Why Does Time Only Move Forward? (*page 48*)

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SCIENTIFIC AMERICAN June 2008 ■ Volume 298 Number 6

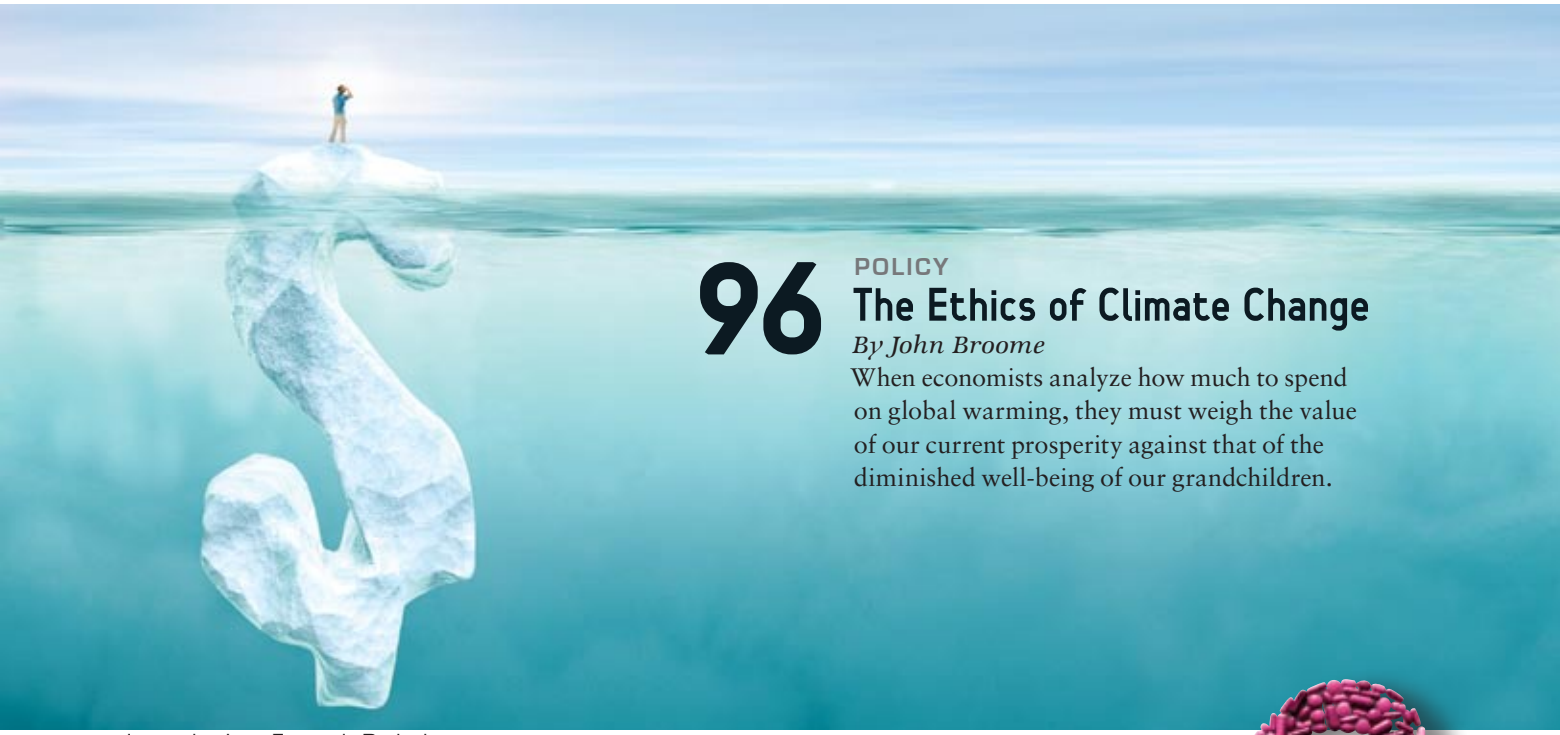

Image by Jean-Francois Podevin

ON THE COVER

Ethics and economics inform every decision about whether to prevent global warming or let future generations deal with it. Image by Jean-Francois Podevin.

MORE FEATURES

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BEN STEIN'S *EXPELLED:* NO INTEGRITY DISPLAYED ▼

Our commentaries on the new antievolution movie *Expelled* detail its shameful attacks on science and its attempts to blame Darwin for the Holocaust. More at **www.SciAm.com/jun2008**

KELLY ENGSTROM

Feature

China's Three Gorges Dam: An Environmental Catastrophe?

Even the Chinese government suspects the massive dam may cause significant environmental damage.

News

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Scientists may have a new clue to how matter beat out antimatter for dominance of the universe.

Ask the Experts

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Video

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Episode 8 of *Scientific American*'s irreverent weekly news roundup deals with all things extraterrestrial.

Podcast

R.I.P.: On the Shoulders of Giants ...

Physicist John Wheeler and geneticist Salome Waelsch both had incredibly long, fruitful careers, providing numerous fundamental insights in their fields.

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DEPARTMENTS

NICOLAS GUERIN

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Escaping from Time

Literature masters the fourth dimension, where physics fears to tread

Time travel is easy. The trick is finding a way to choose your route. Quirks of relativity aside, we never get to see the clock spin in any direction but forward and at a fixed and unvarying rate. (Illusions born of daylight savings time, inter–time zone travel and medication don't count.) However much we might like to stop, divert or roll back time, our sense of it remains linear and progressive. Yesterday always recedes. Tomorrow draws closer.

Only in fiction do characters sometimes have the liberty to experience time differently. One of writer Martin Amis's best known novels is *Time's Arrow,* in which the narrator perceives the flow of time in reverse. For him, people enter the world in coffins disinterred from the soil; once animated, they grow younger and younger and eventually disappear inside their mothers' wombs. That backward perspective turns the most hideous catastrophes into carnivals and the most joyous occasions into tragedies.

ASYMMETRY of time is a puzzle.

Billy Pilgrim, the hero of Kurt Vonnegut's *Slaughterhouse-Five,* is doomed to live the moments of his life in random order. He hops unwillingly between childhood, Dresden during World War II, his drab middle-class existence and his captivity among the aliens of Tralfamadore. In Vonnegut's comic vision, the chaos of 20th-century life seems senseless in every frame of reference.

In *Einstein's Dreams,* by physicist Alan Lightman, a fictional Albert Einstein nightly imagines a month's worth of variations on time: worlds where time is circular, backward, motionless, individualized, altitude-dependent, and so on. One of those visions (can you recognize it?) corresponds to the relativistic spacetime all around us.

But even physicists without literary predilections have been intrigued by time's stubborn insistence on moving one way. Symmetric principles of physics suggest that the universe ought to run forward and backward easily. Yet entropy, the tendency of isolated systems to become more disordered, imposes a bias. Something unbalances the equation and lets entropy increase. Physicists locate that "something" in how the cosmos originated—and, by extension, how it will eventually subside into a nearly empty nothingness.

Physicist Sean M. Carroll reconciles the inherent symmetry of time with its observed asymmetry and concludes that there are parallel universes where Amis's reversed arrow is not just a narrative device. Readers will not find a formula for reversing time in Carroll's article (see page 48), but they will surely find an intellectually enriching way of spending it.

If one could go back in time, surely many meteor buffs would visit Tunguska, Siberia, 100 years ago on June 30. That was when something exploded in midair and flattened uninhabited forest for dozens of miles. Identification of that object as a small asteroid or comet has been hindered by the failure to find any fragments or impact craters from it. Now, however, Luca Gasperini, Enrico Bonatti, Giuseppe Longo and their colleagues suspect that a small lake near the center of the explosion site may be a crater in disguise. Their report, starting on page 80, recounts how their work peeked into the past. ■

JOHN RENNIE
editor in chief

FLYNN LARSEN (*Rennie*); KENN BROWN (*cosmic hourglass*)

Among Our Contributors

JOHN BROOME
is professor of moral philosophy at the University of Oxford and a Fellow of the British Academy, among numerous other honors. His books include *Weighing Goods: Equality, Uncertainty and Time.*

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Land "Tides" ▪ Polar Ice Sheets ▪ Market Morality

FEBRUARY 2008

"A person may not be able to turn down an unfair deal if the alternative is starvation or homelessness. And an executive may be prevented from offering a better deal by the profit motive of his or her corporation."
—*Delano Lopez* APPLETON, WIS.

Tidal Terra Firma

Is Graham P. Collins correct in stating in "The Discovery Machine" [Special Report: The Future of Physics] that the land near Geneva rises 25 centimeters when the moon is full? A shift that large should damage considerable infrastructure.

Charlie Gotschalk
Sequim, Wash.

COLLINS REPLIES: *Because the tidal forces from the sun and moon deform the entire earth, all the land in the vicinity of Switzerland is raised by very nearly the same amount at "high tide." Consequently, at the scale of buildings and towns nothing is displaced enough from anything else to damage infrastructure or even to be particularly noticeable—unless you happen to be running an 8.6-kilometer-diameter accelerator and need to know its circumference to an accuracy of a millimeter. You would have to travel about a quarter of the way around the world (10,000 kilometers as the crow flies) to go from the location of the land's "high tide" to that of the land's "low tide," so it is only over distances of thousands of kilometers that the relative movement is as large as 25 centimeters.*

A 1992 talk on this issue by Gerhard E. Fischer of the Stanford Linear Accelerator Center is available at http://tinyurl.com/2ncx2o. Slides from a 2000 talk by Jorg Wenninger of CERN (pdf file at http://tinyurl.com/2vnpth) show how the effect of the tides on the beam energy of CERN's Large Electron-Positron (LEP) collider was first measured in 1992.

Free-Market Fairness?

After detailing research on the desire for fairness in humans and other primates in "The Mind of the Market" [Skeptic], Michael Shermer concludes that market economies are driven primarily by fairness. His assertion is supported neither by the research discussed nor by history and economics.

Shermer conflates the behavior of markets with that of humans, but corporations, whose only legal and structural motive is profit, conduct the majority of market activity. He also generalizes the results of studies of a presumably random sampling of humans to those who exert a disproportionate influence on the market. Systemic factors may have selected these individuals for ruthlessness. Moreover, Shermer ignores real-world factors: A person may not be able to turn down an unfair deal if the alternative is starvation or homelessness. And an executive may be prevented from offering a better deal by the profit motive of his or her corporation.

Shermer claims that if morality were not the rule, "market capitalism would have imploded long ago," which falsely assumes that an immoral market cannot be stable. (The transatlantic slave market thrived for hundreds of years.) Further, markets implode with great frequency—in crashes and depressions. When such crises occur, it is humans, not markets, that use their political will and governmental agencies to impose regulations and provide social services that restore some degree of justice to their society.

Delano Lopez
Appleton, Wis.

Good-bye, Ice?

"The Unquiet Ice," by Robin E. Bell, describes the effects of the ice sheets of Greenland and Antarctica collapsing completely, but currently there is no evidence that they will fully disappear. Furthermore, Bell's model does not take into account the rebound effect that would take place if those landmasses were free of ice, which would offset some of the sea-level rise. She also does not consider the possibility that there would be a greater movement of water vapor from the ocean to the atmosphere.

Raphael Ketani
Sunnyside, N.Y.

BELL REPLIES: *Ice sheets have come and gone throughout the history of our planet. The recent news of a large part of the Wilkins ice shelf collapsing reminds us of this flux. The results of the ice sheets changing are global and complex. The land underneath a disappearing ice sheet will rebound (today the Nordic countries and northern Canada bounce back almost one centimeter per year from the load of an ice sheet that disappeared more than 15,000 years ago), and the sea level will rise differentially depending on the water temperature and the source of the water. These complexities aside, we will likely continue to see increasing sea-level change from the polar ice sheets. It is difficult to transfer continental-scale ice to a framework we can apply to our own experience. The scientific community certainly does not anticipate a complete collapse of the polar ice sheets, but changing ice will increasingly be a theme of the coming decades.*

NEWLY DISCOVERED NETWORKS of liquid water under ice sheets may make the effects of global warming far more immediate than previously thought.

JAMES BALOG *Aurora Photos*

Smashing for Strings?

The box "Five Goals for the LHC" in "The Coming Revolutions in Particle Physics," by Chris Quigg [Special Report: The Future of Physics], does not mention anything related to string theory as a goal of the upcoming Large Hadron Collider (LHC) at CERN. Are any experiments planned for the LHC that could either support or falsify the theory's claims, expectations or predictions?

Geoff Noakes
San Francisco

QUIGG REPLIES: *String theory is not at the point of making specific predictions for the LHC, but the LHC might make observations that would encourage the string theory project. The discovery of supersymmetry would raise hopes that the incorporation of gravity that string theory has envisaged is a good path. Evidence for extra dimensions could likewise be seen as supporting some string theory ideas. On the other hand, observing certain kinds of new strong interactions might discourage the idea that strings will soon have relevance to our experiments.*

Because string theorists are not yet able to compare a measured number with a predicted one, much of the impact will be in the form of a conversation between an experiment and threads in the string theory worldview. Even before it has begun operation, the LHC has influenced some prominent string theorists to put the theory aside, for the moment, to concentrate on theoretical problems that promise a more immediate dialogue with LHC experiments.

ERRATUM "Building a Future on Science," by Christine Soares, states that Cláudio Mello was a postdoctoral fellow at Duke University in 2002. Mello was an associate professor of neuroscience at Oregon Health & Science University at that time.

CLARIFICATION "Potent Alternative," by JR Minkel [News Scan], incorrectly refers to Dolly the sheep as the first cloned animal. Dolly was the first mammal cloned from an adult cell.

Letters to the Editor

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American Passivity ▪ Wright Brothers' Report ▪ Coal Tar Dye

Compiled by Daniel C. Schlenoff

JUNE 1958

PASSIVE NATION—"Poll after poll among our youngsters has given statistical confirmation of the phenomenon of American life which David Riesman, in his book *The Lonely Crowd,* named 'other-direction'—extreme sensitivity to the opinions of others, with a concomitant conformity. As a nation we seem to have a syndrome characterized by atrophy of the will, hypertrophy of the ego and dystrophy of the intellectual musculature. This rather unpleasant portrait is an inescapable conclusion from the mass of data on the attitudes of the younger generation. More than half believe that the Federal Bureau of Investigation and the local police should be allowed to use wiretapping at will, that the police should be permitted to use the 'third degree,' that people who refuse to testify against themselves should be forced to do so."

BOVINE RESOURCES—"Cattle stand first among the animals serving man. They are outnumbered, it is true, by sheep, and they are outranked in man's esteem by the horse and the dog, but no other domestic animal renders such a variety of important services to human well-being. To the American or European consumer cattle represent beef, veal, milk, butter, cheese and leather; they yield in addition hormones and vitamin extracts, bone meal for feed and fertilizer, and high-protein concentrates for livestock feeding. However, more than a third of the world's 800 million cattle are engaged primarily in the generation of brute energy for the tasks of plowing, hauling and milling [*see illustration*]."

BULL of the Kankrej breed, a working variety of zebu cattle from central India, 1958

JUNE 1908

CARE OF LEPERS—"For the past several hundred years the care of lepers has received considerable attention in the Philippine Islands. If the segregation of lepers would stamp out the disease, this would be a good investment. But in the Philippines, medical evidence is by no means conclusive regarding the efficacy of segregation. A colony has, however, been opened on the little island of Culion, and a large number of lepers collected in it. It is contemplated that only such persons shall be declared lepers as by microscopical examination are found to have leprosy bacilli in their tissues. One noteworthy fact was observed while the lepers were being collected, that only about one-half of those who were previously reported as lepers were, on careful examination, found to be so."

THE WRIGHT BROTHERS WRITE—"The spring of 1908 found us with [government] contracts on hand, the conditions of which required performance not entirely met by our flights in 1905. The best flight of that year, on October 5, covered a distance of a little over 24 miles, at a speed of 38 miles an hour, with only one person on board. The contracts call for a machine with a speed of 40 miles an hour, and capable of carrying two men and fuel supplies sufficient for a flight of 125 miles. Our recent experiments were undertaken with a view of testing our flyer in these particulars, and to enable us to become familiar with the use of the controlling levers as arranged in our latest machines. —Orville and Wilbur Wright"

The entire article from 1908 is available at **www.SciAm.com/jun2008**

JUNE 1858

ANILINE DYES—"F. Grace Calvert, an eminent English chemist, four years ago said 'ere long, some valuable dyeing substance would be prepared from coal.' A few weeks ago he stood before the Society of Arts in London and showed them a beautiful purpleish blue color rivaling that of orchil [a vegetable dye], and having the great advantage of not being destroyed by light. These colors, for there are many of them, have been prepared from the alkalies of coal tar by Messrs. William Henry Perkin and Arthur H. Church, two rising discoverers, and have been called by them nitroso-phenyline and nitroso-naphthyline. The colors have been tried on silk, and found perfectly fast."

SCIENTIFIC AMERICAN, VOL. 198, NO. 6; JUNE 1958

Self-Cleaning Clothes ▪ Titan's Ocean? ▪ Synthetic Success ▪ Crisis Mapping

Edited by Philip Yam

Good-bye, Laundry

Talk of clothing that keeps itself clean, or that at least does not need conventional washing, has percolated for decades. Manufacturers have expressed interest in the technologies underlying such garments, but so far the only advance available commercially is clothing treated with nanoparticles that change the natural characteristics of the fabric to keep stains from soaking into it. That makes dirt easier to wash away. The technology, created by textile company Nano-Tex in 2001, appears in clothing today by retailers Eddie Bauer, Gap and Hugo Boss, to name a few.

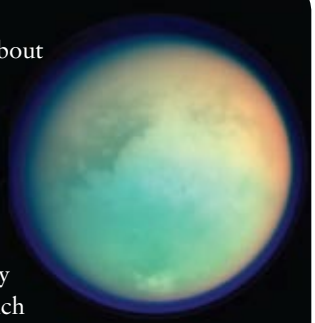
Perhaps the most serious customer for self-cleaning clothing right now, though, is not the average mall shopper but U.S. military personnel, who might face long stretches between clothing changes. Chemist Jeff Owens is working with others at Tyndall Air Force Base in Florida on a process that fuses chemicals onto fabric, resulting in material that resists fire, oil and water and that also kills bacteria. Owens's team is aiming to have the technology ready for preliminary demonstrations in 2009.

Despite today's limited market, the quest for self-cleaning clothing with the potential for broader use continues. Researchers at Monash University in Australia have found a way to coat keratin protein fibers, such as wool, hemp and silk, with titanium dioxide nanocrystals that oxidize food and dirt in sunlight. According to lead researcher Walid Daoud, the process, outlined in the February 26 *Chemistry of Materials,* does not employ toxic reagents and is harmless to skin. The drawback: speed, or lack thereof. It takes 20 hours in the sun for a wine stain to disappear. —*Keren Schultz*

WASH DAZE: Self-cleaning clothes would be a boon to soldiers.

GETTY IMAGES (*soldier hanging up wash*)

Waves below the Crust



Astronomers have wondered about the possibility of water—and, hence, of life—on Saturn's moon Titan [see "The Mystery of Methane on Mars and Titan"; SciAm, May 2007]. Researchers modeling Titan conclude that a huge ocean may lie underneath the surface, which would explain observations by the Cassini probe that found peculiar shifts in Titan's rotation and landmarks on the surface. The ocean may have resulted from heat from radioactivity at the moon's core that melted a layer of frozen water. Luckily, the idea is testable: a subcrustal ocean would speed up Titan's rotation rate in the coming year or two, followed by a slowdown—something that can be measured on succeeding Cassini flybys. —*JR Minkel*

First Artificial Enzyme

With the goal of making synthetic biological components [see "Engineering Life: Building a Fab for Biology"; SciAm, June 2006], researchers have crafted the first artificial enzyme—specifically, an enzyme that removes a proton from a carbon atom. The team, from the University of Washington, the University of California, Los Angeles, and the Weizmann Institute of Science in Rehovot, Israel, used a computational model to devise potential enzymes constructed from 200 amino acids. After finding the enzyme that showed the most activity, the group further improved it by making it undergo evolution in a test tube. Seven rounds of evolution—the introduction of mutations—improved the enzyme's efficiency 200-fold. *Nature* published the study online March 19.

Digital Humanitarianism

Technology helps relief agencies tackle the plight of refugees [see "The Science of Doing Good"; SciAm, November 2007]. Among the newest is an online mapping project by Google and the United Nations High Commissioner for Refugees. Called the Google Earth Outreach program, it enables humanitarian groups to highlight their work in progressively detailed layers, all the way to the schools, water sources and other infrastructure of a refugee camp. The site (www.unhcr.org/events/47f48dc92.html) currently features refugee plights in Colombia, Iraq and the Darfur region of Sudan.

DISASTER IN DETAIL: The U.N.-Google refugee mapping site.

NASA/TERRAMETRICS/GOOGLE (*screen shot*); NASA/JPL/SPACE SCIENCE INSTITUTE (*Titan*)

PALEOANTHROPOLOGY

Hobbit Hullabaloo

New findings challenge the idea of a mini human species on Flores BY KATE WONG

She stood barely more than a meter tall and had a brain the size of a chimpanzee's. That is about all scientists can agree on in the case of the adult human skeleton known as LB1—popularly dubbed the hobbit. Unveiled in 2004, the diminutive bones hail from a cave called Liang Bua on the Indonesian island of Flores. Based on analyses of LB1 and some other, more fragmentary remains, the discovery team concluded that the specimens belonged to a previously unknown human species, *Homo floresiensis*, that lived as recently as 12,000 years ago [see "The Littlest Human," by Kate Wong; Scientific American, February 2005]. But within days skeptics emerged, countering that the tiny remains instead belonged to a small-bodied population of modern humans and that LB1—with her tiny brain and other odd features—was a diseased member of the group.

SMALL WONDER: **Hobbit skull (*left*) housed a brain a third the size of that of a modern human (*right*). Most researchers believe that the hobbit represents a new species. Skeptics, however, argue that it is just a modern human with a growth disorder.**

In recent months researchers have published several papers favoring the minority view of the skeptics. Hobbit proponents, however, think that the evidence for the hobbit as a separate human species is stronger than ever. The stakes are high. Proponents now believe the finds suggest that the first human ancestors to leave Africa may have been far more anatomically primitive—and may have left far earlier—than previously thought. If they are right, the Flores remains rank among the most important paleoanthropological discoveries of all time, one that will revolutionize our understanding of human evolution. If they are wrong, "it will be worse than Piltdown" in terms of its effect on the field, as one anonymous observer put it, referring to the 1912 hoax that combined modern human and orangutan fragments.

Detractors have long argued that LB1 exhibits a number of skeletal and dental anomalies in addition to her minuscule brain case, including various asymmetries in the skull and skeleton. But finding a disorder that can account for those traits has proved challenging. To that end, last June a team of scientists determined that LB1 may have had Laron syndrome, a genetic disease that causes insensitivity to growth hormone. Then, in February, a second research group concluded that she might have suffered from another genetic condition

Dancing around DNA

In the ongoing debate over whether the tiny skeleton known as LB1, or the hobbit, is a separate human species, investigators had hoped that DNA might settle the matter. But according to ancient-DNA expert Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, analysis of mitochondrial DNA retrieved from LB1's teeth has revealed sequences identical to those of living humans. Although such a result could, in theory, support the critics' views, the standard practice in such cases is to assume that the sample has been contaminated with the DNA of someone who handled the bones.

AP PHOTO

BONING UP: Hobbit specimen, LB1, exhibits a host of primitive traits, including short legs and a flaring pelvis.

known as microcephalic osteodysplastic primordial dwarfism type II (MOPD II), which produces individuals with small bodies and small brains who nonetheless are of near-normal intelligence. And in March a third team reported that, based on photographs, LB1's skull seems to have an abnormally large cavity for the pituitary gland. This, the researchers said, was evidence of myxoedematous endemic cretinism; the disorder arises from prenatal nutritional deficiencies that render the thyroid gland unable to function, which in turn supersizes the pituitary.

Within days of the publication of the cretinism paper, investigators led by Lee Berger of the University of the Witwatersrand in Johannesburg announced that they had discovered small modern human bones ranging in age from 1,400 to 2,900 years old in two caves in Palau, Micronesia. In addition to being tiny, the bones display traits that are typically associated with earlier members of our genus, including pronounced browridges and a nonprojecting chin. These characteristics also occur in the hobbits and have been used to help make the case that they represent a new species. But Berger and his colleagues argue that these features may simply arise as a side effect of evolving a small size. And that, they say, supports the possibility that LB1 is a diseased member of a small-bodied modern human population.

Experts dispute all these hypotheses. Dean Falk of Florida State University and Ralph L. Holloway of Columbia University, who have studied CT scans and casts of the interior of LB1's skull, both note that LB1's pituitary was much smaller than the cretinism theorists claim. And in a presentation given to the American Association of Physical Anthropologists in April, Falk rejected the diagnosis of Laron syndrome, noting that many of the 33 traits said to characterize the disease are not present in LB1.

Meanwhile humans around the globe have bones just as small or smaller than these fragments from Palau, says William L. Jungers of Stony Brook University, who has been studying the postcranial skeleton of LB1. "But none of them anywhere in the world are as short as the various individuals of *Homo floresiensis*." Furthermore, he adds, none of them share LB1's suite of primitive skeletal characteristics, such as her apelike wrist bones and her flaring pelvis, which bears an uncanny resemblance to the pelvis of the 3.2-million-year-old fossil from Ethiopia known as Lucy.

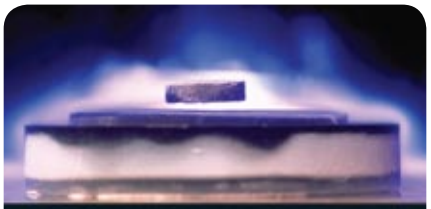
Even hobbit deniers, such as Robert B. Eckhardt of Pennsylvania State University, concede that "it's easy to rule out cretinism and MOPD II." Still, he and others maintain that Laron syndrome is a viable diagnosis. The problem, they say, is that pathologies are complex and the way they manifest varies from person to person. "If you have to match all 33 symptoms, you're not going to find anything," remarks John Hawks of the University of Wisconsin–Madison. "You have to go based on the preponderance of evidence."

WILLIAM L. JUNGERS *Stony Brook University*

PHYSICS

A New Iron Age

A high-temperature superconductor based on iron BY CHARLES Q. CHOI



COLD CASE: A new superconductor could iron out theoretical wrinkles in high-temperature superconductivity, which here produces magnetic levitation with liquid nitrogen.

DAVID PARKER IMI/University of Birmingham High TC Consortium/Photo Researchers, Inc.

For more than 20 years, the only known superconductors that worked far above liquid-helium temperatures were a few dozen compounds—virtually all based on copper. Now scientists have discovered the first high-temperature superconductors based on iron. These novel materials could help unravel one of the biggest mysteries in science—how exactly the high-temperature versions work.

In superconductors electric current flows completely without resistance. For decades, the phenomenon was thought to occur only near absolute zero. The cold tames the vibrations of the atoms making up the substance in such a way that electrons can overcome their natural repulsion for one another. The altered vibrations, called phonons, cause the electrons to pair up; so coupled, they can then move freely through the atomic lattice.

Starting in 1986, however, physicists began discovering a new class of superconductors operating well above absolute zero, to temperatures as high as 160 kelvins (–113 degrees Celsius). These materials, dubbed cuprates, typically consist of copper oxide layers sandwiched between other substances. The structure of the cuprates and the high temperature interfere with the mechanisms that drive conventional superconductors, leading physicists to try to come up with new explanations.

A serendipitous discovery is now forcing investigators to expand their ideas on superconductivity. Materials scientist Hideo Hosono of the Tokyo Institute of Technology and his colleagues were looking to improve the performance of transparent oxide semiconductors but ended up discovering the first iron-based, high-temperature superconductor.

The crystalline material, known chemically as LaOFeAs, stacks iron and arsenic layers, where the electrons flow, between planes of lanthanum and oxygen. Replacing up to 11 percent of the oxygen with fluorine improved the compound—it became superconductive at 26 kelvins, the team reports in the March 19 *Journal of the American Chemical Society*. Subsequent research from other groups suggests that replacing the lanthanum in LaOFeAs with other rare earth elements such as cerium, samarium, neodymium and praseodymium leads to superconductors that work at 52 kelvins.

High-temperature superconductivity in these layered iron compounds completely surprised investigators, who thought that the magnetic nature of iron would disrupt the pairing of electrons. Perhaps, as seems to be the case for cuprates, the electrons get paired with the aid of spin fluctuations—disturbances in the magnetic fields of atoms making up the superconductor. "These iron-based superconductors could give us new hints on how to understand cuprates," says physicist Kristjan Haule of Rutgers University.

On the other hand, the spin fluctuations that could glue together cuprate electrons might not be enough for those in the iron-based materials. Instead orbital fluctua-

tions—or variations in the location of electrons around atoms—might also prove crucial, Haule speculates. In essence, the iron-based materials give more freedom to electrons than cuprates do when it comes to how electrons circle around atoms.

Orbital fluctuations might play important roles in other unconventional superconductors as well, such as ones based on uranium or cobalt, which operate closer to absolute zero, Haule conjectures. Because the iron-based superconductors work at higher temperatures, such fluctuations may be easier to research.

Besides illuminating the theoretical underpinnings of superconductivity, the discovery "makes us ask if there are other high-temperature superconductors we haven't found yet in unexpected places and if there are even higher temperatures these can work at," remarks theoretical physicist David Pines of the University of California, Davis, who is also founding director of the Institute for Complex Adaptive Matter. In trying to boost the critical temperature, experiments should focus not only on swapping in other elements but also on layering the compounds. That should improve them just as it does for cuprate superconductors, Haule thinks.

Being based on iron could make these substances more commercially enticing, too. The fragility of cuprates, which as ceramics are quite brittle, has long hampered applications such as superconducting power lines. If iron-based materials are easier to handle and manufacture than cuprates, "they will become very important," Haule adds.

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

NEURODEGENERATION

Your Brain on Diabetes

More signs that insulin ills set off neurodegenerative conditions BY MELINDA WENNER

Anyone who is diabetic—or knows a diabetic—recognizes the importance of insulin. The hormone helps cells store sugar and fat for energy; when the body cannot produce enough of it (type 1 diabetes) or responds inadequately to it (type 2 diabetes), a range of circulatory and heart problems develop. But that is not all: recent research suggests that insulin is crucial for the brain, too—insulin abnormalities have been implicated in neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's. Among the latest findings is the discovery that a gene linked to insulin processing is located in a chromosomal area linked to Parkinson's.

Historically, scientists believed that insulin was produced only by the pancreas and had no business in the central nervous system. Then, in the mid-1980s, several research groups spotted the hormone and its receptor in the brain. It appeared that the hormone not only crossed the blood-brain barrier but that it was also produced, at low levels, by the brain itself.

Soon afterward, scientists discovered that insulin plays an important role in learning and memory. People who inject or snort insulin immediately get better at recalling stories and performing other memory tasks. Learning also raises insulin levels: rats mastering spatial memory tasks have higher brain insulin levels than sedentary rats do.

These observations led neuropathologist Suzanne de la Monte and her colleagues at Brown University to ask whether brain insulin might have a part in Alzheimer's, which is characterized by severe memory loss. They compared postmortem insulin and insulin receptor levels in healthy brains and brains of Alzheimer's patients. Average insulin levels in the neural parts associated with learning and memory were up to four times higher in the healthy brains, which also had up to 10 times as many insulin receptors.

HERMAN AGOPLAN Getty Images

SWEET TOOTH, SOUR BRAIN: Recent studies emphasize the connection between neurodegeneration and insulin problems, such as those in diabetes.

"That made it clear that one could get exactly the same problems as in regular diabetes except confined to the brain," says de la Monte, who refers to Alzheimer's as "type 3 diabetes." Because brain insulin is linked to insulin in the rest of the body via the blood-brain barrier, diabetics are more likely to develop Alzheimer's, too—nearly twice as likely, according to a 2002 study. They also suffer more memory and learning problems than the general population.

De la Monte and others, including neuroendocrinologist Ignacio Torres Alemán of the Cajal Institute in Madrid, have also found links between Alzheimer's and low brain levels of insulinlike growth factor 1 (IGF-1) and its receptor—proteins similar in structure to insulin and its receptor (insulin occasionally binds to the IGF-1 receptor, and vice versa). "We have suggested that Alzheimer's disease originates because of an exacerbated loss of IGF-1 sup-

port to brain cells," Torres Alemán says.

A handful of recent studies have also linked insulin and IGF-1 to Parkinson's and Huntington's. The prevalence of diabetes in patients with Huntington's is seven times higher than average, and at least half of Parkinson's patients have glucose metabolism problems. Robert Smith, an endocrinologist at Brown, recently discovered a protein called GIGYF2 that interacts with insulin and IGF-1 receptors. To better understand GIGYF2's function, Smith mapped the location of its gene in the human genome. Reporting in the April 11 *American Journal of Human Genetics,* he says, "we found that it was smack dab in the PARK11 site," a region of chromosome 2 that is linked to Parkinson's—although he is not certain what the gene's role in Parkinson's may be.

Indeed, one of the biggest remaining questions is how, exactly, defects in insulin and IGF-1 signaling might hurt the brain. "This is a crucial topic—something we're spending a great deal of effort unraveling," de la Monte says. Some scientists believe that insulin is involved in the production of large protein plaques observed in the brains of patients with Alzheimer's and Parkinson's. When Smith added above normal levels of GIGYF2 to neurons in the lab, large GIGYF2 aggregates formed and killed the cells. Other studies have determined that insulin modulates the production and degradation of amyloid beta, the protein that forms sticky plaques seen in Alzheimer's brains.

Although no one yet knows all the details of what is happening, few scientists in the field doubt that insulin and IGF-1 are crucial players in neurodegenerative disease. Many are working on potential treatments that restore normal insulin function in the hopes of mitigating or even preventing neurodegeneration. For example, compounds that improve insulin response in the brain and body have been shown to lessen cognitive decline in early-stage Alzheimer's patients. "It is so exciting," de la Monte says. "The fact that we have some way to go after it is really cool."

Melinda Wenner is a freelance writer based in New York City.

BANDWIDTH

Fight in White Space

Could future wireless devices destroy HDTV broadcasts? BY LARRY GREENEMEIER

Microsoft, Google and several more of the world's largest and most influential technology companies have found a way to provide wireless Internet access that is so fast it makes today's Wi-Fi networks seem as sluggish as dial-up service. The prospect, however, has big media broadcasters up in arms, because this blazing-fast network access may hamper television signals when they go digital next year. In a test conducted last year by the Federal Communications Commission, wireless devices blanked out digital programming on nearby television sets.

At the heart of the dilemma are so-called white spaces, the chunks of unused bandwidth layered between TV channels that are designed to keep broadcast signals from interfering with one another. These spaces will get even bigger on February 17, 2009, the legally mandated day for TV broadcasts to go completely digital, freeing up more of the airwaves. (Digital signals take up less airwave space than their analog counterparts.)

Tech companies see huge opportunities in these radio-frequency buffer zones. The slices could allow computers, cell phones and other wireless devices to transfer gigabits of data per second (compared with Wi-Fi's megabit-per-second speeds), thereby supporting mesh networks, broadband access in remote areas and wireless hotspots. "You may want to call it Wi-Fi 2.0 or Wi-Fi on steroids," said Rick Whitt, Google's Washington, D.C., telecom and media lawyer, during a recent press conference held to promote the effort. In March, Google filed a petition with the FCC stating its support for white-space-sensing technology—such as that proposed by rival Microsoft. Google's interest in wireless technology stems from the company's desire to promote its open-source Android operating system and software for mobile devices, which Google hopes will be available by this fall.

FREQUENCY FIGHT: New wireless services using the buffer-zone frequencies among television channels could interfere with digital broadcasts.

But broadcasters do not want to invest in a digital infrastructure only to have cell phone and Internet traffic infringe on their channels, essentially making digital TV no more reliable than the analog sets that depended on tinfoil-wrapped rabbit-ear antennas. So before Google and the others can exploit white spaces, they must get permis-

HOLA IMAGES/GETTY IMAGES

sion from the FCC, which wants proof that they can efficiently pinpoint and use them without disrupting broadcast signals or other devices (such as wireless microphones) that already rely on these open frequencies. Five companies—Adaptrum, Microsoft, Motorola, Philips Electronics and Singapore's Institute for Infocomm Research—have submitted prototypes to the FCC. Each of the devices—which represent a form of so-called cognitive radio—tries to identify a slice of pristine airwave space wherein a wireless device could operate without blocking other signals.

So far none of them have received approval. Although some of the prototypes can detect the presence of TV and wireless microphone signals, the ones that have transmission capability have yet to demonstrate reliable function. A recent blow came in late March, when Microsoft acknowledged that its device for sensing white spaces "unexpectedly shut down" during testing; a spokesperson for the company adds, without providing additional detail, that "because of the shutdown, the FCC could not move forward with testing and made a decision to stop testing on this device." This was the second time in two months that a Microsoft device failed to endure FCC scrutiny.

Tech firms believe they will ultimately succeed in devising a technology that can find white spaces on its own and temporarily tap into them without interfering with licensed users. Philips, for instance, plans to send a more advanced version of its spectrum-sensing technology to the FCC soon that can detect signals as well as transmit them without interference, says Kiran Challapali, a project leader in Philips Research North America's wireless communications and networking department. If such systems pass muster, Whitt said, Google would try to put a new crop of wireless devices that could make use of white spaces in consumers' hands by the holiday season of late 2009—without fear of blanking out your pricey big-screen HDTV set.

Gigabucks for Megahertz

This past March the Federal Communications Commission completed its initial auction of licenses to use airwave space that will be freed up once television broadcasters give up their analog channels next year. The FCC raised more than $19 billion in the auction of the 700-megahertz band (which actually ranges from 698 to 806 megahertz). The agency called this auction its largest ever, far exceeding the $10 billion that Congress had estimated. The winning bidders so far include the major cell phone carriers, such as AT&T and Verizon Wireless, which can use the spectrum, for instance, to transmit cell phone signals farther with less power.

EVOLUTION

Need for Speed?

Studies challenge the idea that human evolution recently accelerated

BY DAVID BIELLO

Addis Ababa is the center of the genetic world. Not because of any special skill in genome analysis but because variation in the human genetic code diminishes as distance from the Ethiopian capital increases. After all, modern humans originated in East Africa.

Yet this genetic fact has led to some divergent conclusions. Some researchers have looked at the differing makeup of populations and argued that human evolution must be speeding up to explain all the variation. Others see that variation as yet more proof that a relatively small number of individuals migrated out of Africa and founded the current populations in other parts of the world.

Last December a group of anthropologists and geneticists concluded that human evolution must have accelerated in the past 40,000 years after examining the 3.9 million DNA sequences from 270 people from four populations known as the HapMap. "We found very many human genes undergoing selection," says Gregory Cochran of the University of Utah, a member of the team. "We believe that this can be explained by an increase in the strength of selection as people became agriculturalists, a major ecological change, and a vast increase in the number of favorable mutations as agriculture led to increased population size."

Such mutations include regionally different genes that have lightened skin tone and conferred the ability to digest milk in adulthood. In separate work, Lluís Quintana-Murci of the Pasteur Institute in Paris and his colleagues count about 55 of these mutations in total.

But other studies of changes to individual DNA amino acids (single-nucleotide polymorphisms), DNA sequences (haplotypes) or longer sections of the genetic code (copy number variants) all agree that the peoples of Africa have the most diversity in their genome. People in different regions—say, Africans and Europeans—may have a few different genes, but that minuscule difference is dwarfed by the amount of genetic code all humanity has in common. In fact, two Africans are likely to have greater genetic differences than an African and a European do. "We are a young species," remarks geneticist Noah Rosenberg of the University of Michigan at Ann Arbor, who participated in a comprehensive study of genetic variation that appeared in *Nature* in February. "Different human populations have not been separated for long enough periods of time to develop their own new alleles."

Many geneticists therefore express doubt that genes have evolved very much in the relatively short span of human existence in all parts of the planet. And most genetic instruc-

PIOTR REDLINSKI *Corbis*

SIMILARITY IN DIVERSITY: **The genetic code of humans from different populations is largely the same.**

tions that do vary are more likely to be harmful than helpful, according to another analysis of DNA amino acid variation.

Instead of evolution working on a relatively small number of genes to actively promote functional adaptations—a process known as positive selection—"the alternative is a demographic factor, which is a bottleneck," explains geneticist Marcus Feldman of Stanford University. A bottleneck describes the rise of a new population from a few individuals. Feldman participated in a study of DNA samples from 938 people in 51 different populations, finding evidence for the alternative explanation in declining DNA sequence (haplotype) variation with increasing distance from Africa. The work appeared in *Science* in February.

"A bottleneck followed by population growth may explain the slight increases in the proportion of European-American-specific amino acid variation predicted to adversely impact protein structure and stability," says Carlos Bustamante of Cornell University, who computationally models the changes in genes. Other computational biologists, such as Itsik Pe'er of Columbia University, also point out that demographic changes are consistent with the overall distribution of human genes.

A new initiative, called the 1000 Genomes Project, could settle the question of whether human evolution has picked up. Scheduled for completion in 2011, it should provide a "cornucopia of sequence data from many more individuals from more populations," notes Kirk Lohmueller, a graduate student in Bustamante's lab.

The project will also delve into the genome in greater detail than ever before. "We'll get variants in those samples that are somewhere around the 1 percent or lower frequency," says geneticist Lisa Brooks, director of the National Human Genome Research Institute's Genetic Variation Program. Conversely, she adds, "something that is common in one population is unlikely to be rare in another population. This reflects our common heritage."

Migration: A Force in Evolution

From existing genetic studies, an obvious but sometimes hidden truth has begun to emerge. "An awful lot of people around the world have ancestry in more than one place and, in fact, in more than two places," says geneticist Marcus Feldman of Stanford University. "A lot of mixing has gone on," he says, which can help reveal the most active centers of migration, such as the Middle East. "Where you have large contiguous landmasses, you always see signals for migration, and where you have boundaries, you see the signals of boundaries," he notes. The same signs also appear in linguistics and paleobiology. All those fields, Feldman adds, "are converging to give a consistent picture of modern human evolution."

NEUROBIOLOGY

The Healthy Type

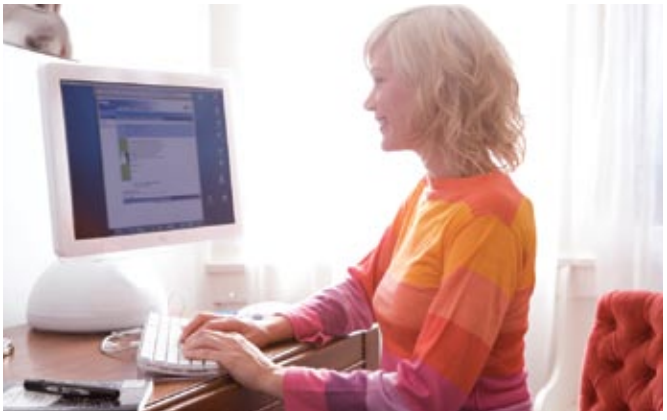
The therapeutic value of blogging becomes a focus of study BY JESSICA WAPNER

Self-medication may be the reason the blogosphere has taken off. Scientists (and writers) have long known about the therapeutic benefits of writing about personal experiences, thoughts and feelings. But besides serving as a stress-coping mechanism, expressive writing produces many physiological benefits. Research shows that it improves memory and sleep, boosts immune cell activity and reduces viral load in AIDS patients, and even speeds healing after surgery. A study in the February issue of the *Oncologist* reports that cancer patients who engaged in expressive writing just before treatment felt markedly better, mentally and physically, as compared with patients who did not.

Scientists now hope to explore the neurological underpinnings at play, especially considering the explosion of blogs. According to Alice Flaherty, a neuroscientist at Harvard University and Massachusetts General Hospital, the placebo theory of suffering is one window through which to view blogging. As social creatures, humans have a range of pain-related behaviors, such as complaining, which acts as a "placebo for getting satisfied," Flaherty says. Blogging about stressful experiences might work similarly.

Flaherty, who studies conditions such as hypergraphia (an uncontrollable urge to write) and writer's block, also looks to disease models to explain the drive behind this mode of communication. For example, people with mania often talk too much. "We believe something in the brain's limbic system is boosting their desire to communicate," Flaherty explains. Located mainly in the midbrain, the limbic system controls our drives, whether they are related to food, sex, appetite, or problem solving. "You know that drives are involved [in blogging] because a lot of people do it compulsively," Flaherty notes. Also, blogging might trigger dopamine release, similar to stimulants like music, running and looking at art.

The frontal and temporal lobes, which govern speech—no dedicated writing center is hardwired in the brain—may also figure in. For example, lesions in Wernicke's area, located in the left temporal lobe, result in excessive speech and loss of language comprehension. People with Wernicke's aphasia speak in gibberish and often write constantly. In light of these traits, Flaherty speculates that some activity in this area could foster the urge to blog.



PUTTING WORDS TO SCREEN may provide health benefits to some people.

Scientists' understanding about the neurobiology underlying therapeutic writing must remain speculative for now. Attempts to image the brain before and after writing have yielded minimal information because the active regions are located so deep inside. Recent functional magnetic resonance imaging studies have shown that the brain lights up differently before, during and after writing, notes James Pennebaker, a psychologist at the University of Texas at Austin. But Pennebaker and others remain skeptical about the value of such images because they are hard to duplicate and quantify.

Most likely, writing activates a cluster of neurological pathways, and several researchers are committed to uncovering them. At the University of Arizona, psychologist and neuroscientist Richard Lane hopes to make brain-imaging techniques more relevant by using those techniques to study the neuroanatomy of emotions and their expressions. Nancy Morgan, lead author of the *Oncologist* study, is looking to conduct larger community-based and clinical trials of expressive writing. And Pennebaker is continuing to investigate the link between expressive writing and biological changes, such as improved sleep, that are integral to health. "I think the sleep angle is one of the more promising ones," he says.

Whatever the underlying causes may be, people coping with cancer diagnoses and other serious conditions are increasingly seeking—and finding—solace in the blogosphere. "Blogging undoubtedly affords similar benefits" to expressive writing, says Morgan, who wants to incorporate writing programs into supportive care for cancer patients.

Some hospitals have started hosting patient-authored blogs on their Web sites as clinicians begin to recognize the therapeutic value. Unlike a bedside journal, blogging offers the added benefit of receptive readers in similar situations, Morgan explains: "Individuals are connecting to one another and witnessing each other's expressions—the basis for forming a community."

Jessica Wapner is a freelance writer based in New York City.

CORBIS

Q&A WITH BRIAN GREENE

A Science Fête Project

A celebration that seeks to reunite the Two Cultures BY GEORGE MUSSER

Was Jason Bourne's amnesia neuroscientifically accurate? What does science have to say about morality or about basketball rebounds? If nothing else, the upcoming World Science Festival (worldsciencefestival.com)—running from May 28 to June 1 in New York City—breaks through the abstruseness barrier. Some three dozen events—panel discussions, science-inspired music and dance performances, and a street festival geared toward kids—aim to reintegrate science into the broader culture. Organized by a group headed by the husband-and-wife team of Columbia University physicist and author Brian Greene and former ABC News television producer Tracy Day, the festival may become an annual event. (*Scientific American* is a media partner.) We asked Greene to describe what motivated him and what he hopes to achieve (a fuller version appears at **www.SciAm.com/jun2008**).

What drove you to start the World Science Festival in the first place?

I'd say the biggest motivation is the recognition that the world is so increasingly reliant on science, and yet a large portion of the general public is intimidated by science. They somehow think it's something that you try to get through in school, but once you get through it, it's something you leave behind. And I've had so many experiences that have shown me that when people are presented science in a way that is accessible and compelling and inspirational, they not only love it, but they also find it opens up a whole new universe of thought, a whole connection to the world around them that they find enormously enriching. So the goal of the festival is to basically increase the number of people that have that experience.

But people are hindered by that sense of intimidation?

It's the intimidation and the cultural willingness to stay away from science. I think if you have a celebratory environment around science—one that gains a critical mass of great scientists, the general public and media attention—you can begin to influence that cultural perspective.

How do you distinguish that cultural, supportive environment from hoopla?

You have programs that are entertaining, exciting and accessible but that also have really high scientific integrity. The bulk of programming doesn't just have things blowing up or loud noises—maybe you have some of that, but you always follow it with the real underlying science.

SETTING THE STAGE: Greene and a Muppet pal announce the World Science Festival.

What was the inspiration for the festival?

I was asked to speak at the Genoa Science Festival—this was in 2005. Tracy and I both went, and the amount of excitement in the streets of Genoa around the festival was so palpable, we just sat there and said there's a real opportunity in New York to do this on a grand scale. Moreover, because Tracy comes from the world of broadcast journalism, she immediately thought there's a way to institute a different model, where the events are highly produced. That way, science events can be elevated to be on par with evening events at the Lincoln Center or Carnegie Hall.

And with such cultural events, what audience are you aiming for?

People who would be put off by the word "science" but who would, say, go to a dance performance. At the Guggenheim Museum, for instance, Karole Armitage is doing a dance piece based on unified theories and quantum gravity, with an onstage discussion that pulls out the science between her and a physicist. This offers ways of connecting with people where you're not having them sit in a lecture where their heads hurt trying to understand the science.

So your ambitions are on multiple levels here: you're trying to bring science to the public by having the event, and you're also doing it in this innovative way.

That is the goal. We've also started this nonprofit foundation whose goal is bigger than the festival itself. For instance, we're building a partnership with the New York City Department of Education with the goal being that what we do is not limited to a festival each May but rather extends to activities throughout the year that will help get kids more excited about science and prepare them for the annual festival.

You hadn't organized such a gigantic event before, had you?

You know, thank God we hadn't organized anything like this before, because we would have known how foolish it was! But I can't tell you the number of times people said, "I can't believe this doesn't already exist." We're in this century of science and technology, and for America not to have a celebratory festival that highlights the power of science … how could this not already exist? And they especially feel that way when they learn that Italy has one, England has two or three, and other countries do, too.

SCOTT GRIES *Getty Images*

Data Points

Cereal Pain

After decades of stability, the global prices of such food staples as wheat, maize and rice have skyrocketed since 2004. Causes include high energy and fertilizer costs, surging demand and economic development, and a move to biofuels. Virtually all of the world's extra corn produced from 2004 to 2007—primarily grown in the U.S.—went to make fuel. Prices may not start to decline until the middle of the next decade. In the meantime, the high costs have put tremendous stress on the world's poor and may exacerbate regional conflicts.

Number of countries in crisis because of food prices: 36

Number in Africa: 21

Metric tons of world cereal stocks in:

2003:	486.3 million
2005:	469.3 million
2008:	405.1 million

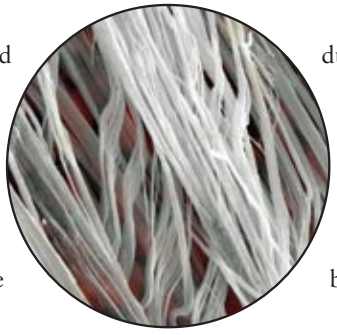
Expected prices, as percent increase above 2004 prices, of:

	2008	2010
Maize	79	76
Rice	101	113
Soybeans	56	44
Wheat	119	104

SOURCES: Rising Food Prices: Policy Options and World Bank Response, *World Bank, April 9, 2008; United Nations Food and Agriculture Organization*

HEALTH

Asbestos Action



ASBESTOS under the microscope.

Breathing in asbestos and silica has long been known to cause lung damage, but how the damage occurs has been a mystery. Using mice, scientists have now zeroed in on a key player known as the Nalp3 inflammasome, a complex of proteins that serves as a potent alarm system in our bodies. Evidently, when the body breaks down inhaled asbestos fibers, it ultimately produces reactive oxygen that triggers the inflammasome, which in turn causes lung inflammation. Mice that lack the Nalp3 inflammasome have a reduced reaction to asbestos. According to study co-author Jürg Tschopp of the University of Lausanne in Switzerland, the finding suggests that people exposed to asbestos should be checked for inflammation of the lung, which may be apparent 10 years after exposure. Also, because Nalp3 lies behind other immune reaction conditions, such as gout, the team speculates that gout medicine might slow the progression of inflammatory lung disease. *Science* published the results online April 10. —*Keren Schultz*

SCENARIOS

Destroyer of Worlds ... and Ozone

A nuclear exchange between India and Pakistan could globally harm the ozone layer, according to computer simulations. If those nations each launched 50 Hiroshima-level nuclear weapons—a total of 1.5 megatons, or just 0.03 percent of the total explosive power of the world's nuclear arsenal—smoke from burning cities would loft up as much as five million metric tons of soot. This ash would eventually rise to stratospheric heights of up to 80 kilometers, where it would trigger ozone-destroying reactions. As much as 70 percent of the ozone above the high northern latitudes would get lost, a depletion comparable to the Antarctic ozone hole. Up to 45 percent of the ozone above the earth's midlatitudes, where most of the world's population lives, would also vanish. As stratospheric ozone diminished, ultraviolet light–triggered cancer and other forms of serious damage would rise sharply. The analysis, which appeared online April 7 in the *Proceedings of the National Academy of Sciences USA*, suggests that the ozone would begin to recover only after five to eight years. —*Charles Q. Choi*

PAKISTANI MISSILE undergoing a test launch can carry a nuclear warhead.

ANDREW SYRED *Photo Researchers, Inc. (top)*; INTERSERVICE PUBLIC RELATIONS DEPARTMENT, HO/AP PHOTO *(bottom)*; ILLUSTRATION BY MATT COLLINS

In Brief

CHARRED FOR LIFE

In the heart of the Amazon River basin 1,500 years ago, tribes mixed soil with charcoal derived from animal bone and tree bark to boost their crop yields. Now scientists conclude that such burned, dead matter fertilizes better than compost and animal manure, helping to transform the soil into the richest earth in the world. The "biochar" also profoundly enhances soil's natural ability to seize carbon, thereby trapping greenhouse gases. Delaware State University researchers presented their findings April 10 at a national meeting of the American Chemical Society.

—Charles Q. Choi

TURNING POLLUTION INTO DVDs

New procedures could turn carbon dioxide (CO_2) from coal-fired power plants and other sources into polycarbonate, a type of plastic derived from petroleum and used to make DVDs and eyeglass lenses. Strategies that rely on catalysts have used CO_2 to make polymer precursors to polycarbonate. Although the chemical reactions produce only water as a waste product, they require high temperatures and pressure. Hence, the processes would only pay off environmentally if clean-energy sources, such as solar or wind power, were used to fuel them.

—David Biello

STARVED FOR BETTER CHEMO

Fasting for 48 hours before receiving chemotherapy could limit the treatment's toxic effects on healthy cells while leaving cancer cells vulnerable. When normal cells are starved, the cells shift into survival mode, revving up repair mechanisms and protective processes. Researchers starved mice that had been injected with malignant cells; then they gave the rodents megadoses of chemotherapy. The animals lost weight, but once treatment ended, they regained it—and their energy. The finding, which stemmed from research on aging, may pave the way for higher and more frequent chemo doses that do not harm normal cells. *—Nikhil Swaminathan*

OLFACTION

Punishing Scents

Danger could make you smell new odors. In testing volunteers, scientists at Northwestern University used odor molecules that have the same chemical formula but are structured to be mirror opposites, like left and right hands. Such molecules ordinarily smell identical to people. But after getting zapped with mild electrical shocks when exposed to one molecule but not when sniffing the other, volunteers rapidly learned to easily tell them apart. Functional MRI scans suggest that strong emotions could make the ancient smell centers of the brain quickly learn subtle differences between odors. The hypersensitivity seen in patients with some anxiety disorders could arise from a faulty ability to distinguish between true signals of danger and similar but less vital stimuli, the Northwestern team speculates, adding that its research could help develop new therapies. The electrifying findings appear in the March 28 *Science*. *—Charles Q. Choi*

STEM CELLS

Skin Job on Parkinson's

Skin cells from an adult mouse reprogrammed to act like embryonic stem cells have silenced symptoms of Parkinson's disease in rats. Scientists injected healthy rats with a toxin that destroyed their dopamine-making neurons, producing motor symptoms reminiscent of Parkinson's. The rodents then received treatment with the modified cells (called induced pluripotent stem cells). Within four weeks most of the rats showed improved balance and coordination; one even had heightened dopamine activity. Still, many issues must be resolved before the procedure can be adapted for humans. For one thing, scientists have yet to exactly mimic Parkinson's in rodents because the disease is so complex. In addition, the retroviruses used to transform the skin cells are known cancer triggers. The findings, published online April 7 by the *Proceedings of the National Academy of Sciences USA*, nonetheless appear to mark the first time manipulated cells have integrated into brain tissue and reversed neurodegenerative damage.

—Nikhil Swaminathan

INFORMATION THEORY

Black Hole Data Retrieval

All that enters a black hole may not be lost; data could leak out over trillions of years as Hawking radiation. A new analysis indicates that the recovery can proceed much faster than previously thought. Imagine Alice hurling some quantum bits into a relatively young black hole; it would take Bob half of the hole's lifetime to recover enough Hawking radiation to reproduce the bits. But things change if Alice holds onto her bits until after the hole has reached the halfway mark and Bob has entangled some of his own bits with Alice's, linking them across any distance.

Alice's dumped bits would spread their entanglement to the outgoing Hawking radiation. Bob could then, in principle, reconstruct Alice's bits by taking the next few bits of Hawking radiation following the data dump and mixing them with his own bits. Bob would need only about 10 percent more Hawking particles than the number of bits that Alice had thrown in—and because black holes could emit as many as 1,000 bits per second, Bob might not need much time at all. *—JR Minkel*

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GAZIMAL Getty Images (top); PAUL KATZ Getty Images (bottom)

SciAm Perspectives

Climate Fatigue

A grassroots approach alone won't make the earth stop warming

BY THE EDITORS

Have you heard enough already about global warming? It's so … last year's news! Plenty of people are "doing something" about it. Becoming carbon-neutral has gone as mainstream as Girl Scout cookies; help is on the way. Can we move on, please?

Unfortunately not. For all the consciousness-raising value of grassroots initiatives, the world is still far from squarely facing up to the issues. Both Hillary Clinton and Barack Obama promise on their Web sites to reduce carbon emissions to just 20 percent of 1990 levels by 2050—a laudable goal. But because what matters is the load of greenhouse gases in the entire atmosphere, reaching those numbers would be hard, to say the least, for the U.S. to do alone. John McCain's Web site simply offers "commonsense approaches to limit carbon emissions by harnessing market forces that will … see to it that … all nations do their rightful share."

If the candidates' statements—perhaps out of political necessity—are short on specifics, the reason is partly that much of the electorate still finds it hard to grasp the size and urgency of the problem. Like the naive passengers onboard an ocean liner, who lean carelessly over the rail as their ship drifts into an iceberg, most of us are oblivious to the magnitude of the impending disaster. The separation closes too slowly for us to appreciate the force of the coming crunch.

What is even more misleading, most climate changes so far seem gentle, even pleasant—an earlier spring, a later fall. Only occasionally does an ungentle reminder break through: this past February 160 square miles of Antarctica's Wilkens ice shelf disintegrated. James Hansen of the NASA Goddard Institute for Space Studies and his colleagues argue in a recent paper submitted to *Science* that the present carbon dioxide (CO_2) level in the atmosphere, 385 parts per million (ppm), has already crossed into dangerous territory. According to their study of past climatic sensitivity to changes in atmospheric CO_2, there is substantial risk that within just a few centuries the earth could lose its great Antarctic and Greenland ice sheets, causing catastrophic rises in sea level, unless CO_2 levels are quickly brought back to 350 ppm.

All six of the scenarios considered by the Intergovernmental Panel on Climate Change (IPCC) assume that by the end of this century atmospheric greenhouse gases will reach the warming equivalent of 600 ppm of CO_2 (600 ppm CO_2-eq). At that level the IPCC pegs the chances at about two thirds that by 2100 the earth will have warmed between two and three degrees Celsius (between 3.6 and 5.4 degrees Fahrenheit) since preindustrial times. If concentrations rise to 1,250 ppm CO_2-eq or above, as they do in two of the IPCC scenarios, the chances become about one in six that the warming will exceed five degrees C (nine degrees F). According to the *Stern Review,* a major report on the economics of climate change, a five-degree increase would be "far outside the experience of human civilisation." It would also risk "irreversible … physical changes, such as the collapse of ocean currents," as well as "mass migrations and social instability." It gets worse. The IPCC puts the chances at 5 percent that even if CO_2-eq levels stabilize at 550 ppm, global temperatures will eventually rise by eight degrees C (14.4 degrees F).

Both the *Stern Review* and John Broome, in his article "The Ethics of Climate Change" (starting on page 96), are explicit about the ethical dimensions of society's response to global warming. At bottom, the issue is much like the one older voters must face when their local government proposes a hike in school taxes. How much do we really care about the well-being of future generations? How much of the good life in the present are we willing to forgo to provide for our children and grandchildren?

Or think about it this way. Imagine you are living in the year 2108, and you are keenly aware that the political dislocations all around you were preventable catastrophes. Decades of turmoil caused by vast migrations of people who could not find enough food or clean drinking water; the crop-destroying volatility in the weather; the drying up of capital as investors withdraw whatever they can from unruly markets; the scourges of insects and disease set loose by the poleward advancement of the tropics—all of these are the legacy of your forebears who should have known better.

Wouldn't you look back and shake your head at the feeble attempts at mitigation by the present age, the endless dithering over the reality of climate change, the head-in-the-sand policies that assumed addressing the problem could be put off for another day and that the future would be clever enough and rich enough to take care of itself? ■

MATT COLLINS

Sustainable Developments

Surging Food Prices and Global Stability

Misguided policies favor biofuels and animal feed over grain for hungry people

BY JEFFREY D. SACHS

The recent surge in world food prices is already creating havoc in poor countries, and worse is to come. Food riots are spreading across Africa, although many have gone unreported in the international press. Moreover, the surge in wheat, maize and rice prices seen on commodities markets has not yet fully percolated into the shops and stalls of the poor countries or into the budgets of relief organizations.

The facts are stark. In early 2006 a metric ton of wheat cost around $375 on the commodity exchanges. In March 2008 it stood at more than $900. Concurrently, maize went from around $250 to $560. Rice prices have also soared.

Several factors are at play in the skyrocketing prices, reflecting both rising global demand and falling supplies. World incomes have been growing at around 5 percent annually in recent years, and 4 percent in per capita terms, leading to an increased global demand for food and for meat as a share of the diet. The rising demand for meat exacerbates the pressures on grain and oilseed prices because several kilograms of animal feed are required to produce each kilogram of meat. The grain supply has also been disrupted by climate shocks, such as Australia's massive droughts.

An even bigger blow has been the U.S. decision to subsidize the conversion of maize into ethanol to blend with gasoline. This wrongheaded policy, pushed by an aggressive farm lobby, gives a 51-cent tax credit for each gallon of ethanol blended into gasoline. The Energy Policy Act of 2005 mandates a minimum of 7.5 billion gallons of domestic renewable-fuel production, which will overwhelmingly be corn-based ethanol, by 2012. Consequently, up to a third of the U.S.'s Midwestern maize crop this year will be converted to ethanol, causing a cascade of price increases across the food chain. (Worse still, use of ethanol instead of gasoline does little to reduce net carbon emissions once the energy-intensive full cycle of ethanol production is taken into account.)

The food price increases are pummeling poor food-importing regions, with Africa by far the hardest hit. Several countries, such as Egypt, India and Vietnam, have cut off their rice exports in response to high prices at home, exacerbating the effects on rice-importing countries. Even small changes in food prices can push the poor into hunger and destitution: as famously expounded by Nobel laureate Amartya Sen, some of the greatest famines in history were caused not by massive declines in grain production but rather by losses in the purchasing power of the poor.

At least four measures should be taken in response to the food price crisis. First, the world should heed the call of United Nations secretary-general Ban Ki-moon to fund a massive increase in Africa's food production. The needed technologies are available—high-yield seeds, fertilizer, small-scale irrigation—but the financing is not. The new African green revolution would initially subsidize peasant farmers' access to better technologies, thus at least doubling grain harvests. The funding would also help farm communities establish long-term microfinance institutions to ensure continued access to improved agricultural inputs after the temporary subsidies end in a few years.

Second, the U.S. should end its misguided corn-to-ethanol subsidies. Farmers hardly need them given world demand for food and feed grain. Third, the world should support longer-term research into higher agricultural production. Shockingly, the Bush administration is proposing to sharply cut the U.S. funding for tropical agriculture studies in the Consultative Group on International Agriculture Research, just when that work is most urgently needed.

Finally, the world should follow through on the promised Adaptation Fund announced last December at the U.N. Climate Change Conference in Bali, to help the poor face the growing risks to food production from increasingly adverse climate conditions. Even as nations stanch the immediate crisis, climate-induced shocks will force wrenching dislocations with increasing frequency. ■

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

SCI AM An extended version of this essay is available at **www.SciAm.com/jun2008**

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

Skeptic

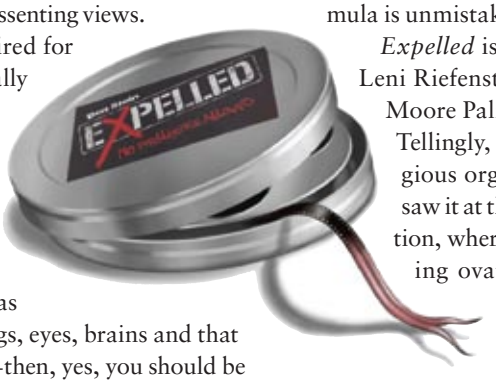
Expelled Exposed

A film challenging evolution by game show host and financial analyst Ben Stein is a case study in antiscience propaganda

BY MICHAEL SHERMER

"Should I be worried about the Crips and the Bloods up here?" These were the first words out of the mouth of Ben Stein as he entered my office at *Skeptic* magazine, located in the racially mixed neighborhood of Altadena, Calif. I cringed and hoped that the two African-American women in my employ were out of earshot of what was perhaps merely Stein's ham-handed attempt at humor before he began interviewing me for what I was told was a film on the intersection of science and religion entitled *Crossroads*.

That is not what the interview was about. And neither is the film, now called *Expelled: No Intelligence Allowed*. The subtitle exposes its motif—intelligent design has been expelled from classrooms and culture, and Ben Stein sees a sinister conspiracy at work. This supercilious financial columnist and ersatz actor and game show host proceeded to grill me on whether or not I think someone should be fired for expressing dissenting views. My answer: it depends. Who is being fired for what, when and where? People are usually fired for reasons having to do with budgetary constraints, incompetence or failure to fulfill the terms of a contract. If you are hired to teach biology according to the curriculum standards of your school district but instead spend the semester telling students that science has no definitive explanation for DNA, wings, eyes, brains and that mystery of mysteries—bacteria flagella—then, yes, you should be fired posthaste. But I know of no instance in which this has happened, and the film's examples of such alleged abuses have reasonable explanations detailed at www.expelledexposed.com, where Eugenie Scott and her tireless crew at the National Center for Science Education have tracked down the specifics of each case.



After asking the question a dozen different ways, Stein finally changed the subject and queried my opinion on the social impact of Darwinism. Having just finished my book on evolutionary economics (*The Mind of the Market*), I drew the connection between Adam Smith's invisible hand and Charles Darwin's natural selection and noted how capitalists have long used social Darwinism to justify unfettered market competition, from the early 20th-century belief in the survival of the fittest corporations to Enron's CEO Jeffrey Skilling, who said his favorite book in Harvard Business School was Richard Dawkins's *The Selfish Gene*. This was not the answer Stein wanted, and he rejoined with a vehemence I did not understand until I saw his film.

Expelled's exegesis is this: Darwinism leads to atheism, communism, fascism and a repetition of the Holocaust. We are in an ideological war between a scientific, natural worldview that leads to the Gulag Archipelago and Nazi gas chambers and a religious, supernatural worldview that leads to freedom, justice and the American way. Expelling intelligent design from American classrooms and culture will inexorably take us down a path of doom, and the film's blunt editing intersperses interview snippets from evolutionary biologists with black-and-white clips of, in ascending scale of ominousness, bullies pounding on a 98-pound weakling; Charlton Heston's character in *Planet of the Apes* being blasted by a water hose by a gorilla thug; Nikita Khrushchev pounding his fist on a United Nations desk; East Germans captured trying to scale the Berlin Wall; and Nazi crematoria remains and Holocaust victims being bulldozed into mass graves. The formula is unmistakable: Darwinism = death.

Expelled is pure propaganda that would make even Leni Riefenstahl blush. The film deserves the Michael Moore Palme d'Or Award for Objective Journalism. Tellingly, it is being marketed to church groups, religious organizations and conservative Christians. I saw it at the National Religious Broadcasters convention, where Stein and the producers received a standing ovation and we were all given an *Expelled* "Event & Resource Kit," which includes movie posters, bumper stickers, teaching outlines, literature from the pro–intelligent design Discovery Institute and even a whistle for "Blowing the whistle on suppression." A DVD includes interviews with intelligent design proponents and suggestions on how to "host a 'Dinner with Darwin' … using the Discussion Guide, DVD and the film as an opportunity to educate yourselves about the 'good science' in support of our faith."

When will Americans learn that evolutionary theory has nothing to do with religion and that "good science" is the product of good data and theory, not "good fit to scripture"? After *Expelled*, will anyone take Ben Stein seriously again? Anyone? Anyone? ■

Michael Shermer is publisher of Skeptic *(www.skeptic.com).*

SCI AM

An expanded version of this review, along with a review by Editor in Chief John Rennie, can be found at **www.SciAm.com/jun2008**

PHOTOGRAPH BY BRAD SWONETZ; ILLUSTRATION BY MATT COLLINS

Antigravity

Call of the Reviled

Brought here on a lark, starlings are now at every turn

BY STEVE MIRSKY

Whistle. Pop. Whirrrr. Zzzt. Repeat. Many, many, many times.

That's the song, if you want to call it that, of the European starling. Two of these relatively drab, chunky little birds are now my next-door neighbors—the pair moved into a hole in the maple tree in front of my house. Whistle. Pop. Whirrrr. Zzzt. Repeat. Incessantly. They fly into the hole. They fly out of the hole. They dig away at the tree's innards and fling the detritus onto the sidewalk below with their little yellow beaks. I might be grateful if I could count on the birds to toss sawdust onto freshly fallen snow so that pedestrians got a firmer footing. But it's already spring; the birds are just digging a deeper hole for themselves.

Like an asteroid put on a collision course with the earth millions of years ago, the starlings invaded my territory because of events set in motion in the distant past. About a decade ago the top of the main trunk of the maple became diseased and saw the business end of a chainsaw. That left a dead top, the kind that cavity-nesting birds love to excavate to build their little homes. Only about 20 feet from the front door of my little home in the Bronx. Zzzt.

The other starting point lies much deeper in the mists of time. In the late 1590s Shakespeare noted the mimicking ability of the starling while writing *Henry IV, Part 1*. Hotspur is contemplating driving King Henry nuts by having a starling repeat the name of Hotspur's brother-in-law Mortimer, whom Henry refuses to ransom out of prisoner status. "Nay, I'll have a starling shall be taught to speak nothing but 'Mortimer,' " Hotspur whines. (In theater and life, in-laws can often be counted on for dramatic conflict.) Whirrrr.

We move on to the late 19th century, when a group called the American Acclimatization Society was reportedly working on their pre-environmental-impact-statement project to introduce to the U.S. every bird mentioned in Shakespeare's scripts. Clearly, the Bard abided birds—his works include references to more than 600 avian species. A Bronx resident, drug manufacturer Eugene Schieffelin (a street bearing his name isn't far from my house) seems to be particularly responsible for the starlings' arrival here. Well, his chickens have come home to roost. Pop. (The society also brought the house sparrow to our shores, a pair of which nest in a vent on the front of my other, human, next-door neighbor's house.)

The Acclimatization Society released some hundred starlings in New York City's Central Park in 1890 and 1891. By 1950 starlings could be found coast to coast, north past Hudson Bay and south into Mexico. Their North American numbers today top 200 million. As bird-watcher Jeffrey Rosen put it in a 2007 *New York Times* article, "It isn't their fault that they treated an open continent much as we ourselves did." Zzzt.

So why are starlings so little loved? Their looks don't help: short, stocky and dark with light speckles, they look like chocolate that's been left out for a few days. And have I mentioned their obnoxious series of sounds, er, song? Another strike against them is their competition with native birds that also make nests in handy cavities. Starlings have thereby been oft indicted as a major reason for the decline of the strikingly beautiful eastern bluebird, state bird of New York and Missouri. (The state bird of Missouri is not the cardinal?)

But perhaps starlings aren't so bad. When the sun hits their feathers just right, they do have a certain iridescent attractiveness. And they have fascinating jaws. That's right, jaws. Most of the world's starlings have conventional jaws that close firmly. But our imported starlings' jaws are wired completely differently—their musculature enables the beak to strongly open. According to *The Birder's Handbook*, "the closed bill is inserted between blades of grass in thick turf or other cover, and then sprung open to expose hidden prey." Which get to observe the unusual musculature of the jaw from the inside. Pop.

And starlings actually appear to be innocent in the case of the missing bluebirds. The feather friends at the Cornell Laboratory of Ornithology contend on their Web site that "a study in 2003 found few actual effects on populations of 27 native species. Only sapsuckers showed declines because of starlings, and other species appeared to be holding their own against the invaders." So when it comes to songbird decline, as Shakespeare almost said, maybe the fault is not in our starlings but in ourselves. Zzzt. ■

PHOTOGRAPH BY FLYNN LARSEN; ILLUSTRATION BY MATT COLLINS

The Cosmic Origins of Time's Arrow

One of the most basic facts of life is that the future looks different from the past. But on a grand cosmological scale, they may look the same

By Sean M. Carroll

KEY CONCEPTS

- The basic laws of physics work equally well forward or backward in time, yet we perceive time to move in one direction only—toward the future. Why?
- To account for it, we have to delve into the prehistory of the universe, to a time before the big bang. Our universe may be part of a much larger multiverse, which as a whole is time-symmetric. Time may run backward in other universes.

—The Editors

The universe does not look right. That may seem like a strange thing to say, given that cosmologists have very little standard for comparison. How do we know what the universe is supposed to look like? Nevertheless, over the years we have developed a strong intuition for what counts as "natural"—and the universe we see does not qualify.

Make no mistake: cosmologists have put together an incredibly successful picture of what the universe is made of and how it has evolved. Some 14 billion years ago the cosmos was hotter and denser than the interior of a star, and since then it has been cooling off and thinning out as the fabric of space expands. This picture accounts for just about every observation we have made, but a number of unusual features, especially in the early universe, suggest that there is more to the story than we understand.

Among the unnatural aspects of the universe, one stands out: time asymmetry. The microscopic laws of physics that underlie the behavior of the universe do not distinguish between past and future, yet the early universe—hot, dense, homogeneous—is completely different from today's—cool, dilute, lumpy. The universe started off orderly and has been getting increasingly disorderly ever since. The asymmetry of time, the arrow that points from past to future, plays an unmistakable role in our everyday lives: it accounts for why we cannot turn an omelet into an egg, why ice cubes never spontaneously unmelt in a glass of water, and why we remember the past but not the future. And the origin of the asymmetry we experience can be traced all the way back to the orderliness of the universe near the big bang. Every time you break an egg, you are doing observational cosmology.

The arrow of time is arguably the most blatant feature of the universe that cosmologists are currently at an utter loss to explain. Increasingly, however, this puzzle about the universe we observe hints at the existence of a much larger spacetime we do not observe. It adds support to the notion that we are part of a multiverse whose dynamics help to explain the seemingly unnatural features of our local vicinity.

The Puzzle of Entropy

Physicists encapsulate the concept of time asymmetry in the celebrated second law of thermodynamics: entropy in a closed system never decreases. Roughly, entropy is a measure of the disorder of a system. In the 19th century, Austrian physicist Ludwig Boltzmann explained entropy in terms of the distinction between the microstate of an object and its macrostate. If you were asked to describe a cup of coffee, you would most likely refer to its macrostate—its temperature, pressure and other overall features. The microstate,

KENN BROWN

[THE AUTHOR]

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on the other hand, specifies the precise position and velocity of every single atom in the liquid. Many different microstates correspond to any one particular macrostate: we could move an atom here and there, and nobody looking at macroscopic scales would notice.

Entropy is the number of different microstates that correspond to the same macrostate. (Technically, it is the number of digits, or logarithm, of that number.) Thus, there are more ways to arrange a given number of atoms into a high-entropy configuration than into a low-entropy one. Imagine that you pour milk into your coffee. There are a great many ways to distribute the molecules so that the milk and coffee are completely mixed together but relatively few ways to arrange them so that the milk is segregated from the surrounding coffee. So the mixture has a higher entropy.

From this point of view, it is not surprising that entropy tends to increase with time. High-entropy states greatly outnumber low-entropy ones; almost any change to the system will land it in a higher-entropy state, simply by the luck of the draw. That is why milk mixes with coffee but never unmixes. Although it is physically possible for all the milk molecules to spontaneously conspire to arrange themselves next to one another, it is statistically very unlikely. If you waited for it to happen of its own accord as molecules randomly reshuffled, you would typically have to wait much longer than the current age of the observable universe. The arrow of time is simply the tendency of systems to evolve toward one of the numerous, natural, high-entropy states.

But explaining why low-entropy states evolve into high-entropy states is different from explaining why entropy is increasing in our universe. The question remains: Why was the entropy low to start with? It seems very unnatural, given that low-entropy states are so rare. Even granting that our universe today has medium entropy, that does not explain why the entropy used to be even lower. Of all the possible initial conditions that could have evolved into a universe like ours, the overwhelming majority have much higher entropy, not lower [see "The Arrow of Time," by David Layzer; SCIENTIFIC AMERICAN, December 1975].

In other words, the real challenge is not to explain why the entropy of the universe will be higher tomorrow than it is today but to explain why the entropy was lower yesterday and even lower the day before that. We can trace this logic all the way back to the beginning of time in our observable universe. Ultimately, time asymmetry is a question for cosmology to answer.

The Disorder of Emptiness

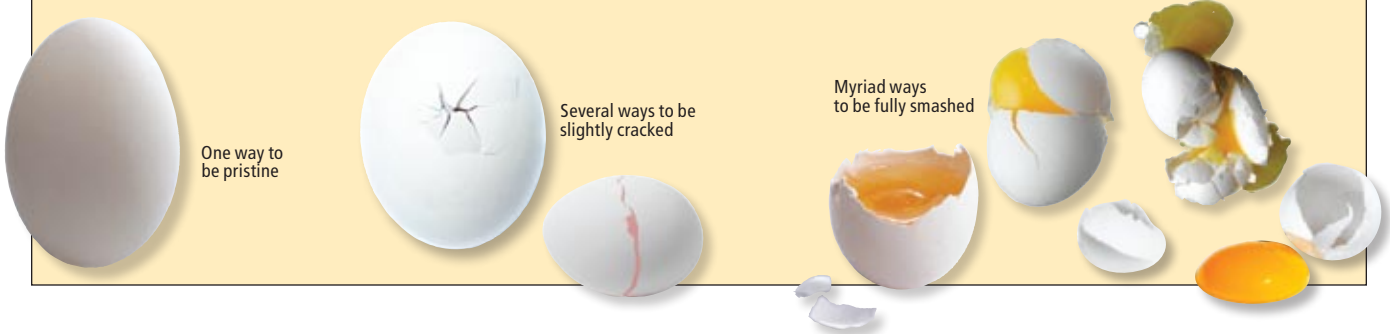
The early universe was a remarkable place. All the particles that make up the universe we currently observe were squeezed into an extraordinarily hot, dense volume. Most important, they were distributed nearly uniformly throughout that tiny volume. On average, the density differed from place to place by only about one part in 100,000. Gradually, as the universe expanded and cooled, the pull of gravity enhanced those differences. Regions with slightly more particles formed stars and galaxies, and regions with slightly fewer particles emptied out to form voids.

Clearly, gravity has been crucial to the evolution of the universe. Unfortunately, we do not fully understand entropy when gravity is involved. Gravity arises from the shape of spacetime, but we do not have a comprehensive theory of spacetime; that is the goal of a quantum theory of gravity. Whereas we can relate the entropy of a fluid to the behavior of the molecules that constitute it, we do not know what constitutes space,

[FROM ORDER TO DISORDER]

ENTROPY IN THE KITCHEN

A raw egg exemplifies the asymmetry of time: a fresh one breaks easily, but a broken one does not spontaneously put itself together again, for the simple reason that there are more ways to be broken than not. In physics jargon, the broken egg has a higher entropy.



KEN WEINGART (*Carroll*); ALL EGG PHOTOGRAPHY COURTESY OF GETTY IMAGES: RICHARD DRURY (*whole*); GRAEME MONTGOMERY (*cracked*); JAN STROMME (*cracked in half*); MICHAEL ROSENFELD (*half with yolk*); JONATHAN KANTOR (*seeping yolk and smashed*); DIAMOND SKY IMAGES (*over easy*)

so we do not know what gravitational microstates correspond to any particular macrostate.

Nevertheless, we have a rough idea of how entropy evolves [*see box below*]. In situations where gravity is negligible, such as a cup of coffee, a uniform distribution of particles has a high entropy. This condition is a state of equilibrium. Even when particles reshuffle themselves, they are already so thoroughly mixed that nothing much seems to happen macroscopically. But if gravity is important and the volume is fixed, a smooth distribution has relatively low entropy. In this case, the system is very far from equilibrium. Gravity causes particles to clump into stars and galaxies, and entropy increases noticeably—consistent with the second law.

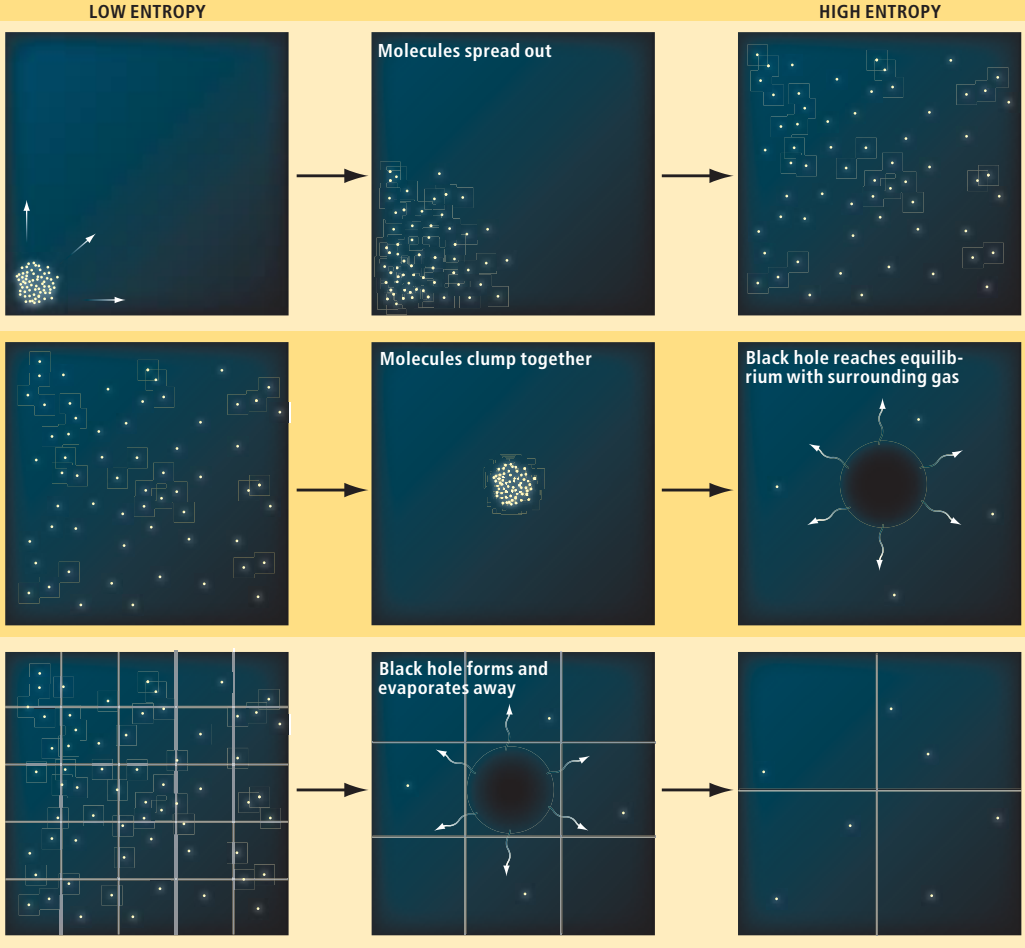
Indeed, if we want to maximize the entropy of a volume when gravity is active, we know what we will get: a black hole. In the 1970s Stephen Hawking of the University of Cambridge confirmed a provocative suggestion of Jacob Bekenstein, now at the Hebrew University of Jerusalem, that black holes fit neatly into the second law. Like the hot objects that the second law was originally formulated to describe, black holes emit radiation and have entropy—a lot of it. A single million-solar-mass black hole, such as the one that lives at the center of our galaxy, has 100 times the entropy of all the ordinary particles in the observable universe.

Eventually even black holes evaporate by emitting Hawking radiation. A black hole does not have the highest possible entropy—but just the highest entropy that can be packed into a certain volume. The volume of space in the universe, however, appears to be growing without limit. In

[ENTROPY OF A GAS]

WHAT GRAVITY DOES TO ENTROPY

What qualifies as low entropy or high entropy depends on the situation. Physicists identify the high-entropy state of a system based on how the system evolves over time. For example, if a diffuse and sufficiently cool gas feels the tug of gravity, it evolves to a clump. The law of entropy increase then implies that the clump has a high entropy, even though at first glance it might appear to be orderly (low entropy).



LUCY READING-IKKANDA

1998 astronomers discovered that cosmic expansion is accelerating. The most straightforward explanation is the existence of dark energy, a form of energy that exists even in empty space and does not appear to dilute away as the universe expands. It is not the only explanation for cosmic acceleration, but attempts to come up with a better idea have so far fallen short.

If dark energy does not dilute away, the universe will expand forever. Distant galaxies will disappear from view [see "The End of Cosmology?" by Lawrence M. Krauss and Robert J. Scherrer; Scientific American, March]. Those that do not will collapse into black holes, which in turn will evaporate into the surrounding gloom as surely as a puddle dries up on a hot day. What will be left is a universe that is, for all intents and purposes, empty. Then and only then will the universe truly have maxed out its entropy. The universe will be in equilibrium, and nothing much will ever happen.

It may seem strange that empty space has such a huge entropy. It sounds like saying that the most disorganized desk in the world is a completely empty desk. Entropy requires microstates, and at first glance empty space does not have any. In actuality, though, empty space has plenty of microstates—the quantum-gravitational microstates built into the fabric of space. We do not yet know what exactly these states are, any more than we know what microstates account for the entropy of a black hole, but we do know that in an accelerating universe the entropy within the observable volume approaches a constant value proportional to the area of its boundary. It is a truly enormous amount of entropy, far greater than that of the matter within that volume.

TIME'S ARROW FAQs, PART I

If entropy always increases, then how do low-entropy objects such as eggs form in the first place? The law of entropy applies to closed systems. It does not forbid decreases in entropy in open systems, including chickens. A hen takes in energy and goes through a great deal of effort to produce an egg.

Don't some particle processes have a built-in arrow of time? The decays of some elementary particles, such as neutral kaons, happen more frequently in one direction of time than the other. (Physicists do not need to travel backward in time to observe this asymmetry; they infer it from experiments on related particle properties.) But these processes are reversible, unlike the growth of entropy, so they do not explain the arrow of time. The Standard Model of particle physics does not seem to be of any help in explaining the low entropy of the early universe.

Past vs. Future

The striking feature of this story is the pronounced difference between the past and the future. The universe starts in a state of very low entropy: particles packed together smoothly. It evolves through a state of medium entropy: the lumpy distribution of stars and galaxies we see around us today. It ultimately reaches a state of high entropy: nearly empty space, featuring only the occasional stray low-energy particle.

Why are the past and future so different? It is not enough to simply posit a theory of initial conditions—a reason why the universe started with low entropy. As philosopher Huw Price of the University of Sydney has pointed out, any reasoning that applies to the initial conditions should also apply to the final conditions, or else we will be guilty of assuming the very thing we were trying to prove—that the past was special. Either we have to take the profound asymmetry of time as a blunt feature of the universe that escapes explanation, or we have to dig deeper into the workings of space and time.

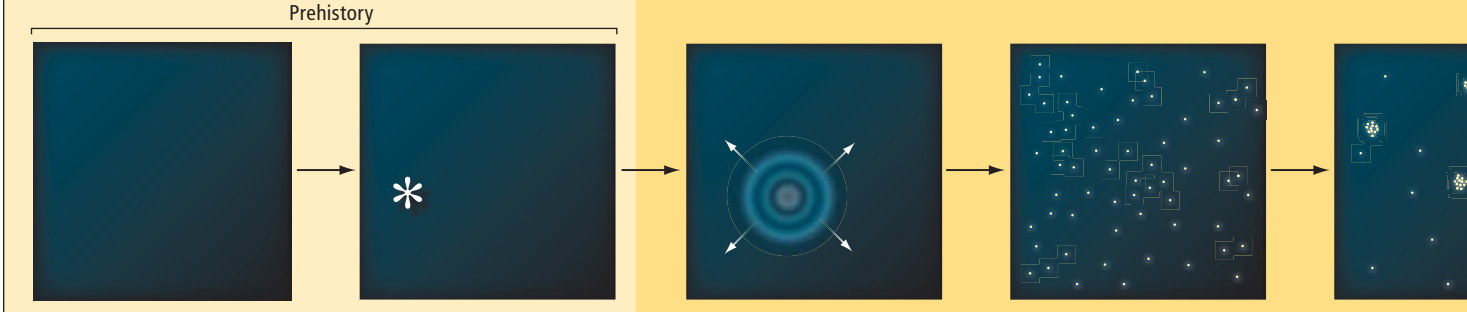
Many cosmologists have tried to attribute the time asymmetry to the process of cosmological inflation. Inflation is an attractive explanation for many basic features of the universe. According to this idea, the very early universe (or at least some part of it) was filled not with particles but rather with a temporary form of dark energy, whose density was enormously higher than the dark energy we observe today. This energy caused the expansion of the universe to accelerate at a fantastic rate, after which it decayed into matter and radiation, leaving behind a tiny wisp of dark energy that is becoming relevant again today. The rest of the story of the big bang, from

LUCY READING-IKKANDA (*timeline*)

[FROM "HEAT BIRTH" TO "HEAT DEATH"]

RESTORING SYMMETRY TO TIME

According to the standard model of cosmology, the universe began as a nearly uniform gas and will end up as nearly empty space—in short, it goes from low entropy to high entropy, a final condition that physicists call "heat death." But this model fails to explain what set up the initial



the smooth primordial gas to galaxies and beyond, simply follows.

The original motivation for inflation was to provide a robust explanation for the finely tuned conditions in the early universe—in particular, the remarkably uniform density of matter in widely separated regions. The acceleration driven by the temporary dark energy smooths out the universe almost perfectly. The prior distribution of matter and energy is irrelevant; once inflation starts, it removes any traces of the preexisting conditions, leaving us with a hot, dense, smooth early universe.

The inflationary paradigm has been very successful in many ways. Its predictions of slight deviations from perfect uniformity agree with observations of density variations in the universe. As an explanation for time asymmetry, however, cosmologists increasingly consider it a bit of a cheat, for reasons that Roger Penrose of the University of Oxford and others have emphasized. For the process to work as desired, the ultradense dark energy had to begin in a very specific configuration. In fact, its entropy had to be fantastically *smaller* than the entropy of the hot, dense gas into which it decayed. That implies inflation has not really solved anything: it "explains" a state of unusually low entropy (a hot, dense, uniform gas) by invoking a prior state of even lower entropy (a smooth patch of space dominated by ultradense dark energy). It simply pushes the puzzle back a step: Why did inflation ever happen?

One of the reasons many cosmologists invoke inflation as an explanation of time asymmetry is that the initial configuration of dark energy does not *seem* all that unlikely. At the time of inflation, our observable universe was less than a centimeter across. Intuitively, such a tiny region does not have many microstates, so it is not so improbable for the universe to stumble by accident into the microstate corresponding to inflation.

FAQs, PART II

Doesn't quantum mechanics have an arrow of time? According to the standard interpretation of quantum mechanics, the measurement of a system causes its wave function to "collapse," a process that is asymmetric in time. But the reason wave functions collapse yet never uncollapse is the same reason that eggs break yet never unbreak—namely, because collapse increases the entropy of the universe. Quantum mechanics does not help explain why the entropy was low in the first place.

Why do we remember the past but not the future? To form a reliable memory requires that the past be orderly—that is, have a low entropy. If the entropy is high, almost all "memories" would be random fluctuations, completely unrelated to what actually happened in the past.

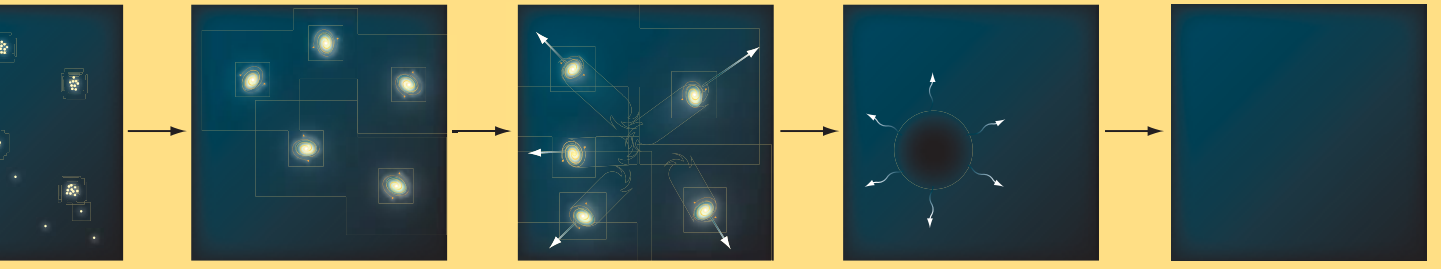
Unfortunately, this intuition is misleading. The early universe, even if it is only a centimeter across, has exactly the same number of microstates as the entire observable universe does today. According the rules of quantum mechanics, the total number of microstates in a system never changes. (Entropy increases not because the number of microstates does but because the system naturally winds up in the most generic possible macrostate.) In fact, the early universe is the same physical system as the late universe. One evolves into the other, after all.

Among all the different ways the microstates of the universe can arrange themselves, only an incredibly tiny fraction correspond to a smooth configuration of ultradense dark energy packed into a tiny volume. The conditions necessary for inflation to begin are extremely specialized and therefore describe a very low entropy configuration. If you were to choose configurations of the universe randomly, you would be highly unlikely to hit on the right conditions to start inflation. Inflation does not, by itself, explain why the early universe has a low entropy; it simply assumes it from the start.

A Time-Symmetric Universe

Thus, inflation is of no help in explaining why the past is different from the future. One bold but simple strategy is just to say: perhaps the very far past is not different from the future after all. Perhaps the distant past, like the future, is actually a high-entropy state. If so, the hot, dense

low-entropy state. The author's model adds a period of prehistory. The universe began empty and will end up empty—the appearance of stars and galaxies is a temporary deviation from its usual equilibrium condition. (This figure is schematic; it does not show space expanding.)



The universe today.

Accelerating expansion pulls galaxies out of sight.

Each galaxy collapses to a black hole, which evaporates into a diffuse gas.

Space is nearly empty.

state we have been calling "the early universe" is actually not the true beginning of the universe but rather just a transitional state between stages of its history.

Some cosmologists imagine that the universe went through a "bounce." Before this event, space was contracting, but instead of simply crashing to a point of infinite density, new physical principles—quantum gravity, extra dimensions, string theory or other exotic phenomena—kicked in to save the day at the last minute, and the universe came out the other side into what we now perceive as the big bang. Though intriguing, bouncing cosmologies do not explain the arrow of time. Either entropy was increasing as the prior universe approached the crunch—in which case the arrow of time stretches infinitely far into the past—or the entropy was decreasing, in which case an unnatural low-entropy condition occurred in the middle of the universe's history (at the bounce). Either way, we have again passed the buck on the question of why the entropy near what we call the big bang was small.

Instead let us suppose that the universe started in a high-entropy state, which is its most natural state. A good candidate for such a state is empty space. Like any good high-entropy state, the tendency of empty space is to just sit there, unchanging. So the problem is: How do we get our current universe out of a desolate and quiescent spacetime? The secret might lie in the existence of dark energy.

In the presence of dark energy, empty space is not completely empty. Fluctuations of quantum fields give rise to a very low temperature—enormously lower than the temperature of today's universe but nonetheless not quite absolute zero. All quantum fields experience occasional thermal fluctuations in such a universe. That means it is not perfectly quiescent; if we wait long enough, individual particles and even substantial collections of particles will fluctuate into existence, only to once again disperse into the vacuum. (These are real particles, as opposed to the short-lived "virtual" particles that empty space contains even in the absence of dark energy.)

Among the things that can fluctuate into existence are small patches of ultradense dark energy. If conditions are just right, that patch can undergo inflation and pinch off to form a separate universe all its own—a baby universe. Our universe may be the offspring of some other universe.

Superficially, this scenario bears some resemblance to the standard account of inflation. There, too, we posit that a patch of ultradense dark energy arises by chance, igniting inflation. The difference is the nature of the starting conditions. In the standard account, the patch arose in a wildly fluctuating universe, in which the vast bulk of fluctuations produced nothing resembling inflation. It would seem to be much more likely for the universe to fluctuate straight into a hot big bang, bypassing the inflationary stage altogether. Indeed, as far as entropy is concerned, it would be even more likely for the universe to fluctuate straight into the configuration we see today, bypassing the past 14 billion years of cosmic evolution.

In our new scenario, the preexisting universe was never randomly fluctuating; it was in a very specific state: empty space. What this theory claims—and what remains to be proved—is that the most likely way to create universes like ours from such a preexisting state is to go through a period of inflation, rather than fluctuating there directly. Our universe, in other words, is a fluctuation but not a random one.

Emit fo Worra

This scenario, proposed in 2004 by Jennifer Chen of the University of Chicago and me, provides a provocative solution to the origin of time asymmetry in our observable universe: we see only a tiny patch of the big picture, and this larger arena is fully time-symmetric. Entropy can increase without limit through the creation of new baby universes.

Best of all, this story can be told backward and forward in time. Imagine that we start with empty space at some particular moment and watch it evolve into the future and into the past. (It goes both ways because we are not presuming a unidirectional arrow of time.) Baby universes fluctuate into existence in both directions of time, eventually emptying out and giving birth to babies of their own. On ultralarge scales, such a multiverse would look statistically symmetric with respect to time—both the past and the future would feature new universes fluctuating into life and proliferating without bound. Each of them would experience an arrow of time, but half would have an arrow that was reversed with respect to that in the others.

The idea of a universe with a backward arrow of time might seem alarming. If we met someone from such a universe, would they remember the future? Happily, there is no danger of such a rendezvous. In the scenario we are describing, the only places where time seems to run backward are enormously far back in our past—long before

FAQs, PART III

Is the multiverse theory testable?
The idea that the universe stretches far beyond what we can see is not really a theory—it is a prediction made by certain theories of quantum mechanics and of gravity. Admittedly, it is a prediction that is hard to test. But all theories of physics force us to go beyond what we can directly see. For instance, our current best model for the origin of cosmic structure, the inflationary universe scenario, requires us to understand the conditions even before inflation.

[RETROCHRONOLOGY]

The History of the Observable Universe

Here is a timeline of important events in the history of our observable universe, according to conventional cosmology:

- Space is empty, featuring nothing but a tiny amount of vacuum energy and an occasional long-wavelength particle formed via fluctuations of the quantum fields that suffuse space.
- High-intensity radiation suddenly sweeps in from across the universe, in a spherical pattern focused on a point in space. When the radiation collects at that point, a "white hole" is formed.
- The white hole gradually grows to billions of times the mass of the sun, through accretion of additional radiation of ever decreasing temperature.
- Other white holes begin to approach from billions of light-years away. They form a homogeneous distribution, all slowly moving toward one another.
- The white holes begin to lose mass by ejecting gas, dust and radiation into the surrounding environment.
- The gas and dust occasionally implode to form stars, which spread themselves into galaxies surrounding the white holes.
- Like the white holes before them, these stars receive inwardly directed radiation. They use the energy from this radiation to convert heavy elements into lighter ones.
- Stars disperse into gas, which gradually smooths itself out through space; matter as a whole continues to move together and grow more dense.
- The universe becomes ever hotter and denser, eventually contracting all the way to a big crunch.

Needless to say, this is not the usual way in which we describe the history of the universe—it is the conventional sequence of events told backward in time. But the laws of physics work equally well run forward or backward in time. Thus, this sequence is as legitimate as the usual one. It serves the purpose of driving home just how unlikely the entire history of our observable universe really is. —*S.M.C.*

our big bang. In between is a broad expanse of universe in which time does not seem to run at all; almost no matter exists, and entropy does not evolve. Any beings who lived in one of these time-reversed regions would not be born old and die young—or anything else out of the ordinary. To them, time would flow in a completely conventional fashion. It is only when comparing their universe to ours that anything seems out of the ordinary—our past is their future, and vice versa. But such a comparison is purely hypothetical, as we cannot get there and they cannot come here.

As of right now, the jury is out on our model. Cosmologists have contemplated the idea of baby universes for many years, but we do not understand the birthing process. If quantum fluctuations could create new universes, they could also create many other things—for example, an entire galaxy. For a scenario like ours to explain the universe we see, it has to predict that most galaxies arise in the aftermath of big bang–like events and not as lonely fluctuations in an otherwise empty universe. If not, our universe would seem highly unnatural.

But the take-home lesson is not any particular scenario for the structure of spacetime on ultralarge scales. It is the idea that a striking feature of our observable cosmos—the arrow of time, arising from very low entropy conditions in the early universe—can provide us with clues about the nature of the *unobservable* universe.

As mentioned at the beginning of this article, it is nice to have a picture that fits the data, but cosmologists want more than that: we seek an understanding of the laws of nature and of our particular universe in which everything makes sense to us. We do not want to be reduced to accepting the strange features of our universe as brute facts. The dramatic time asymmetry of our observable cosmos seems to be offering us a clue to something deeper—a hint to the ultimate workings of space and time. Our task as physicists is to use this and other clues to put together a compelling picture.

If the observable universe were all that existed, it would be nearly impossible to account for the arrow of time in a natural way. But if the universe around us is a tiny piece of a much larger picture, new possibilities present themselves. We can conceive of our bit of universe as just one piece of the puzzle, part of the tendency of the larger system to increase its entropy without limit in the very far past and the very far future. To paraphrase physicist Edward Tryon, the big bang is easier to understand if it is not the beginning of everything but just one of those things that happens from time to time.

Other researchers are working on related ideas, as more and more cosmologists are taking seriously the problem posed by the arrow of time. It is easy enough to observe the arrow—all you have to do is mix a little milk into your coffee. While sipping it, you can contemplate how that simple act can be traced all the way back to the beginning of our observable universe and perhaps beyond. ■

MORE TO EXPLORE

Time's Arrow and Archimedes' Point: New Directions for the Physics of Time. Huw Price. Oxford University Press, 1996.

Spontaneous Inflation and the Origin of the Arrow of Time. Sean M. Carroll and Jennifer Chen. Submitted on October 27, 2004. **www.arxiv.org/abs/hep-th/0410270**

Dark Energy and the Preposterous Universe. Sean M. Carroll in *Sky & Telescope,* Vol. 109, No. 3, pages 32–39; March 2005. Available online at **www.preposterousuniverse.com/writings/skytel-mar05.pdf**

DON DIXON

Gaining Ground on Breast Cancer

The newest targeted therapies are helping doctors to tailor increasingly effective treatments to individual patients

BY FRANCISCO J. ESTEVA AND GABRIEL N. HORTOBAGYI

KEY CONCEPTS

- Breast cancer survival rates have been steadily climbing in North America and Europe, thanks to increased early detection and novel treatment options.
- Many new treatments target specific molecules on tumor cells, allowing doctors to tailor medication to an individual patient's tumor profile.
- Breast cancer was the first solid-tumor type for which molecular-targeted therapy became available, and the success of the approach promises further dramatic advances.

—The Editors

Breast cancer is the most commonly diagnosed malignancy among women and, after lung cancer, the second leading cause of cancer-related deaths in North America. Yet unlike the survival rate for individuals diagnosed with lung cancer, the rate for women diagnosed with breast cancer has been rising dramatically over the past decade—to the point where breast cancer could soon lose its ranking as the second-greatest cancer killer. Nothing would delight clinicians like us more.

This improvement in overall outlook for women diagnosed with breast cancer is attributable in part to earlier detection, which results from greater awareness of, and access to, regular breast screening. But breast cancer patients are also benefiting from accelerated research that has led to a much better understanding of the disease and a wider variety of treatment choices that doctors can mix and match to tailor therapy for a particular patient. In just the past decade, it has even become possible to target drugs to specific molecules within tumors that help to drive the disease.

Breast cancer was, in fact, the first type of solid-tumor cancer to be treated with this molecular-targeting therapeutic approach, when the drug trastuzumab (Herceptin) was approved in 1998. The protein that trastuzumab was designed to attack, called HER2, promotes aggressive tumor growth. Before trastuzumab, diagnosis with a tumor that overproduces HER2 was dreaded news for patients. Now it can be one of the tumor types with the best prognosis, because doctors have an increasing number of effective weapons against HER2.

The next decade promises to be an exciting and productive time in the field of molecular-targeted cancer therapy: additional drugs currently being tested in people and animals are making it possible to go after an increasing variety of molecular tumor features that play a critical role in the initiation and survival of malignancies and in the cancers' progression to increasingly threatening stages. Along with improvements in older therapies and supportive care, this newer generation of drugs gives doctors more options for customizing treatment to cope with a tumor's particular suite of molecular characteristics and reflects our growing realization that breast cancer is not a single disease.

Evolving Treatment Approaches

Although the prospect of tailoring treatment to the molecular features of individual tumors is incredibly encouraging, prior advances are also contributing to the declining mortality rate for women diagnosed with breast cancer. Improved screening techniques, for instance, are definitely helping to catch and confirm more cases at an earlier stage, which is a boon, because breast cancer is highly curable if detected early. Newer imaging methods include digital mammography (which produces a clearer picture than screen-film mammography), ultrasound and magnetic resonance imaging (MRI). Women at high risk of developing breast cancer because of family history or mutations in one of the *BRCA* genes are now offered annual MRI breast screening, although ultrasounds are usually reserved for following up on abnormal findings in a mammogram or physical exam.

JAMES PORTO

In addition, surgical approaches to tumor excision have changed over the past 20 years from radical tissue removal in women whose tumor appears confined to a small part of the breast to breast-conserving therapy. More focused radiation is also less damaging to normal tissues such as those of the heart and lungs. These changes have made treatment less destructive, with equally successful results.

Besides these refinements in the detection and local management of breast tumors, the use of systemic therapies as supplementary, or adjuvant, treatments has become more sophisticated thanks to the availability of new drugs, improvements in their delivery, and management of side effects. Such treatments aim to eradicate any malignant cells not eliminated by surgery or radiation. The approach is often warranted because even tumors that are tiny and apparently self-contained can already have quietly spawned microscopic metastases, undetectable tumors at distant sites in the body. By attacking these invisible tumors, adjuvant chemotherapy can prolong disease-free intervals and overall survival rates.

Adjuvant chemotherapy is also improving the odds for those with more advanced tumors. In the 1970s our clinical group and others began developing multidisciplinary treatment programs for patients with so-called locally advanced breast cancer, which has invaded neighboring tissue. Such patients are often not diagnosed until their cancer is incurable with surgery alone. Our approach is to treat them with preoperative, or neoadjuvant, chemotherapy to shrink their tumors to operable size, after which surgery is performed, followed by additional chemotherapy and radiation therapy. Using this sandwich approach over the past three decades, specialized teams of doctors, nurses and other health professionals have greatly enhanced the cure rate for these patients. Even those whose breast tumor has already metastasized to other organs now have access to novel therapies that prolong their survival and to supportive care that increases their quality of life.

Another mainstay of breast cancer treatment, at least for patients with tumors that are determined to be dependent on estrogen or progesterone, is endocrine therapy. Indeed, hormonal manipulations to treat breast cancer date as far back as the 1890s, when doctors observed tumors regressing after they had removed the ovaries of premenopausal women with advanced breast disease. In 1966 researchers identified hormone receptors—molecules that bind to specific hormones—in various tissues, including that of the breast. Subsequent studies showed that a significant number of invasive breast cancers—as many as 75 percent—contain estrogen receptors or progesterone receptors, or both, causing these molecules to quickly become therapeutic targets.

The antiestrogen drug tamoxifen was first approved in the U.S. in 1977 to treat advanced breast cancer in postmenopausal women. The drug molecule binds to the estrogen receptor, preventing estrogen from doing so. Tamoxifen has since proved effective for patients with localized breast tumors that display estrogen or progesterone receptors and as a preventive therapy in healthy women who are at high risk for breast cancer. Meanwhile newer drugs that inhibit the aromatase enzyme, suppressing natural estro-

FAST FACTS

Inherited mutations in the *BRCA1* gene can multiply lifetime breast cancer risk by 10 times, but only in the past year have researchers discovered why. *BRCA1* is involved in DNA repair, so its malfunction makes errors in other cancer-promoting genes more likely.

Following a 2002 report that hormone replacement therapy (HRT) increased breast cancer risk in postmenopausal women, HRT use fell. The next year there was a dramatic drop in the incidence of both invasive (7.3 percent) and noninvasive (5.5 percent) breast cancers in the U.S.

[TREATMENT MILESTONES]

Doctors started aggressively treating breast cancer in the 19th century, with the first mastectomy performed in 1882. But insights into mechanisms driving the disease that would lead to increasingly targeted therapies began with discoveries in the 1950s.

1880s–1890s

George T. Beatson

Hormonal cancer connection suggested when physicians report significant regression of breast cancer tumors following ovary removal or onset of menopause.

1896: First ovary removal performed as a breast cancer treatment by George T. Beatson.

RAISING AWARENESS of the importance of early detection, as well as raising funding for research, has paid off in notable declines in breast cancer mortality in the developed world.

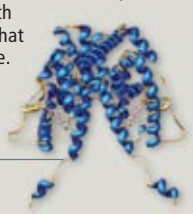
ANGELA ROWLINGS *AP Photo (racers)*; LISA APFELBACHER *(all pills)*; TIMELINE: WELLCOME LIBRARY, LONDON *(Beatson)*; MARK J. WINTER *Photo Researchers, Inc. (estrogen receptor)*; SCIENCE MUSEUM *(tamoxifen)*; P. MARAZZI *Photo Researchers, Inc. (Herceptin)*

1950s–1960s

1951: Estrogen and testosterone found to drive the growth of breast and prostate cancers, respectively.

1958: Cancer researchers identify additional "growth factor" proteins that help tumors thrive.

1966: Estrogen receptor identified.



Estrogen receptor protein structure

1970s–1980s

1976: Cancer-promoting "oncogenes" first discovered in mammals.

Tamoxifen, a selective estrogen receptor modulator

1976: Clinical trials begin to show that lumpectomy with radiation can be as effective as mastectomy.

1977: Hormone-blocking drug tamoxifen approved in U.S. for treatment of breast cancers sensitive to estrogen or progesterone.

1988: Trial results show that preoperative chemotherapy shrinks tumors, making less invasive surgeries possible.

1990s–2008

1994: *BRCA1* gene, known to increase susceptibility to breast cancer, is isolated.

1997: Letrozole, which blocks estrogen synthesis, approved in U.S. for patients whose cancer did not respond to tamoxifen.

1998: Trastuzumab, the first molecular-targeted cancer therapy, approved in U.S. for use in breast cancer.

2007: Lapatinib, an inhibitor of growth signaling, approved in U.S. for use in breast cancer.

2008: Bevacizumab, an inhibitor of blood vessel formation in tumors, approved in U.S. for use in breast cancer.

Trastuzumab, also known by the trade name Herceptin

gen manufacture in the body, have proved superior to tamoxifen in postmenopausal women.

In a sense, then, estrogen and progesterone receptors became the first molecular features of tumors that could be directly targeted by drugs, although an important distinction should be noted between these targets and newer ones identified in the past decade. The sex steroid receptors promote cell proliferation, or growth, in healthy tissues as well as in tumors, so suppressing their ability to transmit growth signals does help to check tumor enlargement. And changes to the receptors' shape or function may sometimes contribute to the general malignant characteristics of tumor cells. But the gene encoding the estrogen receptor is rarely mutated in breast cancers, which means that it is not a true cancer-causing gene.

Perhaps the most important realization in cancer research since the era when sex hormone receptors were discovered is that particular genes, when they become mutated, can cause a normal cell to turn cancerous. Such genes, once they do mutate, are referred to as oncogenes, and they are believed to be responsible both for initiating the transformation of a normal cell into a cancerous one and for driving tumor growth. That is why breast cancer (like all cancers) is described today as fundamentally a disease of genes. An oncogenic mutation, such as a small change in the DNA nucleotide sequence of a gene, might disable a protective gene or boost the activity of a tumor-promoting one. In some cases, entire genes are deleted or duplicated [*see sidebar on page 63*].

Tumors can now be classified according to the genes that are overactive or suppressed in their cells and according to the resulting changes in the manufacture and function of proteins encoded by those genes. The damaged genes can vary from tumor to tumor, and this heterogeneity at the genetic level explains why the breast cancers of individual patients might behave differently. Some cancers have limited invasiveness and metastatic potential, for instance, whereas others spread quickly to distant organs. Knowing the molecular profile of a patient's tumor should permit a doctor to focus on inhibiting the mechanisms driving that particular tumor, one day choosing from an arsenal of drugs a set that will interfere with the specific molecules involved in the initiation, growth and spread of the cancer. The success of trastuzumab and other HER2-targeted therapies illustrates the potential of this approach in combating breast cancer.

Targeting HER2

In the early 1980s the gene that gives rise to HER2 was first discovered in mutated form in rat neural tumors by investigators at the Massachusetts Institute of Technology, who named that oncogene *Neu*. Soon researchers realized that the gene was a mammalian version of one previously identified in viruses called *ERBB*, so *Neu* also came to be known as *ERBB2*. This gene was not done accumulating names, however. When scientists identified the protein encoded by *ERBB2*, they realized that it was closely related to a cell-membrane protein called epidermal growth factor receptor (EGFR). Thus, when they finally isolated the human version of the *ERBB2* gene, they named it human epidermal growth factor receptor 2 (*HER2*).

As it turns out, the entire EGFR family of proteins has proved important to tumor cell growth in a variety of cancers. When activated by specific molecules that bind to them (their ligands), such receptors transmit a proliferation signal to the cell by initiating a cascade of internal molecular interactions—spurring activity by genes whose encoded proteins regulate the activity of still more "downstream" genes. Shortly after the *HER2* gene was discovered, scientists noted that

[THE AUTHORS]

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MEDICAL GRAPHICS & PHOTOGRAPHY/UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER (*left*); JOHN SMALLWOOD (*right*)

it was frequently duplicated in breast cancer cells and that having multiple copies of the gene was associated with a poor prognosis.

Laboratory studies confirmed that adding copies of the *HER2* gene to a normal cell could transform it into a cancer cell—a hallmark ability of oncogenes. Because 20 percent of breast cancer tumors overproduce the HER2 protein, it became a therapeutic target for drug researchers. Genentech scientists created trastuzumab in the late 1980s by manufacturing so-called monoclonal antibodies that bind to the HER2 receptor, preventing it from being activated. In clinical trials, it was found that trastuzumab could lengthen the survival of patients with both early-stage and metastatic breast cancer.

The success of trastuzumab has led to the development of similar antibody-based therapies, such as pertuzumab, which binds to HER2 at a different site than trastuzumab and has the added effect of preventing the receptor from interacting with other members of its family in the cell membrane, such as EGFR and HER3. Blocking such interactions reduces growth signaling along the intracellular pathways of molecular communication downstream of these receptors. Pertuzumab can even disrupt certain types of HER2 activation in tumor cells that have become resistant to trastuzumab. Moreover, we have shown that combining trastuzumab with pertuzumab can boost the rate of cell death in breast cancer cells overproducing HER2.

Still another method of wielding antibodies against the HER2 receptor is to attach a potent toxin to them, which the antibodies then transport into the cancer cell. After the toxin-antibody pair is internalized by a cell, the toxin detaches and kills the cell. This approach has been successful in other types of cancer, such as acute myeloid leukemia, and clinical trials are under way in patients with metastatic breast cancer to determine the safety and efficacy of such trastuzumab-based conjugates.

To send a growth signal into a cell, the intracellular region of the EGFR family of proteins must first be acted on by tyrosine kinases, enzymes that chemically modify a segment known as the tyrosine kinase domain. Tyrosine kinases can thus act as growth-stimulating factors, and inhibiting them directly is another way of squelching EGFR-mediated growth signaling in cells. That is why pharmaceutical companies are avidly pursuing the clinical development of such drugs. Lapatinib (Tykerb) is a dual EGFR/HER2 tyrosine kinase inhibitor that has shown remarkable laboratory results, leading to growth arrest and cell suicide in breast cancer cell lines that overproduce HER2.

One way to improve the effectiveness of HER2-targeted therapy is, therefore, to combine a drug such as trastuzumab with a tyrosine kinase inhibitor such as lapatinib. In breast cancer cell lines, that combination produces greater synergistic growth inhibition and higher rates of cell suicide. Even in cell lines that have developed resistance to trastuzumab after long-term treatment, lapatinib has proved just as effective at inducing cell suicide. A recent large (phase III) clinical trial among patients with HER2-overproducing metastatic breast cancer, whose disease had become resistant to trastuzumab, demonstrated that lapatinib plus capecitabine chemotherapy doubled the median time to progression as compared with capecitabine alone. On the basis of these results, in 2007 the U.S. Food and Drug Administration approved the use of lapatinib combined with capecitabine for treating metastatic disease. Clinical trials to determine lapatinib's value as an adjuvant treatment in a wider variety of circumstances are

JEN CHRISTIANSEN

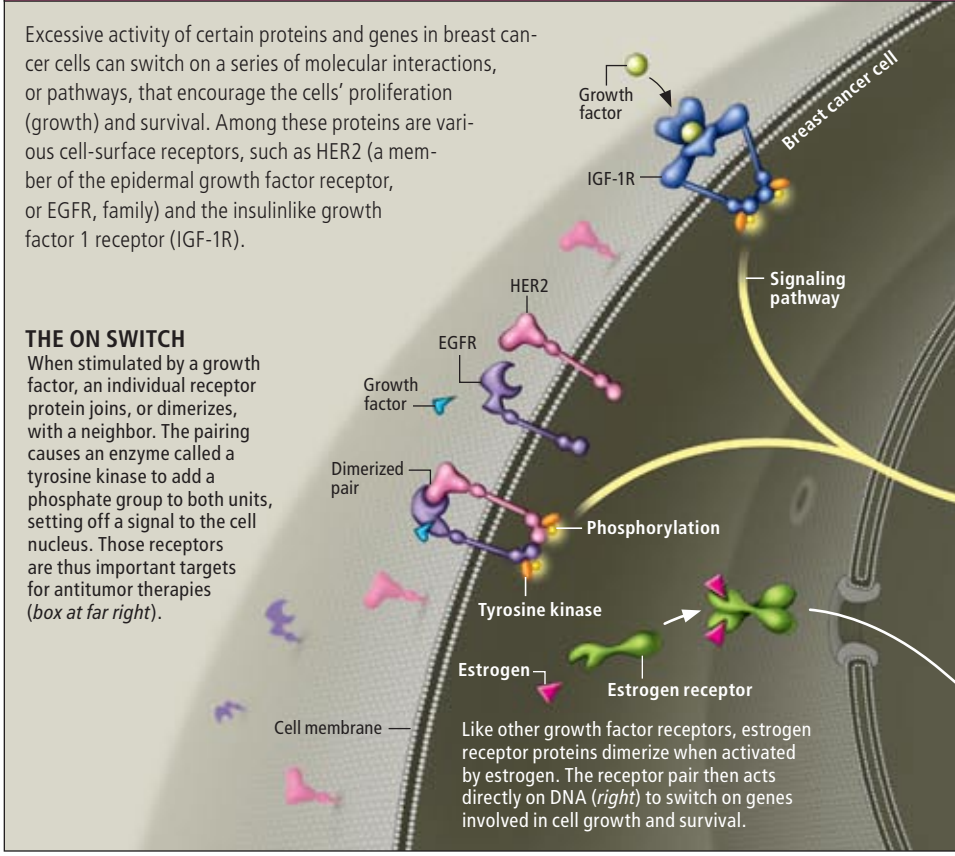
[TARGETS]

TUMOR PATHWAYS

Excessive activity of certain proteins and genes in breast cancer cells can switch on a series of molecular interactions, or pathways, that encourage the cells' proliferation (growth) and survival. Among these proteins are various cell-surface receptors, such as HER2 (a member of the epidermal growth factor receptor, or EGFR, family) and the insulinlike growth factor 1 receptor (IGF-1R).

THE ON SWITCH

When stimulated by a growth factor, an individual receptor protein joins, or dimerizes, with a neighbor. The pairing causes an enzyme called a tyrosine kinase to add a phosphate group to both units, setting off a signal to the cell nucleus. Those receptors are thus important targets for antitumor therapies (*box at far right*).

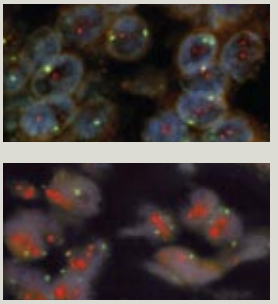


ongoing, as are trials of several other tyrosine kinase inhibitors that target HER2 and EGFR.

Finding alternative means of interfering with the same growth pathways is important because, as can happen with trastuzumab, cancer cells often do eventually find ways to evade individual drugs. Also under way is research into how and why cancer cells develop resistance to trastuzumab, so that investigators can use those insights as a guide to designing more effective combinations or new agents for patients whose tumors overproduce HER2.

In studies of cell cultures and animals, for instance, our laboratory has discovered that cancer cells employ many different mechanisms to survive in the presence of trastuzumab, including increasing their production of other growth factor receptors, either from the EGFR/HER family or from other families, such as the insulinlike growth factor 1 (IGF-1) receptor. The cells may also lose or inactivate the tumor suppressor gene *PTEN*. This gene normally blocks a survival pathway involving the enzyme phosphotidylinositol 3-kinase (PI3K), which allows damaged cells to ignore signals telling them to commit suicide. We have even seen cells lose or disable the extracellular binding site that trastuzumab attaches to on the HER2 receptor.

In light of these observations, identifying additional molecular targets to attack in cells that overproduce HER2, as well as targets in the other 80 percent of tumors that do not have *HER2* mutations, is a high research priority.



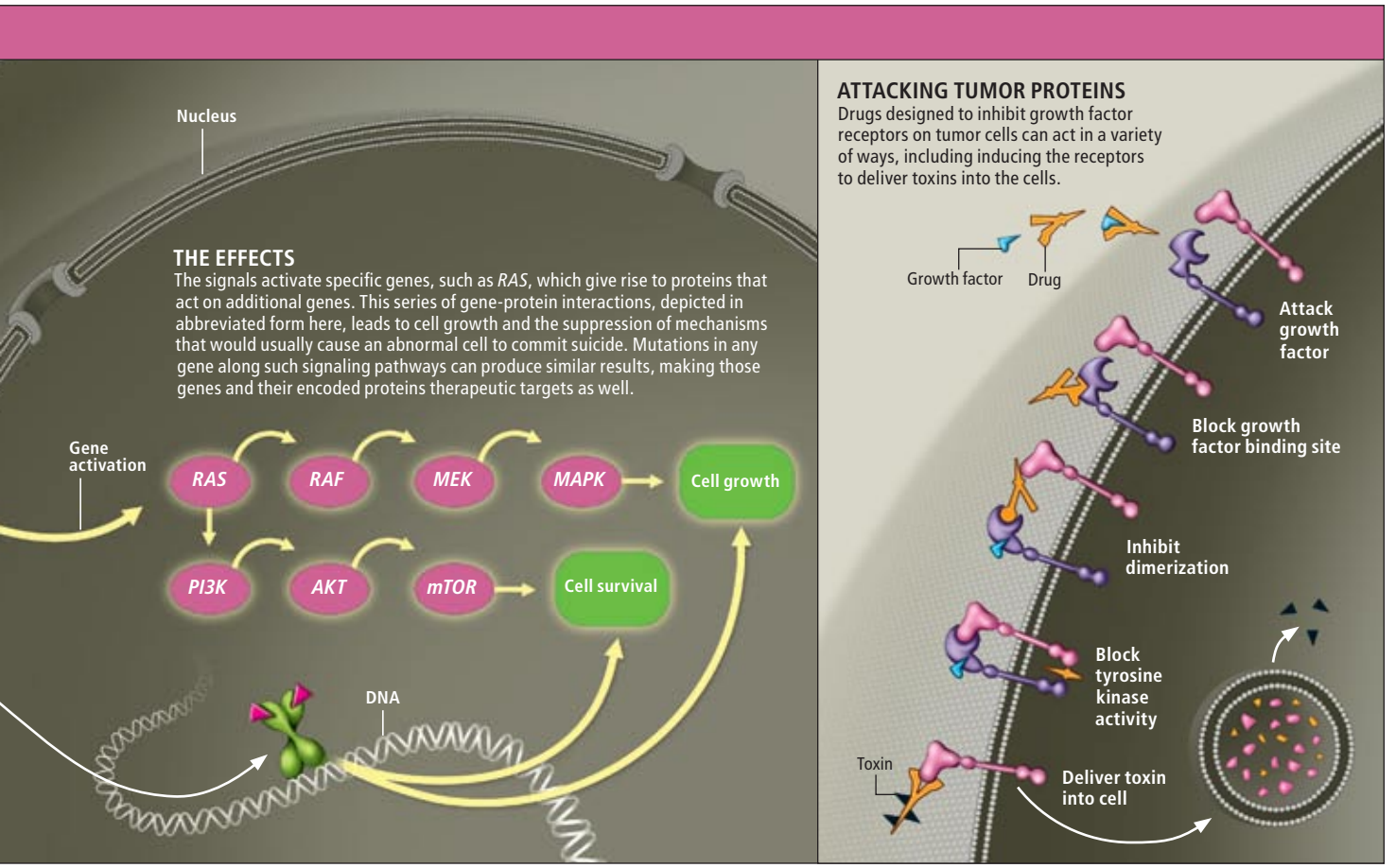
COURTESY OF FRANCISCO J. ESTEVA

HER2 AMPLIFICATION

A gene encoding the HER2 growth factor receptor is tagged with red fluorescence in breast cancer cells (*top*). In HER2-positive cancer cells (*bottom*), the gene is duplicated many times over, leading to overproduction of HER2 proteins that cause the cells to receive excessive growth signals.

Expanding the Arsenal

Among the most promising new targets for breast cancer therapy is the IGF-1 receptor as well as the growth hormone molecules that activate it, IGF-1 and IGF-2. High levels of IGF-1 in the bloodstream have been linked with increased risk of breast cancer, and many laboratory and clinical studies have implicated its receptor in the development, maintenance and progression of multiple cancer types. Signaling by the IGF-1 receptor regulates a variety of cellular processes, including growth, motility and protection from cell suicide. In fact, such signals have been shown to protect tumor cells from the effects of chemotherapy and radiation therapy. Conversely, inhibiting IGF-1 receptor activity during radiation therapy or



chemotherapy has been found to enhance tumor cell suicide rates in animal studies.

In addition to exploring IGF-1 receptor inhibition as a direct therapeutic tool for breast cancer, scientists are evaluating ways to apply it toward preventing or reversing resistance to other treatments, such as endocrine therapies, trastuzumab and lapatinib. Cross talk between the IGF-1 receptor and the various other growth factor receptors—including estrogen, HER2 and additional EGFRs—is a key mechanism for the growth and survival of breast cancer. This codependence and communication between different intracellular pathways is thought to play an important role in drug resistance. Our research group has shown, for example, that blocking the IGF-1 receptor with a monoclonal antibody restores the sensitivity of resistant cells to trastuzumab and disrupts the interaction between the IGF-1 and HER2 receptors. Suppressing the IGF-1 receptor also kills the resistant cells. Furthermore, lapatinib appears to have inhibitory effects on IGF-1 signaling in the trastuzumab-resistant cells, suggesting that its ability to limit tumor cell proliferation may result not only from its anti-EGFR/HER2 activities but also from direct IGF-1 receptor inhibition.

The tangle of signaling pathways leading from the receptors we have been describing to the cellular processes that actually cause a cell to divide or to resist suicide despite DNA damage is highly complex. But scientists are finding that key genes along those pathways are also frequently mutated or dysregulated in tumor cells. Among the best characterized examples is the *PI3K* gene, whose encoded protein chemically modifies another protein known as AKT, which in turn modifies a complex called the mammalian target of rapamycin (mTOR). This PI3K/AKT/mTOR pathway plays a critical role in the body's use of glucose for energy and other important physiological processes in normal cells, but it is pathologically overactivated in cancer cells, prolonging their survival. Because the pathway's effects are ubiquitous in the body, delivering drugs that inhibit it could disrupt healthy cells as well as cancerous ones—a drawback that has so far limited the use of such agents.

Several mTOR inhibitors are nonetheless being tested in clinical trials, both as single agents and combined with other therapies. At the moment, studies using the mTOR-suppressing antibiotic rapamycin, along with an inhibitor of the IGF-1 receptor, suggest that such combinations yield additive antitumor effects as compared with single agents—and that, further, clinically evaluating combined inhibition of both pathways may be a good idea.

Another approach showing great promise is combining direct antitumor agents with compounds that target elements in a tumor's environment. Cancers secrete a variety of growth factors to attract the endothelial cells that build new blood vessels in a process called angiogenesis. Overproduction of the most important of these, vascular endothelial growth factor (VEGF), is thought to make tumors more dangerous, and high levels correlate with worse survival rates in human invasive breast cancers.

TARGETED THERAPIES

A growing list of drugs designed to inhibit specific tumor proteins are approved to treat breast cancer patients (*bold*) or are undergoing clinical trials.

DRUG TYPE

- **Aromatase inhibitor** (blocks an enzyme involved in estrogen and progesterone synthesis)
- **Monoclonal antibody** (impedes activation of cellular receptors)
- **Kinase inhibitor** (inhibits signaling by cellular receptors)
- **Vaccine** (stimulates production of antibodies specific to tumor proteins; can be composed of cells or peptide molecules)
- **Other** (includes direct inhibitors of other molecules or gene therapy to alter cellular protein manufacture)

TARGET	DRUG
Estrogen/ progesterone receptor proteins	**Anastrozole** **Letrozole** **Exemestane** **Tamoxifen** **Fulvestrant**
HER2 receptor protein	**Trastuzumab** **Pertuzumab** **Lapatinib** NeuVax dHER2 MVF-HER-2 E1A (gene therapy)
IGF-1 receptor protein	IMC-A12 CP-751, 871 AMG 479 h7C10 OSI-906
PI3K/AKT/mTOR cell survival pathway	BGT226 BEZ235A RAD001 Rapamycin
VEGF receptor protein (involved in forming tumor blood vessels)	**Bevacizumab** Sunitinib Vatalinib Pazopanib AZD2171 AMG706 AMG386 PTC299
Other targets	Dasatinib (SRC inhibitor) THERATOPE Dendritic cell vaccines P53 peptide vaccine ALT801 (p53 inhibitor) Ad5CMV-p53 (gene therapy) Anti-p53 T-cell reinfusion AZD2281 (PARP protein inhibitor) BSI-201 (PARP inhibitor)

Global Power

Targeted therapies will be most powerful, in principle, when they are used together in combinations tailored to the tumor features driving an individual patient's cancer. Clinical trials to test specific drug combinations provide critical information about which treatments work most effectively on different tumor profiles and reveal unexpected interactions between drugs. But trials take time, often years, to enroll a sufficient number of participants to generate statistically significant results. That is why multinational research consortia based in Europe and the U.S. are pooling resources to conduct a 50-country trial, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Study (ALTTO), which has just begun recruiting in the U.S.

Some 1,500 testing sites will treat patients with early (stage I or II) breast cancers that overproduce the HER2 protein, giving them chemotherapy and either trastuzumab or lapatinib alone, or one of those drugs followed by the other, or both drugs together. The trial will provide the first side-by-side comparison of these HER2-targeted treatments that work by different mechanisms.

With a goal of including as many as 8,000 women on six continents, ALTTO has the potential to quickly generate results that can then be applied to patients everywhere. Moreover, this global data-sharing model can highlight differences in treatment responses or toxicity among different ethnic groups, a phenomenon observed with certain types of chemotherapy because of genetic variations that affect the way the drugs are metabolized by patients' bodies. Having such information about the newer targeted therapies will help doctors to further personalize treatment, tailoring it to both the tumor and the patient. ***—The Editors***

Genentech's bevacizumab (Avastin) is a monoclonal antibody directed against VEGF that was first approved for use in colon cancer in 2004. In more recent clinical trials among patients with heavily treated metastatic breast cancer, bevacizumab alone had limited activity, but certain patients who received it in combination with capecitabine chemotherapy showed improved responses [see "Taming Vessels to Treat Cancer," by Rakesh K. Jain; Scientific American, January]. In another study, HER2-negative metastatic breast cancer progressed more slowly in patients who received paclitaxel chemotherapy with bevacizumab than it did in patients who received paclitaxel alone. Based on such results, bevacizumab was recently approved for use in breast cancer patients, and other VEGF inhibitors are also in development, such as Pfizer's sunitinib (Sutent), a tyrosine kinase inhibitor targeted against the VEGF receptor.

At the same time, very basic biology research is continuing to turn up new molecular targets that both reveal more about the underlying mechanisms of cancer and provide potential leads for drug development. Terumi Kohwi-Shigematsu of Lawrence Berkeley National Laboratory and her colleagues announced one such discovery earlier this year. They identified a gene called *SATB1* as the "master regulator" of activity for more than 1,000 genes involved in breast cancer metastasis. Kohwi-Shigematsu showed that the influence of the SATB1 protein encoded by the gene is both necessary and sufficient for breast cancer cells to become metastatic, which makes it an appealing therapeutic candidate. Her research group is already working on an inhibitor of the SATB1 protein, which could be ready for clinical trials within a few years.

Progress in the molecular targeting of breast cancer and individualized therapy will generally rely on the continuing development of profiling tools to determine whether a patient's tumor overproduces proteins such as HER2, SATB1 and others that might be direct drug targets. In addition, genetic testing can help to characterize a tumor's overall gene activity patterns—a potential signature of a good or poor prognosis. Still other tests already available or nearing approval can help to profile the patient herself to establish whether she has genetic variations that might make her body process a medication more slowly than average—a situation that can be problematic with a drug such as tamoxifen that depends on the body to convert it to active form.

Meanwhile further clinical trials of various drug combinations are needed to validate the effectiveness of attacking multiple targets at once. A 50-country trial has recently begun recruitment in the U.S., for example, to test lapatinib and trastuzumab alone and in combination with each other and with traditional chemotherapies [*see box on this page*].

Such a large international trial exemplifies the considerable resources and attention focused on breast cancer research, in recognition of its importance as a global health threat. The intensive scientific investigation and heightened awareness are certainly bearing fruit. When breast cancer is compared with other types of cancer, such as malignancies of the lung or brain, advances over the past decade have been impressive. Doctors' ability to profile a tumor and tailor treatment to fight it with a growing arsenal of weapons is already making a difference in the survival rates of breast cancer patients, and the coming decade promises even more dramatic progress. ■

MORE TO EXPLORE

Molecular Oncology of Breast Cancer. Edited by Jeffrey S. Ross and Gabriel N. Hortobagyi. Jones and Bartlett Publishers, 2005.

Long-Term Cardiac Tolerability of Trastuzumab in Metastatic Breast Cancer: The M.D. Anderson Cancer Center Experience. Valentina Guarneri et al. in *Journal of Clinical Oncology,* Vol. 24, No. 25, pages 4107–4115; September 1, 2006.

Trastuzumab: Triumphs and Tribulations. Rita Nahta and Francisco J. Esteva in *Oncogene,* Vol. 26, No. 25, pages 3637–3643; May 28, 2007.

Advances in the Treatment of Breast Cancer. Stacy Moulder and Gabriel N. Hortobagyi in *Clinical Pharmacology & Therapeutics,* Vol. 83, No. 1, pages 26–36; January 2008.

Breast Cancer. Second edition. Edited by Kelly K. Hunt, Geoffrey L. Robb, Eric A. Strom and Naoto T. Ueno. Springer, 2008.

DIGITAL IMAGE FORENSICS

Modern software has made manipulation of photographs easier to carry out and harder to uncover than ever before, but the technology also enables new methods of detecting doctored images

By Hany Farid

KEY CONCEPTS

- Fraudulent photographs produced with powerful, commercial software appear constantly, spurring a new field of digital image forensics.
- Many fakes can be exposed because of inconsistent lighting, including the specks of light reflected from people's eyeballs.
- Algorithms can spot when an image has a "cloned" area or does not have the mathematical properties of a raw digital photograph.

—The Editors

History is riddled with the remnants of photographic tampering. Stalin, Mao, Hitler, Mussolini, Castro and Brezhnev each had photographs manipulated—from creating more heroic-looking poses to erasing enemies or bottles of beer. In Stalin's day, such phony images required long hours of cumbersome work in a darkroom, but today anyone with a computer can readily produce fakes that can be very hard to detect.

Barely a month goes by without some newly uncovered fraudulent image making it into the news. In February, for instance, an award-winning photograph depicting a herd of endangered Tibetan antelope apparently undisturbed by a new high-speed train racing nearby was uncovered to be a fake. The photograph had appeared in hundreds of newspapers in China after the controversial train line was opened with much patriotic fanfare in mid-2006. A few people had noticed oddities immediately, such as how some of the antelope were pregnant, but there were no young, as should have been the case at the time of year the train began running. Doubts finally became public when the picture was featured in the Beijing subway this year and other flaws came to light, such as a join line where two images had been stitched together. The photographer, Liu Weiqing, and his newspaper editor resigned; Chinese government news agencies apologized for distributing the image and promised to delete all of Liu's photographs from their databases.

In that case, as with many of the most publicized instances of fraudulent images, the fakery was detected by alert people studying a copy of

THIS IMAGE HAS BEEN MODIFIED in several places. The digital forensic techniques described on the following pages could be used to detect where changes were made. The answers are given on the final page.

the image and seeing flaws of one kind or another. But there are many other cases when examining an image with the naked eye is not enough to demonstrate the presence of tampering, so more technical, computer-based methods—digital image forensics—must be brought to bear.

I am often asked to authenticate images for media outlets, law-enforcement agencies, the courts and private citizens. Each image to be analyzed brings unique challenges and requires different approaches. For example, I used a technique for detecting inconsistencies in lighting on an image that was thought to be a composite of two people. When presented with an image of a fish submitted to an online fishing competition, I looked for pixel artifacts that arise from resizing. Inconsistencies in an image related to its JPEG compression, a standard digital format, revealed tampering in a screen shot offered as evidence in a dispute over software rights.

As these examples show, because of the variety of images and forms of tampering, the forensic analysis of images benefits from having a wide choice of tools. Over the past five years my students, colleagues and I, along with a small but growing number of other researchers, have developed an assortment of ways to detect tampering in digital images. Our approach in creating each tool starts with understanding what statistical or geometric properties of an image are disturbed by a particular kind of tampering. Then we develop a mathematical algorithm to uncover those irregularities. The boxes on the coming pages describe five such forensic techniques.

The validity of an image can determine wheth-

[THE AUTHOR]

Hany Farid has worked with federal law-enforcement agencies and many other clients on uncovering doctored images. Farid is David T. McLaughlin Distinguished Professor of Computer Science and Associate Chair of Computer Science at Dartmouth College and is also affiliated with the Institute for Security Technology Studies at Dartmouth. He thanks the students and colleagues with whom he has developed digital forensic methods, in particular Micah K. Johnson, Eric Kee, Siwei Lyu, Alin Popescu, Weihong Wang and Jeffrey Woodward.

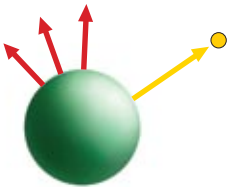
CHRISTOPHE ENA *AP Photo (bicyclists)*; LIU YANG *Redlink/Corbis (woman's head)*; SHEARER IMAGES/CORBIS *(fire hydrant)*

[LIGHTING]

IN A DIFFERENT LIGHT

Composite images made of pieces from different photographs can display subtle differences in the lighting conditions under which each person or object was originally photographed. Such discrepancies will often go unnoticed by the naked eye.

For an image such as the one at the right, my group can estimate the direction of the light source for each person or object (*arrows*). Our method relies on the simple fact that the amount of light striking a surface depends on the relative orientation of the surface to the light source. A sphere, for example, is lit the most on the side facing the light and the least on the opposite side, with gradations of shading across its surface according to the angle between the surface and the direction to the light at each point.



To infer the light-source direction, you must know the local orientation of the surface. At most places on an object in an image, it is difficult to determine the orientation. The one exception is along a surface contour, where the orientation is perpendicular to the contour (*red arrows above*). By measuring the brightness and orientation along several points on a contour, our algorithm estimates the light-source direction.

For the image above, the light-source direction for the police does not match that for the ducks (*arrows*). We would have to analyze other items to be sure it was the ducks that were added. —**H.F.**

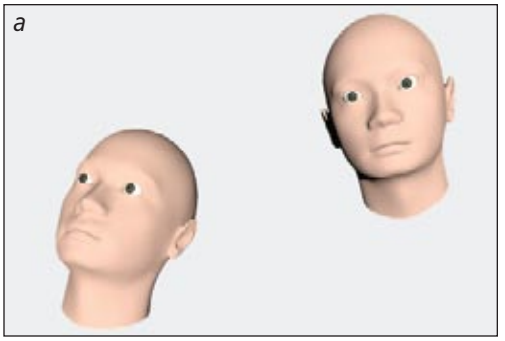
HUGHES LÉGLISE-BATAILLE (*riot*); CHARRO BADGER (*inTheSunStudio (ducks)*; LISA APFELBACHER (*illustration*)

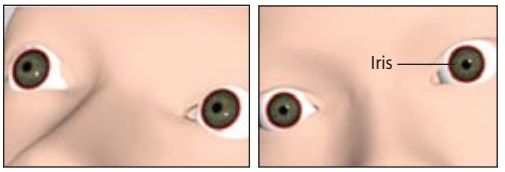
[SHAPES]

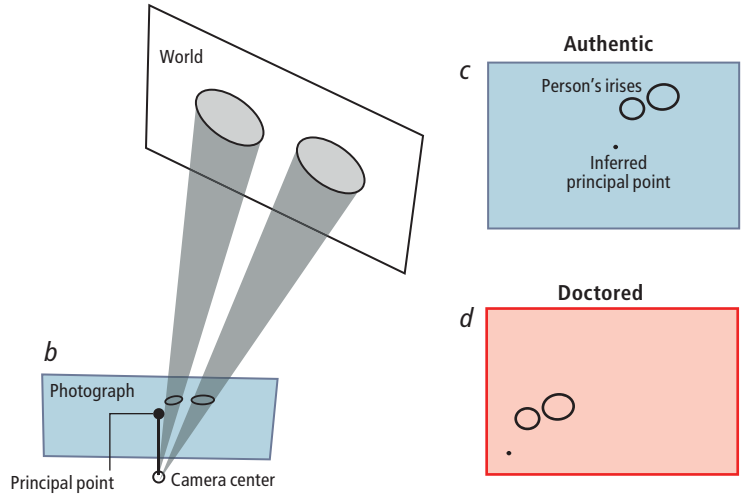
EYES AND POSITION

Because eyes have very consistent shapes, they can be useful for assessing whether a photograph has been altered.

A person's irises are circular in reality but will appear increasingly elliptical as the eyes turn to the side or up or down (*a*). One can approximate how eyes will look in a photograph by tracing rays of light running from them to a point called the camera center (*b*). The picture forms where the rays cross the image plane (*blue*). The principal point of the camera—the intersection of the image plane and the ray along which the camera is pointed—will be near the photograph's center.







My group uses the shape of a person's two irises in the photograph to infer how his or her eyes are oriented relative to the camera and thus where the camera's principal point is located (*c*). A principal point far from the center or people having inconsistent principal points is evidence of tampering (*d*). The algorithm also works with other objects if their shapes are known, as with two wheels on a car.

The technique is limited, however, because the analysis relies on accurately measuring the slightly different shapes of a person's two irises. My collaborators and I have found we can reliably estimate large camera differences, such as when a person is moved from one side of the image to the middle. It is harder to tell if the person was moved much less than that. —**H.F.**

COURTESY OF HANY FARID (*a*); LISA APFELBACHER (*b–d*)

er or not someone goes to prison and whether a claimed scientific discovery is a revolutionary advance or a craven deception that will leave a dark stain on the entire field. Fake images can sway elections, as is thought to have happened with the electoral defeat of Senator Millard E. Tydings in 1950, after a doctored picture was released showing him talking with Earl Browder, the leader of the American Communist Party. Political ads in recent years have seen a startling number of doctored photographs, such as a faux newspaper clipping distributed on the Internet in early 2004 that purported to show John Kerry on stage with Jane Fonda at a 1970s Vietnam War protest. More than ever before, it is important to know when seeing can be believing.

Everywhere You Look

The issue of faked images crops up in a wide variety of contexts. Liu was far from the first news photographer to lose his job and have his work stricken from databases because of digital fakery. Lebanese freelancer Adnan Hajj produced striking photographs from Middle Eastern conflicts for the Reuters news agency for a decade, but in August 2006 Reuters released a picture of his that had obviously been doctored. It showed Beirut after being bombed by Israel, and some of the voluminous clouds of smoke were clearly added copies.

Brian Walski was fired by the *Los Angeles Times* in 2003 after a photograph of his from Iraq that had appeared on the newspaper's front page was revealed to be a composite of elements from two separate photographs combined for greater dramatic effect. A sharp-eyed staffer at another newspaper noticed duplicated people in the image while studying it to see if it showed friends who lived in Iraq. Doctored covers from newsmagazines *Time* (an altered mug shot of O. J. Simpson in 1994) and *Newsweek* (Martha Stewart's head on a slimmer woman's body in 2005) have similarly generated controversy and condemnation.

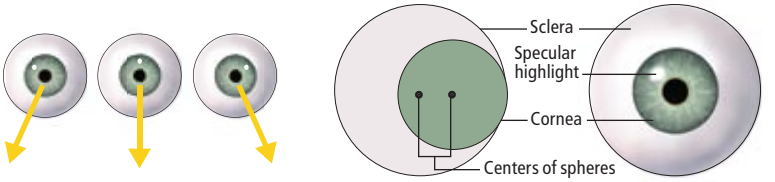
Scandals involving images have also rocked the scientific community. The infamous stem cell research paper published in the journal *Science* in 2005 by Woo Suk Hwang of Seoul National University and his colleagues reported on 11 stem cell colonies that the team claimed to have made. An independent inquiry into the case concluded that nine of those were fakes, involving doctored images of two authentic colonies. Mike Rossner estimates that when he was the managing editor of the *Journal of Cell Biol-*

[SPECULAR HIGHLIGHTS]

TELLTALE TWINKLES

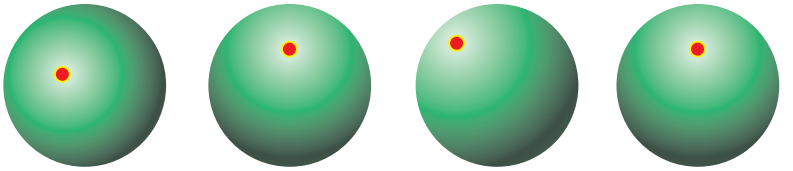
Surrounding lights reflect in eyes to form small white dots called specular highlights. The shape, color and location of these highlights tell us quite a bit about the lighting.

In 2006 a photo editor contacted me about a picture of *American Idol* stars that was scheduled for publication in his magazine (*above*). The specular highlights were quite different (*insets*).



The highlight position indicates where the light source is located (*above left*). As the direction to the light source (*yellow arrow*) moves from left to right, so do the specular highlights.

The highlights in the *American Idol* picture are so inconsistent that visual inspection is enough to infer the photograph has been doctored. Many cases, however, require a mathematical analysis. To determine light position precisely requires taking into account the shape of the eye and the relative orientation between the eye, camera and light. The orientation matters because eyes are not perfect spheres: the clear covering of the iris, or cornea, protrudes, which we model in software as a sphere whose center is offset from the center of the whites of the eye, or sclera (*above right*).



Our algorithm calculates the orientation of a person's eyes from the shape of the irises in the image. With this information and the position of the specular highlights, the program estimates the direction to the light. The image of the *American Idol* cast (*above; directions depicted by red dots on green spheres*) was very likely composed from at least three photographs. —***H.F.***

FOX NEWS (American Idol); LISA APFELBACHER (*eyes*); MELISSA THOMAS (*specular highlights*)

[DUPLICATION]

SEND IN THE CLONES

Cloning—the copying and pasting of a region of an image—is a very common and powerful form of manipulation.

COURTESY OF HANY FARID

This image is taken from a television ad used by George W. Bush's reelection campaign late in 2004. Finding cloned regions by a brute-force computer search, pixel by pixel, of all possible duplicated regions is impractical because they could be of any shape and located anywhere in the image. The number of comparisons to be made is astronomical, and innumerable tiny regions will be identical just by chance ("false positives"). My group has developed a more efficient technique that works with small blocks of pixels, typically about a six-by-six-pixel square (*inset*).

For every six-by-six block of pixels in the image, the algorithm computes a quantity that characterizes the colors of the 36 pixels in the block. It then uses that quantity to order all the blocks in a sequence that has identical and very similar blocks close together. Finally, the program looks for the identical blocks and tries to "grow" larger identical regions from them block by block. By dealing in blocks, the algorithm greatly reduces the number of false positives that must be examined and discarded.

When the algorithm is applied to the image from the political ad, it detects three identical regions (*red, blue* and *green*). —***H.F.***

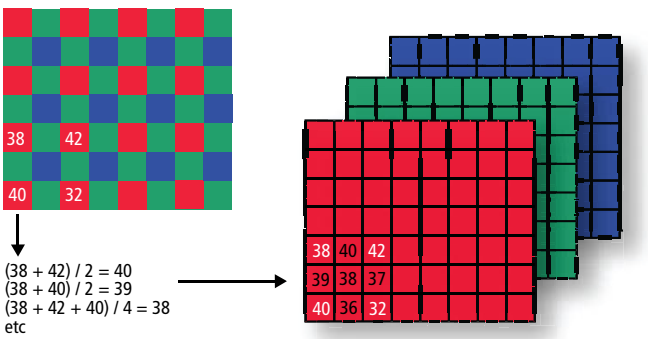
[RETOUCHING]

CAMERA FINGERPRINTS

Digital retouching rarely leaves behind a visual trace. Because retouching can take many forms, I wanted to develop an algorithm that would detect any modification of an image. The technique my group came up with depends on a feature of how virtually all digital cameras work.

A camera's digital sensors are laid out in a rectangular grid of pixels, but each pixel detects the intensity of light only in a band of wavelengths near one color, thanks to a color filter array (CFA) that sits on top of the digital sensor grid. The CFA used most often, the Bayer array, has red, green and blue filters arranged as shown at the right.

Each pixel in the raw data thus has only one color channel of the three required to specify a pixel of a standard digital image. The missing data are filled in—either by a processor in the camera itself or by software that interprets raw data from the camera—by interpolating from the nearby pixels, a procedure called demosaicing. The simplest approach is to take the average of neighboring values, but more sophisticated algorithms are also used to achieve better results. Whatever demosaicing algorithm is applied, the pixels in the final digital image will be correlated with their neighbors. If an image does not have the proper pixel correlations for the camera allegedly used to take the picture, the image has been retouched in some fashion.



RICK WILKING *Reuters (note)*; LISA APFELBACHER (*grids*)

My group's algorithm looks for these periodic correlations in a digital image and can detect deviations from them. If the correlations are absent in a small region, most likely some spot changes have been made there. The correlations may be completely absent if image-wide changes were made, such as resizing or heavy JPEG compression. This technique can detect changes such as those made by Reuters to an image it released from a meeting of the United Nations Security Council in 2005 (*left*): the contrast of the notepad was adjusted to improve its readability.

A drawback of the technique is that it can be applied usefully only to an allegedly original digital image; a scan of a printout, for instance, would have new correlations imposed courtesy of the scanner. —***H.F.***

ogy, as many as a fifth of the accepted manuscripts contained a figure that had to be remade because of inappropriate image manipulation.

The authenticity of images can have myriad legal implications, including cases involving alleged child pornography. In 2002 the U.S. Supreme Court ruled that computer-generated images depicting a fictitious minor are constitutionally protected, overturning parts of a 1996 law that had extended federal laws against child pornography to include such images. In a trial in Wapakoneta, Ohio, in 2006, the defense argued that if the state could not prove that images seized from the defendant's computer were real, then he was within his rights in possessing the images. I testified on behalf of the prosecutor in that case, educating the jurors about the power and limits of modern-day image-processing technology and introducing results from an analysis of the images using techniques to discriminate computer-generated images from real photographs. The defense's argument that the images were not real was unsuccessful.

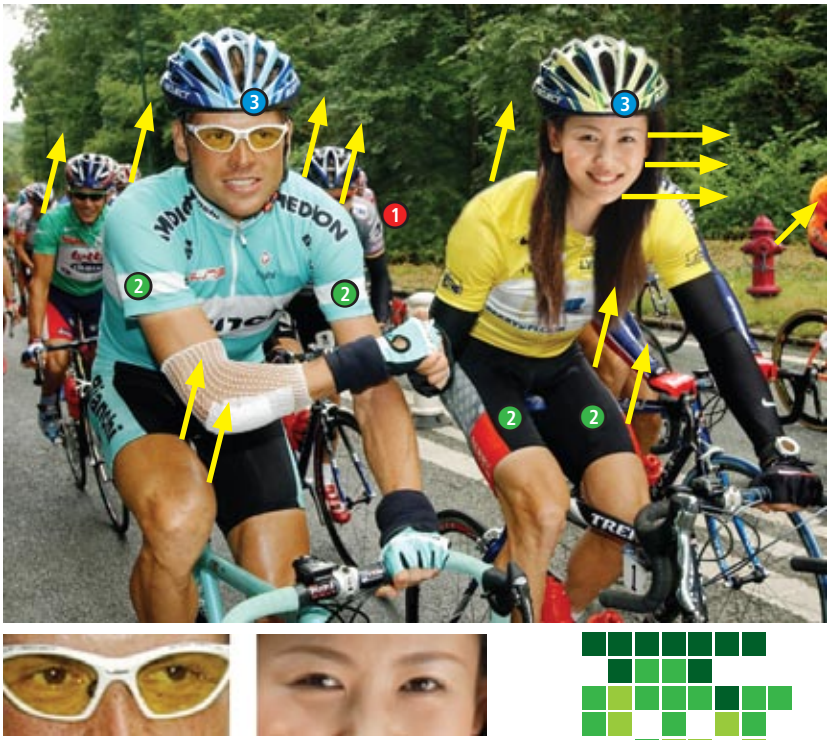
Yet several state and federal rulings have found that because computer-generated images are so sophisticated, juries should not be asked to determine which ones are real or virtual. At least one federal judge questioned the ability of even expert witnesses to make this determination. How then are we to ever trust digital photography when it is introduced as evidence in a court of law?

Arms Race

The methods of spotting fake images discussed in the boxes have the potential to restore some level of trust in photographs. But there is little doubt that as we continue to develop software to expose photographic frauds, forgers will work on finding ways to fool each algorithm and will have at their disposal ever more sophisticated image manipulation software produced for legitimate purposes. And although some of the forensic tools may be not so tough to fool—for instance, it would be easy to write a program to restore the proper pixel correlations expected in a raw image—others will be much harder to circumvent and will be well beyond the average user. The techniques described in the first three boxes exploit complex and subtle lighting and geometric properties of the image formation process that are challenging to correct using standard photo-editing software.

As with the spam/antispam and virus/antivirus game, not to mention criminal activity in general, an arms race between the perpetrator and the forensic analyst is inevitable. The field of image forensics will, however, continue to make it harder and more time-consuming (but never impossible) to create a forgery that cannot be detected.

Although the field of digital image forensics is still relatively young, scientific publishers, news outlets and the courts have begun to embrace the use of forensics to authenticate digital media. I expect that as the field progresses over the next five to 10 years, the application of image forensics will become as routine as the application of physical forensic analysis. It is my hope that this new technology, along with sensible policies and laws, will help us deal with the challenges of this exciting—yet sometimes baffling—digital age. ■



OPENER ANSWER: Inconsistent specular highlights (*bottom*) indicate the two leading cyclists were not photographed together. The light-source direction (*arrows*) for the girl's face conflicts with that of "her" body and the other cyclists. The added fire hydrant has yet another light-source direction. Cloned shrubs, grass and the curbside (1) cover cyclists in the background. Spoiled pixel correlations might reveal areas where retouching removed logos (2) and that the girl's helmet is doctored (3); it is copied from the man's but also has been recolored. The original photograph can be seen at www.SciAm.com/jun2008

MORE TO EXPLORE

Exposing Digital Forgeries in Color Filter Array Interpolated Images. Alin C. Popescu and Hany Farid in *IEEE Transactions on Signal Processing,* Vol. 53, No. 10, pages 3948–3959; October 2005. Available at **www.cs.dartmouth.edu/farid/publications/sp05a.html**

Detecting Photographic Composites of People. Micah K. Johnson and Hany Farid. Presented at the 6th International Workshop on Digital Watermarking, Guangzhou, China, 2007. Available at **www.cs.dartmouth.edu/farid/publications/iwdw07.html**

Lighting and Optical Tools for Image Forensics. Micah K. Johnson. Ph.D. dissertation, Dartmouth College, September 21, 2007. Available at **www.cs.dartmouth.edu/farid/publications/mkjthesis07.html**

Hany Farid's Web site: **www.cs.dartmouth.edu/farid**

What Is a Species?

To this day, scientists struggle with that question. A better definition can influence which animals make the endangered list

By Carl Zimmer

KEY CONCEPTS

- Formal taxonomic systems first identified species based on visual traits such as fins or fur. Later, the species concept changed, specifying that two organisms should be capable of breeding.
- Today biological diversity can be ascertained by sampling DNA and tracking how a species descended from a common ancestor.
- The debate over species definition is far from over and is more than a mere academic spat. Proper classification is essential for designating the endangered list.

—The Editors

If you visit Algonquin Provincial Park in Ontario, you may hear the high, lonesome howls of wolves. You may even be lucky enough to catch a glimpse of a distant pack racing through the forests. But when you show off your blurry pictures back home, what species should you boast that you saw? Depending on the scientist you ask, you may get a different answer. Some may even offer you a few different answers all at once.

In the 18th century European naturalists dubbed the wolves of Canada and the eastern U.S. *Canis lycaon*, because they seemed distinct from *Canis lupus*, the gray wolf of Europe and Asia. By the early 1900s North American naturalists had decided that they were actually gray wolves as well. But in the past few years Canadian researchers who have analyzed wolf DNA have come full circle. They argue that gray wolves only live in western North America. The wolves of Algonquin Provincial Park belong to a separate species, which they want to call *C. lycaon* once more.

Other wolf experts do not think there is enough evidence to split *C. lupus* into two species. And both sides agree that the identity of the Algonquin wolves has become far more murky thanks to interbreeding. Coyotes (another species in the genus *Canis*) have expanded east and begun to interbreed with *C. lycaon*. Now a sizable fraction of these eastern coyotes carry wolf DNA, and vice versa. Meanwhile *C. lycaon* has been interbreeding with gray wolves at the western border of its range. So the Algonquin ani-

JUSTINE COOPER; CANIS INSETS: W. PERRY CONWAY *Corbis (left)*; ALGONQUIN PARK MUSEUM *(center)*; RICHARD HAMILTON SMITH *Corbis (right)*

mals are not just mixing *C. lycaon* DNA with *C. lupus* DNA—they are passing on coyote DNA as well.

Even if *C. lycaon* was once a species, is it a species anymore? Many researchers find that the best way to think of a species is as a population whose members breed mostly among themselves, making the group genetically distinct from other species. When it comes to wolves and coyotes, it is hard to say quite where one species stops and another starts. "We like to call it *Canis* soup," says Bradley White of Trent University in Ontario.

The debate is about much more than naming rights. Wolves in the southeastern U.S. are considered a separate species, the red wolf (*Canis rufus*). This wolf has been the subject of an enormous project to save it from extinction, with a captive breeding effort and a program to reintroduce it to the wild. But the Canadian scientists argue that the red wolf is really just an isolated southern population of *C. lycaon*. If that is true, then the government has not in fact been saving a species from extinction. Thousands of animals belonging to the same species are still thriving in Canada.

As the case of the Algonquin wolves demonstrates, defining species can have a huge effect on whether an endangered group gets protected and whether a habitat is saved or lost. "In one sense, it's a very esoteric subject, but in another, it's a very practical issue," says Alan Templeton of Washington University in St. Louis, "even a legal issue."

▲ **WOLVES illustrate why species classification befuddles. *Canis lycaon* was a wolf species that roamed the woods of Ontario in the 18th century. Biologists reclassified the animals as *C. lupus* in the early 1900s before renaming them *C. lycaon* during the past few years. Some wolf experts now consider them a mix of several species, including coyotes (*C. latrans*) and gray wolves.**

FOLK WISDOM

Early folk classification systems still in use by the San and other indigenous peoples designate plants and animals based on observable features. Later methods, such as Linnaean taxonomy, often made similar categorizations.

An Embarrassment of Definitions

It may come as a surprise to see scientists struggling to agree on something so basic as how to decide that a group of organisms form a species. Perhaps it is the Latin that gives species names the whiff of absolute certainty and that has misled the public into thinking the rules are simple. Perhaps it is the 1.8 million species that scientists have named in the past few centuries. Perhaps it is laws like the Endangered Species Act, which take for granted that we know what species are. But in fact, the very concept of species has fueled debates for decades. "There is no general agreement among biologists on what species are," says Jonathon Marshall, a biologist at Southern Utah University. At last count, there were at least 26 published concepts in circulation.

What makes this disagreement all the more remarkable is that scientists now know vastly more about how life evolves into new forms than when the species debate first started. Not long ago taxonomists could only judge a new species based on what they could see—things like fins, fur and feathers. Today they can read DNA sequences, in which they are discovering a hidden wealth of biological diversity.

Templeton and other experts think that the debate may finally have reached a turning point. They believe it is now possible to combine many competing concepts into a single overarching one. The unification would apply to any kind of organism, from mockingbirds to microbes. And these researchers hope it will lead to powerful tools for recognizing new species.

Long before the dawn of science, humans were naming species. To be able to hunt animals and gather plants, people had to know what they were talking about. Taxonomy, the modern science of naming species, emerged in the 1600s and came into its own in the next century, thanks largely to the work of Swedish naturalist Carl Linnaeus. Linnaeus invented a system to sort living things into groups, inside which were smaller groups. Every member of a particular group shared certain key traits. Humans belonged to the mammal class, and within that class the primate order, and within that order the genus *Homo,* and within that genus the species *Homo sapiens*. Linnaeus declared that each species had existed since creation. "There are as many species as the Infinite Being produced diverse forms in the beginning," he wrote.

Linnaeus's new order made the work of taxonomists much easier, but trying to draw the lines between species often proved frustrating. Two species of mice might interbreed where their ranges overlapped, raising the question of what name to give to the hybrids. Within a species there was confusion as well. The willow ptarmigan in Ireland, for example, has a slightly different plumage than the willow ptarmigan in Scotland, which differs in turn from the one in Finland. Naturalists could not agree about whether they belonged to different ptarmigan species or were just varieties—subsets, in other words—of a single species.

Charles Darwin, for one, was amused by these struggles. "It is really laughable to see what different ideas are prominent in various naturalists' minds, when they speak of 'species,'" he wrote in 1856. "It all comes, I believe, from trying to define the indefinable." Species, Darwin argued, were not fixed since creation. They had evolved. Each group of organisms that we call a species starts out as a variety of an older species. Over time natural selection transforms them as they adapt to their environment. Meanwhile other varieties become extinct. An old variety ends up markedly different from all other organisms—what we see as a species in its own right. "I look at the term 'species' as one arbitrarily given, for the sake of convenience, to a set of individuals closely resembling each other," Darwin declared.

Like the taxonomists before him, Darwin could study species only with the naked eye, observing the color of a bird's feathers or counting the plates on a barnacle. It would not be until the early 20th century that scientists could start to examine the genetic differences among species. Their research led to a new way of thinking. What made a species a species were the barriers to reproducing with other species. Genes could flow among its members as they mated, but these individuals usually remained within the species, thanks to reproductive barriers. Species might spawn at different times of the year, they might find courtship songs of other species unattractive, or their DNA might simply be incompatible.

The best understood way for these barriers to evolve is through isolation. Some members of an existing species—a population—have to become unable to mate with the rest of their species. A glacier could thrust across their range, for example. The isolated population evolves new genes, and some of those new genes may make interbreeding difficult or impossible. Over hundreds of thousands of years so many barri-

At least 26 published concepts attempt to provide a definition of what a species is.

BEVERLY JOUBERT *National Geographic Image Collection*

ers evolve that the isolated population becomes a distinct species.

This understanding of how species evolve led to a new concept of what it meant to be a species. Ernst Mayr, a German ornithologist, boldly declared that species were not convenient labels but real entities, like mountains or people. In 1942 he defined a species as a gene pool, calling it a set of populations that can reproduce with one another and that are unable to mate successfully with other populations. The biological species concept, as it is now called, became the textbook standard.

Eventually many scientists grew dissatisfied with it, finding it too weak to help them make sense of the natural world. For one thing, Mayr's concept did not give any indication of how reproductively isolated a species had to be to qualify as a species. Biologists were left to puzzle over species that looked relatively distinct but interbred regularly. In Mexico, for example, scientists have recently discovered that two species of monkey that split off from a common ancestor three million years ago regularly interbreed. Do they have too much sex to qualify as two species?

Although some species seem to be having too much sex for the biological species concept, others seem to be not having enough. Sunflowers, for example, live in extremely isolated populations across North America. Genes flow rarely from one population to another. One could use Mayr's concept to treat them all as individual species.

Most difficult of all are species that have no sex whatsoever. Take a lineage of microscopic marine animals known as bdelloid rotifers. Most rotifers reproduce sexually, but bdelloid rotifers abandoned sex about 100 million years ago. All bdelloid rotifers are female, and they make embryos without any need for sperm. By the standards of the biological species concept, the rotifers went from being a species to being not a species, whatever that means.

A Sexless Equation

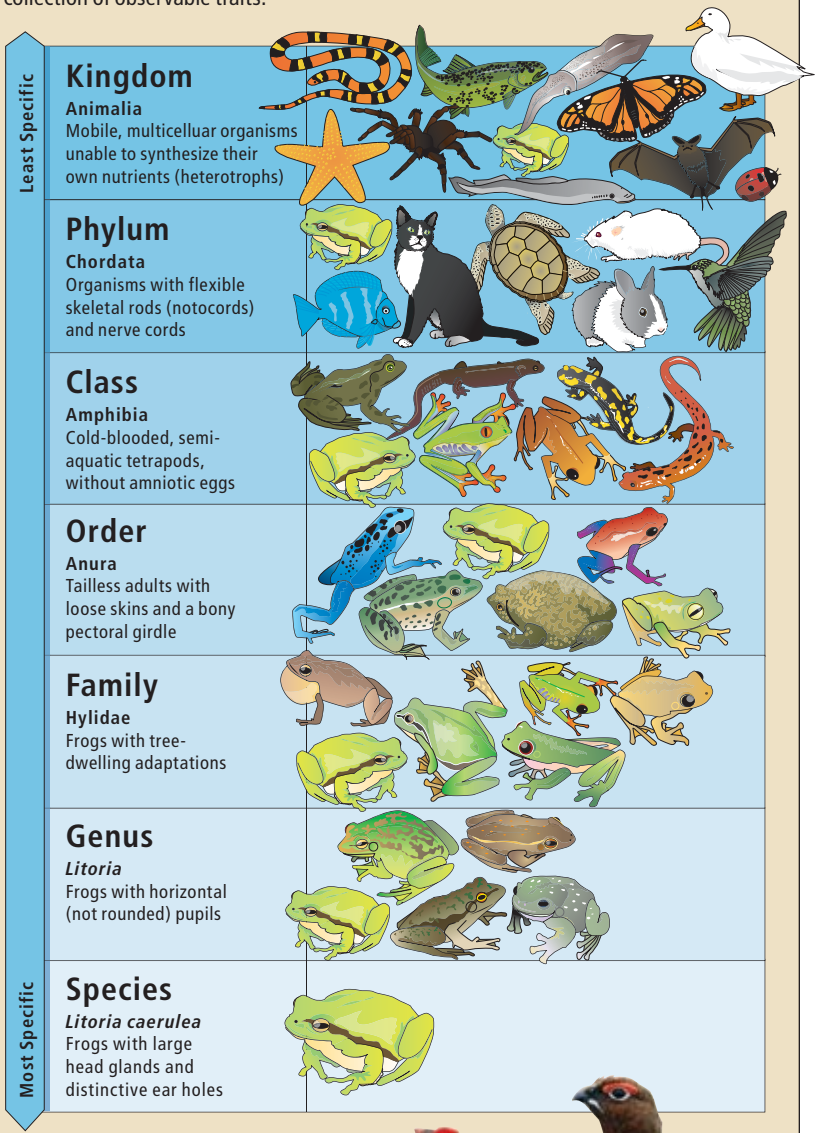
This kind of dissatisfaction led some scientists to devise new species concepts. Each concept was crafted to capture the essence of what it means to be a species. One of the strongest rivals to the biological species concept, called the phylogenetic species concept, takes sex out of the equation and puts descent from a common ancestor in its place.

Related organisms share traits because they share the same ancestry. Humans, giraffes and

[STANDARD TAXONOMY]

Linnaeus's Universe

Carl Linnaeus developed the basis for modern taxonomy in the 1700s, sorting all things biological into hierarchical groupings that range from the kingdom level (such as animals, plants, fungi) down to individual species, each having a unique collection of observable traits.



But . . .

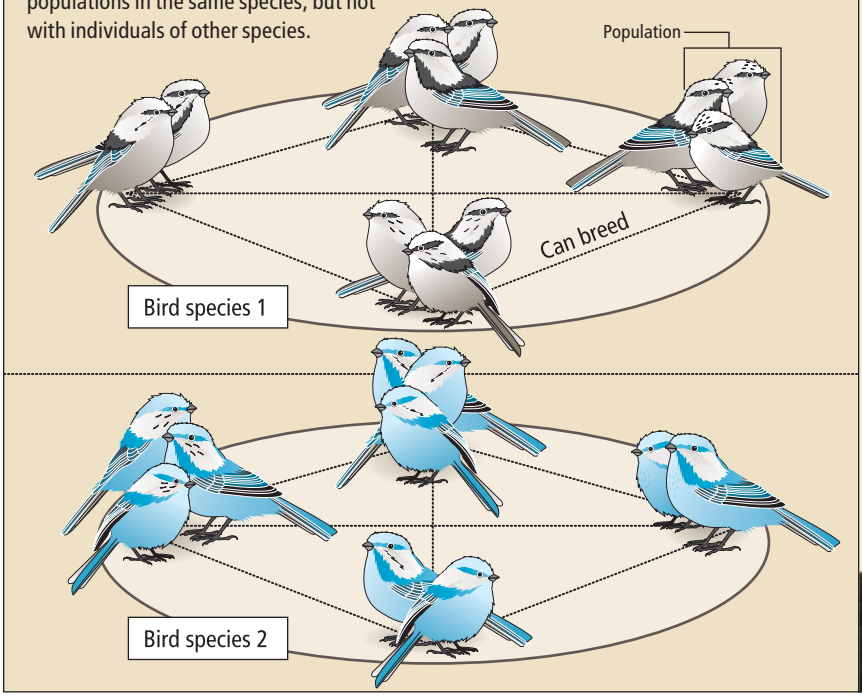
Naturalists often encounter difficulties distinguishing one species from another. The willow ptarmigan in Scotland has distinctive plumage from the one in Finland (*left*)—whether that difference justifies dividing the two creatures into separate species in the Linnaean system is unclear.

LUCY READING-IKKANDA (*illustrations*); CHRISTOPHE SIDAMON-PESSON/BIOSPHOTO *Peter Arnold, Inc. (Finnish willow ptarmigan)*; M. LANE *Peter Arnold, Inc. (Scottish willow ptarmigan)*

[BIOLOGICAL SPECIES CONCEPT]

Biology Is Destiny

Textbooks often define a species—the lowest ranking on the Linnaean hierarchy—as consisting of organisms sharing a cohesive gene pool. The members of a population, according to the biological species concept, can mate successfully with one another and with other populations in the same species, but not with individuals of other species.



But . . .

Some organisms—take the bdelloid rotifers—do not have sex. And two species of Mexican howler monkeys (*photographs*), which diverged from a common ancestor that lived three million years ago, can still mate with each other.

bats all descend from ancient mammals, and as a result they all have hair and milk. Within mammals, humans share a closer common ancestry with other primates. From the common primate ancestor, primates inherited other traits, such as forward-facing eyes. You can zoom in on smaller and smaller sets of organisms this way. Eventually, though, the zooming in comes to a stop. There are organisms that form groups that can no longer be split. These, according to the phylogenetic species concept, are species. In a sense, this concept takes Linnaeus's original system and updates it in light of evolution.

The phylogenetic species concept has been embraced by researchers who need to identify species rather than just contemplate them. Recognizing a species is a matter of finding a group of organisms that shares certain clear-cut traits. Scientists do not have to depend on slippery qualities like reproductive isolation. Recently, for example, the clouded leopards on the Indonesian island of Borneo were declared a species in their own right, distinct from the clouded leopards of southern Asia. All the Bornean clouded leopards shared certain traits not found in the cats on the mainland, including a distinctively dark coat.

Some critics think that there is far too much species splitting going on these days. "The problem with it is that it doesn't give you a natural level at which to stop," says Georgina Mace of Imperial College London. A single mutation might, at least theoretically, be enough to earn a small group of animals a species name. "It's a bit silly when you split them so far," she comments. Mace also argues that a population should be considered ecologically distinct—as defined by geography, climate and predator-prey relations—before someone decides to split it off as a new species.

But other researchers think that they should go where the data lead them rather than worrying about oversplitting. "That's the tail wagging the dog," says John Wiens, a biologist at Stony Brook University. "The argument that there's some sort of ceiling of how many species there should be doesn't seem very scientific."

Confusion over Substance

A few years ago the endless arguments of this kind convinced Kevin de Queiroz, a biologist at the Smithsonian Institution, that the species debate had gone too far. "It was just getting out of control," he says, "and I think a lot of people were just getting sick of it."

[THE AUTHOR]

Carl Zimmer writes frequently about evolution for the *New York Times*, *National Geographic* and other publications. He is the author of six books, including, most recently, *Microcosm: E. coli and the New Science of Life*. His blog, the Loom (www.scienceblogs.com/loom), is a winner of *Scientific American*'s Science and Technology Web Awards. Zimmer wrote about how natural selection may provide some of the tools that allow cancer cells to grow in the January 2007 issue of *Scientific American*.

LUCY READING-IKKANDA (*illustration*); BEN STECHSHULTE (*Zimmer*); THOMAS AND PAT LEESON *Photo Researchers, Inc.* (*A. pigra*); D. TIPLING *Peter Arnold, Inc.* (*A. palliata*)

De Queiroz stepped forward and declared that much of the debate did not deal with substance but rather with confusion. "The confusion is actually a pretty simple one," he says. Most of the competing species concepts actually agree on some basic things. They are all grounded in the notion that a species is a distinct, evolving lineage, for instance. For de Queiroz, that is the fundamental definition of a species. Most of the disagreements about species are not actually about its concept but are about how to recognize a species. De Queiroz thinks that different methods work best in different cases. Strong reproductive isolation is good evidence that a population of birds is a species, for example. But it is not the only yardstick that can be used. For bdelloid rotifers that do not have sex, scientists just have to use other kinds of criteria.

Many (but far from all) other experts on species share de Queiroz's optimism. Instead of trying to use just one gold standard, they are testing new species against several different lines of evidence. Jason Bond, a biologist at East Carolina University, and his student Amy Stockman took this approach in a survey of an enigmatic genus of spiders, *Promyrmekiaphila*, found in California. Taxonomists have long struggled to determine how many *Promyrmekiaphila* species there are. The spiders resist easy classification because they look almost identical. And yet scientists also have known that they probably form very isolated populations, thanks in large part to the fact that each spider is unlikely to move very far from home.

"Once a female digs a good burrow with a trapdoor and a silk lining, it's unlikely she's going to move," Bond says. He has dug up *Promyrmekiaphila* burrows containing three generations of female spiders that have lived there for years. Males will leave their birthplace burrows, but they will not move far before mating with a female from a neighboring burrow.

To identify the species of the spiders, Bond and Stockman adopted methods developed by Templeton. They studied the *Promyrmekiaphila* evolutionary history, measured gene flow between populations and characterized the spiders' ecological role. For the evolutionary history, Bond and Stockman sequenced parts of two genes from 222 spiders at 78 sites in California. They surveyed the DNA for genetic markers that showed how the spiders were related to one another. The evolutionary tree of the spiders turned out to be made up of a number of distinct lineages.

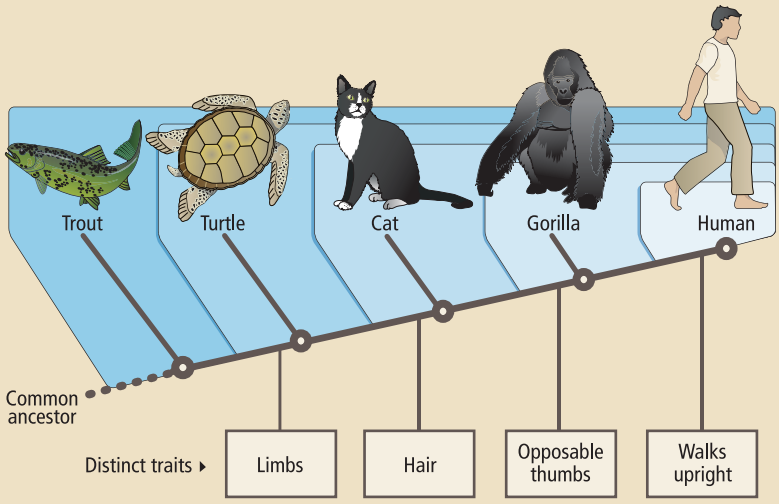
Bond and Stockman then looked for versions of genes in different populations to find evidence of gene flow. And finally, they recorded the climate conditions in which each group of spiders lived. In the end, they identified six species that met all three criteria. If accepted, these findings would double the number of *Promyrmekiaphila* species.

This kind of approach is allowing scientists to study organisms that once seemed not to fit

[PHYLOGENETIC SPECIES CONCEPT]

Linnaeus Updated

The phylogenetic species concept emerged from a new approach to classifying life, known as phylogenetic systematics. Unlike Linnaeus's system, it takes evolutionary history into account. Ignoring the issue of whether two populations can mate, it classifies an individual species as an organism that shares a common ancestor with other species but is set off from others by having acquired newer, distinctive traits. A phylogenetic tree, also known as a tree of life, shows how different species branch off from a common ancestor as they acquire traits the ancestor did not have. The tree below lists some of the traits that land animals and fish accumulated as they evolved.



But ...

Some critics assert that the phylogenetic approach tends to overcategorize. For instance, the clouded leopard on the island of Borneo was recently classified as a species because of a distinctively dark coat and other traits, but some argue that those features may not by themselves warrant grouping it as a separate species from other clouded leopards of southern Asia.

LUCY READING-IKKANDA (*illustration*); ALAIN COMPOST (*leopard*)

Two closely related species of bacteria might be more different than humans are from all other primates.

into species concepts. Because bdelloid rotifers do not have sex, they do not fit well under the biological species concept. Tim Barraclough of Imperial College London and his colleagues used other methods to determine whether the rotifers belong to specieslike groups. They sequenced the DNA and built an evolutionary tree. The tree had just a few long branches, each one topped by a tuft of short twigs. Then they examined the bodies of the rotifers on each tuft and found that they had similar shapes. The diversity of rotifers, in other words, is not just a blur. The animals form clusters, which are probably the result of separate lineages adapting to different ecological niches. If those clusters are not species, they are awfully close.

Where Microbes Fit In

Most of the work that has been done on the species concept in recent years has been directed at animals and plants. That bias is the result of history: animals and plants were the only things that Linnaeus and other early taxonomists could study. But today scientists know that the vast majority of genetic diversity lies in the invisible world of microbes. And microbes have long posed the biggest puzzle of all when it comes to the nature of species.

When microbiologists began naming species in the 1800s, they could not inspect feathers or flowers like zoologists and botanists can. Microorganisms—especially bacteria and archaea—generally look a lot like one another. Some are rod-shaped, for example, and some are tiny spheres. To distinguish two rod-shaped bacteria from each other, microbiologists would run experiments on their metabolism. One kind of microbe might be able to feed on, say, lactose, whereas the other could not. From clues of this sort, microbiologists described such species as *Escherichia coli* or *Vibrio cholerae*. Underlying their work, however, was no clear concept of what it meant for microbes to belong to a species. And when Mayr came up with his biological species concept, it seemed to exclude many microbes. After all, bacteria are not made up of males and females that have to reproduce sexually like animals. They can just split in two.

The confusion got worse when scientists began to analyze the DNA of microbes. They tried to figure out how different the DNA of two microbial species was, selecting small fragments for comparison. To their surprise, the differences could be huge. Two species of bacteria placed in the same genus based on their metabolism might be more different than humans are from all other primates. And the bacteria within a species could make their living in radically different ways. Some strains of *E. coli* live harmlessly in our gut, for example, whereas others can cause fatal diseases. "The genetic variation within a species is so enormous that the term 'species' does not really have the same meaning for bacteria and archaea" as it does for multicellular plants or animals, says Jonathan Eisen of the University of California, Davis.

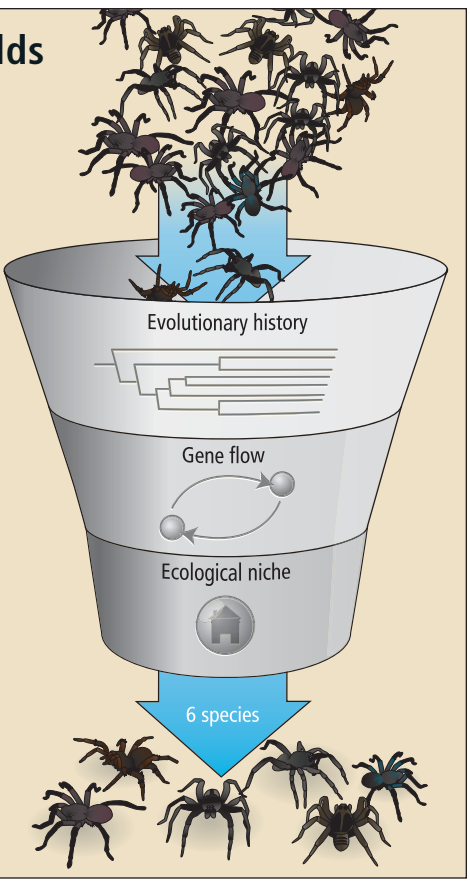
Microbes are not some minor exception to the rule that can be ignored. As investigators have surveyed the microbial world, they have discovered that the diversity of all animals is puny in comparison. "It's always struck me as rather odd that if Mayr is right, then 90 percent of the tree of life doesn't come in species," says John Wilkins, a philosopher of science at the University of Queensland in Australia. "That's got to give you some pause for thought."

Some researchers have argued that perhaps microbes fit the biological species concept, but in their own peculiar way. Bacteria do not mate like animals do, but they do trade genes. Viruses may carry genes from one host to another, or

[A UNIFIED APPROACH]

The Best of All Worlds

Because of the turmoil, some researchers have begun to create phylogenetic classifications by looking beyond evolutionary history and combining it with molecular, ecological, behavioral and biological data. As an example, Jason Bond and one of his students at East Carolina University studied a genus of spider, *Promyrmekiaphila* (*above*), found in California. They studied the spider's evolutionary history and ecological role and sequenced the genes of 222 spiders at 78 sites, using the full collection of information to group the animals into six species.



LUCY READING-IKKANDA (*illustration*); JASON BOND *East Carolina University (spider)*

bacteria may simply slurp up naked DNA, which then slips into their genome. There is some evidence that closely related strains trade more genes than distantly related ones—a microbial version of the barriers between animal species.

But critics have pointed to some problems with the analogy. Although animals and plants can trade genes every time they reproduce, microbes may do so very rarely. And when they do trade genes, they do so with amazing promiscuity. Over millions of years they can acquire many genes, not just from their close relatives but from other microbes that belong to entirely different kingdoms. It would be as if our own genome had hundreds of genes from centipedes, birch trees and truffles. Critics assert that this flow of genes helps to undermine any concept of species in microbes. "I think species are kind of an illusion," says W. Ford Doolittle of Dalhousie University in Nova Scotia.

Some researchers are taking microbial species more seriously. They contend that microbes, like rotifers, are not just a blur of variation but clusters adapted to particular ecological niches. Natural selection keeps their clusters from blurring by favoring new mutants that are even better adapted to their niche. "There's just one slim lineage moving forward," says Frederick Cohan of Wesleyan University. That slim lineage, he argues, is a species.

Cohan and his colleagues have found these microbial species in the hot springs of Yellowstone National Park. The microbes form genetic clusters and ecological clusters. Each genetically related group of microbes lives in a certain niche in the hot springs—enjoying a certain temperature, for example, or requiring a certain amount of sunlight. "It's pretty cool," Cohan says. For him, this evidence is enough to justify calling a group of microbes a species. He and his co-workers are now translating their experiments into a set of rules that they hope others will follow to name new species. "We've decided we have to go beyond nudging people," Cohan asserts.

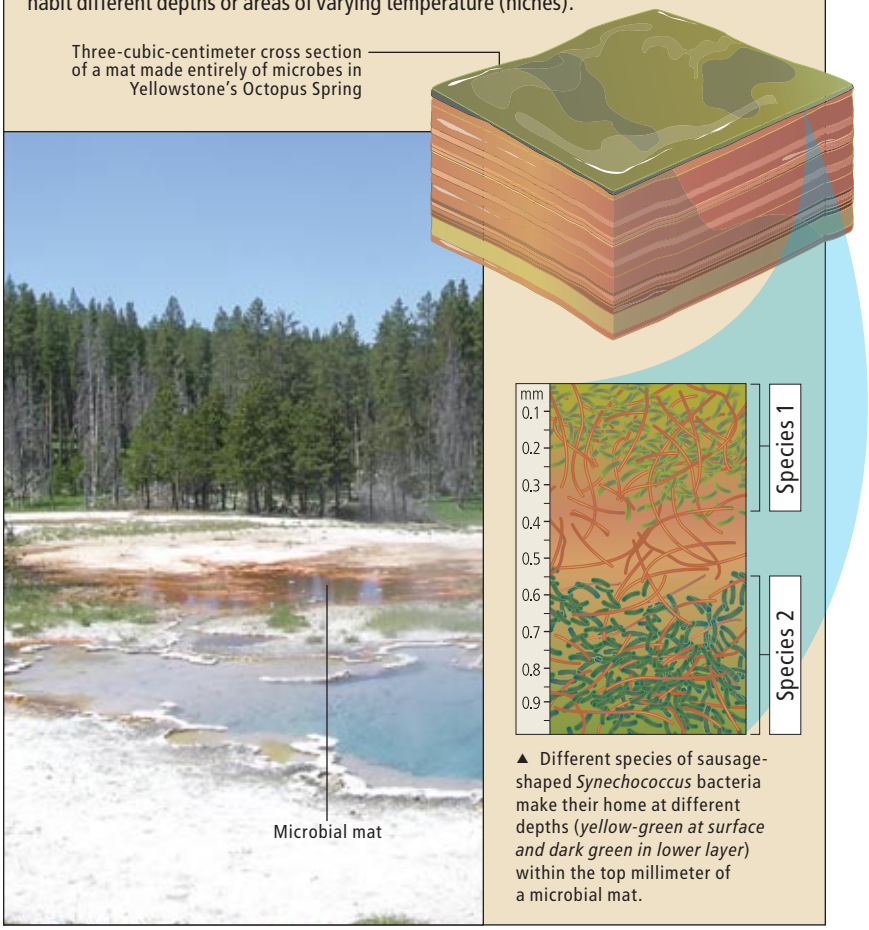
The rules will probably lead scientists to a division of a number of traditional microbial species into many new ones. To avoid confusion, Cohan does not want to come up with completely original names. Instead he wants to add an "ecovar" name at the end ("ecovar" stands for "ecological variant"). The bacterial strain that caused the first recorded outbreak of Legionnaires' disease in Philadelphia, for example, should be called *Legionella pneumophila* ecovar *Philadelphia*.

Understanding the nature of microbial species could help public health workers prepare for the emergence of other novel diseases in the future, Cohan says. Disease-causing bacteria often evolve from relatively harmless microbes that dwell quietly within their hosts. It may take decades of evolution before such organisms cause an epidemic large enough for public health workers to notice. Classifying these new species could let them anticipate outbreaks and give them time to prepare a response. Solving the mystery of species turns out not just to be important for understanding the history of life or preserving biodiversity—our own well-being may depend on it. ■

[BUGS ARE SPECIAL]

Do Microbes Belong to Different Species?

Biologists have always had difficulty grouping microbes into species. Bacteria do not engage in sex as we normally think of it. They just divide in two—and genetic differences between bacteria that purportedly belong to the same species based on similar outward appearance and behavior can be huge. Some researchers assert that bacteria can be classified as separate species by genetics and ecological niche. At a hot spring in Yellowstone National Park (*photograph*), different species of the cyanobacterium *Synechococcus* inhabit different depths or areas of varying temperature (niches).



▲ Different species of sausage-shaped *Synechococcus* bacteria make their home at different depths (*yellow-green at surface and dark green in lower layer*) within the top millimeter of a microbial mat.

LUCY READING-IKKANDA (*illustration*); DAVID M. WARD *Montana State University*

MORE TO EXPLORE

Evolution: The Triumph of an Idea. Carl Zimmer. HarperCollins, 2006.

What Evolution Is. Ernst Mayr. Basic Books, 2001.

Speciation. Jerry A. Coyne and H. Allen Orr. Sinauer Associates, 2004.

Understanding Evolution: Your One-Stop Source for Information on Evolution. A Web site created by the University of California Museum of Paleontology: **http://evolution.berkeley.edu/evolibrary/home.php**

THE TUNGUSKA MYSTERY

Finding a piece of the elusive cosmic body that devastated a Siberian forest a century ago could help save the earth in the centuries to come

By Luca Gasperini, Enrico Bonatti and Giuseppe Longo

JUNE 30, 1908, 7:14 A.M., central Siberia—Semen Semenov, a local farmer, saw "the sky split in two. Fire appeared high and wide over the forest.... From ... where the fire was, came strong heat.... Then the sky shut closed, and a strong thump sounded, and I was thrown a few yards.... After that such noise came, as if . . . cannons were firing, the earth shook ..."

Such is the harrowing testimony of one of the closest eyewitnesses to what scientists call the Tunguska event, the largest impact of a cosmic body to occur on the earth during modern human history. Semenov experienced a raging conflagration some 65 kilometers (40 miles) from ground zero, but the effects of the blast rippled out far into northern Europe and Central Asia as well. Some people saw massive, silvery clouds and brilliant, colored sunsets on the horizon, whereas others witnessed luminescent skies at night—Londoners, for instance, could plainly read newsprint at midnight without artificial lights. Geophysical observatories placed the source of the anomalous seismic and pressure waves they had recorded in a remote section of Siberia. The epicenter lay close to the river Podkamennaya Tunguska, an uninhabited area of swampy taiga forest that stays frozen for eight or nine months of the year.

JAMES PORTO

GIANT FIREBALL in the sky was the first indication that an unknown celestial object had exploded over Siberia. In this artist's conception, Semen Semenov, who witnessed the blast at a distant trading post, starts to feel the heat.

[THE AUTHORS]

Luca Gasperini, Enrico Bonatti and Giuseppe Longo have studied the Tunguska mystery for many years. Gasperini is a research scientist at the Institute of Marine Science in Bologna, Italy. Bonatti is professor of geodynamics at the University of Rome "La Sapienza" and special scientist at Columbia University's Lamont-Doherty Earth Observatory. Longo is professor of physics at the University of Bologna (www-th.bo.infn.it/tunguska).

Ever since the Tunguska event, scientists and lay enthusiasts alike have wondered what caused it. Although most observers generally accept that some kind of cosmic body, either an asteroid or a comet, exploded in the sky above Siberia, no one has yet found fragments of the object or any impact craters in the affected region. The mystery remains unsolved, but our research team, only the latest of a steady stream of investigators who have scoured the area, may be closing in on a discovery that will change our understanding of what happened that fateful morning.

The study of the Tunguska event is important because past collisions with extraterrestrial bodies have had major effects on the evolution of the earth. Some 4.4 billion years ago, for example, a Mars-size planetoid seems to have struck our young planet, throwing out enough debris to create our moon. And a large impact may have caused the extinction of the dinosaurs 65 million years ago. Even today cosmic impacts are evident. In July 1994 several astronomical observatories recorded the spectacular crash of a comet on Jupiter. And only last September, Peruvian villagers watched in awe and fright as a heavenly object streaked across the sky and landed not too far away with a loud boom, leaving a gaping pit 4.5 meters deep and 13 meters wide.

Using satellite observations of meteoric "flares" in the atmosphere ("shooting stars") and acoustical data that record cosmic impacts on the surface of the earth, Peter Brown and his co-workers at the University of Western Ontario and Los Alamos National Laboratory estimated the rate of smaller impacts. The researchers have also extrapolated their findings to larger but rarer incidents such as the Tunguska event. The average frequency of Tunguska-like asteroidal collisions ranges from one in 200 years to one in 1,000 years. Thus, it is not unlikely that a similar strike could occur during our lifetimes. Luckily, the Tunguska impact took place in an unpopulated corner of the globe. Should something like it explode above New York City, the entire metropolitan area would be razed. Understanding the Tunguska event could help us prepare for such an eventuality and maybe even take steps to avoid its occurrence altogether.

The first step in preparing ourselves would be to decide whether the cosmic object that affected Siberia was an asteroid or a comet. Although the consequences are roughly comparable in either case, an important difference is that objects in the solar system that circle far away from the sun on long-period orbits before returning, such as comets, would hit the earth at much greater velocities than close-orbiting (short-period) bodies, such as asteroids. A comet that is significantly smaller than an asteroid thus could release the same kinetic energy in such a collision. And observers have much more difficulty detecting long-period objects before they enter the inner solar system. In addition, the probability that such objects will cross the earth's orbit is low relative to the probability that asteroids will. For these reasons, confirmed comet impacts on the earth are so far unknown. Therefore, if the Tunguska event was in fact caused by a comet, it would be a unique occurrence rather than an important case study of a known class of phenomena. On the other hand, if an asteroid did explode in the Siberian skies that June morning, why has no one yet found fragments?

First Expedition

Part of the enduring mystery of the Tunguska event harks back to the stark physical isolation of central Siberia and the political turmoil that raged in Russia during the early 20th century, a time when the czarist empire fell and the Soviet Union emerged. These two factors delayed scientific field studies for nearly 20 years. Only in 1927 did an expedition led by Leonid Kulik, a meteorite specialist from the Russian Academy of Sciences, reach the Tunguska site. When Kulik got to the site, he was confronted with some

KEY CONCEPTS

- Exactly 100 years ago a comet or an asteroid exploded a few kilometers above the Tunguska region of central Siberia, leaving a huge zone of destruction.
- Despite many searches, no one has found any remnant of the impact body. Such evidence could help scientists gauge the danger posed today by medium-size comets or asteroids.
- A team of Italian scientists has found evidence of a possible impact crater about 10 kilometers from ground zero. They will soon return to recover what may be a fragment of the cosmic object.

—The Editors

[IMPACT ZONE]

The Tunguska Event

Many scientists believe that an asteroid or comet entered the earth's atmosphere over central Siberia (*map inset*) and exploded between five and 10 kilometers above the ground. The airburst flattened about 80 million trees over 2,000 square kilometers, which is about four times the area of Lake Tahoe. If the impactor was an asteroid, investigators estimate its diameter would have ranged from 50 to 80 meters. Searchers have so far found no remains of the object, which seems to have disintegrated.

FELLED FOREST

BLAST ZONE

GROUND ZERO

almost unbelievable scenery. Amazingly, the blast had flattened millions of trees in a broad, butterfly-shaped swath covering more than 2,000 square kilometers (775 square miles). Furthermore, the tree trunks had fallen in a radial pattern extending out for kilometers from a central area where "telegraph poles," a lone stand of partially burned tree stumps, still remained. Kulik interpreted this ravaged landscape as the aftermath of an impact of an iron meteorite. He then began to search for the resulting crater or meteorite fragments.

Kulik led three additional expeditions to the Tunguska region in the late 1920s and 1930s, and several others followed, but no one found clear-cut impact craters or pieces of whatever had hit the area. The dearth of evidence on-site gave rise to various explanatory hypotheses. In 1946, for instance, science-fiction writer Alexander Kazantsev explained the puzzling scene by positing a scenario in which an alien spacecraft had exploded in the atmosphere. Within a few years, the airburst theory gained scientific support and thereafter limited further speculation. Disintegration of a cosmic object in the atmosphere, between five and 10 kilometers above the surface, would explain most of the features investigators observed on the ground. Seismic observatory records, together with the dimensions of the devastation, allowed researchers to estimate the energy and altitude of the blast.

The lack of an impact crater also suggested that the object could not have been a sturdy iron meteorite but a more fragile object, such as a relatively rare, stony asteroid or a small comet. Russian scientists favored the latter hypothesis because a comet is composed of dust particles and ice, which would fail to produce an impact crater. Another explanation for the tumult in the Tunguska region claimed that the destruction resulted from the rapid combustion of methane gas released from the swampy ground into the air.

Laboratory Models

In 1975 Ari Ben-Menahem, a seismologist at the Weizmann Institute of Science in Rehovot, Israel, analyzed the seismic waves triggered by the Tunguska event and estimated that the energy released by the explosion was between 10 and 15 megatons in magnitude, the equivalent of 1,000 Hiroshima atomic bombs.

Astrophysicists have since created numerical simulations of the Tunguska event to try to decide among the competing hypotheses. The airburst of a stony asteroid is the leading interpretation. Models by Christopher F. Chyba, then at the NASA Ames Research Center, and his colleagues proposed in 1993 that the asteroid was a few tens of meters in diameter and that it exploded several kilometers above the ground. Comparison of the effects of nuclear test airbursts with the flattened pattern of the Tunguska forest seems to confirm this suggestion.

More recent simulations by N. A. Artemieva and V. V. Shuvalov, both at the Institute for Dynamics of Geospheres in Moscow, have envisioned an asteroid of similar size vaporizing five to 10 kilometers above Tunguska. In their model, the resulting fine debris and a downward-propagating gaseous jet then dispersed over wide areas in the atmosphere. These simulations do not, however, exclude the possibility that

MARY EVANS *Photo Researchers, Inc.* (*ground zero*); AP PHOTO (*felled forest*); KEVIN HAND (*map illustrations*)

meter-size fragments may have survived the explosion and could have struck the ground not far from the blast.

Late last year Mark Boslough and his team at Sandia National Laboratories concluded that the Tunguska event may have been precipitated by a much smaller object than earlier estimates had suggested. Their supercomputer simulation showed that the mass of the falling cosmic body turned into an expanding jet of high-temperature gas traveling at supersonic speeds. The model also indicated that the impactor was first compressed by the increasing resistance of the earth's atmosphere. As the descending body penetrated deeper, air resistance probably caused it to explode in an airburst with a strong flow of heated gas that was carried downward by its tremendous momentum. Because the fireball would have transported additional energy toward the surface, what scientists had thought to be an explosion between 10 and 20 megatons was more likely only three to five megatons, according to Boslough. All this simulation work only strengthened (and continues to strengthen) our desire to conduct fieldwork at the Tunguska site.

Trip to Siberia

Our involvement with the Tunguska event began in 1991, when one of us (Longo) took part in the first Italian expedition to the site, during which he searched for microparticles from the explosion that might have become trapped in tree resin. Later, we stumbled on two obscure papers by Russian scientists, V. A. Koshelev and K. P. Florensky, that reported their discovery of a small body of water, Lake Cheko, roughly eight kilometers from the suspected epicenter of the phenomenon. In 1960 Koshelev speculated that Lake Cheko might be an impact crater, but Florensky rejected that idea. Florensky instead believed the lake was older than the Tunguska event, based on having found loose sediments as thick as seven meters below the bottom of the lake.

Word that a lake sat close to ground zero piqued our interest in mounting a field trip there because lake-bottom sediments can store a detailed record of events that occurred in the surrounding region, the basis of paleolimnological studies. Although our team knew little of Lake Cheko, we thought that we could perhaps apply paleolimnological techniques and find in the lake's sediments clues to unravel the Tunguska mystery, as if the lake were the black box from a crashed airliner.

A few years later we found ourselves journeying to Russia in the cargo hold of an Ilyushin Il 20M propeller plane, a onetime aerial spy from the cold war era. Having found the necessary funds and having organized our venture in cooperation with research groups at Moscow State University and Tomsk State University in Russia (with the assistance of former cosmonaut Georgi M. Grechko), we were finally on our way to the Tunguska region. After the transport carried most of our Italian team and its equipment to a military base near Moscow, we flew overnight to Krasnojarsk, in central Siberia. We then transferred our equipment and ourselves, plus several researchers from Tomsk State, into the belly of a

SKY VIEW OF TUNGUSKA

If you have access to Google Earth or Microsoft Virtual Earth on your computer, you can view Lake Cheko (*above*), which may have been formed by the Tunguska event, at these map coordinates: 60° 57′ 50.40″ North, 100° 51′ 36.01″ East.

Find the Tunguska impact zone at coordinates 60° 54′ 59.98″ North, 101° 56′ 59.98″ East.

GIUSEPPE LONGO (*Lake Cheko*); KEVIN HAND (*impact illustrations*)

[HYPOTHETICAL SCENARIO]

Was Lake Cheko Created by the Tunguska Event?

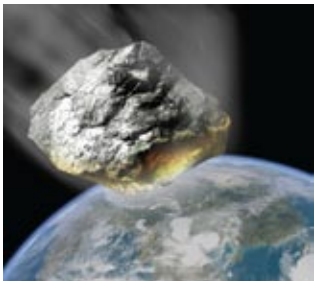
The authors speculate that debris from the posited Tunguska airburst hit the surface, forming Lake Cheko in the following series of events:

1. A meter-size fragment survived the explosion and streaked to the ground some eight kilometers from ground zero, close to the Kimchu River. The slight ellipticity of today's Lake Cheko and its location relative to the blast epicenter suggest that the fragment flew in at a 45-degree angle, hitting the land at a speed slower than one kilometer per second.

2. Energy generated by the fragment's impact melted the permafrost, and the subsequent release of gas and water enlarged the crater to the present size of Lake Cheko—about 350 by 500 meters.

3. Sediments laid down during the intervening years by the inflow of the Kimchu River formed a thin layer on the bottom of the lake.

TRACKING A DEATH STAR



Apophis is a 300-meter-long asteroid that scientists estimate to have a one-in-45,000 chance of hitting the earth in the year 2036. Although such an impact is unlikely, it could obliterate part of our planet, so the Planetary Society, a nonprofit space-advocacy group, wants to send a probe to observe the trajectory of Apophis. Such information should allow scientists to assess the threat it poses and, if needed, determine how best to alter its path. The society offered a $25,000 prize for the best design of a mission to track Apophis. SpaceWorks Engineering in Atlanta won the competition with a simple spacecraft concept dubbed Foresight, a $140-million probe that would orbit the asteroid and report back. The society hopes to find funds for Foresight.

huge Mi 26 heavy-lift helicopter (formerly used by the military). For six hours we squatted among our equipment, deafened by the chopper's twin turboshaft engines, until we finally reached our distant goal in the middle of the endless taiga.

After circling the lake's dark waters warily, the helicopter hovered precariously above the swampy lakeside (which was too soft for a landing) as we jumped down amid a torrential rainstorm. With eight blades rotating furiously above our heads, the resulting hurricane of air and water seemed set to sweep us away when at last we managed to unload our heavy cargo. With a roar, the craft lifted upward, and we were left drenched and exhausted near the edge of the lake, suddenly immersed in the deep silence of the Siberian wilderness. Any small relief we felt when the rain stopped was immediately forgotten as clouds of voracious mosquitoes descended on us like massed squadrons of tiny dive-bombers.

On-Site Studies

We spent the next two days organizing the camp, assembling our survey boat (a catamaran) and testing our equipment. Our studies would require a range of technologies, such as acoustic echo sounders, a magnetometer, subbottom acoustic profilers, a ground-penetrating radar, devices to recover sediment cores, an underwater television camera and a set of GPS receivers to enable study teams to track their position with a resolution of less than a meter.

For two weeks after that, our group surveyed the lake from the catamaran, tormented the entire time by hordes of mosquitoes and horseflies. These efforts focused on exploring the sedimentation and structure of the lake's subbottom. Other team members, in the meantime, busied themselves with their own tasks. With his ground-penetrating radar, Michele Pipan, a geophysicist at the University of Trieste, gradually mapped the subsurface structures (some three to four meters deep) below the 500-meter shore perimeter. Eugene Kolesnikov, a geochemist at Moscow State, and his colleagues excavated trenches in peat deposits near the lake, a tough job given the resistance of the hard permafrost layer below the surface. Kolesnikov's team searched the peat layers for chemical markers of the Tunguska event. At the same time, Romano Serra of Bologna University and Valery Nesvetailo of Tomsk State collected core samples from nearby tree trunks to study possible anomalies in the tree-ring patterns. Meanwhile, high above us, the aircraft that brought us to Krasnojarsk returned and circled the region to take aerial photographs so that we could compare them with those Kulik made some 60 years before.

We had assumed that the lake-bottom sediments might contain markers of the Tunguska event. After completing just a few runs across Lake Cheko with our high-resolution acoustic profiler, it became clear that the sediments blanketing the lake's bottom were more than 10 meters thick. Some sediment particles had been transported to the lake by winds, but most of them came by way of the inflow of the little Kimchu River that fed Lake Cheko. We estimated that sediment deposition in a small body of water that stays frozen for most of the year would probably not exceed a few centimeters a year, so such a thick sediment layer might imply that the lake existed before 1908.

On the other hand, the more we profiled the lake bottom, the more perplexed we became. It appeared that the lake, which is about 50 meters (165 feet) deep in the middle and has steep slopes, is shaped like a funnel or an inverted cone, a structure that is difficult to explain. If the lake were thousands of years old, it would probably have a flat bottom, the result of fine sediments gradually filling it up. We also found it hard to account for the funnel shape using typical erosion-deposition processes that occur when a small river meanders across a relatively flat landscape. Our entire team discussed these questions during the evenings as we sat under rain tarps, dining on delicious Russian kasha seasoned liberally with the bodies of dead mosquitoes.

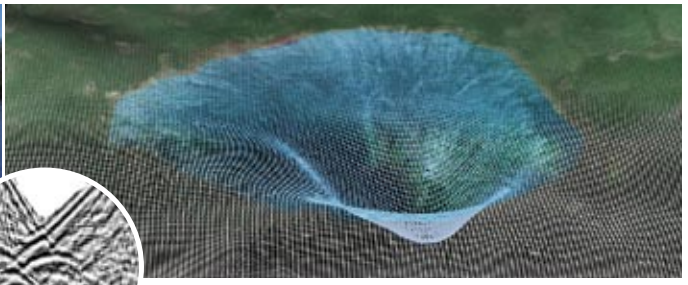
Soon our time in Tunguska was nearly over. The expedition members spent the last day frantically disassembling the boat, packing the equipment and dismantling the camp. When the helicopter arrived at noon the next day, we rushed to load all our stuff and ourselves into the hovering chopper amid the storm of human-made turbulence and finally began our return.

Titillating Evidence

Back in our laboratories in Italy, the three of us completed processing our bathymetric data, which confirmed that the shape of Lake Cheko's bottom differs significantly from those of other Siberian lakes, which typically feature flat bottoms. Most lakes in the region form when water fills the depressions left after the ubiquitous permafrost layer melts. The funnellike shape of Lake Cheko, in contrast, resembles those of known impact craters of similar size—for instance, the so-called Odessa crater, which was

KEVIN HAND

Lake Survey Turns Up Anomalies



After arriving at the Tunguska site, the authors surveyed Lake Cheko using acoustic-echo sounders that they installed on a catamaran (*photograph, left*). The data they obtained revealed that the profile of the lake bottom under its layer of sediment resembles the shape of an impact crater (*digital image, top*). The probe also located an acoustic-echo trace of a dense, meter-size object buried below the crater. The authors are returning this year to determine whether the object is a fragment of the body that exploded overhead in 1908.

created 25,000 years ago by the impact of a small asteroid in what is now Odessa, Tex.

The idea that Lake Cheko might fill an impact crater became more attractive to us. But if the lake is indeed a crater excavated by a fragment of the Tunguska cosmic body, it cannot have been formed earlier than 1908. We sought evidence that the little lake existed before the event. Reliable, pre-1908 maps of this uninhabited region of Siberia are not easy to come by, but we found a czarist military map from 1883 that fails to show the lake. Testimony by local Evenk natives also asserts that a lake was produced by the 1908 explosion. But if the lake was not formed before 1908, how can one explain the thickness of the deposits carpeting its floor? Our seismic-reflection data revealed two distinct zones in the lake's deposits: a thin, roughly meter-thick upper level of laminated, fine sediments typical of quiet deposition overlying a lower region of nonstratified, chaotic deposits.

A recent study by two Italian paleobotanists, Carla Alberta Accorsi of the University of Modena and Luisa Forlani of the University of Bologna, however, has shown that whereas the upper sediment layers contain abundant evidence of aquatic plants, these signs are totally absent in the lower chaotic deposits, which hold plentiful quantities of pollen from forest trees. So it looks as if the lake's true deposits are only about a meter thick, a feature that is compatible with a hypothesis that posits a young age for the lake. A forest seems to have grown on wet ground there before the lake formed.

Our survey team also observed the half-buried remains of tree trunks in the deeper part of the lake via underwater video. And high-frequency acoustic waves reflected back from the same zone showed a characteristic "hairy" pattern that could have resulted from the presence of the remains of trunks and branches. Perhaps these results are a trace of the forest obliterated by the impact.

Suspect Lake Shape

To explain the lower chaotic deposits, we can imagine a cosmic body hitting soggy ground overlying a layer of permafrost several tens of meters thick. The impactor's kinetic energy is transformed into heat, which melts the permafrost, releasing methane and water vapor and expanding the size of the resulting crater by as much as a quarter. At the same time, the impact would have plastered preexisting river and swamp deposits onto the flanks of the impact crater, where they would later be imaged as the chaotic deposits in our acoustic-echo profiles.

Most intriguing, a careful analysis of the seismic-reflection profiles we obtained across the lake has revealed several meters below the deepest point at the center a strong acoustic reflector, probably the echo of a dense, meter-size rocky object. This result is supported by the finding of a small magnetic anomaly above the same spot during our magnetometer survey. Are these indications of a fragment of the Tunguska body?

We are anxious to find out. Our team is now preparing to return later this year to attempt to drill the center of the lake to reach the dense seismic reflector. The year 2008 is the centennial of the Tunguska event. We hope it will also be the year the Tunguska mystery is solved. ■

MORE TO EXPLORE

The 1908 Tunguska Explosion: Atmospheric Disruption of a Stony Asteroid. C. F. Chyba, P. J. Thomas and K. J. Zahnle in *Nature,* Vol. 361, pages 40–44; January 7, 1993.

A Possible Impact Crater for the 1908 Tunguska Event. Luca Gasperini, F. Alvisi, G. Biasini, Enrico Bonatti, Giuseppe Longo, M. Pipan, M. Ravaioli and R. Serra in *Terra Nova,* Vol. 19, No. 4, pages 245–251; August 2007. **www.blackwell-synergy.com/doi/pdf/10.1111/j.1365-3121.2007.00742.x**

The Tunguska Event. Giuseppe Longo in *Comet/Asteroid Impacts and Human Society: An Interdisciplinary Approach.* Edited by Peter T. Bobrowsky and Hans Rickman. Springer-Verlag, 2007.

Lake Cheko and the Tunguska Event: Impact or Non-Impact? Luca Gasperini, Enrico Bonatti and Giuseppe Longo in *Terra Nova,* Vol. 20, No. 2, pages 169–172; 2008. **www.blackwell-synergy.com/doi/pdf/10.1111/j.1365-3121.2008.00792.x**

GIUSEPPE LONGO (*boat with equipment*); SOURCE: "A POSSIBLE IMPACT CRATER FOR THE 1908 TUNGUSKA EVENT," BY L. GASPERINI ET AL., IN *TERRA NOVA*, AUGUST 2007 (*acoustic-echo trace*); KEVIN HAND (*wire frame illustration*)

Our inclination to trust a stranger stems in large part from exposure to a small molecule known for an entirely different task: inducing labor

The Neurobiology of Trust

By Paul J. Zak

KEY CONCEPTS

- The development of trust is essential for appropriate social interactions, so how do people decide whether to trust a new acquaintance or potential business partner?
- Using an experimental task called the trust game, researchers have found that oxytocin, a hormone and neurochemical, enhances an individual's propensity to trust a stranger when that person exhibits non-threatening signals.
- Greater understanding of oxytocin's functions and interactions with other key brain chemicals could lead to insights into many disorders marked by impaired social interactions, such as autism.

—The Editors

If you were asked to fall backward into the arms of a stranger, would you trust the other person to catch you? Such a situation, a common exercise in group therapy, is a bit extreme. But every day most people place some degree of trust in individuals they do not know. Unlike other mammals, we humans tend to spend a great deal of time around others who are unfamiliar. Those who live in cities, for instance, regularly navigate through a sea of strangers, deciding to avoid certain individuals but feeling secure that others will, say, give accurate directions to some destination or will, at the very least, refrain from attacking them.

In the past several years, researchers have begun to uncover how the human brain determines when to trust someone. And my colleagues and I have demonstrated that an ancient and simple molecule made in the brain—oxytocin (ox-ee-TOE-sin)—plays a major role in that process. The findings are suggesting new avenues for discovering the causes and treatments of disorders marked by dysfunctions in social interactions.

Searching for Trust

I came to the study of oxytocin's relation to trust via a somewhat circuitous route. In 1998 Stephen Knack, an economist in the World Bank's Development Research Group, and I began trying to find out why trust among people varies dramatically across different countries. As part of this effort, we constructed a mathematical model that described the kinds of social, legal and economic environments that might be expected to produce high and low levels of trust. In the course of the study, we discovered that trust is among the strongest known predictors of a country's wealth; nations with low levels tend to be poor. Our model showed that societies with low levels are poor because the inhabitants undertake too few of the long-term investments that create jobs and raise incomes. Such investments depend on mutual trust that both sides will fulfill their contractual obligations.

As I thought about the importance of trust in alleviating poverty, I began to wonder how two people decide whether to place faith in each other. Having that information could help policymakers design economic systems that facilitate this process. Laboratory studies had demonstrated that those in the same situation can vary widely in their propensity to trust another individual, but no one had described a coherent mechanism for what goes on in the human brain

TRUSTING STRANGERS can be hard, such as in a group therapy exercise that has a person fall backward into another's arms. Luckily for the smooth running of society, a neurochemical called oxytocin primes people to trust others.

to instill trust. I therefore set about trying to uncover the neural underpinnings of such feelings.

A large body of animal research pointed to oxytocin as a likely contributing factor. This short protein, or peptide, which is composed of just nine amino acids, was known to be produced in the brain, where it serves as a signaling molecule—a neurotransmitter. It also slips into the bloodstream to influence distant tissues, making it a hormone as well. At the time, this peptide was best known in humans for its role in stimulating milk flow in nursing women and in inducing labor; even today about half of women who give birth in the U.S. receive synthetic oxytocin (called pitocin) to hasten uterine contractions. But documenting the peptide's more subtle effects was difficult because its concentrations in the blood are extremely low and it degrades rapidly. The animal work, though, indicated that oxytocin in some way facilitates cooperation—which requires trust—in certain mammals and that a close relative, vasotocin, apparently promotes friendly interactions in other creatures as well.

According to evolutionary biologists, vasotocin appeared first in fish about 100 million years ago. In those animals, it facilitates sexual reproduction by reducing a female's natural fear of being approached by a male when she is ovulating. Biologists conjecture that a mechanism for reducing fear during ovulation evolved because the benefits of sex—offspring and greater genetic diversity—outweigh the danger of becoming the other fish's lunch.

In mammals, vasotocin evolved into two closely related peptides, oxytocin and arginine vasopressin. Research on rodents that began in the late 1970s showed that these molecules, too, promoted affiliation with others. Cort A. Pedersen and his co-workers at the University of North Carolina at Chapel Hill, for instance, demonstrated that oxytocin prompted nurturing behavior in rodent mothers.

Shortly afterward zoologists C. Sue Carter and Lowell L. Getz, both then at the University of Illinois at Urbana-Champaign, examined oxytocin in two genetically and geographically related species of voles: prairie voles and montane voles [see "Monogamy and the Prairie Vole," by C. Sue Carter and Lowell L. Getz; SCIENTIFIC AMERICAN, June 1993]. Male prairie voles are upstanding citizens: they typically cohabitate with their mates for life, live in social groups and are attentive fathers. Male montane voles, in con-

[THE AUTHOR]

Paul J. Zak is professor of economics at and founding director of the Center for Neuroeconomics Studies at Claremont Graduate University. Zak also serves as clinical professor of neurology at Loma Linda University Medical Center. He has a Ph.D. in economics from the University of Pennsylvania and postdoctoral training in neuroimaging from Harvard University. His new book, *Moral Markets: The Critical Role of Values in the Economy,* was published by Princeton University Press this year.

COURTESY OF CENTER FOR NEUROECONOMICS, CLAREMONT GRADUATE UNIVERSITY (*Zak*); MARK ANDERSEN *Getty Images* (*woman*); RYAN McVAY *Getty Images* (*man*)

trast, are cads: they are promiscuous, solitary and indifferent to their offspring. Carter and Getz, as well as several subsequent researchers, showed that the difference between the social behaviors in these vole species could be ascribed to the locations in their brain of receptors for oxytocin and arginine vasopressin. To have an effect on brain cells, molecules first have to bind to specific receptors on the neurons' surface. In prairie voles those receptors are concentrated in brain regions that make monogamy rewarding—in midbrain areas that modulate release of the neurotransmitter dopamine, which reinforces the value to the male of cohabitation and care of offspring.

The Trust Game

Although the animal research did not address the issue of trust formation specifically, the importance of oxytocin in drawing animals together implied to me that it might also underlie trust, presumably a necessary condition for closeness. Around the same time, scientists had found ways to reliably and readily measure small changes in oxytocin levels in blood samples.

My reading of the rodent literature suggested that nonthreatening social signals induced oxytocin production in the brain of signal recipients, and I wondered if, in humans, the approach of strangers who gave positive signals might stimulate release of the peptide in others. My colleagues—Robert Kurzban, a psychologist now at the University of Pennsylvania, and William Matzner, then my graduate student at Claremont Graduate University—and I therefore set out to test that idea and to see if oxytocin production would be affected by, and affect, social behaviors in humans.

We still, however, had to figure out how we might measure the degree of trust between unacquainted people. The rodent researchers could simply drop a strange individual into another's cage to test whether nonthreatening behavior could promote the release of oxytocin, but humans' ability to evaluate potential social situations is far too sophisticated for a similar experimental design. People's reactions can be swayed by many other factors, including physical looks, clothing, and so forth. Luckily, experimental economists Joyce Berg of the University of Iowa and John Dickhaut and Kevin McCabe, both then at the University of Minnesota, had already devised a task in the mid-1990s that would do the trick. In this task, test subjects can signal that they trust a stranger by sacrificing their own money and transferring it to the stranger. They send money to a stranger because they believe the stranger will reciprocate and return more money back to them. The researchers called it the "trust game."

In my lab, the trust game runs as follows: my staff recruits subjects who earn $10 if they agree to spend an hour and a half with us [*see box above*]. We assign the participants randomly into pairs in which the two do not see or communicate directly with each other. Then we have them make decisions about sharing their money with the partner. In each pair, one person is designated subject 1 and the other subject 2. At the start we describe to both individuals how the game works. First subject 1 is prompted by a computer to decide whether to send some of the $10 participation payment to the other person. The amount given is tripled in an account for subject 2. If subject 1 decides to part with $6, for instance, subject 2 will end up with $28 (three times $6 plus $10), and subject 1 will be left with $4.

In the next step, the computer informs subject 2 of the money transfer and allows that person to return some amount of money to subject 1, with the proviso that none need be sent back and the assurance that the participants' identities

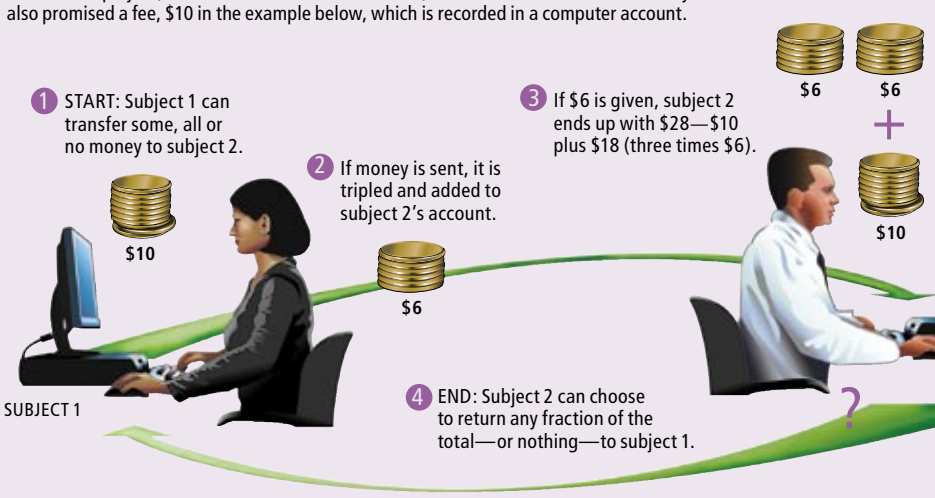
[OXYTOCIN EXPERIMENTS]

PLAYING THE TRUST GAME

To study the role of oxytocin in trust, the author and his colleagues had subjects play what is called the trust game. The team found that receiving a signal of trust led to a rise in oxytocin in the blood (an

THE BASIC GAME

SETUP: Two players, who have no face-to-face contact, are told the rules in advance. They are also promised a fee, $10 in the example below, which is recorded in a computer account.



ANALYSIS: If subject 1 sends money and subject 2 returns enough of the proceeds, both profit. If subject 2 betrays subject 1 and is stingy, subject 1 can lose money. Subject 1's trust is assessed by the amount transferred to subject 2. Trustworthy behavior by subject 2 is measured by the amount returned.

FAST FACTS

- Levels of oxytocin have been shown to spike in men and women during sexual climax. Its presumed role in postcoital affection has earned it the nickname the "cuddle hormone."
- Oxytocin was first isolated and synthesized in 1953 by Vincent du Vigneaud of Weill Cornell Medical College in New York City. He was awarded the Nobel Prize in Chemistry two years later in recognition of this achievement.
- Until recently, oxytocin levels in the blood were difficult to study because the substance is present in extraordinarily low concentrations and degrades to half its original quantity in only three minutes.

PHOTOGRAPH BY PAUL J. ZAK; ILLUSTRATION BY LOGAN PARSONS

indication of greater production by the brain). Further, oxytocin caused an increase both in trust and in trustworthy behavior.

FINDINGS

An oxytocin rise boosts trust:

- After inhaling an oxytocin nasal spray, subject 1s sent 17 percent more money than control subjects who took a placebo did.
- Twice as many subject 1s (almost half the total) who received oxytocin gave all their cash to their partners.

Oxytocin increases trustworthiness:

- Subject 2s showing the highest oxytocin blood levels returned the most money to their partners.

Flaws in the brain's ability to respond to oxytocin might contribute to social disorders:

- A few subject 2s with unusually high oxytocin levels returned nothing. This observation could be explained by a disturbance in the brain's oxytocin system that could suggest pathology.

and decisions will remain confidential. Whatever money subject 2 returns is debited from subject 2's account on a one-to-one basis (that is, the sum is not tripled). No deception is permitted—payments are actually made based on these choices. Immediately after the participants make their decisions, we ask them to provide blood samples so we can measure oxytocin levels.

Interpreting the Game

The consensus view among experimental economists is that the initial transfer measures trust, whereas the return transfer gauges trustworthiness. Researchers have run this trust game numerous times in many countries and for large stakes.

In our experiments, about 85 percent of those in the subject 1 role sent some money to their partners. Of the partners who received the money, 98 percent then went on to return some money to subject 1s. Interestingly, people typically could not articulate why they were trusting or trustworthy. But based on the rodent work, I suspected that being trusted by subject 1s would induce an oxytocin rise and that those who received greater sums from subject 1s would experience the greatest increases.

Indeed, we found that subject 2s' brains produced the peptide when they received money from their partners and thus felt trusted by those strangers. In addition, when people were shown greater trust in the form of more money, their brains released more oxytocin. To be sure that sense of being trusted accounted for the oxytocin rises, we observed a control group of participants who received monetary transfers that clearly occurred at random, not because someone decided to place faith in their reciprocity. Such a control was important to rule out whether money itself caused the oxytocin release—it did not.

We also found that subject 2s with high levels of oxytocin were more trustworthy—that is, they sent more money back to subject 1s who had trusted them. Receiving a signal of trust appears to make people feel positive about strangers who have trusted them.

A possible evolutionary explanation for the strong release of oxytocin in the experimental setting is that humans have a long adolescence and that natural selection favored people who could bond strongly with others over a long time—until youngsters grew up and were able to manage on their own. Our closest genetic relatives, chimpanzees, become sexually mature in seven or eight years, whereas humans may take roughly twice as long and, to thrive, must continue to be looked after by (and remain attached to) their parents throughout that period. An ancillary effect of extended care for the young could be that humans have a powerful propensity for attachment and thus also strongly attach to nonkin who become friends, neighbors or spouses. If that surmise is correct, it is no surprise that humans also bond to pets, places and even their cars.

Boosting Trust Artificially

Our research with the trust game showed that oxytocin release occurred only in subject 2s—those who had received a trust signal. Also, people in the subject 1 role who started the experiment with higher oxytocin levels were not more likely to trust others (to give subject 2s more money). This observation might seem contradictory at first blush, but it is consistent with the animal studies, which showed that oxytocin release happens only when individuals have had social contact with others. It is the rise in oxytocin levels, not the absolute level, that seems to make the difference. One can therefore think of positive social signals and interactions as the flipping of a switch to an "on" state: when the switch goes on, the human brain says, "This person has shown that

OXYTOCIN AND GENEROSITY

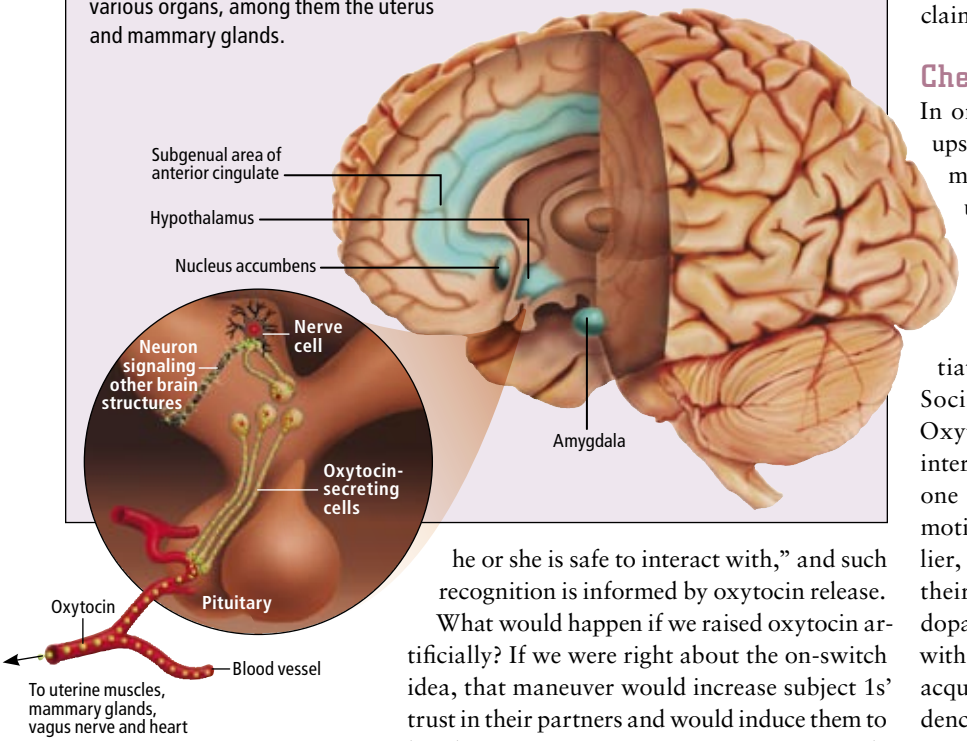
Imagine being asked to split a $10 stake with a stranger. If the stranger accepts your offer, you are both paid, but if your offer is rejected, you both get nothing. What would you offer? And if you received an offer, what is the smallest amount that you would accept?

This game can be used to measure generosity—defined as offering someone more than he or she needs. A study conducted at the author's laboratory recently showed that those who inhaled a dose of oxytocin made offers that were 80 percent higher than those given a placebo. Moreover, subjects who received oxytocin did not demand more money than was offered. These results suggest that oxytocin amplifies our empathy for others and motivates a desire to help them.

[BASIC NEUROBIOLOGY]

OXYTOCIN AND THE BRAIN

Several brain structures (*highlighted in green*) are involved in the release and response to oxytocin. These structures share three features: they have dense fields of oxytocin receptors, which convey oxytocin's "messages" to nerve cells; they control emotions and social behavior; and they modulate midbrain dopamine release, which makes people feel good and so rewards and reinforces specific behaviors. Although the trust-related effects of oxytocin stem from its activity in the brain, the chemical acts elsewhere as well. Some brain cells secrete it into the bloodstream (*detail at bottom left*) to influence various organs, among them the uterus and mammary glands.



he or she is safe to interact with," and such recognition is informed by oxytocin release.

What would happen if we raised oxytocin artificially? If we were right about the on-switch idea, that maneuver would increase subject 1s' trust in their partners and would induce them to hand over more money to strangers. To study this issue, a research team from the University of Zurich headed by economist Ernst Fehr and me had about 200 male investors breathe in a dose of oxytocin formulated as a nasal spray (enabling the drug to reach the brain) and compared their behavior with that of control subjects who inhaled a placebo. We found that those who received oxytocin gave 17 percent more money to their partner. More tellingly, twice as many dosed subject 1s (nearly one half of them) as controls exhibited maximal trust: they transferred all their money. This experiment shows that a rise in oxytocin in the brain reduces our natural (and wholly appropriate) anxiety over interacting with a stranger. It should be noted, though, that some participants who were given oxytocin did not exhibit a high degree of trust. Apparently, for some, a rise in oxytocin is not enough by itself to overcome worry over strangers.

Let me be clear that our experiment had nothing to do with manipulating people's minds to empty their wallets, because it certainly did not turn subjects into will-less automatons. Nor did it offer the possibility that salespeople or politicians could spritz oxytocin into the air or spike people's food or drink to force others to trust them. Oxytocin breaks down in the gut, so oral administration has no effect on the brain. Further, intravenous or nasal delivery is easy to notice, and sniffing it from the air would not raise brain levels appreciably. (Do not be fooled by claims of companies selling "trust in a bottle.")

Chemistry of Distrust

In one experiment, a female subject became upset when she received only a small amount of money from her partner. Her reaction started us thinking about what happens when people are distrusted. Many important systems in the brain are controlled by opposing forces. Eating, for example, is largely driven by hormones that signal when to initiate, and then when to terminate, feeding. Social behaviors may have similar controls. Oxytocin constitutes a positive side of personal interactions; it literally feels good when someone seems to trust you, and this recognition motivates you to reciprocate. As discussed earlier, to induce mammal mothers to attend to their offspring oxytocin causes the release of dopamine in deep midbrain regions associated with rewarding behaviors such as sex and food acquisition. In follow-up research, we found evidence of an opposing, or negative, side to the trust-forming mechanism, at least in males.

When male subject 2s are distrusted (sent little money by a subject 1), they experience a rise in a derivative of testosterone called dihydrotestosterone (DHT). The more distrust men were shown in the game, the higher was their DHT level. This molecule can be thought of as high-octane testosterone; it is primarily DHT that causes the dramatic changes such as body-hair growth, increased muscularity and vocal-cord thickening that hit males during puberty. Elevated levels also boost the desire for physical confrontation in trying social circumstances. Our finding indicates that men have an aggressive response to being distrusted.

Females and males reported equally that they disliked being distrusted, but women did not display the "hot" physiological response of the men. Most male subject 2s who were distrusted returned nothing to their partners, whereas most women were proportional reciprocators across the board; they tended to return about an equal fraction of what they were sent no matter

LOGAN PARSONS

how much money was involved. We think of women as "cooler" responders, although we do not yet fully know the physiological underpinnings for this difference. The possibility of an aggressive response to a signal of distrust may make us more trusting of others. If we know that showing distrust provokes aggression, we may display more trust than we might otherwise to avoid this response.

Measuring brain activity during the trust game using functional magnetic resonance imaging techniques has indicated that trusting a stranger produces strong activity in deep midbrain regions where dopamine binds and contributes to our sense of reward. This result helps to explain why subject 2s who received money usually felt inclined to return some of it to subject 1s even though doing so was economically disadvantageous. The positive feelings subject 2s experienced when reciprocating trust appear to have psychically rewarded them and reinforced a desire to be trustworthy in the future.

Although most people can be deemed trustworthy, 2 percent of subject 2s in our studies were particularly untrustworthy—they kept all or nearly all the money they were sent—and, significantly, they exhibited unusually high levels of oxytocin. This result suggests that these individuals have oxytocin receptors in the wrong brain regions (for instance, those that do not modulate dopamine release) or have dysregulated receptors. In the latter case, the neurons would essentially be deaf to oxytocin release, regardless of how much was made. Tellingly, the highly untrustworthy possess personality traits that resemble those of sociopaths, who are indifferent to or even stimulated by another's suffering.

Future Insights

Today my laboratory focuses on examining whether deficits in oxytocin activity in the brain contribute to disorders marked by disturbed social interactions. People suffering from autism, for instance, have low oxytocin levels. Studies by others have found that replacing the peptide in these subjects did not produce any increase in their social engagement. As was likely true of the untrustworthy people in the trust game, this result suggests that those with autism may have an oxytocin receptor dysfunction.

Similarly, patients with brain lesions in areas normally rich in oxytocin receptors have difficulty determining which people appear trustworthy and which appear untrustworthy. Many neurological and psychiatric disorders involve abnormal social interactions, including schizophrenia, depression, Alzheimer's disease, social anxiety disorder and Huntington's disease. A faulty oxytocin system, as we have seen in those who are untrustworthy, may play a part in these maladies. Greater understanding of its workings may lead to new treatment methods.

Oxytocin's operations within the body appear to be quite dynamic; the peptide interacts with other hormones and neurotransmitters whose levels vary minute by minute and over one's life span. Estrogen, for example, increases the uptake of oxytocin by the body's tissues, whereas progesterone does the opposite. Such effects suggest that both physiological and environmental cues drive our desire to interact socially. They also indicate that our life experiences may "retune" the oxytocin mechanism to a different "set point" and thus to different levels of trust throughout the course of life. Residing in a safe, nurturing environment may stimulate us to release more oxytocin when someone trusts us—and to reciprocate that trust. Stress, uncertainty and isolation all work against the development of a trusting disposition. As our studies continue, we will better understand how this simple peptide allows people to have empathy for and sustain trust in those around them, even complete strangers. ■

LOGAN PARSONS

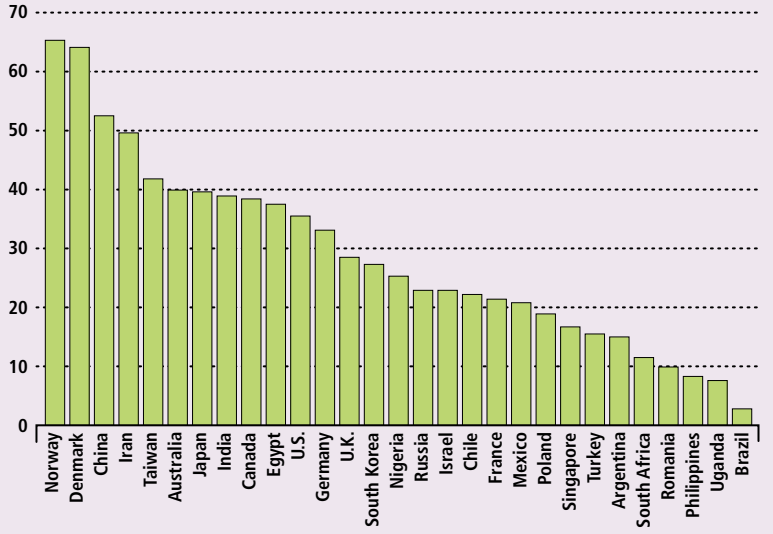
[INTERNATIONAL RESEARCH]

National Trust

The author's research into trust levels in different countries led him to investigate the role of oxytocin in forming trust. This research attempted to identify the social, political and economic conditions that explain the differences among respondents from various countries who answered the question: "Do you think most people can be trusted?"

TRUST LEVEL BY COUNTRY

Percent of respondents who think that most people can be trusted



MORE TO EXPLORE

Neuroendocrine Perspectives on Social Attachment and Love. C. S. Carter in *Psychoneuroendocrinology,* Vol. 23, No. 8, pages 779–818; November 1998.

How Love Evolved from Sex and Gave Birth to Intelligence and Human Nature. C. A. Pedersen in *Journal of Bioeconomics,* Vol. 6, No. 1, pages 39–63; January 2004.

Oxytocin Increases Trust in Humans. M. Kosfeld et al. in *Nature,* Vol. 435, pages 673–676; June 2, 2005.

Oxytocin Is Associated with Human Trustworthiness. P. J. Zak et al. in *Hormones & Behavior,* Vol. 48, pages 522–527; December 2005.

Oxytocin Increases Generosity in Humans. Paul J. Zak, Angela A. Stanton and Sheila Ahmadi in *PLoS ONE,* Vol. 2, No. 11, page e1128; November 2007.

Center for Neuroeconomics Studies: **www.neuroeconomicstudies.org**

The Ethics of CLIMATE CHANGE

Weighing our own prosperity against the chances that climate change will diminish the well-being of our grandchildren calls on economists to make hard ethical judgments

BY JOHN BROOME

What should we do about climate change? The question is an ethical one. Science, including the science of economics, can help discover the causes and effects of climate change. It can also help work out what we can do about climate change. But what we *should* do is an ethical question.

Not all "should" questions are ethical. "How should you hold a golf club?" is not, for instance. The climate question is ethical, however, because any thoughtful answer must weigh conflicting interests among different people. If the world is to do something about climate change, some people—chiefly the better-off among the current generation—will have to reduce their emissions of greenhouse gases to save future generations from the possibility of a bleak existence in a hotter world. When interests conflict, "should" questions are always ethical.

Climate change raises a number of ethical questions. How should we—all of us living today—evaluate the well-being of future generations, given that they are likely to have more material goods than we do? Many people, some living, others yet to be born, will die from the effects of climate change. Is each death equally bad? How bad are those deaths collectively? Many people will die before they bear children, so climate change will prevent the existence of children who would otherwise have been born. Is their nonexistence a bad thing? By emitting greenhouse gases, are the rich perpetrating an injustice on the world's poor? How should we respond to the small but real chance that climate change could lead to worldwide catastrophe?

CHRIS GOULD

Many ethical questions can be settled by common sense. Sophisticated philosophy is rarely needed. All of us are to some extent equipped to face up to the ethical questions raised by climate change. For example, almost everyone recognizes (with some exceptions) the elementary moral principle that you should not do something for your own benefit if it harms another person. True, sometimes you cannot avoid harming someone, and sometimes you may do it accidentally without realizing it. But whenever you cause harm, you should normally compensate the victim.

Climate change will cause harm. Heat waves, storms and floods will kill many people and harm many others. Tropical diseases, which will increase their range as the climate warms, will exact their toll in human lives. Changing patterns of rainfall will lead to local shortages of food and safe drinking water. Large-scale human migrations in response to rising sea levels and other climate-induced stresses will impoverish many people. As yet, few experts have predicted specific numbers, but some statistics suggest the scale of the harm that climate change will cause. The European heat wave of 2003 is estimated to have killed 35,000 people. In 1998 floods in China adversely affected 240 million. The World Health Organization estimates that as long ago as 2000 the annual death toll from climate change had already reached more than 150,000.

In going about our daily lives, each of us causes greenhouse gases to be emitted. Driving a car, using electric power, buying anything whose manufacture or transport consumes energy—all those activities generate greenhouse gases that contribute to climate change. In that way, what we each do for our own benefit harms others. Perhaps at the moment we cannot help it, and in the past we did not realize we were doing it. But the elementary moral principle I mentioned tells us we should try to stop doing it and compensate the people we harm.

This same principle also tells us that what we should do about climate change is not just a mat-

KEY CONCEPTS

- Future generations will suffer most of the harmful effects of global climate change. Yet if the world economy grows, they will be richer than we are.
- The present generation must decide, with the help of expert advice from economists, whether to aggressively reduce the chances of future harm or to let our richer descendants largely fend for themselves.
- Economists cannot avoid making ethical choices in formulating their advice.
- Even the small chance of utter catastrophe from global warming raises special problems for ethical discussion.

—The Editors

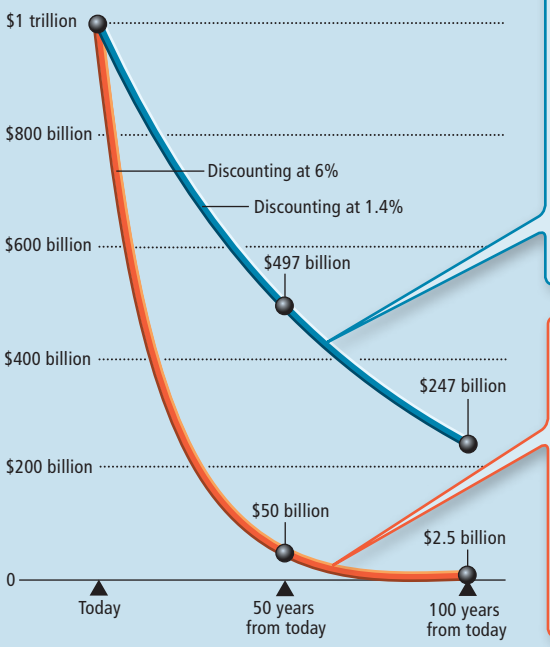
[DISCOUNTING MADE SIMPLE]

HOW MUCH DO WE CARE ABOUT THE FUTURE?

Economists usually value goods received in the future less highly than goods received today. But how much less? If the discount rate is 6 percent a year, goods worth $1 trillion received one year from today are worth only about $940 billion today. (Because economists discount continuously, the actual present value is $941.8 billion.) Economists Nicholas Stern and William Nordhaus have recently reached dramatically divergent conclusions, embodied in the discount rates they apply, about how much to spend today on goods available only to future generations.

HOW DISCOUNTING EVALUATES FUTURE GOODS

The graph shows how the value economists assign today to receiving goods worth $1 trillion in the future depends both on the discount rate and on how far into the future the trillion dollars' worth of goods will be received.



Nicholas Stern's 1.4 percent discount rate places a relatively high value on the well-being of future generations. A trillion dollars' worth of goods received in 100 years is valued at $247 billion today. In fact, Stern argues, the world needs to begin investing 1 percent of its total production, or about $500 billion today, on efforts to reduce greenhouse gases.

William Nordhaus's 6 percent discount rate places far less value than Stern's rate does on the well-being of future generations. A trillion dollars' worth of goods in 100 years is valued at only $2.5 billion today, hardly enough to justify the costs of greatly reducing greenhouse gases.

ter of weighing benefits against costs—although it is partly that. Suppose you calculate that the benefit to you and your friends of partying until dawn exceeds the harm done to your neighbor by keeping her awake all night. It does not follow that you should hold your party. Similarly, think of an industrial project that brings benefits in the near future but emits greenhouse gases that will harm people decades hence. Again suppose the benefits exceed the costs. It does not follow that the project should go ahead; indeed it may be morally wrong. Those who benefit from it should not impose its costs on others who do not.

Ethics of Costs and Benefits

But even if weighing costs against benefits does not entirely answer the question of what should be done about climate change, it is an essential part of the answer. The costs of mitigating climate change are the sacrifices the present generation will have to make to reduce greenhouse gases. We will have to travel less and better insulate our homes. We will have to eat less meat. We will have to live less lavishly. The benefits are the better lives that future people will lead: they will not suffer so much from the spread of deserts, from the loss of their homes to the rising sea, or from floods, famines and the general impoverishment of nature.

How much should we sacrifice today to improve the lives of future people richer than we are?

Weighing benefits to some people against costs to others is an ethical matter. But many of the costs and benefits of mitigating climate change present themselves in economic terms, and economics has useful methods of weighing benefits against costs in complex cases. So here economics can work in the service of ethics.

The ethical basis of cost-benefit economics was recognized recently in a major report, the *Stern Review on the Economics of Climate Change*, by Nicholas Stern and his colleagues at the U.K. Treasury. The *Stern Review* concentrates mainly on comparing costs and benefits, and it concludes that the benefit that would be gained by reducing emissions of greenhouse gases would be far greater than the cost of reducing them. Stern's work has provoked a strong reaction from economists for two reasons. First, some economists think economic conclusions should not be based on ethical premises. Second, the review favors strong and immediate action to control emissions, whereas other economic studies, such as one by William

KENN BROWN AND CHRIS WREN *Mondolithic Studios*

Nordhaus of Yale University, have concluded that the need to act is not so urgent.

Those two issues are connected. Stern's conclusion differs from Nordhaus's principally because, on ethical grounds, Stern uses a lower "discount rate." Economists generally value future goods less than present ones: they discount future goods. Furthermore, the more distant the future in which goods become available, the more the goods are discounted. The discount rate measures how fast the value of goods diminishes with time [*see box on opposite page*]. Nordhaus discounts at roughly 6 percent a year; Stern discounts at 1.4 percent. The effect is that Stern gives a present value of $247 billion for having, say, a trillion dollars' worth of goods a century from now. Nordhaus values having those same goods in 2108 at just $2.5 billion today. Thus, Stern attaches nearly 100 times as much value as Nordhaus does to having any given level of costs and benefits 100 years from now.

The difference between the two economists' discount rates is enough to explain the difference between their conclusions. Most of the costs of controlling climate change must be borne in the near future, when the present generation must sacrifice some of its consumption. The benefits will mostly come a century or two from now. Because Stern judges the present value of those benefits to be higher than Nordhaus does, Stern can justify spending more today on mitigating climate change than Nordhaus can.

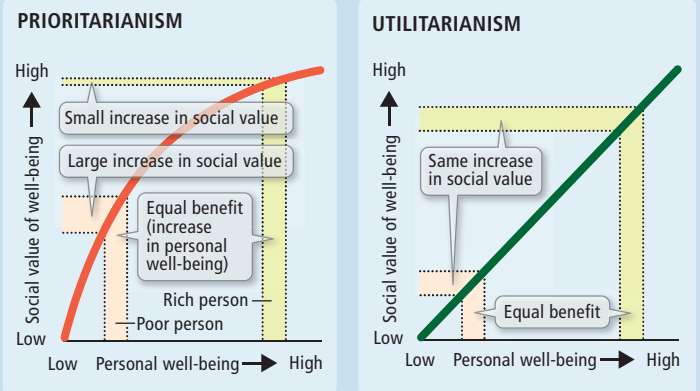
The Richer Future

Why discount future goods at all? The goods in question are the material goods and services that people consume—bicycles, food, banking services and so on. In most of the scenarios predicted for climate change, the world economy will continue to grow. Hence, future people will on average possess more goods than present people do. The more goods you already have, the less valuable are further goods, and so it is sound economic logic to discount them. To have one bathroom in your house is a huge improvement to your life; a second bathroom is nice but not so life-changing. Goods have "diminishing marginal value," as economists put it.

But there may be a second, purely ethical reason for discounting goods that come to relatively rich people. According to an ethical theory known as prioritarianism, a benefit—by which I mean an increase in an individual's well-being—that comes to a rich person should be assigned less social value than the same benefit would have if it had come to a poor person. Prioritarianism gives priority to the less well off. According to an alternative ethical theory known as utilitarianism, however, a benefit has the same value no matter who receives it. Society should simply aim to maximize the total of people's well-being, no matter how that total is distributed across the population [*see box below*].

DEVASTATING COASTAL EROSION in the Alaskan village of Shishmaref, caused by the loss of permafrost and storm-buffering sea ice in a rapidly warming climate, is forcing the villagers to abandon their island homes and relocate to the mainland.

THEORIES OF VALUE disagree about the social value of distributing equal benefits to rich and poor. Prioritarianism assigns greater social value to a given increase in well-being if it reaches a poor person. Utilitarianism assigns the same social value no matter how benefits are distributed.



[THE AUTHOR]

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LUIGI MITTONE (*Broome*); GABRIEL BOUYS *AFP/Getty Images* (*Alaska coast*)

What should the discount rate be? What determines how *fast* the value of having goods in the future diminishes as the future time in question becomes more remote? That depends, first, on some nonethical factors. Among them is the economy's rate of growth, which measures how much better off, on average, people will be in the future than they are today. Consequently, it determines how much less benefit future people will derive from additional material goods than people would derive now from those same goods. A fast growth rate makes for a high discount rate.

The discount rate also depends on an ethical factor. How should benefits to those future, richer people be valued in comparison to our own? If prioritarianism is right, the value attached to future people's benefits should be less than the value of our benefits, because future people will be better off than we are. If utilitarianism is right, future people's benefits should be valued equally with ours. Prioritarianism therefore makes for a relatively high discount rate; utilitarianism makes for a lower one.

The debate between prioritarians and utilitarians takes a curious, even poignant turn in this context. Most debates about inequality take place among the relatively rich, when they consider what sacrifices they should make for the relatively poor. But when we think about future people, we are considering what sacrifices we, the relatively poor, should make for the later relatively rich. Usually prioritarianism demands more of the developed countries than utilitarianism does. In this case, it demands less.

Which is worse, the death of a child in 2108 or the death of a child today?

Temporal Distance

Another ethical consideration also affects the discount rate. Some philosophers think we should care more about people who live close to us in time than about those who live in the more distant future, just because of their temporal distance from us. If those philosophers are right, future well-being should be discounted just because it comes in the future. This position is called pure discounting. It implies we should give less importance to the death of a 10-year-old 100 years in the future than to the death of a 10-year-old now. An opposing view is that we should be temporally impartial, insisting that the mere date on which a harm occurs makes no difference to its value. Pure discounting makes for a relatively high discount rate; temporal impartiality makes for a lower one.

To determine the right discount rate, therefore, the economist must answer at least two ethical questions. Which should we accept: prioritarianism or utilitarianism? And should we adopt pure discounting or be temporally impartial?

These questions are not matters of elementary morality; they raise difficult issues in moral philosophy. Moral philosophers approach such questions by combining tight analytical argument with sensitivity to ethical intuitions. Arguments in moral philosophy are rarely conclusive, partly because we each have mutually inconsistent intuitions. All I can do as a philosopher is judge the truth as well as I can and present my best arguments in support of my judgments. Space prevents me from setting forth my argu-

MEASURING CATASTROPHE?

Climate change raises much harder and more important ethical issues than the appropriate value of the discount rate. One is the chance of utter catastrophe. The Intergovernmental Panel on Climate Change reports several studies of how global temperatures will increase in the long run if atmospheric greenhouse gases reach the warming equivalent of about 550 parts per million of carbon dioxide (a level expected within a few decades). Most of the studies estimate the probability is 5 percent or more that the increase will be above eight degrees Celsius (14.4 degrees Fahrenheit). The disruption caused by such temperatures would pose some risk—no one can say how much—of a devastating collapse of the human population, perhaps even to extinction. Any such event would be so bad that even multiplied by its small chance of occurrence, its badness could dominate all calculations of the harm that climate change will cause. Working out how bad such an event would be is an urgent but very difficult ethical problem.

For example, a population collapse will cause the premature deaths of billions of people. So one must try to estimate how bad, ethically speaking, it is for a person to die early. That may sound like a hard-hearted question, but the value of human life is already recognized as a necessary element in public policy. For example, the World Health Organization has developed a measure of the "burden of disease"—the harm done to people by disease, including the harm suffered by those who are killed by disease. The WHO is already applying the measure to estimate the harm done by climate change.

Catastrophe raises an even harder ethical question. If humanity becomes extinct or the human population collapses, vast numbers of people who would otherwise have existed will not in fact exist. The absence of so much potential humanity seems an overwhelmingly bad thing. But that is puzzling. If nonexistence is a harm, it is a harm suffered by nobody, since there is nobody who does not exist. How can there be a harm that harms nobody?

Some philosophers insist there can be no such harm. They think that extinction or population collapse will do no harm apart from causing early deaths. Other philosophers disagree; they think the loss of future humanity would indeed be exceedingly bad. If they are right, they will still have to judge in quantitative terms just how bad it would be.

The issue remains one of the hardest and most debated problems in practical philosophy. But until a satisfactory answer is found, it will be impossible to properly judge the badness of climate change. —***J.B.***

CLIMATE SHIFT to unprecedentedly dry weather, along with the diversion of water for irrigation, has converted this former reservoir in China's Minqin County into desert.

ments here, but I have concluded that prioritarianism is mistaken and that we should be temporally impartial. For more detail, see chapter 10 of my book *Weighing Goods* (1991) and section 4.3 of my book *Weighing Lives* (2004).

Market Discount Rates?

Stern reaches those same ethical conclusions. Since both tend toward low discounting, they—together with Stern's economic modeling—lead him to his 1.4 percent rate. His practical conclusion follows: the world urgently needs to take strong measures to control climate change.

Economists who oppose Stern do not deny that his practical conclusion follows from his ethical stance. They object to his ethical stance. Yet most of them decline to take any ethical position of their own, even though they favor an interest rate higher than Stern's. As I have explained, the correct discount rate depends on ethical considerations. So how can economists justify a discount rate without taking an ethical position?

They do so by taking their higher discount rate from the money market, where people exchange future money for present money, and vice versa. They adopt the money-market interest rate as their interest rate. How can that be justified?

First, some values are determined by people's tastes, which markets do reveal. The relative value of apples and oranges is determined by the tastes revealed in the fruit market. But the value that should be attached to the well-being of future generations is not determined by tastes. It is a matter of ethical judgment.

So does the money market reveal people's ethical judgments about the value of future well-being? I doubt it. The evidence shows that, when people borrow and lend, they often give less weight to their own future well-being than to their present well-being. Most of us are probably not so foolish as to judge that our own well-being is somehow less valuable in old age than in youth. Instead our behavior simply reflects our impatience to enjoy a present benefit, overwhelming whatever judgment we might make about the value of our own future. Inevitably, impatience will also overwhelm whatever high-minded arguments we might make in favor of the well-being of future generations.

But for the sake of argument, suppose people's market behavior genuinely reflected their judgments of value. How could economists then justify proclaiming an ethically neutral stance and taking the discount rate from the market? They do so, purportedly, on democratic grounds—leaving ethical judgments to the public rather than making them for themselves. The economists who criticize Stern claim the democratic high ground and accuse him of arrogantly trying to impose his own ethical beliefs on others.

They misunderstand democracy. Democracy requires debate and deliberation as well as voting. Economists—even Stern—cannot impose their beliefs on anyone. They can only make recommendations and argue for them. Determining the correct discount rate requires sophisticated theory, and we members of the public cannot do it without advice from experts. The role of economists in the democratic process is to work out that theory. They should offer their best recommendations, supported by their best arguments. They should be willing to engage in debate with one another about the ethical bases of their conclusions. Then we members of the public must reach our own decisions with the experts' help. Without their help, our choices will be uninformed and almost worthless.

Once we have made our decisions through the democratic process, society can act. That is not the job of economists. Their recommendations are inputs to the process, not the output of it. The true arrogance is imagining that you are the final arbiter of the democratic process.

Ethical considerations cannot be avoided in determining the discount rate. Climate change raises many other ethical issues, too; one crucial one, the problem of catastrophic outcomes, is mentioned in the box on page 100. It will require serious work in ethics to decide what sacrifices we should make to moderate climate change. Like the science of climate change, the ethics of climate change is hard. So far it leaves much to be resolved. We face ethical as well as scientific problems, and we must work to solve them. ■

MORE TO EXPLORE

Rational Behavior and Bargaining Equilibrium in Games and Social Situations. John C. Harsanyi. Cambridge University Press, 1977.

Managing the Global Commons: The Economics of Climate Change. William D. Nordhaus. MIT Press, 1994.

A Review of the *Stern Review on the Economics of Climate Change*. Martin L. Weitzman in *Journal of Economic Literature*, Vol. 45, No. 3, pages 703–724; September 2007.

Climate Change 2007. Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press, 2007. Available at **www.ipcc.ch**

Stern Review on the Economics of Climate Change. Nicholas Stern et al. Cambridge University Press, 2007. Available at **www.hm-treasury.gov.uk/independent_reviews/stern_review_economics_climate_change/stern_review_report.cfm**

Beating the Flu in a Single Shot

Walter Fiers found a protein segment on the influenza virus that could lead to a universal flu vaccine, which would end seasonal shots and provide pandemic protection BY ALEXANDER HELLEMANS

Ingmar Bergman's famous 1957 movie *The Seventh Seal* takes place during the 14th century, when Europe is in the midst of a major epidemic of the bubonic plague—the Black Death—which ultimately killed about half the population. A Swedish knight, Antonius Block, returns from the Crusades and finds Death waiting for him. He challenges Death, later seen disguised as a priest, to a chess match, hoping to stave off his own death by devising what he hopes is a winning next move.

For the past three decades, researchers and health workers have engaged in a similar battle against one of the most cunning viruses to afflict humanity and much of the animal world: the dread influenza virus. This pathogen is even smarter than Death; it continuously changes the appearance of its chess pawns—the proteins on its coat—so that immune systems do not recognize the new disguise.

Every year the World Health Organization and other institutions try to predict the next change in the virus's coat. Once the WHO decides on the likeliest alterations, drug manufacturers then have only a few months to develop vaccines. "The whole infrastructure required for the preparation of seasonal vaccines has enormous disadvantages," remarks Walter Fiers, a molecular biologist at Ghent University in Belgium. "It is slow—sometimes we miss the strain that becomes predominant—and if a pandemic should arrive, we will not be prepared." Fiers's goal: a universal vaccine that, like some childhood immunizations, would confer lifelong immunity.

Scientists have dreamed for decades of a one-shot approach to stop the flu—particularly influenza A, the most serious type. But the task is daunting. The appearance-changing coat of the influenza virus is studded with mainly two proteins: hemagglutinin, which allows the virus to attach to and enter a cell; and neuraminidase, which boosts the virus's ability to pass to other cells. (These proteins serve as the basis for influenza nomenclature; for instance, the H5N1 virus refers to specific classes of hemagglutinin and neuraminidase, which in this example correspond to an avian flu subtype.) The genes responsible for these proteins undergo frequent point mutations, resulting in genetic "drift"; moreover, the genes from different animal and human strains may also interchange, resulting in genetic "shift." Both drift and shift make these proteins unrecognizable to the antibodies present in people that were previously inoculated against the flu virus, which now circulates as more than 90 strains.

Unlike the hapless knight Block, the 77-year-old Fiers believes that he has found his adversary's Achilles' heel: although the virus is good at disguising its pawns, there is one on its coat that it cannot change. That pawn, the external part of a protein called M2, should be the target for vaccination, he says.

Fiers has come to this con-

NICOLAS GUERIN

WALTER FIERS

AIMING FOR M2E: Found a protein segment, called M2e, on the influenza virus that may lead to a universal vaccine, thereby eliminating annual shots and protecting against pandemics.

VIRAL TOLL: The influenza virus infects about 10 to 20 percent of the world's population annually, killing 250,000 to 500,000. Past pandemics ensnared about 30 to 50 percent of the population; the 1918 pandemic caused about 50 million deaths.

DELIVERY OPTIONS: In terms of administering a vaccine during a pandemic, Fiers argues for the development of a nasal spray: "Medical workers injecting people will be too slow."

clusion after five decades of work in molecular biology—in particular, decoding genomes. In 1972 he and his team were the first to publish the nucleotide sequence of a complete gene. This gene codes for the coat protein of a bacteria-infecting virus, or bacteriophage. Four years later they published the bacteriophage's complete genome—all four genes of it. "This was the first complete genome that was sequenced," Fiers recalls. Because of its medical importance, he decided around that time to focus on the influenza virus.

In 1980 Fiers first sequenced the gene for hemagglutinin derived from the human influenza strain H3N2 that circulated in 1965. He then compared the hemagglutinin gene of this strain with a similar hemagglutinin gene derived from the strain that had started the 1968 Hong Kong pandemic. His analysis proved that point mutations account for genetic drift.

ANNUAL FLU SHOTS, such as those being given here at a Tupelo, Miss., health fair, could end with a universal vaccine.

Equally important, his studies led him to see how the virus can jump species through genetic shifts. At that time scientists knew that antibodies from people infected by the 1968 pandemic virus also reacted with an influenza strain isolated in 1963 from flu-ridden ducks. Fiers investigated the nucleotide sequence of the hemagglutinin gene of this duck virus and found that it was indeed very closely related to the strain that started the 1968 Hong Kong outbreak. Today infectious disease experts recognize that an avian flu virus could genetically change enough to trigger a human pandemic.

If such a jump occurred, the virus "would not be hindered by any preexisting immunity in the human population," Fiers explains. "It would spread fast over the world because when it arrived here it would look like an entirely different virus. Therefore, you need a vaccine that is not invalidated by drift or shift."

More specifically, he needed a vaccine based on a part of the influenza virus that does not change. Fiers found it in the viral coat protein M2, which creates a pore in the coat. Specifically, he noticed that a section of that protein, called M2e, remains stable even as the other viral surface proteins mutate. The M2 protein, however, occurs only in small numbers on the virus, which is too low to set off a good immune response.

The obvious solution was to amplify the number of M2e segments. But how? Fiers turned to the liver-attacking hepatitis B virus. This pathogen has an inner protein core called HBc, and something intriguing happens when the gene for HBc is inserted into the bacterium *Escherichia coli*. The bacterium starts producing HBc proteins and assembles them to produce viruslike particles. Fiers found that by linking M2e genes to HBc genes, the bacteria would produce viruslike particles studded with M2e.

In tests with mice and, later, ferrets, the M2e-HBc particles caused the formation of antibodies directed against M2e, thereby protecting the animals from a lethal dose of influenza. The vaccine works differently from conventional vaccines in that it does not prevent infection directly. "The target is not the virus, but the target is the virus-infected cell," Fiers says. "If at an early stage, you can kill off these cells, then you will counteract the infection."

THOMAS WELLS *Northeast Mississippi Daily News Journal/AP Photo*

In 1997 Fiers received a patent for the technology, and in 1999 he published a paper in *Nature Medicine* expounding his approach. The British-American company Acambis, based in Cambridge, Mass., and Cambridge, England, has obtained the license to start production of the vaccine. In a phase I trial completed last year, Acambis found that among the 79 volunteers who received the vaccine, 90 percent developed antibodies to the M2e segment.

Whether the antibodies protect against influenza now needs to be determined—no guarantee if the past is any guide. A decade ago a drug based on an internal protein of the flu virus, called NP (for nucleoprotein), set the immune system's killer T cells into action, but it only partially protected mice from the flu.

Because intentionally infecting a volunteer to see if a vaccine works is unethical, the compound will have to face large field trials. "We have to find an area where there is a higher probability that an influenza epidemic will take place," Fiers says. The likeliest places are where dense human populations live near farm animals. Thousands of people will have to be vaccinated to obtain statistically acceptable results. (The current version of the M2 vaccine would protect only against influenza A, the type that has launched pandemics.)

The pharmaceutical industry is showing strong interest, and Arnold Monto, an epidemiologist at the University of Michigan at Ann Arbor, thinks that this universal vaccine is promising. Still, "whether it will be sufficient without having other proteins in there, I'm not sure," Monto says, referring to a possible need to use seasonal flu vaccines as supplements. The chess battle against influenza will have to continue for a while longer, but for now hopes are high that playing the M2 vaccine might be the right strategy to checkmate the virus. ■

Alexander Hellemans is based in Antwerp, Belgium. A Q&A version of his interview with Fiers is at **www.SciAm.com/jun2008**

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Library to Go

By Stuart F. Brown

More and more people are gazing at electronic-book readers—lightweight slates about the size of a thin paperback that can store up to 200 downloaded books. Although prior generations fizzled, Sony's Reader, introduced in 2006, and Amazon's Kindle, which debuted last year, are both selling well. The key difference is the screen.

Researchers had wrestled with e-book readers for decades, but most sported power-thirsty, backlit LCD screens that glared in low light or were drowned out by bright sunlight. The breakthrough this time is a screen made with "electronic paper" from E Ink Corporation in Cambridge, Mass. Sony, Amazon and other makers worldwide are using the material.

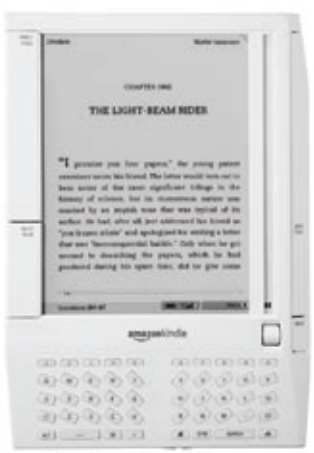
E-paper displays are reflective: ambient light bounces off them, so they look and read like ordinary paper. The screens are very energy efficient, too. "The only power used is when you turn a page," says Isaac Yang, manager of software product development at Sony in San Jose, Calif. No current is needed to sustain the characters on a page once it has been called up [*see main illustration*]. Yang says about 7,500 pages can be turned on a single battery charge. Downloading books consumes additional power.

Sony's Reader, roughly $300, has a stated capacity of about 160 books, which are found by linking it to a computer via a USB cable and going to the company's online bookstore. Amazon's Kindle, $400, can hold about 200 books and can download them by connecting to Sprint's wireless data network. Amazon also offers paid subscriptions to certain newspapers and magazines. Newly released books typically cost around $10. Enthusiasts who have posted online reviews note, however, that the software for downloading and managing files can be a bit cumbersome.

The fonts on both the Sony and Amazon handhelds can be made larger or smaller, and both can display black-and-white JPEG and GIF images, Microsoft Word documents and RSS news feeds. Each item, of course, will occupy some of the roughly 190 megabytes of memory.

Market analysts remain unsure about whether e-books and readers will ever become ubiquitous. Some people are fiercely attached to the tactility—and even the smell—of paper books and periodicals, whereas others love the idea of carrying around heaps of documents in a device weighing 10 ounces. Perhaps the next frontier—color screens—might sway the masses. E Ink is working on prototype e-paper that incorporates the red, green and blue filters needed to show full-color imagery; such a surface could potentially support downloaded video and books on a screen much bigger than a cell phone but much lighter than a laptop.

Stuart F. Brown is a writer in Irvington, N.Y.



Amazon Kindle

Sony Reader

AMAZON.COM, INC. (*Kindle*); SONY ELECTRONICS, INC. (*Reader*)

DID YOU KNOW ...

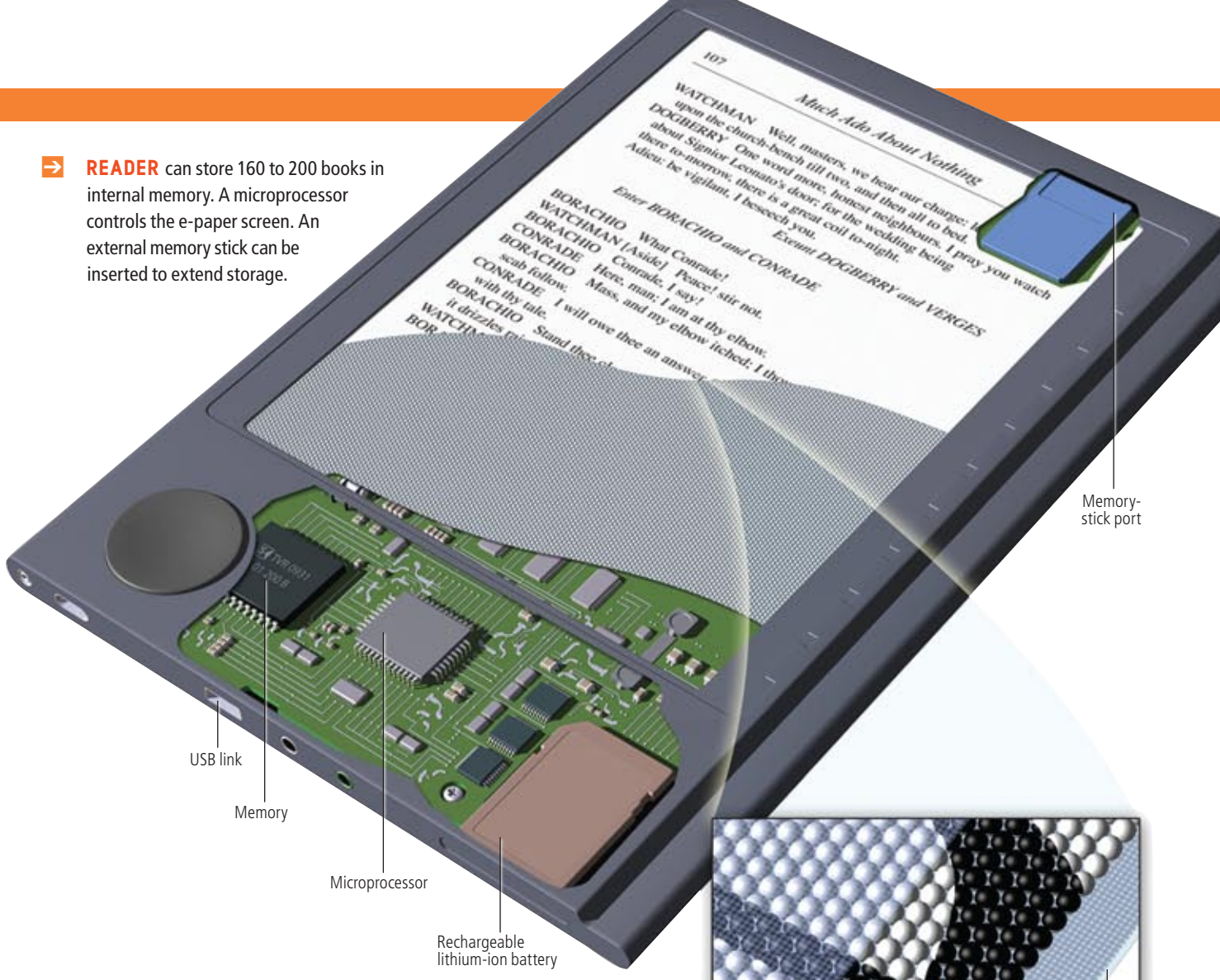
RESOLVED: Reader screens made with E Ink paper have a resolution of 167 dots per inch (dpi). A typical ink-jet printer achieves 300 dpi, a Web page 72 dpi.

CHINA, FRANCE: eRead Technology's STAReBOOK is popular in China, as is Bookeen's Cybook in France. Les Echos, an electronic newspaper publisher in Paris, offers editions that can be downloaded over Wi-Fi connections onto the iLiad reader made by iRex in the Netherlands.

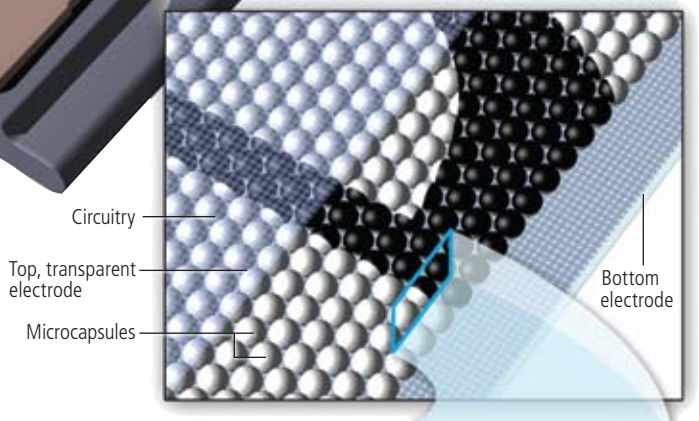
FORERUNNERS: Researchers at Xerox Palo Alto Research Center worked on an oil-filled microcapsule system named Gyricon in the 1970s. In 1971 Michael Hart, a University of Illinois student, obtained mainframe computer time to begin to digitize and archive books and other items, with the goal of someday distributing a massive digital library.

THE LAST BOOK: In 1997 Joseph Jacobson, a young professor at the Massachusetts Institute of Technology's Media Lab and an eventual founder of E Ink, published a paper called "The Last Book." In it he envisioned a hardcover book containing several hundred blank electronic pages. Futuristic memory chips in the book's spine would hold the entire catalogue of the Library of Congress, and a simple control would display any one of those titles on its pages.

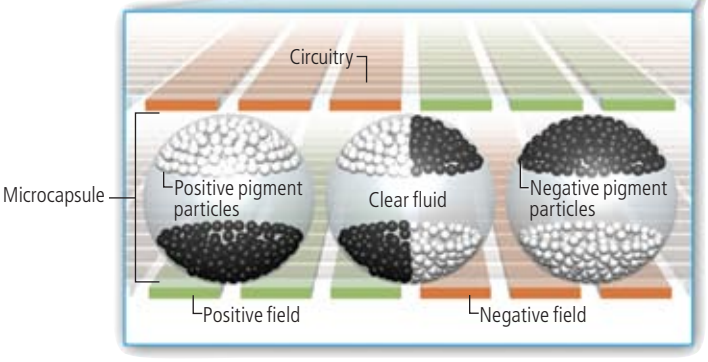
READER can store 160 to 200 books in internal memory. A microprocessor controls the e-paper screen. An external memory stick can be inserted to extend storage.



DISPLAY is made of e-paper from the company E Ink, which exploits electrophoretics. Millions of tiny microcapsules, each about the diameter of a human hair, are held between two thin sheets that function as electrodes.



MICROCAPSULES contain positively charged white particles and negatively charged black particles suspended in a clear fluid. When circuitry in the top sheet applies a negative electric field to a capsule, the white particles move toward it; a corresponding positive field below draws the black particles down (*left*). Reversing the charges makes the pixel dark at the top (*right*). Switching the field for a brief period brings together white and black particles to form gray shades (*not shown*). Once the particles orient, they hold their position with no further power input.



GEORGE RETSECK; SOURCES: SONY (*reader*); E INK (*microcapsule insets*)

SEND TOPIC IDEAS *to workingknowledge@SciAm.com*

Thriller Physics ▪ Virtual Life ▪ Nerd-dom

BY MICHELLE PRESS

COMING OF AGE IN SECOND LIFE: AN ANTHROPOLOGIST EXPLORES THE VIRTUALLY HUMAN

by Tom Boellstorff. Princeton University Press, 2008 ($29.95)

Boellstorff, an anthropologist at the University of California, Irvine, applies the methods and theories of his field to a virtual world accessible only through a computer screen. This world, called Second Life, is owned by Linden Lab, a company that charges roughly $15 a month to "live" there and to buy virtual land. Boellstorff spent two years participating in Second Life and reports back as the trained observer that he is. We read about a fascinating, and to many of us mystifying, world. How do people make actual money in this virtual society? (They do.) How do they make friends with other avatars? The reader unfamiliar with such sites learns a lot—not least, all sorts of cool jargon: people in Second Life, for example, say objects are "rezzing" into existence, a verb that traces its origin to the 1982 movie *Tron.* The jargon of the author's own field is another matter: the reader wearies of specialized terminology and hair-splitting definitions. The title recalls Margaret Mead's *Coming of Age in Samoa*. One wishes this anthropologist had a little more of Mead's flair, but the book is worth the hurdles its scholarly bent sometimes imposes.

AMERICAN NERD: THE STORY OF MY PEOPLE

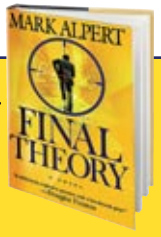
by Benjamin Nugent. Scribner, 2008 ($20)

What a surprise to learn that the first appearance of the word "nerd" in print was probably in Dr. Seuss's *If I Ran the Zoo.* And there are many other surprises in this delightfully written dissection of nerd image and culture that explores online gaming, science-fiction clubs, attire, ethnic implications, and much more. Nugent, a journalist at *Time* magazine, also delves into the correspondence between nerdiness and people with Asperger's syndrome (a form of autism characterized by difficulties in social interaction and by restricted interests and activities). His dissection charms and enlightens. Nerds—and everyone else—will love it.

EXCERPT

FINAL THEORY

by Mark Alpert. Touchstone/Fireside, 2008 ($24)



Physics plays a crucial role in this fast-paced thriller. And not only is the science credible (disclosure: Alpert is an editor at this magazine), so are the characters, who have several more dimensions than those in most thrillers. A young professor runs for his life after he accidentally learns of an unpublished Einstein theory that could destroy the world. A beautiful string theorist joins him in the harrowing scramble to prevent destruction:

"A long dress made from yellow-and-red Kente cloth draped her shoulders, and several gold bracelets hung from each of her brown arms. In the drabness of Jadwin Hall she blazed like a particle shower.

"Women physicists were uncommon enough … but a black female string theorist was a rare phenomenon indeed. The scientists in the auditorium regarded her as they would any other rare phenomenon, with a mixture of awe and skepticism. As soon as she began her presentation, though, they accepted her as one of their own, because she spoke their language, the abstruse tongue of mathematics. Moving to the blackboard, she scribbled a long sequence of equations, each crowded with the symbols representing the fundamental parameters of the universe: the speed of light, the gravitational constant, the mass of the electron, the strength of the nuclear force. Then, with an ease that David could only envy, she manipulated and transformed the dense thickets of symbols until they condensed into a single, elegant equation that described the shape of space around a vibrating string."

NEW AND NOTABLE: FIELD SCIENCE

1 **Life in Cold Blood**
by David Attenborough. Princeton University Press, 2008 ($29.95)
Attenborough travels to the ends of the earth to tell the story of amphibians and reptiles, raising awareness of the threats of environmental destruction along the way. The book accompanies a television series.

2 **Amazon Expeditions: My Quest for the Ice-Age Equator**
by Paul Colinvaux. Yale University Press, 2007 ($32.50)
An adventurous tale of exploration in the days before GPS, with findings that turned a cherished hypothesis on its head.

3 **Mean and Lowly Things: Snakes, Science, and Survival in the Congo**
by Kate Jackson. Harvard University Press, 2008 ($27.95)
Physical and cultural difficulties beset a survey of the amphibians and reptiles of the swamp forest.

4 **The Race to Save the World's Rarest Bird: The Discovery and Death of the Po'ouli**
by Alvin Powell. Stackpole Books, 2008 ($24.95)
A poignant adventure that also examines the workings, and failings, of the Endangered Species Act.

5 **The Snake Charmer: A Life and Death in Pursuit of Knowledge**
by Jamie James. Hyperion, 2008 ($24.95)
The final, fatal expedition of a well-known herpetologist bitten by a many-banded krait.

6 **The Animal Dialogues: Uncommon Encounters in the Wild**
by Craig Childs. Little, Brown, 2007 ($24.99)
A series of eloquent narratives about the author's encounters with, among others, a shark, a peregrine falcon and a mountain lion.

STEPHEN DALTON *NHPA (frog)*; DANIEL J. COX *Getty Images (mountain lion)*

Q *How did people ever find the* ***chemical*** *that makes* ***pupils dilate****?*

Donald Mutti, a professor at the Ohio State University College of Optometry, eyes an answer to this query:

The discovery was probably accidental. Dilating drops block receptors in the muscle that constricts the iris, the colored "curtain" of the eye that controls the amount of light traveling toward the retina. This hindrance allows the muscle that dilates the iris to act unopposed, causing the pupil—which is just a hole in the center of the iris—to enlarge.

Our pupils naturally expand in darkness and shrink in bright light through the actions of the two opposing iris muscles, the iris dilator and the iris sphincter. The dilator muscle, which extends radially through the iris, contracts to pull the iris outward, bunching it up like an open curtain. The iris sphincter is arranged in a circular pattern, similar to a purse string. Its constriction pulls the iris inward and flattens it, like a curtain drawn closed.

DEADLY NIGHTSHADE

These muscles are under the control of the autonomic nervous system, which deals with involuntary reflex actions. Sympathetic output, which is associated with arousal, stimulates the iris dilator muscle to constrict, opening our pupils during a fight-or-flight situation. Parasympathetic output, associated with calming mechanisms, stimulates the iris sphincter to constrict, shrinking our pupils.

Dilating drops are anticholinergic agents, which block the effects of acetylcholine, the neurotransmitter released by parasympathetic nerve cells. Modern dilating drops are synthetic cousins of atropine, an extract of *Atropa belladonna* (also known as deadly nightshade). Atropine is a notorious poison, responsible for the famous quintet of signs that indicate ingestion of the toxin: "hot as a hare, red as a beet, dry as a bone, blind as a bat and mad as a hatter."

One would only have to rub an eye after preparing this extract to discover its pupil-dilating effects. Apparently this property was exploited hundreds of years ago, particularly in Italy, by women who sought large pupils to create a doe-eyed appearance. The sight of one's beloved with pupils enlarged had the desired effect of communicating arousal.

Q *Why don't* ***tornadoes*** *hit cities more often? Could* ***global warming*** *make this event occur more frequently?*

Joshua Wurman, president of the Center for Severe Weather Research in Boulder, Colo., whips up a response:

The glib answer for why tornadoes rarely strike urban areas is: cities are small. Look at Google Maps: the portion of the U.S. covered by urban and suburban areas is pretty minute. And the regions with peak tornado frequencies—from Texas up through Kansas and even out to the Southeast—are fairly open country.

It is very unusual that a tornado encounters a city, as happened in Atlanta this past March. When it happens, however, the storm need not be particularly strong to cause trouble. Tornadoes are rated 0 to 5 on the Enhanced Fujita (EF) scale: violent tornadoes are classified EF4 and EF5, significant ones EF2 and EF3. The tornado that went through Atlanta, which has been rated an EF2, did not raze downtown structures but did claim one casualty and cause millions of dollars in damages.

To address the second question, whereas one could be confident that the global temperature is going to rise, local effects—whether Atlanta or Topeka is going to heat up—are much less clear. On top of that, the effect of local temperature on tornado formation is unknown. Brazil is quite hot but does not have a lot of tornadoes. Oklahoma and Texas are very hot in summer, but those states see the most tornadoes in spring. So it is possible that climate change could shift the timing of the tornado season up, as spring's onset creeps into winter. Perhaps it will affect the geographic distribution of stronger tornadoes. But as for whether global warming will increase the number of tornadoes, making for more urban touchdowns, we may find out soon enough. ■

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

NATURFOTO HONAL/CORBIS (*deadly nightshade*); WEATHERSTOCK/PETER ARNOLD, INC. (*tornado*)