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ScienceNews

MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC ■ FEBRUARY 23, 2013

No Magic Pill

Why new psychiatric drugs are so hard to come by

Dung Beetles Follow the Stars

Deep Brain Stimulation for Autism

The Coming Phosphorus Crisis

The First
The Last
The ONLY!

Actual size is 30.6 mm

50 Years later the 1964 Silver Proof Set still shines bright

On November 25, 1963, just three days after the tragedy in Dallas, the U.S. Mint began work on the 90% Silver Kennedy Half Dollar. It would prove to be one of the most popular half dollar designs in our nation's history. Not surprisingly, when Americans discovered that the brand new Kennedy Half Dollar was the centerpiece of the 1964 U.S. Silver Proof Set, demand immediately soared through the roof!

By January 11th, 1964, the Mint was forced to halt orders for the 1964 Silver Proof Set, and eventually had to reduce the original maximum order of 100 Proof Sets down to just 2 sets per buyer in the face of such staggering demand. Finally, on March 12, even the limit of 2 sets was halted because the Mint received orders for 200,000 Proof Sets in just two days!

Fifty years later, the 1964 Silver Proof Set is still in great demand.

Why? Because this set is chock full of "Firsts", "Lasts" and "Onlys":

1964 Proof Set Firsts, Lasts & Onlys

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- ✔ **The FIRST Proof set to feature a former president on every coin**
- ✔ **The LAST Proof Set struck at the Philadelphia Mint**
- ✔ **The LAST year the Roosevelt Dime, Washington Quarter and Kennedy Half Dollar were struck in 90% silver for regular production**
- ✔ **The ONLY 90% Silver Kennedy Half Dollar Proof ever minted for regular production**
- ✔ **The ONLY Kennedy Half Dollar Proof struck at the Philadelphia Mint**

As we approach the 50th Anniversary of JFK's 1963 assassination this year, the 1964 U.S. Silver Proof Set is back into the spotlight again. Each set contains the 1964 Lincoln Cent and Jefferson Nickel, along with three 90% Silver coins: the Silver Roosevelt Dime, Silver Washington Quarter, and the 1964 Silver Kennedy Half Dollar—the only 90% Kennedy Half Dollar ever struck for regular production.

Saved from destruction—but how many set survived?

Collectors know that the key is to find those sets still preserved in the original U.S. Mint "flat pack" just as issued. And over the past 50 years, that has become more and more difficult! Since this set was issued, silver prices have risen from $1.29 per ounce to over $48 per ounce at the silver market's high mark. During that climb, it is impossible to determine how many of these 1964 Proof Sets have been melted for their precious silver content. The packaging on thousands of other sets has been cut apart to remove the silver coins—so there is no way to know for certain how many 1964 U.S. Proof Sets have survived to this day.

Order now—Satisfaction Guaranteed

We expect our small quantity of 1964 U.S. Silver Proof Sets to disappear quickly, so we urge you to call now to secure yours. You must be satisfied with your set or simply return it within 30 days of receipt for prompt refund *(less s/h)*. ***Limit: 5 per household.***

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ScienceNews

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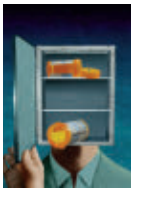

COVER Psychiatrists and patients have waited decades for better drugs. The many obstacles to developing psychiatric medications suggest that the wait will continue. *Michael Morgenstern*

ScienceNews
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FROM THE EDITOR

Finding better drugs may require revised approach

Trial and error. It's how toddlers like my daughter learn which part of a banana to eat (the inside is good, the peel not so much). Without a deeper understanding of how fruits evolved, the method isn't terribly sophisticated. But it can work.

With so much still unknown about the brain and the biological causes of mental illness, scientists are sometimes forced to employ something akin to this process, albeit more systematic and informed. As neuroscience writer Laura Sanders writes on Page 26, finding medications that help people with depression, schizophrenia and other brain disorders has relied heavily on serendipity. And while some patients do get relief from existing drugs, many more do not.

Scientists in the field say that there's a worrisome lack of new psychiatric drugs in the pipeline. It's a knotty problem, made harder by the complexity of the brain itself. Still, many think that the current drug development system is failing people with mental illness. A smarter way to do it, they suggest, is to do what are called "quick-win, fast-fail" studies. The idea is to set up the test in such a way so that if the drug doesn't work, scientists will at least know why, giving them more insight into both the disease and how the brain works in the process. Another effort, dubbed "first in humans" is looking at the feasibility of testing drugs in people much earlier in the process. That could help avoid some of the false hopes created when a drug candidate seems to "cure" a disease in mice but fails to work in people. Both proposals would speed up the research, testing and approval process, which currently averages more than 18 years for drugs that act on the central nervous system. Changes like these might get more help to patients, sooner.

Trial and error often gets a bad rap. But it does have its place in science. On Page 12, Sanders describes a potential new treatment tested in a young man with severe autism. Physicians tried delivering electrical pulses to a few different areas of the amygdala, a part of the brain involved in processing emotions. His symptoms improved only when they stimulated a specific area called the basolateral amygdala. For the first time in his life, the previously nonverbal teen spoke, calling his parents "mama" and "papa."

Trial and error does work sometimes. Just ask my banana-munching, peel-throwing kid.

— Eva Emerson, Editor in Chief

PHILIP CHANNING

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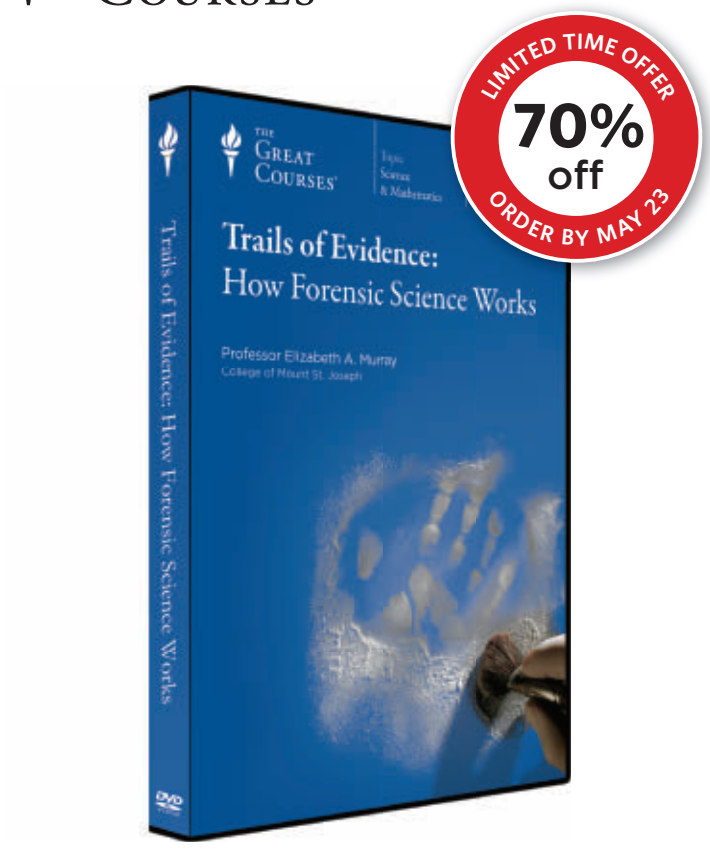

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Say What?

Denudation \ *den-yoo-DAY-shun* \ *n.* The sum of all natural processes that erode Earth's surface, ultimately lowering elevation and carving out landforms (such as this arch at Jordan's Jebel Kharaz, right). Researchers recently used denudation rates from 990 river basins to estimate how much sediment is created annually as rock wears down in quartz-bearing landscapes. The answer: 5.5 billion metric tons globally. The steep slopes of mountains can produce sediments quickly, but low-sloping regions erode more steadily over a larger area and probably form most of the world's sediments each year, Jane Willenbring of the University of Pennsylvania and colleagues report online January 4 in *Geology*. —*Erin Wayman*

Science Past | FROM THE ISSUE OF FEBRUARY 23, 1963

NEW AIR TRANSPORT — Instead of trains on railroads and trucks on expensive highways, the less developed countries in the future are likely to use for their transport hybrid helicopter-airplanes that need only simple landing fields and no roads or rails between. This possibility was offered ... by Dr. Phillip R. Carlson of the Lockheed Aircraft Corporation, Burbank, Calif. The new kind of aircraft would be especially useful in the early stages of area development, operating for distances of less than 500 miles, to establish railroad depots, river ports, and ocean harbors. The new type of craft could be designed, built and put into service in a few years.... Like a helicopter, the proposed craft would be able to rise vertically from unpaved sites, but, like a conventional airplane, forward flight would be possible using wings and airplane engines.

Science Future

March 23
See rare whale specimens, watch a re-creation of a whale hunting a squid and learn how scientists track these giants at the new Whales: Giants of the Deep exhibition at New York City's American Museum of Natural History. See bit.ly/SFamnhwhale

March 28
The Russian Soyuz spacecraft launches from Kazakhstan carrying three crew members headed for the International Space Station. See bit.ly/SFsoyuz35

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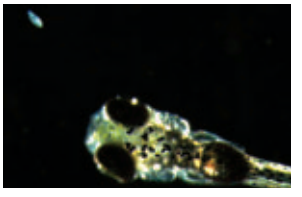
FRAME OF MIND
Laura Sanders ponders turning off depression instantaneously in her column "A new generation of antidepressants could help patients feel better faster."

BODY & BRAIN
See a video of nerves firing in a fish larva's brain (below) as it hunts in "As fish watch prey, researchers watch fish's brains."



LIFE
Anthropologists rethink some fossil cues to hominids' life history in "Chimps' baby teeth don't predict weaning."

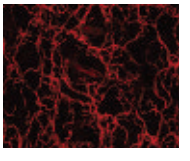
HUMANS
A study finds a link between the types of household chores that men do and how often they have sex. Read "Some chores linked to less sex."

Science Stats | HASHTAG HIGGS

An analysis of Twitter chatter found that tweets about the Higgs boson soared from about 36 per hour before July 2, 2012, to around 36,000 per hour on July 4, when scientists announced that they had found the particle. That day, tweets formerly confined mainly to the United States and Europe went global as people tweeted, and also retweeted, messages from other nations (left).

Network of retweets about Higgs

Introducing | ITCHY NERVE CELLS



Itchiness may finally have its own sensory highway. Until now, all neurons known to respond to itchy sensations also responded to painful ones. But MrgprA3^{+} neurons (right), which transmit signals from the topmost layer of skin, seem to be itch-only sensors, an international team reports online December 23 in *Nature Neuroscience*. Killing these neurons with a chemical injection calmed scratching behaviors in mice triggered by itchy stimuli like dry skin or allergic reactions, but had no effect on the ability to feel painful stimuli such as heat. Targeting the nerve cells may pave the way for new anti-itch therapies, the researchers say. —*Allison Bohac*

CLOCKWISE FROM TOP: ETAN TAL/WIKIMEDIA COMMONS; A. MUTO *ET AL./CURRENT BIOLOGY* 2013; L. HAN *ET AL./NATURE NEUROSCIENCE* 2012; M. DE DOMENICO *ET AL./*ARXIV.ORG 2013

“Poking at small effects you can’t explain can be a way of unraveling a much bigger piece of physics.” —CARL CARLSON, PAGE 8

In the News

STORY ONE

DNA could soon prove practical for long-term data storage

Molecule of life approaches cost of current archival media

By Rachel Ehrenberg

Big data could soon be stored in a very small package: DNA. A team of scientists has demonstrated that storing information in synthetic DNA could represent a feasible approach to managing data in the long term, bumping aside the magnetic tape favored by archivists today.

To illustrate the technique, the research team stored five files — totaling about 750 kilobytes of data — as DNA: Watson and Crick’s classic 1953 paper describing the structure of DNA (a PDF), a color photograph (a JPEG), a 26-second excerpt from Martin Luther King Jr.’s 1963 “I Have a Dream” speech (an MP3), all 154 of Shakespeare’s sonnets (a text file) and another text file containing a code used in the translation process. One sonnet, the researchers estimate, can be stored in 0.3 picograms, less than a trillionth of a gram, of DNA.

“The sweet spot for this is archival applications,” says synthetic biologist Drew Endy of Stanford University, who was not involved in the work.

DNA is most attractive for storing things that people will want to retrieve hundreds or thousands of years from now because it is the information storage medium for life itself. Unlike record players, which are good only for playing music encoded on near-obsolete vinyl discs, machines that make and read DNA will always be in use. “Human beings are never going to stop caring about DNA,” Endy says. DNA is also compact, lightweight and can potentially remain intact for thousands of years if stored in a dark, cool environment.

The new technology, described online January 23 in *Nature*, is the latest in a series of efforts to encode data in DNA.

ACTG or not ACTG? To demonstrate the utility of DNA for data storage, researchers encoded Shakespeare’s sonnets as genetic material and then translated them back into Elizabethan English.

PORTRAIT: GEORGIOSART/ISTOCKPHOTO; DNA: M-X-K/ISTOCKPHOTO

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Last August in *Science*, George Church of Harvard Medical School and colleagues encoded an HTML version of a book coauthored by Church into DNA. The researchers converted the book *Regenesis*, which included illustrations, into a 5.27-megabit file that they translated into DNA, stored on a chip, and then converted back into the digital book.

The new approach stores about three times as much information per gram of DNA compared with the one Church and his colleagues used. The new *Nature* paper also assesses when the costs of DNA storage might begin to match those of archival tape: Its authors estimate that current costs are about $12,400 per megabyte for encoding the information into DNA and about $220 per megabyte to decode it. Their projections suggest that, if the costs of making DNA continue to drop, the approach might be economical for long-term storage in as little as a decade.

"It's genuinely exciting," Endy says. "This is now becoming practical."

Led by Nick Goldman and Ewan Birney, researchers from the European Bioinformatics Institute in England began by converting the five files into digital form (not bits but "trits" — a triplet code comprising zero, one and two). Then they translated that code into one made of As, Cs, Gs and Ts, the "letters" of DNA. So TAGAT replaces the "T" that begins line two of Shakespeare's sonnet 18: "Thou art more lovely and more temperate." The team also incorporated a way to index the data — sort of a DNA version of the Dewey Decimal System — and an error-correction code to keep the data clean.

Then the researchers sent their code to the instrumentation company Agilent Technologies in Santa Clara, Calif. There, scientists read the code and used it to build millions upon millions of DNA molecules, which they sent back to the researchers via FedEx in a test tube inside a cardboard box.

Bioinformaticist Nick Goldman points to a DNA sample in the bottom of a pinkie-sized test tube. He and his colleagues used a similar amount of DNA to encode 750 kilobytes of data.

When the test tube, about the size of a pinkie finger, arrived, Goldman and his colleagues sequenced the DNA the same way researchers read the genomes of organisms, reconstructing the original files using their own version of the genetic code. The translation from data to DNA and back was free of errors, says Goldman.

0.3
picograms
Amount of DNA needed to encode one Shakespeare sonnet

While the approach has now been definitively demonstrated, there's still a lot of exploring to do, says Sriram Kosuri of the Wyss Institute at Harvard University, a coauthor of the *Science* paper with Church. Perhaps artificial genetic molecules called XNAs (*SN: 5/19/12, p. 10*), which are like DNA but have different sugar molecules in their backbone, might also prove useful for storage, he says. "A ton of chemistry could be brought to bear on this."

DNA storage isn't likely to replace thumb drives anytime soon. But in the next decade, it could store information that needs to last at least 50 years, such as government records or library texts. And who knows where it will go, wonders Goldman. Perhaps, he says, "when the cloud sucks things off your computer, it will be to store it as DNA." ■

Back Story | DATA IN DNA

As the technology for deciphering and synthesizing DNA has surged forward, so too have techniques for storing data. In just over a decade, small-scale pilot experiments have given way to the development of methods that may make DNA data storage economically competitive for the archival storage of large amounts of information.

1999
Artist Eduardo Kac adapts a line from Genesis ("Let man have dominion over the fish in the sea, and over the fowl of the air, and over every living thing that moves upon the Earth") and translates it into Morse code, then into a sequence of DNA base pairs. He then inserts the genetic material into bacteria, which produce a protein based on the sequence.

In a different project, researchers encode text in DNA and then mix it into a full human genome that is then printed onto paper as a microdot, a hidden message embedded in a period. Though the technique was secure at the time, modern DNA sequencing technology has made the message-containing DNA fairly easy to isolate from the rest of the genetic material.

2009
Researchers encoded the text and music of the nursery rhyme "Mary Had a Little Lamb," along with a crude sketch of a lamb, in 844 base pairs of DNA.

2010
Researchers at the J. Craig Venter Institute insert a synthetic genome modeled on one bacterium into a different species, and induce the hybrid to reproduce. Before inserting the DNA, they add encoded messages including the names of the project's 46 researchers and quotes from James Joyce and physicist Richard Feynman.

2012
George Church of Harvard Medical School encodes an HTML version of his book *Regenesis* in DNA, and then converts it back into digital form.

2013
Nick Goldman and his colleagues convert image, audio and text files into DNA using a technology that could eventually make the molecule competitive as an archival storage medium.

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Proton's radius revised downward

Surprise measurement could lead to new physics

By Andrew Grant

Only in physics can a few quintillionths of a meter be cause for excitement. A new measurement finds that the proton is about 4 percent smaller than previous experiments suggested. The study, published in the Jan. 25 *Science*, has physicists wondering if the discrepancy between experiments will lead to the discovery of new particles or forces.

"Poking at small effects you can't explain can be a way of unraveling a much bigger piece of physics," says Carl Carlson, a theoretical physicist at the College of William and Mary in Williamsburg, Va., who was not involved in the study. "And this case is particularly intriguing."

For years, physicists have used two indirect methods to determine the size of the proton. They can fire an electron beam at protons and measure how far the flying particles get deflected. Alternatively, physicists can study the behavior of electrons in hydrogen atoms. They shoot a laser at an atom so that the single electron jumps to a higher, unstable energy level; when the electron returns to a low-energy state, it releases radiation whose frequency depends on the size of the proton. Both methods suggest the proton has a radius of about 0.88 femtometers, or quadrillionths of a meter.

That measurement was not in doubt until 2010, when Aldo Antognini at ETH Zurich and his team developed a new technique to probe proton size. They also used hydrogen atoms but instead of electrons used muons — particles similar to electrons but more than 200 times as massive. Muons' additional heft enhances their interaction with protons and makes their behavior more dependent on proton size. After measuring the X-rays emitted by muons shifting between energy states, Antognini's team published a paper in *Nature* saying that the proton radius is 0.84 femtometers — about 4 percent less than previous estimates.

Now the team has reexamined muon-containing hydrogen and measured the X-ray frequencies resulting from two energy level shifts. Both emissions yielded the same, slimmed-down value for the size of the proton. The new study eliminates the possibility of certain systematic errors and improves the measurement's precision by 40 percent.

Carlson says physicists may still be overlooking an error in either the muon or electron experiments. Researchers are on the case, scouring the details of each experiment in the hopes of a consistent value for proton size.

Yet Carlson can't help but entertain the possibility that new physics, not human error, causes the varying size measurements. According to the standard model of physics, electrons and muons should differ only in mass, but theorists are exploring the possibility that there is a yet-undiscovered particle that interacts only with muons. "It would certainly shake things up," he says.

In two or three years, physicists hope to introduce yet another independent method of determining proton size. John Arrington, a physicist at Argonne National Laboratory in Illinois, is helping to develop a muon beam that would fire at protons. If such an experiment yields results similar to those of the muonic hydrogen one, Arrington says, then it's likely that new physics is at work.

F. COMERÓN/ESO

Stellar baby picture

Two bright stars emerge from the darkness in this image of Lupus 3, a stellar nursery about 600 light-years away in the constellation Scorpius. The newborn stars, not even a million years old, formed when regions of a cloud of cool dust and gas (visible at center left) collapsed from gravity. The stars are so young that their brightness comes exclusively from this gravitational contraction; it will take millions more years before they start fusing hydrogen the way the sun and most other stars do. Astronomers believe that this system resembles the one that birthed the sun roughly 4.5 billion years ago. The image, released January 16 by the European Southern Observatory, was captured by a 2.2-meter telescope at the La Silla Observatory in Chile. — *Andrew Grant*

Technology

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Microwave trick simplifies seeing through things

Metamaterials plus math equals quick, cheap system

By Rachel Ehrenberg

A copper strip etched with slightly varying openings acts as an aperture for a fast, simple microwave imaging system that has no lens and no moving parts.

The days of standing still, arms raised, in an airport security scanner may soon be a thing of the past. A new microwave imaging system offers a fast, inexpensive way to see through clothing and other objects by gathering data without complicated moving parts.

The new system, reported in the Jan. 18 *Science*, bounces microwaves off an object and then collects them through holes in a thin copper strip. Elegant math converts the resulting pattern into an image in less than a second.

"This definitely represents a less expensive and potentially faster alternative to current imaging methods," says technologist Kevin Kelly of Rice University in Houston, who was not involved in the research. "You can imagine an MRI or PET scanner where instead of sitting in a machine for 50 minutes you sit in it for five minutes."

In a digital camera, the lens focuses light onto an array of pixels on a detector. If you want a million-pixel image, you essentially need a million detectors, says John Hunt, a Duke University physicist who led the new work. That many-pixel, many-detector approach doesn't work with microwaves, which are longer than waves in the visible part of the electromagnetic spectrum. So microwave imagers — used in airport scanners and car collision avoidance systems for their ability to see through clothing and raindrops — have a single detector that must be slowly moved across a plane with the help of complicated, expensive gears.

The new imaging system also uses a single detector. But its perforated copper aperture eliminates the need for a lens or moving parts. The researchers etched tiny patterns into a superthin piece of copper, turning it into a metamaterial. Metamaterials are exotic arrangements of matter that are often created to manipulate light in ways that are impossible in nature, making them ideal for invisibility cloaking and similar applications. For cloaking purposes, the material controls the direction of light. But in the new study the metamaterial aperture allowed fine control over the frequency of light. Only light of a certain frequency can get through a particular etched section of the metamaterial screen.

"They get exquisite control of microwaves with just a sheet of copper with squiggles in it," says metamaterials pioneer John Pendry of Imperial College London.

By sending out microwaves of different frequencies, recording some of the waves that bounce back to hit the detector and then transforming these data with elaborate algorithms, the researchers were able to reconstruct a scene with far less data than is usually required.

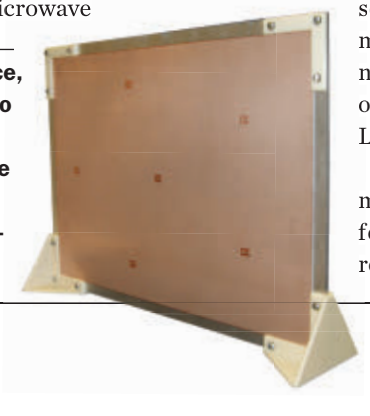
"Instead of taking an organized set of measurements, if you mix them up randomly you can do really cool stuff," says Kelly.

The new system created images with about one-fortieth of the data that would normally be needed. Such compression is commonly done after the fact, resulting in a JPEG or GIF file, but the new approach collects less data to begin with.

"This is a very clever technique of very economical sampling of an environment," Pendry says. "It's an extremely exciting development."

So far, the researchers have taken images only of bright reflective objects in rooms with antireflective material on the walls. But the technology should work anywhere that you want to see shiny metallic objects, says Hunt. The approach might lead to cheap, handheld devices that look through walls at wires and pipes. Or police might have a vest with an imaging surface built into it that can see if a person has a knife concealed in a pocket.

But security is the killer app: One day you might walk through an airport without even knowing that you're being scanned. ■



This two-dimensional device, which could be attached to a wall or laid on the floor, is part of a new microwave imaging system that may lead to cheaper, faster airport security scanners.

BOTH: J. HUNT/DUKE UNIV.

Health & Illness

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Digestive juices blamed in shock

Enzymes leaking from gut may have deadly consequences

By Nathan Seppa

Digestive enzymes that escape from the intestines into adjacent tissues and the bloodstream may be key players in triggering shock, the dangerous condition that sometimes occurs after major medical trauma. A new study finds that giving enzyme inhibitors to rats in shock can alleviate the potentially lethal condition.

The findings could shed some much-needed light on shock, which typically shows up as the result of some other medical problem such as hemorrhage, sepsis, a heart attack or a systemic allergic reaction called anaphylaxis. In all cases, blood pressure plummets, sabotaging circulation and threatening tissue viability.

The new study, in the Jan. 23 *Science Translational Medicine,* suggests that digestive enzymes play a role in this crisis. The enzymes can digest a person's own tissue if not confined to ducts in the pancreas, where they are made, or the small intestine, where they break down food.

A mucosal lining in the intestines keeps the enzymes from escaping the gastrointestinal tract and from damaging the intestines themselves. But hemorrhage, sepsis and other conditions disrupt blood flow to the intestinal wall and hinder maintenance of this barrier, says Geert Schmid-Schönbein, a bioengineer at the University of California, San Diego.

Schmid-Schönbein and his colleagues induced shock in rats through blood loss, bacterial endotoxin poisoning in the intestines to replicate sepsis, or by infecting the peritoneum — the space around the intestines — with fecal matter to mimic intestinal leakage, as might happen with trauma. All three unleashed digestive enzymes into intestinal tissues, the bloodstream and beyond.

One hour after the shock-inducing procedures, researchers injected enzyme blockers into the small intestine of some rats and into the peritoneum of others. Over three months, most of these treated rats survived, whereas most of the untreated rats with shock died of heart or respiratory failure. The treated rats also experienced less intestinal damage, indicating limited barrier breakdown.

The nutrient-absorbing structures in normal rat small intestines (top) break down when the animal is in shock (middle). Researchers have found that blocking digestive enzyme activity can prevent this process (bottom).

"This is a very intriguing approach," says Asrar Malik, a pharmacologist at the University of Illinois at Chicago College of Medicine. "It's very inclusive, covering three models of experimental shock."

The new work should set the stage for tests in larger mammals, Malik says, and if successful, in people — especially patients with sepsis, a leading cause of death for people in intensive care units.

Flu riskier than vaccine to fetus

Illness in mom-to-be boosts odds of miscarriage, stillbirth

By Nathan Seppa

Getting the flu appears to nearly double a pregnant woman's risk of having a miscarriage or stillbirth, data from Norway during the 2009–2010 flu pandemic show. But getting vaccinated during pregnancy greatly reduces a woman's risk of flu, researchers report online January 16 in the *New England Journal of Medicine.*

The study also finds that getting a flu shot during pregnancy is safe. Anecdotal reports had suggested that flu vaccination during gestation might have adverse effects on the fetus, but the new study — as well as two previous reports, from Canada and Denmark — shows no such connection.

"I think this is a strong finding," says Lone Simonsen, an epidemiologist at George Washington University in Washington, D.C. "It's good to see a carefully done, large study like this."

Physician Camilla Stoltenberg of the Norwegian Institute of Public Health in Oslo and her colleagues scanned Norway's national registry of medical information and identified more than 100,000 pregnancies during late 2009. Pregnant women who received the flu vaccine were one-third as likely to get the flu as were unvaccinated pregnant women.

The study team tabulated miscarriages and stillbirths that occurred during the second and third trimesters of pregnancy. Among children born to roughly 26,000 vaccinated mothers, there were 78 fetal deaths; 414 fetal deaths occurred among 87,000 unvaccinated mothers. The researchers calculate that women who got the flu were almost twice as likely to lose the fetus as were uninfected women.

Miscarriages during the first trimester, which experts note are very difficult to track, weren't included in the study.

COURTESY OF FRANK DELANO

49 percent | Portion of infants with one or more late vaccination

More infants get vaccines late

Spacing out shots may boost risk, researchers warn

By Nathan Seppa

As the public resistance to vaccines that emerged a decade ago appears to subside, another public health problem is emerging in the form of delayed vaccination. A new study suggests that half of U.S. babies don't get routine vaccinations on time, in some cases because parents put off the shots. The delay rate has climbed since 2004, researchers report January 21 in *JAMA Pediatrics*.

Scientists reviewed medical records and found that one-eighth of these delays were intentional as parents defied immunization schedules set out by health authorities. Other parents may have inadvertently missed vaccinations or had lapses in insurance coverage, the study authors say.

Some parents see the bunching of recommended vaccinations as risky and try to space out their children's shots, says coauthor Jason Glanz, an epidemiologist at the Institute for Health Research at Kaiser Permanente in Denver. Delaying vaccination, sometimes called alternative scheduling, might appeal to those parents since babies are scheduled to get 23 shots during the first two years of life. "You can see the parents' perspective in saying that's a lot," Glanz says. But delays pose risks, he says, since the shots prevent diphtheria, tetanus, pertussis, hepatitis, measles, mumps, rubella, polio, rotavirus, pneumonia, meningitis and chickenpox.

Edgar Marcuse, a physician at the University of Washington School of Medicine in Seattle, says timely immunization is important precisely because many of these diseases occur in the first years of life. There is no credible, science-based evidence to suggest that putting off vaccines protects children, he says. "Spacing out the vaccines delays protection, increases the risk that some vaccines will be omitted and increases the cost by requiring multiple visits without yielding any demonstrated benefit."

Glanz and his colleagues analyzed the vaccination histories of 320,000 children 2 to 24 months of age in eight managed-care organizations across the United States. The researchers considered the shots to be on time if they came within a one-month grace period of the schedule. For a vaccination or booster due at 6 months, for example, a parent had until the 7-month point before the child would be listed in the records as delayed for that shot. Even with that buffer, 49 percent of children were late for at least one vaccination, the records showed. Of babies late on vaccinations, 20 percent logged more than 100 days in which they were unprotected from a disease, the records showed.

When the researchers looked at common vaccines, they found substantially more first-shot delays in 2008 than in 2004.

Children who had delayed vaccinations had fewer outpatient clinic visits but 20 to 30 percent more hospitalizations than did kids who were vaccinated on time, Glanz says.

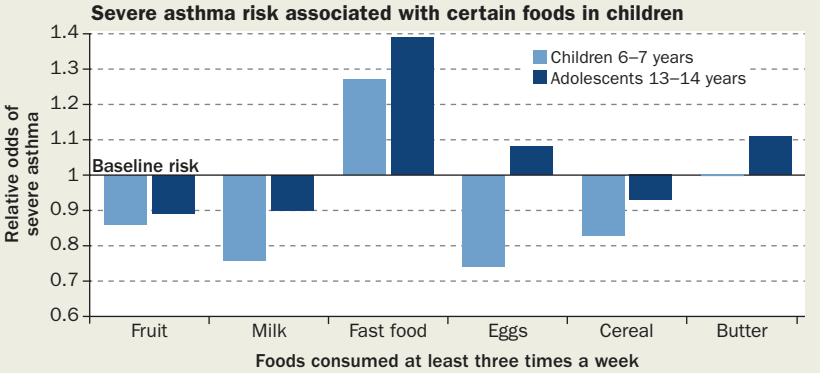
Fast food linked to asthma risk

A diet high in fast food seems to increase the risk of asthma in young children and adolescents, survey data from more than a half-million people finds. Consuming milk and fruit at least three times a week appears to protect against the breathing disorder in all youngsters, while vegetables, eggs and cereal in the diet seem to reduce the odds of asthma in young kids more than in adolescents (examples shown in chart below).

Dozens of countries contributed dietary information from standard questionnaires to the study, published online January 14 in *Thorax* by Philippa Ellwood of the University of Auckland in New Zealand and colleagues. The study accounted for differences among the children apart from diet. The younger group included kids ages 6 and 7; the adolescents were 13 to 14 years old.

The data also suggest a link between fast food and severe eczema, a skin disease, in both age groups, as well as an increased risk of rhinoconjunctivitis, which includes nasal congestion, itchy or runny nose, sneezing and red eyes.

Higher levels of saturated fats, trans-fatty acids, sodium, carbohydrates and sugar were cited by the researchers as "biologically plausible mechanisms" linking junk food to asthma and allergic diseases. —*Nathan Seppa*



SOURCE: P. ELLWOOD *ET AL*/*THORAX* 2013

Mind & Brain

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Brain stimulation aids autistic boy

Implanted electrodes could treat some severe cases

By Laura Sanders

Electrodes implanted deep in the brain of a boy with severe autism have enabled him to live a more normal life. The treatment reduced his destructive behavior and allowed the formerly nonverbal boy to speak a few words, scientists report online January 21 in *Frontiers in Human Neuroscience*.

The case is the first use of brain stimulation to alleviate symptoms of autism. Scientists caution that interpreting the results broadly is impossible without larger, systematic studies. But even so, neurosurgeon Ali Rezai of the Ohio State University Wexner Medical Center in Columbus calls the boy's gains "intriguing and promising."

Researchers have become increasingly interested in deep brain stimulation, a technique in which surgically implanted electrodes act as brain pacemakers. For the last two decades, deep brain stimulation has found use treating movement problems such as the tremors that accompany Parkinson's disease. More recently, scientists have begun experimenting with the technique to treat behavioral and mental problems, including depression, obsessive-compulsive disorder and severe anxiety.

The boy in the study, who was 13 at the time of his experimental surgery, suffered from severe autism symptoms: He couldn't talk or make eye contact, woke up screaming repeatedly during the night and habitually injured himself so badly that his parents restrained him almost constantly to protect him. Multiple rounds of psychiatric drugs failed to stave off his worsening symptoms.

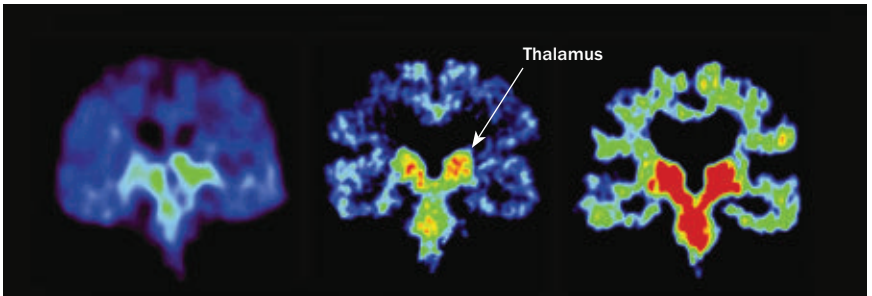
In an effort to help, doctors led by Volker Sturm of the University Hospital of Cologne in Germany implanted electrodes into the boy's brain. Through trial and error, the doctors realized that stimulating a part of the amygdala, a brain structure important for emotions, improved the boy's symptoms. Stimulating other brain areas had no effect or worsened his symptoms.

After eight weeks of continuous electrical stimulation, the boy shifted from "severely ill" to "moderately ill" on a clinical scale that measures signs of aggression and self-injury. The boy also improved on a scale that measures autism symptoms. He began to make eye contact and was better able to control his behavior.

The boy's parents reported even more dramatic improvements: His anxiety and self-harming behavior lessened and he slept better at night. He also began to enjoy activities such as tasting new foods, going on car rides and even playing with a piano. After six months of stimulation, the previously nonverbal boy began saying a few simple words such as "papa" and "mama."

The electrodes' stimulation of the brain seemed to be behind the boy's improvements. After 44 weeks of treatment, the battery on the device ran out. During a monthlong lull in treatment, the boy's symptoms worsened. Once the battery was replaced, his symptoms improved.

The next step is to understand how deep brain stimulation changes the brain, particularly in people with behavioral and cognitive problems, Rezai says. That information could allow clinicians to design better therapies for these complex disorders. ■



UCLA

Trauma revealed in living brains

For the first time, scientists have seen the ravages of repeated concussions in the brains of living people. Brain scans of five retired National Football League players reveal unusual deposits of an ominous protein called tau that used to be identifiable only through autopsy. Tau is a hallmark of chronic traumatic encephalopathy, a disease that causes the gradual appearance of mental and emotional problems in people who have experienced repeated brain trauma.

The new method of looking for tau relies on a chemical that affixes to the protein and serves as a beacon, lighting up in PET scans of the brain (shown in yellow and red above). More tau turned up in the brains of former NFL players (center image shows scan of 59-year-old former NFL linebacker; right is a scan of a 73-year-old former guard) than in other men (one scan shown at left), particularly in the brain areas called the thalamus and the amygdala. Some of the players had thinking and memory problems. The more concussions a player had sustained, the more tau scientists found, Gary Small of UCLA and colleagues report in the February *American Journal of Geriatric Psychiatry*. This ability to track tau changes in players may reveal what happens in brains that get jolted repeatedly during a professional football career. —*Laura Sanders*

"We are made to interact with language and to listen to each other." —PATRICIA TUN

Hearing loss tied to mental decline

Compensating for impairment may divert brainpower

By Laura Sanders

Older people with hearing loss may suffer faster rates of mental decline than their counterparts with normal hearing. People who have hearing trouble show meaningful impairments in memory, attention and learning about three years earlier than people with good hearing, a study published online January 21 in *JAMA Internal Medicine* reveals.

The finding bolsters the idea that hearing loss can have serious consequences for the brain, says Patricia Tun of Brandeis University in Waltham, Mass., who studies aging. "We are made to interact with language and to listen to each other," she says, "and it can have damaging effects if we don't."

Frank Lin of Johns Hopkins School of Medicine and colleagues tested the hearing of 1,984 older adults. Most of the participants, with an average age of 77, showed some hearing loss — 1,162 volunteers had trouble hearing noises of less than 25 decibels, comparable to a whisper or rustling leaves. The volunteers' deficits reflect the hearing loss in the general population: Over half of people older than 70 have trouble hearing.

Over the next six years, these participants underwent mental evaluations that measured factors such as short-term memory, attention and the ability to quickly match numbers to symbols. Everybody got worse at the tasks as time wore on, but people with hearing loss had an especially sharp decline, the team found. On average, a substantial drop in performance would come about three years earlier to people with hearing loss.

Lin cautions that the study has found an association between hearing loss and mental abilities; the researchers can't conclude that hearing loss directly causes the decline. Yet more and more studies are turning up ways that diminished hearing could damage the brain. A person who can't hear well might avoid social situations, for instance, and isolation affects brain function.

More studies are needed to explore exactly how hearing loss relates to mental decline. Lin and his colleagues hope to test whether improvements in hearing brought about by hearing aids or other treatments translate to improvements in mental functioning.

"The ultimate question is: Can we do anything about it?" Lin says. "And we honestly just don't know at this point."

Life

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Cats claim billions of bird and small mammal victims annually

New estimate suggests felines take a big bite out of wildlife

By Susan Milius

Cats kill many more wild birds and small mammals in the United States than scientists thought. The domestic species may rank as the biggest immediate danger that living around people brings to wildlife, researchers say.

America's cats, including house cats that venture outdoors and feral cats, kill between 1.4 billion and 3.7 billion birds in a year, says Peter Marra of the Smithsonian Conservation Biology Institute in Washington, D.C., a member of the team that performed the analysis. Previous estimates of bird kills have varied, he says, but "500 million is a number that has been thrown around a lot."

For wild mammals, the annual toll lies between 6.9 billion and 20.7 billion, Marra and his colleagues report along with the bird numbers January 29 in *Nature Communications*. The majority of these doomed mammals and birds fall into the jaws of cats that live outdoors full time with or without food supplements from people.

"The results are remarkable, not only for the big number, but also for the proportion of deaths from feral cats," says Gary M. Langham, chief scientist for the National Audubon Society. The study assigns 952 million to 3.1 billion bird deaths a year to these free-roaming cats. "These numbers really elevate this threat to a new level."

To figure out how much wildlife cats catch, Marra and his colleagues combed the scientific literature for the best assessments of how many cats live in the United States and of what cats there and in similar climates hunt. Roughly 114 million cats live in the contiguous United States, 84 million of which share people's houses. Forty to 70 percent of those household cats do at least some roaming outside. Between half and 80 percent of those outdoor cats hunt.

Marra says scientists have difficulty judging what proportion of total populations the cat catches represent. Comprehensive mammal numbers are a deep mystery, and estimates for U.S. land birds from volunteer counts lie between 10 billion and 20 billion adults.

"Cats are a nonnative species," he notes, and multiple studies have shown that their hunting often targets natives. In his earlier research, Marra has shown that hunting cats can transform places that would normally be sources of young birds into sinks that drain birds from neighboring populations.

University of Wisconsin–Madison conservation biologist Stanley Temple says that "this huge problem awaits a practical and widely acceptable solution." The practice of catching free-roaming cats to neuter them in hopes of shrinking populations is "simply too difficult, time consuming and expensive," says Temple, a senior fellow at the Aldo Leopold Foundation. "Even if herculean efforts made it feasible at very small local scales, from a conservation perspective, [the trapping and neutering approach] maintains free-ranging cat populations that will continue to harm native wildlife."

An alternative policy of repeatedly rounding up cats and killing them hasn't diminished overall cat numbers, says Becky Robinson, president of Alley Cat Allies, a national advocacy group for protecting cats and reforming animal control based in Bethesda, Md.

"The big message is responsible pet ownership," Marra says. Even though full-time outdoor cats may be the bigger problem, he says, cats with indoor homes still catch some 1.9 billion wild animals a year.

Cat hunting catches have not gotten the serious conservation attention they deserve, he says, because policy makers often dismiss cats as a minor threat compared with the other mortal dangers that wildlife faces. However, the new estimates outstrip assessments of annual bird deaths from pesticide poisonings or from collisions with windows, communication towers or vehicles.

Marra says he hopes the research will encourage dialog, instead of bitter fights, between wildlife conservationists and advocates for cat welfare. "The irony here is that you've got people who love animals on both sides," he says. ■

Cats may be killing far more birds and mammals each year than previously thought, says a new analysis based on hunting studies.

VVVITA/SHUTTERSTOCK

1.4 billion Low estimate of number of birds killed annually by cats

6.9 billion Low estimate of number of small mammals killed annually by cats

Barnacles have sex at a distance

Genetic analysis finds sperm transmission through water

By Susan Milius

Confounding more than a century of received wisdom about crustacean sex, genetic tests show that at least one kind of barnacle can transfer sperm without making direct contact.

Pollicipes polymerus gooseneck barnacles along the northeast Pacific coast have sperm-delivery organs that stretch out about half a body length, which is actually modest by barnacle standards. Many biologists presumed that barnacles deliver sperm only by reaching with these organs into the space within a neighbor's shell.

Yet genetic markers show that the barnacles also reproduce using sperm transported by water, Richard Palmer of the University of Alberta in Edmonton, Canada, and colleagues report in the March 7 *Proceedings of the Royal Society B*.

"The surprise is more that it hasn't been investigated before," says invertebrate zoologist John Zardus of The Citadel in Charleston, S.C.

Biologists have certainly recognized that barnacles are in a fix: The crustaceans essentially glue themselves head-down in one spot for their entire adult lives, which can last decades. Plenty of kinds have evolved sperm-delivery organs two to three times as long as their bodies, and one species can reach eight body lengths. Many barnacles are hermaphrodites, and individuals beyond the reach of potential partners have been presumed to fertilize themselves.

Coauthor Marjan Barazandeh, also at Alberta, examined oddities at single locations in stretches of DNA. This approach allowed her to test the parentage of egg masses from isolated barnacles or barnacles living in pairs.

In a dense crowd of *Pollicipes polymerus* gooseneck barnacles, one oozes sperm. The barnacles can reproduce using sperm released into water.

Loner barnacles' egg masses included markers that couldn't have come from the single parent, indicating fertilization by an out-of-reach individual. Even among barnacles with a potential mate within reach, nearly a quarter of them were fertilized by some out-of-reach donor.

Now, Palmer says, researchers need to see whether the capacity evolved in other barnacle species.

Dung beetles steer by starlight

Nocturnal insects orient using Milky Way, experiments show

By Susan Milius

Even a collector of animal waste can keep its eyes on the stars. Like seals, birds and people, dung beetles use stellar cues, neuroethologist Marie Dacke of Lund University in Sweden and her colleagues report January 24 in *Current Biology*.

Dung-rolling insects collect their prized food source and single-mindedly roll it as directly as possible away from competitors and predators. Beetles can orient using the sun and moon as beacons or by the patterns of polarization in sunlight and moonlight. Beetles don't use landmarks like rocks and trees or, scientists thought, starlight.

That conclusion came from a 2003 publication by Dacke herself. In that work, she and her colleagues reported that beetles lost their sense of direction if they could see the stars but not the moon. So she was mystified years later, when she observed beetles under starlight in a different experiment and found that they weren't lost at all.

The researchers did outdoor experiments blocking the insects' view of the heavens with blinders or using high-walled arenas that allowed them to see nothing but sky. The beetles could orient when they could see the band of light made by the Milky Way but not when they could see only terrestrial landmarks.

Researchers fitted dung beetles with tiny blinders for experiments showing that the insects can use the Milky Way to orient themselves.

Next, Dacke and her colleagues borrowed the Johannesburg planetarium. With the planetarium dome darkened, the nocturnal *Scarabaeus satyrus* dung beetles fumbled and curlicued around. But showing just the Milky Way let the beetles kick along balls of dung in fairly direct paths.

Dacke realized why her earlier experiment had gone wrong: She had tested the beetles in October in South Africa, when the Milky Way was so low in the sky that the animals couldn't get a good view.

The beetles don't steer by the Milky Way with a person's understanding, says Paul Graham of the University of Sussex in England. The blur of stars is just a stable feature for orientation.

FROM TOP: M. BARAZANDEH; MARCUS BYRNE

Environment

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California farms water Southwest

Central Valley irrigation makes Colorado River basin wetter

By Erin Wayman

Farmers in California help make it rain in the American Southwest, a new computer simulation suggests. Water that evaporates from irrigated fields in California's Central Valley travels to the Four Corners region, where it boosts summer rain and increases runoff to the Colorado River, researchers report online January 29 in *Geophysical Research Letters*.

Irrigation in California's Central Valley increases rain and runoff to the Colorado River (shown), hundreds of miles to the east.

This climate link may be crucial to the 40 million people who depend on the Colorado River basin for drinking water. Since the Central Valley's supply of irrigation water faces an uncertain future, it's important to examine how shortfalls in California might affect regional climate, says study coauthor Jay Famiglietti, a hydrologist at the University of California, Irvine.

A study done in 2011 showed that watering the Central Valley's crops cools local temperatures and increases humidity. But the work found no long-distance climate effects because it relied on a regional climate simulation, which had trouble estimating conditions at the boundaries of the study area, Famiglietti says.

To overcome this problem, he and Min-Hui Lo, now at the National Taiwan University in Taipei, simulated global climate over 90 years. They added 350 millimeters of water — coming from groundwater and surface reservoirs — to the Central Valley between May and October each year. The simulations revealed that irrigation doubles evaporation in the Central Valley. That water vapor circulates to the Southwest during the summer monsoon season, which naturally brings rain to the area.

The evaporated water also brings more energy to the atmosphere. And it changes the regional circulation, drawing in even more water vapor from the Gulf of Mexico.

Together, these changes result in a 15 percent increase in summer rainfall in Utah, Colorado, New Mexico and Arizona and a 28 percent increase in runoff to the Colorado River basin compared with simulations lacking irrigation.

"It's a nice first step," says hydrologist Michael Puma of Columbia University. "And it's a link that we need to investigate quite a bit more."

Waste heat warms climate

Energy use in cities may alter atmospheric circulation

By Erin Wayman

The waste heat generated by car engines, power plants, furnaces and other fuel–burning machinery plays an unappreciated role in regional climates, new computer simulations suggest. By altering atmospheric circulation, human-made heat may raise temperatures by as much as 1 degree Celsius during winter in the northernmost parts of the world.

The finding may explain why climate simulations have failed to replicate some winter warming in the northern latitudes, researchers report online January 27 in *Nature Climate Change*. Climate simulations account for the heat-trapping effects of greenhouse gases but not the heat produced by energy use. Studies, including the new one, have found that energy consumption's effect on warming is no more than around 3 percent of the total caused by carbon dioxide emissions.

"The magnitude of their result is quite surprising," says Mark McCarthy, a climate scientist at the Met Office Hadley Centre in Exeter, England.

Climate scientist Ming Cai of Florida State University in Tallahassee and his colleagues ran global climate simulations that took into account energy use in 2006 from 86 of the world's largest metropolitan areas. Together, these cities cover less than 2 percent of Earth's surface but are responsible for about 42 percent of world energy consumption. The researchers assumed that all energy used in these areas converts to waste heat — an overestimate, but not an unrealistic one, Cai says.

The simulations found that temperatures in December, January and February were 1 degree warmer in Russia and northern Asia than they were in simulations that ignored waste heat.

"The largest warming is not in the places where the energy is consumed," Cai notes. That's because the heat itself doesn't cause the temperature spikes. Instead, the heat disrupts normal atmospheric circulation, warming some regions in winter and bringing cooler air to others, the simulations show.

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Science & Society

615 cases — Worldwide H5N1 infections, 2003–2013

364 deaths — Worldwide deaths from H5N1, 2003–2013

Moratorium on H5N1 flu virus research ends

Studies on transmissibility to resume outside U.S.

By Tina Hesman Saey

A self-imposed moratorium by researchers on certain kinds of avian influenza experiments lifted January 23.

In January 2012, influenza researchers imposed a halt on work that would create bird flu viruses that are easily transmissible in mammals. The moratorium came after controversy surrounded two scientific papers describing mutations in the H5N1 avian influenza virus. The mutations enabled the virus to spread among ferrets via airborne droplets. The scientists chose to stop the work until they could explain its benefits and safety to the public, and to give governments and funding agencies a chance to review policies surrounding the research. The halt was supposed to last 60 days, but has lasted for a year because of the complicated issues surrounding the research.

Now, the same group of 40 researchers has declared in a letter published by both *Nature* and *Science* that the goals of the moratorium have been met and that work on the viruses may resume in countries with appropriate policies in place. The United States is not among those countries.

The researchers say they are confident that imposing multiple safety measures can prevent an accidental or malicious release of a version of the H5N1 virus that could pass easily from person to person. "There can never be zero risk," says Yoshihiro Kawaoka of the University of Wisconsin–Madison and the University of Tokyo, but scientists can minimize the risks. Meanwhile, the virus continues to mutate in nature, and some of the mutations identified in the laboratory studies have already been found in wild H5N1 viruses. With resumption of the work, researchers say they can monitor which strains are developing dangerous mutations, identify new mutations and test vaccines and antiviral drugs.

"We believe this research is important to pandemic preparedness," Kawaoka says. He and Ron Fouchier, an influenza researcher from Erasmus Medical Center in Rotterdam, the Netherlands, led the research that originally touched off the controversy.

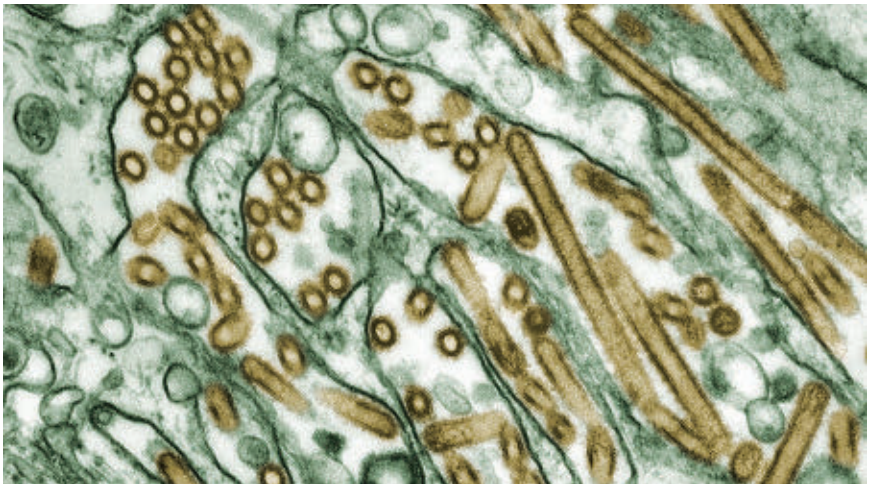
In that work, Fouchier's group found that five to nine mutations could transform the H5N1 virus from one that requires direct contact to one that infects ferrets through the air. Kawaoka's group made similar discoveries using a hybrid of the avian influenza virus and a pandemic flu strain. A U.S. government advisory panel originally deemed both findings too dangerous to publish because of the fear that terrorist groups or rogue governments could use the information to develop biological weapons. The panel later reversed the decision and the papers were published last summer (*SN: 6/2/12, p. 20*).

Although the United States is still working out its guidelines for the research, China, Canada and countries in the European Union have already decided to go ahead, reasoning that the potential benefits outweigh the risks. Fouchier defended the decision to go ahead without the largest funder of infectious disease research. "If this had been the Netherlands," Fouchier asks, "would the U.S. wait?"

The United States is just weeks away from having its own guidelines for avian influenza research, says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases. "We're in the process of saying what we will fund or not fund." The framework emerged from a meeting in December and public comment on the proposal that ended January 10. Final revisions and approval are under way, Fauci says.

Fauci stresses that the U.S. government is not holding researchers back from their work. "The government doesn't have a moratorium," he says. When the new guidelines are in place, NIH will evaluate proposals on a case-by-case basis, he says.

When the moratorium went into effect, only a handful of research groups were conducting studies aimed at discovering what it takes for the bird virus to morph into human flu. "This is really a small slice of research," Fauci says. ■



CYNTHIA GOLDSMITH

Research is set to resume on how the H5N1 avian influenza virus (seen in gold in this false-color micrograph) could become transmissible in mammals. A voluntary moratorium put in place last January had blocked such efforts.

News in Brief

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HEALTH & ILLNESS

Nerve stem cells may treat intestinal disorder

Transplants of nerve stem cells are usually reserved for attempts to repair the brain or spinal cord, but a new study suggests such therapy may improve some intestinal disorders as well. People with Hirschsprung disease have no nerves in parts of the large intestine, so muscles don't contract to produce regular bowel movements. No effective therapies exist for the condition or for similar disorders known as enteric neuropathies. To see if such nerve deficiencies can be repaired, Heather Young of the University of Melbourne in Australia and colleagues transplanted nerve stem cells into the colons of mice. The cells wired into the nervous system and made contact with muscles, suggesting they might be able to correct bowel movement problems. The authors write online February 1 in the *Journal of Clinical Investigation* that the cell therapy could someday replace diseased nerves in the colons of people with some enteric neuropathies. —*Tina Hesman Saey*

Television watching linked to lower sperm counts

Men who watch a lot of television have lower sperm counts than those who don't watch any, researchers report February 4 in the *British Journal of Sports Medicine*. Sperm count is an informal term that refers to the concentration of sperm in a given volume of semen. Researchers gave questionnaires to 189 healthy young men and analyzed their semen. Respondents who watched more than 20 hours of TV per week had sperm counts 44 percent lower than those who didn't watch any. The team, led by Audrey Gaskins and Jorge Chavarro of the Harvard School of Public Health, also found that men who spent the most time doing moderate to vigorous physical exercise had 73 percent higher sperm counts than did the men who were least active. While the findings don't spell out an explanation for these differences, the authors cite the broad physiological benefits of exercise. Cooler scrotal temperatures have been linked to a higher sperm count, and sedentary positions and certain exercises—such as bicycling—have been linked to higher scrotal temperatures. —*Nathan Seppa*

GENES & CELLS

Human gene variant makes flu worse

Chinese people carrying a particular version of an immune system gene are up to six times more likely to develop severe influenza than those lacking the variant. In a previous study involving mostly people of European descent, scientists found that a few individuals carried a particular form of a gene known as *IFITM3* and got hit especially hard by the flu. In China, the variant is much more common. About three-quarters of people carry at least one copy of the form of *IFITM3* that is rare among Europeans, Tao Dong of Capital Medical University in Beijing and Oxford University in England and her colleagues have discovered. The researchers studied 83 people who were hospitalized with the H1N1 flu virus in 2009. Of the 35 people in that group who had two copies of the variant, 22 developed pneumonia or other severe flu symptoms, the researchers report online January 29 in *Nature Communications*. —*Tina Hesman Saey*

EARTH

Indonesian mud volcano running out of steam

The end may be near for an erupting mud volcano that has wreaked havoc in Indonesia. In a few years, the volcano will spew just 10 percent as much mud as it does today, scientists predict. The mud volcano known as Lusi began erupting in May 2006, triggered by either a nearby drilling accident or an earthquake. Since then, the eruption has buried an area about twice the size of New York's Central Park and displaced more than 60,000 people. Based on the amount of muck burped up during the eruption's first three years, scientists had estimated Lusi's fury would last 23 to 50 years. The new estimate takes into account a longer period of Lusi's history. Maxwell Rudolph, now at the University of Colorado Boulder, and colleagues analyzed satellite measurements collected from October 2006 to April 2011 of sinking ground caused by the eruption. Changes in the rate of sinking reflect changes in the pressure inside the volcano, the team says. High pressure fuels the eruption. This pressure has decreased exponentially over time, the researchers found. Currently, Lusi releases 10,000 cubic meters of mud per day. Because of pressure drops, by around 2017 the volcano will erupt less than 1,000 cubic meters daily, the team predicts online January 26 in *Geophysical Research Letters*. —*Erin Wayman*

MIND & BRAIN

Professional athletes have superior perception

Humongous hamstrings, bulging biceps and dangerous delts are obvious attributes of professional athletes. But the brain might be the most important asset on the field, a new study suggests. Pro athletes are better at interpreting abstract moving scenes than are average people, reports Jocelyn Faubert of the University of Montreal. In his study, 102 professional soccer, rugby and hockey players completed a difficult perception task. To perform well, participants had to distribute their attention among multiple targets, ignore distractions, correctly perceive depth and follow lightning-fast dots on a computer screen. The professional athletes outperformed both high-level college athletes and nonathletes, Faubert writes online January 31 in *Scientific Reports*. He does not know whether these superior perceptual skills are innate or learned over years of practicing the sport. —*Laura Sanders*

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Salvage job

With fertilizer prices skyrocketing, scientists scramble to recover phosphorus from waste

By Roberta Kwok

It started with droughts in Australia and Ukraine. Wheat yields dropped and countries clamped down on grain exports. With a hungry biofuel market also gobbling up corn, the cost of food soared.

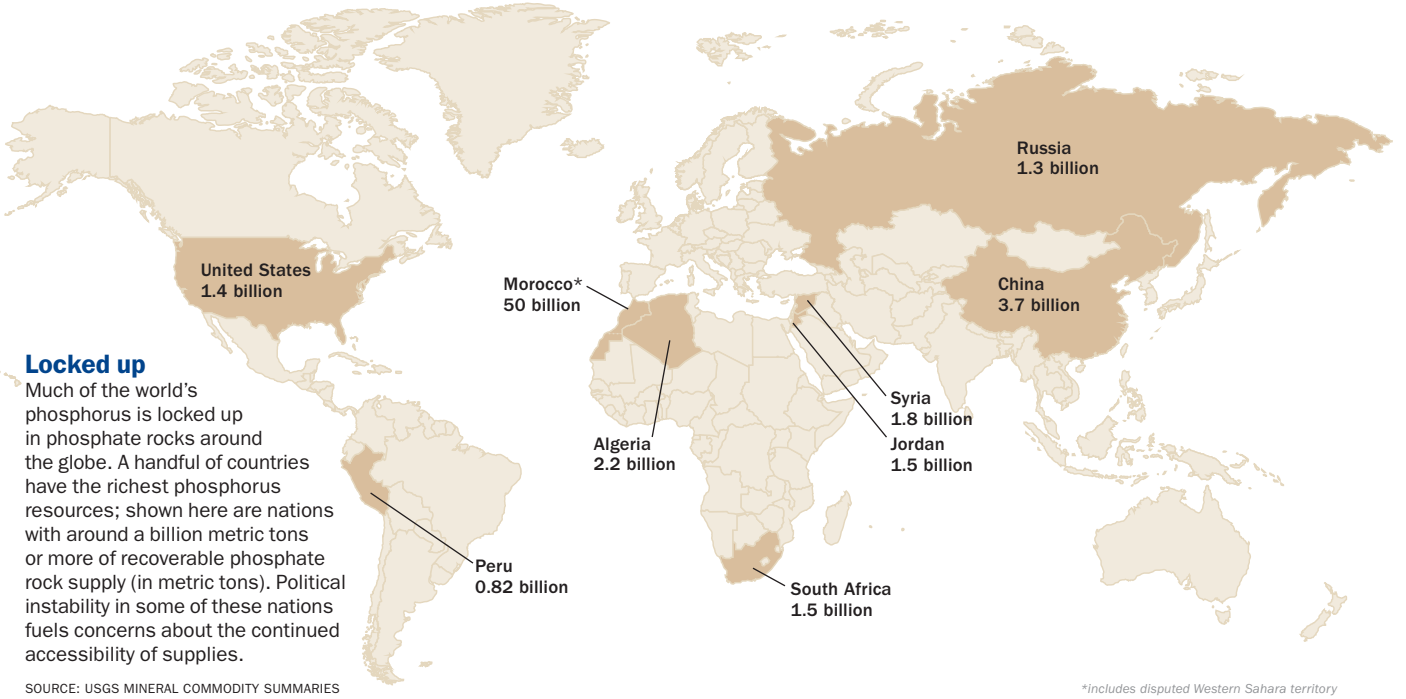
Sensing an opportunity for profit, farmers sought more fertilizer to nourish their fields. But high oil prices had increased the cost of processing phosphate rock, which provides a key ingredient in fertilizer. With rising demand and tight supply, phosphate rock prices leaped from about $45 per metric ton to $80, then $135, then $367 — a roughly 700 percent spike in just one year. As food prices continued to surge, riots erupted from Haiti to Burkina Faso.

The crisis, which unfolded from 2007 to 2008, foreshadows what might happen more regularly if the world runs short of phosphate rock, the main source of phosphorus for fertilizer. Phosphorus, an essential nutrient for life, helps power the growth of crops. By adding the element to fields, farmers boost their yields and churn out the billions of tons of food needed to feed Earth's growing population.

But the planet holds a limited amount of easily accessible phosphate rock. Just a few countries, such as Morocco, China and Algeria, control large deposits that can be mined with existing technology at a reasonable cost. The United States is currently a major supplier, but its

As with oil, the global supply of phosphate rock, needed for fertilizer, will eventually start to dwindle. But how soon this may occur isn't clear (a phosphate and sulfur plant blend, shown).

HEYDENKAYE/ISTOCKPHOTO



Locked up
Much of the world's phosphorus is locked up in phosphate rocks around the globe. A handful of countries have the richest phosphorus resources; shown here are nations with around a billion metric tons or more of recoverable phosphate rock supply (in metric tons). Political instability in some of these nations fuels concerns about the continued accessibility of supplies.

SOURCE: USGS MINERAL COMMODITY SUMMARIES

*includes disputed Western Sahara territory

reserves are dwindling. As high-quality deposits become depleted, remaining untapped reserves generally contain less phosphorus. Some researchers predict that the annual amount of phosphorus retrieved from mined phosphate rock could peak sometime this century.

And how much is left isn't the only concern. Political disputes over ownership of the Western Sahara territory — which along with Morocco contains about three-quarters of the world's remaining known reserves — raise fears that geopolitical instability could threaten the global phosphorus fertilizer supply.

Aware of the growing risk, researchers are investigating how phosphorus in soil and waste can be conserved and recovered. A frequently cited 2009 study in *Global Environmental Change* shows that people waste a flabbergasting amount of this precious resource: Each year, about 80 percent of phosphorus mined for fertilizer is washed off farms, left in livestock manure, dumped into landfills or otherwise squandered before the food even reaches people's mouths. Many farmers still overfertilize their fields, despite initiatives to reduce fertilizer use.

700
percent
Price increase for phosphate rock used to make fertilizer in one year, 2007–2008

To combat these losses, some researchers are engineering plants that suck up leftover phosphorus from the soil, while others are trying to pull phosphorus from wastewater, using everything from nanoparticles to algae.

Through these efforts, scientists and engineers are drawing attention to a neglected problem. Potential fossil fuel and water shortages regularly make headlines, but phosphorus often takes a backseat. "I call it the biggest problem we've never heard of," says James Elser, an ecologist and co-organizer of the Sustainable Phosphorus Initiative at Arizona State University in Tempe.

Lazy plants

Life needs phosphorus. It's part of DNA's backbone and contributes to the structure of cell membranes. "Life without phosphorus would be like life without oxygen or carbon or hydrogen," says Dana Cordell, a sustainability researcher at the University of Technology Sydney and cofounder of the Global Phosphorus Research Initiative. "Life would not exist."

Phosphorus exists primarily in sediments and rock. When marine organisms die or are eaten and excreted by other animals, some of the phosphorus in their bodies sinks to the ocean floor and gets buried in sediment, eventually becoming rock. Over millions of years, that rock shifts and lifts back up to Earth's surface. The rocks weather and break down, forming new soil containing phosphorus that can nourish plant growth. Phosphorus from dead plants

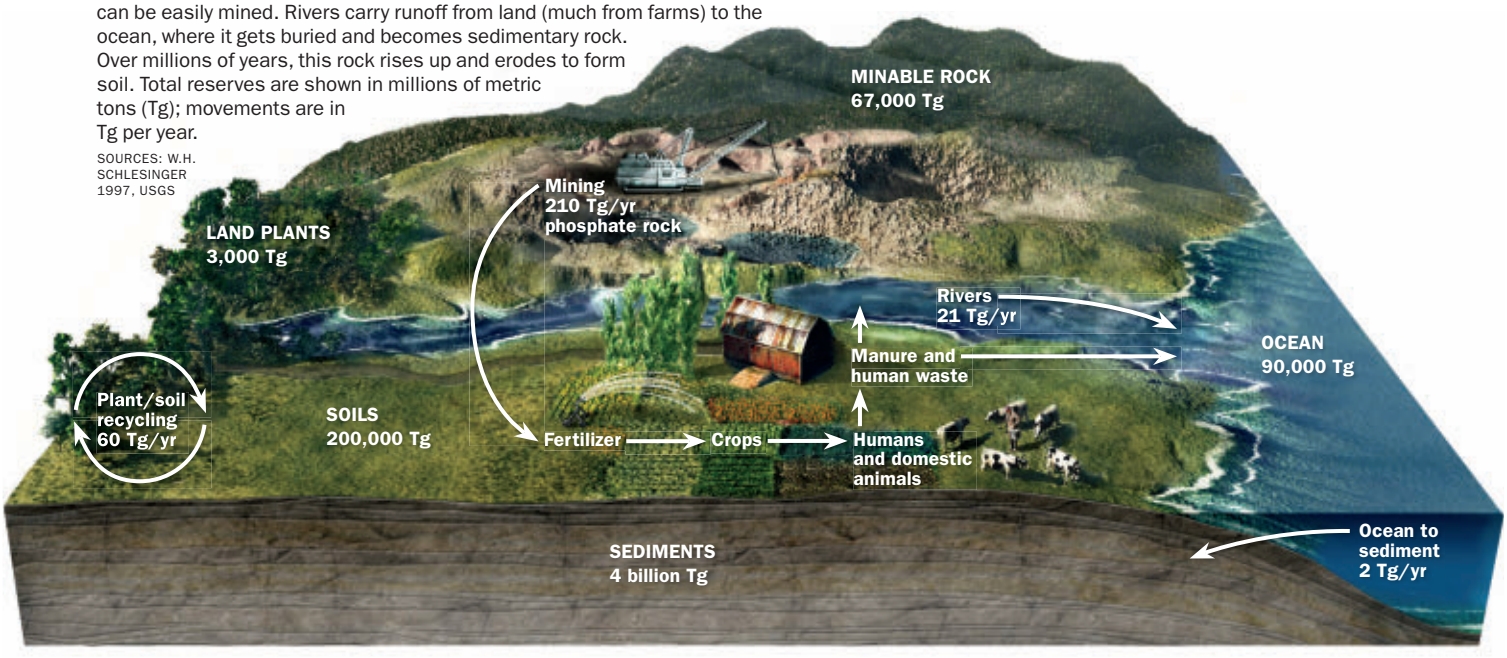
Phosphorus

- **Symbol:** P
- **Atomic number:** 15
- **Atomic mass:** 30.97
- **Chemically similar to:** Arsenic
- **Forms:** In its pure state, P is a solid found in several colors and a colorless form that is highly volatile and spontaneously ignites when exposed to air. In nature P is found only in more stable bound forms.
- **Sources:** Nearly all P on land comes from rock weathering. Unlike other elements important in nature, such as oxygen and nitrogen, it has no significant gaseous form.
- **Biological role:** Found in DNA, RNA and ATP (the energy-carrying molecule in cells); required for life in all known organisms.

REDMAL/ISTOCKPHOTO, ADAPTED BY E. FELICIANO

Follow the P A limited amount of the world's phosphorus is in places that can be easily mined. Rivers carry runoff from land (much from farms) to the ocean, where it gets buried and becomes sedimentary rock. Over millions of years, this rock rises up and erodes to form soil. Total reserves are shown in millions of metric tons (Tg); movements are in Tg per year.

SOURCES: W.H. SCHLESINGER 1997, USGS



and the carcasses or excrement of animals also enters the ground.

Farmers face two big problems in getting to that phosphorus. First, the weathering process is very slow. Second, after phosphorus enters the soil — whether from rock weathering or land animals — much of it ends up bound to iron, aluminum or calcium, which prevent plant roots from absorbing it. So, many soils don't contain enough accessible phosphorus to support vigorous crops.

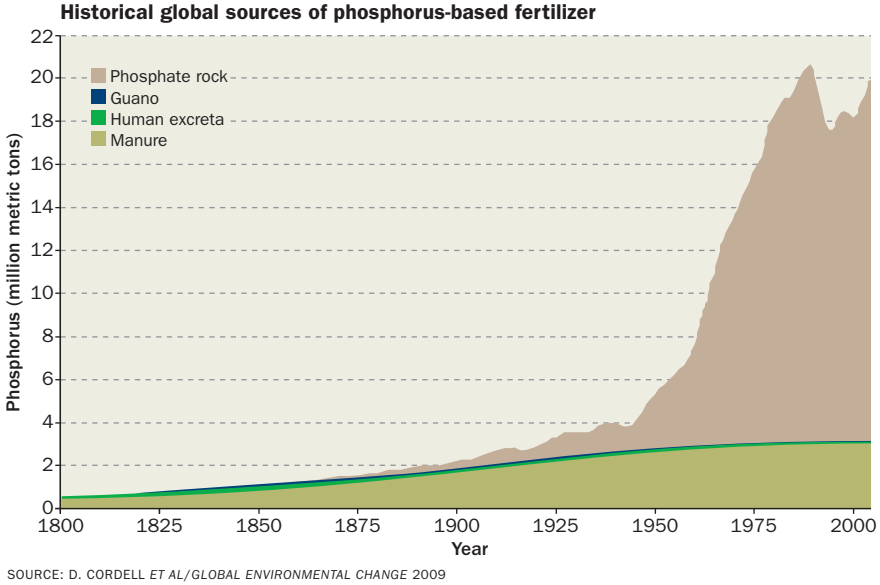
For centuries, people improved crop yields by fertilizing their farms with phosphorus-rich waste such as manure and bat droppings. They didn't always realize they were using phosphorus, but they knew those materials made plants grow better. In the 1900s, companies started ramping up production of chemical fertilizer containing phosphorus, helping trigger a worldwide explosion in farm productivity.

Lavished with a rich supply of fertilizer, domesticated crop plants weren't under any pressure to scrape together phosphorus from nutrient-poor soils. So their roots became lazy, says Roberto Gaxiola, a molecular biologist at Arizona State University and an investigator with the Sustainable Phosphorus Initiative. "The original plants used to grow with whatever they had," he says. "And then we started spoiling them."

In one effort to recover phosphorus, Gaxiola is now coaxing plants to slurp up more phosphorus from the earth. If Gaxiola can get plants to grow bigger roots, they would release more protons, which would acidify the soil. Extra acid frees some phosphorus into a form that plants can take up.

In a 2007 study in *Plant Biotechnology Journal*, Gaxiola's team genetically engineered mouse-ear cress plants to make extra copies of a protein called AVP1. The researchers knew that this protein makes plants grow bigger root systems, though they didn't yet know why. Under low-phosphorus conditions, the

In demand With the start of the Green Revolution in the 1940s, farming became increasingly commercial and large-scale, and the need for fertilizer rose dramatically. Mining of phosphate rock took off (tan), while the use of other phosphorus sources such as manure saw only modest gains. Now efforts focus on increasing the use of such alternative sources.



SOURCE: D. CORDELL *ET AL/GLOBAL ENVIRONMENTAL CHANGE* 2009

TOP: NICOLLE RAGER FULLER

engineered plants sprouted more and bigger leaves than unmodified plants, the team found.

In another experiment, the researchers found a likely cause for the improved growth: Engineered plants grown in the low-phosphorus nutrient mixture turned the mixture more acidic, which would free up more phosphorus.

Next, the team tried similar experiments in crop plants. Tomato plants that made AVP1 could produce more fruit in low-phosphorus soil than unmodified tomatoes could, outweighing them by 82 percent. Engineered rice grew taller, and shoots weighed 50 percent more.

Gaxiola suspects the AVP1 protein helps the plant channel more sugar from the leaves to the roots, allowing a larger root system to flourish. These harder-working crops could recover phosphorus stuck in soil that has been heavily fertilized, he says. For the last two years, Gaxiola's team has grown lettuce in previously fertilized fields and found that the engineered plants perform better than unmodified plants do, even with little or no added fertilizer. Ultimately, engineered plants might mean less fertilizer use from the start.

The research is promising, says Sigrid Heuer, a molecular biologist at the Australian Centre for Plant Functional Genomics in Glen Osmond. But she notes that strict regulations on genetically engineered crops may hinder the approval of transgenic plants. Recent work by Heuer and her colleagues while she was at the International Rice Research Institute in Los Baños, the Philippines, used traditional breeding methods to create rice varieties that can tolerate low-phosphorus conditions.

In a paper published in *Nature* in August, Heuer's team showed that a gene called *PSTOL1*, found in a traditional rice plant variety that had been exposed to little fertilizer, could make modern rice plants grow more grain in phosphorus-deficient soil. The team's new rice varieties containing this gene produce 20 percent higher yields in the field. The researchers hope to make one available to farmers in two to three years.

H. YANG *ET AL*/*PLANT BIOTECHNOLOGY JOURNAL* 2007

Suck it up Genetically engineered plants are able to take up phosphorus from soil more efficiently. *Arabidopsis thaliana* cress plants that were engineered to make more AVP1 protein (middle and right) grew more and larger leaves that had more than twice the total leaf area of control plants (left) after 90 days in the same low-phosphorus soil.

Down the drain

Another major leak in the phosphorus cycle is human waste. Once crops are harvested, they end up on dinner plates or feed livestock later eaten by humans. Since people generally get more phosphorus than they need, they excrete almost all of what they consume. "There's a whole bunch of that going down the drain in the form of wastewater," says Andrew Shilton, an environmental engineer at Massey University in Palmerston North, New Zealand.

Wastewater treatment plants do remove phosphorus from sewage. In the 1960s, people became concerned that phosphorus-laden wastewater released into lakes was triggering the growth of algal blooms. Bacteria consuming the dead algae suck up oxygen, suffocating other aquatic life. To reduce phosphorus levels in wastewater, many treatment plants now add chemicals such as aluminum sulfate, which bind the phosphorus and settle out as sludge. Some treatment plants also use bacteria to gobble up the phosphorus.

But most treatment plants don't recover phosphorus in an easily reusable form. Chemical sludge is often thrown into a landfill. Although treatment plants use processes that digest phosphorus-stuffed bacteria and offer the remains as fertilizer, transporting the bulky, dilute slurry to individual farms is expensive.

One promising strategy is to harvest phosphorus from wastewater as part of a mineral called magnesium ammonium phosphate, or struvite. Struvite forms naturally when phosphate, magnesium and ammonium mix in the right proportions. Wastewater treatment plant operators have generally considered struvite a nuisance because it builds up as concrete-like gunk in magnesium-lined pipes.

But struvite can also be made in a more controllable way. In the early 2000s, researchers at the University of British Columbia in Vancouver built roughly cone-shaped reactors that create enough turbulence in wastewater to trigger the formation and growth of struvite crystals. "Once that crystal forms, it's almost unbreakable," says team leader Don Mavinic, a wastewater treatment and quality researcher. With a little added magnesium, the reactors could produce 98 percent pure, pearl-like struvite pellets, the researchers reported in *Water Science & Technology* in 2008.

That struvite can then serve as fertilizer. A company called Ostara Nutrient Recovery Technologies Inc. in Vancouver now uses the technology pioneered by Mavinic's team to produce struvite fertilizer pellets, named Crystal Green, from wastewater. Ostara has installed its reactors at wastewater plants in Oregon, Virginia and Pennsylvania and is adding reactors to plants in Wisconsin, Saskatchewan and the United Kingdom. Wastewater plants typically call on bacteria to mop up phosphorus first, then digest the microbes to release the phosphorus into a liquid stream that gets channelled to Ostara's reactors. The reactors can recover about 85 to 90 percent of the phosphorus that flows into them, says Phillip Abrary, CEO of Ostara. And the pellets are small and concentrated,

making them easy to transport to farms.

Another phosphorus recovery technique is inspired by methods for removing arsenic from drinking water. Ben Martin, a chemical wastewater engineer at Cranfield University in England, came across a product consisting of small resin beads embedded with iron oxide nanoparticles. When water passes through a column containing the beads, the nanoparticles tightly bind to arsenic-containing molecules.

Since arsenic and phosphorus have similar chemical properties, this material could also bind phosphate, a molecule made of one phosphorus and four oxygen atoms that's commonly found in wastewater.

To find out how well the product removed phosphorus, Martin pumped synthetic, wastewater-mimicking solutions into columns containing the beads. The material captured an average of 98.7 percent of the phosphorus, Martin reported in his 2010 doctoral thesis. He could later release phosphorus from the beads by adding sodium hydroxide.

Other researchers have found that melter slag, a waste product of steelmaking that contains iron oxide, also can remove phosphorus from wastewater. But Martin's approach has the advantage that nanoparticles collectively have a high surface area and can thus bind a lot of phosphorus.

Over the next four years, Martin plans to test the nanoparticle process at a wastewater plant in England. He also wants to investigate whether different types of nanoparticles release phosphorus more easily during the recovery step.

Closing the cycle

Phosphorus is in demand not just for food crops, but also for biofuel production. Algae, for example, produce and store oil in their cells that could be used for biofuel. But growing large amounts of algae requires fertilizer, including phosphorus.

Jonathan Trent, a marine biologist at NASA Ames Research Center in Moffett Field, Calif., wanted to come up with a way to grow algae without competing with farms for land, water and fertilizer. Instead of jockeying for the same resources as farmers, Trent thought, why not take the phosphorus and other nutrients from wastewater that coastal cities dump into the ocean? The water could be redirected into floating reactors off the coast to help algae grow. Later, the algae's oil could be harvested to make biofuel. Phosphorus from other parts of the algae, such as their DNA, might also be recovered to produce fertilizer.

Inspired by arsenic-removal systems, one team has used tiny resin beads (shown) containing nanoparticles to strip phosphorus from wastewater.

Trent's idea led to the development of Offshore Membrane Enclosures for Growing Algae, or OMEGA, described in *Biofuels* in September. His team built 110-liter reactors made of long, flexible plastic tubes and tested them in outdoor tanks in Santa Cruz, Calif. Then the researchers scaled up to a 1,600-liter system in tanks of seawater at a San Francisco wastewater treatment plant. The water contained pharmaceutical and personal-care products such as shampoo, but these didn't hinder algae from growing, the team found. As for the phosphorus, the algae "absorb it almost instantly," says Trent.

The project has drawn interest from countries around the world, including India, Australia, New Zealand, Morocco and Saudi Arabia, says Trent. But to be affordable, the infrastructure will probably need to be multipurpose. For example, seafood producers could grow mussels or oysters beneath the docks that hold the reactors. And researchers still need to find out if the reactors will stand up to storms or have a negative effect on marine ecosystems, says Shilton.

One can imagine other exotic solutions for recovering phosphorus, such as fishing it out of landfills or mining a nearby asteroid. But such strategies are likely to be expensive and difficult. They strike Elser as rather silly when there is already plenty of phosphorus that is more readily accessible. "Why don't we just take better care of our poop?" he asks.

Even as new technologies plug some leaks in the phosphorus cycle, efforts to reduce demand could make a big difference. More farmers are finding ways to reduce fertilizer use, both by more precisely calibrating the amount they need to apply and by better controlling erosion to keep more soil, and thus phosphorus, in the fields. Eating less meat could make a difference too, since a carnivorous diet requires more phosphorus than a vegetarian one, says Cordell.

Developing countries will also need inexpensive, low-tech solutions. In Nepal, researchers have investigated cheap ways of making struvite from urine and are now expanding the work to South Africa. And a product called Peepoo allows people to collect their urine and feces in a single-use, urea-containing bag that converts the waste into sanitized fertilizer. And an international organization called Máshumus has been training Latin American farmers to extract phosphorus from animal bones.

"Why don't we just take better care of our poop?"
JAMES ELSER

In some ways, solving the phosphorus problem is less daunting than managing other resources. With fossil fuels, "once they're burned, you can't unburn them," Elser says. But phosphorus can be reused; it's just a matter of not letting it slip away. "Once we have a closed phosphorus cycle," he says, "it could go on forever." ■

Explore more

■ D. Cordell, J.-O. Drangert and S. White. "The story of phosphorus: Global food security and food for thought." *Global Environmental Change*. May 2009.

Roberta Kwok is a freelance science writer in Burlingame, Calif.

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MICHAEL MORGENSTERN

With drug firms in retreat, the pipeline for new psychiatric medications dries up

By Laura Sanders

Psychiatry seemed poised on the edge of a breakthrough. In early 2011, after decades of no radically new drugs, a fundamentally different schizophrenia treatment promised relief from the psychotic hallucinations and delusions plaguing people with the disease. The new compound, devised by chemists at Eli Lilly and Co., hit a target in the brain that older medicines had ignored.

All signs pointed to success. In mice, a similar molecule could block the schizophrenia-like effects of PCP. In people the new drug, LY2140023, appeared to curb psychotic behavior with few side effects, small pilot studies showed. In March 2011, Lilly began enrolling 1,100 people in a definitive Phase III clinical trial, the final test designed to show conclusively that the new compound worked.

A year and a half later, the drug was dead. After years of work and millions of dollars of investment, the failure was crushing. People with schizophrenia were no better on the new drug than similar people taking a placebo, early results indicated. "I'm disappointed in what these results mean for patients with schizophrenia who still are searching for options to treat this terrible illness," Jan Lundberg, president of Lilly Research Laboratories, said in a press release.

Although the results were devastating, many in the field weren't surprised. For new drugs designed to treat complex brain disorders such as schizophrenia, depression and anxiety, the odds of success are exceedingly slim. Given the current state of affairs in the drug discovery world, some would argue those odds are close to zero. Not a single drug designed to treat a psychiatric illness in a novel way has reached patients in more than

30 years, argues psychiatrist Christian Fibiger of the University of British Columbia in Kelowna, who described the problem in a 2012 *Schizophrenia Bulletin* editorial. "For me, the data are in," says Fibiger, who has developed drugs at several major pharmaceutical companies. "We've got to change. This isn't working."

Fibiger is not alone in thinking the existing approach needs a radical overhaul. Psychiatrists and neuroscientists around the world recently have begun sounding the alarm that the field is in crisis. Drug development for complex psychiatric illnesses is misguided, they argue, stuck churning out slight variations on therapeutic themes that didn't work all that well to begin with. Faulty assumptions, animal models that don't look anything like human diseases, hazy diagnoses and a lack of knowledge about how the brain works have all thwarted the search for better drugs.

Of course, fixing a brain poses challenges that don't apply to other body parts, says neuroscientist Steven Hyman of the Broad Institute of MIT and Harvard. "You can't just open up the hood, take out a chunk and see what's happening," he says. And even if that were possible, it probably wouldn't add much clarity, Hyman argues in the October 10 *Science Translational Medicine*. "Brain research is really hard," says Hyman. "No one should be blamed for how hard this is. But we did get stuck."

Pharmaceutical exodus

At a meeting of the American College of Neuropsychopharmacology late last year, this crisis was the predominant theme. "It's become a topic with a lot of talk and no idea of where to go," Hyman says.

Drug discovery is a tough, slow business. Initial exploratory work to identify a molecular target and a drug that will interact with that target can take years. After that, refined studies are conducted in animals, typically rodents, and then the experiment eventually moves into people. Brain drugs take about 18 years on average to go from preclinical experiments to approval.

This glacial pace is frustrating to the staggering number of people who need better therapies — and to the doctors who treat them.

Many current drugs do exist — by one count, more than 50 different psychiatric medicines together garnered $25 billion in sales in the United States in 2011. But these treatments often don't deliver. "There may be a lot of medicines out there, but they're not doing what we need them to do," says Thomas Insel, director of the National Institute of Mental Health.

> Not a single drug designed to treat a psychiatric illness in a novel way has reached patients in more than 30 years.
> CHRISTIAN FIBIGER

Pharmacies in the United States, for example, filled about 250 million prescriptions for antidepressants in 2011. But these drugs don't work in many people and, even if they do, take weeks to kick in. Antipsychotics, for which roughly 55 million prescriptions were filled in 2011, often do nothing for the most serious symptoms of schizophrenia. On top of that, many of these medicines have side effects so objectionable that people stop taking them.

Despite a dire need for better treatments and a large market — one in four Americans suffers from a diagnosable mental illness in any given year — many drug companies are retreating. Though some small, targeted efforts remain in place, pharmaceutical giants GlaxoSmithKline, AstraZeneca and Novartis recently shuttered their main brain drug discovery programs. "It's pretty scary when you get down to it," says Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development.

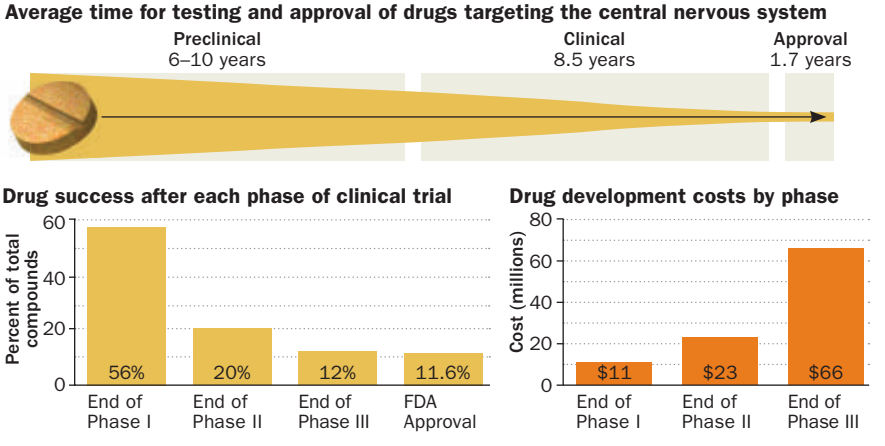
This exodus makes sense: Companies can't afford to spend so much time and money only to have a drug fail in Phase III trials, as LY2140023 did.

A survey of pharmaceutical and biotechnology companies revealed the perils of investing in drugs that target the brain. These drugs are more likely to fail and leak out of the pipeline than other kinds of medications. And brain-targeting drugs spend an average of 8.5 years in human tests alone, more than two years longer than the average for other kinds of drugs. "These tend to be very difficult, expensive clinical trials," Kaitin says. Companies that endure a late-stage failure of a drug after years of testing take a huge financial hit. "Very few companies can withstand that," he says.

Drug firms are also feeling the squeeze from generics, cheaper versions of a drug that can be sold after a certain length of time by companies that didn't have to pay for the original development and testing. To stay profitable, developers need to come up with a fundamentally new drug. "It's really a breakthrough

Broken pipeline For compounds that affect the brain, the chance of failure is high at every step in the testing and approval process (overall success through clinical testing shown below). Generally, these drugs cost more to develop and take longer to reach patients than other drugs.

SOURCE: TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT



S. EGTS

or nothing," Kaitin says. "And breakthroughs are hard to come by."

Some researchers point to reasons for hope. Biomedical advances such as genetic sequencing and brain-scanning technology may usher in a deeper understanding of these complex disorders. Many experts, though, argue that for these discoveries to translate into help for patients, things have to change.

Playing it safe

Most psychiatric drugs in use today originated in serendipitous discoveries made many decades ago. In 1952, doctors noted that patients on the antituberculosis drug iproniazid became euphoric. The observation launched iproniazid, the first antidepressant. A version of the schizophrenia drug chlorpromazine was originally tested in the 1950s as an anesthetic. Around that time, a French surgeon recognized the drug's potential in psychiatry, noting that before surgery patients on the drug became "calm, somewhat somnolent, and relaxed."

Since then, most new psychiatric drugs have been subtle variations on these and a handful of other original molecules. "You get lucky by finding a medicine that helps," Insel says. "Then you create another medicine that looks slightly different."

Derisively termed "me too" drugs, these subtle iterations only rarely make a difference to patients. Instead, Fibiger says, they are created to pad the pockets of drug companies, which aggressively market the drugs as the next new blockbuster. Some are touted as having milder side effects than their predecessors, but critics contend that those side effects are often no better, just different.

As an example, the antipsychotic clozapine, developed in the 1960s, can in rare cases dangerously lower white blood cell counts. Later drugs were developed to mimic clozapine's activity without lowering white blood counts. But the second-generation drugs lead to substantial weight gain and serious metabolic problems.

This copycat process might be a by-product of looking where the light shines brightest. Even basic researchers have a habit of studying what other people are studying. And without an influx of brand new ideas, drug developers are left spinning their wheels. "Even though the technology got better and better, frankly, our success rate got worse and worse," Fibiger says.

After the discoveries of chlorpromazine and another antipsychotic drug, haloperidol, in the 1950s, scientists figured out that these drugs changed the brain's levels of the chemical messenger dopamine. Since then, the relationship between dopamine and schizophrenia has been hotly pursued by the research community, even though it is not exactly clear how those drugs work to combat symptoms. Thousands of studies have been published describing the link between dopamine and schizophrenia. In turn, all of the current drugs for schizophrenia target the brain's dopamine system. (LY2140023 hit a different pathway in the brain called the glutamate system.)

Dopamine probably does play a role in schizophrenia, but other still unexplored factors might be as or more important. The cause of the disease remains unclear. Studies that focus on these neglected unknowns might offer the insights needed to bring about better, faster and more effective drugs, Hyman says.

Another problem that stymies breakthroughs is a heavy reliance on animal models. Scientists often use mice to look for symptoms that can then be applied to human diseases. A mouse that quickly gives up on trying to swim in a tub of water is thought to be despondent. A mouse that doesn't sniff as much as normal around a new mouse is said to be antisocial.

Although these animal behaviors are often the best option for study available, they are a far cry from the human diseases they stand in for, Hyman says. So drugs that can fix these problems in mice don't necessarily translate to people. "Right now, we are in a period of disillusionment with animal models," he says. "People are tired of curing mice."

Hyman believes that human stem cell technology might offer a better solution. Ideas — and eventually drugs — might be tested on groups of carefully cultivated human nerve cells in a dish, for instance. Going further, Hyman and others have started talking seriously about small, carefully designed experiments on people (with oversight and consent, of course). In April, a workshop at the Institute of Medicine will explore the idea of testing drugs first in humans.

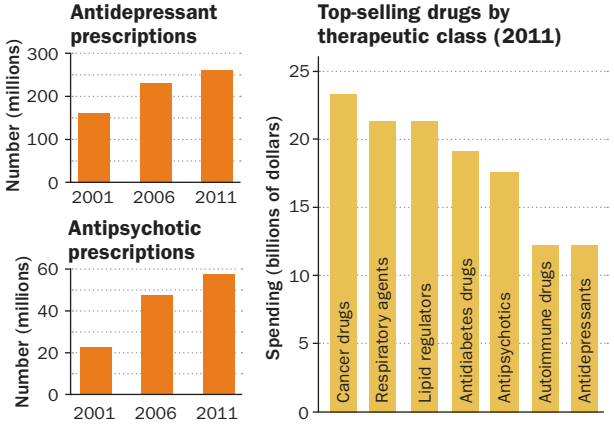
Brain incognito

Perhaps the largest impediment to the development of new psychiatric drugs is the brain itself. A complex web of interconnected systems constantly altered by the environment, the brain is difficult to study.

Even though it's nestled right in our heads, the brain is hard to reach. A blood pressure cuff can be slapped on for an instant and objective measure of what's happening with the heart. A needle biopsy can physically pull out suspected breast cancer cells for further tests. But when it comes to the brain, there is no easy way to identify and

Blockbusters Psychiatric drugs rank among the highest in pharmaceutical sales. But some worry that existing medicines fail to help many people and that efforts to find new therapies are lagging.

SOURCE: T.R. INSEL/*SCIENCE TRANSLATIONAL MEDICINE* 2012



Yesterday's drugs

A large number of the psychiatric drugs in use today are modifications of compounds developed in the 1950s. Many of these compounds' benefits for treating mental disorders were discovered serendipitously.

SOURCE: S.E. HYMAN/*SCIENCE TRANSLATIONAL MEDICINE* 2012

Drug class	Prototype compound	History of use
Mood stabilizer	Lithium	Used to treat gout in the 1800s, its effect on mood was found a century later
Antipsychotic	Chlorpromazine	Synthesized in 1950 and initially tested as an anesthetic
Antidepressant	Imipramine	A failed schizophrenia drug, imipramine turned out to lift depression
Sedative	Chlordiazepoxide	First tested in lions and other zoo animals

measure the thing that isn't working.

When something goes wrong in the brain, as it does in mental illness, the only outward signs are symptoms. And while these symptoms often signify a particular disease, they are far from perfect indicators. For one thing, a particular symptom can accompany multiple diseases. Trouble sleeping often surfaces in depression, schizophrenia and anxiety disorders, for instance. Unlike an unambiguous blood pressure reading, symptoms are subject to interpretation by both patients and doctors, who often rate symptoms on a sliding scale of severity. To muddy the waters even more, symptoms of mental illness can fluctuate, appearing and disappearing over time. Catching someone on an unusually bad or good day can confound a clear view of the disorder.

And even disease diagnoses, often reached by consulting a list of common symptoms, may not offer much insight into what's going on in the brain. Different brain pathologies can yield diseases that appear similar, yet have entirely different causes. Making things even more difficult for would-be developers of new psychiatric medications is the fact that on a biological level most mental disorders are not well understood at all.

All of these factors help explain why it has been impossible to develop a psychiatric drug that makes a disease go away in every person who takes it. In a clinical trial of people with depression, for example, treating patients as one homogenous group obscures meaningful results. If a small subset of the people in the study respond to the drug beautifully, for example, but most people don't, the drug would appear to fail.

"This field is going to have to get past the idea that there will be a perfect pill for these disorders," Insel says. What's needed is a deeper understanding of the brain — the genes, the molecules, the circuits that go awry in some diseases, he writes October 10 in *Science Translational Medicine*. It's much harder to fix something if you don't know what's going wrong.

A reset

The situation is grim, but not hopeless, says Insel. At a time when major pharmaceutical companies are abandoning psychiatric drug development, Insel says he is doubling down, investing federal grant money in places where investors fear to tread. "There are a whole series of pretty amazing developments that I think are worth investing in," he says.

One such project is a newly created funding opportunity for scientists called the Research Domain Criteria, or RDoC. This project has the audacious goal of mapping particular symptoms or behavioral abnormalities to specific causes in the brain. RDoC will bypass the current onerous and problematic disease labels and instead directly investigate what's going on in the brain. Rather than attempting to tie the umbrella disease of schizophrenia to a certain kind of neurotransmitter in the brain, under the RDoC plan a specific part of the disease — hearing voices, for example — might be linked to that neurotransmitter.

Doing small, quick, early-stage trials of prospective compounds in people is another way to move more drugs through the pipeline. In many cases now, a failure in a clinical trial is completely uninformative, Insel says, since it's unclear why a compound failed. By carefully designing studies to test whether a drug hits its target and eases some measurable outcome, these "fast-fail" trials could rapidly identify both promising drugs and ones that don't work. NIMH has requested grant proposals for fast-fail trials aimed at schizophrenia, autism and mood and anxiety disorders.

Some researchers say that the time has come to get back to the roots of psychiatric drug discovery, in which people were given drugs and observant clinicians paid careful attention to the drugs' effects. This is the principle behind the upcoming first-in-humans workshop. And it is the kind of careful observation that can liberate a drug, freeing it to treat problems that it wasn't initially designed to fix. This is how a TB drug and an anesthetic ended up as mood treatments.

Even with many firms pulling back, some pharmaceutical companies are teaming up to work on these tough psychiatric disorders, Kaitin says. Merck and other companies are starting to enter into collaborative agreements with each other and academic centers, spreading the risk but potentially sharing the profits. "I paint a pretty dismal picture when I go out and talk about this, but I think the future is going to be in partnerships and collaborations," Kaitin says.

And of course, more basic experiments on how the brain works will prove instrumental to designing better drugs. If support for that sort of undirected experimentation dries up, so will drug companies' efforts to turn those discoveries into medicine. "At some point, you're going to exhaust the supply," Kaitin says.

Despite the challenges, people are starting to talk seriously about ways to change how psychiatric drugs get discovered, Insel says. "I'm really optimistic," he says. "I think there are great opportunities here." ■

Explore more

- T. Insel. Next-generation treatments for mental disorders. *Science Translational Medicine.* October 10, 2012.

Mastermind: How to Think Like Sherlock Holmes

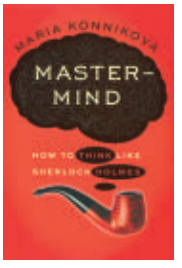
Maria Konnikova

Who *wouldn't* want to think like Sherlock Holmes? Just imagine all the mysteries one could solve: nabbing murderers, foiling villains and locating prize racehorses.

So too might one conquer everyday puzzles, like finding lost car keys. Konnikova, a writer and psychologist, argues that even the dimmest among us can benefit from Sherlockian strategies.

It all sounds a bit self-helpy, but Konnikova unpacks the science behind the brain's process of deduction and how it can falter. Patients with a severed connection between the halves of the brain, for instance, are able to connect facts in ways that seem logical but that don't actually reflect reality. And volunteers incorrectly rank statements packed with more but spurious details as more reliable than statements with fewer but more truthful ones.

By paying attention and putting in some effort, just about anyone can better curate his or her "brain attic," Konnikova claims. The key is to focus on relevant information and throw out the irrelevant stuff. That means not jumping to obvious conclusions right away and making sure all relevant data are in hand before reaching a judgment.



Occasionally the author delves too deeply into Holmes trivia for all but the most devoted fans, and sometimes the science is not deep enough. For instance, a section on priming — how subtle cues unknowingly influence a person's behavior — leaves out recent challenges to some key priming studies (*SN: 5/19/12, p. 26*).

But overall, this enjoyable tour explains usable strategies for sharpening the brain — even for the Dr. Watsons among us. — *Alexandra Witze*

Viking, 2013, 273 p., $26.95

Nature Wars

Jim Sterba

There's a war on in America's neighborhoods. In the past few decades, a confluence of three trends has brought man and beast into increasing conflict: the rebound of wildlife populations from near-historic lows, human populations' growing sprawl and the regrowth of forests on abandoned farmlands, especially in the Northeast.

In *Nature Wars*, longtime reporter Sterba chronicles how the proliferation of trees and greenbelts has turned backyards into battlegrounds, boosting the landscape's ability to support adaptable wildlife at the same time that tolerance of critters such as coyotes is dramatically declining.

And skirmishes in the nature wars aren't restricted to man vs. beast. Patchworks of parks and other predator-free areas where wildlife can thrive have turned some communities into "all-the-pets-you-can-eat" buffets for cougars and coyotes. Likewise, in a landscape where hunters, environmentalists and other interest groups are plentiful and emotions can run high, neighbor can quickly turn against neighbor.

By some estimates, collateral damage is large: Vehicle-wildlife collisions may cost society between $6 billion and $12 billion per year. In just one incident in 2009, US Airways Flight 1549 is believed to have struck a flock of Canada geese, leading to the plane's dramatic landing on the Hudson River.

Such incidents bring a jolt of reality to the public, who may suddenly envision wildlife as a threat to personal safety. Nevertheless, Sterba notes, in an era when individuals are increasingly disconnected from the ecosystems around them, convincing people that wildlife should be actively managed isn't an easy task. — *Sid Perkins*

Crown Publishers, 2012, 343 p., $26

Space Atlas

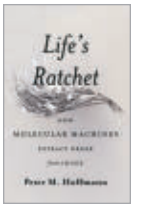
James Trefil

A large-format guide to the universe covers astronomy basics, with eye-catching images plus a foreword by former astronaut Buzz Aldrin. *National Geographic, 2012, 335 p., $50*

I Died for Beauty

Marjorie Senechal

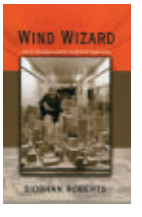
Dorothy Wrinch was best known for losing a feud with Linus Pauling over protein structure, but this biography delves far deeper into her life and contributions to math, physics and more. *Oxford Univ., 2012, 300 p., $34.95*



Life's Ratchet

Peter M. Hoffmann

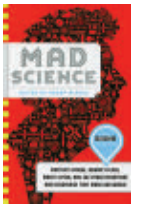
Explore life at the smallest scales in this look at how molecules within cells operate like machines to keep organisms alive. *Basic Books, 2012, 278 p., $27.99*



Wind Wizard

Siobhan Roberts

Skyscrapers and massive bridges would not be the same without Alan Davenport, whose engineering for wind conditions improved the safety of structures around the world. *Princeton Univ., 2013, 278 p., $29.95*



Mad Science

Randy Alfred, ed.

Celebrate a technology anniversary for each day of the year with this compendium of inventions. *Little, Brown and Co., 2012, 390 p., $19.99*

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Dark matter enlightened

Tom Siegfried's article on dark matter ("Light in the dark," *SN: 1/12/13, p. 18*) reminded me of the 19th century search for the luminiferous ether. One can only wonder if history will repeat itself in the 21st century search for dark matter.
Jeffery Miller, Los Angeles, Calif.

The difference is that the ether was only surmised; attempts to observe its effects failed. There is abundant observational evidence for the existence of dark matter. Its actual identity could still, of course, turn out to be very surprising.
— Tom Siegfried

Where did the figure that 17 percent of the universe is composed of ordinary matter come from? The data I have seen is that ordinary matter constitutes less than 5 percent of the universe, 23 percent is dark matter and 72 percent is dark energy.
Dennis Blanchard, San Jose, Calif.

*About 72 percent of the total **mass plus energy** content of the universe is dark energy; nearly all of the remaining 28 percent is matter of some form, either ordinary atomic matter or the mysterious dark matter, which is distinct from dark energy. By the latest calculations, about 4.6 percent of the total mass-energy is ordinary matter, which comes to a little less than 17 percent of the total amount of matter. — Tom Siegfried*

Why is it assumed that dark matter exists in our part of the galaxy? If WIMPs cause the edges of galaxies to rotate much faster than predicted by gravity, wouldn't that imply that they are distributed differently than ordinary matter? For example, they might be confined to a halo surrounding the galaxy.
Bob Eramia, Seattle, Wash.

Scientists have assumed Earth should have more interactions with WIMPs when moving in the direction of the constellation Cygnus. I assume that is because our solar system is moving in that direction within the Milky Way and not simply because of our revolution around the center of the galaxy.
Sam Scrutchins, Benicia, Calif.

"Halo" is a misleading term. If the theory is correct, the galaxy sits embedded in a vast cloud of dark matter which extends well beyond the visible part of the galaxy but also is present within the galaxy, including the solar system. The dark matter particles should be striking the Earth from all directions. The Earth and sun's movement toward Cygnus is a result of the galaxy's rotation; that motion means more impacts with dark matter particles would be expected from that direction.
— Tom Siegfried

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The Science Life

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Leslie Gordon (right, with son Sam and husband Scott Berns) began studying progeria after her son's diagnosis.

Rare disease sets mom's research agenda

When a child is diagnosed with a mysterious disease, the lives of everyone in the family change. But when Leslie Gordon's son Sam was diagnosed with a rare premature aging disease, the lives of dozens of families changed. As a pediatrician and medical researcher at Brown University, Gordon set out to learn what caused her son's condition and how to treat it.

Sam looked fine when he was born, but he didn't grow the way other babies do. His primary teeth didn't come in on time, and he seemed a bit stiff. Doctors couldn't find anything in particular wrong with him, but Gordon knew something was amiss. "I'm his mother," she thought. "I know there's something wrong here."

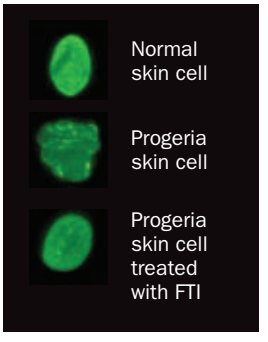
It turned out that Sam has Hutchinson-Gilford progeria syndrome, an extremely rare genetic disease that affects about one in 4 million to 8 million children. An estimated 200 children in the world have the disease. Children with progeria age rapidly, dying on average by age 13.

Gordon had never heard of progeria when her toddler was diagnosed. "Not a word, not a whisper" was uttered about the disease in her medical school or graduate training. Doctors didn't know what caused children with progeria to age rapidly and die of heart attacks or strokes, or how to treat the disease. "Research was a virtual void," Gordon says. The National Institutes of Health had invested little in progeria studies.

That was in 1998. A year later, Gordon, along with her sister and husband, founded the Progeria Research Foundation. The foundation jump-started progeria research by building resources such as a cell and tissue bank that scientists can use to study the disease. Those resources contributed to the discovery of the genetic defect that leads to progeria.

The foundation has helped find 116 kids with the disease worldwide. Many of these children have been enrolled in clinical trials testing possible treatments. Among Gordon's findings is that the kids show hardening of the arteries, even without high cholesterol levels. The sort of progress that the foundation has sparked usually takes decades. "It's an unprecedented pace, on paper, and I'm thrilled," Gordon says.

A documentary about Sam, Gordon and the foundation called *Life According to Sam* premiered at the 2013 Sundance Film Festival and is scheduled to air on HBO in October. Today, Gordon reports that Sam is 16 years old and has just earned an Eagle Scout badge. But asked if she's satisfied with the progress of research, Gordon says, "No. It's never going to be fast enough while there are still children dying of progeria." — *Tina Hesman Saey*



Leslie Gordon's research team has shown that the genetic mutation that causes progeria disrupts a protein important in shaping a cell's nucleus. This change leads to distortions in cell shape. A drug known as a farnesyltransferase inhibitor, or FTI, restored the normal appearance of cells in lab studies (above) and improved weight gain and artery health in children in a clinical trial.

FROM TOP: PROGERIA RESEARCH FOUNDATION; B. CAPELL *ET AL./PNAS* 2005

Chicago Doctor Invents

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More time for less money. We took the ***Buttonwood Watch*** to an independent appraiser who works with auction houses, estate sales and insurance companies. He valued it at $225! We thanked him for his professional opinion and then ignored it. Because even if an experienced appraiser tells us that this watch is valued at over $200, we still want you to wear it for ONLY $59!

Your satisfaction is 100% guaranteed. Try the ***Buttonwood Watch*** for yourself. If you're not completely impressed, send it back within 30 days for a complete refund of your purchase price. But it's much more likely that once you add the ***Buttonwood*** to your portfolio, you'll never want to trade.

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