaining the science is not enough. When two thirds of the public profess a commitment to creationism, argues Stanford University evolutionary biologist Joan E. Roughgarden, the situation is dire. In 2006 Roughgarden wrote what she calls a "religious book" that detailed ideas and examples of evolution written in the Bible. The daughter of Episcopalian missionaries, Roughgarden says she meets believers on their turf—and has even given sermons on evolution from the pulpit. The heart of the debate rests not in theological concepts like explaining evil, she insists, but in the pews.

Sometimes Ayala sounds ready to go there, as when he talks about the vision of God as the author of the universe. But he is unwilling to affirm or deny a personal belief in God, preferring to stick with philosophy. Smart people are being told their faith is incompatible with science. It is his goal, Ayala says, to help believers see evolution as an ally. ■

Sally Lehrman teaches journalism in the public interest at Santa Clara University.

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Dinner and a Show

By Mark Fischetti

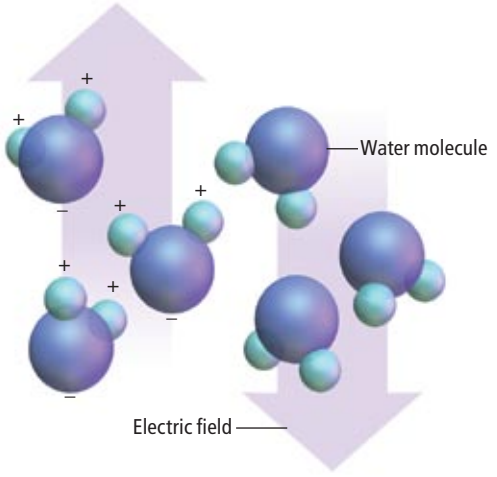
Occasionally it is a treat to remind ourselves how remarkable some of our most common gadgets are. A typical microwave oven ramps up the electricity from a 120-volt wall outlet to an incredible 3,000 volts or more and safely cooks food in just a minute or two, yet it costs less than a pair of good shoes. And we can watch the show through the handy window.

The key component is the magnetron. Although the name conjures up hardware from a questionable science-fiction movie, the sophisticated vacuum tube generates microwaves powerful enough for military radars (for which it was originally developed). Instead of a flame or electric coil generating heat that warms food from the outside, the microwaves penetrate food and create heat from within.

Some people still seem wary of the technology, however, even though microwave ovens have been sold since the 1950s. The classic fear is: Can't the microwaves fly through the window and harm our bodies—especially our eyes? No. The waves reflect off a metal screen embedded in the glass. "The holes are so much smaller than the wavelength of the microwaves that the screen acts like a solid metal mirror," notes Louis A. Bloomfield, a physics professor at the University of Virginia.

Several years ago nutritionists raised concerns that the microwaves depleted nutrients in food. If anything, studies have shown the opposite. All cooking methods can destroy vitamins; the extent of the damage depends on the temperature and the length of cooking time. Most research indicates that microwave ovens result in less extreme temperatures and in fact require less time for cooking than stove-top or oven methods. Boiling food is particularly deleterious.

A recent flap is whether microwave ovens can interfere with Wi-Fi networks. A tightly sealed oven will not do so, because the electromagnetic radiation cannot escape. But tiny leaks could possibly cause problems. "Wireless transmissions are exquisitely sensitive to electromagnetic radiation," Bloomfield says. "So even if a leak were on the order of one part in a billion, our bodies would never notice, but a Wi-Fi signal could."



WATER MOLECULES exist in most foods. They have positive and negative charge at opposite "ends." The electric field of a microwave orients the positive ends in one direction, but the field reverses 4.9 billion times a second, causing the molecules to turn back and forth. As they turn, they bump, creating friction that produces heat. Ceramic and glass containers are water-free and thus remain cool, although hot food might heat them through conduction.

DID YOU KNOW ...

WHOOSH: The whooshing sound a microwave oven makes has nothing to do with the magnetron, which resonates at a frequency far too high for human hearing. The noise is from the fan that blows air across the magnetron to keep it cool.

HUM: Microwave ovens also produce a hum. It comes from the transformer, diode and capacitor, which vibrate as they step up the 60-hertz electric power from a wall outlet.

SPARKS: Despite common wisdom, metal does not necessarily cause sparking inside a microwave; indeed, the cooking chamber walls are metal. Shape matters. Sparks are caused by a buildup of charged particles that suddenly arc when they are pushed by a voltage that changes dramatically over a short distance. A flat, round, metal platter will spread charge around it, preventing buildup; the "crisper" tray that lies underneath some microwaveable pizzas and the sleeve that envelops certain foods (such as Hot Pockets sandwiches) have a metal coating that gets very hot and browns the food yet does not spark. But sharper points, such as fork tines or the many tiny edges in aluminum foil, concentrate charge and also cause localized drops in voltage, which together create corona discharge—a spark.

DEFROST: For decades, ovens achieved "defrost" or any low-power setting simply by turning the magnetron on and off, so that it would generate full-power microwaves for only part of the total cooking time—a cycle that is clearly audible. Some new units have a pulse-width modulator—a hefty electronic circuit that clips the power to the transformer, which lessens the power of the microwaves.

GEORGE RETSECK

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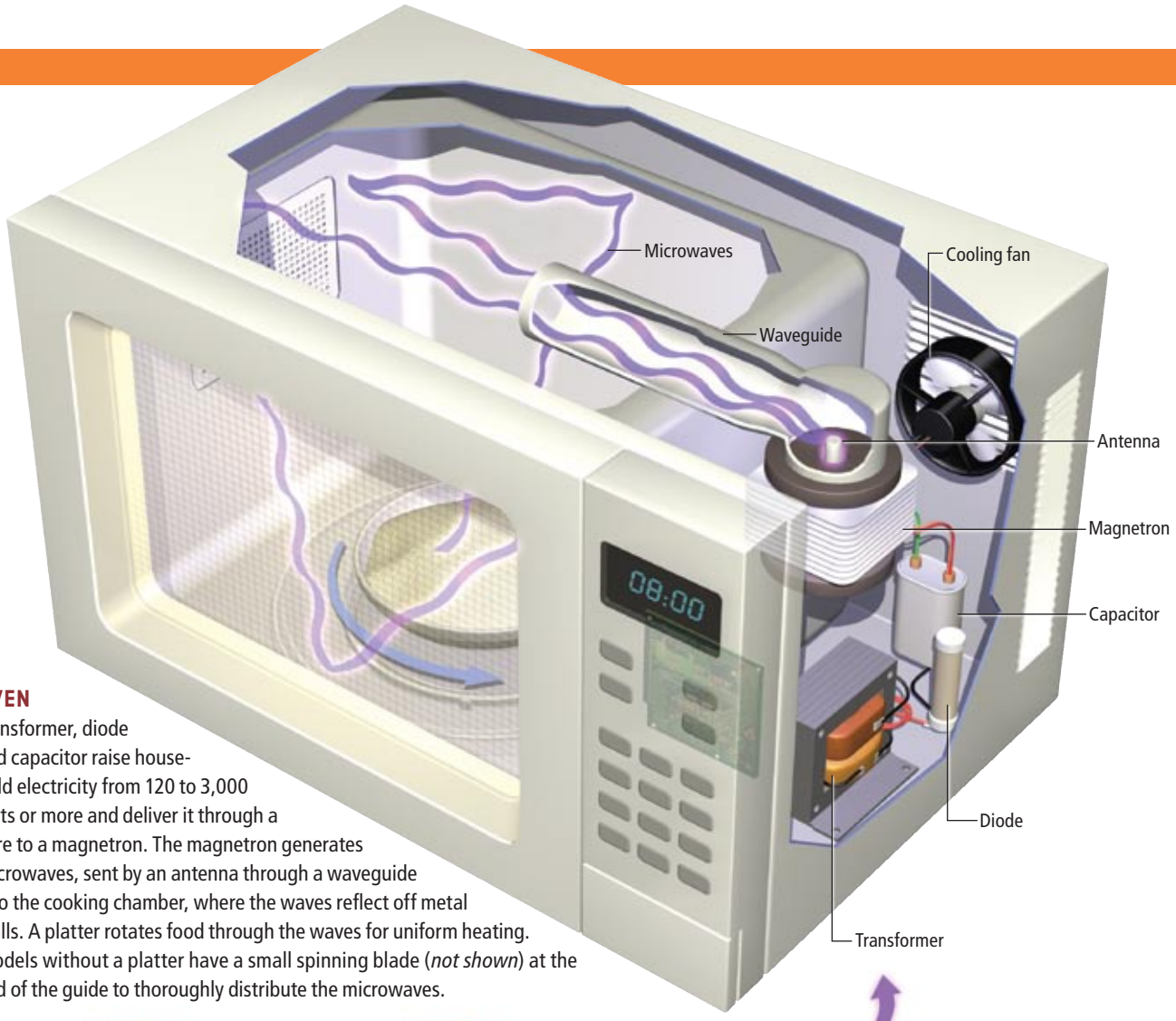
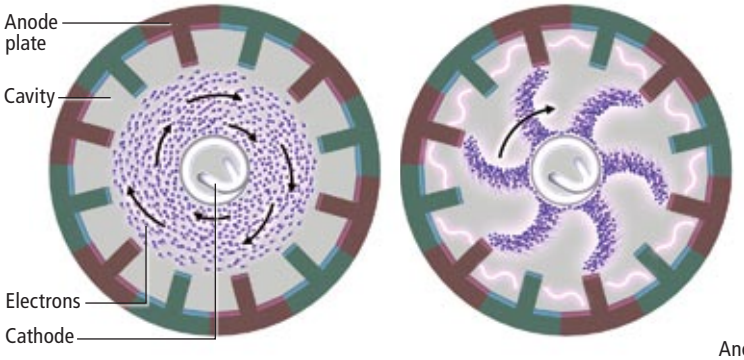
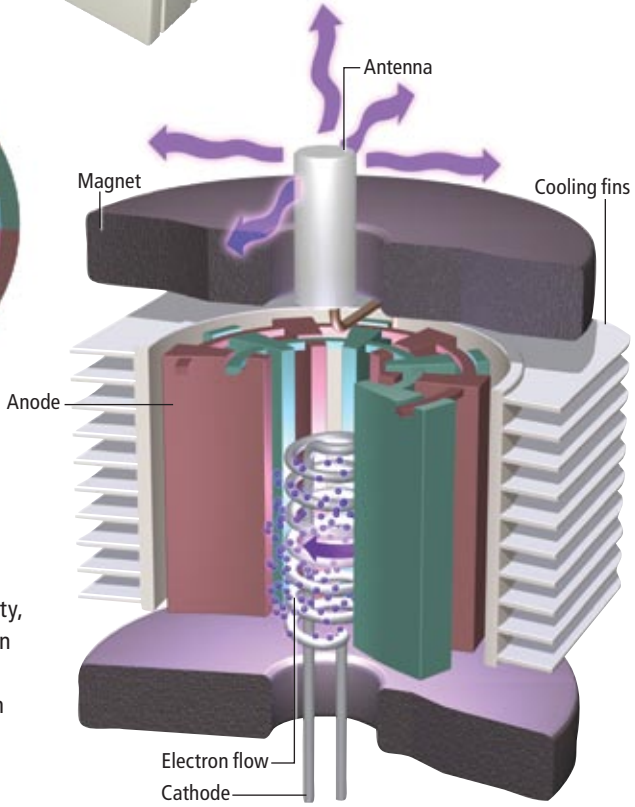


OVEN

Transformer, diode and capacitor raise household electricity from 120 to 3,000 volts or more and deliver it through a wire to a magnetron. The magnetron generates microwaves, sent by an antenna through a waveguide into the cooking chamber, where the waves reflect off metal walls. A platter rotates food through the waves for uniform heating. Models without a platter have a small spinning blade (*not shown*) at the end of the guide to thoroughly distribute the microwaves.





MAGNETRON

High voltage is sent to the cathode filament (*bottom*). After it heats up, it emits electrons that the positively charged anode plates attract. Large magnets impose a field that causes the outward-flowing cloud to revolve (*above left*). As it does, it forms spokes that pass each cavity between the plates (*above right*). A passing spoke provides negative charge to the cavity, which then falls off until the next spoke arrives. The rise and fall creates an electromagnetic field in the cavities that oscillates at 2.45 gigahertz. The attached antenna resonates at that frequency and emits microwaves from its tip—just like a radio-transmission antenna.

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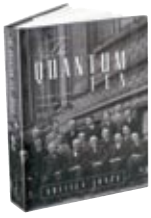
Quantum Drama • Insect Societies • The Unification of Forces

BY MICHELLE PRESS

QUANTUM TEN: A STORY OF PASSION, TRAGEDY, AMBITION, AND SCIENCE

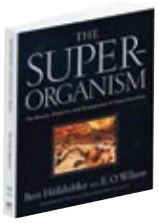
by Sheilla Jones. Oxford University Press, 2008 ($24.95)



In 1927 ten leading physicists met in Brussels to formalize the new science of quantum physics, establishing a set of rules for the microscopic world that was completely incompatible with the existing set for the macroscopic world—and creating a paradox scientists are still trying to resolve. Sheilla Jones, a journalist with a degree in physics, captures the scientific and the human aspects of this meeting. The cast: Albert Einstein, celebrity and lone wolf; Niels Bohr, father figure getting left behind by the new mathematical physics; Paul Ehrenfest, passionate friend to both Einstein and Bohr; Max Born, anxious hypochondriac; Erwin Schrödinger, enthusiastic womanizer; Wolfgang Pauli, clown with a dark side; Louis de Broglie, French aristocrat; Werner Heisenberg, intensely ambitious young man; Paul Dirac, Englishman of few words; and Pascual Jordan, uninvited Aryan nationalist. "This was never a team effort," Jones writes. "Sometimes, two or three would collaborate for a while, but mostly they were rivals who wanted their particular version of the new science to prevail.... A quantum revolution that stalled in a pressure cooker of tension, tragedy and betrayal."

THE SUPERORGANISM: THE BEAUTY, ELEGANCE, AND STRANGENESS OF INSECT SOCIETIES

by Bert Hölldobler and E. O. Wilson. W. W. Norton, 2008 ($65)



The superorganism is a social colony of individuals who, through a sophisticated division of labor, a highly effective communications network and a process of self-organization, form a tightly connected community that functions as a single organism. Fewer than two dozen superorganism species are known to exist: social insects—the colonial bees, wasps, ants and termites—and humans. Fascinating in their own right, superorganisms also offer a window through which we can witness the progression of life from simple to complex forms. Harvard University professor E. O. Wilson and German biologist Bert Hölldobler won a Pulitzer Prize in 1991 for *The Ants*. The current book, they say, is not intended to be as comprehensive but "to present the rich and diverse natural history facts that illustrate superorganismic traits in insect societies." Nevertheless, the book is monumental in every sense, with the same attention to detail and the same elegant style as the earlier volume. More than 100 color photographs and another 100 or so black-and-white drawings make it beautiful as well.

WEAVER ANTS

COURTESY OF BROOKHAVEN NATIONAL LABORATORY (*heavy-ion collision*); COURTESY OF BERT HÖLLDOBLER (*ants*)

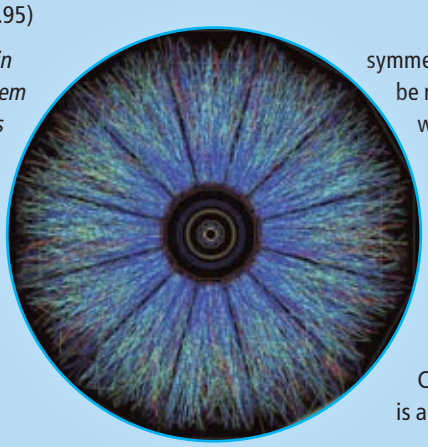
EXCERPT

THE LIGHTNESS OF BEING: MASS, ETHER, AND THE UNIFICATION OF FORCES

by Frank Wilczek. Basic Books, 2008 ($26.95)

Frank Wilczek, winner of the 2004 Nobel Prize in Physics, unwraps exciting new ideas, among them that matter is built from almost weightless units and that space is a dynamic "Grid," a modern ether. He contends, with great wit and style, that we are tantalizingly close to unifying the fundamental forces of nature:

"The striking similarities among our fundamental theories of superficially very different forces hint at the possibility of a synthesis, in which all of them will be seen as different aspects of a more encompassing structure. Their different symmetries might be sub-symmetries of a larger master symmetry. Extra symmetry allows the equations to be rotated into themselves in even more ways.... Thus it opens new possibilities for making connections among patterns that previously seemed unrelated. If our fundamental equations describe partial patterns that we can make more symmetric, by making additions, we're tempted to think that maybe they *really are* just facets of the larger, unified structure. Anton Chekhov famously advised, 'If in Act One there is a rifle hanging over the mantelpiece, it must have been fired by the fifth act.' Now I've hung the rifle of unification."



MINI VERSION of the big bang.

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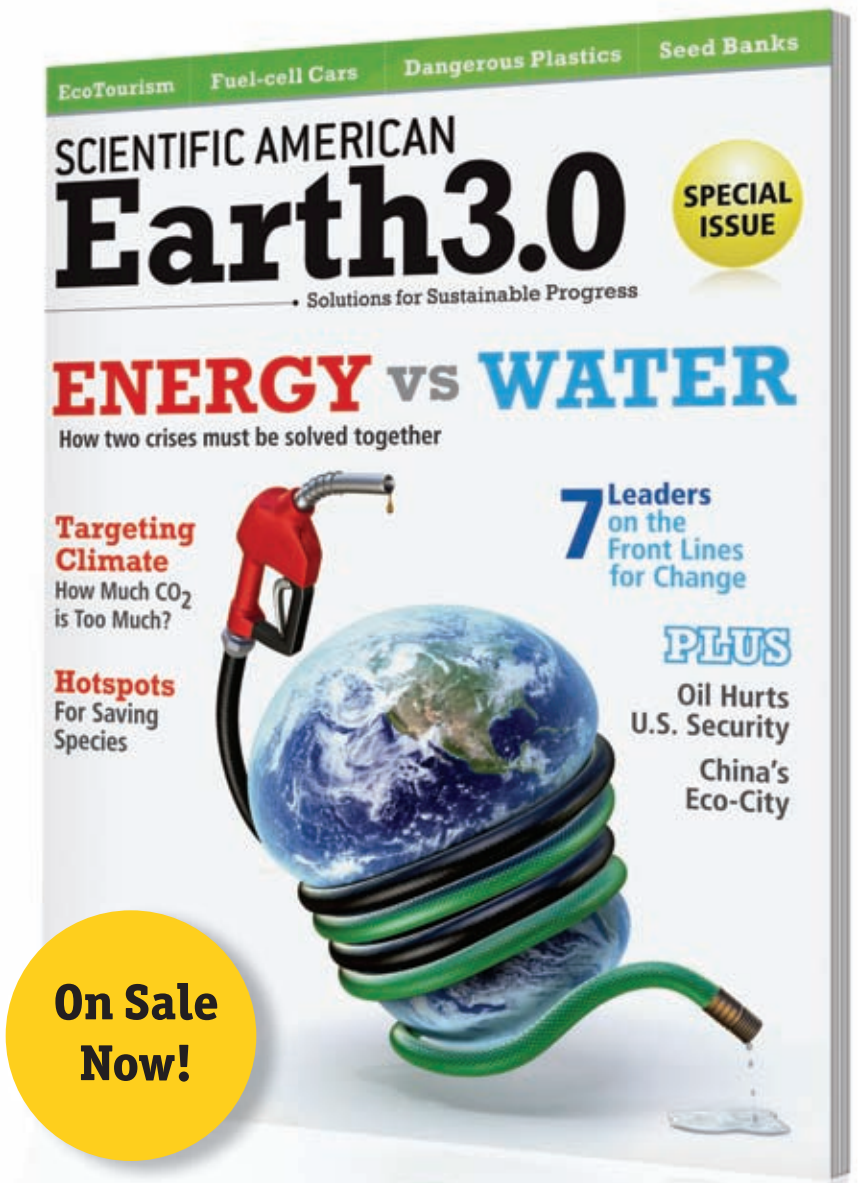

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Q What is touch DNA?

Husband-and-wife forensic experts **Max** and **Lucy Houck** get to the bottom of this mystery:

The touch DNA method is so named because it analyzes skin cells left behind when assailants handle weapons, victims or something else at a crime scene. The technique of analyzing these minute samples for genetic information is relatively new, having appeared only about five years ago.

Touch DNA forensics rose to prominence this past summer, when various news outlets reported that police had used the technique to clear the family of JonBenét Ramsey formally of any wrongdoing in her gruesome 1996 death. In fact, the prosecutor in the Ramsey case, Boulder County (Colorado) district attorney Mary Lacy, learned about touch DNA when she attended a course in the summer of 2007 at the West Virginia University Forensic Science Initiative, which one of us (Max) directs.

In the 1980s, to perform DNA analysis on a piece of evidence or on a victim, forensic investigators needed a blood or semen stain about the size of a quarter. The sample size fell in the 1990s to the size of a dime and then became: "If you can see it, you can analyze it."

Touch DNA does not require you to see anything, however—nor does it require any blood or semen at all. Instead it takes just seven or eight cells from the outermost layer of skin. Naturally, the method has dramatically increased the number of items of evidence that can be used for DNA detection.

Here is how it works: Investigators recover cells from the scene and use a process called polymerase chain reaction (PCR) to make many copies of 13 locations on the DNA. They then mix in fluorescent compounds that attach themselves to those copies. What emerges is a highly specific forensic profile of the person whose cells have been found. The entire process takes a few days.

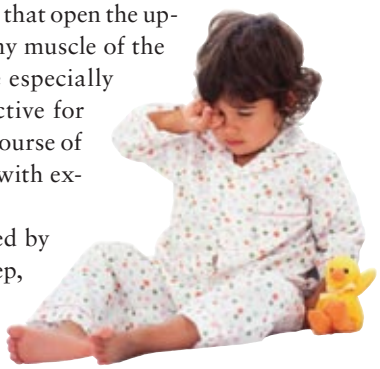
These 13 locations were carefully chosen because they are highly variable among people but do not give away specific information such as race or gender, nor do they reveal levels of personal health or presence of genetic disease. The chance of DNA profiles from two different people having the same genetic signature is vanishingly small.

The trick to finding these cells is context. The forensic specialist on the scene must try to ascertain (or guess) which objects the perpetrator handled and sample them with a cotton swab or a collecting blade. And with the backlogs of evidence common in forensic labs, such a time-consuming process is not always prudent. But in cases such as the Ramsey murder, which has tripped up authorities for more than a decade, it can provide information that leads to a killer—or at least exonerates the innocent.

Q Why do our eyelids get so heavy when we are tired?

Mark A. W. Andrews, professor of physiology and director of the Independent Study Pathway at the Lake Erie College of Osteopathic Medicine, replies:

Generally speaking, heaviness of the muscles around the eyes, including the levator muscles that open the upper eyelids, is similar to fatigue of any muscle of the body. Ocular and brow muscles are especially prone to fatigue because they are active for most of our waking hours. Over the course of the day, they gradually grow leaden with extended use, as our arms and legs do.



Such a feeling may be compounded by general fatigue, including a lack of sleep, or by specific muscle overuse related to long hours of focusing on, say, a computer monitor. Excess skin of the eyelid, or prolapsed fat pads underneath the eyes, makes an individual more prone to this sensation. Chronic allergies and sinus infections may also exacerbate the heaviness, and sun exposure may cause eyelid swelling and thereby increase the probability that the drooping will interfere with vision.

Although heavy eyelids do not typically indicate underlying medical issues, some conditions do cause drooping eyelids, or ptosis. A stroke or a muscular disorder such as myasthenia gravis or myotonic dystrophy can damage facial muscles or their nerves and cause ptosis, as can elective facial surgery or interventions such as Botox injections to the brow. ■

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

ASHLEY COOPER *Corbis (crime scene)*; DORLING KINDERSLEY *(girl)*

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The Evolution of the Genetic Code
Speaker: **Stephen J. Freeland, Ph.D.**

Why should all life use two utterly different chemical languages with which to construct itself? Why did it arrive at a single set of encoding rules for translating between them? How can the precise choice of coding rules influence life's struggle to stay one step ahead of extinction? You'll get the bottom line (as it stands now) on the origin and subsequent evolution of the genetic code from Dr. Freeland, including:

- the central dogma that unifies life
- the non-random "design" of genetic code words
- emergence from an RNA world
- the great unknowns

1859: The Impact of a Dangerous Idea
Speaker: **Jerry Coyne, Ph.D.**

In this session we'll trace the origin of Darwin's "dangerous idea" (actually several ideas) beginning with his famous voyage on the HMS Beagle. We will learn what Darwin really proposed, what impact the ideas of evolution and natural selection had on the Victorian world, and why Darwinism was — and still is — considered a dangerous idea.

Unconscious Design: Natural Selection
Speaker: **Jerry Coyne, Ph.D.**

While the idea of evolution was immediately accepted by 19th-century biologists, the concept of natural selection — the purposeless driving force of evolution and adaptation — has been much more controversial. This talk will describe what natural selection really is and see examples of how it works in nature. We will also examine the complementary theory of sexual selection, which explains the remarkable difference in appearance and behaviour between males and females in many species.

For details contact:
Neil Bauman • 650-787-5665
or neil@InSightCruises.com

On the Origin of Species, Really
Speaker: **Mohamed Noor, Ph.D.**

Although Darwin's book title suggested that he provided us with insights on the origin of species, in fact, he only focused on the process of divergence within species and assumed the same processes "eventually" led to something that could be called a new species. In this session, we'll talk about how species are identified (in practice and in principle), and then how modern evolutionary biologists use this type of information to get a handle on how species are formed.

From Magic to Muons: Why People Believe in Strange Things
Speaker: **Tania Lombrozo, Ph.D.**

Much of our knowledge is about things that we cannot see or touch. By studying human reasoning we can begin to understand both how people make scientific discoveries and how these processes can lead to some surprising errors in understanding our world. We'll consider the debate over evolution and intelligent design as a case study in people's understanding of and preference for different kinds of explanations for the world around us.

The Mathematics of Mind: Exploring the Formal Foundations of Human Thought
Speaker: **Thomas Griffiths, Ph.D.**

Over the last two millennia, scientists and philosophers have used approaches such as logic, artificial neural networks, and probability theory to develop scientific and mathematical models of thought. Dr. Griffiths will talk about current status of work to understand the formal principles that underlie human thought and our ability to solve the computational problems we face in everyday life.

Evolution of Individuality and Complexity Through Cooperation and Conflict
Speaker: **Richard Michod, Ph.D.**

Our understanding of life is being transformed by the realization that evolution occurs not only among individuals within populations, but also through the integration of groups of cooperating individuals into new higher-level individuals — that is, through evolutionary transitions in individuality (ETIs). The major landmarks in the diversification of life and the hierarchical organization of the living world are consequences of a series of ETIs: from genes to gene networks to the first cell; from prokaryotic to eukaryotic cells; from cells to multicellular organisms; from asexually reproducing individuals to sexually reproducing pairs; and from solitary individuals to societies. How do groups become new individuals? Cooperation and conflict play a major role in these evolutionary transitions. Join Dr. Michod and come away with a new perspective on the process of evolution and what it means to be an individual.

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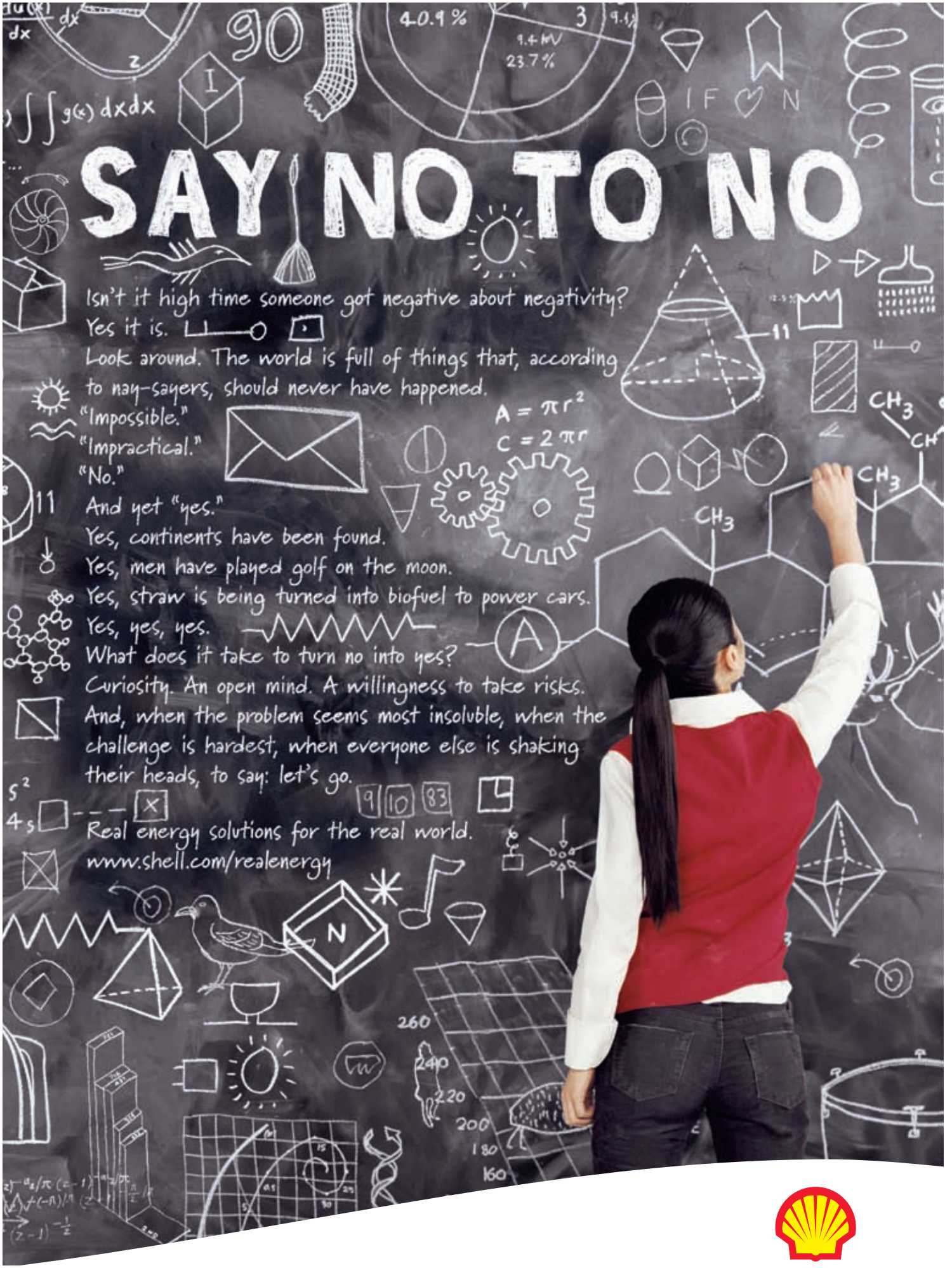

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