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ScienceNews

MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC ■ SEPTEMBER 13, 2008

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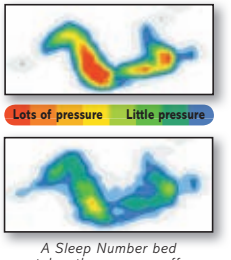

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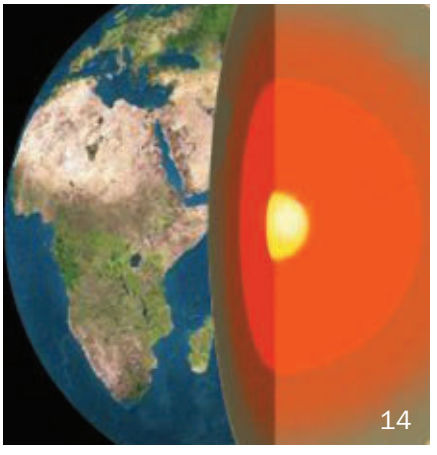

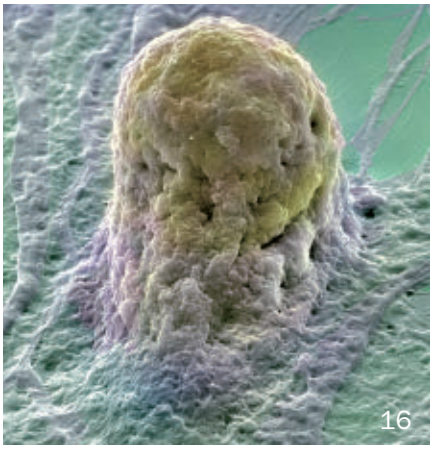

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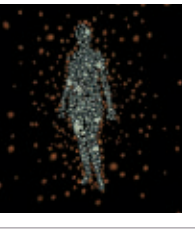

On the cover:
Stem cells divide and differentiate to form the body's great variety of tissues.
Art: Bryan Christie

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Anniversaries inspire timely ruminations

Anniversaries are seldom really newsworthy. They're by definition about something old. But anniversaries often offer good excuses for putting new areas of scientific exploration into historical perspective.

A century ago, Hermann Minkowski put Einstein's brand-new theory of relativity into mathematical perspective, in the process brokering the merger of space with time. The resulting "spacetime continuum" was embraced by science and science fiction alike, and its properties shaped the 20th century's conception of the cosmos. So it is certainly an anniversary worth celebrating. And it provides a convenient context for some 21st century speculations.

As I describe in an essay in this issue (Page 26), Minkowski's vision of spacetime is no longer considered to be a sturdy enough framework for formulating the rest of physics. Many physicists believe that space and time now should be separated, and then some are seeking ways to put them back together again.

One such approach builds on the intriguing realization that time's relationship to the laws of nature is not straightforward. No cosmic clock governs time's flow for the whole universe; the measure of time must spring from the physicists' equations. It turns out, though, that different laws of nature emerge depending on which part of the math is chosen to represent time. So it may be that the observed laws of nature are not ordained by some final theory, but just represent the most likely rules to emerge from an ensemble of possibilities, making the universe something like the outcome of a craps game.

But that's just one idea. The Minkowski anniversary might equally well have provided occasion to explore other speculative ideas about time. One recent paper, for instance, points out that for the early universe, time may be a meaningless concept, as conditions at such remote epochs would not have permitted the existence of any physical system that could serve as a clock. Another new account describes the prospects for a cosmos in which time runs both ways, in which case current events might be influenced by messages (of a sort) sent back from the future.

Another inviting avenue of exploration (well, not that inviting) would be pondering the curiosities of imaginary time, in analogy to the imaginary numbers of mathematics (which figured prominently in Minkowski's work). Unfortunately, there is not enough time available now for that discussion. Or space.

—Tom Siegfried, Editor in Chief

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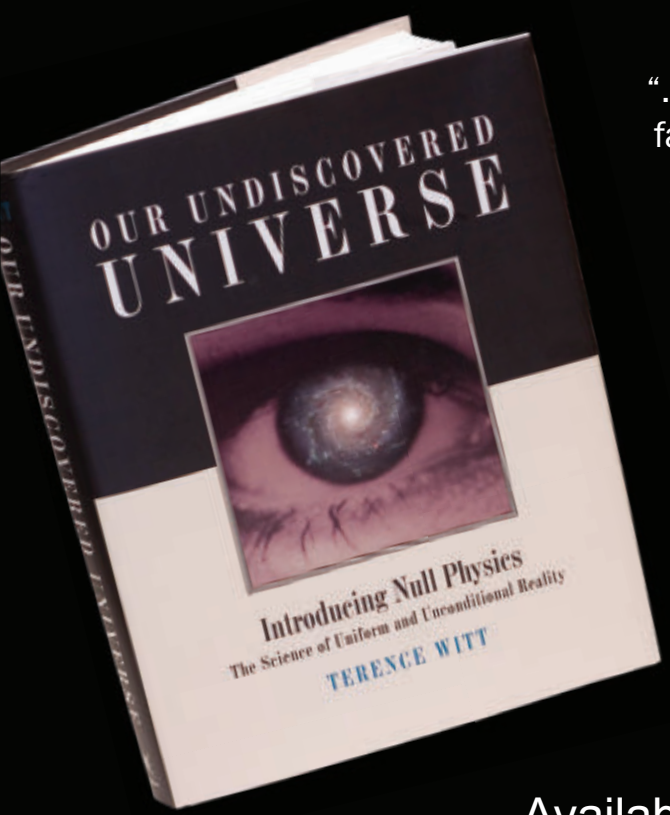

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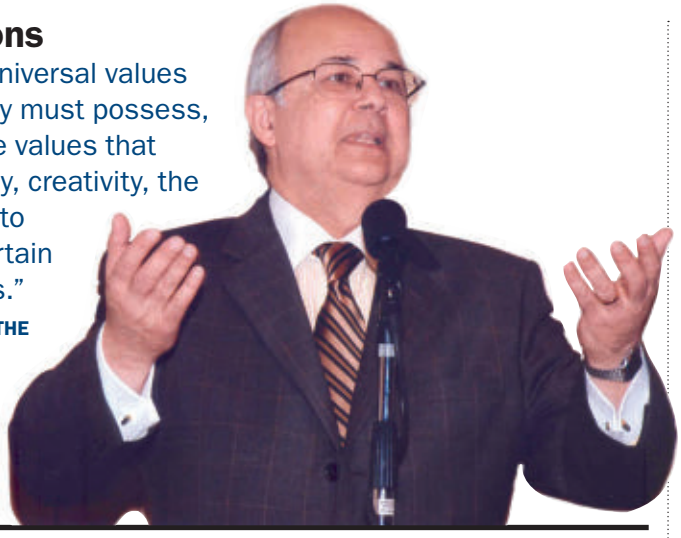
Scientific Observations

"There is a central core of universal values that any truly modern society must possess, and these are very much the values that science promotes: rationality, creativity, the search for truth, adherence to codes of behavior, and a certain constructive subversiveness."

—ISMAIL SERAGELDIN, DIRECTOR OF THE LIBRARY OF ALEXANDRIA IN EGYPT, WRITING ABOUT SCIENCE IN MUSLIM COUNTRIES IN THE AUG. 8 *SCIENCE*.



Science Past:

From *Science News Letter*, September 13, 1958

RNA INFLUENCES CELL DIFFERENTIATION — Ribonucleic acid has been pinpointed as having an essential role in cell differentiation, the process by which the early embryo's look-alike cells become nerve, bone, skin and other organs. Working with extremely small quantities of cellular material, 20 to 50 cells, taken from embryonic newt and salamander tissue, Dr. M. C. Niu of the Rockefeller Institute for Medical Research, New York, found that the presence of ribonucleic acid is critical for the formation of specialized tissues. He used cells removed from two-to-five-day-old fertilized eggs that under ordinary circumstances would become epithelial or skin tissue. These cells, Dr. Niu told Science Service, have the unique characteristic of multi-potentiality.... By growing the cells in a hanging drop of saline solution that included a 97% pure extract of nucleic acid and protein taken from cow tissue, Dr. Niu was able to control cell differentiation.

Science Future

September 7–9

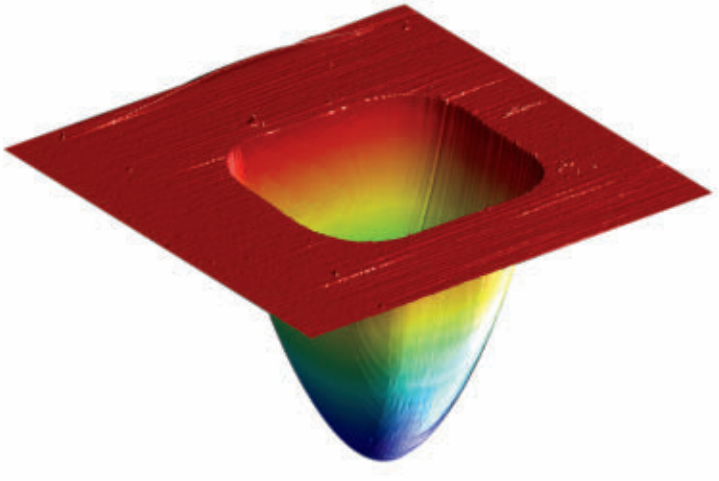
The first INCF Congress of Neuroinformatics. To be held in Stockholm. Visit www.neuroinformatics2008.org

Sept. 21–Nov. 2

The walk-through *Spider Pavilion* opens at the Natural History Museum of Los Angeles County. Visit the museum's website at www.nhm.org

Sept. 27–Oct. 12

Wired magazine's NextFest in Chicago's Millennium Park showcases global innovations. Visit www.wirednextfest.com



The (–est)

This is no party decoration. Researchers at Cornell University have developed the world's thinnest balloon. Made of a single layer of graphite just one atom thick, the membrane is impermeable to even the tiniest airborne molecules. Most likely it will be used in sensors, filters and for imaging at the atomic level, report J. Scott Bunch and colleagues in the August *Nano Letters*.

SN Online

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ENVIRONMENT

The number of oxygen-starved coastal areas, known as dead zones, is on the rise worldwide. Rachel Ehrenberg provides the latest tally and explains the effect on ocean life online in "Coastal dead zones expanding."

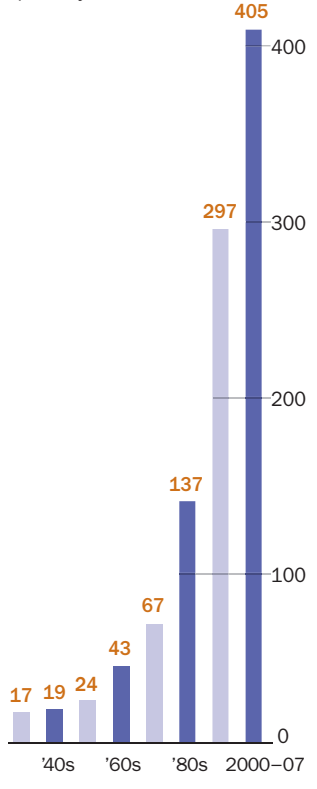
MATH TREK

The nervous system is designed to see images in three dimensions. But in a new series of videos, mathematicians explain how you can view the world in four, Julie J. Rehmeyer reports in her column.

Science Stats

Lacking oxygen

Cumulative number of aquatic dead zones worldwide reported in scientific papers, by decade



SOURCE: R. DIAZ, R. ROSENBERG, *SCIENCE*

JONATHAN ALDEN; THE LIBRARY OF ALEXANDRIA

“There’s always going to be a spore on the grassy knoll.” —VAHID MAJIDI, PAGE 8

In the News

STORY ONE

Doctors debate death definition for transplants

Success with infant hearts shows that timing matters

By Ashley Yeager

A heart stops beating in one person. It is transplanted and restarted in another. Was the individual from whom the heart was taken really dead?

That is a question neurologist James Bernat of the Dartmouth-Hitchcock Medical Center in Lebanon, N.H., asks whenever he considers the ethics involved in organ donation.

Now, a new heart transplant experiment has resparked debate over declaring the death of an organ donor—and over what ethical and medical transplant procedures are appropriate. Bernat is among the thousands of neurologists, cardiologists and medical ethicists who are still struggling to define death in the face of changing technology that sustains and restarts life.

In the new experiment, three babies each received an unorthodox heart transplant. Today they remain healthy, growing infants and toddlers, researchers report in the Aug. 14 *New England Journal of Medicine*. Had the transplants not been done, six babies, rather than three, would have died, says the study’s lead author, Mark Boucek of the Joe DiMaggio Children’s Hospital in Hollywood, Fla.

Each year, roughly 50 U.S. infants are added to the waiting list for a heart transplant. A quarter of the infants die while waiting, Boucek says. He and colleagues at DiMaggio along with doctors from The Children’s Hospital in Aurora, Colo., wanted to provide more hearts. So the team decided to try to transplant hearts from three donor infants who had life-threatening brain injuries, had not been declared brain-dead and had been kept alive only through life support. The parents agreed that the infants not be resuscitated after being taken off life support and that their organs be transplanted upon death, if possible.

A doctor listens to a newborn’s heart to determine if the girl is healthy or has heart damage and will need a transplant. Each year, roughly 50 U.S. babies are added to the heart transplant waiting list.

KARENMOWER/ISTOCKPHOTO

The experimental transplant procedure marks the first time infants have received hearts from infant donors taken off life support. The surgeries, performed in Colorado between May 2004 and May 2007, transplanted the donor hearts into babies less than 1 year old who had malfunctioning or diseased hearts.

After the transplants, the health of the recipients was compared with that of 17 babies who received transplants in the standard way: from infants who had been declared brain-dead but whose hearts were still beating and so weren’t on life support. The three babies who received hearts from infants taken off ventilators are still alive; of the 17 control infants, 14 remain alive.

“Our study is small,” Boucek says, “but it establishes that it is possible to transplant hearts from infants that die of respiratory failure that led to heart failure.” Previously, it was thought that this method would not work because once taken off life support, the donor babies’ circulation stops, causing possible damage to the heart. »

For today's top science news, visit SN Today at **www.sciencenews.org**

» "This experiment was bold," Bernat says, and "it worked." But the procedures involved highlight the question of defining and determining death for organ donors, a question which "needs to be answered before this experimental procedure makes its way into mainstream medicine," he says.

Boucek and colleagues' experimental heart transplants pushed the bounds of the "dead donor rule," an ethical guideline stating that an organ donor must be declared dead before vital organs are prepared for transplantation, Bernat says.

When a person's heart stops irreversibly, the death is ruled a cardiac death; this characterizes the death of individuals taken off life support. Typically, respiration stops, so circulation stops, causing the heart to stop, Boucek explains.

In past research—about 100 recorded cases—a heart has not restarted on its own more than 65 seconds after a person was taken off a ventilator. Based on that limited scientific data and a 2005 medical consensus conference, coroners are asked to wait between two and five minutes after the pulse stops to declare death, Bernat explains. That is the general practice protocol of the dead donor rule.

In the first heart transplant Boucek's team performed, the donor infant's heart stopped 11.5 minutes after the baby was taken off life support. Death was then declared three minutes later and transplant procedures immediately followed.

But as more time elapses between when circulation and the heart stop and when transplantation begins, more damage is caused to the soon-to-be donated organs, Boucek says. So, based on the recommendation of an external ethics review board studying the results of experimental transplants, Boucek's team began each of the final two experimental heart transplants 75 seconds after the donor's pulse ceased. The two babies' hearts stopped 27.5 and 16 minutes after each was taken off life support. The coroner then waited 75 seconds to declare death.

Beginning the transplant after that shorter time period—less time than the accepted dead donor rule limit—raises the issue of whether the donor infants were dead, Bernat says. That practice, in essence, violates the dead donor rule protocol, he says.

But "the dead donor rule was never something we said we were going to have," argues Dr. Robert Truog of Children's Hospital Boston. "It's an implicit assumption that ensured donors were dead before a transplant team removes their organs to, in the past, protect the donors' lives." Now, he says, "we have reached a point in transplantation technology where we have other ways of protecting donors, so now the dead donor rule is getting in the way of successful transplantations."

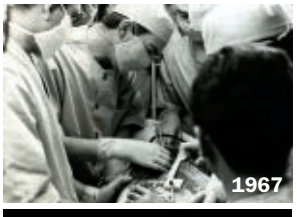
In Boucek's case, three babies were going to die, no matter what, Truog adds. "Parents want to make the best of a tragic situation like that. They want their children's organs donated," and the wait time can jeopardize that, Truog says. He advocates getting rid of the dead donor rule. Donors' prognoses and consent to donate would drive the donation procedure, he says. Timing decisions would be made by the transplant team.

Jettisoning the dead donor rule is radical and risky, Bernat counters. The decision of a patient or a surrogate to end life support should be made before the decision to donate organs, and remain independent of that decision, he says. Separating the two decisions ensures that society's need or a physician's request for organs does not drive the decision to end a person's life—a possibility that may be even more of a concern when the patient and potential organ donor is a child.

Unlike Truog, Bernat advocates a consensus-driven, standard time protocol for organ donations from patients, especially infants and children, who have their life support withdrawn. Developing that consensus will take a joint effort from leaders of the critical care, neurology and transplantation communities to establish acceptable boundaries for organ donation after cardiac death. Waiting 75 seconds is probably not long enough, Bernat adds.

All of this discussion, Boucek notes, is making the transplant process more transparent for society—a result he thinks is healthy for the medical profession. In any case, his team saved three lives, and the method could potentially save hundreds more, he says. ■

Back Story Borrowed hearts



1964 A team at the University of Mississippi Medical Center transplants a chimpanzee heart into a dying patient. The heart beats for 90 minutes before stopping.

1967 South African surgeon Christiaan Barnard performs the first human-to-human heart transplant. The recipient survives for 18 days.

1968 Denton Cooley of Baylor University College of Medicine transplants a heart from a 15-year-old girl into a 47-year-old man. The man survives for 204 days.

1970s Jean Borel investigates the immunosuppressive properties of cyclosporine. The anti-rejection drug later becomes widely used for transplants.

1984 The world's first successful pediatric heart transplants are performed on a 4-year-old boy in New York and on an 8-month-old girl in Texas. Also, a 14-day-old infant girl receives a heart from a baboon.

2007 Roughly 85 infants under age 1, including Zachary Apmann of Denver (pictured at 21 months), receive heart transplants.

AP PHOTO/JACK DEMPSEY; ALFRED PASIEKA/PHOTO RESEARCHERS; PAUL POPPER/POPPERFOTO/GETTY

Understand the Most Brilliant Mind of the 20th Century

Explore the Genius of Albert Einstein

Albert Einstein is undoubtedly one of the most brilliant minds of the 20th century. His ideas on theories of space and time and his earth-shaking equation $E=mc^2$ revolutionized the face of physics. He also achieved fame and influence as a philosopher and humanitarian, involving himself in some of the most profound issues of his day.

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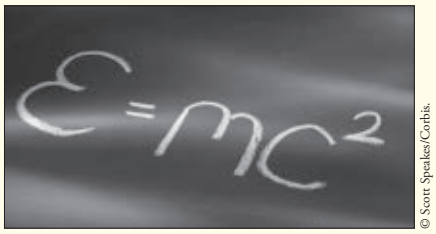

About Your Professor

Dr. Don Howard is a Professor of Philosophy at the University of Notre Dame and Director of Notre Dame's Graduate Program in History and Philosophy of Science. He earned an M.A. and a Ph.D. in Philosophy with a specialization in the Philosophy of Science from Boston University.

Professor Howard has served as an assistant editor and a contributing editor for the Collected Papers of Albert Einstein. He is also a founding coeditor of the Einstein Studies series.

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FBI describes the science used to trace source of anthrax spores

Bacteria's genetic fingerprints prove critical to case

By Rachel Ehrenberg

WASHINGTON — The FBI has offered reporters a glimpse at the science behind the investigation of the 2001 anthrax mailings, which resulted in five deaths. Genetic signatures of the bacteria were prominent clues that eventually led the investigators to an anthrax broth in two Erlenmeyer flasks at the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick in Maryland.

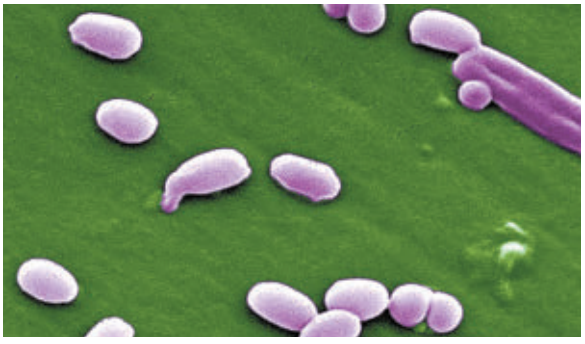
The investigation had implicated Army microbiologist Bruce Ivins as the perpetrator of the anthrax mailings. Ivins committed suicide in July while under investigation. An affidavit released by the FBI in August described Ivins as "sole custodian" of the batch of spores with the telltale DNA.

But in briefings on August 18, officials conceded that about 100 people had access to the batch, called RMR-1029. One other institution, which the FBI would not name, also had anthrax spores with the same genetic signature, investigators said.

In early 2002, the FBI obtained an anthrax sample with DNA that could have linked Ivins to the mailings, but the sample was later destroyed, said Vahid Majidi, assistant director of the FBI's Weapons of Mass Destruction Directorate.

Four mutations lurked in the DNA of the anthrax cultured in the flasks, the same mutations found in samples of the anthrax mailed in the 2001 attacks, officials at the briefings reported. While mutations naturally arise in bacteria, the four mutations the scientists homed in on were stable, said Claire Fraser-Liggett, one of six researchers who discussed the science side of the investigation at the briefings.

"They are not random mutations that come and go," said Fraser-Liggett, director of the newly created Institute for Genome Sciences at the University of Maryland School of Medicine in Baltimore.



The anthrax spores mailed in the 2001 attacks were identified as belonging to the Ames strain (spores shown here).

JANICE HANEY CARR/CDC

Nothing was added to the spores of the rod-shaped bacteria to make them disperse more easily, Majidi said. Tests suggested that some of the mailed spores contained silicon and oxygen, resulting in speculation that the spores were mixed with something that would make them more dangerous. But the silica signal was from inside the spore coat, said Joseph Michael, a materials scientist at Sandia National Laboratories in Albuquerque, N.M. The bacterium may naturally incorporate environmental silica into its spore coat as it develops.

Spores of *Bacillus anthracis* easily drift through the air and take on charge, making them stick to everything, said James Burans of the National Bioforensic Analysis Center in Frederick, Md. That's why labs typically work with anthrax only in liquid form. "People describe it as having a mind of its own," Burans said.

All of the anthrax mailed in the attacks belonged to the Ames strain, which is used in several labs doing basic or vaccine-related research, said Paul Keim, a microbiologist at Northern Arizona University in Flagstaff and director of the Pathogen Genomics Division at the Translational Genomics Research Institute. But a closer look at cultures grown from spores recovered from the mailings revealed phenotypic variation — differences in color, size and texture — that hinted at underlying genetic variation that could help researchers distinguish between batches.

Led by Fraser-Liggett and Jacques Ravel, also of the Institute for Genome Sciences, researchers fully sequenced 12 samples of anthrax from the mailings, with the hope that DNA would lead to the mother stock. Four mutations — specific insertions or deletions of stretches of genetic code — were identified as significant. To determine which labs were using stock with these mutations, investigators obtained more than 1,000 samples of Ames strain anthrax from labs in the United States, the United Kingdom, Canada and Sweden.

Ivins consulted with investigators in 2002 regarding the sampling protocol that should be outlined in the subpoena. But the FBI destroyed the first sample submitted by Ivins because it did not follow the protocol. New samples submitted by Ivins did not contain the four mutations.

Later, investigators realized that Keim, whose lab was keeping a backup of every sample collected, might have the backup of Ivins' original sample. This sample did have the mutations, investigators reported at the briefing.

This investigation was seminal in establishing the field of microbial forensics, said microbiologist Rita Colwell, who was director of the National Science Foundation at the time of the attacks.

Researchers were mum about many of the specifics, saying the results will appear in peer-reviewed journals. Officials said it was unprecedented for the FBI and Department of Justice to hold a briefing on a case that has yet to go to trial.

"I don't think we will ever put all suspicions to bed," said Majidi. "There's always going to be a spore on the grassy knoll." ■

Molecules

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Nanoparticles conspire with free radicals

Dose of carcinogens could be comparable to smoking

By Davide Castelvecchi

PHILADELPHIA — The daily exposure to free radicals from car exhaust, smokestacks and even your neighbors' barbecue could be as harmful as smoking, according to a new study. Many combustion processes, such as those in a car engine, create tiny particles that may act as brewing pots and carriers for free radicals — chemicals believed to cause lung cancer and cardiovascular diseases.

Whether the exposure equates to smoking one cigarette or as many as two packs a day remains difficult to determine, said Barry Dellinger of Louisiana State University in Baton Rouge, who reported the findings August 17 in Philadelphia during a meeting of the American Chemical Society.

His team's experiments, also reported in the July 1 *Environmental Science & Technology*, suggest that noxious chemicals form on soot nanoparticles in the still-hot combustion residue in, for example, car exhaust pipes and catalytic converters.

The chemicals are hydrocarbon-based free radicals. Similar chemicals usually degrade quickly if they float solo. But in this case, the chemicals attach to the nanoparticles and linger in the air far longer than previously thought. "To our enormous surprise, the free radicals survive hours, days, even indefinitely," Dellinger said in an interview.

To mimic the conditions in car exhaust as it cools, Dellinger's team used silica particles 100 nanometers wide and coated with copper oxide. The team then exposed the particles to a hot gas — experimenting with a range of temperatures — containing hydrocarbons typically produced in flames. All are common ingredients in the exhaust of motor vehicles and factories.

The researchers examined the nanoparticles with magnetic fields tuned to identify unpaired electrons, the feature that makes free radicals highly reactive and potentially dangerous to living cells. The data showed a signature typical of free radicals and similar to that of semiquinone, a free radical found in cigarette smoke.

The free radicals, however, showed up only when the initial ingredients had been mixed together at temperatures between 200° Celsius and 600°C. That means free radicals are unlikely to form during actual combustion, which takes place at higher temperatures. Instead, they would probably form once the exhaust begins to cool.

David Pershing, a chemical engineer at the University of Utah in Salt Lake City, says the findings are potentially significant for human health.

Dellinger added that more research is needed to determine not only in what circumstances someone would be exposed to the potentially unhealthy air, but also how much harm it would do to the body.

The exact amount of risk the pollutants pose is hard to estimate, Dellinger said in his presentation. He used air samples provided by the Electric Power Research Institute of Palo Alto, Calif., to determine that the risk could be equivalent to smoking as few as one cigarette a day or as many as 40.

"It's early in the game, and there's a lot of ways of doing these calculations," he said.

The free radicals Dellinger and his team discovered would not show up in ordinary vehicle smog checks, which detect molecules in the gas state and not those attached to solid nanoparticles, he said.

Ironically, even as a catalytic converter breaks down smog-causing pollutants, it may be creating conditions allowing free radicals to form. "You could be destroying some [pollutants] and creating some at the same time," Dellinger says. ■

MEETING NOTES

American Chemical Society
August 17–21, Philadelphia

New coat for spacecraft

A thin-sheet material would make it feasible to build Earth-orbiting satellites as light as five kilograms. Prasanna Chandrasekhar of Ashwin-Ushas Corp. in Lakewood, N.J., said coating spacecraft with the new material could eliminate bulky temperature-control systems. By applying a current, the craft could control the material's darkness and its ability to dissipate heat. Such a shield would help keep temperatures down when the craft is exposed to sunlight, and prevent freezing when it enters Earth's shadow. —*Davide Castelvecchi*

Safer blood thinner

A new way of making heparin, a common blood thinner, could protect against contamination. Mostly extracted from pig intestines, heparin is given to hospital patients to prevent blood clotting. Robert Linhardt of Rensselaer Polytechnic Institute in Troy, N.Y., reported that his team made small amounts of heparin without animal sources. The team used a strain of *E. coli* bacteria to produce a sugar, then used an artificial version of enzymes in pig intestines to turn the sugar into heparin. —*Davide Castelvecchi*

Juice boosts and blocks

Grapefruit juice, known to boost the absorption of some drugs, can also have the opposite effect. David Bailey of the University of Western Ontario in London, Canada, described studies showing that grapefruit juice reduced patients' absorption of the allergy drug fexofenadine (Allegra). Patients drinking grapefruit juice two hours before or while taking the drug had on average only one-fourth as much of the drug in their blood, compared with those who drank water. —*Davide Castelvecchi*

Life

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Magpies check themselves out

Reactions to mirror image suggest self-recognition

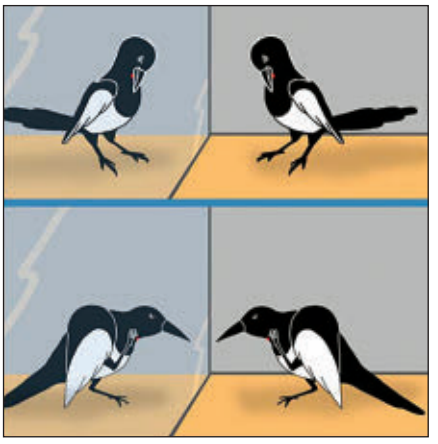
By Bruce Bower

Magpies sing a self-reflective tune that until now has gone unheard. When placed in front of a mirror, these songbirds realize they're looking at themselves, raising the possibility that they have independently evolved the brain power to support basic self-recognition, a new study suggests.

Magpies are the first nonmammal to demonstrate a rudimentary affinity for self-recognition, psychologist Helmut Prior of Goethe University of Frankfurt in Germany and his colleagues report online August 19 in *PLoS Biology*. These members of the corvid family—which includes crows and ravens—join apes, bottlenose dolphins, elephants and humans as the only animals known to understand that a mirror image shows their own body.

"When magpies are judged by the same criteria as primates, they show self-recognition and are on our side of the 'cognitive Rubicon,'" Prior says.

Magpies and other social birds that possess large brains with expanded cortical-like areas should display some level of self-recognition, says Irene Pepperberg of Brandeis University in Waltham, Mass.



Magpies with a red dot painted on their neck tried to touch it with their beak (top) or with their foot (bottom), suggesting self-awareness.

Pepperberg studies thinking and communication in African gray parrots. Her most famous parrot, Alex, could count up to six items and possessed more than 100 vocalizations for objects, actions and colors.

Mirror self-recognition tests, which involve marking an animal with a spot that can be inspected or touched only by looking in a mirror, can be tricky to interpret, Pepperberg adds. Looking in a mirror, one of her parrots scratched a paint mark on his body for nine seconds but ignored the mark for the rest of a 15-minute session. The same bird made no attempt to scratch a barely visible water mark.

Evidence of mirror self-recognition among magpies shows striking parallels to what has been observed in bottlenose dolphins and elephants, comments psychologist Diana Reiss of the City University of New York's Hunter College. The question now is whether magpies' sophisticated social behavior, including intense competition to store food in hidden caches, sets the stage for self-recognition.

In the experiments, each of five magpies first explored a mirror on its own and then again after being marked with paint.

The researchers found that three birds—Gerti, Goldie and Schatzi—preferred to spend time in a cage compartment equipped with a mirror rather than in a cage compartment with a nonreflective plate. The animals closely inspected mirror images, looked behind the mirror and moved back and forth in front of it.

When the researchers applied a bright mark to the feathers of those birds' throats, the birds used the mirror to inspect the marks with care, turning and tilting their heads at close range. On some trials, Gerti and Goldie scratched off marks with their feet. Poorly visible black marks attracted the magpies' attention on only a few occasions. The birds paid the marks no attention when tested without a mirror.

Two other birds, Lilly and Harvey, acted as if their own reflections represented other magpies. They also jumped about and ran around the compartment with the mirror regardless of how they were marked. It's unclear why these two birds failed to recognize their own bodies, Prior says. Studies with chimps have found that mirror self-recognition may decline with age.

ALEXANDRA ACHENBACH/LUDWIG-MAXIMILIANS UNIV.; PRIOR *ET AL.*, *PLOS BIOLOGY*

Slave ants rebel

Tiny ants enslaved inside acorns in the United States may resist their captors with an army of killer nannies. Ants in the genus *Temnothorax* fall prey to a species that doesn't do its own housework. Instead the do-little ants, *Protomognathus americanus*, raid smaller species' nests and steal babies. These youngsters grow up inside the acorn home of the slave-makers' queen, doing her housework and nursemaiding her young. *Temnothorax* sometimes fight raiders, but now Susanne Foitzik of Ludwig-Maximilians University in Munich suggests that post-enslavement resistance also evolves. In lab studies, slave nursemaids (pictured tearing up slave-maker young) killed some 80 percent of their captors' young queens and some 60 percent of the young workers, Foitzik reported at the International Behavioral Ecology Congress held in August at Cornell University. —*Susan Milius*

Body & Brain

20 percent Serious motor vehicle accidents for which sleep deprivation is responsible

Dopamine fends off the zzzzz's

Chemical helps sleep-deprived people stay awake

By Tina Hesman Saey

A reward chemical in the brain is a real eye-opener.

Dopamine, a feel-good brain chemical, helps keep sleep-deprived people awake, researchers from the National Institute on Drug Abuse show in the Aug. 20 *Journal of Neuroscience*. Dopamine is also required for the activity of a drug that treats narcolepsy, Japanese and Chinese scientists report in the same issue.

"Dopamine has been a forgotten neurotransmitter for sleep regulation," says Emmanuel Mignot, a sleep researcher at Stanford University. Increasing evidence points to dopamine as an important ingredient in the brain's recipe for promoting wakefulness.

The new findings suggest that dopamine may naturally increase when a person is sleep-deprived, counteracting a revved-up drive to sleep, says David Dinges of the University of Pennsylvania School of Medicine in Philadelphia. Dinges and Mignot were not involved in the studies.

Sleep deprivation affects some people profoundly, impairing their ability to pay attention and lengthening their reaction times, Dinges says. Other people function nearly as well when mildly sleep-deprived as they do when well-rested. The extent to which dopamine rises in the brain after sleep loss may help explain some of the variability in people's abilities to cope with sleep deprivation, Dinges says.

Dopamine has an undeserved reputation, says Mignot. "People think dopamine equals addiction," he adds. But the chemical plays a role in many brain functions.

Nora Volkow of the National Institute on Drug Abuse led a team at the National Institutes of Health in Bethesda, Md., and the Brookhaven National Laboratory in Upton, N.Y. The researchers recruited 15 healthy volunteers and tested each person's memory and ability to pay attention to visual cues after a good night's sleep and after being kept awake all night. A brain scan called positron emission tomography indirectly measured dopamine levels in the volunteers' brains.

Sleep deprivation increased dopamine in the striatum, a part of the brain that registers motivation and reward. Dopamine also went up in the thalamus, a brain region that helps control alertness, when the volunteers were sleep-deprived. Increases in the brain chemical kept the volunteers awake, and those same increases also correlated with the volunteers reporting that they felt tired.

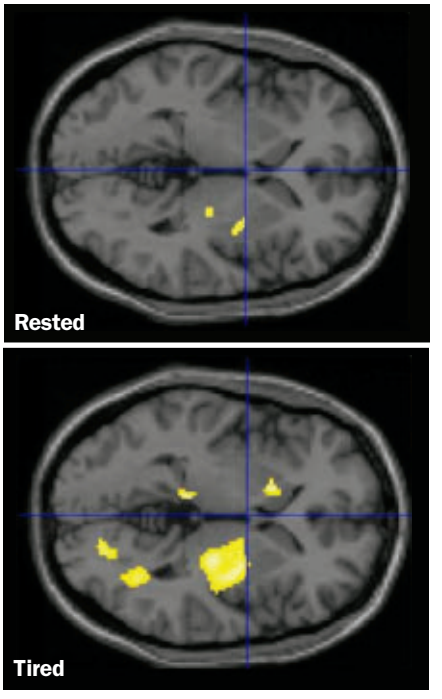
Although increased levels of the neurotransmitter help keep the brain aroused after a sleepless night, higher levels of dopamine don't fend off the thinking and learning problems associated with sleep deprivation, says Volkow, a clinical neuroscientist and director of NIDA.

Some stimulants, such as amphetamines, also increase dopamine in the brain. Previous studies have shown that medical students taking stimulants thought they were more alert. Despite the students' perceptions, their actual performance on tests was worse on the drug.

"A little bit of dopamine is good," says Paul Shaw of Washington University in St. Louis. "More is bad. Less is bad too. You've got to be in the sweet spot."

He speculates that learning and memory may require precise levels of dopamine to work well, but that arousal is controlled by a circuit that is not as sensitive to minor changes in dopamine concentration.

Researchers say the finding fits with Shaw's recent fruit fly study (*SN: 8/30/08, p. 8*). Restoring dopamine activity in flies that started with suboptimal dopamine levels helped them overcome the learning deficits caused by sleep deprivation. In Volkow's study, sleep deprivation appeared to push people past optimal dopamine levels.



In sleep-deprived subjects, dopamine levels rise in some parts of the brain. These brain maps show those changes, measured indirectly. Higher levels of dopamine correlated with reports of feeling fatigued.

Staying awake and alert is a problem for people with the sleeping disorder narcolepsy. The drug modafinil is used to treat the condition, but no one is sure how it works. Previous research has suggested that the drug acts on a wide variety of brain chemicals. But the second new study, by researchers at the Osaka Bioscience Institute in Japan and at Fudan University in Shanghai, China, shows that two proteins sensitive to dopamine's action are essential for modafinil's arousal effect.

Dopamine could be the drug's direct target, but there are not enough data to rule out the possibility that dopamine may just be a key link in a cascade set off by other excitatory molecules, Dinges says.

Other molecules are almost certainly involved, Volkow says. "Sleep is so important that it would be oversimplistic to say that sleep deprivation is only going to change the dopamine system." ■

VOLKOW ET AL./THE JOURNAL OF NEUROSCIENCE

Atom & Cosmos

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Multiverse hosts stellar diversity

Different laws still allow for stars, simulation suggests

By Ron Cowen

Fred Adams sees stars in the most unlikely places.

His calculations suggest that, contrary to some previous claims, stars are not only common in our cosmos but are also ablaze in myriad other universes, where the laws of physics may be drastically different. Even in a cosmos where balls of gas and dust never collapse and ignite to make conventional stars, radiation produced by black holes and clumps of invisible "dark matter" may play the same role as stars, says Adams, a theorist at the University of Michigan in Ann Arbor.

"In fact, all universes can support the existence of stars, provided that the definition of star is interpreted broadly," writes Adams in the August online *Journal of Cosmology and Astroparticle Physics*.

Multiple universes (known collectively as the multiverse) are envisioned by some versions of the Big Bang theory (*SN: 6/7/08, p. 22*). According to one leading version, the cosmos underwent a growth spurt (called inflation) in its first tiny fraction of a second, enlarging from subatomic scale to the size of a grapefruit. This rapid expansion may also have occurred in other patches of space, creating a multitude of universes with different physical laws and numerical constants.

Adams simulated conditions in other universes by simultaneously varying three parameters: the gravitational constant, which determines the strength of gravity; the fine structure constant, which sets the strength of the electromagnetic force; and a number that determines the rate of nuclear reactions, which keep stars shining.

"All universes can support … stars, provided that the definition of star is interpreted broadly."
FRED ADAMS

Other researchers have considered not only multiverse star formation and stellar structure, but also galaxy formation and the existence of life.

"I did a specific approach that is much more detailed on the particular topic of 'can there be stars?' " says Adams.

By allowing three parameters, rather than just one, to vary, he created a simulation that may embrace a larger number of possible universes. He finds that stars are stable entities in roughly one-fourth of the universes he considered. "That's a sizable amount of real estate," he says.

He cautions that his calculations assume that all possible values of each parameter are equally likely. In fact it may be more likely for a universe to have a smaller nuclear reaction rate than a larger one. "We simply do not know," Adams says.

The results are not "particularly surprising, as stars are both fairly simple and fairly robust objects that essentially require [only] a heat source and gravity," says Anthony Aguirre of the University of California, Santa Cruz. "But Adams has done an elegant job of working through the problem to find out exactly how different the universe could be while supporting stars."

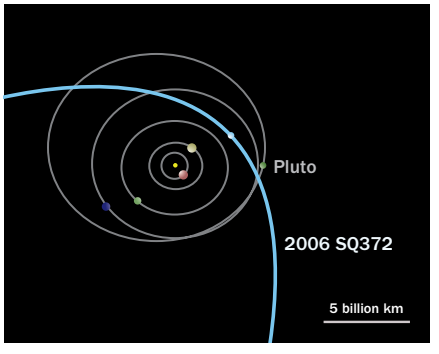
Icy rock takes long way home

Cometlike body traveling back to inner Oort Cloud

By Ron Cowen

A lump of ice and rock now near Neptune apparently came in from the cold — the outermost limits of the solar system — and is on its way back out there.

The roughly 40-kilometer-wide object, dubbed 2006 SQ372, may be the first known visitor to the planetary neighborhood that still makes return trips home to the remote Oort Cloud. This cloud is a proposed reservoir of long-period comets — those that visit the inner solar system no more than once every 200 years — and was first hypothesized to exist in 1950. It is probably thousands of times more distant from the sun than is Earth.



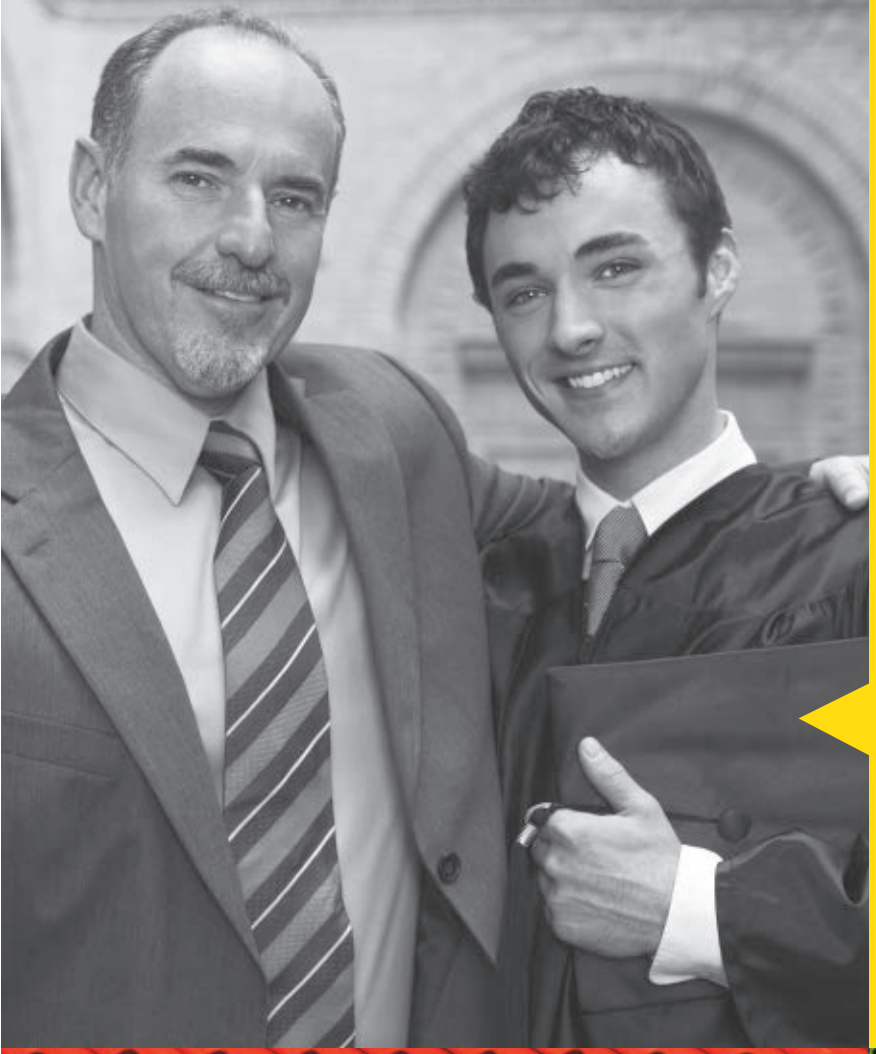
Computer simulations suggest 2006 SQ372 is now returning to the Oort Cloud.

"We believe SQ372 is the first detected member of a comet population in the outer solar system that comes from the, up-until-now, unobserved inner Oort Cloud," says codiscoverer Nathan Kaib of the University of Washington in Seattle. "Comets like SQ372 have the potential to tell us what the entire Oort Cloud looks like … as well as provide clues about the environment that the solar system first formed in." Kaib's team reported the result August 18 in Chicago at a meeting on findings from the Sloan Digital Sky Survey.

Researchers have determined that 2006 SQ372 is now on the return leg of a 22,500-year, highly elongated orbit that will take it back to a region 240 billion kilometers from the sun. That's nearly 1,600 times as far from the sun as Earth is, making 2006 SQ372 the most distant known tourist to visit the outer planets.

SQ372 was first spotted in 2006, but follow-up detections were needed to more accurately determine its orbit.

KAIB



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Earth

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Solid evidence about Earth's core

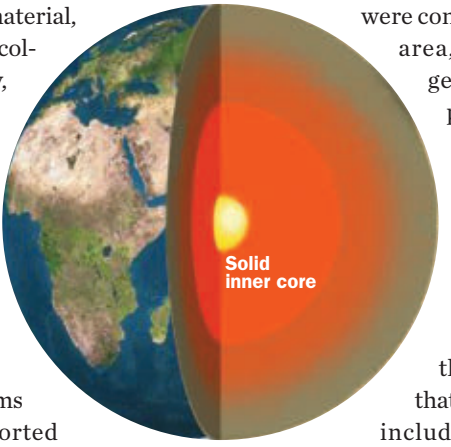
Seismic waves confirm models of the planet's interior

By Sid Perkins

Faint yet distinct ground motions recorded by a large network of seismic instruments in Japan in early 2006 are the strongest, most direct evidence that Earth's inner core is solid.

On February 22, 2006, a magnitude-7 quake rocked Mozambique. The temblor was an unusually large one for southern Africa, but also quick for its size: Motions at the epicenter lasted only eight seconds or so, says George Helffrich, a geophysicist at the University of Bristol in England. While much of the quake's energy spread along the planet's surface, some radiated downward, traveled through Earth's core and then returned to the surface in Japan, where more than 700 seismometers picked up the vibes.

Some types of ground motions triggered by earthquakes can pass either through solid rock or a liquid such as water or molten iron. But the size, shape and timing of vibrations picked up by the Japanese instruments suggest that the waves traveled through the planet's inner core as shear waves, which can travel only through a solid material, says Helffrich. He and colleague James Wookey, also a geophysicist at the University of Bristol, report their findings in the Aug. 14 *Nature*.



Most models of Earth's internal structure include a molten outer core and a solid inner core. Teams have previously reported data hinting that seismic shear waves pass through the inner core, but those reports were inconclusive and direct evidence remained elusive, Helffrich says.

One reason these particular ground motions have been so elusive is their size compared to seismic background noise. Indeed, the ground motions reported by Helffrich and Wookey are "so small, they're easily confused with other vibrations bouncing around inside the Earth after an earthquake," says Ken Creager of the University of Washington in Seattle. But the characteristics of the ground motions the Bristol team noted were consistent over a broad area, a sign that local geological variations probably didn't create spurious reflections that could have confused the analysis, he adds.

The material in the core attenuated the waves less than expected, a sign that the material doesn't include many vibration-damping pockets of melted material, Helffrich suggests. Also, a disparity in travel time between two sets of ground waves suggests that sound travels faster through the material in some directions than it does in others.

Grazers align north to south

Deer, cattle may sense Earth's magnetic field

By Sid Perkins


Cows may have a sixth, magnetic sense.

TENBACK/ISTOCKPHOTO.COM; LUNAR AND PLANETARY INSTITUTE/NASA

Moss covers the north side of trees in a forest. But if you're lost in an open field, look to deer to point you in the right direction.

Herds of grazing and resting deer and cattle tend to align themselves, on average, with Earth's magnetic field lines, report Hynek Burda of the University of Duisburg-Essen in Essen, Germany, and his colleagues online August 25 in *Proceedings of the National Academy of Sciences*.

The researchers observed almost 3,000 red and roe deer in the Czech Republic. Individuals in a grazing herd were generally aligned to face magnetic north. That orientation didn't coincide with any aspect of the terrain, the direction from which the wind was blowing or the direction from which the sun was shining, Burda says.

Data for cattle came from 308 herds captured in images posted on Google Earth. The average orientation of each herd didn't line up with climatic phenomena or with true north, but it did closely match either magnetic north or south.

Many creatures can sense Earth's magnetic field, says John B. Phillips of Virginia Tech in Blacksburg. The ability to detect the field "plays a fundamental role in spatial perception" and may help creatures navigate, even if they move only over short distances, Phillips says.

Environment

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Popular plastics chemical poses another threat: this time diabetes

Bisphenol A blocks protective hormone in human tissue

By Rachel Ehrenberg

The rap sheet for bisphenol A, a chemical commonly found in food and water containers, baby bottles and the lining of aluminum cans, keeps getting longer. But the chemical still has friends at the FDA.

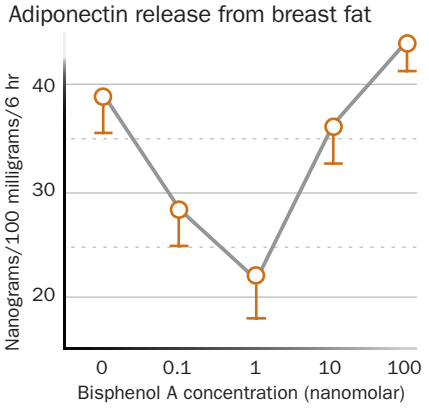
A new study examining the effects of bisphenol A in human fat tissue finds that the chemical suppresses a hormone that protects people from heart attacks and type 2 diabetes. The bisphenol A doses examined in the study are typical of levels found in human blood.

The study appeared online August 14 in *Environmental Health Perspectives*, a day before the Food and Drug Administration released a draft assessment of bisphenol A that decrees the chemical safe at current exposure levels.

"I do not understand why the governments of the United States and Europe put money into studying pollutants like bisphenol A and then later don't listen to what scientists have found," comments Angel Nadal of the Spanish Biomedical Research Network in Diabetes and Associated Metabolic Disorders in Alicante. "They are using a last-century approach to toxicology."

Hundreds of studies have documented bisphenol A's ability to meddle with development and tissue function (*SN: 9/29/07, p. 202*). The chemical, the starter material for many plastics and epoxy resins, has a number of adverse health effects shown to cause reproductive problems, certain cancers and asthma in lab animals.

The FDA responded to requests for comment on the research with an e-mail stating: "FDA is in a legally mandated peer review process, so we are not going to comment on the scientific points regarding individual pieces of data prior to that review process."



The amount of adiponectin hits a low when fat cells from a patient are exposed to the level of bisphenol A typically found in human blood.

Bisphenol A naturally leaches from food and beverage containers, and human exposure is widespread. A 2008 National Center for Environmental Health study detected bisphenol A in the urine of 93 percent of the study's participants.

In the body, bisphenol A mimics the hormone estrogen by attaching to the same cellular sensory molecules that natural estrogens stimulate. But the chemical's precise mode of action remains a puzzle, says Nira Ben-Jonathan, an endocrinologist at the University of Cincinnati in Ohio, who led the new study. "It's really still enigmatic," she says. "No one can put their finger on how it works."

Recently, evidence has accumulated that estrogen-sensing molecules, or receptors, play an important role in metabolic disorders. Mutant mice that don't have certain estrogen receptors eat more, become obese and become resistant to insulin, Nadal says. Estrogen receptors also seem to be involved in the body's management of insulin in the liver and skeletal muscle. So it is not surprising that something like bisphenol A, which also interacts with these receptors, might interfere with metabolism, he says.

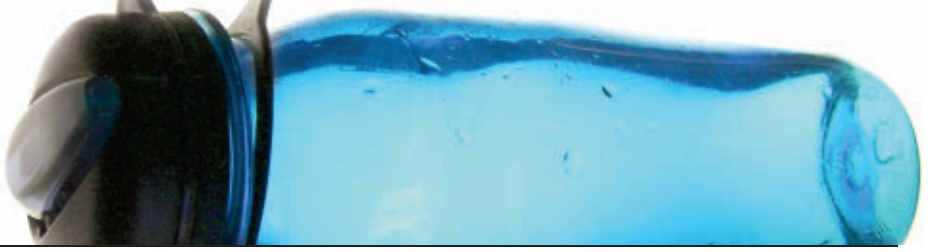
In the new study, Ben-Jonathan's team collected fat tissue surgically removed from people having breast reduction, tummy tucks and gastric bypass surgery at the Christ Hospital in Cincinnati. The researchers exposed some of the tissue to estradiol, a natural form of human estrogen, and some to bisphenol A. Both treatments suppressed the release of the protective hormone adiponectin, which is secreted by fat cells and protects against the suite of conditions that can result in heart attacks and type 2 diabetes.

"These findings provide the molecular basis for bisphenol A being implicated in both obesity and potentially the associated disease that is now being detected in children and adolescents — type 2 diabetes," comments Frederick vom Saal of the University of Missouri in Columbia.

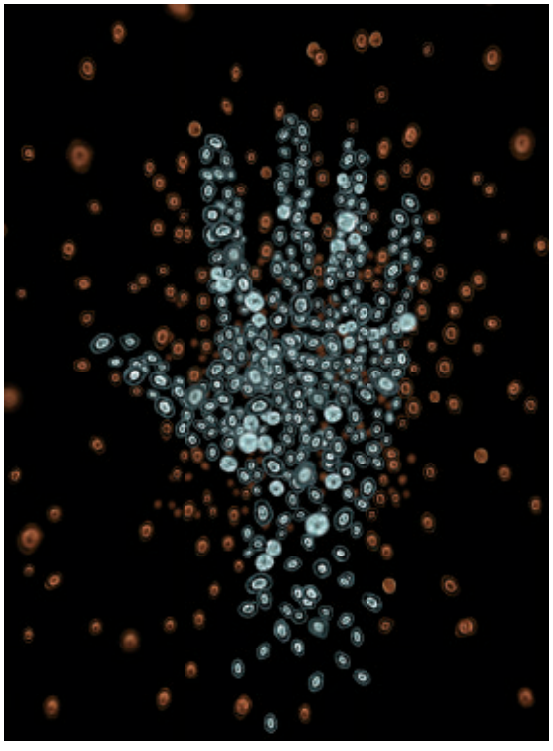
Even though the baseline levels of the protective adiponectin varied greatly from person to person, the work nicely demonstrates that low doses of bisphenol A influence the fat cells' output of adiponectin, Nadal says.

A study of mice by Nadal and colleagues, published in April in *PLoS ONE*, found that bisphenol A makes the pancreatic cells known as beta cells crank up insulin output. This work follows research that demonstrated that low doses of bisphenol A made mice insulin-resistant.

The new study is especially notable because it uses relevant doses and human tissues, says Nadal. ■



T. SIEGFRIED; SOURCE: BEN-JONATHAN



Poten

Stem cells' powers of self-renewal, immort toward understanding them has been slow laboratory. More recently, though, molecu starting to see how stem cells can replenish to turn adult skin cells into cells more like soon harness the capabilities of stem cells,

Essential Stemness

Scientists move closer to understanding the dual fates of embryonic stem cells — to divide or develop

By Tina Hesman Saey

If you think the roadwork in your town is bad, that's nothing compared with the traffic trouble inside a cell. DNA gets repaved with chemicals and proteins almost constantly, maintaining a DNA-protein-chemical infrastructure called chromatin. Chromatin construction helps determine whether a cell's gene activation machinery can zip along like a car-pool van in the HOV lane or gets stuck in a bumper-to-bumper jam. And chromatin prevents cells from wandering off on the wrong developmental road, usually by turning off genes that misdirect cells.

But some cells do things differently. Embryonic stem cells are not stuck in one lane with only one route available. These cells are perpetually poised at a fork in the road, with all options open. They retain the ability to become any type of cell in the body, a property called pluripotency. At the same time, embryonic stem cells have the ability to copy themselves indefinitely. Understanding how these cells accomplish those two feats — dividing indefinitely and choosing multiple identities — is a long-standing mystery of biology.

When seeking the stem cells' secrets, scientists have generally focused on finding the ingredients that confer pluripotency, with less concern for perpetual self-replication. But new research suggests that versatility and immortality are probably not separate traits. The key to making an embryonic stem cell, many researchers believe, lies in balancing the two.

New research shows, for example,

Continued on Page 22

t Promise

ality and potential for medicine inspire those who study them. But progress — it took 20 years just to figure out how to grow embryonic stem cells in the lar techniques have enabled swift movement on two fronts. Researchers are their numbers while giving rise to specialized cells. Others are learning how their embryonic ancestors. These advances offer hope that scientists will at last fulfilling the cells' promise. **Illustrations by Bryan Christie**

Back to the Womb

Reverting adult cells to an embryonic state without creating embryos is a tricky business

By Patrick Barry

The diagnosis is not good; the patient will need surgery. So the doctor plucks a hair from the patient's head and tells her to come back in a few weeks. When the patient returns, the surgeon patches up the faulty organ by implanting healthy cells generated in the lab from the patient's hair follicle. After a few months, the new cells have integrated into the organ and the woman's symptoms recede. A year later, she's healthy and living a normal life.

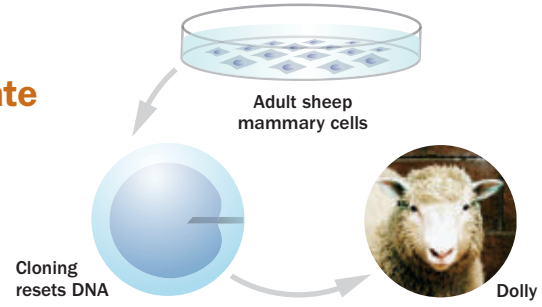
This is the scenario that stem cell researchers hope will be commonplace 10 or 15 years from now. A patient's own cells — perhaps taken from hair follicles, blood or skin — would be transformed into cells of the heart, brain or other organs. Doctors would then transplant these converted cells into the afflicted organ to treat the illness, whether it's multiple sclerosis, Parkinson's disease, heart failure or diabetes.

That dream came closer to reality last November. Two teams of scientists announced that they had wound back the clock on adult human skin cells, regressing those cells to an embryonic state. Just like embryonic stem cells, these reprogrammed cells seemed capable of becoming any of the 200-plus cell types in the human body, an ability called pluripotency (*SN: 11/24/07, p. 323*).

"The fact that you can do something to adult cells to reprogram them was absolutely novel," says Jeanne Loring, director of the Center for Regenerative Medicine

Continued on Page 18

In Dolly, scientists saw proof that the DNA in a mature body cell could be "reset" to an embryonic state and then grow into every kind of cell in a newborn clone's body, from heart muscle cells to nerve cells and bladder cells.



at the Scripps Research Institute in La Jolla, Calif. "It goes against everything that everyone had ever thought about the abilities of adult cells."

Before, the only way to obtain pluripotent human cells had been to extract stem cells from 5-day-old embryos, which made the technique controversial. Reprogramming adult cells doesn't involve making or destroying embryos, so the new cells — called induced pluripotent stem cells, or iPS cells — seemed to offer all the medical promise of embryonic stem cells without the political quagmire.

But nobody really knows how similar these new cells are to embryonic stem cells at the genetic level. Subtle differences in patterns of gene activity could undermine some of the new cells' potential to treat diseases, or even cause the cells to behave abnormally if implanted. Before doctors can safely use reprogrammed cells in people, scientists need to know whether these new cells are truly genetic "twins" of real embryonic stem cells.

Cancer also poses a potential risk. To reprogram adult cells, scientists expose cells to four genetically engineered viruses. Each virus inserts a gene into the cells' DNA at random locations. Such willy-nilly insertions sometimes disrupt the cells' genes, including critical ones such as tumor suppressor genes. This viral disruption can cause cells to grow out of control and form a tumor — another problem that must be solved before physicians can consider treating patients with reprogrammed cells.

Recent research is beginning to overcome these hurdles. Scientists are removing viruses one by one from their cell-conversion recipes. And new genetic studies suggest that these recipes do indeed fully reprogram adult cells — fulfilling a possibility first suggested by the birth of Dolly.

Hitting the reset button

If a sheep could win a Nobel Prize, the prize for paving the way for reprogrammed stem cells would go to Dolly, the first cloned animal.

Lost in the media frenzy that followed Dolly's birth in 1996 was a point more subtle than talk of clone armies and replacement pets. In Dolly, scientists saw proof that the DNA in a mature body cell could be "reset" to an embryonic state and then grow into every kind of cell in a newborn clone's body, from heart muscle cells to nerve cells and bladder cells.

During cloning, inserting the nucleus of an adult cell and its DNA cargo into an emptied egg cell resets the adult DNA. Somehow, egg cells know how to perform this reprogramming feat.

By figuring out which proteins create and maintain this embryonic state, scientists thought they might be able to use those proteins to reset whole adult cells, not just the DNA.

Looking at the genes active in embryonic stem cells, Shinya Yamanaka and Kazutoshi Takahashi from Kyoto University in Japan found a set of four genes that, when inserted into the cells via viruses, did the trick in mouse cells in 2006 and, later, human cells: *Oct3/4*, *SOX2*, *c-Myc* and *KLF4*.

Almost immediately, stem cell researchers around the world flocked to the newly discovered recipe and began experimenting with reprogrammed cells. But work on the more controversial embryonic stem cells wasn't abandoned. Unaltered, true embryonic cells still serve as a gold standard of "stemness" for sizing up the new cells.

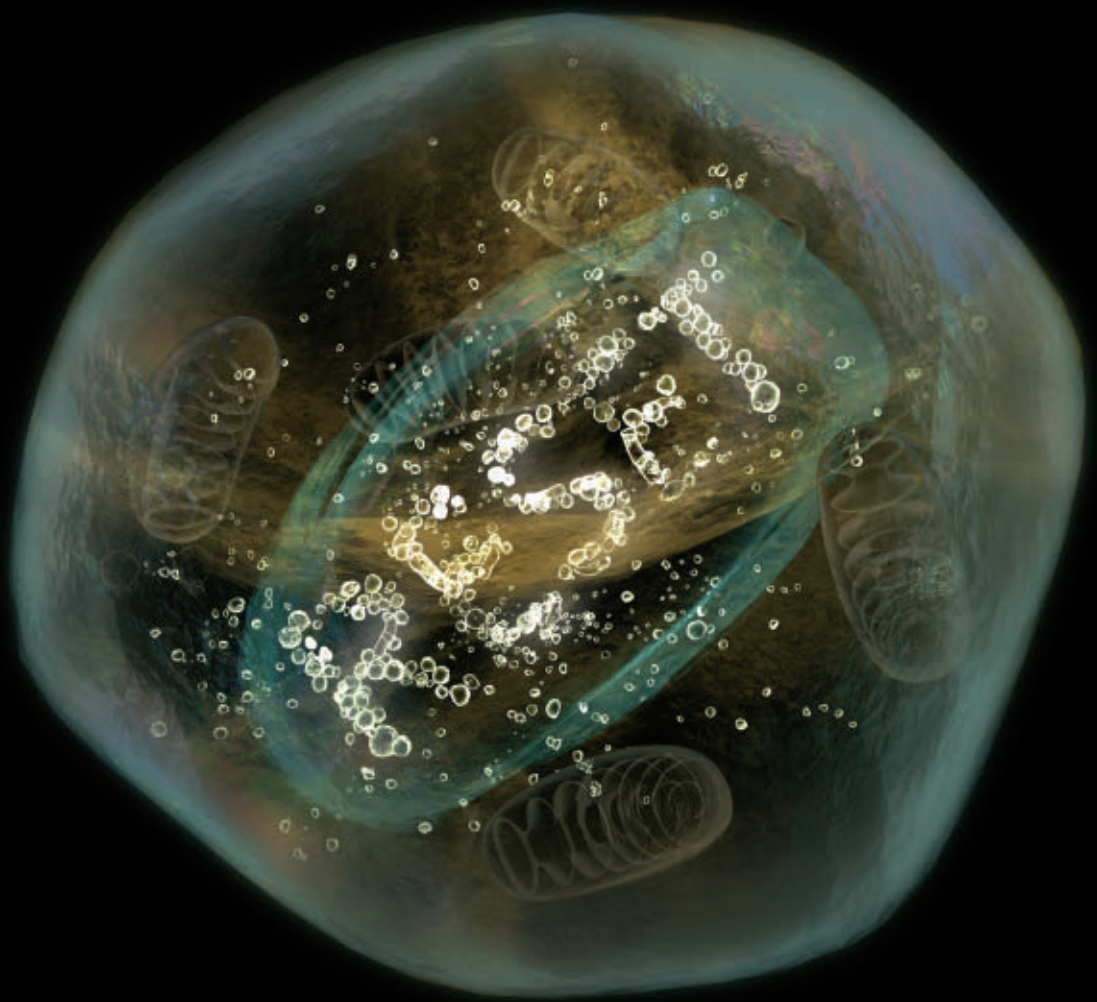
"You never could have made a [reprogrammed] cell without an embryonic stem cell to compare to, to tell you what a pluripotent cell was," says cardiologist Robb MacLellan of the UCLA David Geffen School of Medicine. Reprogrammed cells are "still very preliminary, and they will need a lot of work before you can say that they would be better or equivalent to embryonic stem cells."

Scientists also assess the reprogrammed cells' stemness by using them to treat disease in animals. If iPS cells are truly the same as embryonic stem cells, they should behave the same once converted to heart or nerve cells and implanted in the body.

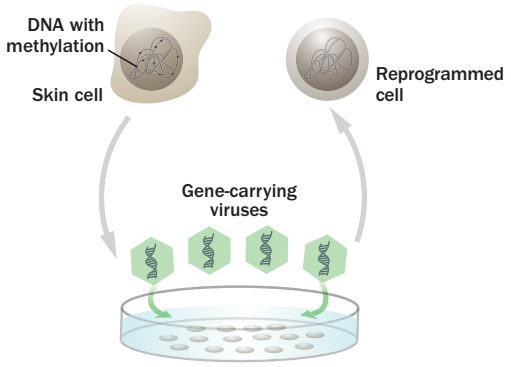
For sickle cell anemia, at least, some evidence suggests that reprogrammed cells can do the job. Rudolf Jaenisch and his colleagues at the Massachusetts Institute of Technology corrected the faulty gene that causes sickle cell anemia in reprogrammed mouse skin cells. After coaxing the cells to develop into mature bone marrow cells, the scientists injected the cells back into the mice. Once the new cells took residence in the mice's bone marrow, those cells began producing normal blood cells and the mice's conditions improved, Jaenisch's team reported last December in *Science*.

Reprogrammed cells can also become nerve cells and treat mice with a condi-

DIAGRAMS: J. KORENBLAT, PHOTO: REUTERS



One way cells shut down unneeded genes is by attaching small molecules called methyl groups to the DNA, a process called methylation. Turning back the clock to return an adult cell to an embryonic state is largely a matter of removing this methylation.



tion analogous to Parkinson's disease, Jaenisch's team showed in research published in the April 15 *Proceedings of the National Academy of Sciences*. In the experiments, reprogrammed cells once again appeared to behave just as embryonic stem cells would.

Another encouraging sign came from comparing which genes are switched off in reprogrammed cells and in embryonic stem cells. As an embryo develops in the womb, cells descended from embryonic stem cells gradually become more and more specialized into, say, liver or bone cells. Specialization primarily consists of shutting down unneeded genes — turning off liver genes in bone cells and vice versa.

One way cells shut down unneeded genes is by attaching small molecules called methyl groups to the DNA, a process called methylation. Turning back the clock to return an adult cell to an embryonic state is largely a matter of removing this methylation. In most studies, methylation patterns of reprogrammed cells have closely mirrored those of embryonic stem, or ES, cells, leading some scientists to view the two as functionally identical.

"They're essentially the same cells," says Michael West, a stem cell researcher and chief executive of BioTime, a biotechnology company based in Alameda, Calif. "They're called iPS cells, but they are ES cells as far as I'm concerned."

Not all scientists agree. "I would say they're not entirely the same, but they're pretty close," says Sheng Ding, a stem cell researcher at the Scripps Research Institute. "There's still sort of imperfect gene activation."

A study appearing online August 24 in *Nature* could finally settle the matter. Loring of Scripps and her colleagues profiled the activity of thousands of genes and proteins in reprogrammed cells, embryonic stem cells, neural stem cells and other stem cells. Comparing these activity profiles revealed a set of 19 proteins that clearly delineate between cells that are pluripotent and others, such as neural stem cells, which are not.

"We can always tell you if a cell falls into that category or not. It's very clear," Loring says. When her team screened reprogrammed cells based on these key proteins, those cells fell cleanly into the same group as embryonic stem cells.

"People who have looked at [reprogrammed] cells before have gotten the impression that they are different, but this shows that they're the same," she says. "If they hadn't been labeled, I wouldn't have been able to tell them apart from [embryonic stem] cells."

The results suggest that, on a genetic level, converted adult cells are so much like true stem cells that they're interchangeable. Except, that is, for those pesky viruses.

Breaking a few eggs

Progress on exorcising viruses from reprogramming recipes has been swift.

In January, research groups led by Yamanaka and Jaenisch separately succeeded in converting cells without the virus carrying *c-Myc*, the groups reported in *Nature Biotechnology* and *Cell Stem Cell*. Because *c-Myc* is known to increase the risk of cancer on its own, it was the first gene scientists aimed to eliminate.

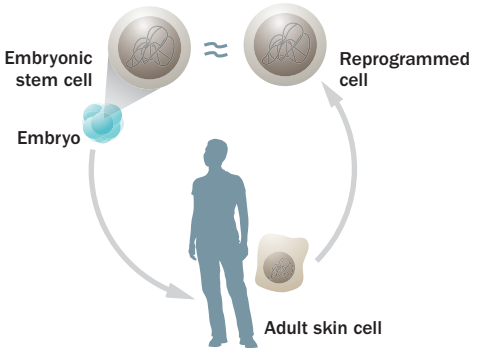
The conversion of mouse skin cells took longer without *c-Myc* — 21 days instead of six — but the cells otherwise appeared to be reprogrammed. During previous experiments, mice grown from embryos containing reprogrammed cells developed tumors because of *c-Myc*, but in these two experiments, the hybrid mice were tumor free. Yamanaka's group also showed that the *c-Myc*–free technique can reset human skin cells.

In later experiments by another group, the *c-Myc*–free technique enhanced with valproic acid converted more than 100 times as many cells after a week as the technique alone did. This improvement offset much of the efficiency lost by removing *c-Myc*, a team led by Douglas Melton of the Harvard Stem Cell Institute in Cambridge, Mass., reported in the July *Nature Biotechnology*.

Using simple chemicals like valproic acid to replace the virus-carried genes could be much safer than dealing with viruses, since the pharmaceutical industry has decades of experience developing and testing small-molecule drugs. These drugs can activate the cell's same native molecular machinery as inserted genes would, thus reprogramming the cells in similar ways.

Replacing the three other virus-gene packages in the reprogramming recipe with chemicals like valproic acid (a compound commonly used in antiseizure medications) is one approach scientists are pursuing to make the conversion process more palatable to the FDA, which would have to approve any medical use of reprogrammed cells. "The FDA brings a whole extra level of scrutiny when there's

"People who have looked at [reprogrammed] cells before have gotten the impression that they are different, but this shows that they're the same," says Jeanne Loring of Scripps. "If they hadn't been labeled, I wouldn't have been able to tell them apart from [embryonic stem] cells."



this genetic modification of cells" by viral insertion of genes, West says.

In unpublished research, Ding's group recently replaced two more of the virus-delivered genes with simple chemicals. "Before it was four genes, now we're down to one, and it's only been about two years" since reprogrammed mouse cells were first created, Ding says. "We were surprised that it wasn't really difficult at all."

Scientists are exploring other ways to solve the virus issue as well, Loring notes. One approach could be to use a different kind of virus. Some viruses deliver genes into a cell without integrating those genes into the cell's DNA. The genes remain free-floating in the cell body, where they can be translated into proteins. Eventually, the cell's enzymes degrade the genes, removing the potential danger created by random insertions of foreign genes into the cell's DNA.

Scientists could also inject the reprogramming proteins directly into the cells, rather than adding the genes that encode those proteins. But the problem with direct protein injection — as well as the nonintegrating viruses — is timing.

"We don't know really how long these inducing factors have to be around in order to reprogram the cells," Loring explains. Without some intervention by scientists, injected proteins would be degraded by the cell in a matter of hours. "If you don't do it for long enough, you might as well not have done it."

Loring is exploring yet another idea: microRNAs, short RNA molecules that silence specific genes. Each cell in a person's body contains a complete set of his or her genetic code, including the four genes in the original reprogramming recipe. So adult cells already have these genes — they're just switched off. Loring hopes to reactivate the cell's own reprogramming genes by using microRNAs to silence the proteins that keep those genes turned off.

Her lab recently identified specific microRNAs that could perform this task. While the experiments are ongoing, Loring says that these microRNAs could be delivered into cells without viruses.

Techniques for each of these approaches are developing rapidly, and many scientists expect that, one way or another, the virus issue will soon be resolved. "It's happening pretty fast," Ding says. "One, two years this will be done."

The hard part

Of course, that's not to say that stem cell therapies will be readily available in only one or two years.

Even after scientists can make virus-free, embryonic-like reprogrammed cells, perfecting the techniques for using these cells in patients will take years.

"You cannot use [converted] cells on their own for anything," Ding notes. "You still have to differentiate the cells into something for it to be useful."

Because reprogrammed cells can become any type of cell in the body, such cells transplanted directly into mice (and presumably people) can develop into teratomas — ghastly tumors consisting of jumbles of hair, teeth, heart and other tissue types, all growing unchecked.

Before transplantation, scientists must first grow the reprogrammed cells in lab dishes under carefully controlled conditions to steer the cells into becoming heart cells, pancreas cells or whatever is needed for the therapy.

These steering techniques involve complex mixtures of signaling molecules. Scientists already know how to direct human stem cells into becoming cells of the heart, brain, pancreas and others, but in experiments on animals, cells made with these techniques don't cope well after transplantation. Typically, the newly minted cells don't integrate well into the organs, and most of the transplanted cells die.

"The actual survival of the cells is so poor," MacLellan says. "This is going to be a huge issue before it will be clinically applicable." These techniques will have to be refined further before they'll be ready for widespread clinical use, Ding says. And that research is slow going.

Researchers estimate that it might take five or 10 years before they'll be ready to begin clinical trials on people using cells derived from reprogrammed cells.

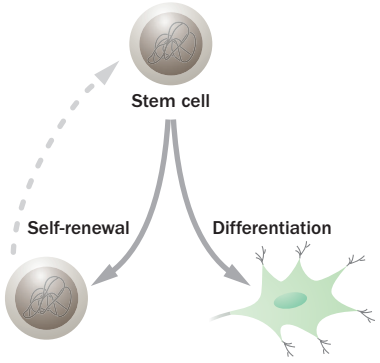
Scientists also want to know the full spectrum of cells in a patient's body that can be reprogrammed. If and when therapies based on converted cells become commonplace, having to extract deep skin cells from each patient wouldn't be particularly convenient.

Ding suggests an easier approach: Perhaps scientists could convert cells from follicles of a patient's hair. ■

Explore more

- To hear Yamanaka discuss his work with iPS cells, follow the link from www.sciencenews.org/Yamanaka.

"Life is just self-renewal and differentiation," says Qi-Long Ying, a stem cell biologist at the University of Southern California. Stem cells are all about the interplay of those two processes.



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that dividing forever may be the natural state of a stem cell's affairs. The cells keep renewing themselves until a signal arrives to differentiate, or transform into another cell type. Another study finds that a family of chemicals involved in choosing identity is also important in guiding cell division. And a network of hundreds of genes involved in pluripotency may also be involved in self-renewal, further research suggests.

These and other studies are leading to deeper understandings of how embryonic stem cells accomplish their defining feats and are allowing scientists to better grasp the essence of stemness.

Stem cell turn signals

Researchers used to think that getting a stem cell to grow required hormones and growth factors, says Qi-Long Ying, a stem cell biologist at the University of Southern California's Keck School of Medicine in Los Angeles. But maybe cells simply keep dividing unless instructed otherwise. In fact, embryonic stem cells will keep making more stem cells unless they get a signal to develop into another type of cell, Ying and colleagues reported in the May 22 *Nature*.

"Life is just self-renewal and differentiation," Ying says. And stem cells are all about the interplay of those two processes.

For instance, by ultimately signaling a cell to turn on certain genes, proteins that take part in a series of reactions called the MAP kinase pathway exert an important influence on differentiation. And MAP kinase and its associates are also required for cell division. At low concentrations, the MAP kinase proteins tell the cell to divide; high levels prompt development of the stem cells into other cell types. So to stay a stem cell, the cell needs to turn down, but not off, activity of the MAP kinase pathway, Ying says. He suspects that several other factors may also walk such a tightrope to maintain stemness.

Other work, reported by an international group of researchers online August 24 in *Nature*, shows that a large network of many genes is responsible for the pluripotency of embryonic stem cells. Circumstantial evidence suggests that the same set of gene and protein interactions are involved in the cells' self-renewal, says study coauthor Franz-Josef Müller of the Center for Integrative Psychiatry in Kiel, Germany.

"This is an active group of genes that are doing something together," Müller says. "I'm pretty sure they're not just suppressing differentiation signals." But what exactly all the genes do is not clear.

Many of the factors identified in the networking study circle around the DNA. Some, like the two "master" ingredients Oct3/4 and SOX2, are what scientists call transcription factors, proteins that direct gene activity. (Those two proteins, along with KLF4 and c-Myc, are the transcription factors used to reprogram skin cells into pluripotent stem cells.)

Certain combinations of the A's, C's, G's and T's that make up the DNA alphabet form what amounts to a reserved parking sign for transcription factors. When the factors find a sign with their name on it, they latch on to the DNA and help to switch nearby genes on or off.

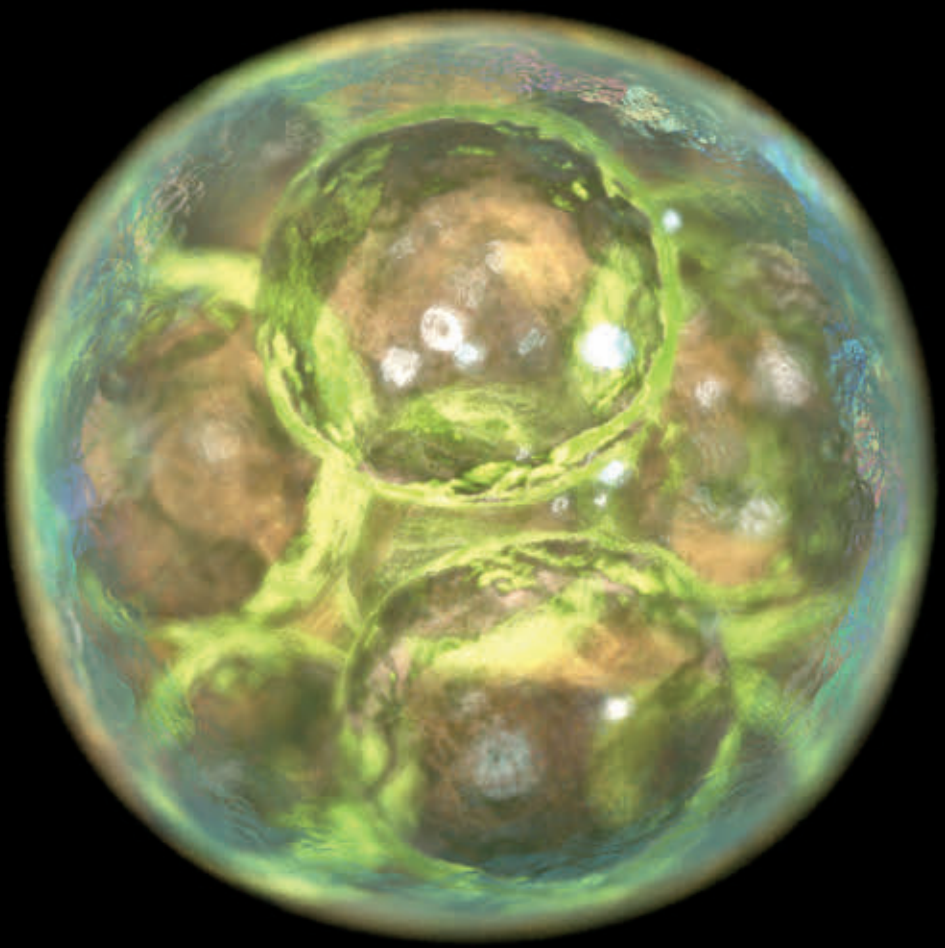
At least that is what would happen if DNA were naked, the equivalent of an empty parking lot. But it's not. The situation is far more complex, thanks to the chromatin infrastructure that guides the cells' machinery for activating genes.

During development, two groups of dueling proteins help direct gene activity. The Polycomb group shuts genes down; the trithorax group turns genes on. Both groups accomplish their task by pinning a chemical called a methyl group to one of DNA's close associates, a protein known as histone H3. The Polycomb group attaches a methyl group to the protein building block lysine at position 27 in the chain of amino acids making up the histone. Trithorax proteins methylate a lysine as well, but at position 4 instead of 27.

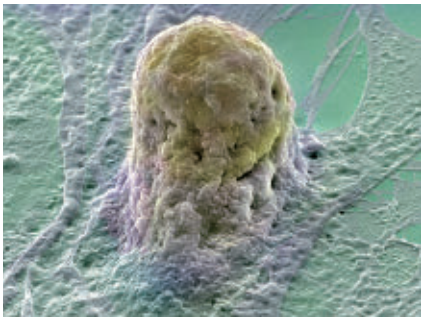
It seems a subtle difference, but to a cell it's a distinction as clear as that between red and green traffic signals.

In embryonic stem cells, genes that encode proteins important in development and about 2,500 other genes carry both Polycomb and trithorax methylation marks, says Bradley Bernstein, a genome scientist and chromatin biologist at Massachusetts General Hospital and Harvard Medical School in Boston. So, much as Schrödinger's hypothetical cat is paradoxically alive and dead at the same time, genes in embryonic stem cells are, in a sense, simultaneously on and off.

Chromatin is packed loosely around these genes, allowing easy access for turning genes on. In embryonic stem cells, the chromatin proteins "breathe," Bernstein says, latching onto DNA and letting go — like pulling into a parking space, backing out, then parking again. That doesn't happen in mature, differentiated



Stem cells' outward simplicity belies the complex traffic inside. Scientists have identified a number of ways that stem cells regulate that traffic to direct the biochemical fine-tuning that leads the cells to divide or head down the pathway toward specialization.



cells. Once cells begin to specialize, the proteins tend to stay parked, Bernstein told colleagues gathered in Philadelphia in June for a meeting of the International Society for Stem Cell Research.

Although the dual methylation marks allow embryonic stem cells to keep their options open, all the doubly marked genes are switched off. As the cells differentiate, the marks made by the Polycomb proteins are erased, giving cells the green light to develop into particular cell types.

Polycomb and trithorax methylation marks may act as homing beacons to transcription factors searching for their parking spaces. Researchers at Harvard University investigated how nine different transcription factors behave and interact in embryonic stem cells. In the March 21 *Cell*, the team reported that Oct3/4, SOX2, NANOG, KLF4, and three other transcription factors tend to carpool, selecting genes marked by both Polycomb and trithorax. Those genes are generally active in embryonic stem cells but get turned off as cells differentiate.

On the other hand, genes that have only one type of methylation mark tend to attract single transcription factors, or smaller groups of transcription factors. Those genes are usually shut off in stem cells but get turned on as cells differentiate. A small number of genes have no methyl groups on their histones. Those genes are largely ignored by transcription factors, the Harvard group reports.

Still other genes seem to be turned on at low levels in stem cells all the time, Bernstein says. Those genes may help direct the cell down a developmental path.

This type of promiscuous gene activity is also found in oocytes — immature egg cells, says John Gurdon, a developmental biologist at the University of Cambridge in England. Oocytes will often turn on genes normally found in muscle cells or other adult cells. And the oocytes do it without the help of transcription factors, Gurdon says. That means the earliest cells open up the entire genome, stripping the DNA and histones bare. Development then becomes an exercise in shutting down things that aren't wanted.

Red light, stop

One method of shutting things down is to stick methyl groups on DNA. The groups gum up the works, closing the on-ramps to the gene-activation fast lane. In embryonic stem cells, some regulatory regions called CpG islands get away scot-free, while other areas of the genome are heavily methylated, Bernstein says.

Louise Laurent, a stem cell biologist at the University of California, San Diego, and her colleagues examined DNA methylation patterns in several different embryonic stem cell lines. The researchers compared the stem cells with many types of differentiated cells to see if stem cells contain other hidden methylation patterns that distinguish them from adult cells.

The group did the same sort of comparison for another type of master regulator in the cells. Those regulators are tiny snippets of RNA only 20 letters, or bases, long. Their diminutive size has earned them the name microRNAs, but the molecules do a big job, controlling much of the protein production in the cell. Usually microRNAs act a lot like building inspectors, shutting down protein-building until certain conditions are met. Each microRNA may help regulate production of hundreds to thousands of proteins.

On human chromosome 14, the team found a cluster of microRNAs located "bang, one right after the other," Laurent says. This cluster is turned off in embryonic stem cells. The team soon discovered why. Located nearby is a gene, called *maternally expressed gene 3*, that makes RNA, but no protein. Only the copy of the gene inherited from the mother is turned on because a special chemical alteration keeps the copy from the father switched off. Scientists call this imprinting.

Imprinting is akin to a genetic custody fight. People inherit two copies of almost all genes, one from mom and one from dad. Most of the time, both copies get to make RNA and proteins, but in a few cases, it's important that only one copy be active. In those cases, cells decide which parent's gene will get the honor, by serving the other parent's gene with a methylation mark. In the case of *maternally expressed gene 3*, the father's gene is shut off by methylation while mom's gene makes RNA. The cluster of microRNAs is imprinted in the same way so that only the mother's copy is active. The situation may be reversed for other genes.

Many important genes are imprinted, and disrupting this balance leads to diseases and disorders, such as Angelman syndrome and Prader-Willi syndrome.

Curiously, in every embryonic stem cell line the team examined, both the mother's and father's chromosome carried a methylation mark. That is not supposed to happen. It's as if a judge decides that neither parent should get custody and the child

ANNIE CAVANAGH, DAVE MCCARTHY

ends up in an orphanage instead. The consequence is that the microRNA cluster is silenced in embryonic stem cells.

The result was unexpected, and Laurent is still trying to sort out how the methylation later gets erased from the mother's chromosome, allowing the microRNAs to be made. The scientists also don't know why embryonic stem cells handle imprinting so differently from other cells.

"One possibility is that we don't really understand imprinting as well as we thought we did," Laurent says. "The other possibility is that imprinting in embryonic stem cells is not stable."

Driving forward

These types of dysfunctional family battles could help explain why some cloned animals have health problems. Imprinting defects might also limit the use of stem cells as therapies for people.

Just as embryonic stem cells do things differently from mature cells, embryonic stem cells from other species also have particular characteristics, Ying says. Even though human embryonic stem cells and mouse embryonic stem cells both come from embryos at what appears to be the same stage of development, the cells differ in their abilities. Human embryonic stem cells can produce placenta, while mouse embryonic cells can't. That seems to indicate that human cells are at a slightly earlier stage of development with more possibilities open to them, but Ying says most data suggest human cells are slightly more advanced than mouse cells in a developmental sense.

Ying and his colleagues have succeeded in isolating embryonic stem cells from rat embryos, a feat scientists have been trying to accomplish for more than 30 years. Rat cells are different from either human or mouse cells and must be grown under special conditions, Ying says. He has been able to make the rat cells do almost everything human and mouse embryonic stem cells can do, including producing about 95 percent of the cell types in the animal. But the rat cells haven't yet formed cells that will produce sperm and eggs, crucial for classification as true embryonic stem cells.

But Ying thinks focusing on differences will teach only a limited amount about how stem cells work. He wants to compare human, rat and mouse embryonic stem cells to see what traits are alike. Stem cells are just too important for evolution to have taken a different tack in every species, he says.

"The real mechanism must be shared between species, so we're trying to look at what's common," Ying says.

Even with rats and mice as guides, it may still be years before scientists know all the secret ingredients and tricks embryonic stem cells use to achieve stemness. ■

Explore more

■ N.R. Dunn. "Self-renewal made simple." *Cell Stem Cell*. July 3, 2008.

It's Likely That Times Are Changing

A century ago, mathematician Hermann Minkowski famously merged space with time, establishing a new foundation for physics; today physicists are rethinking how the two should fit together

By Tom Siegfried

Einstein hated dice. Or at least he hated what dice represented: a world in which chance trumped fate. Einstein believed in a cosmic time that ticked into the future along a preordained route, each moment the inevitable product of the one preceding. Einstein's universe had no room for luck.

Or so Einstein's deterministic view of reality is often represented. Actually, his time didn't even tick. It preexisted. His time was just a dimension in a vast continuum, with no point having a better claim to representing "now" than any other. "Physicists," Einstein once wrote, meaning physicists like him, "believe the separation between past, present, and future is only an illusion."

Einstein's belief that time is illusory did not stem from a mere devotion to Newtonian determinism. After all, he had disregarded Newton before, rewriting the laws of motion that underpinned deterministic philosophy in the first place. In so doing, Einstein introduced a new notion of time, more radical than even he at first realized. In fact, the view of time that Einstein adopted was first articulated by his onetime math teacher in a famous lecture delivered one century ago. That lecture, by the German mathematician Hermann Minkowski, established a new arena for the presentation of physics, a new vision of the nature of reality redefining the mathematics of existence. The lecture was titled "Space and Time," and it introduced to the world the marriage of the two, now known as spacetime.

It was a good marriage, but lately physicists' passion for spacetime has begun to diminish. And some are starting to whisper about possible grounds for divorce.

Minkowski's lecture featured one of the most quoted passages in the history of science, frequently appearing in basic

AIP EMILIO SEGRE VISUAL ARCHIVES

expositions of Einstein's theory of special relativity. "Henceforth space by itself, and time by itself, are doomed to fade away into mere shadows, and only a kind of union of the two will preserve an independent reality," Minkowski declared in Cologne on September 21, 1908, at the Assembly of German Natural Scientists and Physicians.

A decade earlier, he had been a professor at the Zurich Polytechnic university, where the young Einstein often skipped his math classes. Minkowski was sure Einstein would never amount to anything. But shortly after 1905, when Einstein authored a lifetime's worth of revolutionary results in a single year, Minkowski took notice, turning his mathematical prowess to better formulate Einstein's physics. Before long, Minkowski saw deep consequences of Einstein's ideas, especially how they implied that time and space could not be torn asunder. Einstein's famous insistence that the velocity of light is a cosmic speed limit made sense, Minkowski saw, only if space and time were intertwined.

"Nobody has ever noticed a place except at a time," he avowed, "or a time except at a place."

Minkowski perceived new meaning in Einstein's proof that distant events cannot be unambiguously simultaneous (different observers, moving rapidly with respect to each other, may not always perceive the same time-order of events). Thus Minkowski's math described a world consisting not of a dynamic set of events occurring in some specific sequence, but rather a four-dimensional realm consisting of everything, with all "events" occupying points distributed throughout an eternal spacetime continuum. "Distances" between such points no longer reflected mere linear separation in space, but the combined separation of space plus time. The speed of light

is constant, and inviolable, because it is a conversion factor, converting between time units and length units.

In the century since Minkowski spoke, spacetime has become the stage for all of physical science's portrayals of nature, the conceptual framework for formulating scientific descriptions of reality. Building on Minkowski's foundation, Einstein generalized his theory of relativity to describe the interplay of spacetime with matter, thereby rewriting the law of gravity. All the rest of physics, it seemed, fit in the framework that Minkowski and Einstein constructed. Through the lens of spacetime, scientists glimpsed deep and surprising truths about the origin and history of the cosmos.

Yet for all its successes, spacetime has somehow fallen short of solving all the mysteries the universe poses, and recently its primacy has been challenged. Making Einstein's relativity mesh with quantum mechanics has proven so tough that scientists are now willing to seek answers from beyond spacetime (as it is ordinarily conceived). Many physicists now believe that at its roots, nature is built from elements more basic, that space and time emerge from something messier, and then merge into the mirage that human inquiry is able to access. Physicists of the 21st century therefore face the task of finding the true reality obscured by the spacetime mirage.

Doing so, some scientists think, will require looking more closely at how space and time fit together. In particular, some investigators suggest, it might be time to rethink time.

Since Saint Augustine confessed that he knew what time was until somebody asked him to explain it, philosophers and physicists alike have never ceased grappling with its elusiveness. Newton tried to define "absolute time" as "duration" — flowing "equably without regard to anything external." But Einstein demolished that idea, pointing out that time travels at different rates for rapid travelers. Most scientists, though, don't waste time worrying about time's ultimate essence — for them, time is simply what clocks measure. But therein lies a problem: how to choose the clock.

Andreas Albrecht, a cosmologist at the University of California, Davis, has thought deeply about choosing clocks, leading him to some troubling realizations.

Clock as homewrecker

In a lab, time is simple. You can watch experiments and record what happens as time passes simply by referring to the clock on the wall (or the computerized timers on the lab bench). But suppose you are studying the universe as a whole, attempting to formulate the laws of quantum gravity that rule the cosmos. There is no wall enclosing the universe on which to hang a clock, no external timekeeper to gauge the whenness of being.

Yet quantum physics requires time to tell the universe what to do — time is necessary for things to happen. Or, as the famous restroom graffito puts it, time is nature's way of keeping everything from happening at once.

In quantum math, time is represented in a formula called a wave function, which describes a multiplicity of possible realities. For an electron, the wave function does not specify, say, a precise position, but tells the odds of finding that electron in various possible locations. Those odds are not forever constant, but change as time goes by; the part of the math that specifies those changes is, in some abstract sense, a clock. On a cosmic scale, the situation is similar — the quantum math describes multiple possible states of the universe, as well as how the universe changes as "time" proceeds — as the cosmic clockwork turns the future into the past. You can compute what happens to the universe as one piece of the math alters in value, like the ever-changing angle that a second hand makes as it sweeps around a clockface.

But when deriving that math to begin with, there's no way to know in advance which part corresponds to the master

FMNG/ISTOCKPHOTO, J. KORENBLAT

cosmic clock. You have to choose something to represent time from within your equations, Albrecht notes. "Your first job is to identify what you mean by time," he says.

But here's where it gets tricky. When you choose one piece of the math to describe time, the rest of the math becomes the formula for the laws of nature, describing how the universe behaves. Suppose, though, that you choose a different part of the equations to play the role of clock. Now you have a different formula for the laws of nature — what happens in the universe doesn't stay the same, Albrecht figured out.

"I showed that you could make different choices of what you mean by time and get any laws of physics you want," he says. Freedom to choose "time" therefore implies that the laws of physics aren't indelibly inscribed with Sharpies on indestructible stone tablets, but are more like multiple drafts of legislative bills with details still at the whim of editors wielding word processors. Some of those laws might not even include any provision for space, leaving time partnerless.

Albrecht calls this time-choice conundrum the clock paradox, described with his UC Davis collaborator Alberto Iglesias in a paper published this year in *Physical Review D*. "We tried to show that there was something wrong with this picture, that the freedom to choose any clock would somehow contradict itself," Albrecht says. But it didn't.

In that paper and a subsequent one available online (arxiv.org/abs/0805.4452), Albrecht and Iglesias further explore the implications of this time-freedom for the laws of nature. If you can choose any time you like and get different laws, it makes no sense to say that the universe is ruled by a single Constitution of Physics. The cosmos becomes more like the United Nations, a hodgepodge of jurisdictions with diverse codes of conduct. "The clock ambiguity suggests that we must view physical laws as emergent from a random ensemble of all possible laws," Albrecht and Iglesias write.

In other words, there is no one set of laws, but a whole library of different cosmic law books. Yet somehow physics finds order from chaos; there must be some principle behind the regularities that govern the interaction of entities. Albrecht suggests that the universe offers such a principle: the idea that individual entities exist at all.

> **"You could make different choices of what you mean by time and get any laws of physics you want."**
>
> ANDREAS ALBRECHT

Space time reunion

"The remarkable thing about our experience as observers in the universe is we are fairly isolated from the universe, so we have our own isolated existence," Albrecht says. "The universe doesn't instantly destroy us." Stars, planets and people aren't blended in a cosmic mixmaster, but remain somewhat separate — exhibiting what Albrecht calls "quasiseparability."

"Quasiseparability means the universe can be separated into different things, different objects, that have their own identity," he says. "That's how we stay safe in a universe full of potentially antagonistic physical objects."

And that's how it's possible to experience meaningful laws of physics even in a universe without a master clock. Freedom to choose different clocks means choosing from among a multitude of possible laws, some wildly different from those in human textbooks. But quasiseparability places limits on which sets of laws humans could possibly experience. Only those laws consistent with quasiseparability would permit systems containing objects like physicists.

This separability requirement brings something like space back into the cosmic picture. In a sense, time and space get back together not because that's the way the world is, but because that's the only way that humans can comprehend it.

So even though many laws of nature are possible, some should, in an inhabited universe, be statistically much more likely than others. With quasiseparability as a guiding principle, Albrecht and Iglesias show that even a random choice of clock is very likely to produce laws that look like the ones that physics already knows, describing fields of matter and energy that act locally to generate the behavior of the whole cosmos.

This development is strikingly analogous to the original quantum revolution, which established the idea that science's laws were not absolute but statistical — producing the cosmic dice-playing that Einstein deplored. Now, it seems, even the laws themselves may not be absolute, but merely — given quasiseparability — the most likely set of rules drawn from a statistical distribution of all possible rules. "Maybe we should have seen it coming," Albrecht says.

What he and other pioneers on the spacetime frontiers have seen coming is an intellectual crisis. The approaches of the past seem insufficiently powerful to meet the challenges remaining from Einstein's century — such as finding a harmonious mathematical marriage for relativity with quantum mechanics the way Minkowski unified space and time. And more recently physicists have been forced to confront the embarrassment of not knowing what makes up the vast bulk of matter and energy in the universe. They remain in the dark about the nature of the dark energy that drives the universe to expand at an accelerating rate.

Efforts to explain the dark energy's existence and intensity have been ambitious but fruitless. To Albrecht, the dark energy mystery suggests that it's time for physics to drop old prejudices about how nature's laws ought to be and search instead for how they really are. And that might mean razing Minkowski's arena and rebuilding it from a new design.

"It seems to me like it's a time in the development of physics," says Albrecht, "where it's time to look at how we think about space and time very differently." ■

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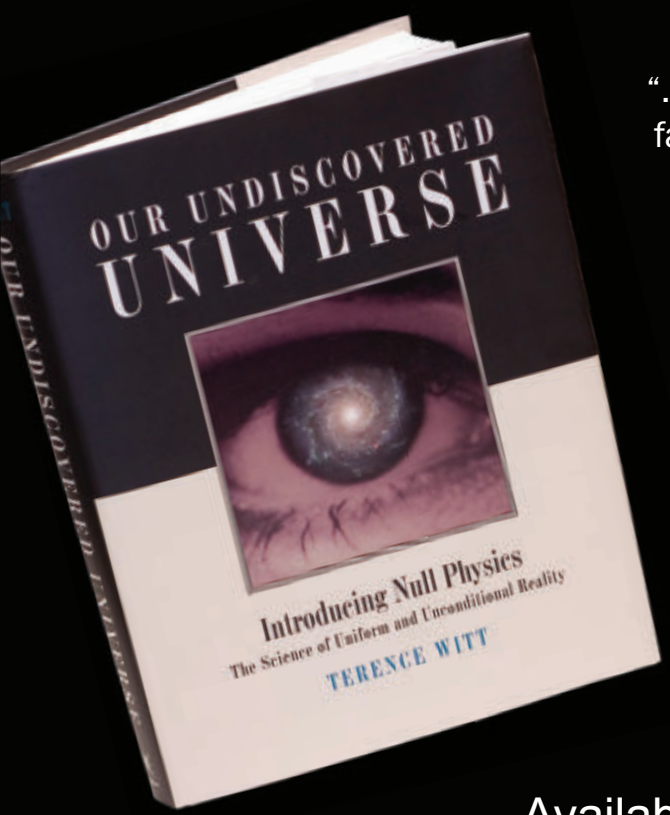

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The Gulf Stream: Tiny Plankton, Giant Bluefin, and the Amazing Story of the Powerful River in the Atlantic

Stan Ulanski

The Gulf Stream, dramatized by painter Winslow Homer, has had many admirers ranging from Juan Ponce de Léon, who claims to have discovered it, to Ernest Hemingway, who fished its waters.

Ulanski starts this book with a whirlwind tour. Warm waters dead-end in the Caribbean Sea and the Gulf of Mexico,

spill out around the Florida coast, barrel north toward Cape Hatteras and bounce eastward. But contrary to a widely held belief, the Gulf Stream warms Northern Europe only slightly. It has a greater impact on New England northeasters, which form when warm winds collide with polar air.

Ulanski likens the Gulf Stream to a huge living organism moving below the surface. Its waters contain plankton, jellyfish, sargassum weed, dolphin and wahoo. But its stars are giant bluefin tuna, weighing 300 to 600 pounds.

"The Gulf Stream doesn't discriminate with regard to its passengers," Ulanski says. "It's just the conveyor."

Ulanski ends with a fascinating account of the Gulf Stream's role in history. John Cabot, who explored the east coast of North America in 1497, rode the Gulf Stream and prevailing westerly winds of the North Atlantic back to England in only two weeks. Later explorers followed suit. In contrast, the rule of thumb upon leaving Europe became "sail south until the butter melts," then turn west.

Benjamin Franklin appears to be the first scientist to test the stream, finding it milder than the surrounding Atlantic. It's warmer by 15 to 20 degrees Fahrenheit. This coursing body of water-bound energy affects climate, ocean life and history, and explains Cabot's remark that the beer in his hold became oddly warm off the coast of America. **—Nathan Seppa**

Univ. of North Carolina, 2008, 212 p., $28.

Central Park in the Dark: More Mysteries of Urban Wildlife

Marie Winn

Marie Winn's tale of adventures in Central Park begins with darkness. She explores the cultural and literary associations between night and death, and the backstory of why humans are afraid of the dark. But, for her, curiosity and logic override fear—these days more crime occurs in the park during the day. So Winn sets off and running on a nighttime safari through the 800-plus acres that make up one of the world's most fabled green spaces.

Screech owls, slugs, beetles and bats are among the wonders Winn and her compatriots stalk during 11 years of forays. Winn delves into each species' natural history, including not only information gleaned from field guides and scientists, but also quotes from Thoreau, Shakespeare and Ogden Nash.

Her tone is conversational and infused with enthusiasm. The reader is a listener at a cocktail party, and Winn's stories are peppered with asides. She references her moods and those of her companions, which include a group of amateur astronomers who hang out on the Great Lawn (the star guys) and her poem-writing friend Charles (the sun drops/the cold slides in/owl time).

A writer for the *Wall Street Journal* and

author of *Red-Tails in Love*, Winn interweaves hard facts with narratives. City dwellers and visitors will appreciate the precise descriptions of specific benches, trees or outcrops where Winn saw a silver-haired bat chasing insects or a black witch moth. The book may well prompt more people to abandon their fears and visit Central Park in the dark. **—Rachel Ehrenberg**

Farrar, Straus and Giroux, 2008, 304 p., $25.

Dire Predictions: Understanding Global Warming

Michael E. Mann and Lee R. Kump

This user-friendly guide to climate change illustrates key concepts with plenty of graphics.

DK Publishing, 2008, 208 p., $25.

Out of the Blue

John S. Friedman

Ancient beliefs, scientific discoveries and survivor accounts of lightning strikes.

Delacorte Press, 2008, 290 p., $24.

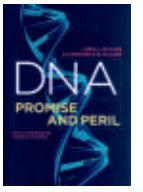
What's the Big Idea? Four Centuries of Innovation in Boston

Stephen Krensky

A children's history of discoveries, from the smallpox vaccine to modern computers.

Charlesbridge, 2008, 64 p., $18.95.

DNA: Promise and Peril



Linda L. McCabe and Edward R.B. McCabe

How advances in genetics could affect health insurance, forensic testing, reproductive technology and more.

Univ. of California Press, 2008, 339 p., $39.95.

The Complete Herb Book

Jekka McVicar

This book includes descriptions, medicinal uses and recipes for more than 150 aromatic plants, from lemongrass to dandelion.

Firefly Books, 2008, 304 p., $29.95.

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Feedback

> "Objectivity and truth in reporting are not exactly encouraged in the current clinical medical research climate."

Disturbing numbers

I found the "Sizing up science" Science Stat (*SN: 8/2/08, p. 4*) somewhat disconcerting with regard to the opinion about medicine. Basic medical research, in which ties to pharmaceutical companies and the like are not limited, may be "scientific" in the usual sense, but once you enter the arena of clinical research, the "scientific" is scarcely applicable. Objectivity and truth in reporting are not exactly encouraged in the current clinical medical research climate.

It should be unsettling that a paper reporting an important negative result—one that neither the industry nor the "opinion leaders" wish to see or address—has little chance of being published in a major journal, especially if the entity potentially affected by the result is a supporter of the journal. The results of such research rarely reach practicing physicians. Fortunately, over time such information usually comes to the fore, but it can take decades.

HARRY A. KIESEL, PHILADELPHIA, PA.

Seeing within

I was confused by the article on the use of Raman spectroscopy to detect tumors ("Insightful light," *SN: 8/2/08, p. 22*). The article implied that the tumors were internal, but unless the tumor is on or near the surface so the laser light can penetrate it, I do not see how this can work.

CHESTER GABRIEL, CUPERTINO, CALIF.

In addition to developing nanoparticles that attach to tumor cells, researchers are also designing microendoscopic probes to look for diseased tissue inside the body. Nanoparticles attached to this tissue will release a signal when the probe delivers laser light to the region. —ASHLEY YEAGER

It's in the timing

I enjoyed reading "Decoding the quantum mystery" (*SN: 8/2/08, p. 26*), but two things struck me as unusual. Both were timely comments that showed the article was not written last December, edited in February, approved in April and printed in July. It is the timeliness of *Science News* that I look for. And when you quietly remind us of the timeliness, it is appreciated. The two comments were: "a cosmic horse race in which Big Brown usually wins" and "more reliably victorious even than Tiger Woods on good knees." You couldn't have known in December.

PAUL EBEL, AIKEN, S.C.

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Eugene Spafford

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Protecting the Internet from the criminal element

Eugene Spafford is executive director of Purdue University's Center for Education and Research in Information Assurance and Security, one of the world's leading centers for information security. His research focuses on issues related to securing computers, networks and their data against criminal activities and failures. He has testified before various congressional committees, advised agencies within the executive branch and worked with the U.S. military and the FBI. Here, freelance science writer Susan Gaidos questions Spafford about computer security issues.

You've been tracking computer security breaches for 30 years. What trends have you seen over that time, and what new problems are emerging?
The change in the computational environment has led to changes in what we've seen as "incidents." In the 1990s, most of what we saw as "untoward behavior" was neither malicious nor criminal. Some of it came from individuals who were new to the Internet and didn't have a complete handle of what it was they were doing. Others — the classic hackers — did it for bragging rights or to prove to others their skill.

We're now seeing a tremendous amount of criminal fraud perpetrated through the Internet, and much of it organized with an international reach. Things like credit card fraud and phishing for identity theft fall into this category. We're also seeing greater sophistication in ... theft of intellectual property and information by transnational organizations and governments. Here we're talking about the invasion of corporate and government machines to steal advanced designs, or to extract political and personal information.

Who's policing the Internet and how is that being done?
It isn't, and that's part of the problem. I've been working with some law enforcement agencies trying to track down fraud that appears to be coming from other countries. Some of it may be originating in those other countries, but some of it may be originating down the street where somebody is using a computer in another country as a way of hiding their participation.

Whichever is the case, traditional law enforcement is strongly bound to physical national boundaries. These distinctions really don't exist on the Internet, so that makes law enforcement by local agencies very difficult.

What action needs to be taken to make information more secure?
As a society, we haven't been particularly willing to pay the extra required to actually build in good security. In addition, we've been very forgiving of the flaws and incidents that have occurred. For security to get better, both of those things need to change.

In some cases, we're using systems and protocols that were never really designed to be secure. E-mail, for example, evolved as a means of sharing and was designed before there was commercial use of the Internet. Spam and phishing — e-mail that looks like it came from your bank or some other known source — are examples of ways that criminals can exploit weaknesses in the system to get information from users. We have to find ways to increase accountability, authenticity and attribution without doing away with some of the freedom of expression that is part of the benefit of having the Internet.

The probable direction we're going to have to go in is to build very robust, highly protected enclaves, or protected systems of computers.

It's going to be some time before we can work out the laws and etiquette of having instant communication in different cultures.

How vulnerable are the computers that we use at work and at home?
In the worst case, the systems have already been taken over by the bad guys through the use of botnets or spyware, and the owners of the systems don't know it.... The software gets inserted automatically into someone's system and is under the control of a remote operator.... These programs can be used to steal information or to disable a system.

What challenges lie ahead?
We now have a more global network, so we see a lot more individuals with a broad range of ideologies and motives. As the use of the network spreads, we encounter more and more users whose cultural outlook and political and economic motivations differ from our own.

This gives rise to some challenges. For example, where some people might view the ability of the citizens in China to upload a video of violent suppression of Tibetan protests as free speech, the Chinese authorities might view it as a criminal act promoting civil unrest. It's going to be some time before we can work out the laws and etiquette of having instant communication in different cultures with very different perspectives.

Right now, we have a lot of people who aren't thinking globally when they put things out online. As computers get smaller and phone networks converge with the Internet, so that everyone's walking around with a connection in their purse or on their belt, it will just further add to the concerns we have. ■

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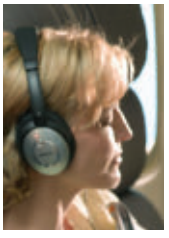

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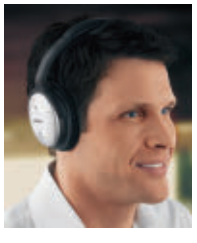

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