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SCIENCE NEWS MAGAZINE
SOCIETY FOR SCIENCE & THE PUBLIC
NOVEMBER 30, 2013

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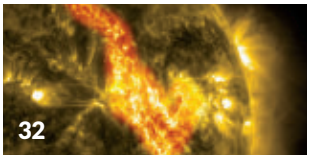
ScienceNews

Features

News



Departments

COVER Immune cells that prune unneeded connections in the developing brain and remove molecular debris throughout life may play a role in late-stage brain diseases such as Alzheimer's. *Colin Anderson/Getty Images, Belterz, Fabler, Egeeksen/all iStockphoto, paraflyer/Flickr, adapted by Stephen Egts*

FROM TOP: © JIM WEST/ALAMY; SOLAR DYNAMICS OBSERVATORY/NASA; ALAN COUCH/FLICKR

U.S. science funding sends young people a mixed message

Much effort is expended on informing young people about the wonders of science. Lab classes at school, hands-on museums, television shows, competitions and publications such as our own *Science News for Students* are designed to cultivate an appreciation for knowledge and to encourage students to pursue careers in science. I wholeheartedly endorse efforts to improve and expand STEM (short for science, technology, engineering and mathematics) education. I think science, and more specifically scientific thinking, is the most powerful tool for understanding the world. Everyone should learn how to think like a scientist.

Some doubts about the depths of U.S. support for STEM, however, began to creep into my mind while reading staff writer Beth Mole's article on Page 14 about the acute effects of the government shutdown and sequester amid chronic underfunding of U.S. basic research. The story highlights the broad array of important science that depends on federal dollars, from studies of disease and climate to investigations of the cosmos. Unfortunately, at this moment in history, being dependent on federal funding puts any enterprise, no matter how worthy, in an extremely vulnerable position. More and more aspiring researchers are finding that instead of marking the beginning of a research career, earning a Ph.D. means the end of their professional lives as scientists. "Of current biomedical doctoral students," Mole writes, "only about 25 percent are projected to get tenure-track faculty positions and carry out independent research in the next five years."

I still see the value in strong STEM education. Science education is much more than pre-professional training — at its best, science teaches people how to think critically and provides access to a deeper understanding of the physical world. But I find myself wondering about our nation's commitment to sustaining a robust scientific community. Why work so hard to convince young people to devote themselves to science if there are fewer and fewer research opportunities?

Those who have dedicated a substantial portion of their young lives to earning an advanced science degree ought to have at least a decent shot at a research career. To make this happen, the United States needs to invest more in science, and reverse the ebb in funding seen over the last decade.

That investment would mean more than simply jobs. It would also ensure that our nation remains a global leader in science, driving the engine of discovery to new frontiers. Now, that kind of commitment just might inspire the next generation of scientists. — *Eva Emerson, Editor in Chief*

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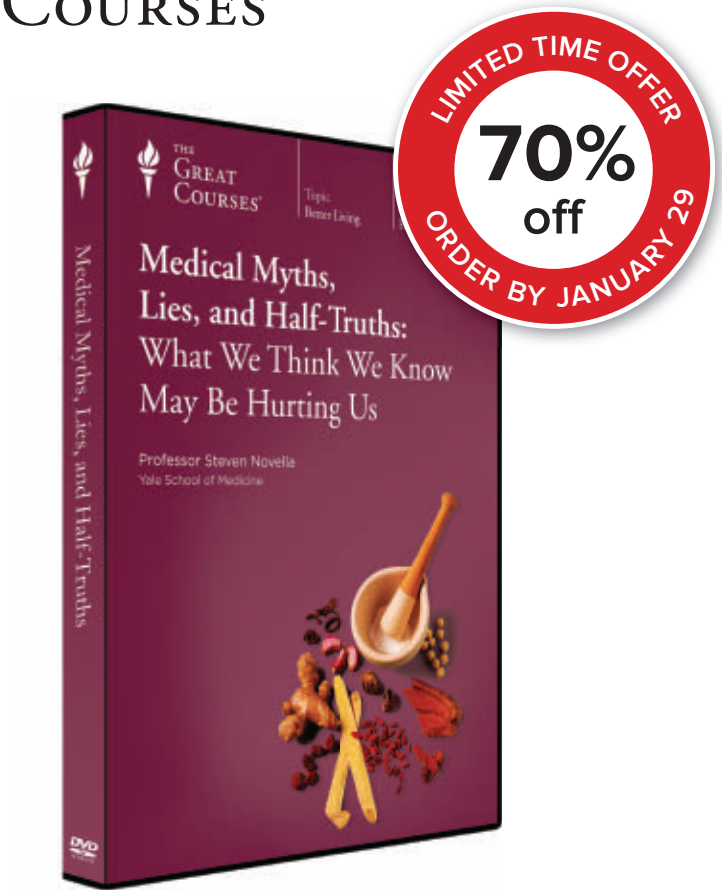

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Excerpt from the November 30, 1963, issue of *Science News Letter*

50 YEARS AGO

Moon Material on Earth

Material blasted off the moon's surface by the impact of giant meteorites has dropped upon the earth on at least three separate occasions in the geological past. Strange glassy objects — called "tektites" and "impactites" — are found by the thousands in sites scattered across the earth. One theory is that tektites are solidified droplets of lunar material melted and splashed into space when large meteorites crashed into the moon. Impactites are thought to be products of the impact of large extraterrestrial objects against the earth. Evidence linking the formation of tektites and impactites was provided by a new technique for dating geological specimens.

UPDATE: Moon rocks collected by the Apollo missions put holes in the theory that tektites were of lunar origin; the two were just too different. Scientists now think that tektites are a type of impactite, formed during the rapid heating and cooling of material ejected when a meteorite strikes Earth.

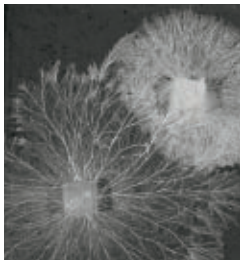
A lion's mane fungus (*Hericium erinaceus*) roars out territorial challenges via silent chemical secretions. Battle lines between fungi can appear as dark streaks inside logs.

IT'S ALIVE

Fungal fight club

Battles between mushrooms don't make a sound, but they're violent. "Good fighters can kill the less-good ones and take over their territories," says mycologist Lynne Boddy of Cardiff University in Wales. "There are battles royal going on all the time."

Combat between fungal individuals is a bit like war between heaps of spaghetti. The main bodies of fungi are networks of long, thin strands called hyphae that insinuate themselves into anything they can eat: tree trunks, plant roots, dung and so on. Defending a food source or wresting a few more millimeters of turf away from a rival can prolong life. So fungi don't let a lack of teeth, claws or eyes diminish their ferocity. Boddy studies toadstool-forming basidiomycetes, a group rife with combatants that poison opponents or release enzymes that dissolve their flesh.



"I'm a great fight-goer," Boddy says. Hundreds of times, she estimates, she has brought fungi in from the wild, set up matches in lab dishes or wood blocks and documented duels lasting weeks. She watches for the hairlike strands to exude chemical droplets, sometimes blood-red. Then she tests the air above the drops for toxic gases wafting toward the enemy. "It's like gas warfare in the trenches," she says.

Fungi struggling for territory remind Boddy of a sports league. She has found that bear's head tooth fungus (*Hericium coralloides*), which bursts out of tree trunks in delicate, white cascades, usually whips an artist's conk fungus. But the bear's head in turn succumbs to a species called hairy parchment. A death match found that the strands of the ferocious sulfur tuft mushroom (inset, upper right) got whomped by *Phanerochaete velutina* (inset, bottom left).

Some fungi excel at both offense and defense, others at just one or the other. A few, poor things, are skilled at neither. But as in sports rankings, "sometimes there can be a giant killer from low down," she says, and a weak competitor beats a favorite.

And as in sports, heat or soggy conditions brings out the greatness in some competitors but dooms others. Boddy's sports analogy has its limits, though. Climate change can affect who wins fights, she and her colleagues reported this year in *Fungal Ecology*, but the outcomes depend on more than weather. Shifts in league rank also depend on the extent of nibbling by small woodland arthropods. — *Susan Milius*

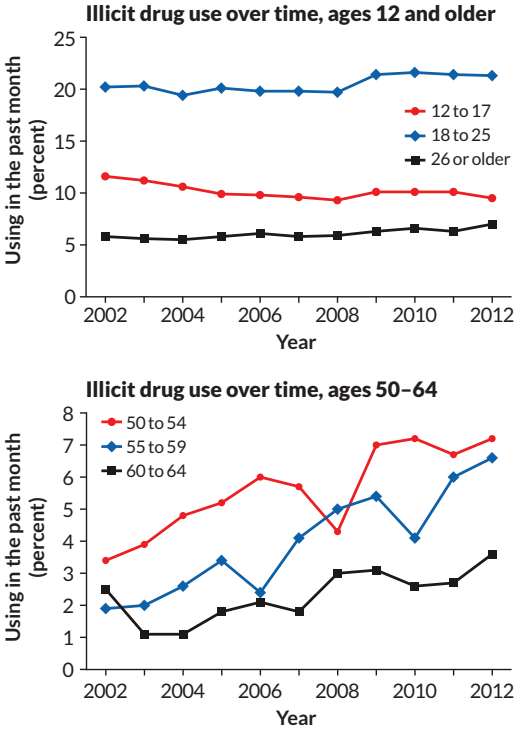
FROM TOP: LEBRAC/WIKIMEDIA COMMONS; COURTESY OF L. BODDY

Watch video of fighting fungi **bit.ly/fungifight**

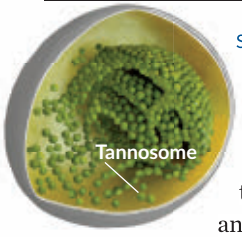
SCIENCE STATS

Drug use on the rise in older set

The use of illicit drugs has declined slightly over the last decade among teens but is growing more common in people over age 50. New data from the U.S. Substance Abuse and Mental Health Services Administration show that 23.9 million Americans over age 12 had used drugs in the previous month. Marijuana use is most common and rose from 5.8 to 7.3 percent of people over 12 from 2007 to 2012. The trend over age 50 reflects the entry into the age group of the baby boom generation, with higher drug-use rates than older generations, researchers say.



SOURCE: NATIONAL SURVEY ON DRUG USE AND HEALTH 2012



SAY WHAT?

Tannosome *TAN-noh-sohm*\ n.

A newly discovered structure where mouth-puckering compounds called tannins form inside plant cells. Plants from oak trees to corn make tannins, which discourage nibbling insects and reduce damage from UV light. Tannosomes are tiny organelles that arise in chloroplasts, structures that capture light energy. There, sacs of green pigment break into little spheres. The chloroplast membrane creates a pocket around clusters of these spheres, and the pocket eventually breaks loose and shuttles to the cell's large fluid-filled vacuole. During the shuttle ride, tannosomes earn their name by filling with tannins, researchers report in the Oct. 6 *Annals of Botany*. Learning how plants build tannins feeds the dream of tweaking flavor in wine, tea, chocolate or other tannin-containing pleasures. —*Susan Milius*

THE LIST

World's worst polluted

A new report by Green Cross Switzerland and the Blacksmith Institute, which screened more than 3,000 contaminated sites, lists places posing the greatest risk to human health. Here are the top 10, in alphabetical order:

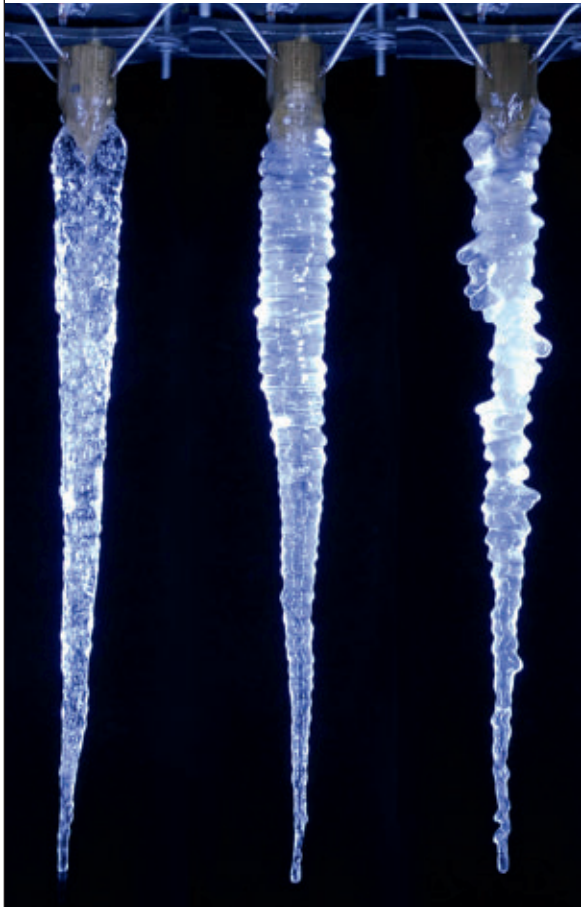
1. Agbobloshie (Ghana)
2. Chernobyl (Ukraine)
3. Citarum River (Indonesia)
4. Dzershinsk (Russia)
5. Hazaribagh (Bangladesh)
6. Kabwe (Zambia)
7. Kalimantan (Indonesia)
8. Matanza Riachuelo (Argentina)
9. Niger River Delta (Nigeria)
10. Norilsk (Russia)

SOURCE: THE WORLD'S WORST 2013

MYSTERY SOLVED

Ripple effect

If you want ripples in your icicles, just add salt. This recipe comes from physicists reporting in the October *New Journal of Physics*. Antony Chen and Stephen Morris of the University of Toronto built a tabletop machine that allowed nearly ice-cold water to drip through a nozzle onto a slowly rotating support, where the water froze. Distilled water produced an unrippled, carrot-shaped icicle (below, left). When the scientists added a pinch of sodium chloride, or table salt, regularly spaced ripples formed (center). When they added more, the ripples became wildly irregular (right). The researchers have not been able to find a theory to explain why salt is crucial to ripple formation. Fortunately, nature doesn't need a theory; the team found that water running off Toronto roofs had enough dissolved ions to make ripples on its own. —*Gabriel Popkin*



FROM LEFT: J.M. BRILLOUET; A. SZU-HAN CHEN AND S.W. MORRIS/*NEW J. OF PHYSICS* 2013

ATOM & COSMOS

Large meteor strikes underestimated

Chelyabinsk-sized rocks may hit Earth once every 30 years

BY ANDREW GRANT

Meteor impacts such as February's explosion over Chelyabinsk, Russia, the most powerful observed in a century, may occur more frequently than thought. An analysis of recorded impacts over the last 20 years suggests that Chelyabinsk-sized objects strike the planet every few decades, on average, rather than once every century or two.

"There were inklings of this before, but this is the strongest statement that's been made," says Paul Chodas, a planetary scientist with NASA's Near Earth Object Program at the Jet Propulsion Laboratory in Pasadena, Calif. If confirmed, scientists will need to reassess the risk of impacts and come up with new strategies for spotting space rocks tens of meters in diameter, which can cause widespread damage and injuries.

It's impossible to find and track each of the millions of objects whose orbits cross Earth's path. Instead, astronomers maintain a census of objects detected by ground-based telescopes and use those numbers to estimate how often asteroids of various sizes should strike the planet. According to those predictions, an impact like that of the 19-meter-wide Chelyabinsk meteor, which released the energy equivalent of about 500,000 tons of TNT, should take place roughly once in 120 years. Impacts as powerful as the famous Tunguska event of 1908, which was comparable to a 10-million-ton blast, should take place every few thousand years.

Concerned by multiple supposedly low-probability events having occurred over the last century, planetary scientist Peter Brown of Canada's University of Western Ontario decided to analyze the energies of actual impacts recorded worldwide during the last 20 years. As expected, high-energy events corresponding to larger meteors occurred less frequently than less energetic ones.

But the frequency did not drop off as quickly as telescope surveys predict. In a study published November 6 in *Nature*, Brown's team shows that objects between 10 and 50 meters across strike Earth at least three times as frequently as expected. Chelyabinsk becomes a once-in-30-years event, while a Tunguska-like impact should occur once every few hundred years on average.

"We need to try to find the source of the discrepancy," Chodas says. He says the data suggest that either a subset of Chelyabinsk-sized objects have particularly Earth-threatening orbits, or telescope surveys severely underestimate the total number of those objects.

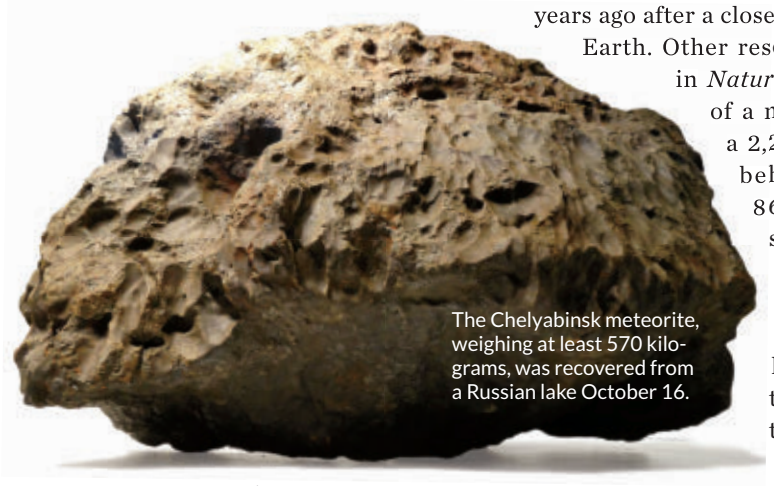
Clues may lie in two other studies also published November 6. In *Science*, researchers chemically analyzed meteorite fragments from the Chelyabinsk object and suggest that it split off from a larger asteroid as recently as 1.2 million years ago after a close encounter with Earth. Other researchers report in *Nature* that the orbit of a nearby asteroid, a 2,200-meter-wide behemoth called 86039, is very similar to that of the Chelyabinsk object. The two rocks may once have been part of the same object, the researchers conclude. Chodas says it's possible, though far from proven, that a family of asteroids derived from one parent body might have Earth-threatening orbits.

Researchers in these two studies used videos from Russian citizens' cell phones and car dashboard cameras to reconstruct the Chelyabinsk asteroid's trajectory. The researchers calculate that the 12,000-metric-ton object plunged into Earth's atmosphere at more than 68,000 kilometers per hour; that makes it more than 25 times as massive as a fully loaded Boeing 747 and almost 75 times as fast.

Friction from plowing through the atmosphere caused the rock to fracture about 30 kilometers above the surface, unleashing a fireball 30 times as bright as the sun and a shock wave aimed toward Chelyabinsk, an industrial city of over a million people.

The Chelyabinsk meteor event shattered windows in more than 7,000 buildings and sent 112 people to hospitals within an area 180 kilometers from north to south and 80 kilometers from east to west. But the damage was not nearly as bad as scientists would have predicted for a 19-meter-wide object. That's because current damage predictions are based on explosions of nuclear bombs, Brown says; compared with a meteor, bombs fall from the sky much more slowly and release energy far more quickly.

Still, the meteor made a major impression on the people who saw it and felt it that February morning. Peter Jenniskens, an astronomer at the SETI Institute in Mountain View, Calif., and coauthor of the *Science* study, spent 16 days in March visiting 50 villages in the region, where he and colleagues interviewed hundreds of witnesses, assessed building damage and analyzed meteorite fragments. A coal miner reported that the fireball caused sunburn so severe that some of his skin flaked off. "Everybody we met had a story to tell," Jenniskens says. ■



The Chelyabinsk meteorite, weighing at least 570 kilograms, was recovered from a Russian lake October 16.

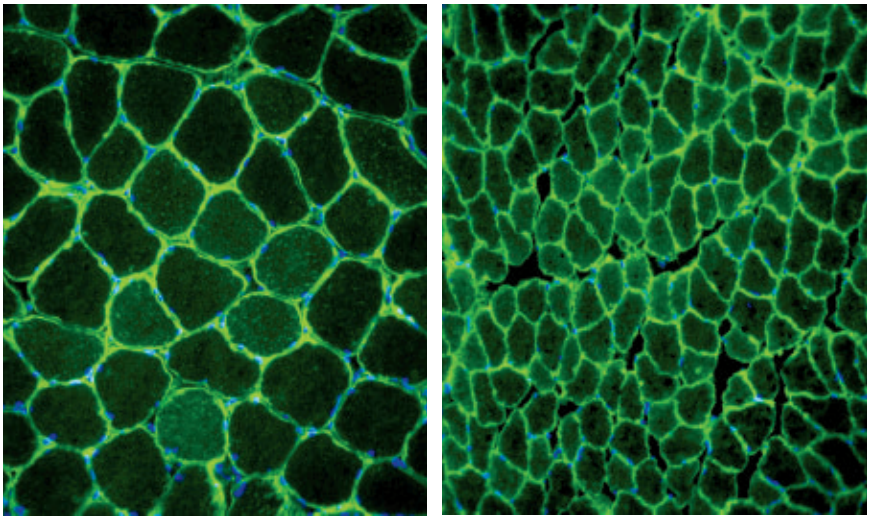
COURTESY OF *SCIENCE*/AAAS

GENES & CELLS

Steroids boost muscles for the long haul

In mice, effects don't end when doping does

BY TINA HESMAN SAEY



Mouse muscles treated with steroids (left) grow bigger than ones in undrugged animals (right). Steroids increase the number of nuclei in a muscle cell, which may help the muscle pump back up long after the steroids are gone.

J.C. BRUUSGAARD/UNIV. OF OSLO

Steroids may continue to boost muscle-building capacity long after a person stops taking the drugs, a study of mice suggests. The finding could mean that athletes who cheat by taking anabolic steroids should be suspended from competition for a decade or longer.

The research also suggests that building muscles in youth by any means may have benefits that last into old age.

In the study, researchers led by Kristian Gundersen, a physiologist at the University of Oslo, tested the effect of testosterone on female mice. The team had previously found that exercise builds new nuclei in muscle cells (*SN: 9/11/10, p. 15*). Nuclei are the cellular compartments that store DNA, and muscle cells typically have multiple nuclei. Increasing the number of nuclei gives muscles the capacity to build more proteins.

Doses of testosterone, an anabolic steroid, caused the mice to add nuclei to their muscles, the researchers report October 28 in the *Journal of Physiology*. After two weeks of steroid treatment, the muscle cells had up to 66 percent more nuclei per muscle fiber. Mice that didn't get steroids, but had surgery that cut certain muscles to make another work harder, had 51 percent more nuclei in the overworked muscle. Mice that got both steroids and surgery built 92 percent more nuclei in their uncut muscle.

The mice's muscle cells bulked up too, eventually shrinking to pre-steroid size after the drugs were stopped. But the new nuclei didn't go away, Gundersen's team found. Steroid-treated muscles kept their additional nuclei for at least three months, which corresponds to about a decade in a human's life span. The effect may last even longer, but the researchers did not extend the experiment to find out.

When muscles were worked three months after the steroid treatment stopped, the muscle mass of animals that previously took testosterone bounced back right away, bulking up 31 percent in the first six days. Mice that never took steroids added only about 6 percent to their muscle mass in the same time frame.

"In my career it has been rare to see such clear results," Gundersen says. "It is more dramatic than I thought it would be."

Other researchers are also impressed with the results.

"There's no question it's very interesting data and it's very strong," says Bengt Saltin, a physiologist at the University of Copenhagen. "This should be a hotter topic in muscle research and physiology," he says. Elderly people often have trouble with muscle wasting, and the study suggests that working out in young adulthood could help old muscles regain vigor with exercise later.

Lawrence Schwartz, a cell biologist at the University of Massachusetts Amherst, agrees. "The implication is once you have these nuclei, you never lose them."

Both researchers also say that similar research to see how long steroids exert their influence should be done on humans before antidoping agencies decide how long cheating athletes should be barred from competition.

"I suspect the basics of muscle physiology are going to be very similar," Schwartz says of mice and humans. But given the side effects of steroids and the difficulty of closely examining muscle in people without causing harm, "I don't see any easy or even an ethical way of doing this in humans." ■

JUST THE FACTS

Male body image

7.6%

Fraction of U.S. males age 16 to 22 who are very concerned about muscularity and take steroids, growth hormones or other supplements

SOURCE: A.E. FIELD *ET AL*/*JAMA PEDIATRICS* 2013

"These individuals may represent the male equivalent of purging disorder."

A.E. FIELD *ET AL*

Using supernova measurements from the Pan-STARRS PS1 telescope on Maui, researchers calculated a cosmological parameter related to dark energy. If verified, the findings could force cosmologists to develop a new explanation for this energy, which pushes the universe apart.

ATOM & COSMOS

Dark energy search gets murkier

Supernova measurements muddle scientists' efforts to explain universe's accelerating expansion

BY GABRIEL POPKIN

New measurements of light from distant supernovas could complicate cosmologists' already frustrating attempts to explain the mysterious dark energy that is pushing apart the universe.

In the new analysis, scientists combined data from 146 recently discovered supernovas with previously published results and calculated an important cosmological parameter. Their result is inconsistent with the simplest explanation for the universe's accelerating expansion, which suggests that the strength of dark energy has remained constant over the history of the universe.

If confirmed, the finding could imply that matter in the universe will eventually be torn apart, a scenario known as the Big Rip (*SN: 1/3/09, p. 9*). But before reaching that conclusion, the researchers say they must ferret out potential sources of error and uncertainty in their measurements. "It's very possible, and I think a lot of people would say likely, that one of the big measurements is off," says study coleader Daniel Scolnic, an astrophysicist at Johns Hopkins University.

> If confirmed, the finding could imply that matter in the universe will eventually be torn apart.

Dark energy first made headlines in 1998, when researchers found that light from faraway supernovas was dimmer than expected, suggesting that the universe is expanding at a faster and faster pace. To explain this acceleration, scientists proposed the existence of dark energy, which imbues the cosmos with a negative pressure that pushes space outward. Most physicists suspect that dark energy is a form of vacuum energy known as the "cosmological constant" because its strength never varies. If so, a number called w, which relates the pressure pushing space apart to the density of dark energy, must equal –1.

But the new analysis, posted October 14 at arXiv.org, arrives at a different value. Combining data from the Hawaii-based Panoramic Survey Telescope & Rapid Response System, or Pan-STARRS, with previous astronomical surveys, the researchers calculate w to be –1.186. If correct, this value of w would force cosmologists to pursue

ATOM & COSMOS

Single electron caught in action

Researchers observe behavior of one particle at a time

BY ANDREW GRANT

In a feat akin to plucking a single water molecule from a vast ocean, physicists have for the first time isolated a single electron from an electronic sea. The study gives scientists a chance to learn more about the elementary particles and to employ them for quantum communication and computing devices.

The world is flush with electrons, yet they are very difficult to study individually. In metal wires and electrodes, individual electrons are virtually indistinguishable from each other because they sit together in a vast reservoir called the Fermi sea. One trick physicists have used is to strip a wire free of electrons and then inject it with particles one at a time, but those electrons don't behave the same way they would if they were immersed in the sea. Like zoologists interested in looking at the behavior of an animal in the wild, physicists want to study individual electrons in their natural environment.

In 1996, MIT physicist Leonid Levitov and colleagues proposed a way to do that. They surmised that applying a particular voltage pulse across a circuit would cause electrons within the sea to interact and eject a single electron at high energy; all the other electrons would remain in a low-energy state. The high-energy electron would glide across the surface of the Fermi sea like a lone wave in the ocean, making it easy to study.

Now, 17 years later, a European team including physicist Christian Glattli of the Saclay Nuclear Research Center near Paris has experimentally confirmed Levitov's prediction. The researchers set up a circuit, cooled it to a few hundredths of a degree above absolute zero and sent through an electric pulse. An instrument called a beam splitter counted the electrons carried in each pulse. By acting like an audio recorder on a tin roof in the rain, the splitter could detect the tiny splat of a single raindrop — an electron — rather than the thrashing of many drops. Sure enough, the beam

more complicated theories about the universe's expansion, in which the strength of dark energy increases over time.

That reconsideration of theory is not happening yet. Even the study's authors stress that they are not advocating throwing out the cosmological constant. "My gut feeling is that w is probably –1," says study coleader Armin Rest, an astronomer at the Space Telescope Science Institute in Baltimore.

Rest thinks the finding most likely results from some kind of systematic error. In a companion paper also posted online October 14 at arXiv.org, the team determines that the largest source of error involves differences in how the Pan-STARRS telescope and other groups' telescopes captured the supernovas' light. Errors can also arise from interference from dust in the Milky Way, an incomplete understanding of supernova physics and other factors.

George Efstathiou, director of the Kavli Institute for Cosmology at the University of Cambridge, believes that whether due to systematic error or as-yet-undiscovered physics, the results provide useful information. "These are very difficult measurements to make," he says. "The more independent data there is, the better it is for the field." ■

splitter confirmed that each pulse triggered a lone electron to glide across the sea, the researchers report in the Oct. 31 *Nature*.

The study sets physicists on a path toward using electrons in quantum experiments the way they use photons, Glattli says. Photons are far easier to isolate and manipulate than electrons, so they have been the particle of choice for designing secure communication networks and rudimentary quantum computers. A new generation of quantum electronics could integrate more easily with other electronic devices.

Fittingly, Glattli and his team coined the term leviton for the single-electron pulse. "It is a terrific paper," Levitov says. "And I say that not because [of the word] leviton." ■

COURTESY OF MATT KAPUST/SANFORD UNDERGROUND RESEARCH FACILITY

ATOM & COSMOS

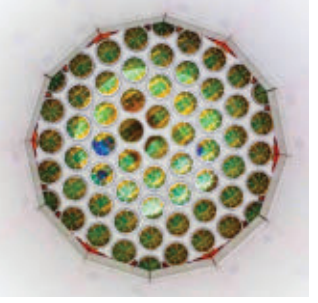
Candidates for dark matter bite the dust

Sensitive experiment finds that earlier results were artifacts

BY ANDREW GRANT

The elusive substance that makes up more than a quarter of the universe is now even more of a mystery. A supersensitive search for dark matter has come up empty, researchers announced in an October 30 press conference, casting serious doubt on the findings of experiments that have claimed detections or hints of dark matter particles.

Dark matter is the ultimate tease: Scientists know it permeates the universe because of its gravitational influence on distant galaxies, but they can't see it and don't know what it's made of. Theoretical physicists have proposed that dark matter could come in the form of weakly interacting massive particles, or WIMPs, and have predicted how those particles might behave. Scientists around the world have built giant underground experiments, shielded by soil and rock from the bombardment of other particles, to try to detect WIMPs.



LUX's photomultiplier tubes, such as these, should detect flashes of light caused by putative dark matter particles striking xenon nuclei.

The Large Underground Xenon detector, or LUX, is located in a former gold mine 1.5 kilometers beneath Lead, S.D. The experiment consists of a phone-booth-sized titanium tank that holds liquid and gaseous xenon. WIMPs rarely interact with ordinary matter, but every now and then one should collide with the nucleus of a xenon atom, causing two distinct flashes of light. Particles such as neutrons and electrons can cause similar signals upon striking xenon, but LUX researchers say they can eliminate false positives with unprecedented accuracy.

LUX operated for three months this summer and recorded 84 million potential detections, LUX physicist Richard Gaitskell of Brown University announced. Yet after a detailed analysis, the LUX team found no signals that were convincingly caused by WIMPs.

The finding (or lack thereof) has implications for evaluating the results of other experiments. For example, in April physicists with the Cryogenic Dark Matter Search in Soudan, Minn., announced the possible detection of three WIMPs, each with a strikingly low mass about 10 times that of a proton (*SN: 5/18/13, p. 10*). If that were the correct mass, Gaitskell said, LUX should have detected more than 1,500 WIMPs because it is 20 times as sensitive to such low-mass particles as any previous experiment.

The LUX results also clash with claimed detections from the CoGeNT Dark Matter Experiment, also in Soudan, Minn., and the DAMA/LIBRA experiment near L'Aquila, Italy. "We are just not consistent with observations that other dark matter experiments have made," Gaitskell said, adding that physicists in other experiments probably were fooled by false positives. "We're ruling out those low-mass WIMPs." LUX will follow up its initial observations with almost a year of operation, providing the increased sensitivity that could reveal WIMPs now sneaking just below the threshold for detection.

Katherine Freese, a theoretical astrophysicist at the University of Michigan in Ann Arbor, isn't quite ready to give up on previous findings, even though she calls LUX really well done. She says that WIMPs may interact differently with xenon than they do with silicon, germanium and sodium iodide, which make up the detectors in other experiments. "I'm going to do my damnedest to save" low-mass WIMPs, she says. "But to be honest, it's not looking too good." ■

BODY & BRAIN

Scorpion venom kills pain in mice

Toxin works with nerve proteins to block distress signals' journey to brain

An Arizona bark scorpion makes a tasty meal for the carnivorous southern grasshopper mouse. A protein in the mouse's nerves prevents pain signals triggered by the scorpion's sting from reaching the brain.

COURTESY OF MATTHEW AND A. ROWE

BY MEGHAN ROSEN

Tiny desert rodents have found a way to take the sting out of scorpion venom.

A protein in the nerves of southern grasshopper mice hijacks the venom's toxins, silencing pain signals that usually race to the brain when scorpions strike. The protein and venom together can even numb the animals to other types of agony, researchers report in the Oct. 25 *Science*.

"In these mice, the venom actually works like a painkiller," says neuroscientist Frank Bosmans of Johns Hopkins University, who was not involved with the work.

The Arizona bark scorpion, *Centruroides sculpturatus*, wields particularly nasty venom. "It's pretty painful," says study coauthor Ashlee Rowe, an evolutionary neurobiologist at Michigan State University in East Lansing. "People say it feels like being branded, or burned with a cigarette, and then driving a nail in." A hefty dose of bark scorpion venom can kill infants and small children.

Because the venom is so toxic to mammals, Rowe thought that bark scorpions must use it to defend themselves from mammalian predators. She decided to take a look at southern grasshopper mice, *Onychomys torridus*, carnivorous rodents known to chow down on scorpion species less toxic than bark scorpions. Other researchers had guessed that grasshopper mice might shun bark scorpions, or somehow dodge their stings.

About a decade ago, Rowe collected wild scorpions and mice in Arizona and placed the animals in a terrarium. The mice devoured the pests and didn't seem to mind getting stung.

To investigate the animals' high pain tolerance, Rowe and her team injected a drop of venom into the hind paws of house mice and grasshopper mice, and then timed how long the animals tended their wounds. House mice licked their injured paws for about four minutes, while grasshopper mice licked for just a few seconds. In the grasshopper mice, the venom injection even blocked pain from a follow-up injection of formalin, a chemical that provokes a burning sensation.

The researchers suspected that bark scorpion venom might somehow halt pain messages' journey to the brain. In humans and house mice, venom toxins switch on a pain signal via proteins embedded in nerve cells in the skin. These proteins, called sodium channels, operate tiny gates to control the flow of sodium into the cell.

Venom cues the gates to open, letting sodium flood in and triggering neighboring gates to open. The domino effect lets a pain signal race to the brain.

But when the researchers dissected pain-sensing nerves from grasshopper mice and added venom, one type of sodium channel behaved differently and stopped the usual flow of sodium.

If sodium can't flow in, the pain signal peters out, says neuroscientist Thomas Park of the University of Illinois at Chicago. When scorpions sting the mice, he says, "the nerves say, 'no, I'm not going to send that signal up.'" And when venom is around, the nerves can block pain signals from other sources too.

The mice's pain-avoiding strategy is similar to that used by naked mole rats in Africa, Park says. Those animals resist pain from acidic environments by shutting down a different type of sodium channel. Park thinks other animals may also deal with pain in similar ways.

The findings will probably interest people designing pain-relieving drugs, says molecular neurobiologist Gary Lewin of the Max Delbrück Center for Molecular Medicine in Berlin. "Drug companies have been trying for at least the last 15 years to make specific molecules that block these channels," he says.

"What's nice about this story is that here comes evolution and actually shows how it can be done." ■

Genes help determine a person's microbial mix

In mice and humans, genetic variants seem to control which bacteria live on and in bodies

BY TINA HESMAN SAEY & BETH MOLE

BOSTON — Humans may be in charge of which bacteria live in and on them, researchers report. Scientists used to think that what people ate and where they lived were the main determinants of the microbes that colonize human bodies, but new studies suggest that the immune system plays a big role in selecting its microbial companions.

The selection process may make it harder to change which microbes call a person's body home.

Studies of mice and humans presented at the annual meeting of the American Society of Human Genetics suggest that a host's genetic makeup may determine which microbes set up shop in the intestines, on the skin and in other parts of the body. And a paper appearing October 29 in *Genome Research* finds that people with immune disorders host a wider variety of bacteria and fungi, some harmful, on their skin than do healthy people.

The set of microbes living in and on a host organism — known as the microbiome — is highly individual, said Andrew Benson of the University of Nebraska-Lincoln. Even mice that live in the same laboratory conditions may have widely varying microbiomes.

To find out why animals develop a certain microbiome, Benson and colleagues studied microbes of genetically diverse mice. When the researchers characterized which bacteria lived in the mice's intestines, they saw "a shotgun blast of diversity," Benson reported October 23.

Which microbes are present may not be as important as what they do for the host, so Benson's team determined the services the bacteria provide. The team found that mice with some genetic variants tend to harbor bacteria that make molecules important for communication between immune cells.

Mice with variants in proteins that bind to certain amino acids tended to have more bacteria that produce those same amino acids, the team found. Variants in some of the mice's immune system genes were also associated with particular microbial mixes. The mice's own genes seem to encourage the growth of some microbes while discouraging others, Benson said.

"It's beautiful work," said Ran Blekhman of the University of Minnesota, Twin Cities. Blekhman has come to similar conclusions using data gleaned from the human microbiome project, an effort to catalog people's microbes (*SN: 6/16/12, p. 15*).

The more similar two people's genetic makeups are, the more similar their microbiomes, Blekhman reported October 24. In particular, human genes involved in regulating the immune system are associated with the types of microbes that reside in a person.

That may mean that the human immune system picks and chooses its bacterial buddies. People with genetic variants that affect an appetite-controlling hormone called leptin or with variants in genes associated with colon cancer harbor distinct microbial mixes, Blekhman found. The finding suggests that microbes may work with human genes to produce obesity, cancer or other diseases.

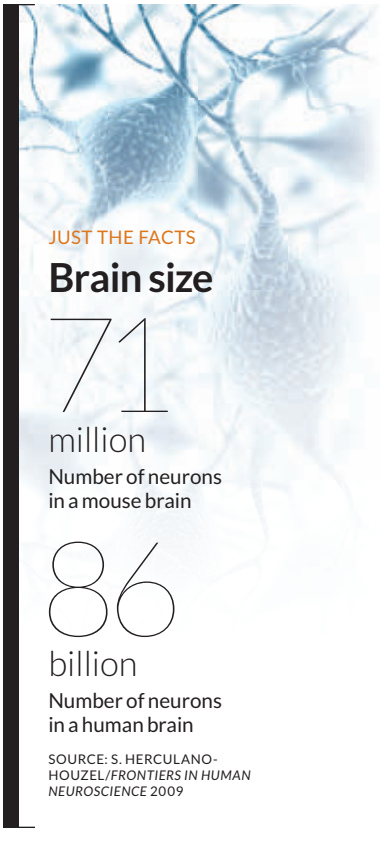
In the *Genome Research* report, dermatologist Heidi Kong of the National Institutes of Health in Bethesda, Md., and colleagues compared the microbial communities on the skin of 49 healthy people with those on 41 people who have rare immune disorders that make them prone to eczema-like skin problems. The patients had one of three disorders, each caused by a defect in a single gene.

The team found more variety in the microbial populations on the immune-deficient patients' skin, suggesting that functional immune systems usually rein in skin microbes. Kong thinks that having a haphazard collection of microbes may increase a patient's risk of infection. If true, doctors could develop treatments that restore a healthy balance of microbes, rather than killing off specific bacteria with antibiotics.

But a problem for people hoping to improve health by altering their microbiomes is that a person's genes don't change. Introducing beneficial bacteria through yogurt or dietary supplements called probiotics might be for naught if the immune system is set against those microbes. Plus, new bacteria may have a hard time taking hold in an already thriving microbial community, Benson said.

"Giving a probiotic is like introducing a new species into a rainforest," he said.

Previous studies have indicated that diet, antibiotics and other environmental changes may shift the microbe mix temporarily, but by adulthood, the microbiome is usually quite stable. The new studies may help explain that finding. ■



KTSIMAGE/ISTOCKPHOTO

HUMANS & SOCIETY

Aboriginal hunting helps lizards

Reptiles thrive in Australian desert where people eat them

BY JESSICA SHUGART

Indigenous Australian hunters create prime habitat for a desert-dwelling lizard.

"It's simply not the case that human activity always has a negative impact on ecological circumstances," says ecological anthropologist Doug Bird of Stanford University.

The Martu, an aboriginal people in Western Australia, burn patches of brush to expose dens of the lizard *Varanus gouldii*, known as sand goannas. Then people dig out the prey and roast the morsels over a coal fire.

Lizards called goannas (*Varanus gouldii*) live in the desert of Western Australia and have larger populations where indigenous people hunt.

The frequent burning creates a patchy mosaic of charred lands and regrowing vegetation. Unlike lightning-triggered fires that can wipe out large swaths of vegetation, the small human-lit fires promote a diverse collection of habitats.

Aboriginal peoples have lived in Western Australia for at least 36,000 years, and ancient lizard remains found at archeological sites show that people have hunted goannas for much of that time. To understand how the Martu have maintained their food supply for so long, Bird, Stanford collaborator Rebecca Bliege Bird and colleagues spent a decade monitoring changes in lizard group sizes, hunting success and habitat throughout a more than 46,000-square-kilometer section of Martu land.

Goanna populations were densest where the Martu hunted most. The finding, reported October 22 in the *Proceedings of the Royal Society B*, reveals that the lizards prefer to dig their burrows in patches of mature vegetation within frequently burned regions. The lizards prefer these spots because emerging vegetation from recently burned patches bears more food that attracts goannas' prey, the researchers speculate.

The Martu understand their place in the desert as a key part of the relationships among plants and animals, rather than as landscape managers, says Doug Bird. So they believe that the ecosystem will collapse if they stop foraging and burning, he says. In fact, when the Martu and other desert foragers were forced to leave their lands between the 1950s and 1970s, surveys showed that 10 to 20 native mammal species went extinct. When the Martu returned in the 1980s, they reignited the small fires and biodiversity gradually increased, according to surveys conducted by the Birds and other scientists.

The research compellingly argues that "small-scale human societies can actually exist in an ecosystem without damaging it over a very long period of time," says archaeologist Bruce Smith of the Smithsonian National Museum of Natural History. "It's just wonderful science." ■

MATTER & ENERGY

Beads of water act as test tubes

Superheated floating drops create nanoparticles

BY BETH MOLE

Droplets of water dancing over a hot skillet may be the chemical factories of the future.

On a hot surface, water droplets hover on a cushion of their own evaporation. The drops become superheated and negatively charged, which creates ideal conditions for making nanoproducts, researchers demonstrate October 29 in *Nature Communications*.

"The experiment itself is very simple," says study coauthor Mady Elbahri, a nanochemist at the University of Kiel in Germany. "All you need is a hot plate."

Elbahri got the idea to use the droplets in 2006 while making pancakes at home. After washing his hands, he accidentally shook some water onto a hot plate and noticed the levitating water droplets that resulted.

Intrigued, Elbahri and his colleagues used a heat-sensing camera to find that, on a surface heated to 250° Celsius, water droplets' bottoms undergo evaporation, causing the water to become charged. Negatively charged hydroxyl ions stay in the water, creating a basic pH in the droplet.

To do nanochemistry in a drop, the researchers combined water and an acidic solution of salt containing gold atoms. When they dripped the liquid onto a hot surface, the basic environment in the drop converted the salt to gold nanoparticles that formed metal clusters, coloring the solution red.

Because the reaction requires only water, instead of hazardous or waste-producing solvents, Elbahri and colleagues say the technique offers a cheap, environmentally friendly way to manufacture nanoscale materials.

Using other salts, the team found that the hot drops could also form nanoscale coatings around tiny objects; porous metals that, because of their absorption of light, could find use in solar energy; and a hybrid metal-polymer foam that could be useful on spacecraft because of its light weight and heat resistance.

Bryce Tappan, a nanochemist at Los Alamos National Laboratory in New Mexico, says the method could allow nonspecialists to make a wide variety of nanomaterials.

In all, Tappan calls the technique a "triumph of clever over complicated." ■

ALAN COUCH/FLICKR

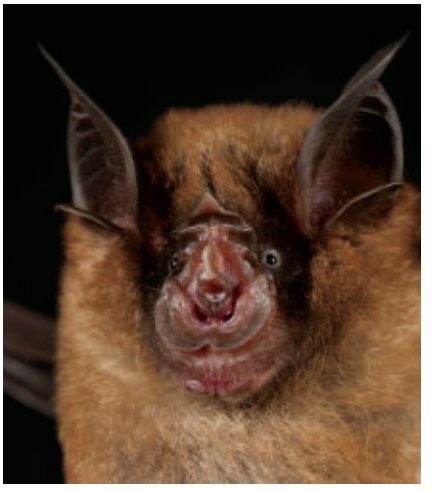
GENES & CELLS

SARS virus may trace back to bats

Chinese horseshoe bats carry two viruses that are closely related to the coronavirus that causes severe acute respiratory syndrome, or SARS, in people. The discovery, reported October 30 in *Nature*, provides the strongest evidence yet that SARS originated in bats. The spread of SARS in 2002–2003 caused a pandemic that sickened more than 8,000 people and killed 774. Scientists have identified several SARS-like coronaviruses in bats in China, Europe and Africa and have proposed that the animals may have spread the virus to humans. But there's been no convincing data to support the idea. In the new study, Xing-Yi Ge of the Wuhan Institute of Virology in China and colleagues analyzed the genomes of the newly identified bat coronaviruses. The results show that these viruses are more closely related to the SARS virus than to other SARS-like viruses previously identified in bats. The new viruses can also invade cells using the same human cell receptor protein that SARS uses. *—Ashley Yeager*

Antibody treatment shows progress against HIV

Antibodies that latch onto viral proteins can suppress HIV-like disease in rhesus macaques for weeks or even months, researchers report October 30 in two studies in *Nature*. Such antibodies, patterned after ones made in rare people who can keep HIV infection in check, might someday benefit other patients chronically infected with HIV, say the research teams. The antibodies are broadly neutralizing, meaning that they can hit diverse forms of the virus. That makes them more potent than antibodies identified in earlier studies. The scientists used monkeys infected with a virus containing portions of the HIV and simian immunodeficiency viral genomes. The hybrid has the protein shell of HIV, which it uses to enter cells and cause disease. A cocktail injection of multiple kinds of antibodies dramatically lowered blood concentrations of the virus in the monkeys. The virus later rebounded,



LIBIAO ZHANG/SOUTH CHINA INSTITUTE OF ENDANGERED ANIMALS

but since the antibodies attack the virus differently than HIV drugs do, a combination of the therapies might thwart the virus better than standard treatment does. *—Nathan Seppa*

EARTH & ENVIRONMENT

Mercury pollution to linger in California for 10,000 years

California's gold rush ended more than a century ago, but the contamination it caused will last thousands of years, a new analysis shows. Some hydraulic gold mining processes use the toxic metal mercury to separate gold from gravel. In the mid-1800s, gold mining released more than a cubic kilometer of mercury-laden sediments into Northern California's Sierra Nevada foothills. The sediments fanned out and inundated rivers that flow into the San Francisco Bay. Researchers estimate that 90 percent of the mercury is still trapped in the sediments. To understand how flooding and erosion may trigger future releases of the metal, researchers led by Michael Bliss Singer of the University of St. Andrews in Scotland measured mercury in sediments at 105 locations upstream of the bay. Drawing on historical flood data to predict sediment flow, the team reports October 28 in the *Proceedings of the National Academy of Sciences* that the mining sediments will continue to release mercury into waterways over at least the next 10,000 years. These flood-driven discharges might pose contamination risks for people living in the region. *—Jessica Shugart*

ATOM & COSMOS

Milky Way home to billions of potentially habitable planets

The galaxy contains billions of potentially habitable Earth-sized planets, according to even the most conservative estimate using data from NASA's Kepler space telescope. Although a mechanical failure recently put the telescope out of commission (*SN: 6/15/13, p. 10*), Kepler's census of planets orbiting roughly 170,000 stars is enabling astronomers to predict how common planets similar to Earth are across the galaxy. The authors of a study published November 4 in the *Proceedings of the National Academy of Sciences* conclude that 14 to 30 percent of stars similar in mass and temperature to the sun host a possibly habitable planet. Such planets orbit in a star's habitable zone, a temperate region where liquid surface water could exist, and have diameters at least as large as Earth's but no more than twice that. The estimate comes from identifying, and then extrapolating from, suitable worlds around more than 42,000 stars. The estimate is rough: If applied to the solar system, the researchers' definition of habitable zone would include the orbits of Venus and Mars, planets that are certainly not Earthlike (though they may have been in the past). Using tighter constraints, the researchers estimate that 4 to 8 percent of sunlike stars host an Earth-sized world with a 200- to 400-day orbit. Still, even 4 percent would yield a galactic population of more than a billion potentially habitable Earth-sized planets. *—Andrew Grant*

SCIENCE slowdown

Recent federal shutdown just the latest shock in a deepening funding crisis

By Beth Mole

The Green Bank radio telescope in West Virginia was idled by October's government shutdown, which scientists say exacerbated an already difficult funding situation.

For two weeks in October, the largest maneuverable radio telescope in the world stood still. With the federal government shut down and the employees who control the Green Bank telescope on furlough, the research of astronomers around the world came to an abrupt halt.

Astronomers Sheila Kannappan and David Stark of the University of North Carolina at Chapel Hill had been allotted 80 hours of observing time on the gigantic West Virginia telescope to study how gases flow between galaxies and fuel star formation. Now it's unclear when, if ever, they will get to complete those observations.

Astronomers are used to working around things like bad weather and tight schedules, Stark says. But being waylaid by politics felt especially irritating.

"You fight tooth and nail for this time," he says. "It's just adding insult to injury."

The recent federal government shutdown, which furloughed more than 800,000 government workers and may have cost the nation as much as $24 billion, has sent ripples through the nation's scientific research enterprise. In just 2½ weeks, experiments were spoiled, careers derailed and proposed research initiatives delayed or suspended. Yet as scientists struggle to recover, many say that this is just the latest blow to a research community already weakened by funding cuts and fiscal uncertainty.

Since the post–World War II era, the U.S. government has pushed to support basic research. The space race of the 1960s, which culminated with the moon landing, drove interest in federal research funding until the 1970s and 1980s, when energy development was of top concern. In the late 1990s, Democrats and Republicans alike pushed for a doubling of the National Institutes of Health budget, which was achieved in 2003 primarily with additional funds for bioterrorism research.

But in the last decade, federal funding for basic and biomedical research has stagnated. The budget for the NIH, for instance, has dropped nearly 23 percent since 2003 after accounting for inflation. The sequester, a 5 percent, across-the-board budget cut that went into effect in March, has exacerbated already ailing science budgets.

"It's terrible, and it's not just the shutdown," says Alan Leshner, CEO of the American Association for the Advancement of Science and secretary of the board of trustees of the Society for Science & the Public, which publishes *Science News*. "The decrease in funding has been dramatic, but the sequester has been catastrophic." The U.S. scientific community, Leshner says, is "beleaguered," while competitors abroad are boosting their research investments. China, for instance, has increased its science funding more than fivefold since 1999.

Researchers struggle to win grant money that will pay for their experiments, maintain their laboratories and support graduate student education. Just 15 years ago, the NIH awarded funding to more than 30 percent of all proposals. Today, around 20 percent of grant proposals submitted to the NIH and the National Science Foundation in Arlington, Va., will receive funding. Some research programs, such as those that fund minority health research, accept only 10 percent of grant applications. As a result, scientists around the country report that established labs have closed and early-career scientists are having a harder time getting their labs running.

Careers jeopardized

For Stark, who is finishing his Ph.D. dissertation research and preparing to graduate, the career outlook is dicey. "I'm keeping a very open mind about where I end up," he says.

Staying in academic research after completing a doctorate increasingly requires taking a postdoctoral position before trying for a faculty job and starting a lab. But even those bridging positions are in jeopardy due to the funding climate, says reproductive biologist Andrew Singson of Rutgers University in Piscataway, N.J. "It's certainly causing us to lose people," he says.

After some of his funding ran out in April, Singson had to lay off one of the four postdoctoral researchers working in his lab, which aims to identify genetic components linked to infertility in humans. That postdoc applied for government unemployment benefits while he looked for a new job.

The layoff came about after one of Singson's grant proposals to the National Institute of Child Health and Human Development, an institute within the NIH, scored in the 11th percentile, which was not high enough to receive funding. "Eleven percent almost certainly would have been funded before sequester," Singson says. When another postdoc in the lab left for a faculty job last summer, Singson was not able to hire a new researcher to replace him.

By late summer, Singson finally got some good news: His latest proposal scored in the top 2 percent. But the NIH planned to start the funding on October 1 — the day the government shutdown began.

"We've seemed to hit a perfect storm of all these gridlocks in Washington," Singson says. While he's been able to keep his research going, others haven't fared so well. "It's just heartbreaking to see beautiful science not getting funded," he says.

In this era of perpetual uncertainty, says Cathy Trower, research director of the Collaborative on Academic Careers in Higher Education at Harvard University, adaptability is key. She urges young researchers to start opening their minds to more entrepreneurial endeavors and to find alternative sources of funding.

Graduate student Maximiliaan Schillebeeckx at Washington University in St. Louis is taking that advice. He and his peers have started a nonprofit organization that links graduate students and postdocs with local biotech start-up companies. The companies receive consulting on how to better target their products to the research community, while the young scientists get an entrée to industry. The goal, Schillebeeckx says, is to boost each participant's skill set, and thus potential job options.

Of current biomedical doctoral students, only about 25 percent are projected to get tenure-track faculty positions and carry out independent research in the next five years. The majority of newly minted Ph.D. researchers are looking to careers that scientists once considered alternative, such as private industry, patent law and publishing.

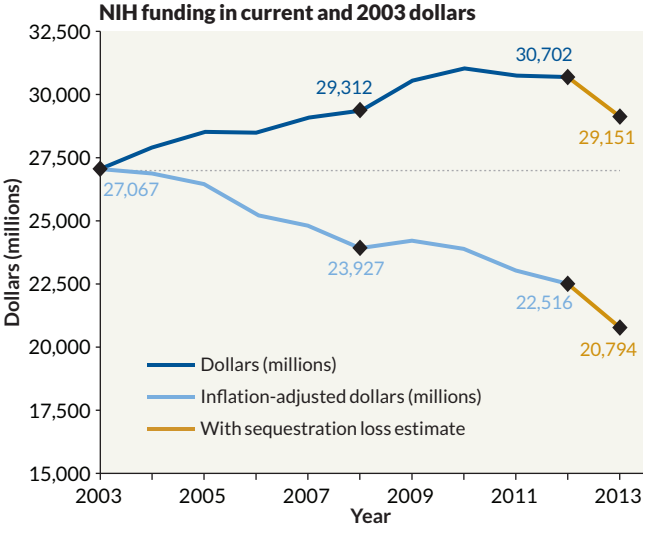
"We're not doing this to be rebels," Schillebeeckx says. "We're still very dedicated to our Ph.D.s." But with the state of science, he says, the more career options young researchers have, the better. "The funding situation is surely pushing you to be more creative."

Larry Suva, an orthopedic researcher at the University of Arkansas for Medical Sciences in Little Rock, worries that the current challenges are scaring off the country's next generation of scientists. For the first time in his 30-year career, Suva, who came to America from Australia to do science, saw one of his graduate students take a job abroad to avoid the U.S. funding climate. "I couldn't believe it," he says. "We used to have people who wanted to come here, and the opposite is happening."

Even a few years ago, the United States was by far the world's leader in research funding, paying for 36 percent of research in the world in 2007. But its lead is now shrinking. China, which has been steadily increasing its research investment since the early 2000s (*SN: 12/1/12, p. 20*), is poised to surpass the United States in science funding and published discoveries.

Suva says he can't blame students who leave the United States. Even for the few scientists who do manage to win

Funding fade-out After accounting for inflation, the National Institutes of Health budget has decreased steadily for a decade. With the sequester, which mandates across-the-board cuts beginning this year, the 2013 NIH budget was 23 percent smaller in real dollars than it was in 2003. SOURCE: FASEB



E. OTWELL

funding, the business of science has become stressful amidst continual government snags and shutdowns. Experiments often require lengthy preparation, multiple collaborators and extended commitment, which hiccups in funding can destroy.

"It's not like you come into lab and think 'I think I'll do an experiment today,'" Suva says.

His lab, for example, collaborates with researchers at the Arkansas Children's Nutrition Center to study how bone diseases link to metabolic syndromes such as obesity. The experiments involve giving mice daily dietary supplements. But because the U.S. Department of Agriculture funds the nutrition center, some of his collaborators were furloughed during the recent shutdown and couldn't give the mice their supplements.

Stop-and-go science

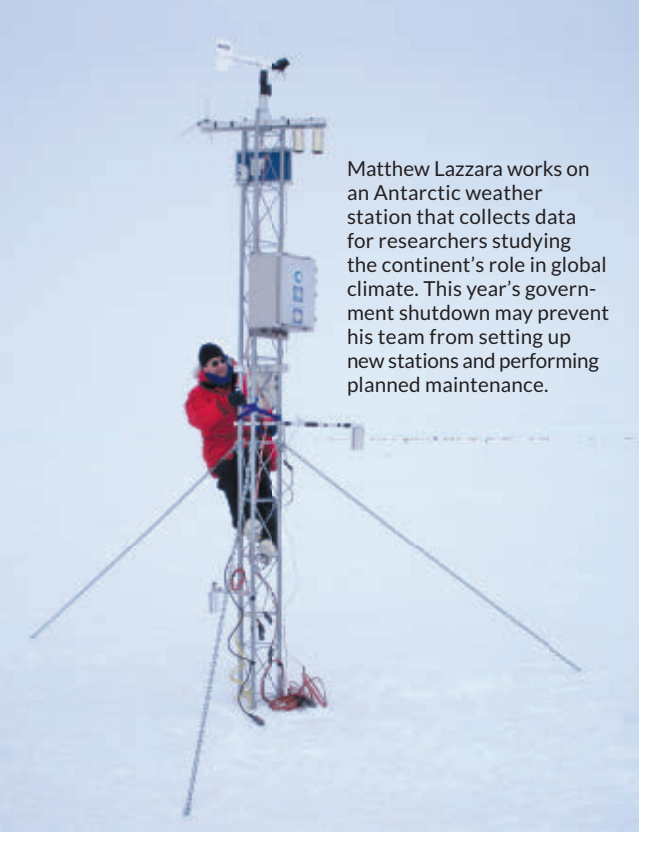
Researchers who do fieldwork in Antarctica already contend with delays and disruptions due to weather, mechanical breakdowns and logistical problems. So it was especially frustrating for scientists funded by the U.S. Antarctic Program, whose research season unofficially begins October 1, that the federal shutdown began the very same day. During the shutdown, the NSF began shifting its three Antarctic research stations into a caretaker status, emptying facilities and powering down equipment just as hundreds of scientists planned to begin research for the 2013–2014 austral summer.

Scientists around the world take part in the program, which coordinates and sponsors Antarctic research on everything from native Adélie penguins to astrophysics and glaciers. Meteorologist Matthew Lazzara of the University of Wisconsin–Madison, who studies Antarctica's role in global climate, planned to send four researchers to the cold continent midway through the four- to five-month warm season.

With the shutdown now over, the NSF has begun the daunting process of firing up the icy stations and assessing which researchers will get priority for transportation and services. Though his team will still go this season, it will likely not have enough time to collect data from as many weather monitoring stations, which will make future analyses difficult. "It's hard to fill a data hole when you don't have anything to fill it with," Lazzara says.

Stable funding and long-term planning is critical to running a successful experiment in the Antarctic, he says. "To have it cut from under you right when you're ready to go is pretty hard."

At the NIH, biomedical researchers are scrambling to salvage the current grant review cycle. During the 16-day shutdown, the NIH had to cancel more than 200 grant review meetings. Thousands of volunteer researchers would have convened around the NIH campus in Bethesda for in-person panel reviews of more than 11,000 submitted proposals.



Matthew Lazzara works on an Antarctic weather station that collects data for researchers studying the continent's role in global climate. This year's government shutdown may prevent his team from setting up new stations and performing planned maintenance.

COURTESY OF M. LAZZARA

Rescheduling those meetings has been a logistical nightmare, says Darren Boehning, a cell biologist at the University of Texas Health Sciences Center at Houston. "The shutdown came at a very inopportune time," he says, because October is a peak time for peer review panels to meet and decide the fate of grant proposals for the next year. Peer reviewers are already under intense pressure, he adds, having to make hair-splitting decisions between exceptional grants that get funding and exceptional grants that do not.

32%

Approximate success rate for NIH research grant proposals in 2000

18%

Approximate success rate for NIH research grant proposals in 2012

To be able to fund as many grants as possible, many institutes within the NIH trim money off funding packages. Boehning, for instance, won a five-year NIH grant of more than $1 million, which due to sequester was converted to a four-year grant with 26 percent less money annually.

Perhaps more worrisome: The funding cuts, pauses and uncertainty aren't over yet. When Congress passed legislation to reopen the government on October 17, it did so only until January 15, at which point another budget battle will likely ensue.

It's starting to look like this isn't just a blip or a temporary downturn, says Trower of Harvard's Collaborative on Academic Careers in Higher Education. "We've seen year after year of cut and cut, down to the bone. People are realizing that it's never going to come back," she says. "I don't like to be gloom and doom, but I don't think it will." ■

Explore more

- *AAAS Report XXXVIII: Research and Development FY 2014.* Available at: www.aaas.org/spp/rd/rdreport2014

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OLD DRUG, NEW TRICKS

Metformin, cheap and widely used for diabetes, takes a swipe at cancer

By Nathan Seppa

Like an aging actor rediscovered after being typecast for years, the long-standing diabetes drug metformin is poised to reinvent itself. A wealth of studies suggests the drug has cancer-fighting properties, and clinical trials are now under way to prove it.

Metformin's impact could be huge. "We believe that if this drug works, it will save between 100,000 and 150,000 lives a year worldwide because it is readily administered in countries that don't have a lot of money for drugs," says Vuk Stambolic, a molecular biologist at the University of Toronto. Also encouraging is the wide array of cancers metformin may treat — uterine, liver, pancreatic, colon, lung, ovarian and breast. Metformin may even help prevent cancer in people at high risk.

Metformin, also sold as Glucophage, has a long safety record and side effects that are milder than most cancer drugs. It is easy to store and take because it's a pill, not an injection. As a result, metformin is on a fast track to clinical testing. Even while some scientists are still testing metformin in the lab, others are already pitting it against placebo in breast cancer patients.

In addition to getting repurposed as a cancer therapy, metformin shows great promise in the treatment of polycystic ovary syndrome (see sidebar Page 21). Other recent studies hint that it might counteract dementia and Parkinson's disease, and trigger growth of nerve cells. And early studies in animals suggest the drug could even extend life.

Yet metformin seems an odd candidate for the spotlight. It is an old medication, a generic that sells for less than a dollar a dose. Even if the drug gets cleared to treat cancer, don't expect to see it featured on TV in expensive, slow-motion commercials. You won't be hearing, "Ask your doctor about metformin." At the clinic, no well-dressed drug reps will be passing out free samples.

The drug is also unlikely to ever get top billing in the chemo credits. Instead, metformin is being cast in a supporting role, the kind of medication given along with standard cancer drugs to attack a tumor from multiple directions.

If it works, says Michael Pollak, an oncologist at McGill University in Montreal, "it would be a nice story. You buy it by the kilogram." That's in contrast to most new cancer drugs, which must plow through years of expensive trials before they reach a druggist's shelf. That translates into costs of tens of thousands of dollars for a standard treatment regimen of drugs such as bevacizumab (Avastin) and cetuximab (Erbitux).

Known as goat's rue, holy hay, French lilac and Italian fitch, *Galega officinalis* was an ancient herbal remedy. Now its derivative, the diabetes drug metformin, may find new uses treating cancer and other diseases.

Unexpected tumor fighter

On the surface, a diabetes drug would seem to offer little for cancer patients. But people with diabetes are more likely to get cancer. And various lines of research have revealed an often-overlooked connection between the two diseases.

The notion that metformin might substantially hinder cancer in large numbers of people didn't gain traction until 2005, when a modest two-page study in the *British Medical Journal* showed that diabetes patients who took metformin were less likely to develop cancer than those who didn't.

That report from the University of Dundee in Scotland looked like a head-scratcher until an avalanche of similar findings followed. Researchers at the University of Alberta in 2006 found that patients who had diabetes and cancer were less likely to die if they were taking metformin, compared with patients getting insulin or another diabetes drug.

A 2005 study showed that diabetes patients who took metformin were less likely to develop cancer than those who didn't.

The metformin effect showed up again in 2009 when Ana Gonzalez-Angulo, a surgical oncologist at the M.D. Anderson Cancer Center in Houston, and her colleagues looked back at 155 breast cancer patients treated between 1990 and 2007 who also had diabetes. Fully 24 percent of the patients getting metformin had no detectable tumor after standard chemotherapy, compared with only 8 percent of similar patients not getting metformin.

"It's hard to find a cancer that hasn't had a [research] paper about metformin," says Iris Romero, an obstetrician-gynecologist at the University of Chicago. She found in 2012 that patients with ovarian or related cancers who had taken metformin were substantially less likely to die of cancer-related causes over five years than similar patients not getting the drug. A Mayo Clinic study in the same year yielded similar results.

Epidemiological studies raise possibilities but don't cure anyone, not even a mouse. "They give us the basis to see if we have enough evidence to move forward," says Gonzalez-Angulo. That's where randomized trials come in. More than 3,600 breast cancer patients who have been through surgery and/or chemotherapy have now been randomly assigned to get metformin or a placebo.

It's a leap to go this quickly from population studies to a big randomized trial, but metformin's record makes it the exception. "The general consensus was that this is an appropriate time to ask the question," says Pamela Goodwin, the University of Toronto medical oncologist leading the trial. Dozens of smaller trials are testing metformin against other cancers.

Blocking growth

A fast-forward to the clinic hasn't stopped scientists from pursuing molecular clues to metformin's cancer-suppressing activity.

Metformin controls type 2 diabetes by lowering patients' blood sugar levels, which reduces the need for insulin production by the pancreas. A hormone, insulin regulates cells' uptake and use of the simple sugar glucose for energy, and people with diabetes or prediabetes often have cells that take up glucose inefficiently.

But cancer cells do just fine in a milieu of high glucose and high insulin. By lowering both, studies indicate, metformin indirectly inhibits cancerous growth in people. The drug also seems to attack cancer by a more straightforward route. Metformin can slam the brakes on cancer-abetting mechanisms at work inside cells by turning on a protein called AMP-activated protein kinase. By revving up the AMPK protein, metformin bogs down a troublesome growth-spurring protein called mTOR.

Metformin, Romero says, "has a very biologically plausible mechanism."

The drug must get inside tumor cells to turn on AMPK, so the effect should show up in tissues that come into contact with lots of metformin. Metformin is an oral drug that must pass through the intestines before entering the bloodstream, Stambolic says. Colorectal cells are likely to encounter the drug, which puts colorectal cancer high on the list of diseases the drug could target.

That's why researchers were impressed by the results of a study done at Yokohama City University in Japan, in which scientists used magnified colonoscopy to identify 23 volunteers without diabetes who had tiny clusters of abnormal tubelike growths in their rectal tissue. These growths are the earliest precancerous lesions found in colorectal tissues and some develop into polyps, which can turn malignant.

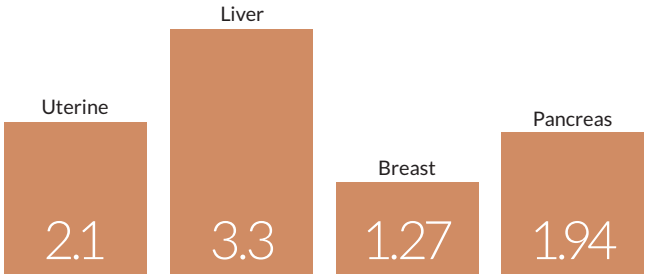
Nine of the volunteers were randomly assigned to get metformin. These people showed a drop in the number of growths from 8.8 on average to 5.1 after only one month of taking the drug. Fourteen other volunteers who didn't get metformin over that time saw their lesion clusters remain practically unchanged, rising from 7.2 to 7.6, the researchers reported in *Cancer Prevention Research* in 2010.

Metabolic effects

But metformin also seems to have an effect on tumor cells that reside far from the colon, Stambolic says. In those cases, metformin apparently works by a roundabout mechanism — lowering glucose in the blood, which leads to less insulin production and contributes to weight loss.

People with diabetes are about twice as likely as those without diabetes to develop liver, uterine or pancreatic cancer, and diabetes patients also have some increased risk for breast, bladder and colorectal cancers. Enter metformin. People with type 2 diabetes usually make plenty of insulin, but it gets left in the blood because their cells resist its effects. Metformin relieves this insulin resistance by taking away some of the liver's capacity to make glucose and dump it into the bloodstream, lowering demand for insulin production, Stambolic says. This mimics

The diabetes-cancer link Simply having diabetes places a person at an increased risk (a value of 1 is the average risk) of developing certain cancers. SOURCE: S. GANDINI *ET AL/J. CLIN. ONC.* 2013



the benefits of calorie restriction (*SN: 8/1/09, p. 9*) and induces cells to process glucose more effectively.

Insulin promotes growth by turning on a biochemical pathway in the cell. Insulin's progrowth signals can ultimately activate mTOR and shut down failsafe anticancer processes. By lowering insulin and glucose in the blood, metformin removes the punch bowl from this cancer party. If metformin does its job, less insulin reaches a cancer cell's front door — the receptor proteins to which insulin binds to exert its effects.

This insulin pathway appears important in certain cancers. About 90 percent of breast tumors display insulin receptors, Stambolic says. And insulin can also interact with other cellular docking stations called IGF-1 receptors and abet cell growth. While not all tumor cells display a multitude of these receptors, Pollak says their presence or absence may clarify which patients would benefit from metformin. The drug might work best on tumors that are clearly responsive to insulin and in people with high blood glucose, he says, "so there is room for their insulin to fall."

Romero agrees. "Metformin might be more effective in cancer where there's a double whammy" of obesity and high blood glucose. "For gynecologists that would be uterine cancer."

Alastair Thompson, a surgeon at the University of Dundee, says weight gain is linked with breast cancer risk in postmenopausal women. And Stambolic points out that "more and more women who are showing up at clinics with breast cancer are obese."

The good news: In Goodwin's trial, early returns show the metformin group is losing weight.

Cancer by cancer

Many scientists are looking to metformin to help out in hard-to-treat cancers. For instance, some breast tumors don't respond to standard drugs because they lack receptors for the hormones estrogen and progesterone and for the progrowth HER2/neu protein. But these triple-negative cancers often have one thing in common — active mTOR that's stoking tumor growth, Thompson says.

Metformin seems to have other tricks up its sleeve, and one could benefit uterine cancer patients. Overexposure to estrogen can gin up cancer in uterine cells, but the effect is toned down by progesterone. When progesterone binds to its receptor protein on cells, it keeps estrogen-fueled growth in check. Metformin promotes progesterone receptor activation by suppressing mTOR, researchers in Beijing reported in 2011 in the *Journal of Steroid Biochemistry and Molecular Biology*.

Taking metformin might also prevent some cancers. Randomized cancer prevention trials are nearly impossible to do because they would need healthy people to take drugs or placebos for years to show an effect. But Romero says preventing ovarian cancer in a unique group of women — those carrying a mutation in the *BRCA* gene — might fit the bill. Women with a *BRCA* mutation face a sharply increased lifetime risk of ovarian cancer.

"Here's how I see this coming into play," she says. "The clinical trials approach *BRCA*-mutation carriers and suggest metformin as an option until their ovaries get taken out. They would lose a little weight. I think they would be really into it."

Other frontiers

Quite apart from combating diabetes or cancer, metformin might find use in thwarting certain neurological diseases. For instance, type 2 diabetes seems to increase the risk of Parkinson's disease, but when researchers in Taiwan tapped into a huge health database in 2012 they found no Parkinson's increase in diabetic patients on metformin. Comparing only people with diabetes against each other, they found that those on metformin were less likely to develop Parkinson's disease than those getting other diabetes drugs called sulfonylureas, the team reported in *Parkinsonism & Related Disorders*.

Metformin can also stimulate new neuron growth. The drug improved problem-solving and memory in mice negotiating a water maze, a U.S.-Canadian team reported in 2012 in *Cell Stem*

Metformin through the ages

1700s and earlier
In medieval times, tea from goat's rue, the plant from which metformin is derived, is used to treat snake bites, plague, frequent urination and worms. The plant, which grows in southern Europe, eventually falls out of use.

1800s
Goat's rue is found to increase cows' milk output.

1920s
Derivatives of goat's rue called biguanides are shown to lower blood sugar in rabbits. But the discovery of insulin leads to a focus on using that hormone to treat diabetes. Biguanides are largely ignored for decades.

1950s
French researchers develop pills that include three biguanides and France approves them for use in patients with type 2 diabetes.

1970s
Two of the biguanides are pulled from the market due to side effects, leaving only metformin. The French call it Glucophage, literally "glucose eater."

1990s
Metformin/Glucophage is approved by the U.S. Food and Drug Administration for diabetes in 1994.

Cell. Elsewhere, data are now being analyzed from a randomized trial in overweight people aimed at determining whether metformin preserves memory and general cognition.

On another front, metformin shows hints of extending life. Of 16,417 heart failure patients with diabetes who were discharged from hospitals, a Denver-based research team found in 2005 that 25 percent of those on metformin had died within a year, compared with 30 percent on another diabetes drug and 36 percent of those getting neither drug. Metformin also retards aging in worms and mice, albeit in higher doses than people get. The biological mechanisms underlying these observations are still being investigated.

A 'dirty' drug

Despite all the promising results, the buzz about metformin seems muted. At a cancer research meeting in Washington in April, the session on metformin was only half full.

Clinical trials aren't done yet. Some scientists might think metformin will flop in its new role. And there is no assurance that the relatively safe doses used for diabetes will work against cancer. Besides, metformin isn't worry-free. It can cause side effects such as intestinal bloating, muscle pain and diarrhea, especially when people first start on it. A less common but more serious side effect is lactic acidosis, marked by low pH in blood and tissues. Anyone showing it must stop the drug.

There's just a lot about metformin at the cellular level that's unclear, Pollak says. "We now have a mixed bag of very important clues that must be followed up, but they are only clues."

Thompson sees a bright side there. "It's a relatively 'dirty' drug, in the nicest sense," he says. "It seems that it doesn't work on only one molecule, and in cancer that can be quite beneficial." Compared with other cancer drugs, "metformin might work more subtly, by gently suppressing, and not completely strangling, cancer tissues. And that might be a more sustainable effect."

Meanwhile, metformin will keep its day job, hiding in plain sight as a diabetes drug prescribed to 120 million people a year worldwide. ■

Explore more

- Begoña Martin-Castillo *et al*. "Metformin and cancer: doses, mechanisms and the dandelion and hormetic phenomena." *Cell Cycle*. March 15, 2010.

1990s
Researchers find that metformin is useful in treating polycystic ovary syndrome.

2000s
Metformin begins to be sold as a generic drug.

2005
Researchers first document a link between metformin use and lower cancer rates in people with type 2 diabetes.

2013
The largest trial pitting metformin against cancer completes enrollment of patients.

Treating polycystic ovaries

Metformin has already established itself as a weapon against polycystic ovary syndrome, in which cysts enlarge the ovaries, leading to irregular menstrual cycles, lack of ovulation and hence low fertility. Women with the condition who do get pregnant face a heightened risk of complications.

While the cause of polycystic ovaries is unclear, roughly 40 percent of women with the condition are obese. Even more show insulin resistance. Both result in excess insulin in the blood, fingering insulin as a chief suspect in the condition. Since a 1994 study first suggested that metformin might help these patients, many reports have backed it up:

- A 2003 review of 13 studies by a British-Australian team found that the drug increases the chance of ovulating nearly fourfold in women with the condition.
- In 2011, researchers in Egypt and the Netherlands tracked women who got pregnant despite having polycystic ovaries. Those on metformin were one-sixth as likely to develop gestational diabetes and one-third as prone to a complication called preeclampsia as women not getting the drug.
- In Finland, scientists randomly assigned women with polycystic ovaries who had previously tried to get pregnant using fertility drugs to take metformin or a placebo. Women on metformin were substantially more likely to get pregnant and to have a live birth, the scientists reported in the *Journal of Clinical Endocrinology & Metabolism* in 2012.
- While obese patients seem most apt to benefit from metformin, so can normal-weight women with polycystic ovaries, according to a 2011 randomized trial in four Nordic countries. Normal-weight women with polycystic ovary syndrome who were using assisted fertilization were more likely to get pregnant if they were among those randomly assigned to get the drug.

Not all studies of women with polycystic ovaries find a benefit from metformin, and even the many positive findings haven't led to regulatory approval for this condition. But that hasn't stopped doctors from giving it to patients. In the United States, doctors can prescribe approved drugs for such "off-label" uses if they deem it necessary.

"Any OB/GYN on the street will tell you it's one of the first-line treatments for polycystic ovary syndrome," says Iris Romero, an obstetrician-gynecologist at the University of Chicago.

— Nathan Seppa

The Inconstant GARDENER

Microglia, the same immune cells that help sculpt the developing brain, may do damage later in life **By Susan Gaidos**

Like the cavalry in old Western movies, certain immune cells in the brain rush to answer distress calls and save the day. If a nerve cell is injured or a toxin attacks the brain, these microglia ride to the rescue, moving to the injury site and destroying any bad guys they encounter.

But even in the movies the cavalry, mistakenly or intentionally, sometimes mows down innocent bystanders. A similar scenario may be playing out in the brain with processes that normally limit damage: Microglia may be improperly activated late in life and play a role in neurodegenerative disease.

Take Alzheimer's as an example. People with Alzheimer's disease lose millions of nerve cells in brain areas crucial for memory. As the losses grow, the brain also becomes cluttered with clumps of plaque containing a protein fragment called amyloid-beta, or A-beta. Where these plaques emerge, microglia appear as well.

COMPOSITE: FABLER/ISTOCKPHOTO, DEM10/ISTOCKPHOTO, EGEEKSEN/ISTOCKPHOTO, ADAPTED BY S. EGTS

For years, researchers have believed that the microglia are there to help clear out dead cells and debris left behind as the plaques progressively damage the brain. But new research suggests a different scenario. Long before the plaques collect, microglia may be called in and compelled to attack healthy cells.

A protein called C1q may set up the brain for this destruction. C1q is found in abundance in young brains. During development, the protein works with microglia to target and prune unused connections between brain cells, making way for new connections to form in response to experience and learning.

C1q also accumulates in aging brains, according to recent research. The protein collects at synapses, the junctions between nerve cells where communication between the cells takes place. Information is processed and stored in the brain through these delicate connections. Each nerve cell can have thousands of synapses, creating a total of billions of connections inside the brain.

What impact does accumulating C1q — and its troops, the microglia — have on the older brain?

Stanford neuroscientist Ben Barres speculates that microglia may be reactivated later in life in response to a head injury, stroke or severe illness. This reactivation, he says, may explain the massive loss of neurons seen in neurodegenerative disease.

"Our findings suggest that long before the [nerve] cells die, their synapses are dying," Barres says. "It may be that the neuron dies only after it has lost a sufficient number of synapses."

His lab and a few others are exploring this hypothesis. They say their findings may implicate microglial cells in an array of conditions, including Alzheimer's, Parkinson's, glaucoma and multiple sclerosis, that result from the loss of large numbers of synapses.

That microglia have the potential to act as both protector and attacker doesn't come as a complete surprise. But whether these immune cells are helpful or harmful in these diseases has remained unclear.

While pruning of synapses during development is necessary for wiring the nervous system, activation of microglia in old age can occur through various means and is a detrimental process, says R. Douglas Fields, chief of the nervous system development and plasticity section at the National Institute of Child Health and Human Development.

"This is somewhat similar to the situation where the action of the body's immune system is normally crucial, but in autoimmune disorders such as multiple sclerosis, pathological consequences can result from the mechanism intended to protect the body," Fields says.

By studying how microglia respond to various proteins and signals in the brain, in both health and disease, scientists aim to clarify microglia's role in synapse loss and disease. Some researchers are also devising ways to tweak microglia's function in the body by inhibiting immune responses that call microglia to action or replacing faulty microglia with healthy ones.

Guardian and housekeeper

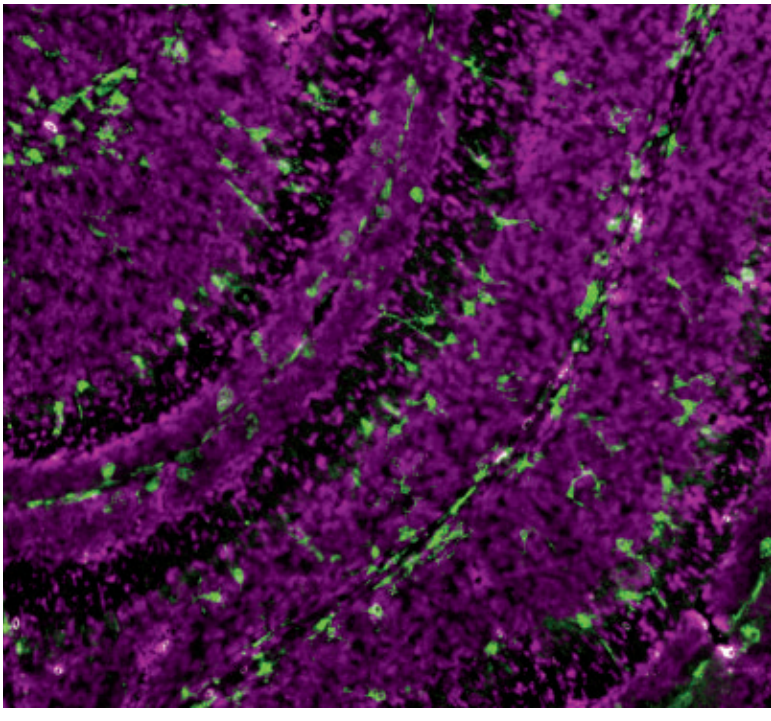
Microglia belong to a class of brain cells called glia — the name literally means glue — which also includes astrocytes and oligodendrocytes. Together, these cells outnumber neurons 3 to 1. While neurons do the heavy work of transmitting and processing information, glial cells produce proteins necessary for the health and survival of the neurons.

Astrocytes ferry nutrients to neurons and help control where synaptic connections form. They also promote neuron survival by stimulating the growth of axons, the long nerve fibers that transmit neuron impulses. Oligodendrocytes coat the axons with an insulating sheath called myelin. Because axons serve as nerve cells' communication fibers, much like electrical wires, the insulating myelin coat helps to boost signal speeds.

Hard-working microglia serve as both guardian and housekeeper. If something bad happens in the nervous system — a blow to the head or a bacterial infection — these small cells take action. Pulling in their long, skinny appendages, they puff up in size and move toward the injury. Once there, they release chemical substances to kill invaders then gobble up any bits of debris, including dead or dying cells. By keeping the environment around the neurons and synapses clean, microglia help keep things running smoothly.

For decades, microglia were considered supporting players that remained "at rest" unless called on to respond to an emergency. As better imaging tools became available and allowed

Cleanup crew In the brain's developing visual system, microglia engulf unnecessary connections and prune them away. This slide shows microglia (green) in cleanup mode, interacting with cells (nuclei labeled purple) in a mouse brain during the animal's first few days of life.



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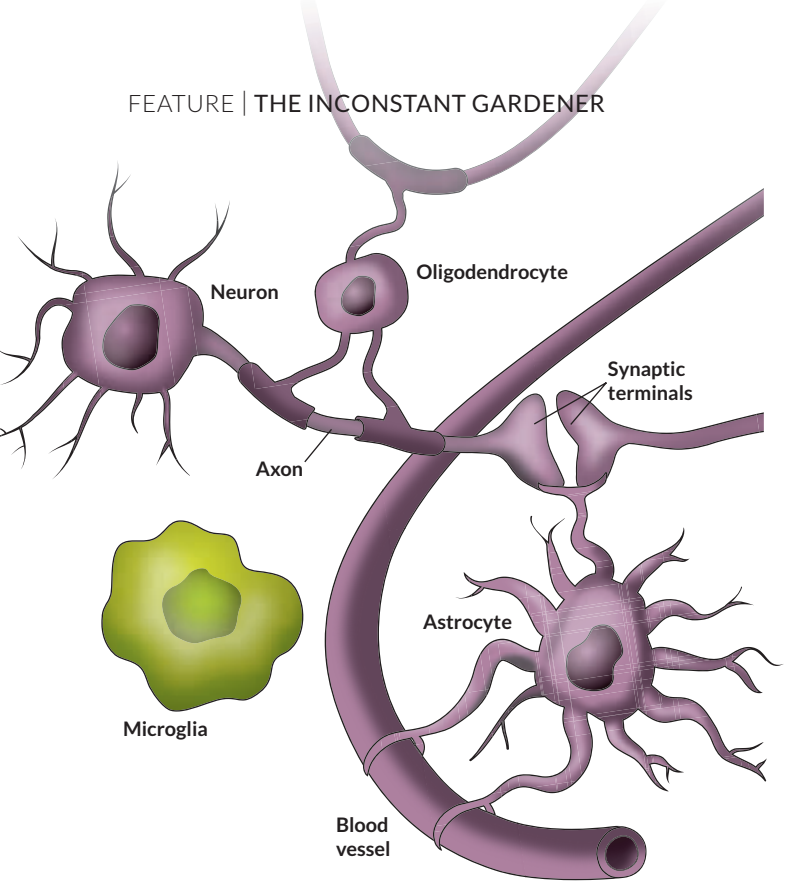


Supporting cast Specialized glial cells help maintain neurons. Astrocytes provide oxygen and nutrients, connecting neurons to their blood supply. Oligodendrocytes coat the axons with a myelin sheath to speed up neural signals. Microglia fight infection, promote repair and help sculpt the developing brain. SOURCE: N.J. ALLEN AND B.A. BARRES/*NATURE* 2009

scientists to peer inside the brains of living animals, it became clear that, for these cells, there is no rest.

In 2005, Axel Nimmerjahn, then a graduate student at the Max Planck Institute for Medical Research in Heidelberg, Germany, and colleagues released images of microglia in action, taken from a live mouse over a period of hours. The images show the cells' branchlike projections in constant motion, extending and withdrawing from surrounding tissue, presumably to check for damage.

In 2007, Beth Stevens, a postdoctoral fellow in Barres' lab, made an even more surprising observation while spying on brain cells of young mice. The microglia she saw were not only brimming with activity, they were already in their puffed-up fighter mode. Last year, Stevens, now a Harvard neuroscientist, confirmed that microglia help sculpt the brain's circuits by pruning unneeded connections between neurons during early development, when the brain forms more neurons and synapses than it needs.

In the study, Stevens showed that microglia take their cues, in part, from a set of signals that trigger an immune response called the complement cascade. In the body, complement proteins bind to invading pathogens or dying cells, sparking their destruction by immune cells called macrophages. The multistep process involves about 20 different proteins, which one by one glom onto unwanted bits and debris, ultimately calling upon the macrophages to gobble up the invader.

In the brain, microglia do the work of macrophages but with an added job: pruning. Stevens' group found one complement protein in particular, called C3, on synapses destined for pruning during early development. Microglia have proteins that lock onto C3, which acts as a biochemical bugler calling microglia to action.

Stevens' group used dyes to track microglial activity in the visual system of mice and caught microglia in the act of pruning synapses tagged with C3. In the study, published last year in *Neuron*, Stevens noted that microglia engulfed synapses only during development, when extra synapses are forming and unused synapses need clearing away. Stevens' lab is studying whether microglia play a role in maintaining the brain's synaptic architecture in adult mice.

Coaxed into battle

In most cases, the complement system works for the brain's benefit, calling on microglia to clear unwanted debris or unneeded connections. But if left unchecked, complement proteins can coax microglia into battle with the cells they should be protecting. That's something that Barres believes happens in a number of neurodegenerative conditions.

He has some evidence to back this up. Barres' group found that synapse elimination is reactivated very early in glaucoma, a neurodegenerative disease that is a major cause of blindness. In the 2007 study, his team showed that the earliest sign of the disease was the activation of the complement cascade at synapses. Soon after came massive synapse loss.

Synapse loss is a hallmark of a number of diseases, including Alzheimer's. Pointing to recent findings that show C1q, a key complement protein, increasingly collects at the synapses with age, Barres says immune signaling may be at play in such diseases as well.

C1q is first in the series of proteins that initiate the complement cascade. Examinations of mouse and human brain tissue show as much as a 300-fold increase of the protein in aging brains, even healthy ones. Studies from other labs have shown the presence of both microglia and C1q in areas where A-beta plaques accumulate in patients' brains.

"By the time you get to be a 2-year-old mouse or a 77-year-old human, the C1q is pretty much everywhere throughout the brain," Barres says.

What's more, the most dramatic increases are seen in the hippocampus and the substantia nigra, brain regions that are typically ravaged by Alzheimer's and Parkinson's diseases.

But just because C1q is present doesn't mean microglia are going to come running. Unlike C1q seen in brain development, C1q found in the healthy, aging brain is not activated, a step needed to draw other complement proteins and microglia to the site.

What it does mean, Barres says, is that these delicate connections are "primed" with complement protein, poised to call out for help if injury or major illness strikes. Because various stresses lead to a full-blown immune response, a stroke, a

ADAPTED BY S. EGTS

blow to the head or even a bad case of pneumonia could put the tagged synapses on a path toward destruction by calling microglia into action.

"There's always been this mystery: Why is the old brain selectively vulnerable to neurodegenerative disease?" Barres says. "I believe that this could be the missing link. It's only the old brain that has already got the complement system essentially charged up and ready to go."

Spreading destruction

Nerve cells are uniquely vulnerable to activation of the complement cascade. Other cells in the body have complement-inhibiting agents to prevent the loss of healthy tissue during an immune attack. Such fail-safe mechanisms allow the complement system to attack bacteria on the liver without harming the liver itself.

But neurons have little or no complement inhibitors. If the complement system gets out of control and microglia begin gobbling C1q-coded connections in an aged brain, according to Barres' theory, a spreading "fire" may burn through the synapses, destroying neural circuits and the memories that go with them.

"You can imagine in the brain, where you have this dense network of synaptic connections, all jam-packed next to each other, if the complement system gets set off at one of those synapses, there will be innocent bystander killing," he says.

This scenario has yet to be tested. But it could help explain the massive synapse loss seen in a host of neurodegenerative disorders. In the Aug. 14 *Journal of Neuroscience*, Barres and his group report that mice genetically deficient in C1q age with fewer memory problems than normal mice.

Scientists are trying to figure out why C1q targets some synapses and not others, or what series of events puts C1q on the path of destruction. If researchers could find the key players involved, they may be able to develop new treatment approaches to prevent synapse loss, Barres says.

Even as they expand their studies to see what happens between C1q buildup and microglia activation in the brain, Barres and his colleagues are developing a drug to inhibit immune responses that call microglia to action in aging brains. Barres has created a start-up company, called Annexon, to develop drugs to block the action of C1q and other proteins in the complement cascade. One drug is already being tested in animals.

Fatigued fighters

Attacking healthy cells may not be the only way that microglia contribute to disease. Some scientists point to another possibility: With age, microglia may lose the oomph they need to counter an assault.

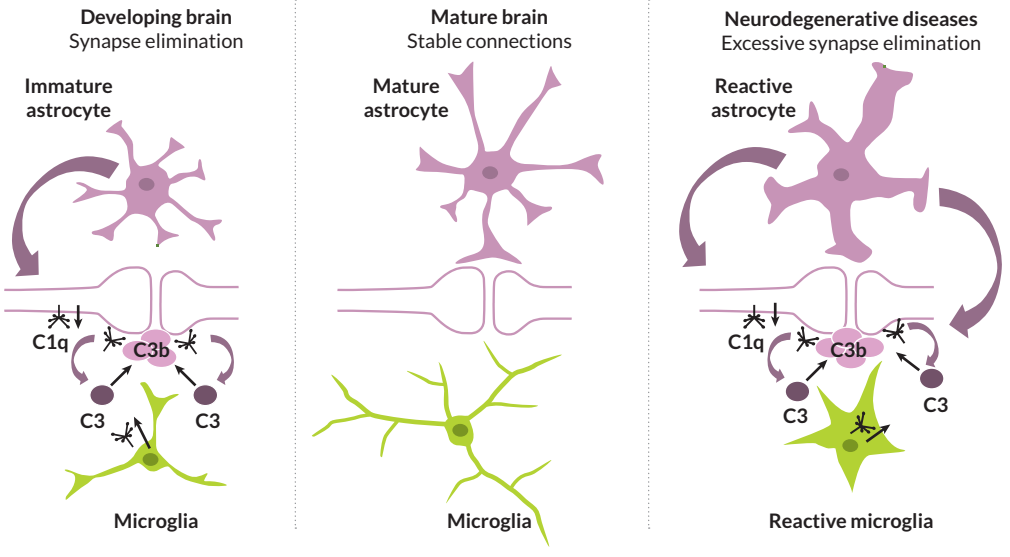
Microglia become activated in increasing numbers in aging brains, Fields says, which has long been considered a sign of the cells' hard work to protect the brain from accumulating insults. It's also thought to be a reason people recover from strokes better at younger ages.

"If the brain's microglia are already activated chronically before a stroke, they cannot mount a response to the injury that is as aggressive as if they were quiescent in a younger brain," he says.

The situation may be made worse by disease. Researchers led by Helmut Kettenmann of the Max Delbrück Center for Molecular Medicine in Berlin recorded moving images of microglia surrounding plaque deposits in the brains of mice with an Alzheimer's-like condition using two-photon microscopy. The microglia could not perform normal custodial functions: They did not clear cell fragments or other structures from the brain and lost their ability to move about in their surroundings.

When the scientists injected the mice with an antibody against the A-beta protein, prompting the rodents to produce

Microglia in developing, mature and diseased brains



ADAPTED BY S. EGTS

Cutback cues

Early in the brain's development, the first complement protein, C1q, lodges at the site of weak or unused synapses, tagging them for destruction. Another protein, C3, is converted to its active form, C3b, which calls microglia to the scene. In a mature, healthy brain, microglia stand watch, ready to respond to injury. With advancing age, C1q appears to accumulate at higher-than-normal levels at synapses, perhaps triggering the destruction of healthy cells by reactivated microglia.

SOURCE: A.H. STEPHAN *ET AL/ANNUAL REVIEW OF NEUROSCIENCE* 2012

Do microglia fail in Rett syndrome?

Some microglia may develop an aversion to housekeeping long before old age. Studies by Jonathan Kipnis of the University of Virginia School of Medicine in Charlottesville and colleagues have found a link between faulty microglia and Rett syndrome, a severe autism spectrum disorder that strikes in early childhood.

Rett syndrome affects motor skills and often leaves young victims wheelchair bound, unable to talk or use their hands and gasping for breath. The syndrome is caused by mutations in a single gene, called *MECP2*, on the X chromosome. Because they have only one X chromosome, boys born with the mutation usually die within weeks of birth. Girls with one faulty copy generally begin to show symptoms of decline before 18 months of age.

Microglia are suspects in causing some of the dysfunction because the brains of mice with Rett-like disease become cluttered with cellular debris, according to Kipnis. In a study published last year in *Nature*, he showed that replacing faulty microglia with healthy cells made a difference in mice with the disease.

Microglia are the only cell type in the brain that can be "feasibly" replaced, Kipnis says. That's because microglia are part of the immune system, and bone marrow transplantation results in a partial replacement of these cells.

First, Kipnis' team exposed 4-week-old mice with Rett-like symptoms to radiation to wipe out their existing immune cells, including microglia. Then the team injected the animals with bone marrow cells that had a working copy of the *MECP2* gene.

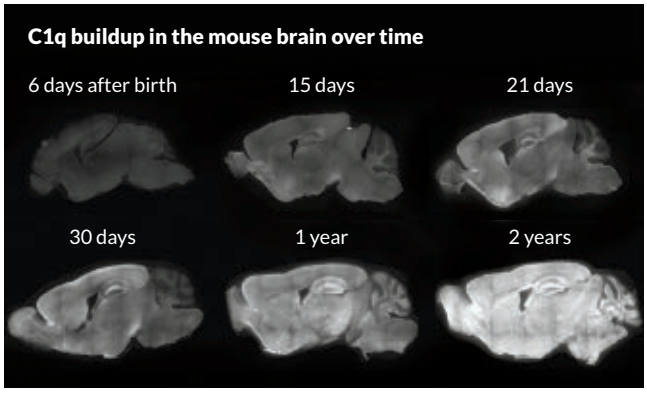
The treatment reduced and slowed progression of the symptoms in both males and females. Males grew stronger, gained weight and began to walk. Females also showed improvement in walking and breathing.

To be sure that the improvements were because of microglia in the brain and not immune cells elsewhere in the body, the scientists gave bone marrow transplants to Rett mice that did not get a dose of radiation to their brains, sparing the faulty microglia. The transplant did nothing for these mice.

Though unconventional, the approach shows how treatments focused on the immune system can correct problems in the brain, Kipnis says.

"What drives our interest about the immune system, and microglia in particular, is that even though neurological disorders are disorders of neurons, it's impossible to treat them directly," he says.

"We can't fix neurons, we can't replace them and we can't change them." — *Susan Gaidos*



Vulnerable brains A series of cross sections of the mouse brain from 6 days to 2 years of age shows the accumulation of the C1q protein (white). Early on, the brain appears dark. By old age, the brain turns ghostly white, indicating a heavy buildup of C1q.

fewer plaques, the microglial cells resumed their normal functions.

How microglial cells become weakened in Alzheimer's is not fully understood, Kettenmann says. His group is now studying the roles of various receptors in microglia. For example, different receptors on microglia may initiate tissue repair, inflammation or neurodegeneration. He's also studying how microglia participate in other diseases, such as cancer. Four years ago, his group published findings that show microglial cells support the growth of some tumor cells, helping them spread through the brain.

"In the old days we thought that microglia activation worked like an action potential — an all or nothing process," says Kettenmann. "Now, we recognize that the activation process is quite diverse," depending in part on the condition that sets off the alarm.

As scientists explore the workings of microglia in disease, other efforts aim to see how microglia perform in normal, healthy brains.

"We know almost nothing about their functions in a normal brain," Kettenmann says. "It's likely that many of the mechanisms which are used in pathology are also used in development and plasticity."

This seems to be the case in other kinds of cells, he says. Rather than inventing a new path for destruction, cells take an untimely misstep on pathways meant for normal development or growth.

"Somehow the microglial cell may get put back on that pathway," Kettenmann says. And maybe there's a way to set it right again. ■

Explore more

■ Alexander H. Stephan *et al.* "The complement system: an unexpected role in synaptic pruning during development and disease." *Annual Review of Neuroscience.* July 2012.

A.H. STEPHAN *ET AL./JOURNAL OF NEUROSCIENCE* 2013

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SCREENTIME

Cruise through a collider

The doors to CERN, the particle physics lab near Geneva where the Higgs boson was discovered last year, are closed to most folks. But the researchers there let in a team from Google Maps Street View, and now anyone can tour the Large Hadron Collider and other CERN experiments in 360-degree photo panoramas online. Virtual visitors can "walk" through a tunnel housing part of the collider's 27-kilometer-long particle accelerator. Or you can explore brightly painted particle detectors such as the Compact Muon Solenoid experiment (shown), which scientists used to find many of the ephemeral particles created in the LHC's high-energy collisions. — *Sarah Zielinski*

GOOGLE STREET VIEW

BOOKSHELF

The Accidental Species

Misunderstandings of Human Evolution

Henry Gee

This is not a typical book about human evolution. There's no chronology of fossil discoveries, no detailed description of hominid species or even an illustration of human family trees. In fact, the book is largely about what we don't know about human evolution — and what we've gotten wrong.

Gee, an editor at *Nature* and a former paleontologist, begins by taking a swipe at the oversized human ego. Despite what many people, including some scientists, seem to think, *Homo sapiens* is not the pinnacle of evolution. "Human beings are special in many ways — of course we are — but so is every other species," Gee writes. There's nothing exceptional about the way evolution shaped the human lineage, and the hallmarks of humankind — such as upright walking, large brains and language — can be found in varying degrees in other animals, he points out.

Another misconception is that extinct hominids represent "missing links," stepping stones on the way to becoming human. In reality, natural selection has no endpoint in sight, Gee reminds readers. It can act only on whatever raw material an organism has and can shape only current conditions, resulting in traits that are "contingent, makeshift compromises made in response to a number of different factors."

Yet many evolutionary biologists attempt to single out an overarching explanation for a particular human trait. Some researchers argue upright walking evolved as an efficient way to move between patches of shrinking forest, while others claim the need to free up the hands led to a two-legged stance.

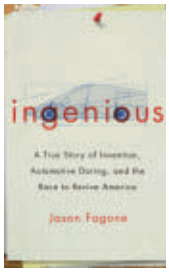
Such theories, or stories as Gee calls them, are nearly impossible to test because the fossil record is so spotty. In the end, that realization may leave readers unsatisfied. Gee has no pat solutions for understanding our past, just a needed reality check. — *Erin Wayman*
University of Chicago Press, $26

Ingenious

A True Story of Invention, Automotive Daring, and the Race to Revive America

Jason Fagone

The challenge was to build a safe, mass-producible vehicle that can carry two people 100 miles using no more than the energy in a gallon of gas. In 2007, the X Prize Foundation offered $10 million to be shared by teams that could pull it off, and in 2010, three groups claimed the prize.



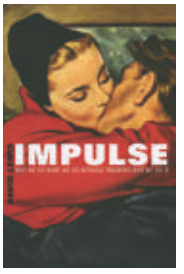
Fagone, a journalist, chronicles the three-year scrum of engineering

See the CERN Street View at bit.ly/SNviewCERN

inspired by this bold challenge. Many teams sought to boost gas mileage by reducing aerodynamic drag, but one also enhanced performance by making the car incredibly light (less than 360 kilograms, or 800 pounds). Some vehicles were electric, others gas/electric hybrids, and one was a Frankensteinish hodgepodge with an electric motor, a motorcycle engine and a Ford chassis.

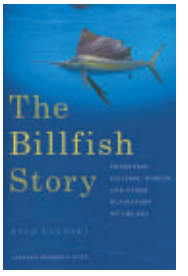
Of hundreds of would-be car moguls, Fagone followed four teams closely, including a well-funded start-up from Southern California, high schoolers from West Philadelphia and an Illinois team that built its vehicle in a barn.

Ingenious recounts the heartbreaks and triumphs that unfold as the competition takes a dramatic toll on bank accounts and on professional and personal relationships. The book provides keen insights into the process of innovation. More than that, though, it is a fascinating behind-the-scenes tale of engineering obsession. — *Sid Perkins*
Crown, $26

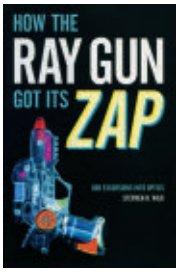


Impulse
David Lewis
A neuropsychologist examines why people often act on impulse rather than logically, and why that may be good for mental health. *Belknap, $27.95*

The Inheritor's Powder
Sandra Hempel
The story of an early forensic investigation of poisoning shows the importance of studying arsenic, which was once so frequently used by potential beneficiaries of wills that it was known as "inheritor's powder." *W.W. Norton, $25.95*



The Billfish Story
Stan Ulanski
An oceanographer weaves together ecology and human history with this group, which includes sailfish, swordfish and marlins. *Univ. of Georgia, $26.95*



How the Ray Gun Got Its Zap
Stephen R. Wilk
A collection of the author's essays on optics ranges in subject from lasers and photographs to ancient studies of light. *Oxford Univ., $34.95*

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OCTOBER 19, 2013

Facelifts

Science News has had several makeovers during the last decade or so, most recently in October.

JANUARY 19, 2002

APRIL 5, 2008

OCTOBER 6, 2012

NOVEMBER 30, 2013

SN gets a new look

The October 19 issue of *Science News* showed off a makeover with a clean, modern design and expanded department sections.

Remembering the passionate reader response to a more extensive redesign in 2008, *Science News* editors braced for a flood of letters. So far, the reaction to our changes has been mostly positive. **Burt Kessler**, a reader since 1970, e-mailed to say how much he likes the new design. "I have not enjoyed an issue so much in years. I am particularly pleased to see the return of very short articles, just a few column inches." And the new Feedback design got a thumbs-up from **Ron Belcher**, who e-mailed that he really likes the summarized format. "Much easier to read," he says.

Our new cover style also garnered attention, especially the SN logo that replaced the traditional title. The new, smaller logo helps us feature our cover designs in digital formats with smaller screens, such as the iPad tablet edition, and ties in with the SN logo appearing across the online world. But some readers are already nostalgic for the way things were. The large SN "puts me in mind of snuff, snot, sneak, snarl, snafu and Snidely Whiplash," **Connie Thomas** e-mailed. "Please just call it like it is, and was and always should be: *Science News*!" Thomas writes. A few readers have questioned our choice of new font styles as well. While we did update headlines, captions and some other text in the redesign, the main body text of all our stories remains in the same Chronicle font used since 2008 and much loved for its readability.

View on Voyager

"Voyager's View" by **Andrew Grant** (*SN: 10/19/13, p. 19*) charted the course of the Voyager 1 spacecraft into interstellar space on a three-page foldout.

The story noted that it will take 30,000 years for the two Voyager probes to pass through the Oort cloud, a huge sphere of ice chunks that extends as far as 100,000 astronomical units from the sun. "But I thought I read that as 300 years elsewhere," asked **Betsy Wilson** by e-mail. "Which is correct?" Wilson won a NASA medal for her work on the Voyager probes, which she began in 1975. We double-checked our work. **Grant** replies: "Voyager 1 will reach the inner edge of the Oort Cloud in about 300 years, but the outer edge of the cloud is about 100,000 astronomical units from the sun. Voyager is chugging along at 3.5 astronomical units per year, so traveling 100,000 AU will take nearly 30,000 years."

Taking *Gravity*'s measure

Andrew Grant spoke with NASA experts to assess the likelihood that the space disasters in the movie *Gravity* could happen in real life ("Gravity," *SN: 10/19/13, p. 34*).

Readers were eager to point out other inconsistencies in the film that were unrelated to disasters or accidents. Sandra Bullock's character strips off her spacesuit to reveal shorts and a sports bra, for instance, without the liquid cooling and ventilation garment that astronauts wear on spacewalks. That garment covers the whole body and "contains a labyrinth of internal tubes that connect to external hoses, which in turn connect to the life-support system on the back of the spacesuit. Water is continuously pumped through the tubes to remove excess body heat," e-mailed **Wiley Knight**. On the *Science News* website, **KBerg95** pointed out that the Hubble Space Telescope and the International Space Station are much too far apart for astronauts to travel by jet pack from one to the other. "As they say in Maine, "Ya can't get theah from heah," he writes. The story also referred to a real-life 1997 accident on the Russian space station Mir, noting that an "oxygen canister" ignited. That description attracted notice from online readers who pointed out that oxygen itself is not flammable. That's correct; we were using a shorthand to describe the device, which uses chemical reactions to generate oxygen gas. In the Mir device, contaminants in the canisters created the fire hazard.

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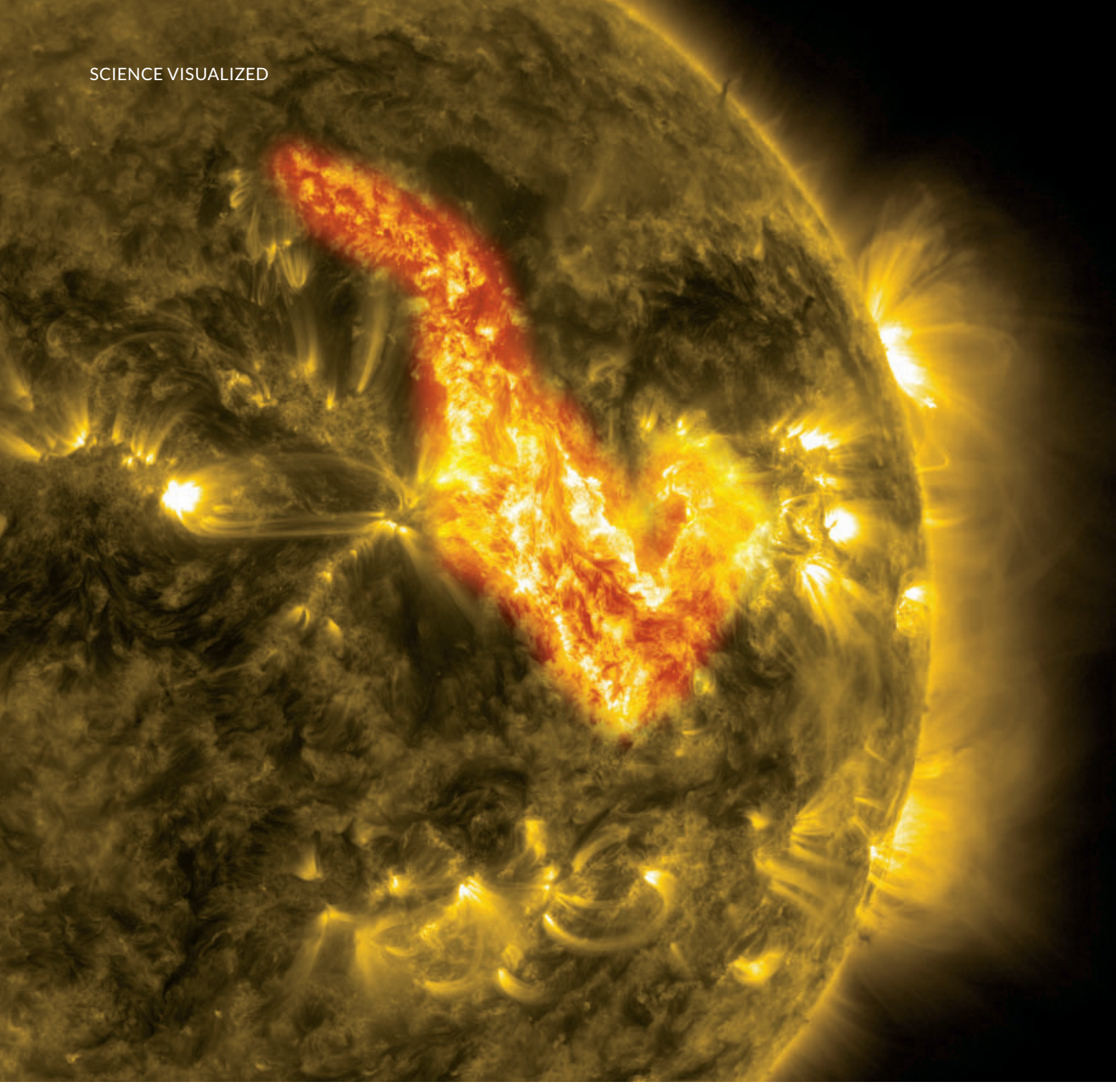

Solar explosion forms 'Canyon of Fire'

Just when the sun was looking especially lethargic, a violent eruption left behind a vast chasm of superheated gas on the solar surface. On September 29–30, a searing filament of charged particles blasted away from the sun at more than 3 million kilometers per hour. The event left behind a scar (shown above in red-orange) that marks where the filament escaped into space. NASA's Solar Dynamics Observatory captured this image by combining two different wavelength views. Yellow highlights plasma moving along the sun's magnetic fields, and red-orange helps highlight the sun's plasma at 50,000° Celsius.

The prominent pockmark caught astronomers' attention because, for the most part, the sun has been unexpectedly quiet in the peak year of its 11-year solar cycle. In fact, the sun is on track to have its quietest peak year since the early 1900s (*SN: 11/2/13, p. 22*). Still, what NASA has dubbed the Canyon of Fire is a sobering reminder that the sun is a tempestuous and unpredictable place. —*Andrew Grant*

SOLAR DYNAMICS OBSERVATORY/NASA

See video of the explosion at **bit.ly/SNsunfire**

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Unfortunately, the window on this exciting emerald opportunity is closing fast. Not long after Stauer acquired their cache, a recent auction saw Zambian emerald prices hit a new record high. The time to act on this great gem value is now, before it's too late. Please call our U.S.-based client service team at 1-888-277-8375 or visit us online at www.stauer.com.

Emerald Is THE Gem of 2014

The rise of emeralds is more than just a passing trend. An article in the *Financial Times of London* from June of this year pointed to the reason. In "Emeralds: Shades of Green Start to Outshine Diamonds," the newspaper reported that emerald demand is soaring worldwide even as diamond demand softens. Rarity is key as fine emeralds are much rarer than most diamonds.

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