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JANUARY 2005
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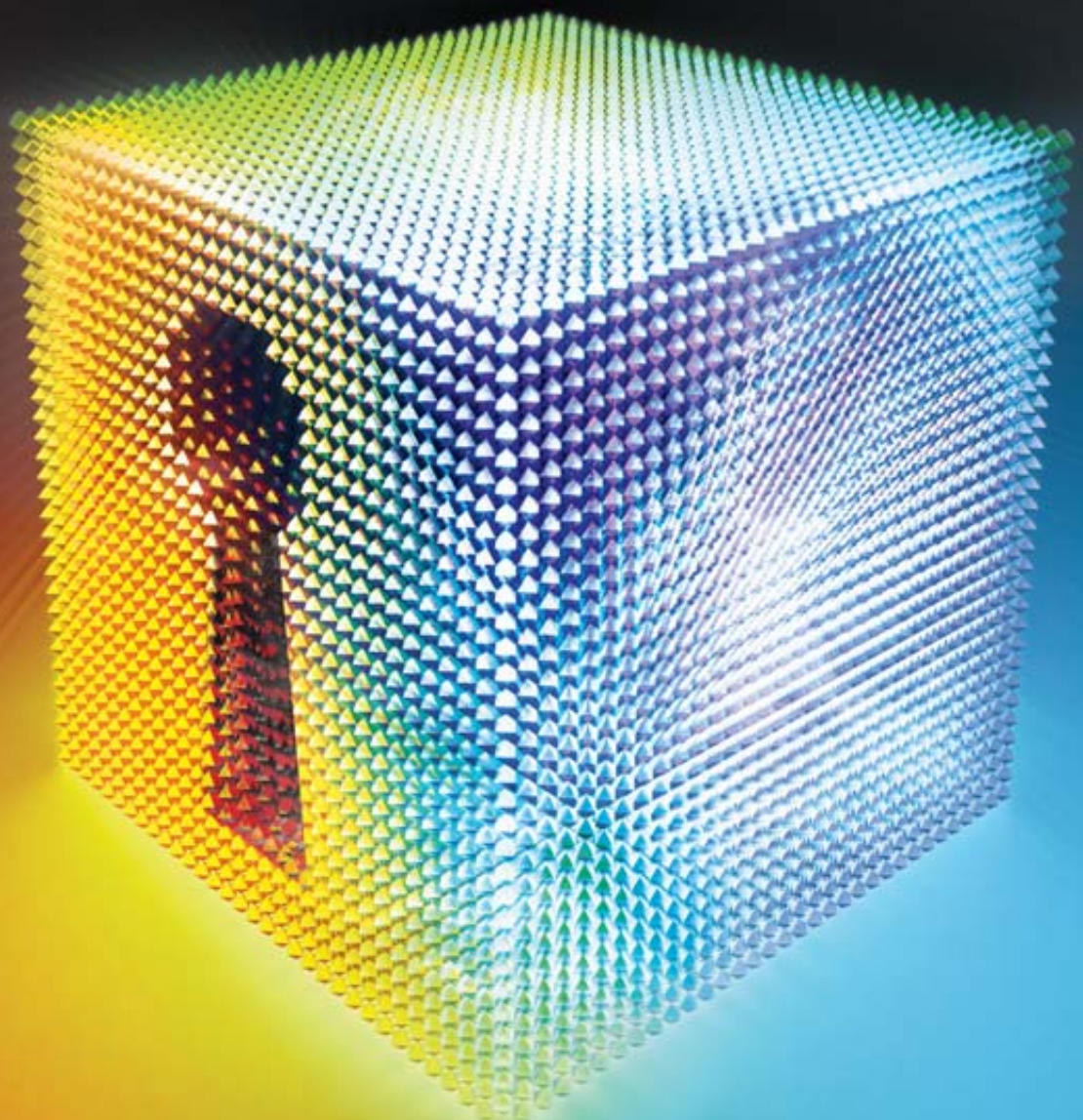
BEST-KEPT SECRETS

Unbreakable Quantum Encryption Has Arrived

Reanimating a Killer to Stop Flu Pandemics

A Cosmic Midlife Crisis

Computers That Learn Your Priorities



january 2005

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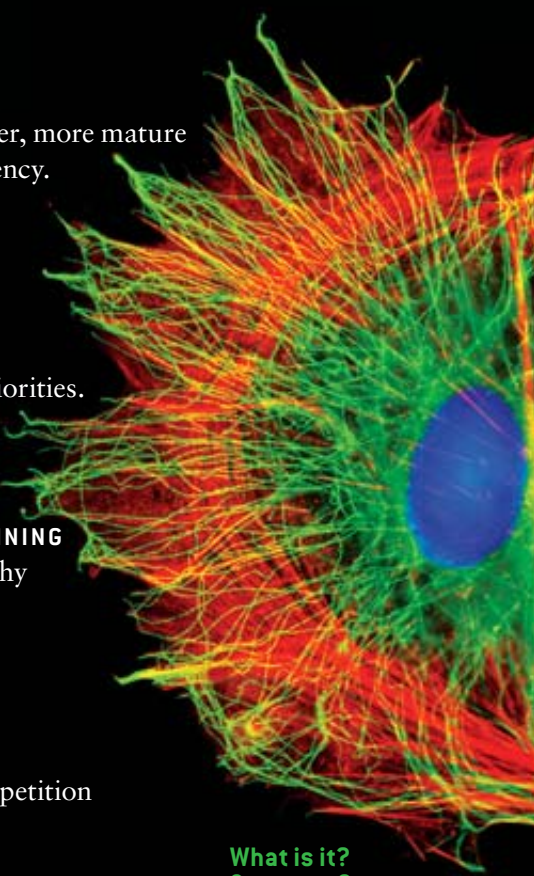

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WHAT IS IT? Hamster kidney cells fluoresce in culture. Photograph on page 5: Albert Tousson, University of Alabama at Birmingham, courtesy of Nikon Instruments.

Cover image by Kenn Brown; photograph at left by Scott Goldsmith.

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Worth a Pound of Cure

A global influenza pandemic is closer than at any time in a generation. Klaus Stöhr, head of flu surveillance at the World Health Organization, made that uncharacteristically dramatic declaration back in November, before convening an emergency summit of vaccine manufacturers and national health agency officials. The reason was the escalating avian influenza crisis in 10 Asian countries, which poses a direct threat to human health.

SUSPECT DUCKLING eyed by Chinese health workers.

Because the avian virus, known as H5N1, is lethal in chickens, identifying local outbreaks was easy. Stöhr was alarmed by evidence that the virus is also widespread in the region's domestic ducks, which show no symptoms. With asymptomatic ducks waddling through barnyards, backyards and kitchens shedding virus, hope of stamping out this largest avian flu outbreak in history has dimmed. And the likelihood of human exposure to the virus, which could spark a pandemic, has increased. "We know the recipe, and all the ingredients are there," Stöhr said.

Flu pandemics are caused by viruses with surface proteins unfamiliar to human immune systems. In the pandemic strains of 1957 and 1968, such proteins came from flu viruses that previously infected only birds. That was possible because flu is a promiscuous gene swapper. If an avian strain meets a flu strain adapted to spreading among mammals, their progeny may possess the deadly combination of protein novelty and easy transmissibility between humans. The exchange can happen inside animal hosts susceptible to both avian and human flu strains, such as pigs. Or it might happen inside a farmer's child infected with this season's circulating human flu strain, whose healthy-looking pet duckling then gives her H5N1. In the past year more than 40 people in Thailand and Vietnam have already contracted the avian virus, and more than 30 of them have died from it.

Beginning on page 62 of this issue, Jeffery K. Taubenberger and his colleagues describe their resurrection, literally from the grave, of the virus that killed upward of 40 million people in 1918–1919. And they offer a chilling conclusion about its origin. Although certain genes in that virus may have come from a bird strain, the genes look as though they spent significant time evolving in yet another animal before the virus emerged among humans. This unknown source of the 1918 pandemic might even have been a type of bird or animal that we don't recognize as a flu carrier.

Systematic surveillance for influenza is currently limited to humans, chickens, swine and horses, with wild waterfowl and shore birds tested less regularly. But few of these samples are closely analyzed, and scientists do not know the dynamics or true scope of the influenza ecosystem. The National Institutes of Health just announced plans to sequence the genomes of existing flu samples. In addition, the Armed Forces Institute of Pathology, the Centers for Disease Control and Prevention, and several partners want to create a high-capacity laboratory network dedicated to expanding flu surveillance capability and molecular analysis of influenza viruses. Studying how they evolve and move through human and animal populations might identify new flu reservoirs and enable the emergence of new strains to be predicted.

Start-up costs would equal the price of the two million emergency H5N1 vaccine doses the Department of Health and Human Services ordered in September. The money would be well spent for an ounce of prevention against future flu pandemics.

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Compound Stymies Key Step in Alzheimer's

Small molecules make better drugs than large ones do, because they can more easily enter cells and gum up chosen chemically active sites. But their size makes it hard for them to stop larger molecules such as proteins from interacting with one another, which is critical to many diseases. Now, borrowing a trick from soil bacteria, researchers have designed a small molecule that effectively forms a new drug on the spot by teaming up with a large protein that is common inside cells. The resulting complex binds to fragments of beta-amyloid protein and keeps them from sticking together to form the "plaques" that are a hallmark of Alzheimer's disease.

Scientists Identify Source of Potent Animal Toxin

"You are what you eat," so the adage goes. For some species, this maxim holds especially true because what they consume plays an integral role in how they defend themselves. New work identifies a potential dietary source for the toxins found in poison-dart frogs and certain birds.

Ask the Experts

How long can people survive without food?

Alan D. Lieberson, a medical doctor, lawyer and author of *Treatment of Pain and Suffering in the Terminally Ill* and *Advance Medical Directives*, explains.

COURTESY OF ISABELLA A. GRAEF (*top*); COURTESY OF *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA* (*bottom*)

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Letters

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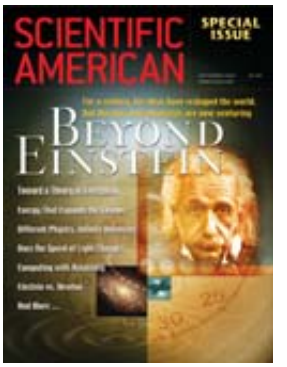


THE RESPONSES to the September single-topic issue on Albert Einstein were philosophical, thoughtful, contentious and abundant. Comments about the SA Perspectives, "Einstein = Man of Conscience^2," suggest that $E = mc^2$ could also stand for Einstein commentaries = much controversy^2.

Less disputatious were recollections of Einstein the person. Ralph Townsend of Oxford, England, related an encounter with the great physicist that shows it is the little things that demonstrate character: A friend of his who worked in Princeton, N.J., "had a young daughter who had difficulty understanding math problems, which he would try to elucidate, but with little success. When she asked him, 'Who could explain this to me?' he replied, 'I'm afraid it would take Einstein.' The resourceful child found Einstein's address and, on the way to school, visited him, saying, 'My father says that only Einstein could explain this problem.' She was invited in, and Einstein enlightened her. When her parents discovered, after she had become habitually late for school, that these meetings had become routine, they apologized to the Einsteins, who replied that they enjoyed seeing her and continued to let her visit."

Following are more comments on this physics revolutionary, who by setting the universal speed limit diminished the limits on our understanding of the universe.

EINSTEIN = MAN OF CONSCIENCE^2

You indicate that Albert Einstein [SA Perspectives] would have found causes for moral outrage today, giving as an example that "though a Zionist, he had always insisted that Jews must live peaceably with Arabs." But with whom would he be outraged?

The Israeli Jews wanted nothing more than to live peaceably with Arabs when they accepted a small fraction of the original Palestine Mandate in the 1948 U.N. partition, but they were attacked by all neighboring Arab states. After surviving this, they wanted to live peaceably with Arabs, but they were continually harassed by boycotts and border raids and excluded from using the Suez Canal.

In 1967 they were again attacked by Arab states, even though Israel then held no part of the West Bank or Gaza Strip. After surviving this, they wanted to live peaceably with Arabs, though now inside defensible borders. Since then, Israeli Jews have made many offers to withdraw from most of Gaza and the West Bank and live peaceably with their Arab inhabitants, but these offers have always been refused. They were attacked again by Arab armies in 1973, coming close to defeat, and their citizens continue to be murdered by Arab terrorists. They have always peacefully coexisted with the Arab citizens of Israel, who enjoy more civil liberties than in any Arab country.

Yes, I think Einstein would be outraged. He never forgave Germany for what it had done to the Jews of Europe, and I don't think he would forgive Arab leaders for what they have done to the Jews of Israel.

Steven Weinberg
Department of Physics
University of Texas at Austin

I applaud your celebration of Einstein. He was truly a genius of the first order. Unfortunately, I feel it was diminished by your comments in SA Perspectives. The editors "speculate that Einstein … would have opposed his adoptive nation's foray into Iraq." I disagree. First, how could you divine the opinion of a man 50 years dead, even if he was well known for opinions on war? He was also outspoken against genocide during the Holocaust. Saddam didn't kill as many people as Hitler, but he is a mass murderer. May this have led to a more nuanced position by Einstein?

If you feel the war was wrong, that's your privilege. But don't attach your

opinion as a postscript to humankind's greatest thinker.

Kris Stone
Fresno, Calif.

THE EDITORS REPLY: We think that Einstein might have found reasons for outrage on both sides of the Arab-Israeli conflict; poor phrasing made it seem we were siding against Israel when we were not. Some readers seem unclear about the meaning of "speculate." They are welcome to disagree with our guess. Whatever Einstein's views on these topics would have been, our point was that history suggests he would have been outspoken.

Regarding Einstein, you write: "It's only natural that a man who showed how to bend space and stretch time should become a titan of science. Yet Einstein also attained a wider renown than many of his equally brilliant peers in physics.... Surely the reason is that the public had feelings for him beyond admiration."

You suggest that there were many "Einsteins," but only one acquired the exceptional admiration and renown that we all abundantly bestow on him. Closer is the description that should be added to the editors' words above: ... *and* that he discovered $E = mc^2$.

Alex Blum
Bar-Ilan University
Ramat-Gan, Israel

ALBERT AND ISAAC

Alan Lightman in "Einstein and Newton: Genius Compared," makes the provocative statement that nobody before Newton can be compared with Einstein.

What about Euclid and Archimedes? The indispensable achievements of scientists of antiquity are often overlooked. Although Euclid was a mathematician, his work comprises one of the first attempts to describe the fundamental principles of nature through mathematics, and every physicist owes him a debt. Enormously influential, Euclid's *Elements* was a standard into the 19th century, and proofs today still use the forms he established. As for Archimedes, he is one of the towering figures in mathematics and engineering; his work on statics and hydrostatics is the foundation of both. Whereas some of his best work had little impact because it was so far ahead of its time, other writings of his influenced scientists for centuries.

No historian of science should overlook either of these men just because they lived so long ago.

Gillian Bradshaw
Coventry, England

LIGHTMAN REPLIES: Bradshaw writes that I had claimed that no person before Newton had the scientific accomplishments of Einstein. I did not state that claim in categorical language but only suggested it, using the word "might." I agree that Archimedes and Euclid were powerful thinkers. It would be hard for anyone to argue convincingly that Einstein's accomplishments were more or less than their achievements. What is important is that we must reach through the centuries for any comparison to Einstein.

EINSTEIN AND NEWTON: On whose shoulders do they stand?

UNTANGLING STRING THEORY

As a nonscientist, the very idea of string theory makes my heart sink, and articles about it usually leave me more confused than before I started. So congratulations to Raphael Bousso and Joseph Polchinski for writing "The String Theory Landscape," a clear and enlightening piece on this abstruse topic.

Richard Tagart
Antwerp, Belgium

Reading the string theory article brought to mind some questions concerning the formation of bubble universes: What will happen if a new bubble, with different physical laws, starts to form in a neighboring galaxy? Will we see it? What will it look like? Will it engulf us?

Karl Dahlke
Troy, Mich.

BOUSSO AND POLCHINSKI REPLY: The formation of a new bubble releases an enormous amount of energy, which goes into growing and accelerating the bubble wall. For this reason, the wall moves nearly at the speed of light. Barely a moment after we first catch sight of the bubble, it will already have engulfed us.

This is a catastrophic event. The particles we know will decay, along with all memory devices made from them.

The good news is that this apocalypse is unlikely to occur soon, even by astronomical standards.

ERRATA On page 48 of the timeline in "The Patent Clerk's Legacy," by Gary Stix, the caption for the year 1931 misidentified the man standing to the right of Albert Einstein as Edwin Hubble. He is Robert Millikan.

The first sentence of the letter from William Donelson of Wimbledon, London was incorrectly edited to read, "Whereas emissions of *carbon monoxide* will drop in a hydrogen economy...." The writer stated that emissions of *carbon dioxide* would drop. We very much regret the error.

In "Everyday Einstein," by Philip Yam, it was stated that the gravitational pull on GPS satellites is one quarter the attraction they would experience on Earth's surface. The statement should have referred explicitly to gravitational potential, which varies linearly with the inverse of the distance (and is used to calculate time-dilation corrections). In a GPS orbit, gravitational force—which varies with the inverse square of the distance—is $^1/_{16}$ of that on the ground.

HULTON-DEUTSCH COLLECTION/CORBIS (*left*); BETTMANN/CORBIS (*right*)

50, 100 & 150 Years Ago

FROM SCIENTIFIC AMERICAN

Personality Clash ▪ War Worries ▪ Heavenly Revolutions

JANUARY 1955

UNSOCIAL SCIENTISTS—"Are the social traits that characterize so many scientists to be regarded as defects of personality bordering on the abnormal? The answer is no. Mental or emotional breakdowns were no more common among scientists than among nonscientists in our gifted sample of the population. At any rate, in our gifted group the physical scientists and engineers are at the opposite pole from the businessmen and lawyers in abilities, in occupational interests and in social behavior. These basic personality differences may well account for much of the current friction between scientists and the government officials who are responsible for their security clearances and for the restrictions imposed upon them."

DOWN WITH LOVE—"In a study of 1,297 telephone operators, researchers found that the typical ill operator was a married woman, widow or divorcee who had hoped to be a housewife and mother. Deprived of her husband's support by death, desertion or incompatibility, she had been forced to continue working, often while rearing small children. The healthiest operators, on the other hand, tended to be single women with little drive toward marriage and whose ambitions did not go much beyond the modest satisfactions of their jobs."

HELICOPTERS—"The helicopter's versatility and uses are formidable and growing, but none of them yet adds up to mass transportation. The helicopter's future assuredly rests on its unique property of being able to take off from the center of a crowded city, overleap the traffic jams of surface travel and land in an equally crowded center. It can do this with good speed and superlative safety. Sabena Airlines recently demonstrated that a helicopter cruising at only 75 miles per hour could get passengers from downtown Brussels to London more quickly than a 250-mile-per-hour airliner whose passengers had to taxi to and from the airports."

JANUARY 1905

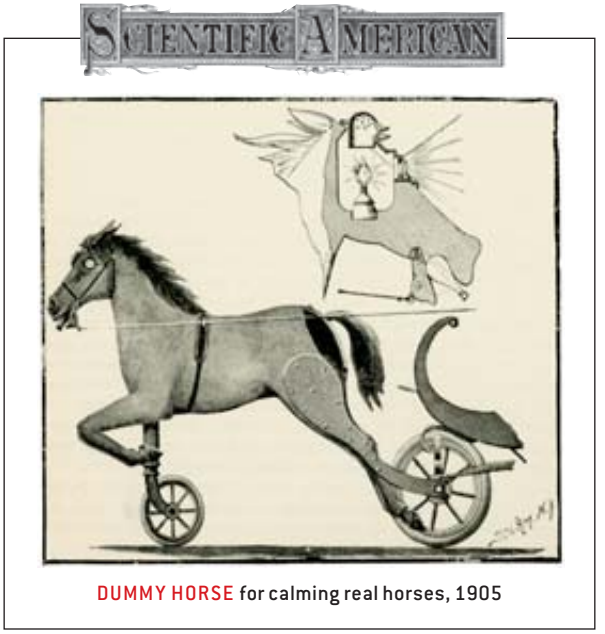
HORSE NERVES—"A resident of Canada proposes to humor the skittish horse by attaching life-size dummy horses in front of automobiles [*see illustration*], so that they will present the appearance of horse-drawn vehicles. Aside from its office of deceiving timid and high-strung horses, the head of the horse carries a search light for use at night [*see inset in illustration*], and in its mouth the animal carries an automobile horn."

RUSSO-JAPANESE WAR—"Most sincerely does the SCIENTIFIC AMERICAN regret the fact, as disclosed by the present war, that the refinements of science, instead of mitigating, as we had many of us fondly hoped they would, the horrors of war, have multiplied them. The dream of the philanthropist that science had made modern warfare so shocking and terrifying as to render its continuance impossible, fades pitifully away in the presence of that awful panorama at Port Arthur, where the bodies of brave men lie rotting by the thousand on the snow-covered slopes of the fortifications, truce for burial being deemed incompatible with the exigencies of successful warfare."

JANUARY 1855

COMETARY ORBITS—"The orbits of all the planets, and probably of nearly every comet, are ellipses, having the sun in one of their foci. No attracting body can exist in the upper focus of the orbit of any comet which is known to be periodical, it being impossible for a body to remain motionless at such a point. The nearest fixed star whose distance has been ascertained, *Alpha Centauri,* is more than two hundred thousand radii of the earth's orbit from the sun. It requires light, moving continually at the rate of 192,000 miles per second, above 3 1/4 years to traverse this interval. How long then would it require a comet to complete the double tour? That comets do not reach our system from the regions of the fixed stars is quite evident."

BAD HAIR ROOM—"Hair used in plaster for new houses is, very frequently, so dirty as to emit unpleasant effluvia, which is quite sickening, and calculated to keep a room unhealthy for years afterwards. Hair used for mixing in mortar should be thoroughly washed—re-washed, and dried, and thus deprived of the putrid matter that often adheres to it. The lime in mortar is not sufficient to cleanse the hair. It will generate an unpleasant sickly effluvia whenever the room is heated."



DUMMY HORSE for calming real horses, 1905

PUBLIC HEALTH

Polio Postponed

POLITICS SLOW POLIO'S ERADICATION—AND CAUSE IT TO SPREAD **BY CHRISTINE SOARES**

The celebration started January 15, 2004, when health ministers of the last six countries where the poliovirus still circulated—Afghanistan, India, Pakistan, Egypt, Nigeria and Niger—gathered in Geneva to commence a very public countdown. After 15 years and some $3 billion, the Global Polio Eradication Initiative was going to halt all transmission of the "wild" virus by the end of the year and thereafter consign polio to the same fate as smallpox, declared officially banished in 1980.

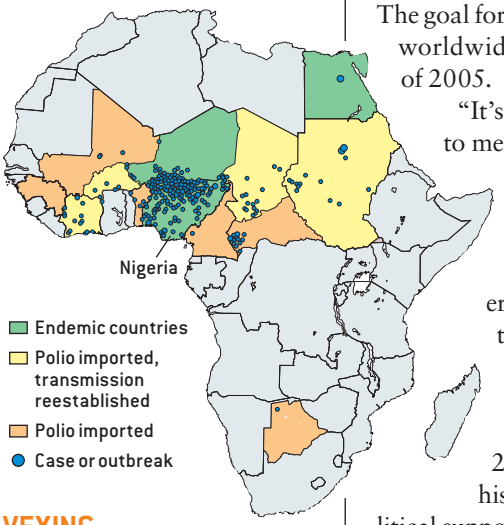
MOBILE IMMUNIZATION TEAM in northern Nigeria carries insulated boxes of oral polio vaccine during a mass-vaccination campaign in early October.

UNICEF/HQ04-0733/MUDI YAHAYA

Unfortunately, polio has proved to be a much trickier disease, and the world is a different place than it was in the 1970s. Rather than having been eliminated, polio is now present in 10 countries. The polio program has succeeded in many difficult areas, says University of Pittsburgh professor D. A. Henderson, who led the smallpox eradication program and guided polio eradication in the Americas. "But at this time they're running into some very heavy weather," he warns.

Polio's perfect storm started in the summer of 2003 in northern Nigeria. In the Kano state, politicians and clerics claimed that the polio vaccine was a "Western" ploy, tainted with HIV or with hormones meant to render Muslim women infertile. The resulting resistance to the eradication program led to immunizations being suspended for 11 months. By the summer of 2004, outbreaks in Nigeria had spread to 10 surrounding nations that had been polio-free for years, leaving nearly 700 children paralyzed and reestablishing polio in four countries.

A massive mop-up campaign began in October, involving one million volunteers in 23 African countries attempting to vaccinate 80 million children by year's end. The unexpected setback cost the cash-strapped eradication program an additional $100 million.



WILD POLIO was exported to 10 polio-free countries from Nigeria in 2004.

VEXING VACCINE

Wild poliovirus is present in India, Pakistan, Afghanistan, Nigeria, Niger, Egypt, Ivory Coast, Burkina Faso, Chad and Sudan. These nations hope to eliminate the disease by the end of 2005. The World Health Organization will wait three years before certifying that wild virus is no longer circulating in the world. Then the agency faces another hurdle: banning further use of the oral polio vaccine (OPV) and destroying any remaining stockpiles. The live virus in OPV can mutate back into pathogenic form, and at least four polio outbreaks have been attributed to the vaccine itself. The Global Polio Eradication Initiative does not want to eradicate polio only to combat vaccine-derived outbreaks.

The goal for ending wild-virus transmission worldwide has now slipped to the end of 2005.

"It's certainly biologically feasible" to meet the new target date, says David L. Heymann of the World Health Organization. Since Heymann took over the polio program in mid-2003, the veteran epidemiologist has observed that political will is the real wild card [see "A Strategy of Containment," by Christine Soares; SCIENTIFIC AMERICAN, March 2004]. So he has spent much of his tenure traveling to drum up political support for polio eradication.

One of Heymann's first big accomplishments was gaining an endorsement from the Organization of the Islamic Conference (OIC), a confederation of 56 Muslim nations. Polio has hit the group hard: five of the six original endemic countries and two where wild virus was reestablished are members. Malaysia and the United Arab Emirates, both in the OIC, each made $1-million contributions to the eradication program last year. The organization's support also softened opposition in Nigeria. By last spring, Kano officials agreed to resume vaccinations but made a show of purchasing the vaccine from Muslim Indonesia, and sending it to India to be safety-tested. (Ironically, India, where polio is still endemic, has yet to resolve two past incidents of locally manufactured vaccine being contaminated—either accidentally or intentionally—by a virulent wild strain of the poliovirus.)

Meeting an end-of-2005 target in Africa will require a "heroic effort," according to Henderson. The 13 African countries where outbreaks occurred last year cover an area bigger than the 48 contiguous states and have a population of some 300 million people. Because polio only causes a detectable "acute flaccid paralysis" in one of every 200 victims, it is much harder to ferret out than smallpox, Henderson adds, and 800 documented cases in Africa mean that 160,000 people were probably infected.

India, Pakistan and Afghanistan are in far better shape. By early November, India had detected only 81 cases. According to Heymann, all three Asian countries should "finish up" efforts to halt wild-virus transmission early in 2005. Doing the same in Africa by the end of the year is essential, he says: "If countries don't do it now, it won't happen. This is the best chance we'll ever have."

The polio program's tribulations may already have dampened enthusiasm for the concept of total disease eradication. Measles was supposed to be next, but measles fighters are only "talking about mortality reduction and catch-up" these days, Heymann remarks.

"There's been an undue emphasis on the idea that we're going to eradicate things," Henderson says, despite his own successes against smallpox and polio. Noting tremendous progress in controlling childhood diseases, such as neonatal tetanus and rubella, Henderson thinks that if nothing else, "the polio program has served to show countries what could be done with large-scale immunization, when you mobilize a whole community to act."

CARLI MORGENSTEIN

SPACE

A Bad Fix for Hubble?

ROBOTIC REPAIR MAY BE RISKIER THAN FIRST THOUGHT **BY STEVEN ASHLEY**

The decision to repair the Hubble Space Telescope with robotics technology seemed a natural given the safety concerns raised by the crash of the space shuttle *Columbia* in 2003. That way the observatory prized by scientists and admired by the public could function for at least five more years with upgraded sensors. And all the experience gained by using teleoperated manipulators would form the basis of future semiautonomous servicing operations in space. Now, however, independent analyses have cast fresh doubts on whether a robotic mission can reliably save Hubble.

According to the original scheme, spacewalking astronauts would have replaced failing batteries, gyroscopes and fine-guidance sensors. In addition, new scientific instruments—including a wide-field camera and a spectrograph—would have boosted Hubble's observational ability by a factor of 10 or more.

But after the *Columbia* disaster, NASA scaled back its shuttle plans. Unlike flights to the International Space Station, a mission to Hubble provides no repair depot and safe haven for the shuttle and its crew in an emergency. In its stead, the space agency contemplated unmanned rescue efforts.

Various technical obstacles confront an unmanned mission, explains Preston Burch, program manager for the NASA Goddard Space Flight Center. One, the self-guided orbital repair module will have to "rendezvous and soft-dock" with Hubble without any assistance from the telescope or ground staff. (Previous automated dockings have been little more than "controlled crashes.") He notes that these advanced maneuvers will be demonstrated in the near future by a trio of NASA and Defense Department spacecraft. Two, the robot arms will have to unfasten several types of latches, connect cables, and exchange a variety of fragile devices, often in tight spaces. The dual robotic manipulator arms, fitted with tiny video cameras and precision positioning sensors, must accomplish the work mostly autonomously with only limited supervision from earthbound operators. (Because of the distance and other factors, communications face a delay of a few seconds.)

MANHANDLED: The Hubble Space Telescope is brought into the space shuttle's cargo bay by its teleoperated arm during the 1999 servicing mission.

Nevertheless, detailed analysis and laboratory tests of key procedures with full-scale facsimile hardware give the Goddard staff and their contractors a good deal of confidence. Clever workarounds should ease matters considerably as well. Engineers, for example, would place the otherwise difficult-to-install gyroscopes inside the wide-field camera, which is to be attached to the internal telescope structure from the outside. Robotic repair "will be very slow—maybe 10 times slower than by the astronauts, but it's definitely doable," Burch says.

A National Research Council committee, led by Louis J. Lanzerotti of Bell Laboratories and the New Jersey Institute of Technology, does not seem so sure, however. In an interim study report, the panel stated: "The proposed Hubble robotic servicing mission involves a level of complexity, sophistication, and technology maturity that requires significant development, integration, and demonstration to reach flight readiness." The committee warned that the proposed unmanned mission is essentially an experiment that is expected to accomplish difficult real-world objectives and that relying on untested procedures is risky. It urged NASA to "take no actions that would preclude a space shuttle servicing mission." Not exactly a ringing endorsement.

The Aerospace Corporation, a nonprofit private research, development and advisory organization headquartered in El Segundo, Calif., is also skeptical. According to those who have seen its confidential assessment, the study concludes that the probability of success of a robotic mission attempting only minimal goals (extending Hubble's life) is 58 percent. Worse, the odds are one in three for a more ambitious automated effort to install a "deorbit module" (a rocket motor to control reentry) and to upgrade scientific instruments. These odds are less than those of a manned shuttle mission, which offers a 63 percent chance of success, say sources who asked to remain unidentified.

Then there is the issue of cost. Burch says NASA's "conservative" estimate for a robotic mission is $1.3 billion, whereas in-

WHY NOT LET HUBBLE DIE?

A refurbished Hubble Space Telescope has much yet to contribute. The new instruments that are to be installed, including the Wide Field Camera 3 and the Cosmic Origins Spectrograph, "are at least an order of magnitude more powerful than their predecessors in orbit," declares astronomer Garth Illingworth of the University of California's Lick Observatory.

"If serviced, Hubble could do unique and pioneering observations on nearly everything from planets circling nearby stars to the most distant and enigmatic gamma-ray burst objects to the unknown dark energy," states John Bahcall of the Institute for Advanced Study in Princeton, N.J. "If successful, the best days of Hubble are in the future because we have learned how to use it so well."

NASA/STScI

formants indicate that the Aerospace analysis pegs it at about $2 billion. The latter also reportedly set the price tag of a shuttle servicing flight at around the same amount.

Finally, the estimates of the time necessary to build the required technologies are said to differ. The Goddard team thinks they can be ready by late 2007, whereas the Aerospace group estimates completion in 2010—a severe hitch because Hubble's current main batteries are likely to fail by 2009, placing the observatory permanently out of action.

As an alternative to robotic repair, the Aerospace evaluation considered orbiting a new vehicle containing the improved observational instruments. Many observers, however, deem this $2-billion "rehosting" option unrealistic because of the long delay until the spacecraft could be constructed. NASA has slated the launch of Hubble's replacement, the James Webb Space Telescope, for 2011.

Given the pessimism surrounding robotic rescue, NASA may have to opt for what many scientists and astronauts favor—a return to "plan A." Servicing Hubble with humans is uncertain, but that seems to be a risk astronauts are willing to take. "Frankly, we use robotics whenever we can," says Apollo astronaut Walter Cunningham, who drafted a petition, endorsed by 26 former astronauts, supporting the restoration of the shuttle effort. "But very few people feel that robotics are sophisticated enough to do what the shuttle servicing mission would accomplish."

FISHERIES

Sound Findings

SONAR OFFERS A WAY TO COUNT SALMON ACCURATELY

BY DAVID KOSUB

The debate is as fierce and perennial as the surf pounding the Alaska coastline. On one side, commercial and sports fishermen complain that calculated fishing quotas do not match the number of fish actually in the water. On the other, conservation authorities worry that overfishing will deplete the sockeye and chinook salmon stocks plying the Pacific Northwest waters. New techniques using existing acoustic sonar equipment may help both sides by determining how many salmon are in the water as well as distinguishing one species from the other. And that could make counting and catching them a lot easier.

In sonar setups such as fish finders, pulses of sound bounce off the water's bottom—and off any creatures that happen to swim by. Typically devices record the strength of the return echo, thereby indicating the rough numbers of fish and their sizes.

Echo pulses have other characteristics, too, such as width, shape and kurtosis (the size of the pulse's top half relative to that of the bottom half). Sci-

SALMON SPOTTING relied on a collection of four sonar transducers mounted on a plate; each one generates a particular frequency (70, 120, 200 and 400 kilohertz, from the largest to the smallest transducer).

COURTESY OF DEBBY BURWEN

entists have largely ignored these features, because they believed that background noises obscure whatever information they may contain.

Some investigators decided to challenge that belief. This past summer researchers at Fisheries and Oceans Canada and the U.S. National Marine Fisheries Service in Alaska mounted four acoustic transducers on a metal plate beside Alaska's Kenai River. The transducers then fired simultaneous sound waves, each at different frequencies, at approximately 40 chinook and sockeye salmon tethered to the river bottom with fishing line.

"We've learned," says physicist Tim Mulligan with Fisheries and Oceans Canada, "that, indeed, the fish's shape" and its positioning measurably alter the return echo, a finding "that wasn't really documented until now." For instance, the degree to which a salmon's head and tail point toward the transducer correlates strongly with the width of the echo pulse; other changes in the returning echo, including the kurtosis, also indicate the orientation of the fish. The next step will be to correlate echo components with other fish features, such as tail strength and swim speed, and to determine how those sonar characteristics vary according to species. Nailing down the differences between sockeye and chinook salmon could take years, however.

Mulligan insists the significance of the correlation between fish swimming behavior and long-ignored echo characteristics cannot be overstated. It "opens many more opportunities for fish-type discrimination based on behavior," he says. Alaska's Kenai River Sportfishing Association, which helped to finance the project, evidently agrees. Its hope: that conservation officials will have more accurate assessments of the yearly salmon runs up the Kenai and other rivers and be able to identify fish by species before netting or reeling them in. That could settle disputes between officials and fishers over just how much salmon can be harvested.

David Kosub is based in Victoria, B.C.

PHYSICS

A Glimpse of Supersolid

SOLID HELIUM CAN BEHAVE LIKE A SUPERFLUID **BY GRAHAM P. COLLINS**

Solids and liquids could hardly seem more different, one maintaining a rigid shape and the other flowing to fit the contours of whatever contains it. And of all the things that slosh and pour, superfluids seem to capture the quintessence of the liquid state—running through tiny channels with no resistance and even dribbling uphill to escape from a bowl.

A superfluid solid sounds like an oxymoron, but it is precisely what researchers at Pennsylvania State University have recently witnessed. Physicists Moses Chan and Eun-Seong Kim saw the behavior in helium 4 that was compressed into solidity and chilled to near absolute zero. Although the supersolid behavior had been suggested as a theoretical possibility as long ago as 1969, its demonstration poses deep mysteries.

Rotation is one way that superfluids reveal their peculiar properties. Take a bucket of ordinary liquid helium and rotate it slowly, then cool it down to about two kelvins, so that some of the helium becomes superfluid. The superfluid fraction will not rotate. Because part of the helium is motionless, the amount of force required to set the bucket and helium rotating is less than it would be otherwise. Technically, the helium's rotational inertia decreases.

Chan and Kim observed such a decrease of rotational inertia in a ring of solid helium. They applied about 26 atmospheres of pressure to liquid helium, forcing the atoms to lock in place and thereby form a fixed lattice. They observed the oscillations of the helium as it twisted back and forth on the end of a metal rod. The period of these torsional oscillations depended on the rotational inertia of the helium; the oscillations occurred more rapidly when the inertia went down, just as if the mass of the helium decreased. Amazingly, they found that about 1 percent of the helium ring remained motionless while the other 99 percent continued rotating as normal. One solid could somehow move effortlessly through another.

So how can a solid behave like a superfluid? All bulk liquid superfluids are caused by Bose-Einstein condensation, which is the quantum process whereby a large number of particles all enter the same quantum state. Chan and Kim's result therefore suggests that 1 percent of the atoms in the solid helium somehow form a Bose-Einstein condensate even while they remain at fixed lattice positions. That seems like a contradiction in terms, but the exchange of atoms between lattice sites might allow it. A characteristic of helium would tend to promote such an exchange—namely, its large zero-point motion, which is the inherent jiggling of atoms that represents a minimum amount of movement required by quantum uncertainty. (It is the reason helium ordinarily only occurs as a gas or a liquid: the extremely lightweight atoms jiggle about too much to form a solid.) Supporting the idea of condensation, the two researchers did not see superfluidity in solid helium 3, an isotope of helium that as a liquid undergoes a kind of condensation and becomes superfluid only at temperatures far below that needed by liquid helium 4.

Another possibility is that the crystal of helium contains numerous defects and lattice vacancies (yet another effect of the zero-point motion). These defects and vacancies

SUPERSOLID HELIUM partly rotates and partly stays still as its suspended aluminum-shelled container rotates.

JOHN PASSANEAU, COURTESY OF MOSES CHEN, *Pennsylvania State University* (*top*); LUCY READING (*bottom*)

THE IMPORTANCE OF BEING PURE

Pennsylvania State University physicists Moses Chan and Eun-Seong Kim recently succeeded in creating a solid that acts like a superfluid. They used helium 4 (the original superfluid, which goes "super" when the liquid is cooled below 2.17 kelvins) that was extremely pure. It contained no more than 0.3 part per million of helium's other isotope, helium 3 (which goes super in a more complicated fashion at the much chillier temperature of two millikelvins).

In a previous experiment, using helium embedded in the nanoscopic interstices of porous glass, the two physicists observed evidence of supersolidity, but only in samples containing less than 0.01 percent helium 3. The results suggest why previous efforts to observe supersolid helium failed—insufficiently pure helium.

could be what, in effect, undergo Bose-Einstein condensation.

But all those theories seem to imply that the superfluidity would vary with the pressure, yet Chan and Kim see roughly the same effect all the way from 26 to 66 atmospheres. Douglas D. Osheroff of Stanford University, the co-discoverer of superfluidity in helium 3, calls the lack of pressure dependence "more than a bit bewildering." He says that Chan and Kim have done "all the obvious experiments to search for some artifact." If they are correct, Osheroff adds, then "I don't understand how supersolids become super. I hope the theorists are thinking about it seriously."

ASTRONOMY

Through Titan's Haze

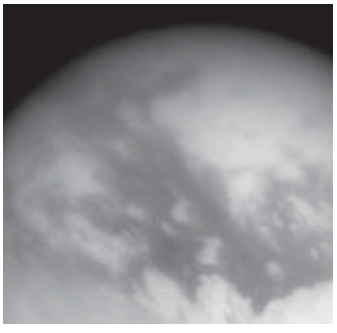
SATURN MOON HAS A SURFACE THAT IS DYNAMIC—AND PUZZLING BY CHARLES Q. CHOI

After taking spectacular close-ups of Saturn and its rings, the Cassini spacecraft turned its attention to Titan, Saturn's largest moon. Using imaging radar, the spacecraft peered through Titan's smog blanket—its thick orange atmosphere, consisting primarily of nitrogen and trace amounts of at least a dozen kinds of organic compounds, extends hundreds of kilometers above the surface. Making its closest approach of 1,200 kilometers on October 26, Cassini was able to resolve features down to 300 meters across while traveling at 21,800 kilometers per hour. It mapped roughly 1 percent of a satellite world larger than either Mercury or Pluto.

The images returned so far have astonished scientists. Cassini has not detected any signs of the long-predicted gasolinelike seas of methane, propane or butane that are speculated to be as much as three kilometers deep. But investigators were quick to point out that the data did not preclude their existence, either. Perhaps more surprising, Cassini found hardly any evidence of impact craters. The lack of craters suggests that Titan, made of equal parts water ice and rocky matter, is continuously reshaping itself.

Indeed, one strikingly bright feature looks very much like something oozed across the freezing (–178 degrees Celsius) surface—perhaps icy "lava" spewed by a "cryovolcano." Elsewhere, streaks on the surface could be flowing liquid hydrocarbons, a moving ice sheet like a glacier, or matter blown over the ground by wind. Another region resembling a feline's head, dubbed "the Halloween cat," might be a lake, judging by its relative smoothness. On Christmas Eve, Cassini was to have deployed the European Space Agency's piggybacked Huygens probe to streak through the moon's atmosphere for a better look. If all goes well, it will land—or splash down—on Titan on January 14.

ICY "LAVA" is one explanation for the "oozing" seen on the surface of Titan. This artist rendition is based on Cassini data, such as the image showing surface material streaking across the moon (*right*).



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

RON MILLER (*top*); NASA/JPL/SSCI (*bottom*)

ECOLOGY

Snaking Its Way In

FEARED SNAKEHEAD FISH SETS UP HOUSE IN THE U.S. **BY AIMEE CUNNINGHAM**

Few invasive species play their threatening parts with as much panache as the northern snakehead. With its toothy mug, scaly head, predatory nature and decidedly unfishlike need to breathe air, this interloper from the waters of eastern Asia made headlines as "Frankenfish" when it was discovered in a Maryland pond in 2002. Worried that a heavy rain could wash the fish into the nearby Little Patuxent River—harming native species in a large, open ecosystem—wildlife officials poisoned the pond, killing a population of some 1,300 northern snakeheads that most likely began with a local resident's release of a few fish. Having launched a public education campaign on the dangers of freeing nonnative species in the wild, officials hoped the snakehead was gone for good.

FUTILE FIGHT? Battle against snakeheads in Pine Lake in Wheaton, Md., began in April with temporary removal of native fish before lake drainage (*top*). But adults later turned up in the Potomac River (*bottom*).

MATT HOUSTON AP Photo

Two years later they got a troubling answer: the fish, *Channa argus,* turned up in the waters of the Potomac River, the result of one or perhaps multiple releases along its shores. In May an angler caught a female in a Virginia tributary, and as the summer progressed, the river's tally rose to 19. The biggest blow came September 29, when a juvenile northern snakehead fell out of the aquatic weeds tangled around a boat trailer that was pulled from Virginia's Dogue Creek, another tributary. The result of a midsummer spawn, the juvenile points to a reproducing population in a waterway with tens of thousands of acres of habitat. "This time you can't get rid of them," says Walter Courtenay, Jr., a U.S. Geological Survey research fishery biologist.

No clear control measures exist. Because anglers have caught most of the Potomac snakeheads, wildlife officials are bringing the fishing community onboard in their removal efforts. It is not known, however, if fishing will make a significant difference. Traditional sampling techniques, using special nets or electric current to stun fish, do not work well in the shallow, heavily vegetated areas that northern snakeheads prefer. "Prevention was everything," explains Steve Minkkinen, a fisheries biologist with the U.S. Fish and Wildlife Service. "Once they get out there, it can be very difficult."

Officials will keep sampling the river and educating the public, but "it's going to take time to see what happens," Courtenay says. Based on the precedent set by other nonnative species, the outcome is not promising. The European green crab, another predatory invader with a taste for native clams and crabs, caused a five- to 10-fold decrease in their populations three years after arriving in Bodega Bay Harbor, Calif. Nor is the northern snakehead very likely to remain an East Coast problem: in October an angler caught an adult in Burnham Harbor in Lake Michigan. "The problem is, it only takes one person" to let an invasive species loose, says Steve Early, a biologist in the Maryland Fisheries Service. "People just don't recognize the consequences."

PROBLEM FOR THE POTOMAC

No one can say for sure how a growing population of northern snakeheads, with no natural predators, will affect the Potomac River. "We really have nothing on which to base an opinion," says Becky Wajda, assistant division director with the Virginia Department of Game and Inland Fisheries. The fish have yet to establish long-standing U.S. populations, and little is known about the species, such as what keeps it in check in its native waters. Most worrisome is the invader's probable effect on the area's prized largemouth bass population, because it will compete for the same food and habitat.

DATA POINTS: CLEARING THE AIR

In maintaining clean rooms, engineers try to keep out particles 0.5 micron and larger. A key device is the high-efficiency particulate air (HEPA) filter, which traps at least 99.97 percent of particulates 0.3 micron wide. (It does even better with bigger particulates.) Other measures, however, must be included, because additional particulates are constantly being created—walking, for instance, generates about five million of them per minute. For ultralow penetration air (ULPA) filters, the target is 0.12 micron with 99.999 percent efficiency.

Number of particles less than 0.5 micron wide suspended in a cubic foot of air in:

Office building: 500,000 to 1 million

Room in a U.S. home: 350,000

Hospital operating room: 1,000 to 10,000

NASA clean room: 100

Computer-chipmaking clean room: 10 to 1,000

Biohazard Level 4 lab: 10

Typical size, in microns:

Bacterium: 1 to 10

Virus: 0.02 to 0.45

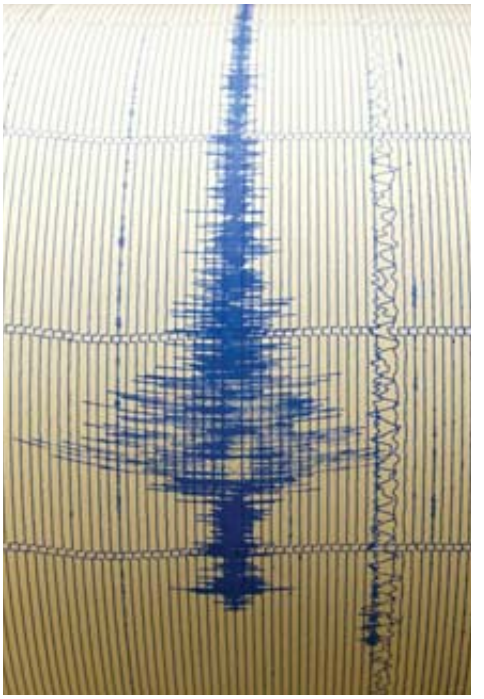
Compiled by Barry E. DiGregorio

SOURCES: NASA; Coastwide Laboratories; The Quarantine and Certification of Martian Samples *(National Academies Press, 2002); Wikipedia.org, orders of magnitude (length)*

GEOPHYSICS

Shaky Gravity Boost

Earthquakes jostle matter within the crust, thereby modifying local gravity. But because of imprecise, unstable instruments, scientists could monitor these changes only with the aid of long records before and after quakes. Japanese investigators have devised a much quicker method. They monitored how superconducting balls respond to gravity while trapped floating in ultrastable magnetic fields generated by superconducting coils. After accounting for the separate pulls of the sun, moon, air, ocean and the earth's rotation, the researchers detected a permanent increase in gravity roughly a half billionth that of the earth's pull southeast off the coast of Hokkaido, the epicenter of the magnitude 8 Tokachi-oki quake in 2003. The results, in the October 15 *Science,* agree with theoretical predictions, suggesting that superconducting gravimeters can help satellites chart the earth's gravity to map changes in polar ice cap thickness, seawater levels, atmospheric density and planetary geology. —*Charles Q. Choi*



TREMORS can modify the local gravitational force.

HEALTH

Mercurial Spread

A neurotoxic poison, mercury is especially worrisome to developing fetuses. A nationwide study reveals that a significant number of women of child-bearing age have too much of the metal in their systems. Researchers at the University of North Carolina at Asheville based their results on hair samples from nearly 1,500 people of all ages. As hair grows, it incorporates mercury from the bloodstream. Interim results from the Greenpeace-commissioned survey released October 20 revealed that one fifth of those studied had mercury levels above the EPA recommendation of one part per million in hair. The investigators report no other pollutant has anywhere near this high a percentage of the U.S. population with exposure levels above federal standards. The biggest sources of airborne mercury are coal-fired power plants. The investigators will gather an estimated 5,000 samples or more in total and issue their final report in March. —*Charles Q. Choi*

MERCURY exposure appears far too common.

CHARLES REX ARBOGAST *AP Photo (top);* DIRK WIERSMA *Science Photo Library (bottom);* ILLUSTRATION BY MATT COLLINS

BEHAVIOR

Face Painters, Begone!

Some animals signal vitality through high-maintenance "badges of status," such as the peacock's plume, whereas others have badges that seem to impose no inherent cost to the creature, raising the question of why such individuals do not simply cheat. Researchers surmise that social punishment of liars keeps such signals truthful. Now entomologists have observed the first unequivocal evidence supporting the idea. They discovered that female paper wasps with larger, more fragmented or blotchier black markings above their mouths tend to win in clashes for dominance. When the researchers painted the wasps to give them the markings of higher or lower dominance, they found that both kinds of liars were harassed more than unpainted wasps, indicating that the wasps frown on lying per se. The investigators, who describe their work in the November 11 *Nature*, suspect that some behavioral or chemical cue gives the liars away. —*JR Minkel*

PAPER WASPS don't put up with phonies.

MEMORY

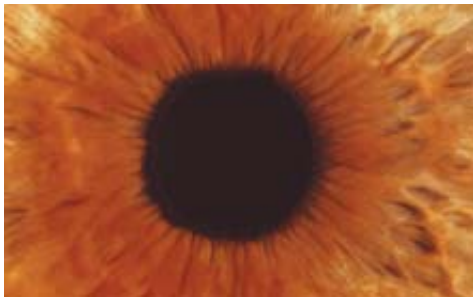
Alternative Reality

In "Just My Imagination," the Temptations sang of a vision that "couldn't be a dream, for too real it all seems." Scientists now have pinpointed how the imagination can make false memories. Volunteers lying in a magnetic resonance imaging scanner were shown a list of words and told to picture each item. For half the words, a photograph of the matching object was flashed. Afterward, volunteers listened to a random sequence of words corresponding either to photographs they saw, to objects they were only told to imagine, or to items neither seen nor imagined. When volunteers falsely remembered seeing photographs of objects they had only imagined, brain regions critical to generating images became highly activated. Mental images created by these areas leave traces in the brain that are later mistaken for objects actually perceived, suggest researchers at Northwestern University in the October *Psychological Science*. —*Charles Q. Choi*

BIOLOGY

Eyeing Stem Cells

Humans appear to have true, self-renewing retinal stem cells. Brenda Coles and her colleagues at the University of Toronto minced up eyes donated from deceased people and cultured the cells. They found that about one in 500 cells from the black ring around the iris could divide indefinitely and adopt the full variety of retinal cell types. (Past studies had found retinal stem cells of limited capacity, unable to divide indefinitely and transforming into only a few cell types.) When transplanted into embryonic mice or chicks, the stem cells turned into cells of the type found in that animal at that stage of development. Their next experiment, Coles says, is to transplant the cells into mice with degenerating retinas to see if they restore function and later to figure out how to activate and manipulate them. See the November 2 *Proceedings of the National Academy of Sciences USA*. —*JR Minkel*



IRIS could be a source for stem cells.

BRIEF POINTS

- **Rather than just an X-Y pair, the duck-billed platypus requires five chromosomal pairs to determine sex. One pair has avian similarity, suggesting that the sex-determining systems of birds and mammals may be linked.**

  Nature online, October 24, 2004; *Proceedings of the National Academy of Sciences USA*, November 16, 2004

- **Selling aspirin and acetaminophen in smaller doses reduced the suicide rate from these drugs by nearly 25 percent and the need for liver transplants from related damage by 30 percent in the U.K., where 1998 legislation cut the package sizes.**

  BMJ, November 6, 2004

- **According to rat studies, alcoholics who lay off the hooch might restore their ability to grow new neurons, a process inhibited by alcohol dependency.**

  Journal of Neuroscience, October 27, 2004

- **New evidence confirms not only the presence of methane on Mars but also larger quantities of it than previously inferred. The gas could have originated from biological processes.**

  American Astronomical Society meeting, November 11; www.sciam.com/ontheweb

E. A. TIBBETTS (*top*); DAVID PARKER *Science Photo Library* (*bottom*)

BY THE NUMBERS

Nurses in Short Supply

THE PROFESSION IS HEADING TOWARD ITS BIGGEST CRISIS **BY RODGER DOYLE**

At least since the 1990s, the U.S. has faced a growing shortage of registered nurses. According to the Department of Health and Human Services (DHHS), in 2020 the demand for nurses could exceed the supply by 40 percent if nothing is done to stop this trend. The 20th century has seen recurrent shortages, but this one is different, in part because of an unprecedented demographic squeeze. The workforce made up of those aged 20 to 35, the prime recruiting pool for nurses, will decline at the same time baby boomers begin to reach retirement and consume medical services at a faster rate. But perhaps a more important factor is the low status of nurses. At one time, low status was far less of a deterrent, but now, when virtually all professions are open to women, nursing has become a relatively unattractive career choice. Moreover, the work is physically demanding: it is so strenuous that nurses generally cannot work much beyond their mid-50s. Indeed, the top concerns of nurses are their increasing workload and long hours.

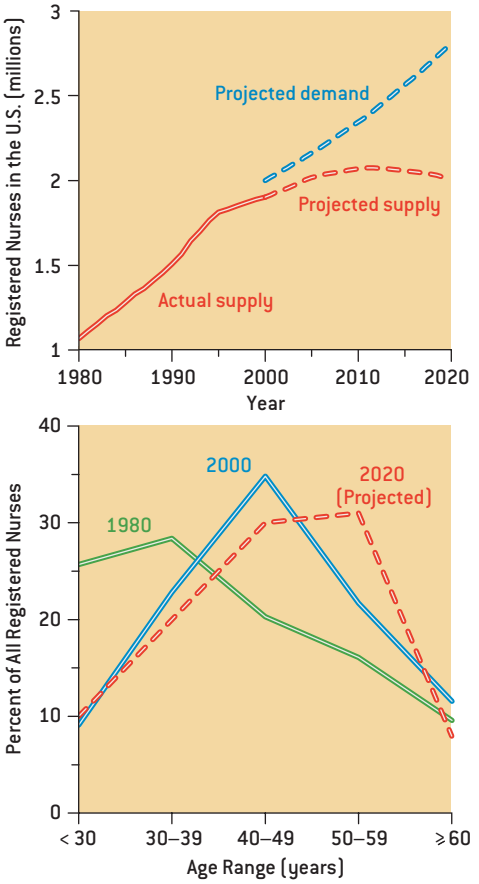
Furthermore, pay lags behind other occupations that have similar educational requirements: an elementary schoolteacher, for example, earned $14,000 more than a nurse in 2001, according to the DHHS. Registered nurses are leaving the workforce at a faster rate than ever: currently, almost 500,000 RNs do not work in nursing.

Demand for nurses is rising because of population growth, more elderly persons and medical advances that require greater skill. Health industry economics also drives demand. Since 1990, an average of 85 percent of the population have had some form of health insurance and so have been covered, at least partially, for nursing care. At the same time, real per capita disposable income has grown steadily, making it easier to pay for noncovered health care.

Nursing seems to defy the normal laws of supply and demand, given that pay has lagged at a time of higher demand. A possible explanation lies in the superior bargaining power of hospitals—the major employers of RNs—combined with the relative lack of organization of nurses. Only 38 percent of hospital nurses are unionized. Another factor affecting pay is the failure of nurses to develop a strong constituency among the general public. In contrast, schoolteachers have forged strong community bonds through local parent-teacher organizations.

Broadening the recruitment base—nurses are now 86 percent white—would help alleviate the shortage, but long-term solutions most likely will have to deal with the more fundamental nature of the field. In addition to higher wages, the key to resolving the shortage may lie in giving nurses more power over working conditions and over health care decisions now made by physicians.

Rodger Doyle can be reached at rdoyle2@adelphia.net



SOURCE: U.S. Department of Health and Human Services

FAST FACTS: WEAK WAGES

Average hourly pay of:

Registered nurse: $25.96

Physical therapist: $28.07

Dental hygienist: $29.66

Elementary schoolteacher: $31.74

Secondary schoolteacher: $31.88

SOURCE: Bureau of Labor Statistics, National Compensation Survey. Data from July 2003.

FURTHER READING

Health Care's Human Crisis: The American Nursing Shortage. Bobbi Kimball and Edward O'Neil. Robert Wood Johnson Foundation, April 2002. www.rwjf.org

Projected Supply, Demand, and Shortages of Registered Nurses: 2000–2020. National Center for Health Workforce Analysis, U.S. Department of Health and Human Services, July 2002. http://bhpr.hrsa.gov/

Changing Demographics: Implications for Physicians, Nurses, and Other Health Workers. National Center for Health Workforce Analysis, U.S. Department of Health and Human Services, Spring 2003. http://bhpr.hrsa.gov/

RODGER DOYLE

Quantum Quackery

A surprise-hit film has renewed interest in applying quantum mechanics to consciousness, spirituality and human potential By MICHAEL SHERMER

In spring 2004 I appeared on KATU TV's *AM Northwest* in Portland, Ore., with the producers of an improbably named film, *What the #$*! Do We Know?!* Artfully edited and featuring actress Marlee Matlin as a dreamy-eyed photographer trying to make sense of an apparently senseless universe, the film's central tenet is that we create our own reality through consciousness and quantum mechanics. I never imagined that such a film would succeed, but it has grossed millions.

The film's avatars are New Age scientists whose jargon-laden sound bites amount to little more than what California Institute of Technology physicist and Nobel laureate Murray Gell-Mann once described as "quantum flapdoodle." University of Oregon quantum physicist Amit Goswami, for example, says in the film: "The material world around us is nothing but possible movements of consciousness. I am choosing moment by moment my experience. Heisenberg said atoms are not things, only tendencies." Okay, Amit, I challenge you to leap out of a 20-story building and consciously choose the experience of passing safely through the ground's tendencies.

What the #$*! is going on here?

The work of Japanese researcher Masaru Emoto, author of *The Hidden Messages in Water,* is featured to show how thoughts change the structure of ice crystals—beautiful crystals form in a glass of water with the word "love" taped to it, whereas playing Elvis's "Heartbreak Hotel" causes other crystals to split in two. Would his "Burnin' Love" boil water?

The film's nadir is an interview with "Ramtha," a 35,000-year-old spirit channeled by a woman named JZ Knight. I wondered where humans spoke English with an Indian accent 35,000 years ago. Many of the films' participants are members of Ramtha's "School of Enlightenment," where New Age pabulum is dispensed in costly weekend retreats.

The attempt to link the weirdness of the quantum world to mysteries of the macro world (such as consciousness) is not new. The best candidate to connect the two comes from University of Oxford physicist Roger Penrose and physician Stuart Hameroff of the Arizona Health Sciences Center, whose theory of quantum consciousness has generated much heat but little light. Inside our neurons are tiny hollow microtubules that act like structural scaffolding. Their conjecture (and that's all it is) is that something inside the microtubules may initiate a wave-function collapse that results in the quantum coherence of atoms. The quantum coherence causes neurotransmitters to be released into the synapses between neurons, thus triggering them to fire in a uniform pattern that creates thought and consciousness. Because a wave-function collapse can come about only when an atom is "observed" (that is, affected in any way by something else), the late neuroscientist Sir John Eccles, another proponent of the idea, even suggested that "mind" may be the observer in a recursive loop from atoms to molecules to neurons to thought to consciousness to mind to atoms….

In reality, the gap between subatomic quantum effects and large-scale macro systems is too large to bridge. In his book *The Unconscious Quantum* (Prometheus Books, 1995), University of Colorado physicist Victor Stenger demonstrates that for a system to be described quantum-mechanically, its typical mass (m), speed (v) and distance (d) must be on the order of Planck's constant (h). "If mvd is much greater than h, then the system probably can be treated classically." Stenger computes that the mass of neural transmitter molecules and their speed across the distance of the synapse are about two orders of magnitude too large for quantum effects to be influential. There is no micro-macro connection. Then what the #$*! is going on here?

Physics envy. The lure of reducing complex problems to basic physical principles has dominated the philosophy of science since Descartes's failed attempt some four centuries ago to explain cognition by the actions of swirling vortices of atoms dancing their way to consciousness. Such Cartesian dreams provide a sense of certainty, but they quickly fade in the face of the complexities of biology. We should be exploring consciousness at the neural level and higher, where the arrow of causal analysis points up toward such principles as emergence and self-organization. Biology envy.

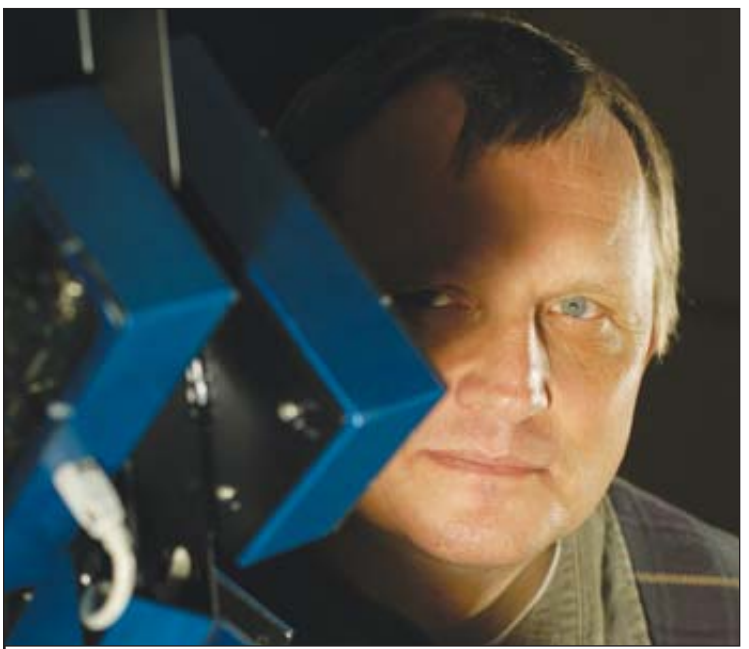
Michael Shermer is publisher of Skeptic *(www.skeptic.com) and author of* The Science of Good and Evil.

BRAD HINES

You, Robot

He says humans will download their minds into computers one day. With a new robotics firm, Hans Moravec begins the journey from warehouse drones to *robo sapiens* By CHIP WALTER

When word got around that Hans Moravec had founded an honest-to-goodness robotics firm, more than a few eyebrows were raised. Wasn't this the same Carnegie Mellon University scientist who had predicted that we would someday routinely download our minds into robots? And that exponential advances in computing power would cause the human race to invent itself out of a job as robots supplanted us as the planet's most adept and adaptive species? Somehow, creating a company seemed ... uncharacteristically pragmatic.



SCOTT GOLDSMITH

HANS MORAVEC: A FUTURE OF ROBOTS

- **Constructed his first robot at age 10 out of tin cans, batteries, a motor and lights; as a child, deeply affected by science fiction, especially the writings of A. E. van Vogt and Arthur C. Clarke.**
- **Predicts that by 2040 faster processing will enable robots to become self-aware and experience emotions.**
- **Why a robotics industry is necessary for real advances: "I've seen robotics research at universities, and it's pretty interesting, but it's primarily a lot of one-shot projects."**

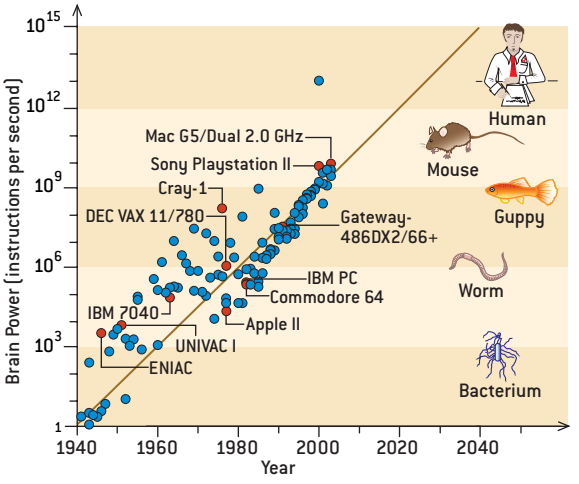
But Moravec doesn't see it that way. He says he didn't start Seegrid Corporation because he was backing off his predictions. He founded the company because he was planning to help fulfill them. "It was time," he says, slowly rubbing his hand across his bristle-short hair. "The computing power is here."

The 56-year-old Moravec should know. Born in Kautzen, Austria, and raised in Montreal, he has been pushing the envelope on robotics theory and experimentation for the past 35 years, first as the graduate student at Stanford University who created the "Stanford Cart," the first mobile robot capable of seeing and autonomously navigating the world around it (albeit very slowly), and later as a central force in Carnegie Mellon's vaunted Robotics Institute. His iconoclastic theories and inventive work in machine vision have both shocked his colleagues and jump-started research; Seegrid is just the next logical step.

Moravec pulls an image up onto one of the two massive monitors that sit side by side on his desk, like great unblinking eyes. It's six o'clock in the evening, but an inveterate night owl, he's just starting his "day." "I have been drawing these graphs for years about what will be possible," he comments. His mouse roams along dots and images that plot and compare the processing power of old top-of-the-line computers with their biological equivalents. There is the ENIAC, for example, that in 1946 possessed the processing capacity of a bacterium and then a 1990 model IBM PS/2 90 that once harnessed the digital horsepower of a worm. Only recently have desktop computers arrived that can deliver the raw processing muscle of a spider or a guppy (about one billion instructions per second). "At guppy-level intelligence," he explains, "I thought we could manage 3-D mapping and create a robot that could get around pretty well without any special preparation of its environment."

But no one was creating that robot, so in the late 1990s Moravec says he began to grow "very antsy" about getting one built. In 1998 he wrote an ambitious grant proposal that outlined software for a robotic vision system. The Defense Advanced Research Projects Agency quickly funded the proposal, and three and a half years and $970,000 later, with PCs just reaching guppy smarts, a working demonstration was complete.

"It proved the principle," Moravec says. "We really could map with stereo vision, if we did things just right." But doing things just right required more than prototype software. Robotic evolution, he adds, "has to be driven forward by a lot of trial and error, and the only way to get enough is if you have an industry where one company is trying to outdo another." To help things along, he and Pittsburgh physician and entrepreneur Scott Friedman founded Seegrid in 2003. Their focus: the unglamorous but potentially huge "product handling" market.



RAW COMPUTING MUSCLE, as exemplified by a plot of 120 top machines of their time since 1940, is today on par with the brain of a guppy. It may reach the human equivalent around 2040.

Industrial robots already flourish in tightly constrained environments such as assembly lines. Where they fail is in locations loaded with unpredictability. So Seegrid concentrated on creating vision systems that enable simple machines to move supplies around warehouses without any human direction.

Not exactly the stuff of science fiction, Moravec agrees, and a long way from superintelligent robots, but he says you have to start somewhere. Nearly everything sold has to be warehoused at some point, and at some point it also has to be rerouted and shipped. Right now human workers move millions of tons of supplies and products using dollies, pallet jacks and forklifts. Seegrid's first prototype devices automate that work, turning wheeled carts into seeing-eye machines that can be loaded and then walked through various routes to teach them how to navigate on their own. The technology is built on Moravec's bedrock belief that if robots are going to succeed, the world cannot be adapted to them; they have to adapt to the world, just like the rest of us.

Other approaches can guide robots, but they typically rely on costly, precision hardware such as laser range finders or on extravagant arrangements that prewire and preprogram the machines to move through controlled spaces. Seegrid's system uses off-the-shelf CCD cameras and simple sonar and infrared sensors. Although these components gather imprecise information, the software compensates. It statistically compares the gathered data to develop a clean, accurate 3-D map. "If the same information keeps coming up, then the program decides that it's probably really there," Moravec explains. The robot then knows to stop or roll around it. This approach is how you might make your way through a dark room with a flashlight, in which you slowly build up a mental picture of what is around.

Creating warehouse drones as a first step toward the startling robotic world Moravec foresees might seem an unlikely concession to reality. But those who know Moravec say it is no surprise: he is an unusual mix of whimsy, wild vision and rigorous pragmatism. He has been known to be so lost in thought during his daily walks to his office that he bumps into mailboxes, yet none of that eccentricity has tarnished his reputation as a first-rate engineer and programmer.

"Some of Hans's ideas are pretty outrageous," admits Raj Reddy, who as director of the Robotics Institute brought Moravec to Carnegie Mellon in 1980, "but his work has always been very practical." Seegrid co-founder Friedman says it is exactly Moravec's vision and dogged persistence that separates him from the pack: "He's a genius, *and* he works hard."

The same themes run through his view of the future of robotics. Evolution moves in tiny steps, Moravec notes, but accomplishes amazing things. Machine evolution will do the same as it incrementally nudges robots from their clumsy beginnings to the heights of human-level intelligence and mobility. "We don't need a lot of Einsteins to do this; we need a lot of engineers working diligently to make little improvements and then test them out in the marketplace," Moravec insists. And that, he says, will ultimately lead to robots becoming vastly more intelligent and adaptable than we are.

That seems to leave us only one destination: the endangered species list. "Something like 99 percent of all species go extinct," Moravec observes. Why, he asks, should we be any different? Not that he sees us being destroyed by what he calls our "mind children" exactly. "It's not going to be like *Terminator,*" he reassures. But children do often exceed the accomplishments of their parents. And in our evolutionary dotage, he is sure they will take good care of us, as parents' children often do. "They will create the perfect welfare state," he says.

At least, we hope so. SA

Chip Walter is working on his third science book, Six Traits (That Make Us Human).

LUCY READING

INITIAL ENCOUNTER with germs, or pathogens, sets off the "innate" arm of the immune system, which turns out to be more sophisticated than anyone guessed.

Immunity's Early-Warning System

By Luke A. J. O'Neill

The innate immune response constitutes the first line of defense against invading microbes and plays a role in inflammatory disease. Surprising insights into how this system operates could lead to new therapies for a host of infectious and immune-related disorders

A woman is riding an elevator when her fellow passengers start to sneeze. As she wonders what sort of sickness the other riders might be spreading, her immune system swings into action. If the bug being dispersed by the contagious sneezers is one the woman has met before, a battalion of trained immune cells—the foot soldiers of the so-called adaptive immune system—will remember the specific invader and clear it within hours. She might never realize she had been infected.

But if the virus or bacterium is one that our hapless rider has never wrestled, a different sort of immune response comes to the rescue. This "innate" immune system recognizes generic classes of molecules produced by a variety of disease-causing agents, or pathogens. When such foreign molecules are detected, the innate system triggers an inflammatory response, in which certain cells of the immune system attempt to wall off the invader and halt its spread. The activity of these cells—and of the chemicals they secrete—precipitates the redness and swelling at sites of injury and accounts for the fever, body aches and other flulike symptoms that accompany many infections.

The inflammatory assault, we now know, is initiated by Toll-like receptors (TLRs): an ancient family of proteins that mediate innate immunity in organisms from horseshoe crabs to humans. If TLRs fail, the entire immune system crashes, leaving the body wide open to infection. If they work too hard, however, they can induce disorders marked by chronic, harmful inflammation, such as arthritis, lupus and even cardiovascular disease.

Discovery of TLRs has generated an excitement among immunologists akin to that seen when Christopher Columbus returned from the New World. Scores of researchers are now setting sail to this new land, where they hope to find explanations for many still mysterious aspects of immunity, infection and disorders involving abnormal defensive activity. Study of these receptors, and of the molecular events that unfold after they encounter a pathogen, is already beginning to uncover targets for pharmaceuticals that may enhance the body's protective activity, bolster vaccines, and treat a range of devastating and potentially deadly disorders.

Cinderella Immunity

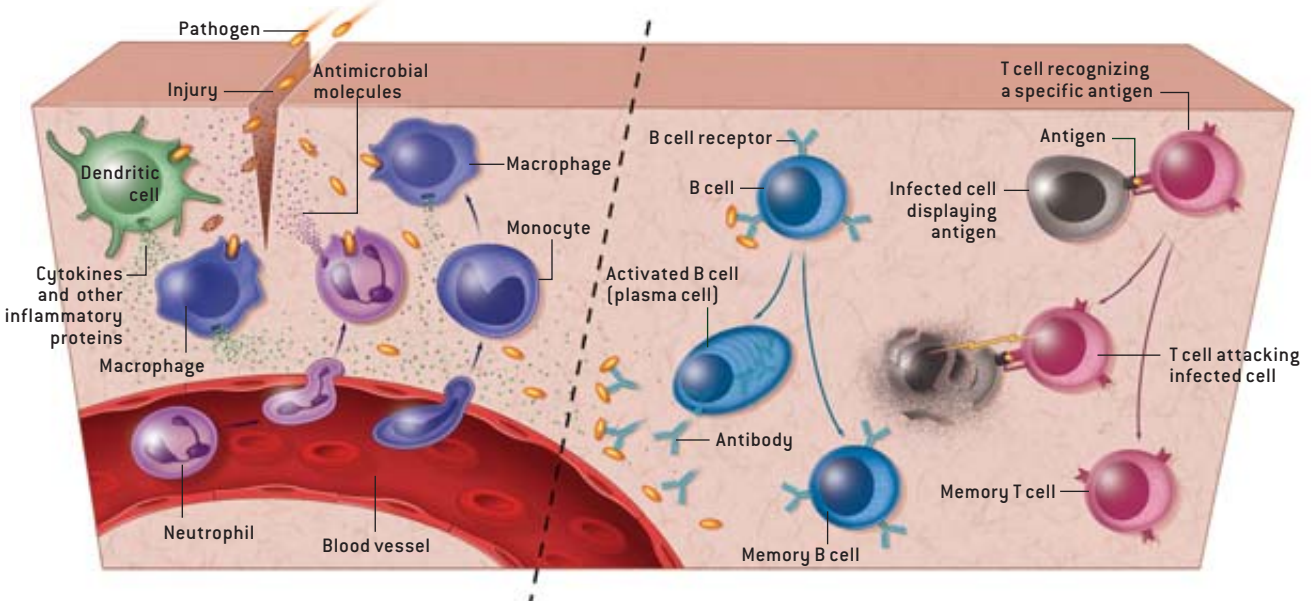
UNTIL ABOUT FIVE YEARS AGO, when it came to the immune system, the adaptive division was the star of the show. Textbooks were filled with details about B cells making antibodies that latch onto specific proteins, or antigens, on the surface of an invading pathogen and about T cells that sport receptors able to recognize fragments of proteins from pathogens. The response is called adaptive because over the course of an infection, it adjusts to optimally handle the particular microorganism responsible for the disease.

Adaptive immunity also grabbed the spotlight because it endows the immune system with memory. Once an infection has been eliminated, the specially trained B and T cells stick around, priming the body to ward off subsequent attacks. This ability to remember past infections allows vaccines to protect us from diseases caused by viruses or bacteria. Vac-

JAMES SALZANO

THE DIVISIONS OF THE IMMUNE SYSTEM

The mammalian immune system has two overarching divisions. The innate part (*left side*) acts near entry points into the body and is always at the ready. If it fails to contain a pathogen, the adaptive division (*right side*) kicks in, mounting a later but highly targeted attack against the specific invader.



INNATE IMMUNE SYSTEM

This system includes, among other components, antimicrobial molecules and various phagocytes (cells that ingest and destroy pathogens). These cells, such as dendritic cells and macrophages, also activate an inflammatory response, secreting proteins called cytokines that trigger an influx of defensive cells from the blood. Among the recruits are more phagocytes—notably monocytes (which can mature into macrophages) and neutrophils.

ADAPTIVE IMMUNE SYSTEM

This system "stars" B cells and T cells. Activated B cells secrete antibody molecules that bind to antigens—specific components unique to a given invader—and destroy the invader directly or mark it for attack by others. T cells recognize antigens displayed on cells. Some T cells help to activate B cells and other T cells (*not shown*); other T cells directly attack infected cells. T and B cells spawn "memory" cells that promptly eliminate invaders encountered before.

cines expose the body to a disabled form of a pathogen (or harmless pieces of it), but the immune system reacts as it would to a true assault, generating protective memory cells in the process. Thanks to T and B cells, once an organism has encountered a microbe and survived, it becomes exempt from being overtaken by the same bug again.

The innate immune system seemed rather drab in comparison. Its components—including antibacterial enzymes in saliva and an interlocking set of proteins (known collectively as the complement) that kill bacteria in the bloodstream—were felt to be less sophisticated than targeted antibodies and killer T cells. What is more, the innate immune system does not tailor its response in the same way that the adaptive system does.

In dismissing the innate immune response as dull and uninteresting, however, immunologists were tiptoeing around a dirty little secret: the adaptive system does not work in the absence of the allegedly more crude innate response. The innate system produces certain signaling proteins called cytokines that not only induce inflammation but also activate the B and T cells that are needed for the adaptive response. The posh sister, it turns out, needs her less respected sibling to make her shine.

By the late 1990s immunologists knew a tremendous amount about how the adaptive immune system operates. But they had less of a handle on innate immunity. In particular, researchers did not understand how microbes activate the innate response—or exactly how this stimulation helps to drive the adaptive response of T and B cells. Soon after, though, they would learn that much of the answer lay with the TLRs, which are produced by various immune system cells. But the path scientists traveled to get to these proteins was a circuitous one,

Overview/*Innate Immunity*

- Innate immunity serves as a rapid response system for detecting and clearing infections by any infectious agent. The response is mediated by a family of molecules called Toll-like receptors (TLRs), made by many defensive cells.
- When TLRs detect an invader, they trigger the production of an array of signaling proteins that induce inflammation and direct the body to mount a full-fledged immune response.
- If TLRs are underactive, the immune system fails; if overactive, they can give rise to disorders such as rheumatoid arthritis and even cardiovascular disease. Learning how to manipulate TLRs or the proteins with which they interact could provide new options for treating infectious and inflammatory diseases.

TAMI TOLPA

winding through studies of fruit fly development, the search for drugs to treat arthritis, and the dawn of the genomic era.

Weird Protein

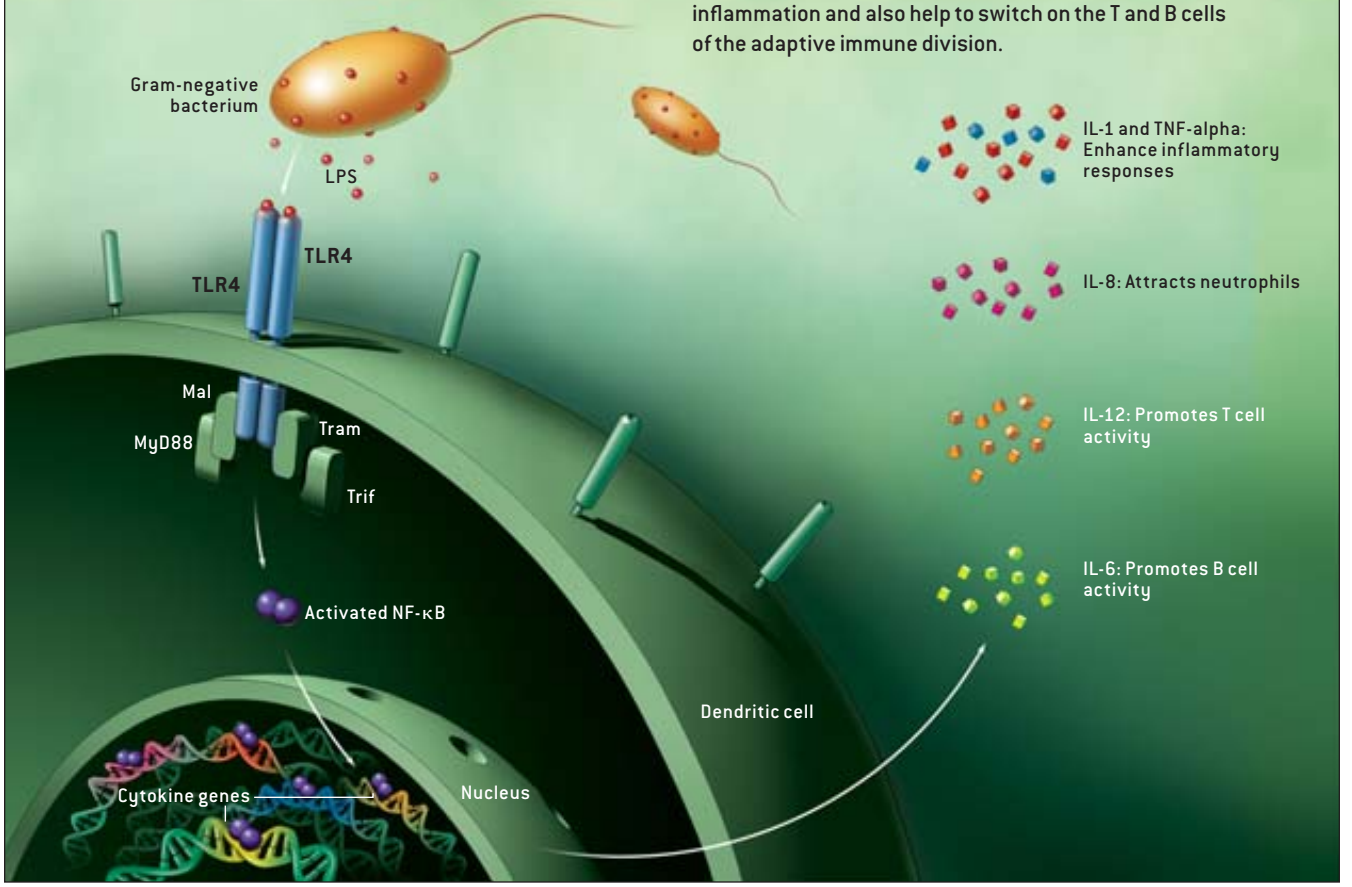
THE PATH ACTUALLY HAD its beginnings in the early 1980s, when immunologists started to study the molecular activity of cytokines. These protein messengers are produced by various immune cells, including macrophages and dendritic cells. Macrophages patrol the body's tissues, searching for signs of infection. When they detect a foreign protein, they set off the inflammatory response. In particular, they engulf and destroy the invader bearing that protein and secrete a suite of cytokines, some of which raise an alarm that recruits other cells to the site of infection and puts the immune system in general on full alert. Dendritic cells ingest invading microbes and head off to the lymph nodes, where they present fragments of the pathogen's proteins to armies of T cells and release cytokines—activities that help to switch on the adaptive immune response.

To study the functions of various cytokines, researchers needed a way to induce the molecules' production. They found that the most effective way to get macrophages and dendritic cells to make cytokines in the laboratory was to expose them to bacteria—or more important, to selected components of bacteria. Notably, a molecule called lipopolysaccharide (LPS), made by a large class of bacteria, stimulates a powerful immune response. In humans, exposure to LPS causes fever and can lead to septic shock—a deadly vascular shutdown triggered by an overwhelming, destructive action of immune cells. LPS, it turns out, evokes this inflammatory response by prompting macrophages and dendritic cells to release the cytokines tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1).

Indeed, these two cytokines were shown to rule the inflammatory response, prodding immune cells into action. If left unchecked, they can precipitate disorders such as rheumatoid arthritis, an autoimmune condition characterized by excessive inflammation that leads to destruc-

TOLLS IN CHARGE

Toll-like receptors (TLRs), made by many cells of the innate system, have been found to both orchestrate the innate immune response and play a critical role in the adaptive response. TLR4, for example, elicits these defenses when gram-negative bacteria begin to invade. TLR4 detects the incursions by binding to lipopolysaccharide (LPS), a sugar unique to gram-negative bacteria. Having recognized LPS, pairs of TLR4s signal to four molecules inside the cell—MyD88, Mal, Tram and Trif—which, in turn, trigger molecular interactions that ultimately activate a master regulator of inflammation (NF-κB). This regulator then switches on genes that encode immune activators, including cytokines. These cytokines (*far right*) induce inflammation and also help to switch on the T and B cells of the adaptive immune division.



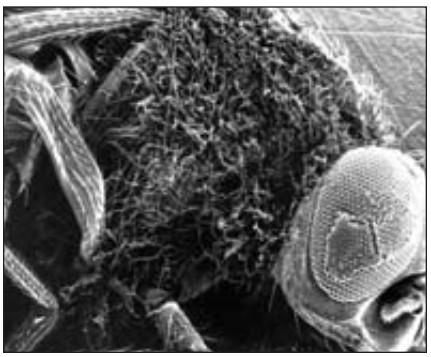
TAMI TOLPA

tion of the joints. Investigators therefore surmised that limiting the effects of TNF-alpha and IL-1 might slow the progress of the disease and alleviate the suffering of those with arthritis. To design such a therapy, though, they needed to know more about how these molecules work. And the first step was identifying the proteins with which they interact.

In 1988 John E. Sims and his colleagues at Immunex in Seattle discovered a receptor protein that recognizes IL-1. This receptor resides in the membranes of many different cells in the body, including macrophages and dendritic cells. The part of the receptor that juts out of the cell binds to IL-1, whereas the segment that lies inside the cell relays the message that IL-1 has been detected. Sims examined the inner part of the IL-1 receptor carefully, hoping it would yield some clue as to how the protein transmits its message—revealing, for example, which signaling molecules it activates within cells. But the inner domain of the human IL-1 receptor was unlike anything researchers had seen before, so he was stymied.

Then, in 1991, Nick J. Gay of the University of Cambridge—working on a completely unrelated problem—made a strange discovery. He was looking for proteins that were similar to a fruit-fly protein called Toll. Toll had been identified by Christiane Nusslein-Volhard in Tübingen, Germany, who gave the protein its name because flies that lack Toll look weird (*Toll* being the German word for "weird"). The protein helps the developing *Drosophila* embryo to differentiate its top from its bottom, and flies without Toll look jumbled, as if they have lost their sidedness.

Gay searched the database containing all the gene sequences then known. He



FRUIT FLY that lacked the protein Toll fell victim to a rampant fungal infection; spores cover the body like a fur coat. (The head is at the bottom right.) This outcome, reported in 1996, was one of the first indications that fruit flies require Toll proteins for protection against disease.

was looking for genes whose sequences closely matched that of Toll and thus might encode Toll-like proteins. And he discovered that part of the Toll protein bears a striking resemblance to the inner part of the human IL-1 receptor, the segment that had mystified Sims.

At first the finding didn't make sense. Why would a protein involved in human inflammation look like a protein that tells fly embryos which end is up? The discovery remained puzzling until 1996, when Jules A. Hoffmann and his collaborators at CNRS in Strasbourg showed that flies use their Toll protein to defend themselves from fungal infection. In *Drosophila*, it seems, Toll multitasks and is involved in both embryonic development and adult immunity.

Worms, Water Fleas and You

THE IL-1 RECEPTOR and the Toll protein are similar only in the segments that are tucked inside the cell; the bits that are exposed to the outside look quite different. This observation led researchers to search for human proteins that resemble Toll in its entirety. After all, evolution usually conserves designs that work well—and if Toll could mediate immunity in flies, perhaps similar proteins were doing the same in humans.

Acting on a tip from Hoffmann, in 1997 Ruslan Medzhitov and the late Charles A. Janeway, Jr., of Yale University discovered the first of these proteins, which they called human Toll. Within six months or so, Fernando Bazan and his colleagues at DNAX in Palo Alto, Calif., had identified five human Tolls, which they dubbed Toll-like receptors (TLRs). One, TLR4, was the same human Toll described by Medzhitov and Janeway.

At that point, researchers still did not know exactly how TLRs might contribute to human immunity. Janeway had found that stuffing the membranes of dendritic cells with TLR4 prompted the production of cytokines. But he could not say how TLR4 became activated during an infection.

The answer came in late 1998, when Bruce Beutler and his co-workers at the Scripps Institute in La Jolla, Calif., found that mutant mice unable to respond to LPS harbor a defective version of TLR4. Whereas normal mice die of sepsis within an hour of being injected with LPS, these mutant mice survive and behave as if they have not been exposed to the molecule at all; that is, the mutation in the TLR4 gene renders these mice insensitive to LPS.

This discovery made it clear that TLR4 becomes activated when it interacts with LPS. Indeed, its job is to sense LPS. That realization was a major breakthrough in the field of sepsis, because it revealed the molecular mechanism that underlies inflammation and provided a possible new target for treatment of a disorder that sorely needed effective therapies. Within two years, researchers determined that most TLRs—of which 10 are now known in humans—recognize molecules important to the survival of bacteria, viruses, fungi and parasites. TLR2 binds to lipoteichoic acid, a component of the bacterial cell wall. TLR3 recognizes the genetic material of viruses; TLR5 recognizes flagellin, a protein that forms the whiplike tails used by bacteria to swim; and TLR9 recognizes a signature genetic sequence called CpG, which occurs in bacteria and viruses in longer stretches and in a form that is chemically distinct from the CpG sequences in mammalian DNA.

TLRs, it is evident, evolved to recognize and respond to molecules that are fundamental components of pathogens. Eliminating or chemically altering any one of these elements could cripple an infectious agent, which means that the or-

THE AUTHOR

LUKE A. J. O'NEILL received his Ph.D. in pharmacology from the University of London in 1985 for work on the pro-inflammatory cytokine interleukin-1. O'Neill is Science Foundation Ireland Research Professor and head of the department of biochemistry at Trinity College in Dublin. He is founder of Opsona Therapeutics, a drug development company in Dublin.

FROM BRUNO LEMAITRE, EMMANUELLE NICOLAS, LYDIA MICHAUT, JEAN-MARC REICHHART AND JULES A. HOFFMANN IN *CELL*, VOL. 86, NO. 6, PAGES 973–983; SEPTEMBER 20, 1996

ganisms cannot dodge TLRs by mutating until these components are unrecognizable. And because so many of these elements are shared by a variety of microbes, even as few as 10 TLRs can protect us from virtually every known pathogen.

Innate immunity is not unique to humans. In fact, the system is quite ancient. Flies have an innate immune response, as do starfish, water fleas and almost every organism that has been examined thus far. And many use TLRs as a trigger. The nematode worm has one that allows it to sense and swim away from infectious bacteria. And plants are rife with TLRs. Tobacco has one called N protein that is required for fighting tobacco mosaic virus. The weed *Arabidopsis* has more than 200. The first Toll-like protein most likely arose in a single-celled organism that was a common ancestor of plants and animals. Perhaps these molecules even helped to facilitate our evolution. Without an efficient means of defense against infection, multicellular organisms might never have survived.

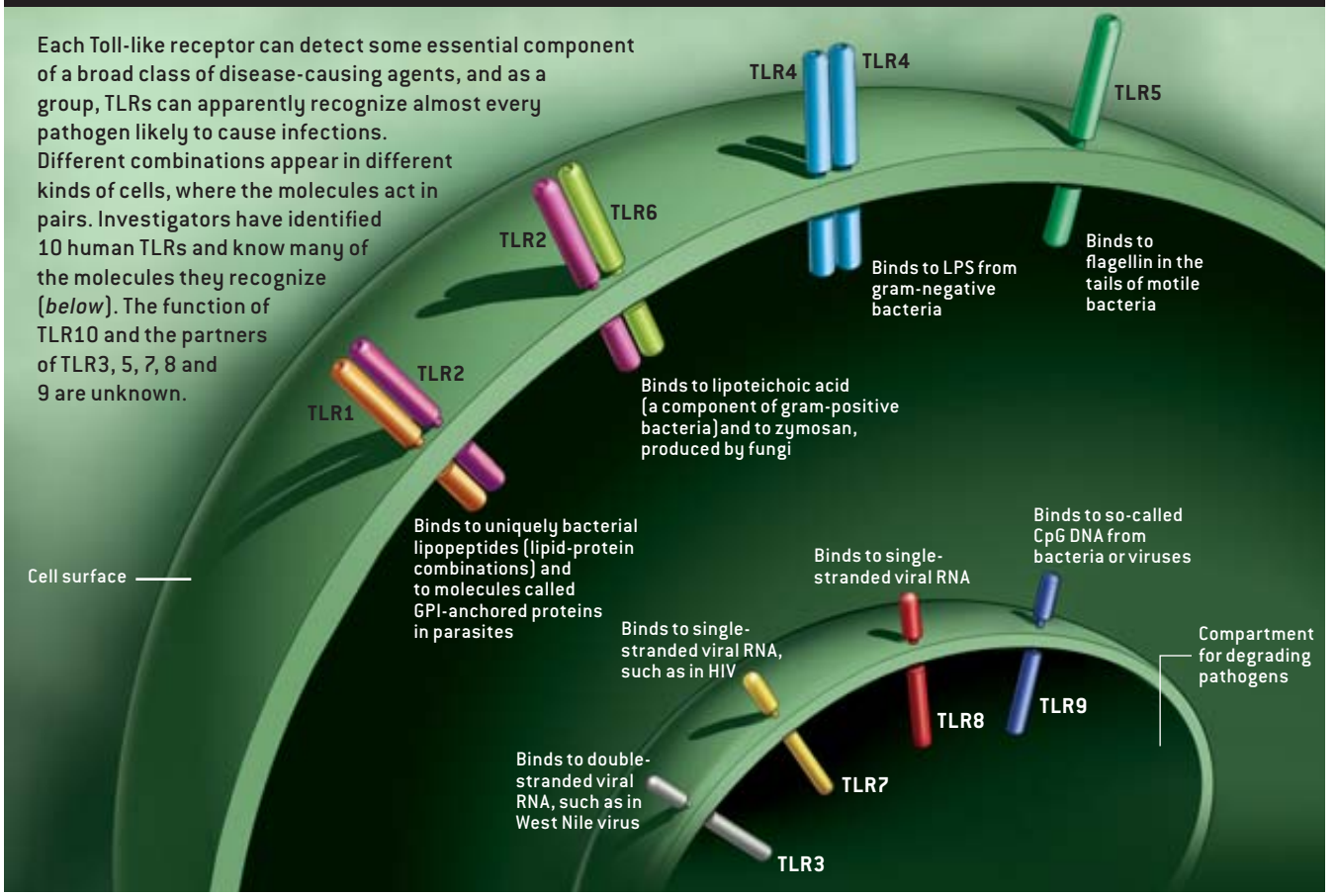
Storming the Castle

THE INNATE SYSTEM was once thought to be no more elaborate than the wall of a castle. The real action, researchers believed, occurred once the wall had been breached and the troops inside—the T and B cells—became engaged. We now know that the castle wall is studded with sentries—TLRs—that identify the invader and sound the alarm to mobilize the troops and prepare the array of defenses needed to fully combat the attack. TLRs, in other words, unleash both the innate and adaptive systems.

The emerging picture looks something like this. When a pathogen first enters the body, one or more TLRs, such as those on the surface of patrolling macrophages and dendritic cells, latch onto the foreign molecules—for example, the LPS of gram-negative bacteria. Once engaged, the TLRs prompt the cells to unleash particular suites of cytokines. These protein messengers then recruit additional macrophages, dendritic cells and other immune cells to wall off and nonspecifically attack the marauding microbe. At the same time, cytokines released by all these busy cells can produce the classic symptoms of infection, including fever and flulike feelings.

Macrophages and dendritic cells that have chopped up a pathogen display pieces of it on their surface, along with other molecules indicating that a disease-causing agent is present. This display, combined with the cytokines released in response to TLRs, ultimately activates B and T cells that recognize those specific pieces, causing them—over the course of several days—to proliferate and launch a powerful, highly focused attack on the particular invader. Without the priming effect of TLRs, B and T cells would not become engaged and the body would not

THE JOBS OF TOLL-LIKE RECEPTORS



TAMI TOLPA

be able to mount a full immune response. Nor could the body retain any memory of previous infections.

Following the initial infection, enough memory T and B cells are left behind so that the body can deal more efficiently with the invader should it return. This army of memory cells can act so quickly that inflammation might not occur at all. Hence, the victim does not feel as ill and might not even notice the infection when it recurs.

Innate and adaptive immunity are thus part of the same system for recognizing and eliminating microbes. The interplay between these two systems is what makes our overall immune system so strong.

Choose Your Weapon

TO FULLY UNDERSTAND how TLRs control immune activity, immunologists need to identify the molecules that relay signals from activated TLRs on the cell surface to the nucleus, switching on genes that encode cytokines and other immune activators. Many investigators are now pursuing this search intensively, but already we have made some fascinating discoveries.

We now know that TLRs, like many receptors that reside on the cell surface, enlist the help of a long line of signaling proteins that carry their message to the nucleus, much as a bucket brigade shuttles water to a fire. All the TLRs, with the exception of TLR3, hand off their signal to an adapter protein called MyD88. Which other proteins participate in the relay varies with the TLR: my laboratory studies Mal, a protein we discovered that helps to carry signals generated by TLR4 and TLR2. TLR4 also requires two other proteins—Tram and Trif—to relay the signal, whereas TLR3 relies on Trif alone. Shizuo Akira of Osaka University in Japan has shown that mice engineered so that they do not produce some of these intermediary signaling proteins do not respond to microbial products, suggesting that TLR-associated proteins could provide novel targets for new anti-inflammatory or antimicrobial agents.

Interaction with different sets of signaling proteins allows TLRs to activate different sets of genes that hone the cell's response to better match the type of pathogen being encountered. For example, TLR3 and TLR7 sense the presence of viruses. They then trigger a string of molecular interactions that induce the production and release of interferon, the major antiviral cytokine. TLR2, which is activated by bacteria, stimulates the release of a blend of cytokines that does not include interferon but is more suited to activating an effective antibacterial response by the body.

The realization that TLRs can detect different microbial products and help to tailor the immune response to thwart the enemy is now overturning long-held assumptions that innate immunity is a static, undiscriminating barrier. It is, in fact, a dynamic system that governs almost every aspect of inflammation and immunity.

From *Legionella* to Lupus

ON RECOGNIZING the central role that TLRs play in initiating immune responses, investigators quickly began to suspect that hobbled or overactive versions of these receptors could contribute to many infectious and immune-related disorders. That hunch proved correct. Defects in innate immunity lead to greater susceptibility to viruses and bacteria. People with an underactive form of TLR4 are five times as likely to have severe bacterial infections over a five-year period than those with a normal TLR4. And people who die from Legionnaire's disease often harbor a mutation in TLR5 that disables the protein, compromising their innate immune response and rendering them unable to fight off the *Legionella* bacterium. On the other hand, an overzealous immune response can be equally destructive. In the U.S. and Europe alone, more than 400,000 people die annually from sepsis, which stems from an overactive immune response led by TLR4.

Other studies are pointing to roles for TLRs in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Here TLRs might respond to products from damaged cells, propagating an inappropriate inflammatory response and promoting a misguided reaction by the adaptive immune system. In lupus, for example, TLR9 has been found to react to the body's own DNA.

Innate immunity and the TLRs could also play a part in heart disease. People with a mutation in TLR4 appear to be less prone to developing cardiovascular disease. Shutting down TLR4 could protect the heart because inflammation appears to contribute to the formation of the plaques that clog coronary arteries.

MECHNIKOV'S FLEAS

The discovery of Tolls and Toll-like receptors extends a line of research begun more than 100 years ago, when Russian biologist Ilya Mechnikov essentially discovered innate immunity. In the early 1880s Mechnikov plucked some thorns from a tangerine tree and poked them into a starfish larva. The next morning he saw that the thorns were surrounded by mobile cells, which he surmised were in the process of engulfing bacteria introduced along with the foreign bodies. He then discovered that water fleas (*Daphnia*) exposed to fungal spores mount a similar response. This process of phagocytosis is a cornerstone of innate immunity, and its discovery earned Mechnikov a Nobel Prize in 1908.

MECHNIKOV was a character. Speaking of the era when he worked at the Pasteur Institute, his Nobel Prize biography notes, "It is said of him that at this time he usually wore overshoes in all weathers and carried an umbrella, his pockets being overfull with scientific papers, and that he always wore the same hat, and often, when he was excited, sat on it."

HULTON ARCHIVE/GETTY IMAGES

TLRs AS DRUG TARGETS

Agents that activate TLRs and thus enhance immune responses could increase the effectiveness of vaccines or protect against infection. They might even prod the immune system to destroy tumors. In contrast, drugs that block TLR activity might prove useful for dampening inflammatory disorders. Drugs of both types are under study (*below*).

DRUG TYPE	EXAMPLES
TLR4 activator	MPL, an allergy treatment and vaccine adjuvant (immune system activator) from Corixa (Seattle), is in large-scale clinical trials
TLR7 activator	ANA245 (isatoribine), an antiviral agent from Anandys (San Diego), is in early human trials for hepatitis C
TLR7 and TLR8 activator	Imiquimod, a treatment for genital warts, basal cell skin cancer and actinic keratosis from 3M (St. Paul, Minn.), is on the market
TLR9 activator	ProMune, a vaccine adjuvant and treatment for melanoma skin cancer and non-Hodgkin's lymphoma from Coley (Wellesley, Mass.), is in large-scale clinical trials
TLR4 inhibitor	E5564, an antisepsis drug from Eisai (Teaneck, N.J.), is in early human trials
General TLR inhibitor	RDP58, a drug for ulcerative colitis and Crohn's disease from Genzyme (Cambridge, Mass.), is entering large-scale clinical trials
General TLR inhibitor	OPN201, a drug for autoimmune disorders from Opsona Therapeutics (Dublin, Ireland), is being tested in animal models of inflammation

Manipulation of TLR4 might therefore be another approach to preventing or limiting this condition.

Volume Control

MANY OF THE BIG pharmaceutical companies have an interest in using TLRs and their associated signaling proteins as targets for drugs that could treat infections and immune-related disorders. With the spread of antibiotic resistance, the emergence of new and more virulent viruses, and the rising threat of bioterrorism, the need to come up with fresh ways to help our bodies fight infection is becoming more pressing.

Work on TLRs could, for example, guide the development of safer, more effective vaccines. Most vaccines depend on the inclusion of an adjuvant, a substance that kick-starts the inflammatory response, which in turn pumps up the ability of the adaptive system to generate the desired memory cells. The adjuvant used in most vaccines today does not provoke a full adaptive response; instead it favors B cells over T cells. To elicit a stronger response, several companies have set their sights on compounds that activate TLR9, a receptor that recognizes a broad range of bacteria and viruses and drives a robust immune response.

And TLRs are teaching us how to defend ourselves against biological weapons, such as poxviruses. A potential staple in the bioterrorist arsenal, these viruses can shut down TLRs and thereby avoid detection and elimination. In collaboration with Geoffrey L. Smith of Imperial College London, my lab found that by removing the viral protein that disables TLRs, we could generate a weakened virus that could serve as the basis of a vaccine unlikely to provoke an unintended fatal pox infection.

Armed with an understanding of TLRs and innate immunity, physicians might be able to predict which patients will fare poorly during infection and treat them more aggressively. If, for instance, patients came to a clinic with a bacterial infection and were found to have a mutant TLR4, the doctor might bombard them with antibiotics or with agents that could somehow bolster their immune response to prevent the infection from doing lasting damage.

Of course, a balance must be struck between stimulating an immune response that is sufficient to clear a microbe and precipitating an inflammatory response that will do more harm than good. Similarly, any medications that aim to relieve inflammation by quelling TLR activity and cytokine release must not, at the same time, undercut the body's defense against infection.

Anti-inflammatory drugs that interfere with TNF-alpha, one of the cytokines produced as a result of TLR4 activation, offer a cautionary tale. TNF-alpha produced during infection and inflammation can accumulate in the joints of patients with rheumatoid arthritis. The anti-inflammatory compounds alleviate the arthritis, but some people taking them wind up with tuberculosis. The infection is probably latent, but reining in the inflammatory response can also dampen the pathogen-specific responses and allow the bacterium to reemerge.

In short, TLRs are like the volume knob on a stereo, balancing adaptive immunity and inflammation. Researchers and pharmaceutical companies are now looking for ways to tweak these controls, so they can curtail inflammation without disabling immunity.

Given that TLRs were unheard of seven years ago, investigators have made enormous progress in understanding the central role these proteins play in the body's first line of defense. Innate immunity, long shrouded in oblivion, has suddenly become the belle of the ball. SA

MORE TO EXPLORE

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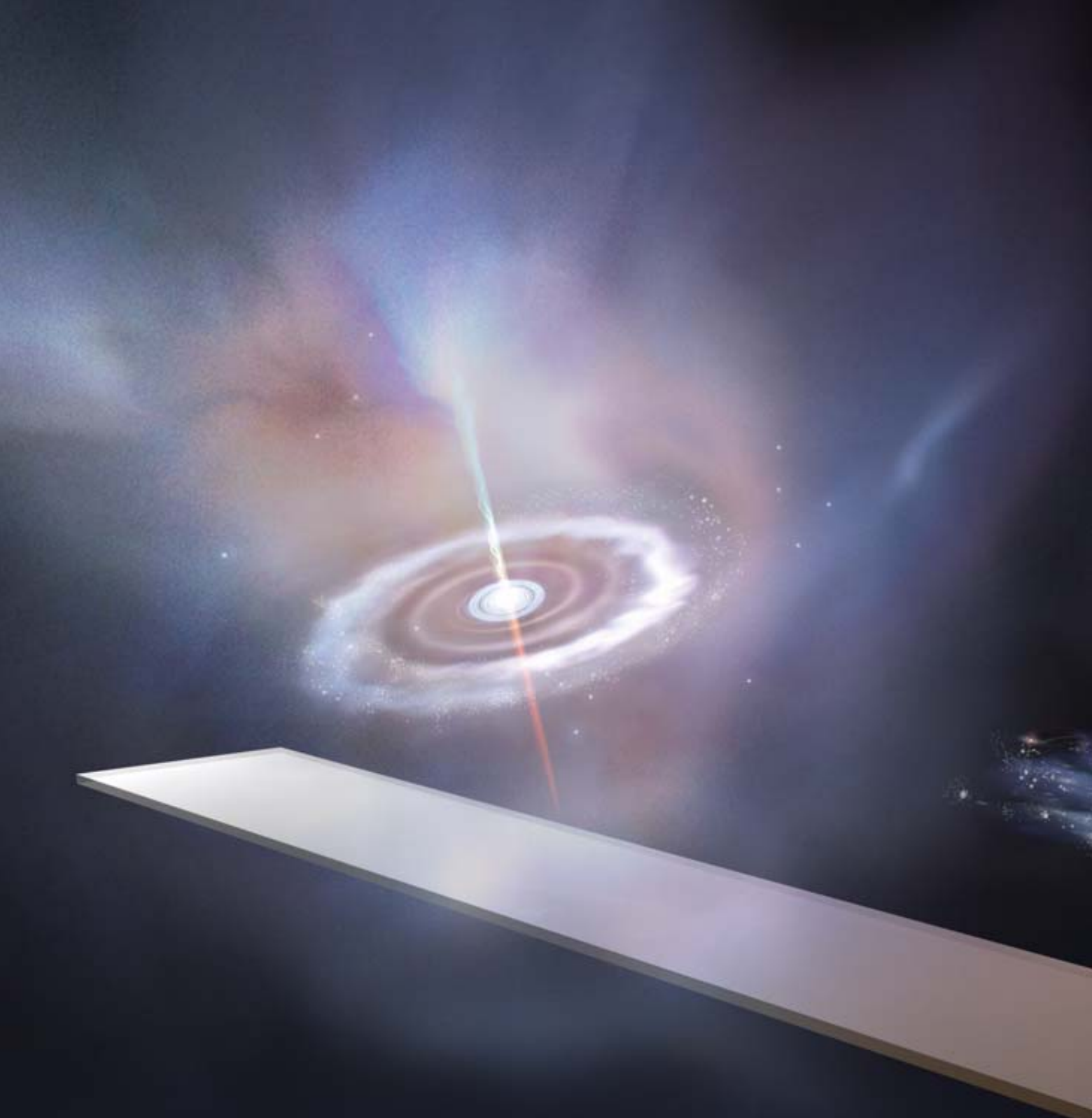
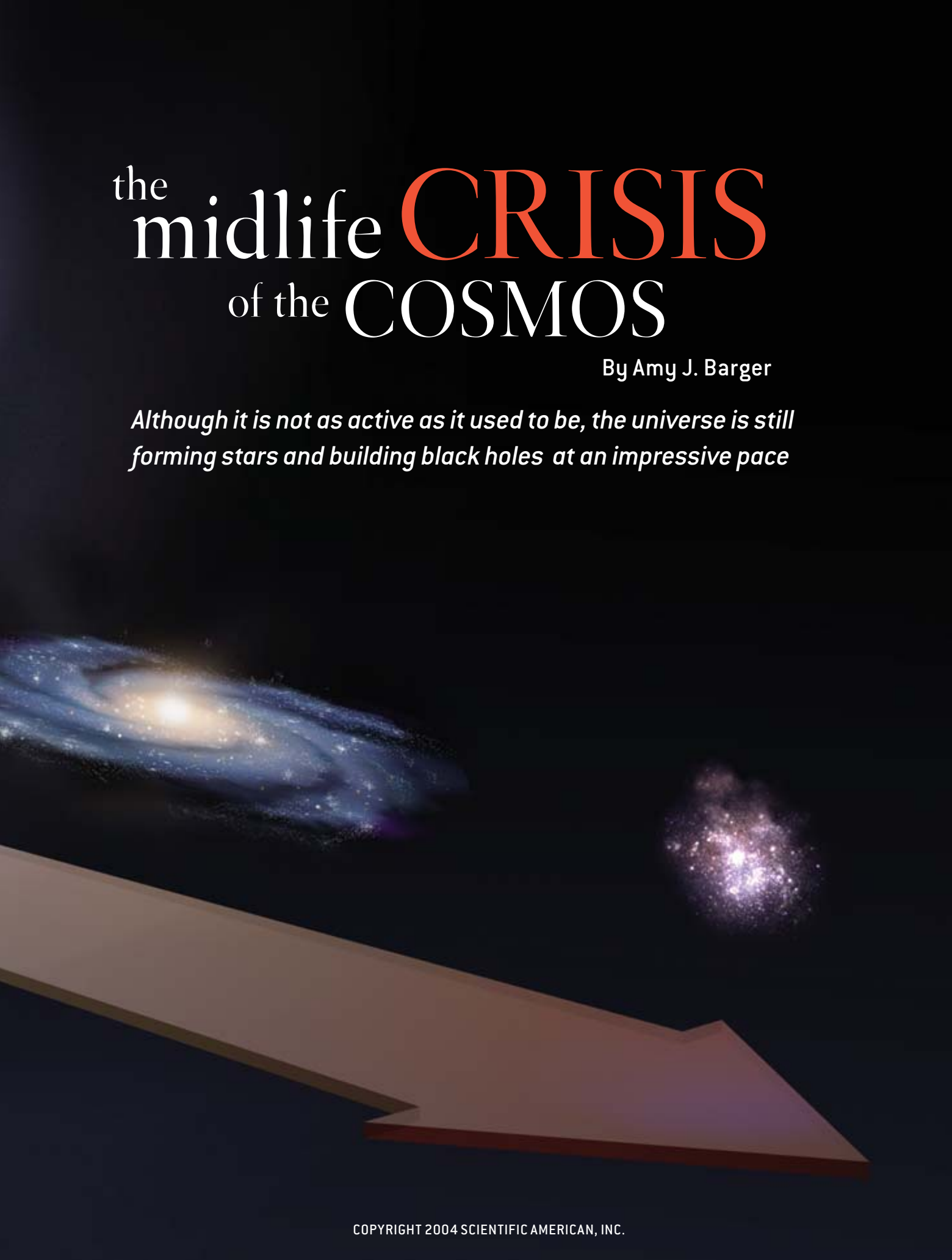


COSMIC DOWNSIZING has occurred over the past 14 billion years as activity has shifted to smaller galaxies. In the first half of the universe's lifetime, giant galaxies gave birth to prodigious numbers of stars and supermassive black holes that powered brilliant quasars (*left*). In the second half, activity in the giant galaxies slowed, but star formation and black hole building continued in medium-size galaxies (*center*). In the future, the main sites of cosmic activity will be dwarf galaxies holding only a few million stars each (*right*).

the midlife CRISIS of the COSMOS

By Amy J. Barger

Although it is not as active as it used to be, the universe is still forming stars and building black holes at an impressive pace



Until recently, most astronomers believed that the universe had entered a very boring middle age. According to this paradigm, the early history of the universe—that is, until about six billion years after the big bang—was an era of cosmic fireworks: galaxies collided and merged, powerful black holes sucked in huge whirlpools of gas, and stars were born in unrivaled profusion. In the following eight billion years, in contrast, galactic mergers became much less common, the gargantuan black holes went dormant, and star formation slowed to a flicker. Many astronomers were convinced that they were witnessing the end of cosmic history and that the future held nothing but the relentless expansion of a becalmed and senescent universe.

In the past few years, however, new observations have made it clear that the reports of the universe's demise have been greatly exaggerated. With the advent of new space observatories and new instruments on ground-based telescopes, astronomers have detected violent activity occurring in nearby galaxies during the recent past. (The light from more distant galaxies takes longer to reach us, so we observe these structures in an earlier stage of development.) By examining the x-rays emitted by the cores of these relatively close galaxies, researchers have discovered many tremendously massive black holes still devouring the surrounding gas and dust. Furthermore, a more thorough study of the light emitted by galaxies of different ages has shown that the star formation rate has not declined as steeply as once believed.

The emerging consensus is that the early universe was dominated by a small number of giant galaxies containing colossal black holes and prodigious bursts of star formation, whereas the present universe has a more dispersed nature—the creation of stars and the accretion of material into black holes are now occurring in a large number of medium-size and small galaxies. Essentially, we are in the midst of a vast downsizing that is redistributing cosmic activity.

Deep-Field Images

TO PIECE TOGETHER the history of the cosmos, astronomers must first make sense of the astounding multitude of objects they observe. Our most sensitive optical views of the universe come from the Hubble Space Telescope. In the Hubble Deep Field studies—10-day exposures of two tiny regions of the sky observed through four different wavelength filters—researchers have found thousands of distant galaxies, with the oldest dating back to about one billion years after the big bang. A more recent study, called the Hubble Ultra Deep Field, has revealed even older galaxies. Obtaining these deep-field images is only the beginning, however. Astronomers want to understand how the oldest and most distant objects evolved into present-day galaxies. It is somewhat like learning how a human baby grows to be an adult. Connecting the present with the past has become one of the dominant themes of modern astronomy.

A major step in this direction is to determine the cosmic stratigraphy—which objects are in front and which are more distant—among the thousands of galaxies in a typical deep-field image. The standard way to perform this task is to obtain a spectrum of each galaxy in the image and measure its redshift. Because of the universe's expansion, the light from distant sources has been stretched, shifting its wavelength toward the red end of the spectrum. The more the light is shifted to the red, the farther away the source is and thus the older it is. For example, a redshift of one means that the wavelength has been stretched by 100 percent, that is, to twice its original size. Light from an object with this redshift was emitted about six billion years after the big bang, which is less than half the current age of the universe. In fact, astronomers usually talk in terms of redshift rather than years, because redshift is what we measure directly.

Obtaining redshifts is a practically foolproof technique for reconstructing cosmic history, but in the deepest of the deep-field images it is almost impossible to measure redshifts for all the galaxies. One reason is the sheer number of galaxies in the image, but a more fundamental problem is the intrinsic faintness of some

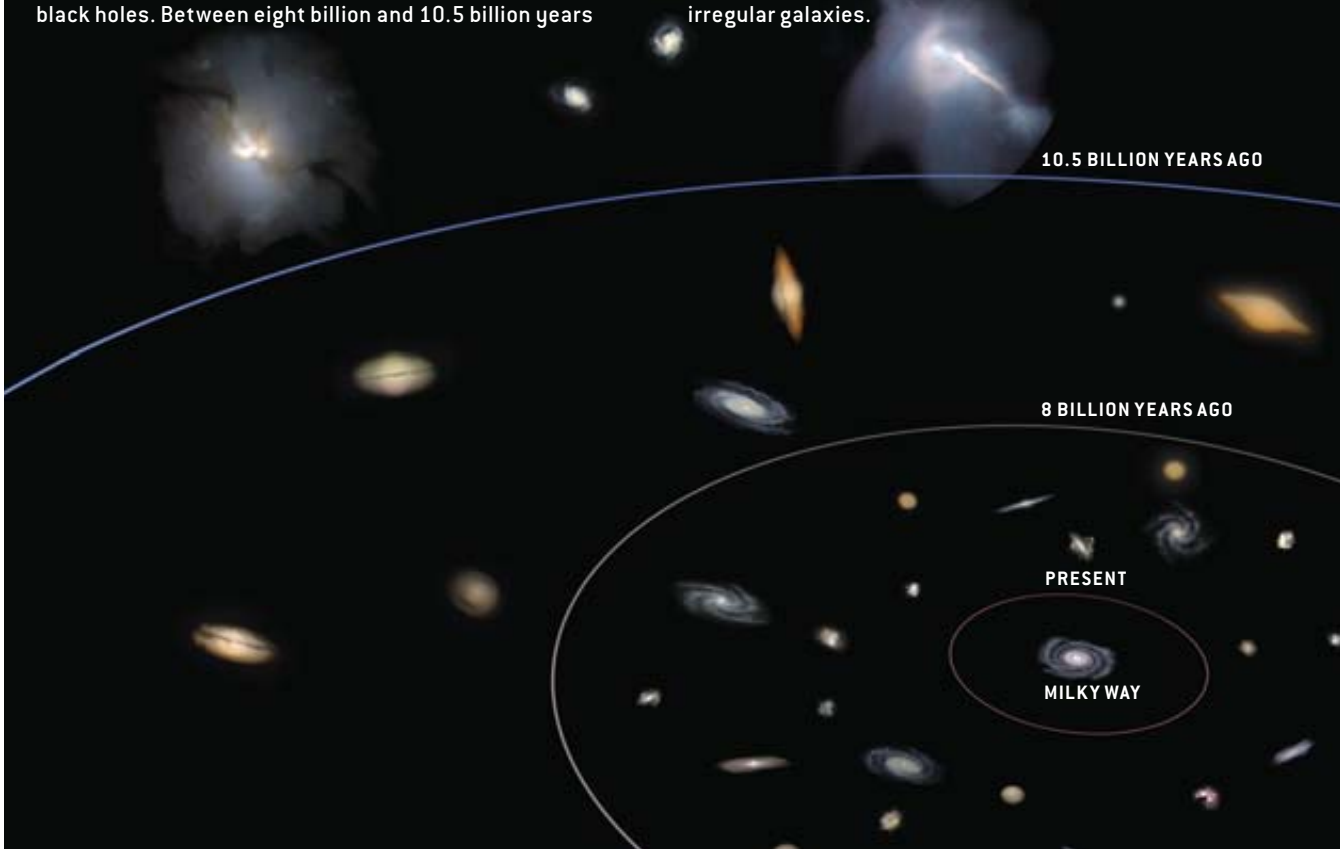
Overview/*Middle-Aged Cosmos*

- The early history of the universe was a turbulent era marked by galactic collisions, huge bursts of star formation and the creation of extremely massive black holes. The falloff in cosmic activity since then has led many astronomers to believe that the glory days of the universe are long gone.
- In recent years, though, researchers have found powerful black holes still actively consuming gas in many nearby galaxies. New observations also suggest that star formation has not dropped as steeply as once believed.
- The results point to a cosmic downsizing: whereas the early universe was dominated by a relatively small number of giant galaxies, activity in the current universe is dispersed among a large number of smaller galaxies.

ALFRED T. KAMAJIAN (*preceding pages*)

EVOLUTION OF THE UNIVERSE

As astronomers peer into the depths of space, they also look back in time, because the light from distant objects takes longer to reach us. More than 10.5 billion years ago, tremendous galaxies collided and merged, triggering bursts of star formation and the accretion of gas into supermassive black holes. Between eight billion and 10.5 billion years ago, stars continued to form at a high rate, and black holes continued to grow inside the galactic cores. In more recent times, star formation and black hole activity began to die down in the bigger galaxies; in the present-day universe, most of the star formation takes place in smaller spiral and irregular galaxies.



ALFRED T. KAMAJIAN

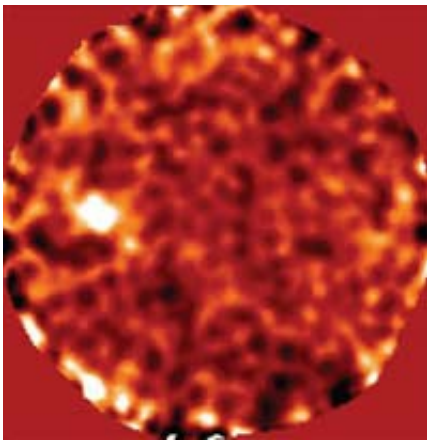
of the galaxies. The light from these dim objects arrives at a trickle of only one photon per minute in each square centimeter. And when observers take a spectrum of the galaxy, the diffraction grating of the spectrograph disperses the light over a large area on the detector, rendering the signal even fainter at each wavelength.

In the late 1980s a team led by Lennox L. Cowie of the University of Hawaii Institute for Astronomy and Simon J. Lilly, now at the Swiss Federal Institute of Technology in Zurich, developed a novel approach to avoid the need for laborious redshift observations. The researchers observed regions of the sky with filters that selected narrow wavebands in the ultraviolet, green and red parts of the spectrum and then measured how bright the galaxies were in each of the wavebands [*see box on page 51*]. A nearby star-forming galaxy is equally bright in all three wavebands. The intrinsic light from a star-forming galaxy has a sharp cutoff just beyond the ultraviolet waveband, at a wavelength of about 912 angstroms. (The cutoff appears because the neutral hydrogen gas in and around the galaxy absorbs radiation with shorter wavelengths.) Because the light from distant galaxies is shifted to the red, the cutoff moves to longer wavelengths; if the redshift is great enough, the galaxy's light will not appear in the ultraviolet waveband, and if the redshift is greater still, the galaxy will not be visible in the green waveband either.

Thus, Cowie and Lilly could separate star-forming galaxies into broad redshift intervals that roughly indicated their ages. In 1996 Charles C. Steidel of the California Institute of Technology and his collaborators used this technique to isolate hundreds of ancient star-forming galaxies with redshifts of about three, dating from about two bil-

THE AUTHOR

AMY J. BARGER studies the evolution of the universe by observing some of its oldest objects. She is an associate professor of astronomy at the University of Wisconsin–Madison and also holds an affiliate graduate faculty appointment at the University of Hawaii at Manoa. Barger earned her Ph.D. in astronomy in 1997 at the University of Cambridge, then did postdoctoral research at the University of Hawaii Institute for Astronomy. An observational cosmologist, she has explored the high-redshift universe using the Chandra X-ray Observatory, the Hubble Space Telescope, and the telescopes on Kitt Peak in Arizona and on Mauna Kea in Hawaii.



EXTREMELY LUMINOUS GALAXIES in the early universe have been discovered using the Submillimeter Common-User Bolometer Array (SCUBA) on the James Clerk Maxwell Telescope on Mauna Kea in Hawaii. The bright blob on the left is believed to be an ancient dust-enshrouded galaxy that spawned stars at a phenomenal rate, forming the equivalent of more than 1,000 suns every year.

lion years after the big bang. The researchers confirmed many of the estimated redshifts by obtaining very deep spectra of the galaxies with the powerful 10-meter Keck telescope on Mauna Kea in Hawaii.

frame ultraviolet light, researchers can estimate the number of high-mass stars in the galaxy.

Because high-mass stars live for only a few tens of millions of years—a short time by galactic standards—their number closely tracks variations in the galaxy's overall star formation rate. As the pace of star creation slows, the number of high-mass stars declines soon afterward because they die so quickly after they are born. In our own Milky Way, which is quite typical of nearby, massive spiral galaxies, the number of observed high-mass stars indicates that stars are forming at a rate of a few solar masses a year. In high-redshift galaxies, however, the rate of star formation is 10 times as great.

When Cowie and Lilly calculated the star formation rates in all the galaxies they observed, they came to the remarkable conclusion that the universe underwent a veritable baby boom at a redshift of about one. In 1996 Piero Madau, now at the University of California at Santa Cruz, put the technique to work on the Hubble Deep Field North data, which were ideal for this approach because of the very precise intensity measurements in four wavebands. Madau combined his results with those from existing lower-redshift optical observations to refine the estimates of the star formation history of the universe. He inferred that the rate of star formation must have peaked when the universe was about four billion to six billion years old. This result led many astronomers to conclude that the universe's best days were far behind it.

cal telescopes cannot detect every source in the early universe. The more distant a galaxy is, the more it suffers from cosmological redshifting, and at high enough redshifts, the galaxy's rest-frame ultraviolet and optical emissions will be stretched into the infrared part of the spectrum. Furthermore, stars tend to reside in very dusty environments because of the detritus from supernova explosions and other processes. The starlight heats up the dust grains, which then reradiate this energy at far-infrared wavelengths. For very distant sources, the light that is absorbed by dust and reradiated into the far-infrared is shifted by the expansion of the universe to submillimeter wavelengths. Therefore, a bright source of submillimeter light is often a sign of intense star formation.

Until recently, astronomers found it difficult to make submillimeter observations with ground-based telescopes, partly because water vapor in the atmosphere absorbs signals of that wavelength. But those difficulties were eased with the introduction of the Submillimeter Common-User Bolometer Array (SCUBA), a camera that was installed on the James Clerk Maxwell Telescope on Mauna Kea in 1997. (Located at a height of four kilometers above sea level, the observatory is above 97 percent of the water in the atmosphere.) Several teams of researchers, one of which I led, used SCUBA to directly image regions of the sky with sufficient sensitivity and area coverage to discover distant, exceptionally luminous dust-obscured sources. Because the resolution is fairly coarse, the galaxies have a bloblike appearance [*see illustration above*]. They are also relatively rare—even after many hours of exposure, few sources appeared on each SCUBA image—but they are among the most luminous galaxies

New observations make it clear that reports of the UNIVERSE'S DEMISE have been greatly exaggerated.

Once the redshifts of the galaxies have been measured, we can begin to reconstruct the history of star formation. We know from observations of nearby galaxies that a small number of high-mass stars and a larger number of low-mass stars usually form at the same time. For every 20 sunlike stars that are born, only one 10-solar-mass star (that is, a star with a mass 10 times as great as the sun's) is created. High-mass stars emit ultraviolet and blue light, whereas low-mass stars emit yellow and red light. If the redshift of a distant galaxy is known, astronomers can determine the galaxy's intrinsic spectrum (also called the rest-frame spectrum). Then, by measuring the total amount of rest-

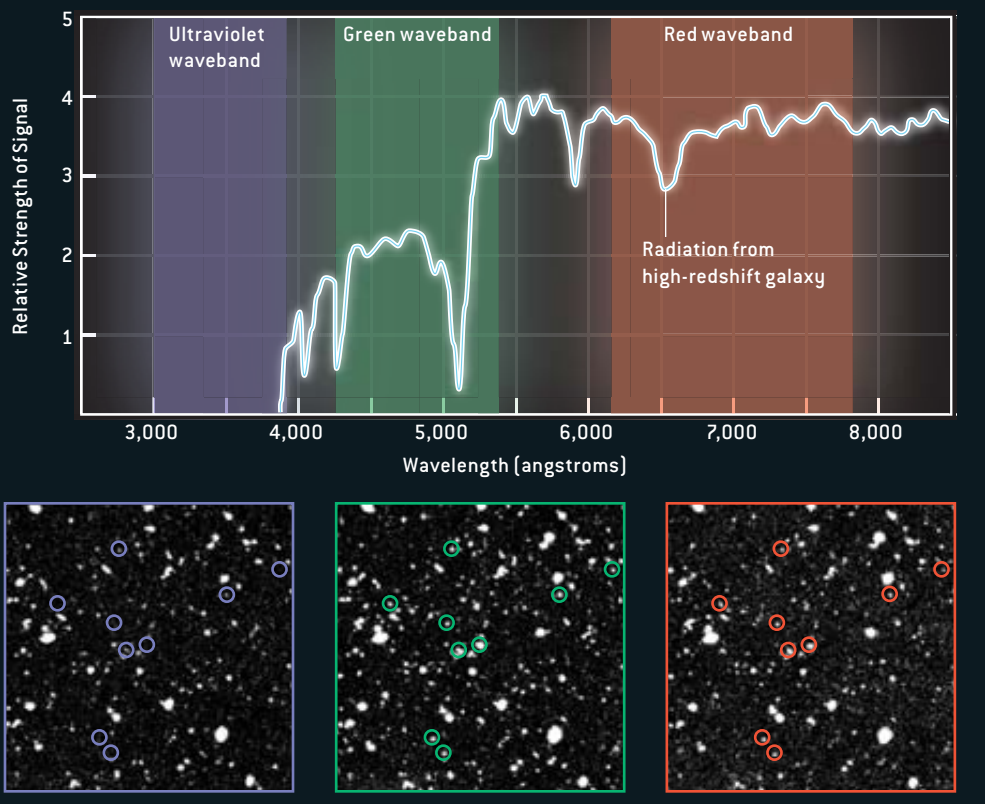
An Absorbing Tale

ALTHOUGH MADAU'S ANALYSIS of star formation history was an important milestone, it was only a small part of the story. Galaxy surveys using opti-

A. J. BARGER, L. L. COWIE, D. B. SANDERS, E. FULTON ET AL. *James Clerk Maxwell Telescope*

FINDING ANCIENT GALAXIES

To efficiently detect the oldest galaxies in a survey field, astronomers have developed a technique employing filters that select wavebands in the ultraviolet, green and red parts of the spectrum. Because of the expansion of the universe, the light from the oldest galaxies has been shifted toward the red end; the graph (*top*) shows how a relatively high redshift (about three) can push the radiation from a distant galaxy out of the ultraviolet waveband. As a result, the ancient galaxies appear in images made with the red and green filters but not in images made with the ultraviolet filter (*bottom*).



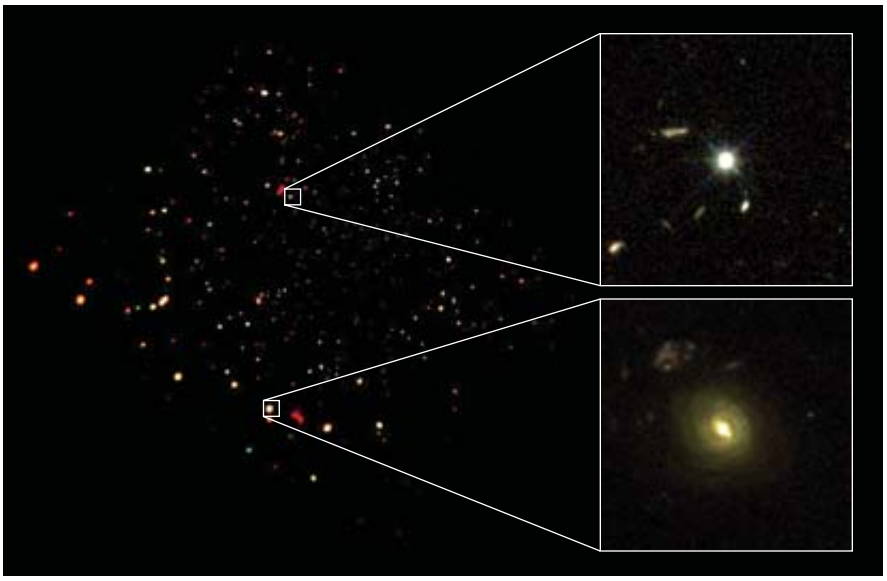
in the universe. It is sobering to realize that before SCUBA became available, we did not even know that these powerful, distant systems existed! Their star formation rates are hundreds of times greater than those of present-day galaxies, another indication that the universe used to be much more exciting than it is now.

Finding all this previously hidden star formation was revolutionary, but might the universe be covering up other violent activity? For example, gas and dust within galaxies could also be obscuring the radiation emitted by the disks of material whirling around supermassive black holes (those weighing as much as billions of suns). These disks are believed to be the power sources of quasars, the prodigiously luminous objects found at high redshifts, as well as the active nuclei at the centers of many nearby galaxies. Optical studies in the 1980s suggested that there were far more quasars several billion years after the big bang than there are active galactic nuclei in the present-day universe. Because the supermassive black holes that powered the distant quasar activity cannot be destroyed, astronomers presumed that many nearby galaxies must contain dead quasars—black holes that have exhausted their fuel supply.

These dormant supermassive black holes have indeed been detected through their gravitational influence. Stars and gas continue to orbit around the holes even though little material is swirling into them. In fact, a nearly dormant black hole resides at the center of the Milky Way. Together these results led scientists to develop a scenario: most supermassive black holes formed during the quasar era, consumed all the material surrounding them in a violent fit of growth and then disappeared from optical observations once their fuel supply ran out. In short, quasar activity, like star formation, was more vigorous in the distant past, a third sign that we live in relatively boring times.

This scenario, however, is incomplete. By combining x-ray and visible-light observations, astronomers are now revisiting the conclusion that the vast majority of quasars died out long ago. X-rays are important because, unlike visible light, they can pass through the gas and dust surrounding hidden black holes. But x-rays are blocked by the earth's atmosphere, so researchers must rely on space telescopes such as the Chandra and XMM/Newton X-ray observatories to detect black hole activity [see "The Cosmic Reality Check," by Günther Hasinger and Roberto Gilli; SCIENTIFIC AMERICAN, March 2002]. In 2000 a team consisting of Cowie, Richard F. Mushotzky of the NASA Goddard Space Flight Center, Eric A. Richards, then at Arizona State University, and I used the Subaru telescope at

TOMMY MOORMAN (*graph*); COURTESY OF CHARLES C. STEIDEL *California Institute of Technology* (*images*)



X-RAY VISION can be used to find hidden black holes. The Chandra X-ray Observatory detected many black holes in its Deep Field North survey (*left*). Some were ancient, powering brilliant quasars that flourished just a few billion years after the big bang (*top right*). But others lurked in the centers of relatively nearby galaxies, still generating x-rays in the modern era (*bottom right*).

Mauna Kea to identify optical counterparts to 20 x-ray sources found by Chandra in a survey field. We then employed the 10-meter Keck telescope to obtain the spectra of these objects.

Our result was quite unexpected: many of the active supermassive black holes detected by Chandra reside in relatively nearby, luminous galaxies. Modelers of the cosmic x-ray background had predicted the existence of a large population of obscured supermassive black holes, but they had not expected them to be so close at hand! Moreover, the optical spectra of many of these galaxies showed absolutely no evidence of black hole activity; without the x-ray observations, astronomers could never have discovered the supermassive black holes lurking in their cores.

This research suggests that not all supermassive black holes were formed in the quasar era. These mighty objects have apparently been assembling from the earliest times until the present. The supermassive black holes that are still active, however, do not exhibit the same behavioral patterns as the distant quasars. Quasars are voracious consumers, greedily gobbling up the material around them at an enormous rate. In contrast, most of the nearby sources that Chandra detected are more moderate eaters and thus radiate less intensely. Scientists have not yet determined what mechanism is responsible for this vastly different behavior. One possibility is that the present-day black holes have less gas to consume. Nearby galaxies undergo fewer collisions than the distant, ancient galaxies did, and such collisions could drive material into the supermassive black holes at the galactic centers.

Chandra had yet another secret to reveal: although the moderate x-ray sources were much less luminous than the quasars—generating as little as 1 percent of the radiation emitted by their older counterparts—when we added up the light produced by all the moderate sources in recent times, we found the amount to be about one tenth of that produced by the quasars in early times. The only way this result could arise is if there are many more moderate black holes active now than there were quasars active in the past. In other words, the contents of the universe have transitioned from a small number of bright objects to a large number of dimmer ones. Even though supermassive black holes are now being built smaller and cheaper, their combined effect is still potent.

Star-forming galaxies have also undergone a cosmic downsizing. Although some nearby galaxies are just as extravagant in their star-forming habits as the extremely luminous, dust-obscured galaxies found in the SCUBA images, the density of ultraluminous galaxies in the present-day universe is more than 400 times lower than their density in the distant universe. Again, however, smaller galaxies have taken up some of the slack. A team consisting of Cowie, Gillian Wilson, now at NASA's Infrared Processing and Analysis Center, Doug J. Burke, now at the Harvard-Smithsonian Center for Astrophysics, and I has refined the estimates of the universe's luminosity density by studying high-quality images produced with a wide range of filters and performing a complete spectroscopic follow-up. We found that the luminosity density of optical and ultraviolet light has not changed all that much with cosmic time. Although the overall star formation rate has dropped in the second half of the universe's lifetime because the monstrous dusty galaxies are no longer bursting with stars, the population of small, nearby star-forming galaxies is so numerous that the density of optical and ultraviolet light is declining rather gradually. This result gives us a much more optimistic outlook on the continuing health of the universe.

Middle-Aged Vigor

THE EMERGING PICTURE of continued vigor fits well with cosmological theory. New computer simulations suggest that the shift from a universe dominated by a few large and powerful galaxies to a universe filled with many smaller and meeker galaxies may be a direct consequence of cosmic expansion. As the universe expands, galaxies become more separated and mergers become rarer. Furthermore, as the gas surrounding galaxies grows more diffuse, it becomes easier to heat. Because hot gas is more energetic than cold gas, it does not gravitationally collapse as readily into the galaxy's potential well. Fabrizio Nicastro of the Harvard-Smithsonian Center for Astrophysics

D. M. ALEXANDER, F. E. BAUER, W. N. BRANDT, G. P. GARMIRE ET AL. *NASA/Pennsylvania State University (Chandra image)*; A. J. BARGER AND M. GIAVALISCO *NASA/Great Observatories Origins Deep Survey (optical images)*

and his co-workers have recently detected a warm intergalactic fog through its absorption of ultraviolet light and x-rays from distant quasars and active galactic nuclei. This warm fog surrounds our galaxy in every direction and is part of the Local Group of galaxies, which includes the Milky Way, Andromeda and 30 smaller galaxies. Most likely this gaseous material was left over from the galaxy formation process but is too warm to permit further galaxy formation to take place.

Small galaxies may lie in cooler environments because they may not have heated their surrounding regions of gas to the same extent that the big galaxies did through supernova explosions and quasar energy. Also, the small galaxies may have consumed less of their surrounding material, allowing them to continue their more modest lifestyles to the present day. In contrast, the larger and more profligate galaxies have exhausted their resources and are no longer able to collect more from their environments. Ongoing observational studies of the gaseous properties of small, nearby galaxies may reveal how they interact with their environments and thus provide a key to understanding galactic evolution.

But a crucial part of the puzzle remains unsolved: How did the universe form monster quasars so early in its history? The Sloan Digital Sky Survey, a major astronomical project to map one quarter of the entire sky and measure distances to more than a million remote objects, has discovered quasars that existed when the universe was only one sixteenth of its present age, about 800 million years after the big bang. In 2003 Fabian Walter, then at the National Radio Astronomy Observatory, and his collaborators detected the presence of carbon monoxide in the emission from one of these quasars; because carbon and oxygen could have been created only from the thermonuclear reactions in stars, this discovery suggests that a significant amount of star formation occurred in the universe's first several hundred million years. Recent results from the Wilkinson Microwave Anisotropy Probe, a satellite that studies the cosmic background radiation, also indicate that star formation began just 200 million years after the big bang.

Furthermore, computer simulations have shown that the first stars were most likely hundreds of times as massive as the sun. Such stars would have burned so brightly that they would have run out of fuel in just a few tens of millions of years; then the heaviest stars would have collapsed to black holes, which could have formed the seeds of the supermassive black holes that powered the first quasars. This explanation for the early appearance of quasars may be bolstered by the further study of gamma-ray bursts, which are believed to result from the collapse of very massive stars into black holes. Because gamma-ray bursts are the most powerful explosions in the universe since the big bang, astronomers can detect them at very great distances. This past November, NASA was expected to launch the Swift Gamma-Ray Burst Mission, a $250-million satellite with three telescopes designed to observe the explosions in the gamma-ray, x-ray, ultraviolet and optical wavelengths. By measuring the spectra of the gamma-ray bursts and their afterglows, the Swift satellite could provide scientists with a much better understanding of how collapsing stars could have started the growth of supermassive black holes in the early universe.

In comic books, Superman looked through walls with his x-ray vision. Astronomers have now acquired a similar ability with the Chandra and XMM/Newton observatories and are making good use of it to peer deep into the dust-enshrouded regions of the universe. What is being revealed is a dramatic transition from the mighty to the meek. The giant star-forming galaxies and voracious black holes of the universe's past are now moribund. A few billion years from now, the smaller galaxies that are active today will have consumed much of their fuel, and the total cosmic output of radiation will decline dramatically. Even our own Milky Way will someday face this same fate. As the cosmic downsizing continues, the dwarf galaxies—which hold only a few million stars each but are the most numerous type of galaxy in the universe—will become the primary hot spots of star formation. Inevitably, though, the universe will darken, and its only contents will be the fossils of galaxies from its glorious past. Old galaxies never die, they just fade away. SA

What is being revealed is a dramatic transition from the MIGHTY TO THE MEEK. Dwarf galaxies will become the PRIMARY HOT SPOTS of star formation.

MORE TO EXPLORE

Star Formation History since z = 1 as Inferred from Rest-Frame Ultraviolet Luminosity Density Evolution. Gillian Wilson et al. in *Astronomical Journal,* Vol. 124, pages 1258–1265; September 2002. Available online at **www.arxiv.org/abs/astro-ph/0203168**

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Digital gadgets demand ever more of our attention with their rude and thoughtless interruptions. Engineers are now testing computers, phones and cars that sense when you're busy and spare you from distraction

CONSIDERATE COMPUTING

By W. Wayt Gibbs

"YOUR BATTERY IS NOW FULLY CHARGED," ANNOUNCED THE LAPTOP COMPUTER to its owner, Donald A. Norman, with enthusiasm—perhaps even a hint of pride?—in its synthetic voice. Norman, a chief advocate of the notion that computers and appliances ought to be programmed with something akin to emotions, might normally have smiled at the statement. Instead he blushed—and no doubt wished that his computer could share his embarrassment. For at that moment, Norman was onstage at a dais, having addressed a conference room of cognitive scientists and computer researchers, and his Powerbook was still plugged into the public address system. Many in the audience chuckled at the automated faux pas and shook their heads. The moderator, flustered, shot Norman a less than sympathetic look.

And yet we've all been there. Our cell phones ring during movies. Telemarketers interrupt our dinners with friends. Our laptops throw up screensavers in the middle of presentations. "You've got mail!" derails our train of thought just as we get in the groove.

To be sure, distractions and multitasking are hardly new to the human condition. "A complicated life, continually interrupted by competing requests for attention, is as old as procreation," laughs Ted Selker of the Massachusetts Institute of Technology Media Lab. But increasingly, it is not just our kids pulling us three ways at once; it is also a relentless barrage of e-mail, alerts, alarms, calls, instant messages and automated notifications, none of them coordinated and all of them oblivious to whether we are busy—or even present. "It's ridiculous that my own computer can't figure out whether I'm in front of it, but a public toilet can," exclaims Roel Vertegaal of Queen's University in Ontario.

Humanity has connected itself through roughly three billion networked telephones, computers, traffic lights—even refrigerators and picture frames—because these things make life more convenient and keep us available to those we care about. So although we could simply turn off the phones, close the e-mail program, and shut the office door when it is time for a meeting or a stretch of concentrated work, we usually don't. We just endure the consequences.

"We take major productivity hits with each interruption," says Rosalind Picard, a cognitive scientist at the M.I.T. Media Lab. People juggle the myriad demands of work and daily life by maintaining a mental list of tasks to be done. An interruption of just 15 seconds causes most people to lose part of that to-do list, according to experiments by Gilles O. Einstein of Furman University.

Numerous studies have shown that when people are unexpectedly interrupt-

PETER HOEY

> **"It's ridiculous that my own computer can't figure out whether I'm in front of it, but a public toilet can."**

ed, they not only work less efficiently but also make more mistakes. "It seems to add cumulatively to a feeling of frustration," Picard reports, and that stress response makes it hard to regain focus. It isn't merely a matter of productivity and the pace of life. For pilots, drivers, soldiers and doctors, errors of inattention can be downright dangerous.

"If we could just give our computers and phones some understanding of the limits of human attention and memory, it would make them seem a lot more thoughtful and courteous," says Eric Horvitz of Microsoft Research. Horvitz, Vertegaal, Selker and Picard are among a small but growing number of researchers trying to teach computers, phones, cars and other gadgets to behave less like egocentric oafs and more like considerate colleagues.

To do this, the machines need new skills of three kinds: sensing, reasoning and communicating. First a system must sense or infer where its owner is and what he or she is doing. Next it must weigh the value of the messages it wants to convey against the cost of the disruption. Then it has to choose the best mode and time to interject.

Each of these pushes the limits of computer science and raises issues of privacy, complexity or reliability. Nevertheless, "attentive" computing systems have begun appearing in newer Volvos [*see box on opposite page*], and IBM has introduced Websphere communications software with a basic busyness sense. Microsoft has been running extensive in-house tests of a much more sophisticated system since 2003. Within a few years, companies may be able to offer every office worker a software version of the personal receptionist that only corner-suite executives enjoy today.

But if such an offer should land in your inbox, be sure to read the fine print before you sign. An attentive system, by definition, is one that is always watching. That considerate computer may come to know more about your work habits than you do.

Minding Your Busyness

MOST PEOPLE AREN'T AS BUSY as they think they are, which is why we can usually tolerate interruptions from our inconsiderate electronic paraphernalia. James Fogarty and Scott E. Hudson of Carnegie Mellon University recently teamed up with Jennifer Lai of IBM Research to study 10 managers, researchers and interns at work. They videotaped the subjects and periodically had them rate their "interruptibility." The amount of time the workers spent in leave-me-alone mode varied from person to person and day to day, ranging from 10 to 51 percent. On average, the subjects wanted to work without interruption about one third of the time. In studies of Microsoft employees, Horvitz has similarly found that they typically spend more than 65 percent of their day in a state of low attention.

Today's phones and computers, which naively assume that the user is never too busy to take a call, read an e-mail, or click "OK" on an alert box, thus are probably correct about two thirds of time. (Hudson and Horvitz acknowledge, however, that it is not yet clear how well these figures generalize to other jobs.) To be useful, then, considerate systems will have to be more than 65 percent accurate in sensing when their users are near their cognitive limits.

Fortunately, this doesn't seem to require strapping someone into a heart monitor or a brain scanner. Fogarty and his collaborators have found that simply using a microphone to detect whether anyone is talking within earshot would raise accuracy to 76 percent. That is as good as the human judgment of coworkers who viewed videotapes of the subjects and guessed when they were uninterruptible. When Fogarty's group enhanced the software to detect not only conversations but also mouse movement, keyboard activity and the applications running on machines, the system's accuracy climbed to 87 percent for the two managers. Curiously, it rose only to 77 percent for the five scientists, perhaps because they are a chattier bunch.

Bestcom/Enhanced Telephony, a Microsoft prototype based on Horvitz's work, digs a little deeper into each user's computer to find clues about what they are up to. Microsoft launched an internal beta test of the system in mid-2003. By last October, Horvitz says, about 3,800 people were using the system to field their incoming phone calls.

Horvitz himself is one of those testers, and while we talk in his office in

Overview/*Sensing Attention*

- Computers continue to grow cheaper, more powerful and more pervasive. Human attention, in contrast, is a scarce and fixed resource. As we spend more of our time surrounded by "smart" devices, their productivity-sapping, stress-inducing interruptions increasingly detract from their value.
- Researchers at corporate and academic labs have developed several powerful techniques that enable computerized machines to estimate their user's cognitive load and focus of attention.
- Engineers are testing prototype systems that can automatically prioritize, reschedule or forward incoming phone calls and digital messages, much as a personal receptionist might. Similar attention-sensing technology has begun to appear in cars and may lead to more "considerate" everyday appliances.
- Monitoring a person's attention requires sophisticated reasoning based on in-depth surveillance. The work thus raises issues of privacy and reliability.

Attentive Autos

First the eyelids droop, then the head begins to bob. The car drifts out of its lane, then jerks back erratically. The signs of a drowsy or distracted driver are not hard to spot, but one must look for them. Many vehicles soon will.

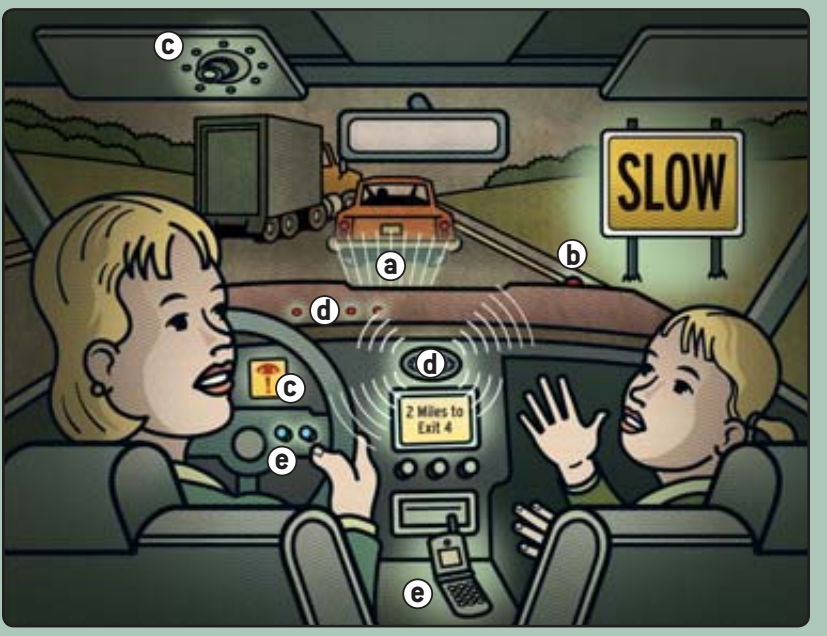
The U.S. National Highway Traffic Safety Administration (NHTSA) figures that 20 to 30 percent of crashes reported to the police—about 1.5 million every year—result at least in part from inattentive drivers. Technology contributes to this problem, cluttering up the cabin with phones, DVD players, touch-screen maps and other doodads. Now technology of a different kind may help to solve it.

In 2003 Volvo added an attention management system to its S40 sedans. Sensors pick up steering actions, accelerator position and other vehicle dynamics. They feed into a computer, which looks for evidence of swerving, overtaking or hard braking. When it notices such demanding maneuvers, the system suppresses nonsafety-critical messages from the onboard phone, navigation system, warning lights, and so on. In June, Motorola and DaimlerChrysler demonstrated a minivan outfitted with a similar system. More recently, Volvo has been testing cameras that can detect drowsy eyelids and suspicious lane crossings [*see illustration at right*].

Last March the European Union launched a four-year, €12.5-million project to develop industrywide standards for adaptive driver-vehicle interfaces by 2008. Engineers must still solve many tricky issues.

"Liability is a major stumbling block in the U.S.," observes Trent Victor, who designs driver awareness systems for Volvo. Automakers must be certain the computer will not make a bad situation worse, even if the driver uses it improperly.

Indeed, it seems inevitable that as the system adapts to drivers, drivers will adapt right back. "There are people today who use the rumble strips [which buzz when a car approaches the edge of a road] as a way to help them watch TV," Trent says. —*W.W.G.*



"CONSIDERATE CARS" of the future could combine a variety of systems to sense the attention level of the driver and prevent dangerous distractions. In this example, Alice is driving at high speed in heavy traffic, but her concentration is interrupted by a rambunctious daughter. The car ahead has begun to brake as it enters a construction zone. But at the same moment, Alice's mobile phone receives a call, and the onboard navigation system decides to alert her to an upcoming exit.

(a) **MIND THE GAP:** A short-range radar mounted on the front of the car notices that the vehicle ahead is getting closer. The adaptive cruise-control system automatically eases off the gas and gently applies the brake to maintain separation. Such systems are already available on certain luxury cars.

(b) **IT'S A SIGN:** A forward-looking video camera watches the road. An onboard computer continually scans the video for lane markers and road signs. It recognizes the construction warning ahead and raises the car's estimate of the current burden on the driver's attention. Alexander Zelinsky and his co-workers at the Australian National University have demonstrated such sign-reading systems.

(c) **WATCHING THE WATCHER:** LEDs on the visor shine invisible infrared light into Alice's eyes; a small infrared camera picks up the reflections from her pupils and deduces the direction of her gaze. If the driver takes her eyes off the road or shows signs of drowsiness, an icon in the instrument panel lights up, and the car goes on high alert. It vibrates the steering wheel if needed to rouse her. Zelinsky started a company, Seeing Machines, to commercialize such gaze monitors, and Volvo and others have tested them in cars and trucks.

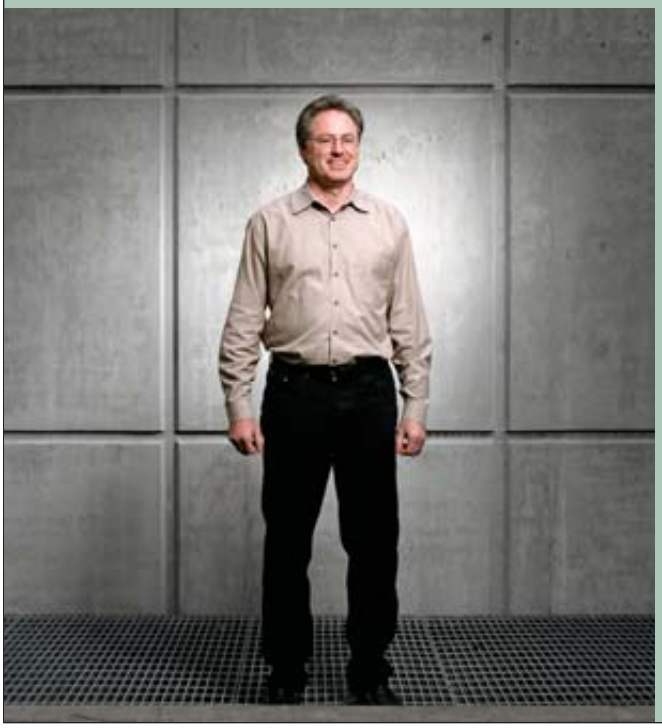
(d) **EYES ON THE ROAD:** Because Alice is looking away at a moment when the demands on her attention are high, the system emits an alert sound through the car speakers and flashes a sequence of lights on the dash that draws her attention back to the car ahead. Tests by Volvo have shown this method to be effective.

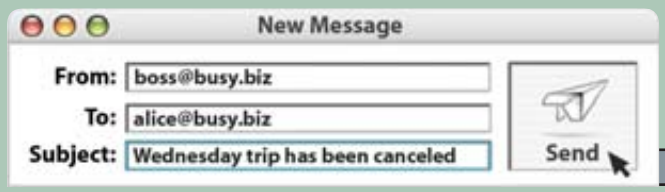
(e) **NOT NOW, PLEASE:** The onboard computer has a model of the driver's abilities and is always monitoring the cognitive load, so it knows that now is a bad time for a phone call or a navigational alert. The computer turns off the ringer on the cell phone and instead lights an unobtrusive "incoming message" button on the steering wheel that Alice can press to take the call when it is safe to do so. The car likewise lights another button to let her know that the navigation system has an instruction for her. Chrysler has built such gentle notification devices into some of its prototype cars.

PETER HOEY

AN AUTOMATED PERSONAL RECEPTIONIST

Notification Platform, a prototype system developed by Horvitz and his co-workers at Microsoft, performs triage on incoming communications much as a receptionist would. The system, which runs on a central server, analyzes messages to decide whether, when and how to notify the recipient of their arrival. It would handle the same e-mail message to Alice from her boss differently if she were conducting a job interview (*scenario 1*), reading e-mail (*2*) or packing for a business trip (*3*). One part of the system estimates the value of the message and how that value decays with time. A second part uses sensors and a statistical model to guess the focus and intensity of Alice's attention, what devices she is using, how likely she is to see the message without an alert, and how these variables will change in the future. A third part decides what kind of alert to issue.





ERIC HORVITZ (*left*) pioneered the use of sensors and statistical models (*above*) to build attention-aware communications systems.

Redmond, Wash., Bestcom silently handles one call after another. First it checks whether the caller is listed in his address book, the company directory, or its log of people he has called recently. Triangulating these sources, it tries to deduce their relationship. Family members, supervisors and people he called earlier today ring through. Others see a message on their computer that he is in a meeting and won't be available until 3 P.M. The system scans Horvitz's and the caller's calendar and offers to reschedule the call at a time that is open for both. Some callers choose that option; others leave voice mail. E-mail messages get a similar screening. When Horvitz is out of the office, Bestcom automatically offers to forward selected callers to his cell phone—unless his calendar and other evidence suggest that he is in a meeting.

Most large companies already use computerized phone systems and standard calendar and contact management software, so tapping into those "sensors" should be straightforward. Not all employees will like the idea of having a microphone on all the time in their office, however, nor will everyone want to expose their datebook to some program they do not ultimately control. Moreover, some managers might be tempted to equate a "state of low attention" with "goofing off" and punish those who seem insufficiently busy.

The researchers seem to appreciate these risks. Hudson argues that an attentive system should not record audio, keystrokes or the like but simply analyze the data streams and discard them after logging "conversation in progress," "typing detected," and so on. "We built a privacy tool into Bestcom from the beginning," Horvitz emphasizes, "so users can control who is allowed to see the various kinds of information it collects about them."

Watching the Watcher

AS DIGITAL CAMERAS fall in price, that information may come to include video. With a simple $20 webcam, Horvitz's software can tell when a person is in view and whether she is alone or in a meeting. Fancier cameras can use the eyes as a window to the mind and perhaps extend the reach of considerate computers into the home.

Vertegaal has filled the Human Media Lab at Queen's University with everyday appliances that know when you are looking at them. "When I say 'on,' the lamp over there doesn't do any-

KC ARMSTRONG (*photographs*); PETER HOEY (*scenarios*); JEN CHRISTIANSEN (*diagram*)

SCENARIO 1

Monday, 10:07 A.M.

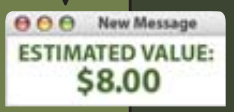
SCENARIO 2

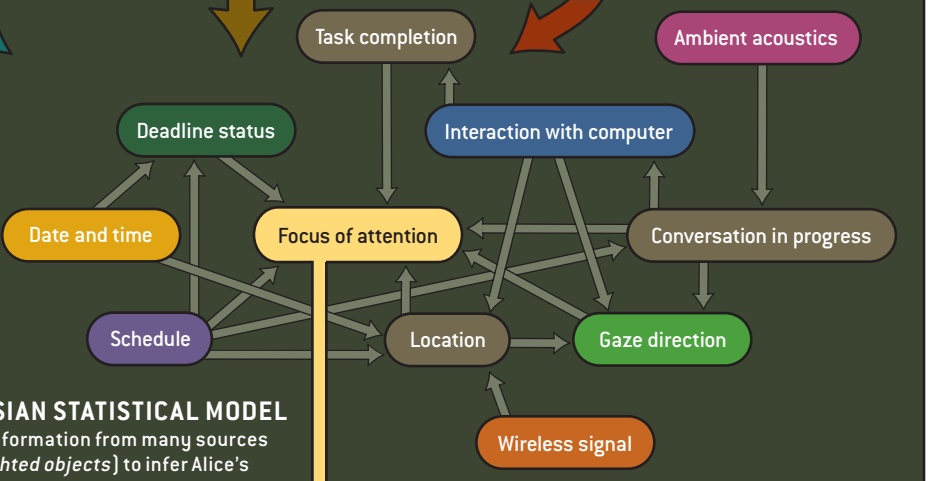
Tuesday, 9:00 A.M.

SCENARIO 3

Wednesday, 6:15 A.M.

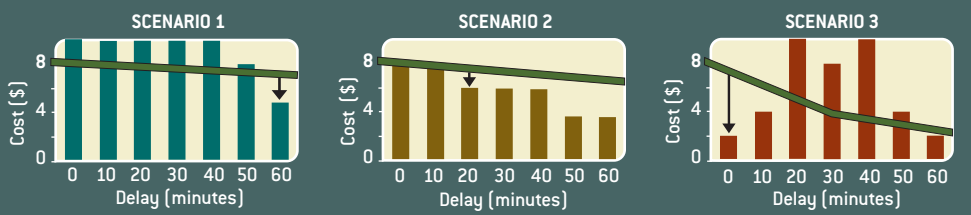
URGENCY CLASSIFIER consults its database to determine the relationship between the sender and recipient and their communication history. A linguistic analyzer scans the text for times, dates and key words. The classifier "stamps" the message with a dollar value that can fall as the communication grows stale.

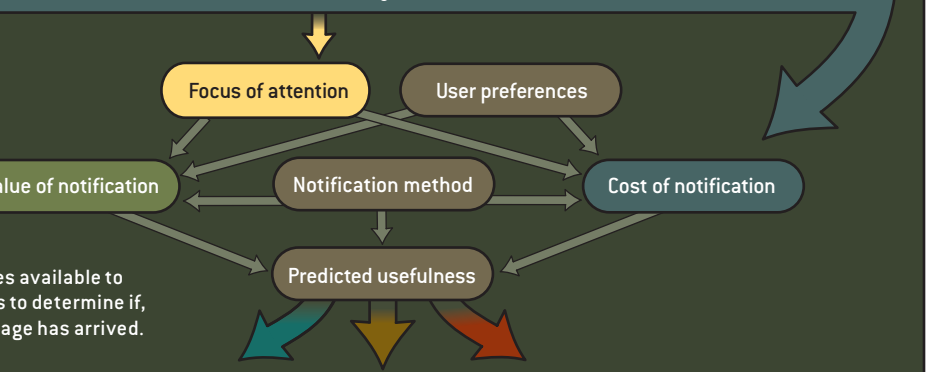




BAYESIAN STATISTICAL MODEL fuses information from many sources (*highlighted objects*) to infer Alice's current focus of attention.

The system also estimates the cost of interrupting Alice now and in the near future. It alerts her to the message only when the cost of a distraction falls below the value of a notification (*arrows*).





DECISION MODEL surveys the devices available to Alice and performs a cost-benefit analysis to determine if, when and how to signal her that this message has arrived.

SCENARIO 1

The Notification Platform adds the e-mail from Alice's boss to her inbox but does not notify her about the message until one hour later, after her appointment with the job candidate has ended.

SCENARIO 2

The system senses that Alice is at her PC and is composing an e-mail. It waits for her to finish writing, then chimes and displays a small alert box in the corner of the screen, notifying her about the message from her boss.

SCENARIO 3

The system matches the subject of the e-mail to an entry in Alice's schedule for today and assigns it highest priority. The e-mail is forwarded to her "considerate" cell phone, which signals her with an urgent ring tone.

WATCHING THE EYES TO FOLLOW THE MIND

Roel Vertegaal (*left*) and his students at Queen's University in Kingston, Ontario, have been enhancing televisions, phones, computers and video-conferencing systems with the ability to sense human eye contact. They have also put the technology to artistic use in AuraMirror (*right*). Hidden infrared lights, cameras and a computer transform a large monitor into a virtual magic mirror that superimposes nebulous "auras" over the images of people in front of it. The blobs extend outward and merge when two observers look at each other, giving visible form to an intangible human connection (*far right*).

> "Eye contact is the most accurate measure of attention that we have. But it's not perfect by any means."

thing," Vertegaal says, pointing over his shoulder. He turns to face the object.

"On," he says. LEDs mounted on a small circuit board stuck to the lamp shoot invisible infrared light into his pupils. The light reflects off his retinas, and an infrared camera on the board picks up two bright spots in the image, one from each eye. A processor does some quick pattern and speech recognition, and the lamp switches on.

Gaze detection can endow quotidian machines with seemingly magical behavior. Vertegaal answers a ringing telephone by looking at it and saying "Hello." When he stops talking and turns away from the phone, it hangs up. The TV in the lab pauses a DVD or mutes the sound on a broadcast show whenever it notices that there are no longer any eyes watching it. Some of Vertegaal's students walk around with eye-contact sensors on their hat or glasses. When the wearer enters a conversation, the sensor passes that information via a wireless link to the cell phone in his pocket, which then switches from ring mode to vibrate.

Although the technology is steadily improving, gaze detectors are still too expensive, bulky, ugly and unreliable for everyday use. "Eye contact is the most accurate measure of attention that we have—about 80 percent accurate in conversational settings," Vertegaal says. "But it's not perfect by any means."

Attentive appliances are mere parlor tricks, moreover, when they act independently. The real payoff will only come from larger, smarter systems that can both divine the focus of our attention and moderate our conversation with all our personal machines. Doing that reliably will require a nice bit of reasoning.

Trusting the Black Box

BROADLY SPEAKING, computers can use two techniques—rules or models—to decide when and how to transmit a particular piece of information. Both approaches must face the bugbear of complexity.

If the system is limited to following a few rules, users can predict exactly how it will treat a given message. Many e-mail programs, for example, manage spam by maintaining lists of known spammers and of legitimate contacts. When each e-mail arrives, its sender is compared against both lists and either deleted or delivered. Such systems are simple and clear—but infamously inaccurate.

Spam filters and network firewalls improved significantly when they began to rely on statistical models, called Bayesian networks, that are built by machine-learning algorithms. The user gives the algorithm many examples of desirable messages and also some counterexamples of undesired traffic. "The software identifies all the variables that influence the property that you are interested in [for example, not spam], then searches over all feasible relationships among those variables to find the model that is most predictive," Horvitz explains.

Bayesian networks can be eerily accurate. "They use probabilities, so they are wise in the sense that they know that they can't know everything," Horvitz

> "Artificial intelligence couldn't deliver the personal secretary. I'm pretty sure we can deliver a personal receptionist."

KC ARMSTRONG

elaborates. "That allows them to capture subtle behaviors that would require thousands of strict rules." In January he plans to present the results of a field trial of a model trained on 559 past appointments taken from a manager's datebook. When challenged with 100 calendar entries it had never seen, the model correctly predicted whether the manager would attend the meeting 92 percent of the time. And in four out of every five cases, the model matched the manager's own estimate of the cost of interruption during the meeting.

That sounds impressive, but some experts in the field remain skeptical. Users may have a very low tolerance for a system that erroneously suppresses one out of every 10 important calls. "The more 'attentive' things become, the more unpredictable they are," warns Ben Shneiderman of the University of Maryland. "We have a history in this community of creating 'smart' devices that people don't use because they can't understand how they operate."

Indeed, Vertegaal reflects, "artificial intelligence couldn't deliver the personal secretary, because it was too complicated." Nevertheless, he adds, "I'm pretty sure we can deliver a receptionist."

That would be welcome, but will considerate computing really reduce interruptions and boost productivity? At least for certain specialized tasks, the answer is: unquestionably.

Consider Lockheed Martin's HAIL-SS (Human Alerting and Interruption Logistics-Surface Ship) system. In much the way that Bestcom interposes itself between the phone system and an office worker, HAIL-SS keeps an eye on the sailors operating an Aegis naval weapons system and mediates the many alerts that Aegis produces. In combat simulations, HAIL-SS cut the number of interruptions by 50 to 80 percent, allowing sailors to handle critical alerts up to twice as quickly. The software lowered the perceived difficulty and stressfulness of the job by one quarter. The U.S. Navy now plans to deploy HAIL-SS throughout the fleet.

No comparable studies have yet been done in the office environment, however. Even with Bestcom diverting callers to voice mail and squelching e-mail alerts, Horvitz was interrupted 14 times in the course of our five-hour interview. Two fire alarms, a FedEx deliveryman and numerous colleagues poking their head into the office were merely examples of a large class of disruptions that will never disappear, because they benefit the interrupter.

Vertegaal is optimistic nonetheless. "By opening up these new sources of information about how available someone is, people will naturally adapt and use them to apply existing social rules of etiquette," he predicts. "So just by virtue of letting people know when you're busy, you'll get fewer interruptions." SA

W. Wayt Gibbs is senior writer.

MORE TO EXPLORE

Attentive User Interfaces. Special section. Edited by Roel Vertegaal in *Communications of the ACM,* Vol. 46, No. 3, pages 30–72; March 2003.

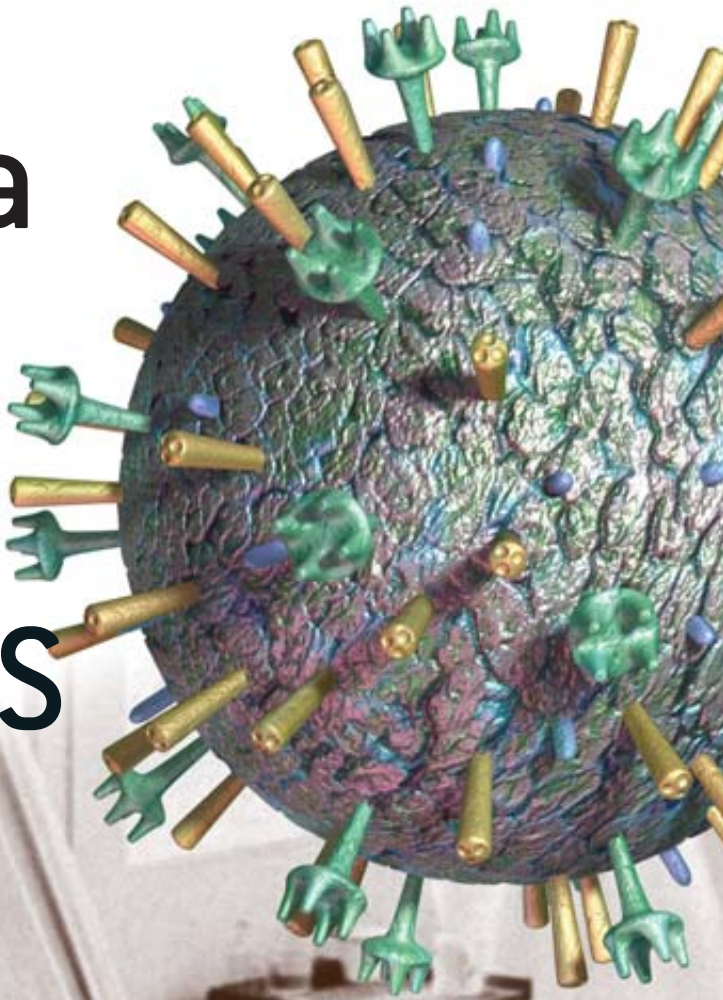
Learning and Reasoning about Interruption. Eric Horvitz and Johnson Apacible. Proceedings of the Fifth International Conference on Multimodal Interfaces, November 2003.

Proceedings of the International Workshop on Progress and Future Directions of Adaptive Driver Assistance Research. Washington, D.C., May 2004. Available online at **www.volpe.dot.gov/opsad/saveit/**

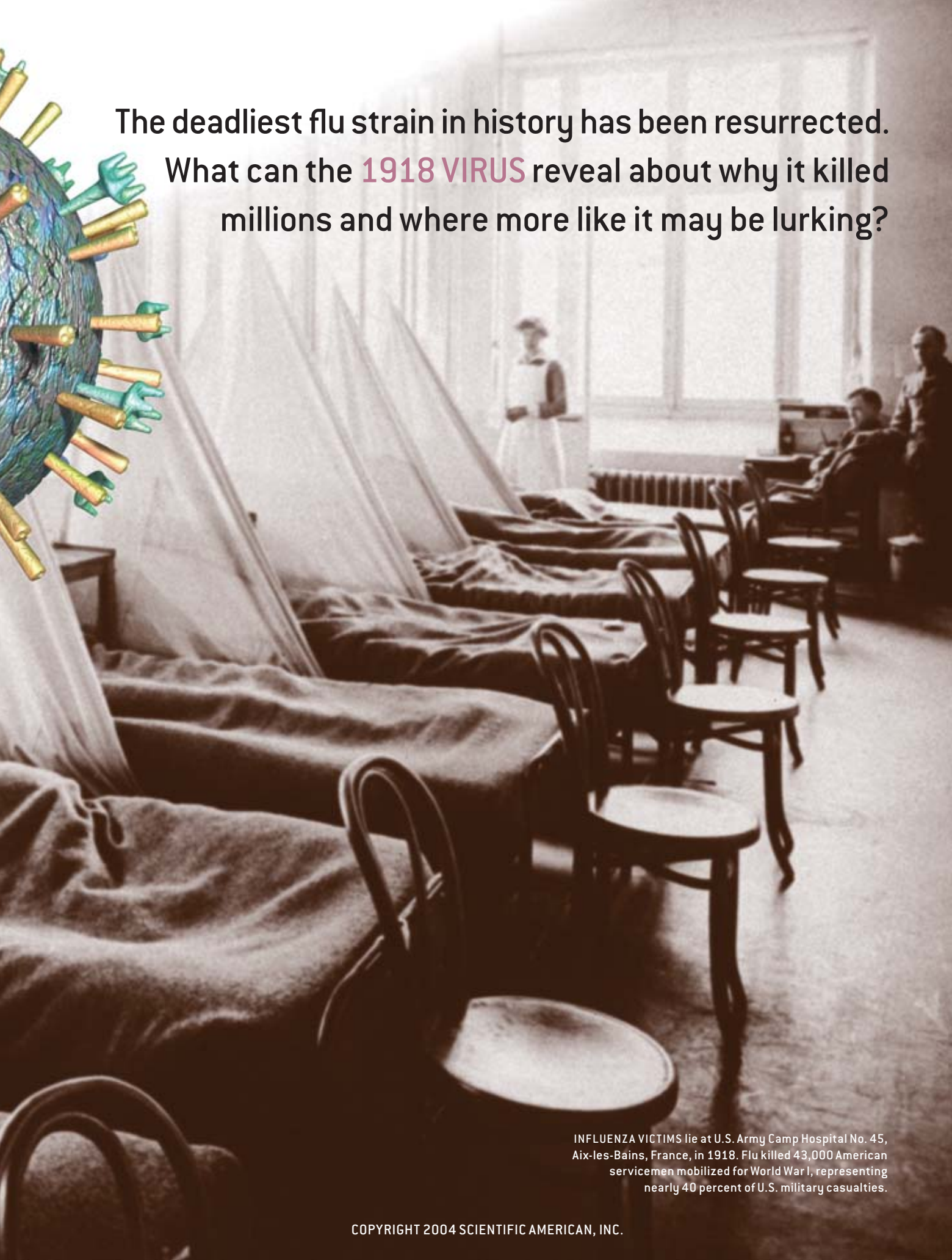
A variety of relevant technical articles are available online at **http://interruptions.net**

KC ARMSTRONG

Capturing a Killer Flu VIRUS



By Jeffery K. Taubenberger, Ann H. Reid and Thomas G. Fanning



The deadliest flu strain in history has been resurrected. What can the 1918 VIRUS reveal about why it killed millions and where more like it may be lurking?

INFLUENZA VICTIMS lie at U.S. Army Camp Hospital No. 45, Aix-les-Bains, France, in 1918. Flu killed 43,000 American servicemen mobilized for World War I, representing nearly 40 percent of U.S. military casualties.

RED CROSS NURSES in St. Louis carry a flu patient in 1918. Health workers, police and a panicked public donned face masks for protection as the virus swept the country. Nearly a third of all Americans were infected during the pandemic, and 675,000 of them died.

On September 7, 1918, at the height of World War I, a soldier at an army training camp outside Boston came to sick call with a high fever. Doctors diagnosed him with meningitis but changed their minds the next day when a dozen more soldiers were hospitalized with respiratory symptoms. Thirty-six new cases of this unknown illness appeared on the 16th. Incredibly, by September 23rd, 12,604 cases had been reported in the camp of 45,000 soldiers. By the end of the outbreak, one third of the camp's population would come down with this severe disease, and nearly 800 of them would die. The soldiers who perished often developed a bluish skin color and struggled horribly before succumbing to death by suffocation. Many died less than 48 hours after their symptoms appeared, and at autopsy their lungs were filled with fluid or blood.

Because this unusual suite of symptoms did not fit any known malady, a distinguished pathologist of the era, William Henry Welch, speculated that "this must be some new kind of infection or plague." Yet the disease was neither plague nor even new. It was just influenza. Still, this particularly virulent and infectious strain of the flu virus is thought to have killed as many as 40 million people around the world between 1918 and 1919.

This most lethal flu outbreak in modern history disappeared almost as quickly as it emerged, and its cause was long believed lost to time. No one had preserved samples of the pathogen for later study because influenza would not be identified as a virus until the 1930s. But thanks to incredible foresight by the U.S. Army Medical Museum, the persistence of a pathologist named Johan Hultin, and advances in genetic analysis of old tissue samples, we have been able to retrieve parts of the 1918 virus and study their features. Now, more than 80 years after the horrible natural disaster of 1918–1919, tissues recovered from a handful of victims are answering fundamental questions both about the nature of this pandemic strain and about the workings of influenza viruses in general.

The effort is not motivated merely by historical curiosity. Because influenza viruses continually evolve, new influenza strains continually threaten human populations. Pandemic human flu viruses have emerged twice since 1918—in 1957 and 1968. And flu strains that usually infect only animals have also periodically caused disease in humans, as seen in the recent outbreak of avian influenza in Asia. Our two principal goals are determining what made the 1918 influenza so virulent, to guide development of influenza treatments and preventive measures, and establishing the origin of the pandemic virus, to better target possible sources of future pandemic strains.

Overview/*The Mystery of 1918*

- The flu pandemic that swept the globe in 1918–1919 was exceptional for the sheer numbers it killed, especially the number of young people who succumbed to the unusually virulent flu virus.
- What made the strain so deadly was a longstanding medical mystery until the authors devised techniques that allowed them to retrieve the 1918 virus's genes from victims' preserved tissues.
- Analysis of those genes and the proteins they encode revealed viral features that could have both suppressed immune defenses and provoked a violent immune reaction in victims, contributing to the high mortality.
- Known bird and mammal influenza hosts are unlikely sources of the pandemic virus, so its origin remains unsolved.

Hunting the 1918 Virus

IN MANY RESPECTS, the 1918 influenza pandemic was similar to others before it and since. Whenever a new flu strain emerges with features that have never been encountered by most people's immune systems, widespread flu outbreaks are likely. But certain unique characteristics of the 1918 pandemic have long remained enigmatic.

For instance, it was exceptional in both its breadth and depth. Outbreaks swept across Europe and North America, spreading as far as the Alaskan wilderness and the most remote islands of the Pacific. Ultimately, one third of the world's population may have been infected. The disease was also unusually severe, with death rates of 2.5 to 5 percent—up to 50 times the mortality seen in other influenza outbreaks.

GEORGE RETSECK (*flu virus*); CORBIS (*hospital*) (*preceding pages*); AMERICAN RED CROSS MUSEUM (*this page*)

By the fall of 1918 everyone in Europe was calling the disease the "Spanish" influenza, probably because neutral Spain did not impose the wartime censorship of news about the outbreak prevalent in combatant countries. The name stuck, although the first outbreaks, or spring wave, of the pandemic seemingly arose in and around military camps in the U.S. in March 1918. The second, main wave of the global pandemic occurred from September to November 1918, and in many places yet another severe wave of influenza hit in early 1919.

Antibiotics had yet to be discovered, and most of the people who died during the pandemic succumbed to pneumonia caused by opportunistic bacteria that infected those already weakened by the flu. But a subset of influenza victims died just days after the onset of their symptoms from a more severe viral pneumonia—caused by the flu itself—that left their lungs either massively hemorrhaged or filled with fluid. Furthermore, most deaths occurred among young adults between 15 and 35 years old, a group that rarely dies from influenza. Strikingly, people younger than 65 years accounted for more than 99 percent of all "excess" influenza deaths (those above normal annual averages) in 1918–1919.

Efforts to understand the cause of the 1918 pandemic and its unusual features began almost as soon as it was over, but the culprit virus itself remained hidden for nearly eight decades. In 1951 scientists from the University of Iowa, including a graduate student recently arrived from Sweden named Johan Hultin, went as far as the Seward Peninsula of Alaska seeking the 1918 strain [*see box on page 71*]. In November 1918 flu spread through an Inuit fishing village now called Brevig Mission in five days, killing 72 people—about 85 percent of the adult population. Their bodies had since been buried in permafrost, and the 1951 expedition members hoped to find the 1918 virus preserved in the victims' lungs. Unfortunately, all attempts to culture live influenza virus from these specimens were unsuccessful.

In 1995 our group initiated an attempt to find the 1918 virus using a different source of tissue: archival autopsy specimens stored at the Armed Forces Institute of Pathology (AFIP). For several years, we had been developing expertise in extracting fragile viral genetic material from damaged or decayed tissue for diagnostic purposes. In 1994, for instance, we were able to use our new techniques to help an AFIP marine mammal pathologist investigate a mass dolphin die-off that had been blamed on red tide. Although the available dolphin tissue samples were badly decayed, we extracted enough pieces of RNA from them to identify a new virus, similar to the one that causes canine distemper, which proved to be the real cause of the dolphin deaths. Soon we began to wonder if there were any older medical mysteries we might solve with our institute's resources.

A descendant of the U.S. Army Medical Museum founded in 1862, the AFIP has grown along with the medical specialty of pathology and now has a collection of three million specimens. When we realized that these included autopsy samples from 1918 flu victims, we decided to go after the pandemic virus. Our initial study examined 78 tissue samples from victims of the deadly fall wave of 1918, focusing on those with the severe lung damage characteristic of patients who died rapidly. Because the influenza virus normally clears the lungs just days after infection, we had the greatest chance of finding virus remnants in these victims.

The standard practice of the era was to preserve autopsy specimens in formaldehyde and then embed them in paraffin, so fishing out tiny genetic fragments of the virus from these 80-year-old "fixed" tissues pushed the very limits of the techniques we had developed. After an agonizing year of negative results, we found the first influenza-positive sample in 1996, a lung specimen from a soldier who died in September 1918 at Fort Jackson, S.C. We were able to determine the sequence of nucleotides in small fragments of five influenza genes from this sample.

But to confirm that the sequences belonged to the lethal 1918 virus, we kept looking for more positive cases and identified another one in 1997. This soldier also died in September 1918, at Camp Upton, N.Y. Having a second sample allowed us to confirm the gene sequences we had, but the tiny quantity of tissue remaining from these autopsies made us worry that we would never be able to generate a complete virus sequence.

A solution to our problem came from an unexpected source in 1997: Johan Hultin, by then a 73-year-old retired pathologist, had read about our initial results. He offered to return to Brevig Mission to try another exhumation of 1918 flu victims interred in permafrost. Forty-

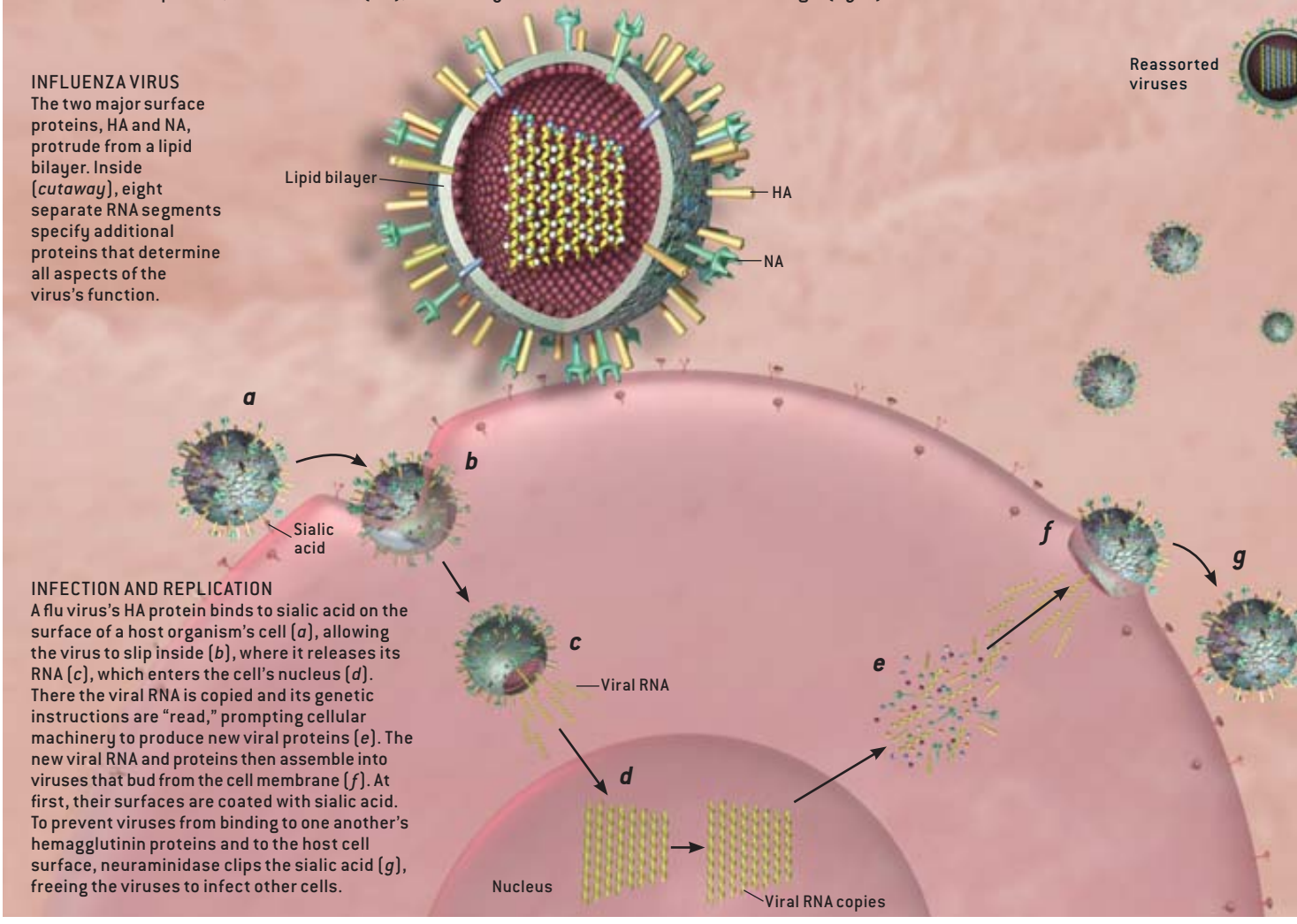
After an AGONIZING YEAR of negative results, we found THE FIRST CASE in 1996.

THE AUTHORS

JEFFERY K. TAUBENBERGER, ANN H. REID and *THOMAS G. FANNING* work together at the Armed Forces Institute of Pathology in Rockville, Md. In 1993 Taubenberger, a molecular pathologist, helped to create a laboratory there devoted to molecular diagnostics—identifying diseases by their genetic signatures rather than by the microscopic appearance of patients' tissue samples. Early work by Reid, a molecular biologist, led the group to devise the techniques for extracting DNA and RNA from damaged or decayed tissue that allowed them to retrieve bits and pieces of 1918 flu virus genes from archived autopsy specimens. Fanning, a geneticist with expertise in the evolution of genomes, helped to analyze the genes' relationships to other animal and human flu viruses. The authors wish to note that the opinions expressed in this article are their own and do not represent the views of the Department of Defense or the AFIP.

FLU HIJACKS HOSTS TO REPLICATE AND EVOLVE

Influenza is a small and simple virus—just a hollow lipid ball studded with a few proteins and bearing only eight gene segments (*below*). But that is all it needs to induce the cells of living hosts to make more viruses (*bottom*). One especially important protein on influenza's surface, hemagglutinin (HA), allows the virus to enter cells. Its shape determines which hosts a flu virus strain can infect. Another protein, neuraminidase (NA), cuts newly formed viruses loose from an infected cell, influencing how efficiently the virus can spread. Slight changes in these and other flu proteins can help the virus infect new kinds of hosts and evade immune attack. The alterations can arise through mistakes that occur while viral genes are being copied. Or they can be acquired in trade when the genes of two different flu viruses infecting the same cell intermingle (*right*).



INFLUENZA VIRUS
The two major surface proteins, HA and NA, protrude from a lipid bilayer. Inside (*cutaway*), eight separate RNA segments specify additional proteins that determine all aspects of the virus's function.

INFECTION AND REPLICATION
A flu virus's HA protein binds to sialic acid on the surface of a host organism's cell (*a*), allowing the virus to slip inside (*b*), where it releases its RNA (*c*), which enters the cell's nucleus (*d*). There the viral RNA is copied and its genetic instructions are "read," prompting cellular machinery to produce new viral proteins (*e*). The new viral RNA and proteins then assemble into viruses that bud from the cell membrane (*f*). At first, their surfaces are coated with sialic acid. To prevent viruses from binding to one another's hemagglutinin proteins and to the host cell surface, neuraminidase clips the sialic acid (*g*), freeing the viruses to infect other cells.

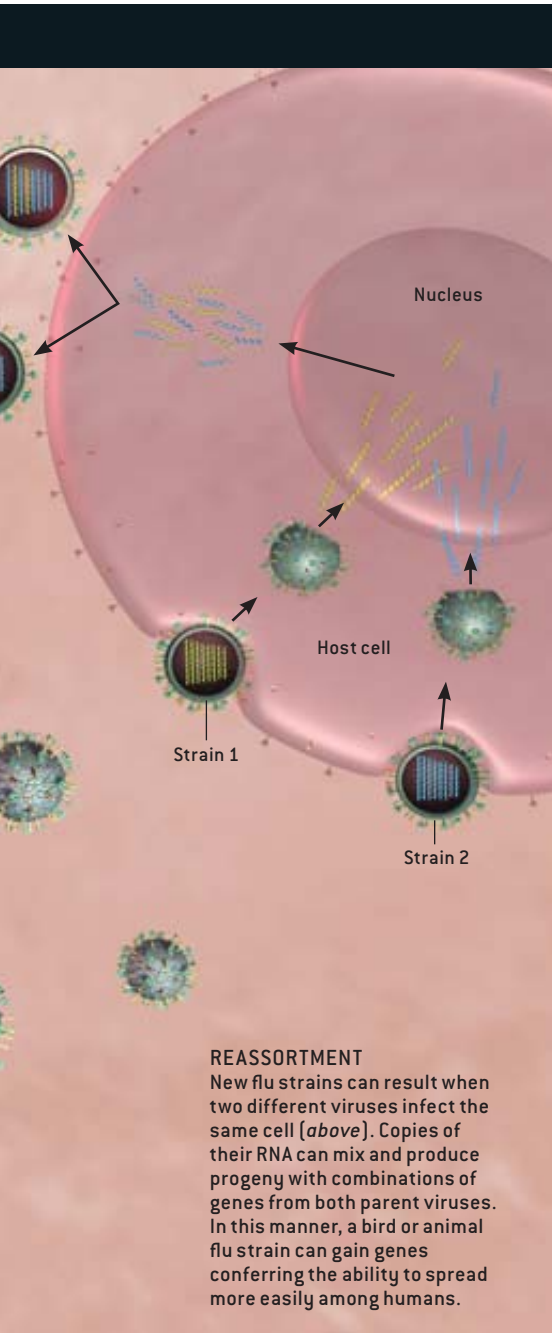
six years after his first attempt, with permission from the Brevig Mission Council, he obtained frozen lung biopsies of four flu victims. In one of these samples, from a woman of unknown age, we found influenza RNA that provided the key to sequencing the entire genome of the 1918 virus.

More recently, our group, in collaboration with British colleagues, has also been surveying autopsy tissue samples from 1918 influenza victims from the Royal London Hospital. We have been able to analyze flu virus genes from two of these cases and have found that they were nearly identical to the North American samples, confirming the rapid worldwide spread of a uniform virus. But what can the sequences tell us about the virulence and origin of the 1918 strain? Answering those questions requires a bit of background about how influenza viruses function and cause disease in different hosts.

Flu's Changing Face

EACH OF THE THREE novel influenza strains that caused pandemics in the past 100 years belonged to the type A group of flu viruses. Flu comes in three main forms, designated A, B and C. The latter two infect only humans and have never caused pandemics. Type A influenza viruses, on the other hand, have been found to infect a wide variety of animals, including poultry, swine, horses, humans and other mammals. Aquatic birds, such as ducks, serve as the natural "reservoir" for all the known subtypes of influenza A, meaning that the virus infects the bird's gut without causing symptoms. But these wild avian strains

GEORGE RETSECK



REASSORTMENT
New flu strains can result when two different viruses infect the same cell (*above*). Copies of their RNA can mix and produce progeny with combinations of genes from both parent viruses. In this manner, a bird or animal flu strain can gain genes conferring the ability to spread more easily among humans.

can mutate over time or exchange genetic material with other influenza strains, producing novel viruses that are able to spread among mammals and domestic poultry.

The life cycle and genomic structure of influenza A virus allow it to evolve and exchange genes easily. The virus's genetic material consists of eight separate RNA segments encased in a lipid membrane studded with proteins [*see top illustration on opposite page*]. To reproduce, the virus binds to and then enters a living cell, where it commandeers cellular machinery, inducing it to manufacture new viral proteins and additional copies of viral RNA. These pieces then assemble themselves into new viruses that escape the host cell, proceeding to infect other cells. No proofreading mechanism ensures that the RNA copies are accurate, so mistakes leading to new mutations are common. What is more, should two different influenza virus strains infect the same cell, their RNA segments can mix freely there, producing progeny viruses that contain a combination of genes from both the original viruses. This "reassortment" of viral genes is an important mechanism for generating diverse new strains.

Different circulating influenza A viruses are identified by referring to two signature proteins on their surfaces. One is hemagglutinin (HA), which has at least 15 known variants, or subtypes. Another is neuraminidase (NA), which has nine subtypes. Exposure to these proteins produces distinctive antibodies in a host, thus the 1918 strain was the first to be named, "H1N1," based on antibodies found in the bloodstream of pandemic survivors. Indeed, less virulent descendants of H1N1 were the predominant circulating flu strains until 1957, when an H2N2 virus emerged, causing a pandemic. Since 1968, the H3N2 subtype, which provoked the pandemic that year, has predominated.

The HA and NA protein subtypes present on a given influenza A virus are more than just identifiers; they are essential for viral reproduction and are primary targets of an infected host's immune system. The HA molecule initiates infection by binding to receptors on the surface of certain host cells. These tend to be respiratory lining cells in mammals and intestinal lining cells in birds. The NA protein enables new virus copies to escape the host cell so they can go on to infect other cells.

After a host's first exposure to an HA subtype, antibodies will block receptor binding in the future and are thus very effective at preventing reinfection with the same strain. Yet flu viruses with HA subtypes that are new to humans periodically appear, most likely through reassortment with the extensive pool of influenza viruses infecting wild birds. Normally, influenza HAs that are adapted to avian hosts bind poorly to the cell-surface receptors prevalent in the human respiratory tract, so an avian virus's HA binding affinity must be somewhat modified before the virus can replicate and spread efficiently in humans. Until recently, existing evidence suggested that a wholly avian influenza virus probably could not directly infect humans, but 18 people were infected with an avian H5N1 influenza virus in Hong Kong in 1997, and six died.

Outbreaks of an even more pathogenic version of that H5N1 strain became widespread in Asian poultry in 2003 and 2004, and more than 30 people infected with this virus have died in Vietnam and Thailand.

The virulence of an influenza virus once it infects a host is determined by a complex set of factors, including how readily the virus enters different tissues, how quickly it replicates, and the violence of the host's immune response to the intruder. Thus, understanding exactly what made the 1918 pandemic influenza strain so infectious and so virulent could yield great insight into what makes any influenza strain more or less of a threat.

A Killer's Face

WITH THE 1918 RNA we have retrieved, we have used the virus's own genes as recipes for manufacturing its component parts—essentially re-creating pieces of the killer virus itself. The first of these we were eager to examine was the hemagglutinin protein, to look for features that might explain the exceptional virulence of the 1918 strain.

We could see, for example, that the part of the 1918 HA that binds with a host cell is nearly identical to the binding site of a wholly avian influenza HA [*see illustration on page 69*]. In two of the 1918 isolates, this receptor-binding site differs from an avian form by only one amino acid building block. In the other three isolates, a second amino acid is also altered. These seemingly subtle mutations may represent the min-

REVERSE ENGINEERING THE FLU

When analyzing the genes of the 1918 virus revealed no definitive reasons for the pandemic strain's virulence, our group turned to reverse genetics—a method of understanding the function of genes by studying the proteins they encode. In collaboration with scientists from the Mount Sinai School of Medicine, the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the University of Washington and the Scripps Research Institute, we "built" influenza viruses containing one or more of the 1918 virus's genes, so we could see how these recombinant viruses behaved in animals and human cell cultures.

To construct these viruses, we employed a new technique called plasmid-based reverse genetics, which requires first making DNA copies of flu genes that normally exist in RNA form. Each DNA gene copy is then inserted into a tiny ring of DNA called a plasmid. Different combinations of these plasmids can be injected into living cells, where cellular machinery will execute the genetic instructions they bear and manufacture flu viruses with only the desired combination of genes.

Reverse genetics not only allows us to study the 1918 virus, it will allow scientists in the U.S. and Europe to explore how great a threat the H5N1 avian flu virus poses to humans. Since January 2004, that strain—which is now present in birds in 10 Asian countries—has infected more than 40 people, killing more than 30 of them. One of the casualties was a mother who is believed to have contracted the virus from her daughter, rather than directly from a bird.

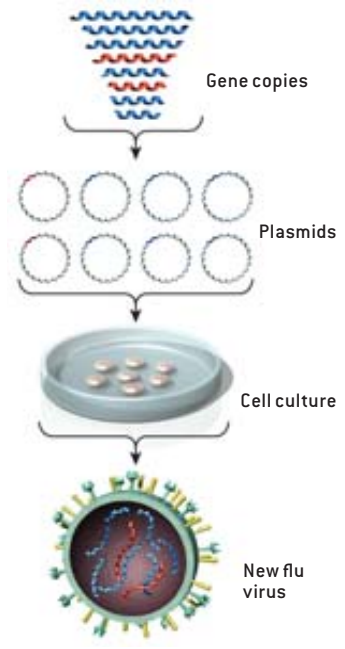
Such human-to-human transmission could suggest that in their case the avian virus had adapted to be more easily spread between humans, either by mutating or by acquiring new genes through reassortment with a circulating human flu strain. That dreaded development would increase the possibility of a human pandemic. Hoping to predict and thereby prevent such a disaster, scientists at the CDC and Erasmus University in the Netherlands are planning to test combinations of H5N1 with current human flu strains to assess the likelihood of their occurring naturally and their virulence in people.

What these experiments will reveal, as in our group's work with the 1918 virus genes, is crucial to understanding how influenza pandemics form and why they cause disease. Some observers have questioned the safety of experimenting with lethal flu strains, but all of this research is conducted in secure laboratories designed specifically to deal with highly pathogenic influenza viruses.

What is more, re-creating the 1918 virus proteins enabled us to establish that currently available antiviral drugs, such as amantadine or the newer neuraminidase inhibitors, such as oseltamivir (Tamiflu), would be effective against the 1918 strain in the case of an accidental infection. The H5N1 viruses are also sensitive to the neuraminidase inhibitors.

Scientists in the U.S. and U.K. also recently employed plasmid-based reverse genetics to create a seed strain for a human vaccine against H5N1. They made a version of the H5N1 virus lacking the wild strain's most deadly features, so that manufacturers could safely use it to produce a vaccine [see "The Scientific American 50," December 2004]. Clinical trials of that H5N1 vaccine were scheduled to begin at the end of 2004.

—J.K.T., A.H.R. and T.G.F.



PLASMID-BASED reverse genetics lets scientists custom-manufacture flu viruses. DNA copies of genes from two different flu strains (*blue* and *red*) are inserted into DNA rings called plasmids. The gene-bearing plasmids are then injected into a culture of living cells, which manufacture whole flu viruses containing the desired combination of genes.

imal change necessary to allow an avian-type HA to bind to mammalian-type receptors.

But while gaining a new binding affinity is a critical step that allows a virus to infect a new type of host, it does not necessarily explain why the 1918 strain was so lethal. We turned to the gene sequences themselves, looking for features that could be directly related to virulence, including two known mutations in other flu viruses. One involves the HA gene: to become active in a cell, the HA protein must be cleaved into two pieces by a gut-specific protein-cutting enzyme, or protease, supplied by the host. Some avian H5 and H7 subtype viruses acquire a gene mutation that adds one or more basic amino acids to the cleavage site, allowing HA to be activated by ubiquitous proteases. In chickens and other birds, infection by such a virus causes disease in multiple organs and even the central nervous system, with a very high mortality rate. This mutation has been observed in the H5N1 viruses currently circulating in Asia. We did not, however, find it in the 1918 virus.

The other mutation with a significant effect on virulence has been seen in the NA gene of two influenza virus strains that infect mice. Again, mutations at a single amino acid appear to allow the virus to replicate in many different body tissues, and these flu strains are typically lethal in laboratory mice. But we did not see this mutation in the NA of the 1918 virus either.

Because analysis of the 1918 virus's

GEORGE RETSECK

genes was not revealing any characteristics that would explain its extreme virulence, we initiated a collaborative effort with several other institutions to re-create parts of the 1918 virus itself so we could observe their effects in living tissues.

A new technique called plasmid-based reverse genetics allows us to copy 1918 viral genes and then combine them with the genes of an existing influenza strain, producing a hybrid virus. Thus, we can take an influenza strain adapted to mice, for example, and give it different combinations of 1918 viral genes. Then, by infecting a live animal or a human tissue culture with this engineered virus, we can see which components of the pandemic strain might have been key to its pathogenicity.

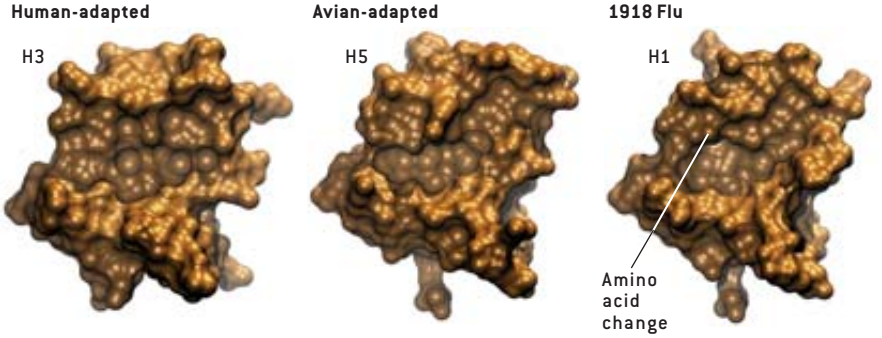
For instance, the 1918 virus's distinctive ability to produce rapid and extensive damage to both upper and lower respiratory tissues suggests that it replicated to high numbers and spread quickly from cell to cell. The viral protein NS1 is known to prevent production of type I interferon (IFN)—an "early warning" system that cells use to initiate an immune response against a viral infection. When we tested recombinant viruses in a tissue culture of human lung cells, we found that a virus with the 1918 NS1 gene was indeed more effective at blocking the host's type I IFN system.

To date, we have produced recombinant influenza viruses containing between one and five of the 1918 genes. Interestingly, we found that any of the recombinant viruses possessing both the 1918 HA and NA genes were lethal in mice, causing severe lung damage similar to that seen in some of the pandemic fatalities. When we analyzed these lung tissues, we found signatures of gene activation involved in common inflammatory responses. But we also found higher than normal activation of genes associated with the immune system's offensive soldiers, T cells and macrophages, as well as genes related to tissue injury, oxidative damage, and apoptosis, or cell suicide.

More recently, Yoshihiro Kawaoka of the University of Wisconsin–Madison reported similar experiments with 1918 flu genes in mice, with similar results. But when he tested the HA and NA genes separately, he found that only the 1918 HA produced the intensive immune response, suggesting that for reasons as yet unclear, this protein may have played a key role in the 1918 strain's virulence.

These ongoing experiments are providing a window to the past, helping scientists understand the unusual characteristics of the 1918 pandemic. Similarly, these techniques will be used to study what types of changes to the current H5N1 avian influenza strain might give that extremely lethal virus the potential to become pandemic in humans [*see box on opposite page*]. An equally compelling question is how such virulent strains emerge in the first place, so our group has also been analyzing the 1918 virus's genes for clues about where it might have originated.

Seemingly subtle mutations may allow an AVIAN hemagglutinin to bind to MAMMALIAN receptors.



HEMAGGLUTININ (HA) of the 1918 flu strain was re-created from its gene sequence by the authors' collaborators so they could examine the part that binds to a host cell's sialic acid and allows the virus to enter the cell. HA binding sites usually are shaped differently enough to bar cross-species infection. For instance, the human-adapted H3-type HA has a wide cavity in the middle of its binding site (*left*), whereas the avian H5 cavity (*center*) is narrow. The 1918 H1-type HA (*right*) more closely resembles the avian form, with only a few minor differences in the sequence of its amino acid building blocks. One of these alterations (*above right*) slightly widens the central cavity, apparently just enough to have allowed a flu virus with this avian-type HA to infect hundreds of millions of humans in 1918–1919.

Seeking the Source

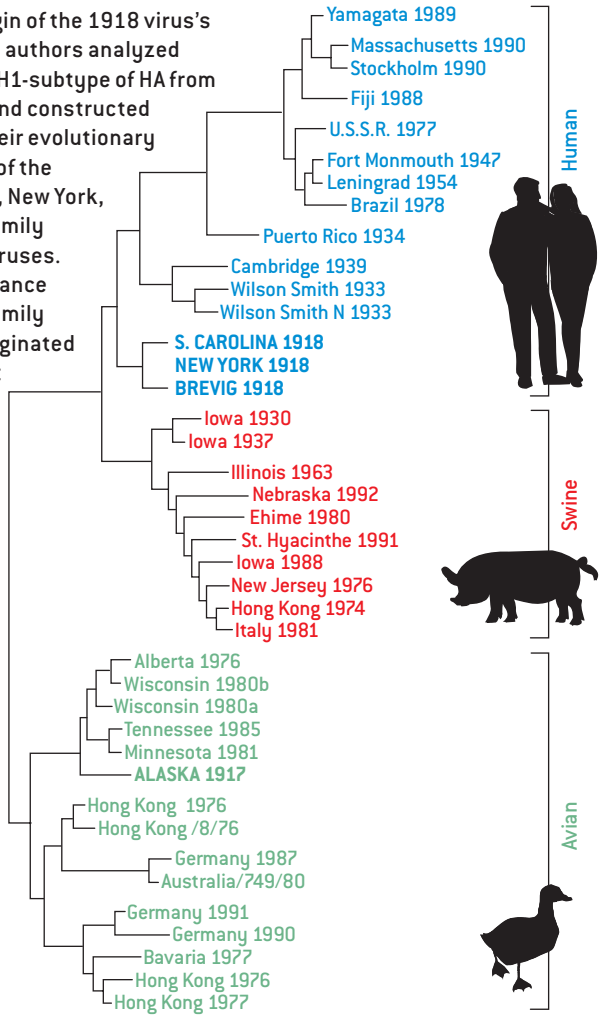
THE BEST APPROACH to analyzing the relationships among influenza viruses is phylogenetics, whereby hypothetical family trees are constructed using viral gene sequences and knowledge of how often genes typically mutate. Because the genome of an influenza virus consists of eight discrete RNA segments that can move independently by reassortment, these evolutionary studies must be performed separately for each gene segment.

We have completed analyses of five of the 1918 virus's eight RNA segments, and so far our comparisons of the 1918 flu genes with those of numerous human, swine and avian influenza viruses always place the 1918 virus within the human and swine families, outside the avian virus group [*see box on next page*]. The 1918 viral genes do have some avian features, however, so it is probable that the virus originally emerged from an avian reservoir sometime before 1918. Clearly by 1918, though, the virus had acquired enough adaptations to mammals to function as a human pandemic virus. The question is, where?

When we analyzed the 1918 hemagglutinin gene, we found that the sequence has many more differences from

Flu Family Tree

Seeking clues to the origin of the 1918 virus's hemagglutinin (HA), the authors analyzed gene sequences for the H1-subtype of HA from a variety of flu strains and constructed a phylogeny showing their evolutionary relationships. Samples of the 1918 strain (S. Carolina, New York, Brevig) fell within the family of human-adapted flu viruses. The 1918 H1 gene's distance from the known avian family could indicate that it originated in an avian flu strain but spent time evolving in an unidentified host before emerging in 1918. Supporting this conclusion, a contemporary avian strain found in a preserved Brant goose (Alaska 1917) was evolutionarily distant from the 1918 strain and more similar to modern bird flus.



avian sequences than do the 1957 H2 and 1968 H3 subtypes. Thus, we concluded, either the 1918 HA gene spent some length of time in an intermediate host where it accumulated many changes from the original avian sequence, or the gene came directly from an avian virus, but one that was markedly different from known avian H1 sequences.

To investigate the latter possibility that avian H1 genes might have changed substantially in the eight decades since the 1918 pandemic, we collaborated with scientists from the Smithsonian Institution's Museum of Natural History and Ohio State University. After examining many preserved birds from the era, our group isolated an avian subtype H1 influenza strain from a Brant goose collected in 1917 and stored in ethanol in the Smithsonian's bird collections. As it turned out, the 1917 avian H1 sequence was closely related to modern avian North American H1 strains, suggesting that avian H1 sequences have changed little over the past 80 years. Extensive sequencing of additional wild bird H1 strains may yet identify a strain more similar to the 1918 HA, but it may be that no avian H1 will be found resembling the 1918 strain because, in fact, the HA did not reassort directly from a bird strain.

In that case, it must have had some intermediate host. Pigs are a widely suggested possibility because they are known to be susceptible to both human and avian viruses. Indeed, simultaneous outbreaks of influenza were seen in humans and swine during the 1918 pandemic, but we believe that the direction of transmission was most probably from humans to pigs. There are numerous examples of human influenza A virus strains infecting swine since 1918, but swine influenza strains have been isolated only sporadically from humans. Nevertheless, to explore the possibility that the 1918 HA may have started as an avian form that gradually adapted to mammalian hosts in swine, we looked at a current example of how avian viruses evolve in pigs—an avian H1N1 influenza lineage that has become established in European swine over the past 25 years. We found that even 20 years of evolution in swine has not resulted in the number of changes from avian sequences exhibited by the 1918 pandemic strain.

When we applied these types of analyses to four other 1918 virus genes, we came to the same conclusion: the virus that sparked the 1918 pandemic could well have been an avian strain that was evolutionarily isolated from the typical wild waterfowl influenza gene pool for some time—one that, like the SARS coronavirus, emerged into circulation among humans from an as yet unknown animal host.

Future Investigations

OUR ANALYSES of five RNA segments from the 1918 virus have shed some light on its origin and strongly suggest that the pandemic virus was the common ancestor of both subsequent human and swine H1N1 lineages, rather than having emerged from swine. To date, analyzing the viral genes has offered no definitive clue to the exceptional virulence of the 1918 virus strain. But experiments with engineered viruses containing 1918 genes indicate that certain of the 1918 viral proteins could promote rapid virus replication and provoke an intensely destructive host immune response.

In future work, we hope that the 1918 pandemic virus strain can be placed in the context of influenza viruses that immediately preceded and followed it. The direct precursor of the pandemic virus, the first or spring wave virus strain, lacked the autumn wave's

JOHNNY JOHNSON

exceptional virulence and seemed to spread less easily. At present, we are seeking influenza RNA samples from victims of the spring wave to identify any genetic differences between the two strains that might help elucidate why the autumn wave was more severe. Similarly, finding pre-1918 human influenza RNA samples would clarify which gene segments in the 1918 virus were completely novel to humans. The unusual mortality among young people during the 1918 pandemic might be explained if the virus shared features with earlier circulating strains to which older people had some immunity. And finding samples of H1N1 from the 1920s and later would help us understand the 1918 virus's subsequent evolution into less virulent forms.

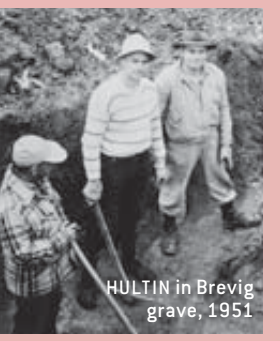
We must remember that the mechanisms by which pandemic flu strains originate are not yet fully understood. Because the 1957 and 1968 pandemic strains had avian-like HA proteins, it seems most likely that they originated in the direct reassortment of avian and human virus strains. The actual circumstances of those reassortment events have never been identified, however, so no one knows how long it took for the novel strains to develop into human pandemics.

The 1918 pandemic strain is even more puzzling, because its gene sequences are consistent neither with direct reassortment from a known avian strain nor with adaptation of an avian strain in swine. If the 1918 virus should prove to have acquired novel genes through a different mechanism than subsequent pandemic strains, this could have important public health implications. An alternative origin might even have contributed to the 1918 strain's exceptional virulence. Sequencing of many more avian influenza viruses and research into alternative intermediate hosts other than swine, such as poultry, wild birds or horses, may provide more clues to the 1918 pandemic's source. Until the origins of such strains are better understood, detection and prevention efforts may overlook the beginning of the next pandemic. SA

ASSOCIATED PRODUCERS (*top*), JOHAN HULTIN (*bottom*)

Persistence Pays Off

Visiting Alaska in the summer of 1949, Swedish medical student Johan Hultin met Lutheran missionaries in Fairbanks who told him of the 1918 flu pandemic's toll on Inuit villages. One, a tiny settlement on the Seward Peninsula called Teller Mission, was all but wiped out in November 1918. Overwhelmed missionaries had to call in the U.S. Army to help bury 72 victims' bodies in a mass grave, which they marked by two crosses.


HULTIN in Brevig grave, 1951

Haunted by the story, Hultin (*right, center* and *below*) headed to the University of Iowa to begin his doctoral studies in microbiology. There he kept thinking about the 1918 pandemic and wondering if the deadly virus that caused it could be retrieved for study from bodies that may have been preserved by the Alaskan permafrost. In the summer of 1951, Hultin convinced two Iowa faculty, a virologist and a pathologist, to visit the village, then called Brevig Mission. With permission from tribal elders, the scientists excavated the grave and obtained tissue specimens from what remained of several victims' lungs.

Back in Iowa, the team tried and tried to grow live virus from the specimens but never could. In retrospect, that was perhaps just as well since biological containment equipment for dangerous pathogens did not exist at the time.

Hultin's disappointment led him to abandon his Ph.D. and become a pathologist instead. Retired and living in San Francisco in 1997, Hultin read our group's first published description of the 1918 genes we retrieved from autopsy specimens, and it rekindled his hope of finding the entire 1918 virus. He wrote to me, eager to try to procure new lung specimens from Brevig Mission for us to work with. He offered to leave immediately for Alaska, and I agreed.

At the same time, Hultin tracked down his 1951 expedition mates to ask if they had kept any of the original Brevig specimens. We reasoned that those tissue samples obtained just 33 years after the pandemic and then preserved might be in better condition than specimens taken later. As it turned out, one of Hultin's colleagues had kept the material in storage for years but finally deemed it useless and threw it out. He had disposed of the last specimens just the year before, in 1996.

Fortunately, Hultin once again got permission from the Brevig Mission Council to excavate the 1918 grave in August 1997. And this time he found the body of a young woman who had been obese in life. Hultin said later that he knew instantly her tissue samples would contain the 1918 virus—together with the cold temperature, her thick layer of fat had almost perfectly preserved her lungs. He was right, and her tissue provided us with the entire genome of the 1918 pandemic virus. —*J.K.T.*


HULTIN in Brevig grave, 1997

MORE TO EXPLORE

Devil's Flu: The World's Deadliest Influenza Epidemic and the Scientific Hunt for the Virus That Caused It. Pete Davies. Henry Holt and Co., 2000.

America's Forgotten Pandemic: The Influenza of 1918. Second edition. Alfred W. Crosby. Cambridge University Press, 2003.

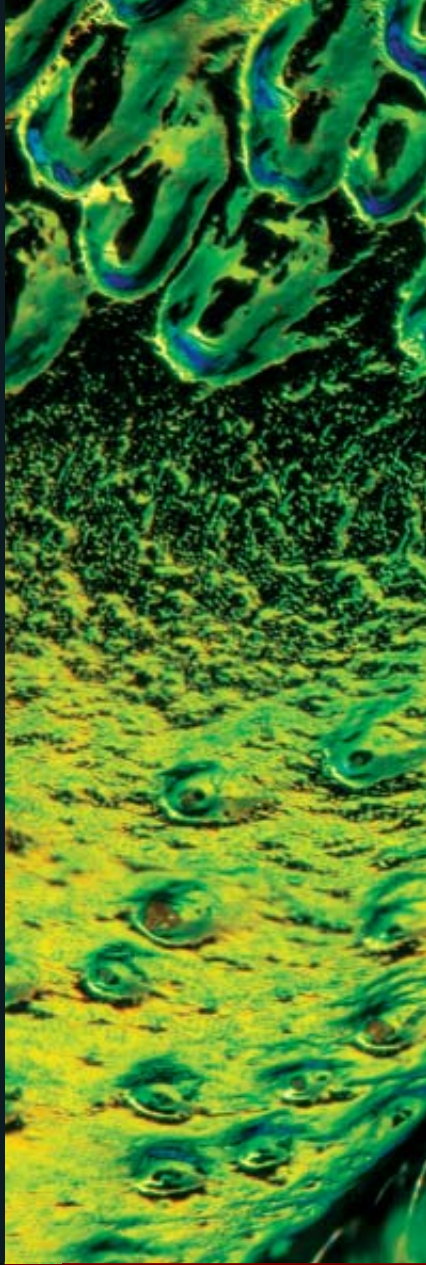
The Origin of the 1918 Pandemic Influenza Virus: A Continuing Enigma. Ann H. Reid and Jeffery K. Taubenberger in *Journal of General Virology,* Vol. 84, Part 9, pages 2285–2292; September 2003.

Global Host Immune Response: Pathogenesis and Transcriptional Profiling of Type A Influenza Viruses Expressing the Hemagglutinin and Neuraminidase Genes from the 1918 Pandemic Virus. J. C. Kash, C. F. Basler, A. Garcia-Sastre, V. Carter, R. Billharz, D. E. Swayne, R. M. Przygodzki, J. K. Taubenberger, M. G. Katze and T. M. Tumpey in *Journal of Virology,* Vol. 78, No. 17, pages 9499–9511; September 2004.

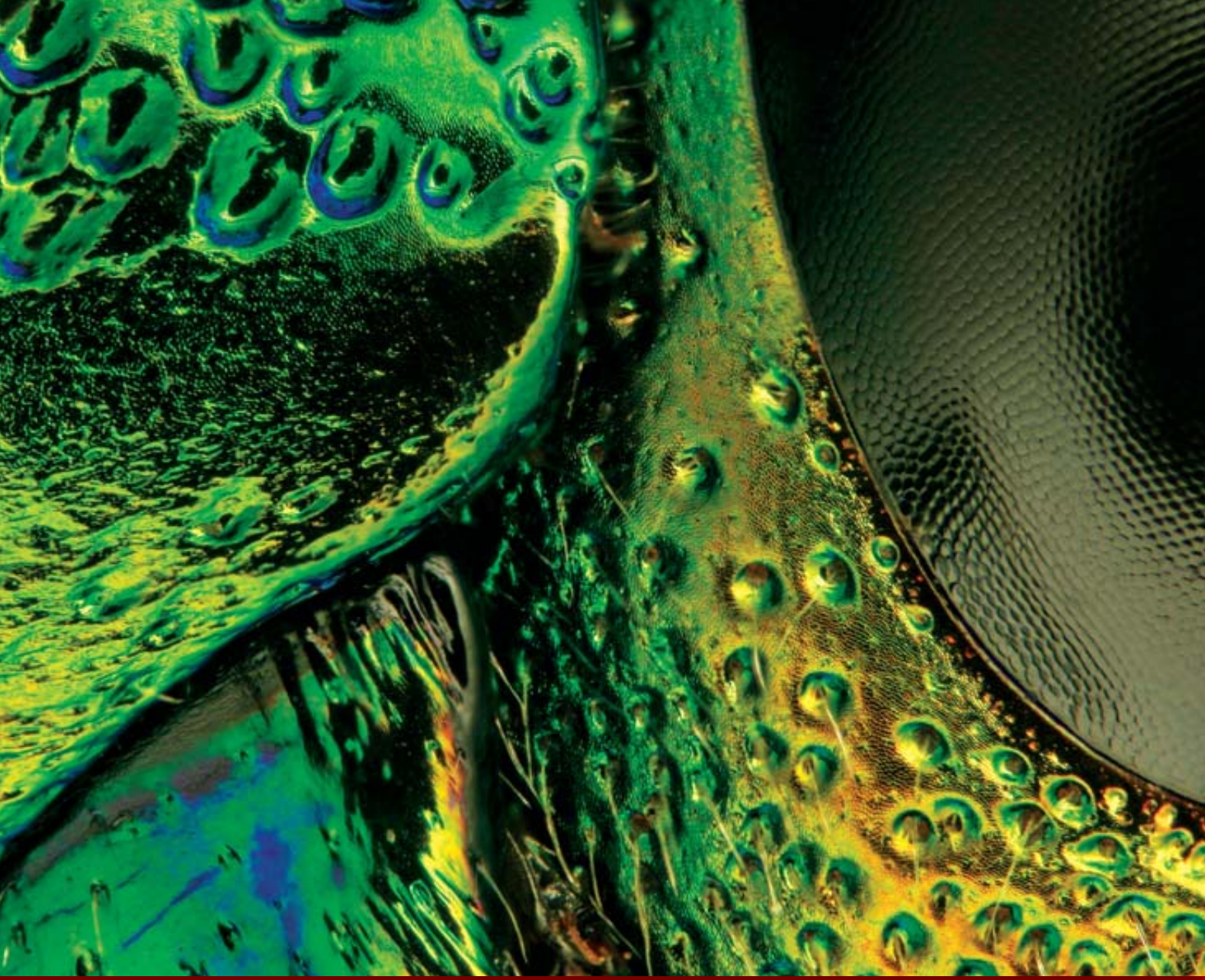
Eye of the Beholder

Wonders under the lens of the optical microscope

Text by Emily Harrison



A SEA OF SWIMMING goldfish and a slick of oil on pavement—or so could seem these close-ups of a Madagascar moon moth and a metallic beetle. Kevin Mackenzie of the University of Aberdeen, Scotland, used brightfield and fiber-optic illumination for this detail of *Argema mittrei*'s wing (100×). Charles B. Krebs of Issaquah, Wash., captured this image of the eye and thorax of the beetle *Chrysochroa fulminans* (45×) using reflected light.



There is infinite beauty in the world, if only we find the means to see it. And when it comes to seeing more, science holds a marvelous tool chest of techniques. With materials that may be as fundamental as light and lens, the art of scientific observation expands the visible world far beyond the depths and distances our unaided eyes can access. While optical telescopes extend our view deep into space, to distances billions of light-years away from the eye's everyday demesne, optical microscopes turn our vision inward, taking it to deep inner space. They resolve slivers of the world as small as a wavelength of light, 1,000 times as small as anything we notice in the macroscopic world.

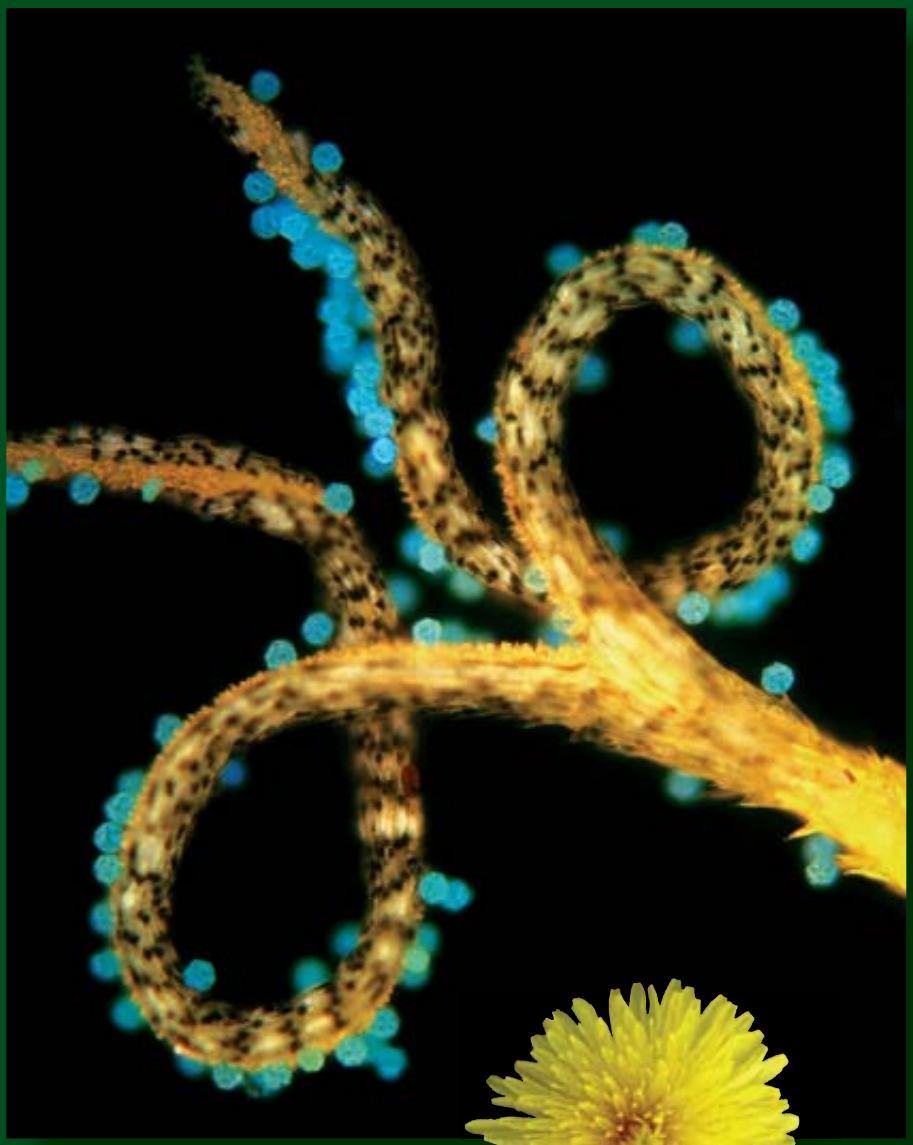
The pairs of images here, selected from entries to Nikon's annual Small World Competition, epitomize the art of looking closer, as captured by some modern masters of photomicrography. Each one offers a slice of life as the eye does not, ordinarily, have the opportunity to know it.

Continued on page 77

ALL MICROSCOPE IMAGES COURTESY OF NIKON INSTRUMENTS; MARK LASKO (*moon moth*); CLIVE PRATT (*beetle*)

PAOLO MAZZEI (*silkworm, opposite page*)

EXTRAVAGANT GEOMETRY abounds, even among the worms. Using a technique called darkfield illumination, Greg W. Rouse of the South Australian Museum in Adelaide snapped this view (*above*) of the polygonous polychaete *Myrianida pachycera* (45×). Ian C. Walker of Huddersfield, England, illuminated the trachea of a silkworm (70×).



PUNCTUATED BY POLLEN, these intimate views show the beginning stages of the botanical life cycle. Shirley A. Owens of Michigan State University found fortune cookie–shaped pollen on the anther of the spiderwort *Trandescantia virginiana* (1,450×), photographed with a confocal laser technique. The spindly tree strung with holiday lights (*above right*) is actually the stigma of the dandelion *Taraxacum* (160×), as captured with fluorescence by Róbert Márkus of the Hungarian Academy of Sciences in Szeged.

Continued from page 73

Magnification, resolution and contrast—the same properties a composer manipulates aurally to create a dynamic piece of music—bring the very tiny and the often very transparent into view at the eyepiece of a microscope. To visualize patterns in a sample under study, a microscopist may stain its sugars, tag its various proteins with different fluorescent markers, imbue it with a rainbow of illuminations, or shadow it from multiple angles to highlight its contours. And the resulting images, when successful, each yield a tiny symphony of light—and insight. SA

Emily Harrison is photography editor of Scientific American.

THOMAS G. BARNES (*spiderwort*); CHARLIE KANE (*dandelion*)

BEST-KEPT SECRETS

Quantum cryptography has marched from theory to laboratory to real products

By Gary Stix

At the IBM Thomas J. Watson Research Laboratory, Charles Bennett is known as a brilliant theoretician—one of the fathers of the emerging field of quantum computing. Like many theorists, he has not logged much experience in the laboratory. His absentmindedness in relation to the physical world once transformed the color of a teapot from green to red when he left it on a double boiler too long. But in 1989 Bennett and colleagues John A. Smolin and Gilles Brassard cast caution aside and undertook a groundbreaking experiment that would demonstrate a new cryptography based on the principles of quantum mechanics.

The team put together an experiment in which photons moved down a 30-centimeter channel in a light-tight box called "Aunt Martha's coffin." The direction in which the photons oscillated, their polarization, represented the 0s or 1s of a series of quantum bits, or qubits. The qubits constituted a cryptographic "key" that could be used to encrypt or decipher a message. What kept the key from prying eavesdroppers was Heisenberg's uncertainty principle—a foundation of quantum physics that dictates that the measurement of one property in a quantum state will perturb another. In a quantum cryptographic system, any interloper tapping into the stream of photons will alter them in a way that is detectable to the sender and the receiver. In principle, the technique provides the makings of an unbreakable cryptographic key.

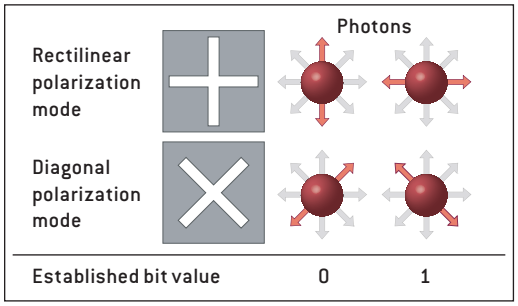
Today quantum cryptography has come a long way from the jury-rigged project assembled on a table in Bennett's office. The National Security Agency or one of the Federal Reserve banks can now buy a quantum-cryptographic system from two small companies—and more products are on the way. This new method of encryption represents the first major commercial implementation for what has become known as quantum information science, which blends quantum mechanics and information theory. The ultimate technology to emerge from the field may be a quantum computer so powerful that the only way to protect against its prodigious code-breaking capability may be to deploy quantum-cryptographic techniques.

The challenge modern cryptographers face is for sender and receiver to share a key while ensuring that no one has filched a copy. A method called public-key cryptography

JEAN-FRANCOIS PODEVIN

QUANTUM MECHANICS HIDES A SECRET CODE KEY

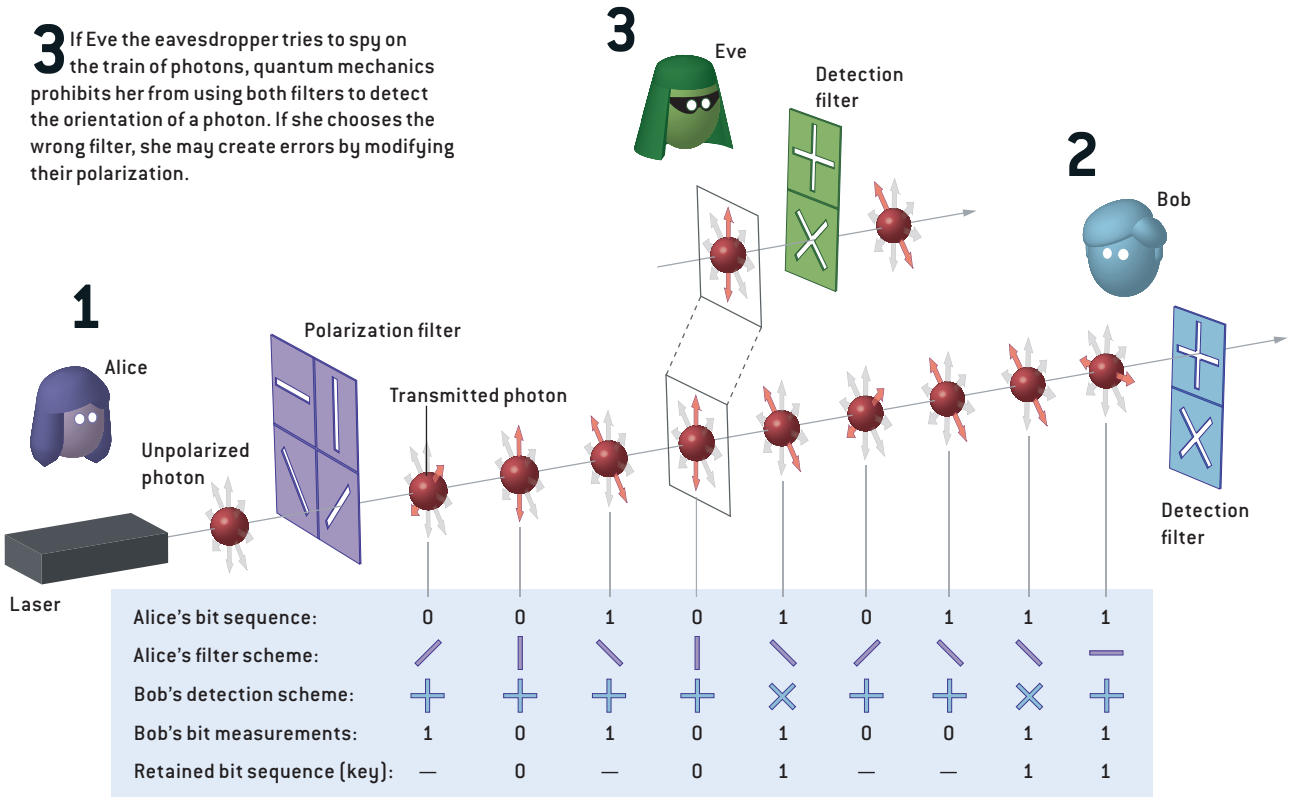
Alice and Bob try to keep a quantum-cryptographic key secret by transmitting it in the form of polarized photons, a scheme invented by Charles Bennett of IBM and Gilles Brassard of the University of Montreal during the 1980s and now implemented in a number of commercial products.



1 To begin creating a key, Alice sends a photon through either the 0 or 1 slot of the rectilinear or diagonal polarizing filters, while making a record of the various orientations.

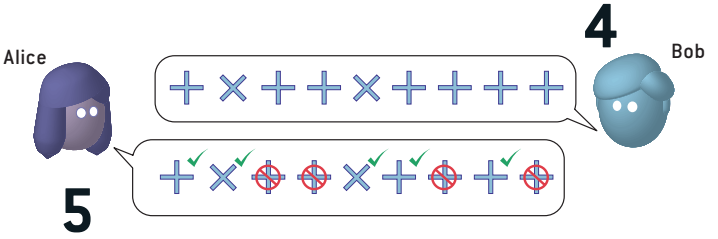
2 For each incoming bit, Bob chooses randomly which filter slot he uses for detection and writes down both the polarization and the bit value.

3 If Eve the eavesdropper tries to spy on the train of photons, quantum mechanics prohibits her from using both filters to detect the orientation of a photon. If she chooses the wrong filter, she may create errors by modifying their polarization.



4 After all the photons have reached Bob, he tells Alice over a public channel, perhaps by telephone or an e-mail, the sequence of filters he used for the incoming photons, but not the bit value of the photons.

5 Alice tells Bob during the same conversation which filters he chose correctly. Those instances constitute the bits that Alice and Bob will use to form the key that they will use to encrypt messages.



TOMMY MOORMAN; ADAPTED FROM *THE CODE BOOK: THE SCIENCE OF SECRECY FROM ANCIENT EGYPT TO QUANTUM CRYPTOGRAPHY*, BY SIMON SINGH (1999)

is often used to distribute the secret keys for encryption and decoding of a full-length message. The security of public-key cryptography depends on factorization or other difficult mathematical problems. It is easy to compute the product of two large numbers but extremely hard to factor it back into the primes. The popular RSA cipher algorithm, widely deployed in public-key cryptography, relies on factorization. The secret key being transferred between sender and receiver is encrypted with a publicly available key, say, a large number such as 408,508,091 (in practice, the number would be much larger). It can be decrypted only with a private key owned by the recipient of the data, made up of two factors, in this case 18,313 and 22,307.

The difficulty of overcoming a public-key cipher may hold secret keys secure for a decade or more. But the advent of the quantum information era—and, in particular, the capability of quantum computers to rapidly perform monstrously challenging factorizations—may portend the eventual demise of RSA and other cryptographic schemes. "If quantum computers become a reality, the whole game changes," says John Rarity, a professor in the department of electrical and electronics engineering at the University of Bristol in England.

WHO SELLS "UNBREAKABLE" KEYS

COMPANY	TECHNOLOGY
id Quantique Geneva, Switzerland	An optical-fiber-based system sends quantum-cryptographic keys over tens of kilometers
MagiQ Technologies New York City	An optical-fiber system sends quantum-cryptographic keys up to 100 kilometers; also includes hardware and software for integration into existing networks
NEC Tokyo	Scheduled to release an optical-fiber product at the earliest next year after a 2004 demonstration that transferred keys over a record 150 kilometers
QinetiQ Farnborough, England	Provides systems on a contract basis that transfer keys through the air at distances up to 10 kilometers; has supplied a system to BBN Technologies in Cambridge, Mass.

The arrival of the quantum computer may portend the EVENTUAL DEMISE OF CIPHERS based on factorization.

Unlike public-key cryptography, quantum cryptography should remain secure when quantum computers arrive on the scene. One way of sending a quantum-cryptographic key between sender and receiver requires that a laser transmit single photons that are polarized in one of two modes. In the first, photons are positioned vertically or horizontally (rectilinear mode); in the second, they are oriented 45 degrees to the left or right of vertical (diagonal mode). In either mode, the opposing positions of the photons represent either a digital 0 or a 1. The sender, whom cryptographers by convention call Alice, sends a string of bits, choosing randomly to send photons in either the rectilinear or the diagonal modes. The receiver, known as Bob in crypto-speak, makes a similarly random decision about which mode to measure the incoming bits. The Heisenberg uncertainty principle dictates that he can measure the bits in only one mode, not both. Only the bits that Bob measured in the same mode as sent by Alice are guaranteed to be in the correct orientation, thus retaining the proper value [*see box on opposite page*].

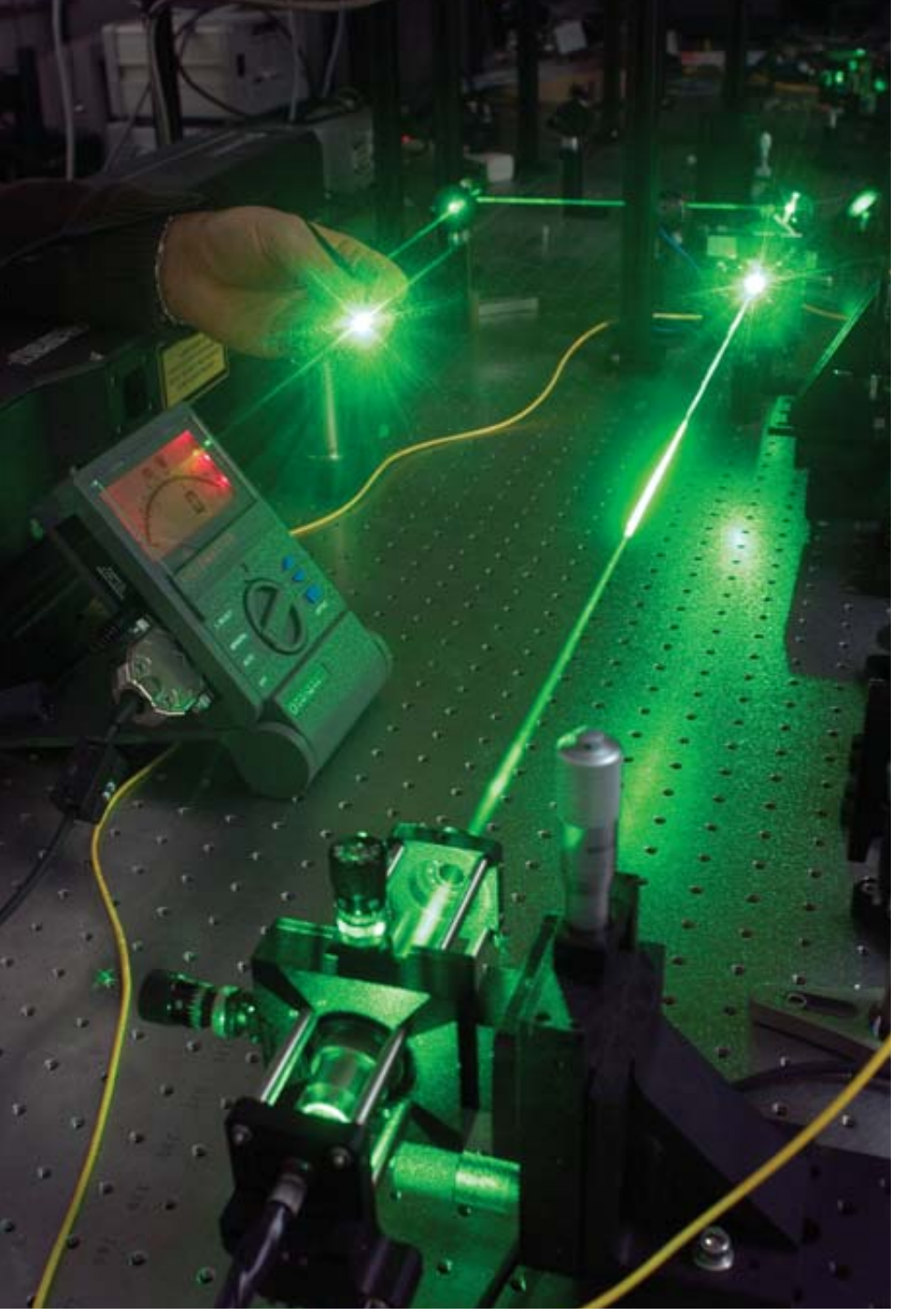
After transmission, Bob then communicates with Alice, an exchange that need not remain secret, to tell her which of the two modes he used to receive each photon. He does not, however, reveal the 0- or 1-bit value represented by each photon. Alice then tells Bob which of the modes were measured correctly. They both ignore photons that were not observed in the right mode. The modes measured correctly constitute the key that serves as an input for an algorithm used to encrypt or decipher a message.

If someone tries to intercept this stream of photons—call her Eve—she cannot measure both modes, thanks to Heisenberg. If she makes the measurements in the wrong mode, even if she resends the bits to Bob in the same way she measured them, she will inevitably introduce errors. Alice and Bob can detect the presence of the eavesdropper by comparing selected bits and checking for errors.

Beginning in 2003, two companies—id Quantique in Geneva and MagiQ Technologies in New York City—introduced commercial products that send a quantum-cryptographic key beyond the 30 centimeters traversed in Bennett's experiment. And, after demonstrating a record transmission distance of 150 kilometers, NEC is to come to market with a product at the earliest next year. Others, such as IBM, Fujitsu and Toshiba, have active research efforts [*see table above*].

The products on the market can send keys over individual optical-fiber links for multiple tens of kilometers. A system from MagiQ costs $70,000 to $100,000. "A small number of customers are using and testing the system, but it's not widely deployed in any network," comments Robert Gelfond, a former Wall Street quantitative trader who in 1999 founded MagiQ Technologies.

Some government agencies and financial institutions are afraid that an



ENCRYPTION involving quantum states utilizes such advanced technologies that much of the work still resides in laboratories such as this one at MagiQ Technologies.

encrypted message could be captured today and stored for a decade or more—at which time a quantum computer might decipher it. Richard J. Hughes, a researcher in quantum cryptography at Los Alamos National Laboratory, cites other examples of information that must remain confidential for a long time: raw census data, the formula for Coca-Cola or the commands for a commercial satellite. (Remember Captain Midnight, who took over HBO for more than four minutes in 1986.) Among the prospective customers for quantum-cryptographic systems are telecommunications providers that foresee offering customers an ultrasecure service.

The first attempts to incorporate quantum cryptography into actual networks—rather than just point-to-point connections—have begun. The Defense Advanced Research Projects Agency has funded a project to connect six network nodes that stretch among Harvard University, Boston University and BBN Technologies in Cambridge, Mass., a company that played a critical role in establishing the Internet. The encryption keys are sent over dedicated links, and the messages ciphered with those keys are transmitted over the Internet. "This is the first continuously running operational quantum-cryptography network outside a laboratory," notes Chip Elliott of BBN, who heads the project. The network, designed to merely show that the technology works, transfers ordinary unclassified Internet traffic. "The only secrets I can possibly think of here are where the parking spaces are," Elliott says. Last fall, id Quantique and a partner, the Geneva-based Internet services provider Deckpoint, put on display a network that allowed a cluster of servers in Geneva to have its data backed up at a site 10 kilometers away, with new keys being distributed frequently through a quantum-encrypted link.

The current uses for quantum cryptography are in networks of limited geographic reach. The strength of the technique—that anyone who spies on a key transmittal will change it unalterably—also means that the signals that carry quantum keys cannot be amplified by network equipment that restores a weakening signal and allows it to be relayed along to the next repeater. An optical amplifier would corrupt qubits.

To extend the distance of these links, researchers are looking beyond optical fibers as the medium to distribute quantum keys. Scientists have trekked to mountaintops—where the altitude minimizes atmospheric turbulence—to prove the feasibility of sending quantum keys through the air. One experiment in 2002 at Los Alamos National Laboratory created a 10-kilometer link. Another, performed that same year by QinetiQ, based in Farnborough, England, and Ludwig Maximilian University in Munich, stretched 23 kilometers between two mountaintops in the southern Alps. By optimizing this technology—using bigger telescopes for detection, better filters and antireflective coatings—it might be possible to build a system that could transmit and receive signals over more than 1,000 kilometers, sufficient to reach satellites in low earth orbit. A network of

SAM OGDEN

satellites would allow for worldwide coverage. The European Space Agency is in the early stages of putting together a plan for an earth-to-satellite experiment. (The European Union also launched an effort in April to develop quantum encryption over communications networks, an effort spurred in part by a desire to prevent eavesdropping by Echelon, a system that intercepts electronic messages for the intelligence services of the U.S., Britain and other nations.)

Ultimately cryptographers want some form of quantum repeater—in essence, an elementary form of quantum computer that would overcome distance limitations. A repeater would work through what Albert Einstein famously called "*spukhafte Fernwirkungen*," spooky action at a distance. Anton Zeilinger and his colleagues at the Institute of Experimental Physics in Vienna, Austria, took an early step toward a repeater when they reported in the August 19, 2004, issue of *Nature* that their group had strung an optical-fiber cable in a sewer tunnel under the Danube River and stationed an "entangled" photon at each end. The measurement of the state of polarization in one photon (horizontal, vertical, and so on) establishes immediately an identical polarization that can be measured in the other.

Entanglement spooked Einstein, but Zeilinger and his team took advantage of a link between two entangled photons to "teleport" the information carried by a third photon a distance of 600 meters across the Danube. Such a system might be extended in multiple relays, so that the qubits in a key could be transmitted across continents or oceans. To make this a reality will require development of esoteric components, such as a quantum memory capable of actually storing qubits without corrupting them before they are sent along to a subsequent link. "This is still very much in its infancy. It's still in the hands of physics laboratories," notes Nicolas Gisin, a professor at the University of Geneva, who helped to found id Quantique and who has also done experiments on long-distance entanglement.

A quantum memory might be best implemented with atoms, not photons. An experiment published in the October 22 issue of *Science* showed how this might work. Building on ideas of researchers from the University of Innsbruck in Austria, a group at the Georgia Institute of Technology detailed in the paper how two clouds of ultracold rubidium atoms could be entangled and, because of the quantum linkage, could be inscribed with a qubit, the clouds storing the qubit for much longer than a photon can. The experiment then transferred the quantum state of the atoms, their qubit, onto a photon, constituting information transfer from matter to light and showing how a quantum memory might output a bit. By entangling clouds, Alex Kuzmich and Dzmitry Matsukevich of Georgia Tech hope to create repeaters that can transfer qubits over long distances.

The supposed inviolability of quantum cryptography rests on a set of assumptions that do not necessarily carry over into the real world. One of those assumptions is that only a single photon represents each qubit. Quantum cryptography works by taking a pulsed laser and diminishing its intensity to such an extent that typically it becomes unlikely that any more than one in 10 pulses contains a photon—the rest are dark—one reason that the data transfer rate is so low. But this is only a statistical likelihood. The pulse may have more than one photon. An eavesdropper could, in theory, steal an extra photon and use it to help decode a message. A software algorithm, known as privacy amplification, helps to guard against this possibility by masking the values of the qubits.

But cryptographers would like to have better photon sources and detectors. The National Institute of Standards and Technology (NIST) is one of many groups laboring on these devices. "One very interesting area is the development of detectors that can tell the difference between one, two or more photons arriving at the same time," says Alan Migdall of NIST. Researchers there have also tried to address the problem of slow transmission speed by generating quantum keys at a rate of one megabit per second—100 times faster than any previous efforts and enough to distribute keys for video applications.

Quantum cryptography may still prove vulnerable to some unorthodox attacks. An eavesdropper might sabotage a receiver's detector, causing qubits received from a sender to leak back into a fiber and be intercepted. And an inside job will always prove unstoppable. "Treachery is the primary way," observes Seth Lloyd, an expert in quantum computation at the Massachusetts Institute of Technology. "There's nothing quantum mechanics can do about that." Still, in the emerging quantum information age, these new ways of keeping secrets may be better than any others in the codebooks. SA

Entanglement SPOOKED EINSTEIN, but researchers have used the phenomenon to "TELEPORT" quantum information.

MORE TO EXPLORE

Quantum Cryptography. Charles H. Bennett, Gilles Brassard and Artur K. Ekert in *Scientific American,* Vol. 267, No. 4, pages 50–57; October 1992.

The Code Book. Simon Singh. Anchor Books, 1999.

Information about quantum-cryptographic products can be found at the Web sites of id Quantique (**idquantique.com**) and MagiQ Technologies (**magiqtech.com**).

EXPLODING THE SELF-ESTEEM MYTH

By Roy F. Baumeister, Jennifer D. Campbell, Joachim I. Krueger and Kathleen D. Vohs

Boosting people's sense of self-worth has become a national preoccupation. Yet surprisingly, research shows that such efforts are of little value in fostering academic progress or preventing undesirable behavior

People intuitively recognize the importance of self-esteem to their psychological health, so it isn't particularly remarkable that most of us try to protect and enhance it in ourselves whenever possible. What *is* remarkable is that attention to self-esteem has become a communal concern, at least for Americans, who see a favorable opinion of oneself as the central psychological source from which all manner of positive outcomes spring. The corollary, that low self-esteem lies at the root of individual and thus societal problems and dysfunctions, has sustained an ambitious social agenda for decades. Indeed, campaigns to raise people's sense of self-worth abound.

Consider what transpired in California in the late 1980s. Prodded by State Assemblyman John Vasconcellos, Governor George Deukmejian set up a task force on self-esteem and personal and social responsibility. Vasconcellos argued that raising self-esteem in young people would reduce crime, teen pregnancy, drug abuse, school underachievement and pollution. At one point, he even expressed the hope that these efforts would one day help balance the state budget, a prospect predicated on the observation that people with high self-regard earn more than others and thus pay more in taxes. Along with its other activities, the task force assembled a team of scholars to survey the relevant literature. The results appeared in a 1989 volume entitled *The Social Importance of Self-Esteem*, which stated that "many, if not most, of the major

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problems plaguing society have roots in the low self-esteem of many of the people who make up society." In reality, the report contained little to support that assertion.

The California task force disbanded in 1995, but a nonprofit organization called the National Association for Self-Esteem (NASE) has picked up its mantle, aiming (according to its mission statement) to "promote awareness of and provide vision, leadership and advocacy for improving the human condition through the enhancement of self-esteem." Vasconcellos, now a California state senator, is on the advisory board.

Was it reasonable for leaders in California to start fashioning therapies and social policies without supportive data? Perhaps so. After all, practicing psychologists and lawmakers must deal with the problems facing them, even before all the relevant research is done. But one can draw on many more studies now than was the case 15 years ago, enough to assess the value of self-esteem in several spheres. Regrettably, those who have been pursuing self-esteem-boosting programs, including the leaders of NASE, have not shown a desire to examine the new work, which is why the four of us recently came together under the aegis of the American Psychological Society to review the scientific literature.

In the Eye of the Beholder

GAUGING THE VALUE of self-esteem requires, first of all, a sensible way to measure it. Most investigators just ask people what they think of themselves. Naturally enough, the answers are often colored by the common tendency to want to make oneself look good. Unfortunately, psychologists lack any better method to judge self-esteem, which is worrisome because similar self-ratings of other attributes often prove to be way off. Consider, for instance, research on the relation between self-esteem and physical attractiveness.

Several studies have explored correlations between these qualities, generally finding clear positive links when people rate themselves on both properties. It seems plausible that physically attractive people would end up with high self-esteem because they are treated more favorably than unattractive ones—being more popular, more sought after, more valued by lovers and friends, and so forth. But it could just as well be that those who score highly on self-esteem scales by claiming to be wonderful people all around also boast of being physically attractive.

Some findings even suggest that artificially boosting self-esteem may lower subsequent academic performance.

In 1995 Edward F. Diener and Brian Wolsic of the University of Illinois and Frank Fujita of Indiana University South Bend examined this possibility. They obtained self-esteem scores from a broad sample of the population and then photographed everybody, presenting these pictures to a panel of judges, who evaluated the subjects for attractiveness. Ratings based on full-length photographs showed no significant correlation with self-esteem. Head-and-shoulders close-ups fared slightly better, but even this finding is dubious, because individuals with high self-esteem might take particular care to present themselves well, such as by wearing attractive clothing and jewelry. The 1995 study suggests as much: when the judges were shown pictures of just the participants' unadorned faces, the modest correlation between attractiveness and self-esteem fell to zero. In that same investigation, however, self-reported physical attractiveness was found to have a strong correlation with self-esteem. Clearly, those with high self-esteem are gorgeous in their own eyes but not necessarily so to others.

This discrepancy should be sobering. What seemed at first to be a strong link between physical good looks and high self-esteem turned out to be nothing more than a pattern of consistency in how favorably people rate themselves. A parallel phenomenon affects those with low self-esteem, who are prone to floccinaucinihilipilification, a highfalutin word (among the longest in the Oxford English Dictionary) but one that we can't resist using here, it being defined as "the action or habit of estimating as worthless." That is, people with low self-esteem are not merely down on themselves; they are negative about everything.

This tendency has certainly distorted some assessments. For example, psychologists once thought that people with low self-esteem were especially prejudiced. Early studies, in which subjects simply rated groups to which they did not belong, seemingly confirmed that notion, but thoughtful scholars, such

Overview/*Self-Esteem*

- Self-esteem is viewed as a communal problem for Americans, who worry that inadequate self-esteem leads to various undesirable behaviors.
- Bullies, contrary to popular perception, do not typically suffer from low self-esteem. Neither do those who become sexually active at an early age, nor do those prone to abusing alcohol or illicit drugs.
- Raising self-esteem is not likely to boost performance in school or on the job.
- People with high self-esteem tend to show more initiative and appear to be significantly happier than others.

as Jennifer Crocker of the University of Michigan at Ann Arbor, questioned this conclusion. After all, if people rate themselves negatively, it is hardly proper to label them as prejudiced for rating people not like themselves similarly. When one uses the difference between the subjects' assessments of their own group and their ratings of other groups as the yardstick for bias, the findings are reversed: people with *high* self-esteem appear to be more prejudiced. Floccinaucinihilipilification also raises the danger that those who describe themselves disparagingly may describe their lives similarly, thus furnishing the appearance that low self-esteem has unpleasant outcomes.

Given the often misleading nature of self-reports, we set up our review to emphasize objective measures wherever possible—a requirement that greatly reduced the number of relevant studies (from more than 15,000 to about 200). We were also mindful to avoid another fallacy: the assumption that a correlation between self-esteem and some desired behavior establishes causality. Indeed, the question of causality goes to the heart of the debate. If high self-esteem brings about certain positive outcomes, it may well be worth the effort and expense of trying to instill this feeling. But if the correlations mean simply that a positive self-image is a result of success or good behavior—which is, after all, at least as plausible—there is little to be gained by raising self-esteem alone. We began our two-year effort to sort out the issue by reviewing studies relating self-esteem to academic performance.

School Daze

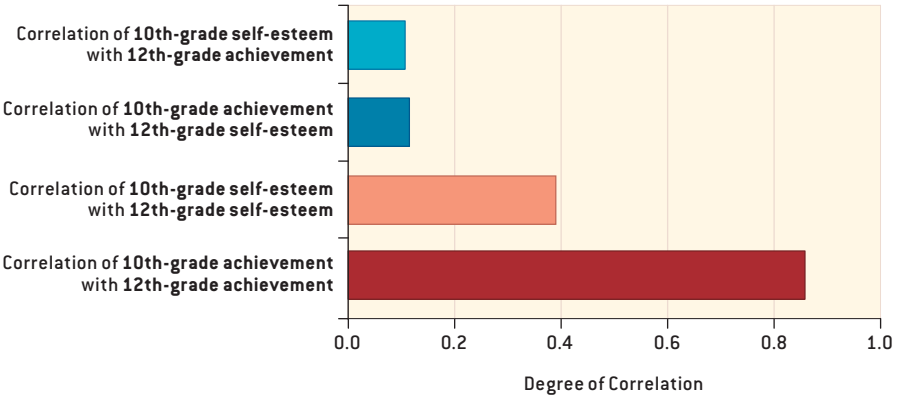
AT THE OUTSET, we had every reason to hope that boosting self-esteem would be a potent tool for helping students. Logic suggests that having a good dollop of self-esteem would enhance striving and persistence in school, while making a student less likely to succumb to paralyzing feelings of incompetence or self-doubt. Early work showed positive correlations between self-esteem and academic performance, lending credence to this notion. Modern efforts have, however, cast doubt on the idea that higher self-esteem actually induces students to do better.

Such inferences about causality are possible when the subjects are examined at two different times, as was the case in 1986 when Sheila M. Pottebaum, Timothy Z. Keith and Stewart W. Ehly, all then at the University of Iowa, tested more than 23,000 high school students, first in the 10th and again in the 12th grade. They found that self-esteem in 10th grade is only weakly predictive of academic achievement in 12th grade. Academic achievement in 10th grade correlates with self-esteem in 12th grade only trivially better. Such results, which are now available from multiple studies, certainly do not indicate that raising self-esteem offers students much benefit. Some findings even suggest that artificially boosting self-esteem may lower subsequent performance [*see illustration on page 89*].

Even if raising self-esteem does not foster academic progress, might it serve some purpose later, say, on the job? Apparently not. Studies of possible links between workers' self-regard and job performance echo what has been found with schoolwork: the simple search for correlations yields some suggestive results, but these do not show whether a good self-image leads to occupational success, or vice versa. In any case, the link is not particularly strong.

SELF-ESTEEM AND ACADEMIC ACHIEVEMENT

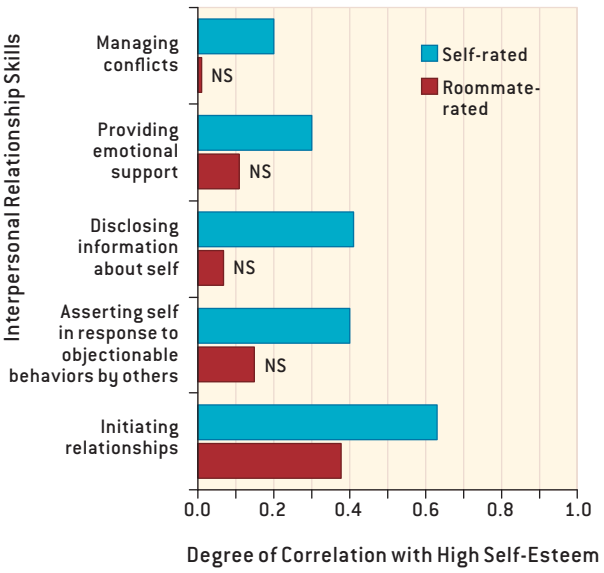
In an attempt to gauge whether high self-esteem leads to good academic performance, researchers surveyed thousands of high school students in their sophomore and senior years. The correlation between self-esteem sophomore year and academic performance senior year proved to be about the same as the correlation between academic performance sophomore year and self-esteem senior year. Thus it is hard to know which causes which—or whether some third factor gives rise to both high self-esteem and superior academic achievement.



SOURCE: S. M. Pottebaum, T. Z. Keith and S. W. Ehly in Educational Research, *Vol. 79, pages 140–144; 1986.*

STONE+

SELF-ESTEEM AND RELATIONSHIPS



A study of college students revealed strong links between self-esteem and various interpersonal skills—when the subjects rated themselves. Using skill ratings provided by their roommates provided a different picture: for four of the five skills surveyed, the correlations with self-esteem dropped to levels that were not significant (NS) statistically. Nevertheless, the connection between self-esteem and prowess in initiating relationships remained reasonably robust, as one might expect.

SOURCE: D. Buhrmester, W. Furman, M. T. Wittenberg and H. T. Reis in Journal of Personality and Social Psychology, *Vol. 55, pages 991–1008; 1988.*

The failure to contribute significantly at school or at the office would be easily offset if a heightened sense of self-worth helped someone to get along better with others. Having a good self-image might make someone more likable insofar as people prefer to associate with confident, positive individuals and generally avoid those who suffer from self-doubts and insecurities.

People who regard themselves highly generally state that they are popular and rate their friendships as being of superior quality to those described by people with low self-esteem, who report more negative interactions and less social support. But as Julia Bishop and Heidi M. Inderbitzen-Nolan of the University of Nebraska–Lincoln showed in 1995, these assertions do not reflect reality. The investigators asked 542 ninth-grade students to nominate their most-liked and least-liked peers, and the resulting rankings displayed no correlation whatsoever with self-esteem scores.

A few other methodologically sound studies have found that the same is true for adults. In one of these investigations, conducted in the late 1980s, Duane P. Buhrmester, now at the University of Texas at Dallas, and three colleagues reported that college students with high levels of self-regard claimed to be substantially better at initiating relationships, better at disclosing things about themselves, better at asserting themselves in response to objectionable behaviors by others, better at providing emotional support and better even at managing interpersonal conflicts. Their roommates' ratings, however, told a different story. For four of the five interpersonal skills surveyed, the correlation with self-esteem dropped to near zero. The only one that remained statistically significant was with the subjects' ability to initiate new social contacts and friendships. This does seem to be one sphere in which confidence indeed matters: people who think that they are desirable and attractive should be adept at striking up conversations with strangers, whereas those with low self-esteem presumably shy away from initiating such contacts, fearing rejection.

One can imagine that such differences might influence a person's love life, too. In 2002 Sandra L. Murray of the University at Buffalo and four colleagues found that people low in self-esteem tend to distrust their partners' expressions of love and support, acting as though they are constantly expecting rejection. Thus far, however, investigators have not produced evidence that such relationships are especially prone to dissolve. In fact, high self-esteem may be the bigger threat: as Caryl E. Rusbult, Gregory D. Morrow and Dennis J. Johnson, all then at the University of Kentucky, showed back in 1987, those who think highly of themselves are more likely than oth-

THE AUTHORS

ROY F. BAUMEISTER, JENNIFER D. CAMPBELL, JOACHIM I. KRUEGER and KATHLEEN D. VOHS collaborated on a more technical paper on self-esteem published in *Psychological Science in the Public Interest* [see "More to Explore," on page 91]. Baumeister, formerly a professor of psychology at Case Western Reserve University, became Eppes Professor of Psychology at Florida State University in 2003. Campbell is emeritus professor of psychology at the University of British Columbia in Vancouver. Krueger is professor of psychology at Brown University. Vohs holds the Canada Research Chair in Marketing Science and Consumer Psychology in the Sauder School of Business at the University of British Columbia.

RANDY FARIS *Corbis*

ers to respond to problems by severing relations and seeking other partners.

Sex, Drugs, Rock 'n' Roll

HOW ABOUT TEENAGERS? How does self-esteem, or the lack thereof, influence their love life, in particular their sexual activity? Investigators have examined this subject extensively. All in all, the results do not support the idea that low self-esteem predisposes young people to more or earlier sexual activity. If anything, those with high self-esteem are less inhibited, more willing to disregard risks and more prone to engage in sex. At the same time, bad sexual experiences and unwanted pregnancies appear to lower self-esteem.

If not sex, then how about alcohol or illicit drugs? Abuse of these substances is one of the most worrisome behaviors among young people, and many psychologists once believed that boosting self-esteem would prevent such problems. The thought was that people with low self-esteem turn to drinking or drugs for solace. The data, however, do not consistently show that low adolescent self-esteem causes or even correlates with the abuse of alcohol or other drugs. In particular, in a large-scale study in 2000, Rob McGee and Sheila M. Williams of the University of Otago Medical School in New Zealand found no correlation between self-esteem measured between ages nine and 13 and drinking or drug use at age 15. Even when findings do show links between alcohol use and self-esteem, they are

MIXED MESSAGES

A 1999 study by Donelson R. Forsyth and Natalie A. Kerr of Virginia Commonwealth University suggests that attempts to boost self-esteem among struggling students may backfire. Here the subjects were students taking a college course in psychology.

Those getting grades of D or F were divided into two groups, arranged initially to have the same grade-point average. Each week, students in the first group received an e-mail message designed to boost their self-esteem (*such as the example shown at left*). Those in the second group received a message intended to instill a sense of personal responsibility for their academic performance (*right*).

By the end of the course, the average grade for students in the first group dropped below 50 percent—a failing grade. The average for students in the second group was 62 percent—a D minus, which is poor but still passing.

Group 1

WHAT CAUSES GOOD AND BAD GRADES?

Past research suggests that when students get back their tests, they tend to lose confidence: they say things like "I can't do this," or "I'm worthless," or "I'm not as good as other people in college."

Other studies suggest, though, that students who have high self-esteem not only get better grades, but they remain self-confident and assured.

In fact, in one study researchers had students write down what "went through their minds" when they were trying to get better grades. Students who improved with each test were thinking:

"I can be proud of myself."
"I can do this."
"I am better than most of the other people in this school."
"I am satisfied with myself."

Students who did not improve were thinking:

"I'm ashamed of myself."
"I don't deserve to be in college."
"I'm worthless."

BOTTOM LINE: Hold your head—and your self-esteem—high.

Group 2

WHAT CAUSES GOOD AND BAD GRADES?

Past research suggests that when students get back their tests, they tend to blame poor scores on external factors: they say things like "the test was too hard," or "the prof didn't explain that," or "the questions are too picky."

Other studies suggest, though, that students who take responsibility for their grades not only get better grades, but they also learn that they, personally, can control the grades they get.

In fact, in one study researchers had students write down what "went through their minds" when they were trying to get better grades. Students who improved with each test were thinking:

"I need to work harder."
"I can learn this material if I apply myself."
"I can control what happens to me in this class."
"I have what it takes to do this."

Students who did not improve were thinking:

"It's not my fault."
"This test was too hard."
"I'm not good at this."

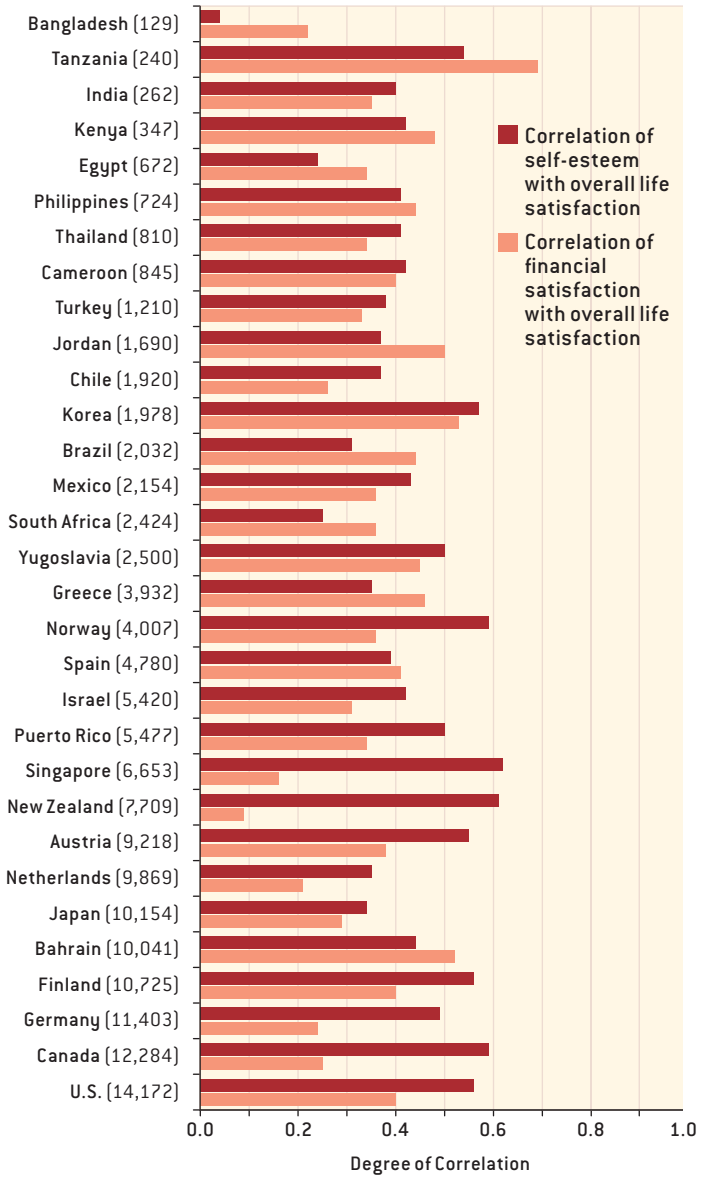
BOTTOM LINE: Take personal control of your performance.

mixed and inconclusive. A few studies have shown that *high* self-esteem is associated with frequent alcohol consumption, but another suggests the opposite. We did find, however, some evidence that low self-esteem contributes to illicit drug use. In particular, Judy A. Andrews and Susan C. Duncan of the Oregon Research Institute found in 1997 that declining levels of academic motivation (the main focus of their study) caused self-esteem to drop, which in turn led to marijuana use, although the connection was rather weak.

Interpretation of the findings on drinking and drug abuse is probably complicated by the fact that some people approach the experience out of curiosity or thrill seeking, whereas others may use it to cope with or escape from chronic unhappiness. The overall result is that no categorical statements can be made. The same is true for tobacco use, where our study-by-study review uncovered a preponderance of results that show no influence. The few positive findings we unearthed could conceivably reflect nothing more than self-report bias.

Another complication that also clouds these studies is that the category of people with high self-esteem contains individuals whose self-opinions differ in important ways. Yet in most analyses, people with a healthy sense of self-respect are, for example, lumped with those feigning higher self-esteem than they really feel or who are narcissistic. Not surprisingly,

SELF-ESTEEM AND HAPPINESS



Around the world, a person's overall satisfaction with life tends to go hand in hand with his or her level of self-esteem, as shown by the high degree of correlation between the two. Note that in most countries overall life satisfaction correlates better with self-esteem than with financial satisfaction. Exceptions tend to be countries with low per capita GDP (*bracketed values*).

SOURCE: E. Diener and M. Diener in Journal of Personality and Social Psychology, *Vol. 68, pages 653–663; 1995.*

MELISSA SZALKOWSKI

the results of such investigations may produce weak or contradictory findings.

Bully for You

FOR DECADES, psychologists believed that low self-esteem was an important cause of aggression. One of us (Baumeister) challenged that notion in 1996, when he reviewed assorted studies and concluded that perpetrators of aggression generally hold favorable and perhaps even inflated views of themselves.

Take the bullying that goes on among children, a common form of aggression. Dan Olweus of the University of Bergen was one of the first to dispute the notion that under their tough exteriors, bullies suffer from insecurities and self-doubts. Although Olweus did not measure self-esteem directly, he showed that bullies reported less anxiety and were more sure of themselves than other children. Apparently the same applies to violent adults, as Baumeister discussed in these pages a few years ago [see "More to Explore," below].

After coming to the conclusion that high self-esteem does not lessen a tendency toward violence, that it does not deter adolescents from turning to alcohol, tobacco, drugs and sex, and that it fails to improve academic or job performance, we got a boost when we looked into how self-esteem relates to happiness. The consistent finding is that people with high self-esteem are significantly happier than others. They are also less likely to be depressed.

One especially compelling study was published in 1995, after Diener and his daughter Marissa, now a psychologist at the University of Utah, surveyed more than 13,000 college students, and high self-esteem emerged as the strongest factor in overall life satisfaction. In 2004 Sonja Lyubomirsky, Chris Tkach and M. Robin DiMatteo of the University of California at Riverside reported data from more than 600 adults ranging in age from 51 to 95. Once again, happiness and self-esteem proved to be closely tied. Before it is safe to conclude that high self-esteem leads to happiness, however, further research must address the shortcomings of the work that has been done so far.

First, causation needs to be established. It seems possible that high self-esteem brings about happiness, but no research has shown this outcome. The strong correlation between self-esteem and happiness is just that—a correlation. It is plausible that occupational, academic or interpersonal successes cause both happiness and high self-esteem and that corresponding failures cause both unhappiness and low self-esteem. It is even possible that happiness, in the sense of a temperament or disposition to feel good, induces high self-esteem.

Second, it must be recognized that happiness (and its opposite, depression) has been studied mainly by means of self-report, and the tendency of some people toward negativity may produce both their low opinions of themselves and unfavorable evaluations of other aspects of life. In other instances, we were suspicious of self-reports, yet here it is not clear what could replace such assessments. An investigator would indeed be hard-pressed to demonstrate convincingly that a person was less (or more) happy than he or she supposed. Clearly, objective measures of happiness and depression are going to be difficult if not impossible to obtain, but that does not mean self-reports should be accepted uncritically.

People with high self-esteem are significantly happier than others. They are also less likely to be depressed.

What then should we do? Should parents, teachers and therapists seek to boost self-esteem wherever possible? In the course of our literature review, we found some indications that self-esteem is a helpful attribute. It improves persistence in the face of failure. And individuals with high self-esteem sometimes perform better in groups than do those with low self-esteem. Also, a poor self-image is a risk factor for certain eating disorders, especially bulimia—a connection one of us (Vohs) and her colleagues documented in 1999. Other effects are harder to demonstrate with objective evidence, although we are inclined to accept the subjective evidence that self-esteem goes hand in hand with happiness.

So we can certainly understand how an injection of self-esteem might be valuable to the individual. But imagine if a heightened sense of self-worth prompted some people to demand preferential treatment or to exploit their fellows. Such tendencies would entail considerable social costs. And we have found little to indicate that indiscriminately promoting self-esteem in today's children or adults, just for being themselves, offers society any compensatory benefits beyond the seductive pleasure it brings to those engaged in the exercise. SA

MORE TO EXPLORE

The Social Importance of Self-esteem. Edited by Andrew M. Mecca, Neil J. Smelser and John Vasconcellos. University of California Press, 1989.

Violent Pride. Roy F. Baumeister in *Scientific American,* Vol. 284, No. 4, pages 96–101; April 2001.

Does High Self-Esteem Cause Better Performance, Interpersonal Success, Happiness, or Healthier Lifestyles? Roy F. Baumeister, Jennifer D. Campbell, Joachim I. Krueger and Kathleen D. Vohs in *Psychological Science in the Public Interest,* Vol. 4, No. 1, pages 1–44; May 2003.

KEYLESS ENTRY

Open Sesame

You exit a busy store, point your key fob across the crowded parking lot, press a button and "Pop!"—your car door unlocks. How does the car know it's you? And why don't other cars open, too?

Most new vehicles offer what the industry calls remote keyless entry. Manufacturers program a microprocessor in each car and in its dedicated key fob with an algorithmic formula that generates a secret, encrypted code that changes each time a button is pressed [*see illustration*]. Each formula is unique, so one person's fob cannot open any other vehicle. Current-day garage door openers work similarly. "The scheme has been around for 10 years and has proven very secure," says Fanie Duvenhage, product marketing manager at Microchip Technology, a Chandler, Ariz., firm whose code-generating processors run the majority of U.S. automotive fobs. "We have not seen any successful attack on the algorithm."

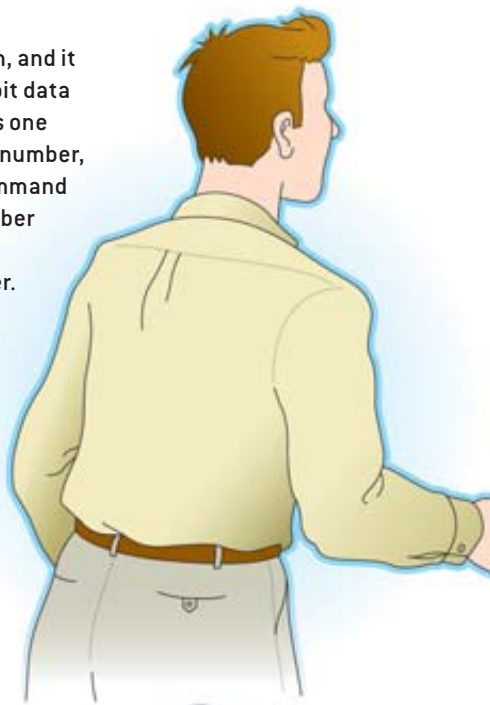
Success has spawned even greater convenience and protection. In "passive keyless entry," a driver standing beside a door begins to lift its handle, and a transceiver inside the car compares code with a key fob or smart card in the driver's pocket or handbag—handy for someone carrying an armful of groceries or packages. "Immobilization" systems will not allow a car to start after a key is inserted into the ignition unless a chip built into the key head provides the right code to a chip inside the ignition housing. In European countries that have mandated immobilizers in new cars, theft of current models has decreased by more than 50 percent.

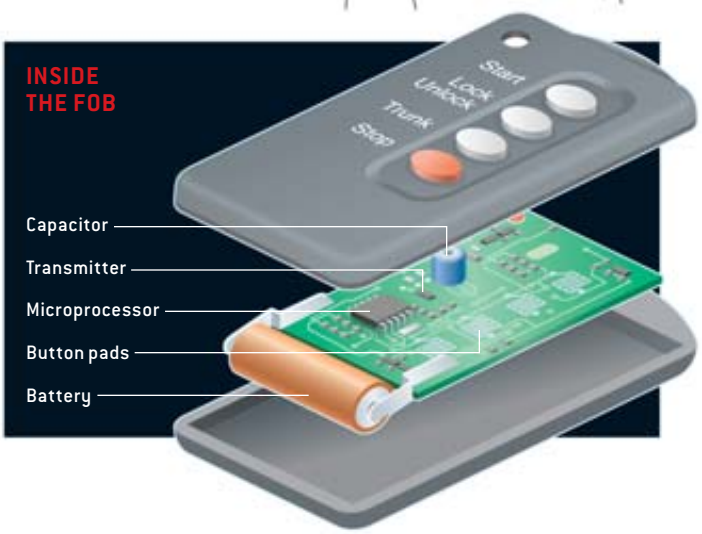
Immobilizer and passive entry communications take place at the relatively low frequency of 125 kilohertz. Remote keyless systems tap much higher frequencies, typically 315 megahertz in the U.S. and Japan, in part to span a parking lot or front lawn. European manufacturers have been using 433 megahertz, notes Alec Makdessian, business manager at integrated-circuits maker Maxim Integrated Products in Sunnyvale, Calif., "but they are moving up to 868 megahertz because the lower bands are becoming congested." About two million new keyless gadgets worldwide add to the saturation every year.

—Mark Fischetti

1 Auto manufacturer programs a car's receiver and a key fob with a software algorithm that will generate a unique 32-bit number each time they are activated. The number is created along a preset pattern determined by a formula that only that vehicle and fob share, so one person's fob can't open another's car.

2 Driver presses a fob button, and it transmits a stream of 64-bit data packets. The receiver captures one full packet comprising a serial number, a new secret number and a command (unlock door). If the serial number matches, the receiver also generates a new secret number. If the numbers agree, the receiver instructs the car's controller to open the door. The number is created with encryption technology so a thief cannot decipher it if he manages to capture the transmission with a radio scanner.





SAMUEL VELASCO; SOURCES: COILCRAFT, INC.; MAXIM INTEGRATED PRODUCTS

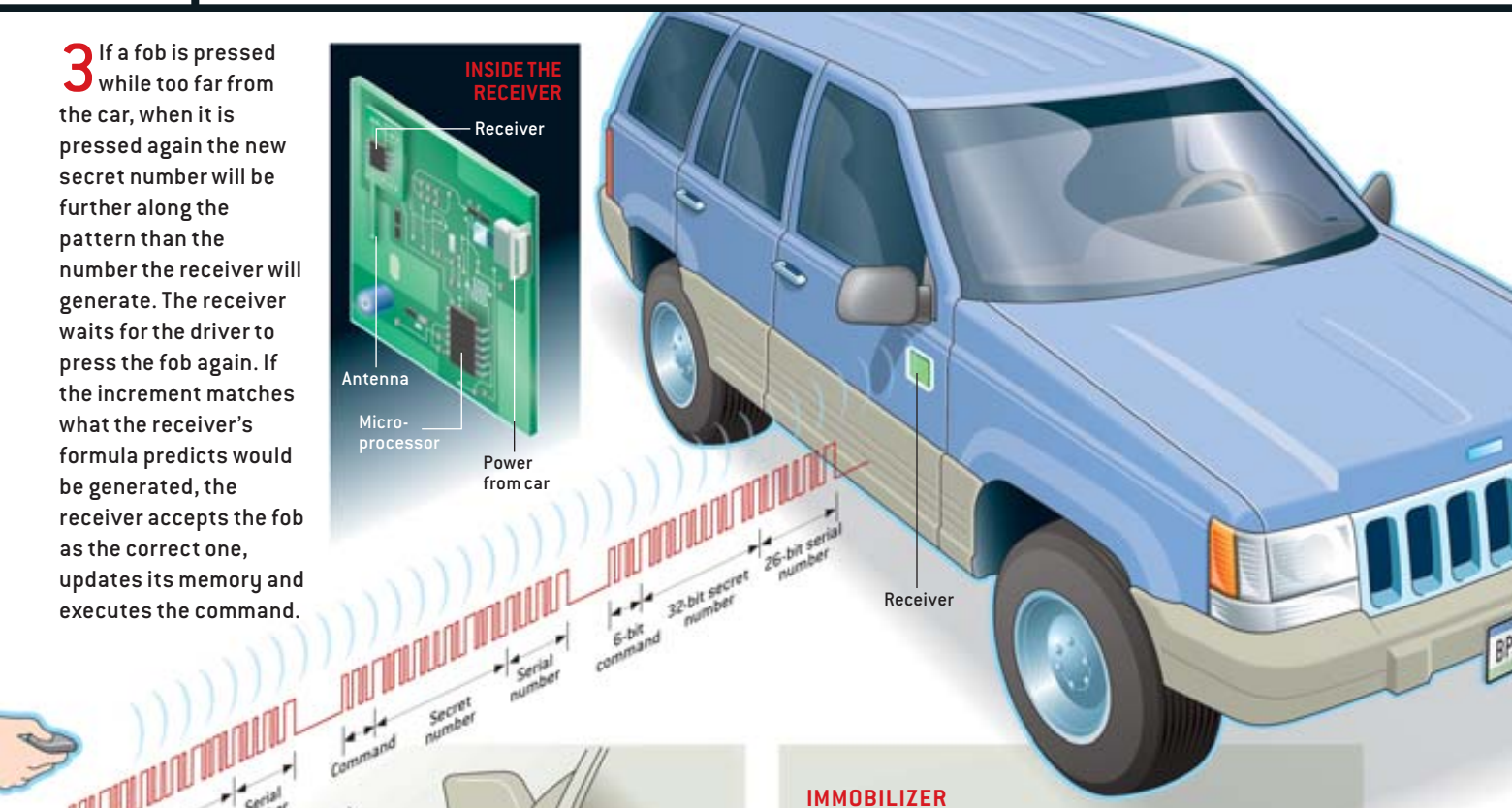
DID YOU KNOW...

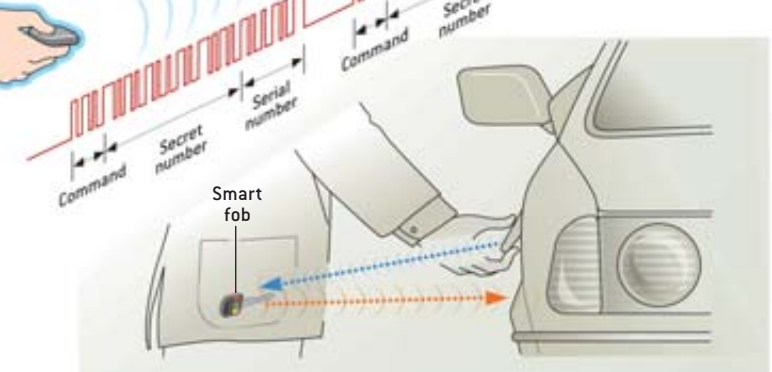
➤ TIRES: Low tire pressure can lead to dangerous steering or a blowout. Recent federal law mandates that new vehicles must eventually be equipped with tire-pressure monitoring systems. The leading option, already offered on some models, is a sensor housed in a fob inside a tire, behind the valve stem. If pressure drops 25 percent below recommended inflation, the fob's battery-powered radio transmitter (much like a key fob's) alerts the car's computer, which lights a warning icon on the dashboard.

➤ GARAGES: The first garage door openers appeared in the 1950s. They sent a simple "open" or "close" command over a single frequency. As they slowly proliferated, one person could drive down the street and open neighbors' doors. By the 1970s the "clicker" and the door controller each had an integrated circuit switch with eight little pins that were manually set to agree, providing one of 256 possible codes—better, but still not very secure. Today's openers use the same electronic algorithms as auto key fobs do; a 32-bit code offers more than four billion possible combinations.

➤ HOUSES, TOO: Some homes now have keyless dead bolts that communicate with a key fob. They typically display a red light that indicates when a door is locked. No more fumbling for keys when hands are full or scraping for the keyhole in the dark. Just be sure the button isn't depressed on that spare fob hidden under the flowerpot.

3 If a fob is pressed while too far from the car, when it is pressed again the new secret number will be further along the pattern than the number the receiver will generate. The receiver waits for the driver to press the fob again. If the increment matches what the receiver's formula predicts would be generated, the receiver accepts the fob as the correct one, updates its memory and executes the command.



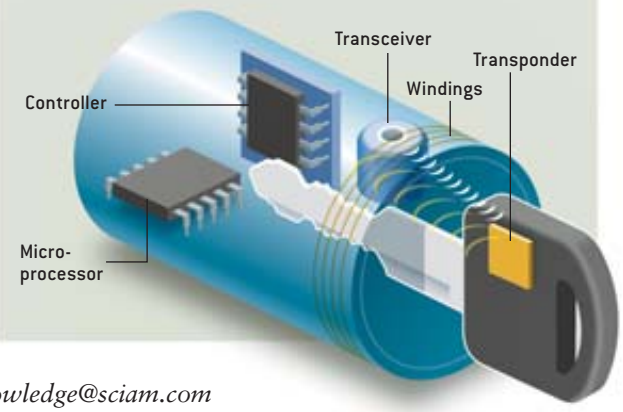


PASSIVE KEYLESS ENTRY

When a person lifts a door handle, the car's transceiver broadcasts a radio signal to see if a smart fob is within five feet of the door. If so, the transceiver generates a secret number and challenges the fob to do the same. If it does, the transceiver tells the car's controller to unlock the door.

IMMOBILIZER

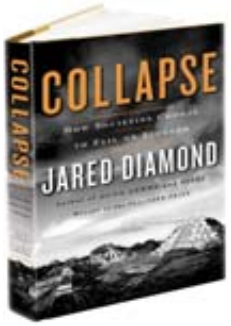
Driver inserts a key into the ignition. Windings emit a magnetic field that induces current in the key's transponder. The ignition microprocessor generates a secret number. If the transponder can match it, the controller allows the ignition to start.



Topic was suggested by numerous readers. Send ideas to workingknowledge@sciam.com

How Are the Mighty Fallen?

THE RISE AND FALL OF MONTANA, MAYA AND OTHER SOCIETIES **BY ROBERT S. DESOWITZ**



COLLAPSE: HOW SOCIETIES CHOOSE TO FAIL OR SUCCEED
By Jared Diamond
Viking, 2005
($29.95)

According to scripture, "How are the mighty fallen in the midst of battle" (II Samuel 1:25). To war, Jared Diamond in his new book, *Collapse: How Societies Choose to Fail or Succeed,* adds self-inflicted environmental degradation, climate change, disastrous trading relations, and unwise responses to societal problems. In his earlier, Pulitzer Prize–winning *Guns, Germs and Steel,* Diamond, a professor of geography at the University of California at Los Angeles, celebrated the rise of communities and nations despite microbial and self-imposed adversities.

Collapse is the downside of those dynamics, the societies that didn't make it, barely made it, or are destined, as Diamond sees it, for the fall. In this exhaustively researched new book, he presents carefully detailed case histories of failed societies—islands in warmish waters (Easter, Pitcairn, Haiti), an island in coolish waters (Greenland), a continental semidesert (the Anasazi of the Southwest U.S.), a continental tropical forest (the Maya of Mexico).

Diamond begins with the failed state of Montana. Montana? Well, a Pulitzer Prize–winning tenured professor can take the liberty of giving priority to his passions. So Diamond the ardent fly-fisherman, defender of ecological pristineness, sympathetic friend of the farming "locals" has come to the sad conclusion that Montana is going to the dogs. Once one of the richest states of the union, it now ranks among the poorest, having squandered its nonrenewable mineral resources and savagely overlogged its forests. Maybe worst of all, some cad put pike into the trout waters.

Although Montana is not about to fall off the map, leaving us with 49 states, the elements responsible for its decline are also responsible for societies that *have* fallen by the wayside. Diamond's central proposition is that wherever these globally disparate societies failed the chief cause had been anthropogenic ecological devastation, especially deforestation, imposed on ecosystems of limited resources. Those other western Americans, the Anasazi, settled in the New Mexico area about A.D. 600. There they built spectacular cliff housing, worked their marginal agricultural land, and chopped down all the trees without any plans for reforestation. Starving to the desperate point of cannibalism, wracked by internecine warfare, they met their end some 600 years later.

To the south, the Maya mostly had it all: technological knowledge to build architecturally wonderful cities, writing, and crops of corn. What they did not have were large domestic animals, or the foresight to replant after they clear-cut forests, or the political sense to refrain from inter-city warfare. Mayan soldiers and city dwellers were, as Diamond puts it, "parasites on farmers," who could no longer produce surplus food on their now barren, treeless land. The Maya began to go into decline about A.D. 1000 and said goodbye to the world about 1675, mopped up by the Spanish.

Diamond argues that the isolated island societies suffered a similar fate to the Anasazi and Maya for similar reasons. Pitcairn Island, Easter Island and Greenland all collapsed after the settlers had exhausted the fragile food and timber resources. Deforestation was particularly critical; after the larger trees were harvested, nothing was left to make the seagoing canoes needed for voyaging to other sources of food and material and for recruiting new people, especially wives, into their dwindling, interbreeding populations.

In these historical accounts of fallen societies, untrammeled population growth did not play a significant role. Not until the section on modern societies with modern troubles does Diamond invoke Malthus, offering Rwanda as the

JOEL W. ROGERS *Corbis*

PATTERN OF CATASTROPHE in the collapse of past civilizations included deforestation and other environmental degradation.

prime Malthusian model of too many people with too little land. He makes an unconventional interpretation of the savage Rwandan conflict. It was not a mutually genocidal affair propelled by ancient hatreds. At the village level the Hutu and Tutsi had lived together amicably—until geometric population growth far exceeded the arithmetic increase in land and improved agricultural technology, fulfilling the thesis of Malthus's 1798 *Essay on the Principle of Population*. The brutal killing was, according to Diamond, primarily over your neighbor's land, not his tribal affiliation.

As the book's subtitle suggests, there *are* societies that have come to success by right thought and action. The Japanese, for example, saw the light and preserved and replanted their forests (although they have not renounced their national wood esthetic; the trees now come from the forests of vulnerable states such as Papua New Guinea). The Dominican Republic preserved its forests and prospered. Its neighbor Haiti ravished both land and forests. And look what happened to them.

I wrote these last words while flying home from a National Academy of Sciences meeting called to reconsider bringing back that contentious, effective and dirt-cheap chemical, DDT. Now the choice will have to be made between the ultraconservationists' prohibition of DDT and the equally ardent arguments of a new coterie of American scientists who are demanding the return of DDT to try to halt the carnage of the malaria parasite, which kills two million to three million children and pregnant women every year. Sorry, Professor Diamond, even in our time of enlightened science, societies don't always have an easy, clear choice to survive, let alone succeed.

Collapse is a big book, 500-plus pages. It may well become a seminal work, although its plea for societal survival through ecological conservation is rather like preaching to the choir. It is not a page-turner, especially for slow readers of short attention span (like this reviewer). Some of Diamond's "case studies" may be overkilled by overdetail. The last section, on practical lessons, seems disconnected from the central *Collapse* story and almost constitutes a separate book. But, having discharged the reviewer's obligation to be critical, my recommendation would definitely be to read the book. It will challenge and make you think—long after you have turned that last 500th-plus page. SA

Robert S. Desowitz is emeritus professor of tropical medicine at the

University of Hawaii. He is author of five books on ecological and political issues relating to infectious diseases, the most recent being Federal Bodysnatchers and the New Guinea Virus *(W. W. Norton, 2003).*

THE EDITORS **RECOMMEND**

BOOKS ON EINSTEIN

A shelfful of books greets the centennial of Albert Einstein's "miracle year," which witnessed the theory of special relativity and four other seminal papers. Here is a sampling of the books our staff enjoyed.

EINSTEIN'S COSMOS: HOW ALBERT EINSTEIN'S VISION TRANSFORMED OUR UNDERSTANDING OF SPACE AND TIME

By Michio Kaku. W. W. Norton, 2004 ($22.95)

Thanks to Kaku's insight (he is a theoretical physicist) and his flair for explaining dense scientific concepts (he is a best-selling author), this brief book weaves Einstein's life and work into a seamless, hard-to-put-down narrative. The organizing metaphor is how Einstein thought in terms of simple physical pictures—speeding trains, falling elevators, moving clocks. Excellent for the neophyte or readers who want to refresh their knowledge about Einstein without being talked down to or bored.

EINSTEIN'S CLOCKS, POINCARÉ'S MAPS: EMPIRES OF TIME

By Peter Galison. W. W. Norton, 2004 ($14.95, paperbound)

Two scientists closed in on one groundbreaking theory. Poincaré posited something so close to Einstein's theory of relativity that it is surprising in retrospect he did not take the final step. The story is told in this new (paperbound) edition of a book that appeared in 2003. Described then as "absolutely brilliant," "a stroke of genius," "fresh, idiosyncratic," and "meticulously detailed ... perhaps the most sophisticated history of science ever attempted in a popular science book," it is all of the above, but it is not for the intellectually faint of heart.

THE INVISIBLE CENTURY: EINSTEIN, FREUD, AND THE SEARCH FOR HIDDEN UNIVERSES

By Richard Panek. Viking, 2004 ($24.95)

A less likely pairing emerges in this book—Einstein and Sigmund Freud. Although they met just once and didn't know what to make of each other's work, Einstein and Freud became the foremost proponents of research on the frontier of the invisible, the search for the next level of scientific data—evidence we can't see.

EINSTEIN DEFIANT: GENIUS VERSUS GENIUS IN THE QUANTUM REVOLUTION

By Edmund Blair Bolles. Joseph Henry Press, 2004 ($27.95)

Bolles intertwines a rich combination of scientific explanation and literary drama, painting a picture of Einstein's persona, the Euro-

EMILY HARRISON

pean mind-set, and the soap opera of quantum physics. The focus is on Einstein's battle for causality, the idea that every event has a cause and can thus be predicted.

ALBERT EINSTEIN'S VISION: REMARKABLE DISCOVERIES THAT SHAPED MODERN SCIENCE

By Barry Parker. Prometheus Books, 2004 ($28)

Parker follows Einstein's train of thought into the 20th century, examining the developments that resulted from his works. The book provides readers with enough information to recognize current buzzwords but not necessarily to understand them.

EINSTEIN A TO Z

By Karen C. Fox and Aries Keck. John Wiley, 2004 ($17.95)

Every Einstein book talks about relativity, but not many tell you about the mortician who ran away with his brain. From absentmindedness to Zionism, Fox and Keck offer sharp, bite-size pieces of Einstein-related people, concepts and quirks in a fun book ideal for trivia lovers and the science-wary.

THE EINSTEIN ALMANAC

By Alice Calaprice. Johns Hopkins University Press, 2004 ($24.95)

In a complete, concise guide, the author (who was in-house editor of the Princeton University Press series *The Collected Papers of Albert Einstein*) sets brief descriptions of 300 of Einstein's publications into the context of concurrent events in his personal life, the world in general, and the realm of physical science.

THE EXPANDED QUOTABLE EINSTEIN

Collected and edited by Alice Calaprice. Princeton University Press, 2000 ($19.95)

In her expanded edition, Calaprice has added a surprising number of new quotes to her quirky biography for the impatient reader. Most quotes are ordinary statements that convey a sense of Einstein's character rather than his mind-boggling intelligence.

THE COMPLETE IDIOT'S GUIDE TO UNDERSTANDING EINSTEIN

By Gary F. Moring. Second edition. Alpha Books (Penguin), 2004 ($18.95)

While the complete idiot may think that Einstein = relativity, Moring goes back as far as the ancient Greeks to set a solid stage for Einstein's myriad accomplishments in fields ranging from physics to philosophy. The book's explanations are complete enough to both satisfy the reader and pacify the scientist, and the cheeky writing style is amusing without being annoying.

The books reviewed are available for purchase through www.sciam.com

Captive Audience

"TO FERRET" MEANS TO BRING TO LIGHT BY SEARCHING BY STEVE MIRSKY

In October researchers announced in the journal *Nature* what could prove to be one of the greatest scientific discoveries of all time—the fossil remains of a miniature species of humans. The island of Flores, already famous in paleontological circles for having been home to pygmy elephants, also seems to have encouraged the downsizing of a stray group of *Homo erectus* who wound up there. Small stature was selected until adults were just over three feet tall and deserved to be classified as a new species. Islands, with limited resources, promote this kind of diminution—*Scientific American*'s offices are on the island of Manhattan, and some of us need a boost just to type uppercase letters.

You'll be able to read a full-length feature article about the not-quite-full-length people of Flores in our February issue. But I am forced to abandon my consideration of them at this point in favor of a discussion of other research. Because, at the end of September, *Nature* published a study in which scientists made ferrets watch the movie *The Matrix*. I'll wait while you read that last sentence again.

Indeed, researchers at the University of Rochester made a dozen ferrets watch *The Matrix*. (The idea of 12 sentient beings exposed to bad acting from stiff guys dressed in cheap suits particularly disturbs me, but that's probably because I was just on jury duty.) Of course, you are no doubt wondering why serious scientists made ferrets watch *The Matrix*. This question can be answered in three different ways:

1. Why did researchers make ferrets watch *The Matrix*? Answer: Because there are some things that rats just won't do.
2. Why did researchers make ferrets watch *The Matrix*? Answer: Because if they had made ferrets watch *The Matrix Reloaded*, animal-rights groups would have been storming the laboratory.
3. Why did researchers make ferrets watch *The Matrix*? Answer: To get a better handle on the nature of the perception of reality.

Seriously. *The Matrix* was an ironic choice, because that particular movie poses questions about whether what we commonly perceive is objective reality or just an imposed fiction. But because the investigators were interested in how a brain processes visual stimulation, they could have shown the ferrets anything other than *My Dinner with Andre* or C-SPAN's coverage of Congress.

A surprise for the scientists was that watching the movie made an adult ferret brain's visual system work only a bit harder than its baseline output. The ferrets' visual neurons were cranking along at about 80 percent of capacity even in a completely dark room. "In this framework," the researchers write, "ongoing activity may not be noise upon which visual responses are superimposed, but rather an integral component of sensory processing." That thing going bump in the night is your brain.

A provocative conjecture is that most of the brain's visually related activity is devoted to continuously manufacturing its learned representation of the world—its reality matrix—even in the complete absence of any current stimuli. And new, real-time action is overlaid on that internal representation.

"Because of the high-energy consumption of baseline neural activity in the brain," the scientists write, "it would be inefficient to maintain the observed high level of spontaneous activity unless it had an essential role in sensory processing." Perhaps it's simply easier to keep the matrix handy at all times than to ask the brain to build reality from scratch every moment. Which leads to this parting thought from the great mythologist Joseph Campbell: "Life is like arriving late for a movie, having to figure out what was going on without bothering everybody with a lot of questions, and then being unexpectedly called away before you find out how it ends." Especially if you're a ferret. SA

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

ASK THE EXPERTS

How do computer hackers "get inside" a computer?

—D. Ikavuka, La Mirada, Calif.

Julie J.C.H. Ryan, assistant professor at George Washington University and co-author of *Defending Your Digital Assets against Hackers, Crackers, Spies, and Thieves*, explains:

Essentially, hackers get inside a computer system by taking advantage of software or hardware weaknesses that exist in every system. Before explaining how they do this, a few definitions are in order. The term "hacker" is fairly controversial: some use this word to describe those whose intrusions into computer systems push the boundaries of knowledge without causing intentional harm, whereas "crackers" want to wreak havoc. I prefer "unauthorized user" (UU) for anyone who engages in unsanctioned computer access. "Getting inside" can mean one of three things: accessing the information stored on a computer, surreptitiously using a machine's processing capabilities (to send spam, for instance) or capturing information being sent between systems.

So how does a UU get inside a computer? The easiest weakness to exploit is a poorly conceived password. Password-cracking programs can identify dictionary words, names and even common phrases within a matter of minutes. Many of these programs perform a "dictionary attack": they take the encryption code used by the password system and encrypt every word in the dictionary. Then the UU plugs in the encrypted words until the password match is found. If a system has a complex password, the UU could try a "technical exploit," which means using technical knowledge to break into a computer system (as opposed to nontechnical options such as stealing documentation about a system). This is more challenging, because the UU must first learn what kind of system the target is and what the system can do. A proficient UU can do this remotely by utilizing a hypertext transfer protocol (http) that gains World Wide Web access. Web pages usually record the browser being used. The UU could write a program that takes advantage of this procedure, making the Web page ask for even more information. With this knowledge in hand, the UU then writes a program that circumvents the protections in place in the system.

MATT COLLINS

Although you cannot eliminate all possible weaknesses, you can take steps to protect against unauthorized access. Make sure you have the latest patches for your operating system and applications. Create a complex password with letters, numbers and symbolic characters. Consider installing a firewall program, which blocks unwanted Internet traffic. Make sure your antivirus software is up-to-date and check frequently for new virus definitions. Finally, back up your data, so you can recover important material if anything does happen.

Why do traffic jams sometimes seem to appear out of nowhere?

— H. Smith, New York City

Benjamin Coifman, assistant professor of electrical and computer engineering at Ohio State University who studies traffic patterns, offers this answer:

Drivers encounter the end of the line in a traffic jam seemingly out of nowhere because the number of waiting cars could stretch several miles away from the original bottleneck. The bottleneck could have arisen because of an accident or because of features in the roadway, such as a sharp curve, where drivers must slow down. The difference between the bottleneck's capacity and the demand upstream determines how fast the line grows. The end of the line typically has the worst conditions because cars there suffer from accumulated delays caused by the original obstruction, especially since vehicles entering from ramps worsen the problem by occupying additional space. Speeds tend to improve as drivers progress, making it easy to miss the actual trouble site when you finally pass it. SA

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