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Matt Crenson Janet Raloff Lila Guterman Lynn Addison Erika Engelhaupt Kate Travis Bruce Bower Nathan Seppa Rachel Ehrenberg Erin Wayman Susan Milius Tina Hesman Saey Laura Sanders Andrew Grant Meghan Rosen Allison Bohac Puneet Kollipara Laura Beil, Susan Gaidos,

Alexandra Witze

DESIGN

DESIGN DIRECTOR Beth Rakouskas ASSISTANT ART DIRECTORS Marcy Atarod, Stephen Egts, Erin Otwell

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FROM THE EDITOR

Seeing cells as they are —alive and dynamic



Think of a cell. If you are like me, the first image that comes to mind is a static, two-dimensional drawing from your college biology textbook. Or perhaps a leaf cell seen through a low-powered light microscope: a flat, blank space surrounding a dark nucleus. Like the serene monk's cells they were originally named after, these cells are strangely quiet,

almost lifeless, their various organelles inked into place like heavy furniture that cannot be shifted. But real cells are not flat, fixed in place or serene. Biologists' studies of cells reveal these compartments to be vibrant, dynamic — even hectic — dens of activity with lots of moving parts.

The disconnect stems from the difficulty of imaging living cells and the small structures found within. Most cells emit no light; their organelles are tiny and their proteins and other biomolecules smaller still. Seeing cells under a microscope often involves flattening them and flooding them with light, usually killing them in the process. Engineering cells to precisely produce fluorescent proteins has enabled much better views of cellular structures and molecules, but these images also have tended to look fuzzy at the nanometer scale.

But in the last decade, advances in imaging and the use of fluorescent compounds have produced unparalleled — and beautiful — super-resolution views of cells. Rachel Ehrenberg's photo essay on Page 20 features a small sampling of these.

"We are entering a Hubble era of imaging," physicist Eric Betzig told Ehrenberg during a visit to his lab at Howard Hughes Medical Institute's Janelia Farm in Ashburn, Va. "We're doing for microscopy what Hubble did for space." With Janelia Farm colleague Harald Hess, Betzig invented PALM, a microscopy technique that can produce 3-D images of cells on a nanometer scale. The two former Bell Lab physicists, then unemployed, came up with the prototype for PALM in the living room of Hess' San Diego condo.

This and other new views to a cell are expected to lead to a raft of insights. New tools will allow biologists to move away from the study of cells under cover slips and toward the study of cells in organisms. "A huge unanswered question is how much we can learn from fixed cells," Betzig says. "It's like roadkill. That raccoon that's been sitting out there for a few weeks is not a raccoon."

One day soon, those stale textbook diagrams may be replaced with 3-D video. – *Eva Emerson, Editor in Chief*

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How Bizarre | ETERNAL FLAMES

A natural gas seep has been fueling a flame under a waterfall near Buffalo, N.Y., for centuries or millennia. The fire (left) can go out, but is periodically reignited either naturally or by people. Scientists don't know when the blaze will extinguish for good, but they've pinpointed the gas' source to shale rock 400 meters deep. Shale is normally impermeable, so companies artificially fracture, or "frack," the rock to extract gas. In this case, tectonic activity probably cracked the shale and allowed gas to vent, researchers report in the May *Marine and Petroleum Geology*. That means some shale gas deposits in tectonically active places may not require much fracking, which critics say can contaminate groundwater. — *Erin Wayman*

Say What?

MYRMECOCHORY \Mur-mee-koh-KOH-ree\ n. Seed dispersal by ants. Enticed by a fleshy attachment on certain seeds, scavenging ants carry them back to the colony. After feeding the nutrient-rich attachments to their larvae, the ants often discard the actual seeds, which have better odds of



germinating in or near the ant nest than they do farther away. There, seeds enjoy less competition with other seedlings and protection from predators and fire. Researchers in Spain now suggest that while the plants reap many rewards from this relationship, the ants may get the short end of the stick. They expend energy to carry the whole seed but can eat only a small part, gaining no nutritional advantage over other diets, the team reports May 14 in *Ecological Entomology. – Kelly Servick*

50 Years Ago

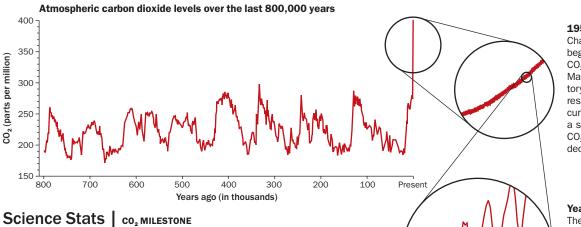
Excerpt from the June 15, 1963, issue of Science News Letter



THIRTY YEARS TO MARS

Men should land on Mars before the century's end. Some optimists say this could happen by the late 1970s but others argue that the formidable problems to be solved make any time period less than some 30-odd years unrealistic. Unless, they add, there is a now unforeseen breakthrough in launching giant loads into orbit or propelling such loads through interplanetary space. Even before man lands on Mars, however, the question of whether some form of life exists there will be answered ... next year when the National Aeronautics and Space Administration will send Mariner on a Mars fly-by.

UPDATE: 50 years later, we are still nearly 30 years to Mars. President Obama said in 2010 that astronauts could orbit the Red Planet by the mid-2030s. Mariner 4 sent photos of Mars' lifeless surface in 1965; since then dozens of manned mission plans have been scrapped. Payload capacity remains limiting.



Atmospheric carbon dioxide levels recently hit 400 parts per million at Hawaii's Mauna Loa Observatory. Ice cores show that today's concentration far exceeds any in the last 800,000 years. The last time CO_2 passed 400 ppm was probably more than 3 million years ago, when temperatures were 3 to 4 degrees Celsius warmer than today. Source: NOAA, SCRIPPS INST. OF OCEANOGRAPHY

1958-present

Charles Keeling began measuring CO_2 at Hawaii's Mauna Loa Observatory in 1958. The resulting "Keeling curve" shows a sharp rise in CO_2 over recent decades.

Yearly cycles

The Keeling curve's sawtooth pattern reflects plants in the Northern Hemisphere (which has more plants) taking up more CO₂ during summer growth.

14 Kepler contributed enormously, and now we're excited to go on to the next steps. **77** — **DAVID LATHAM**, **PAGE 10**

In the News

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STORY ONE

Human cloning advance raises personalized medicine hopes

Embryonic stem cells made with nuclear transfer method

By Meghan Rosen

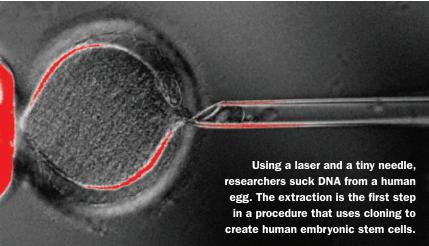
or the first time, scientists have created human embryonic stem cells by transferring the nucleus of a mature cell into an egg. The cloning technique could nudge the dream of personalized medicine closer to reality, researchers suggest May 15 in *Cell*.

"It's a huge, landmark achievement," says stem cell biologist George Daley of Children's Hospital Boston and Harvard University. Creating embryonic stem cells by nuclear transfer in humans, he says, is "the next major technological advance since Dolly."

The famous sheep was the first mammal cloned by the nuclear transfer technique, which inserts the nucleus of a cell from one adult animal into the egg of another. Since Dolly's birth in 1996, scientists around the world have tried to duplicate the technique in human cells.

If cloned human cells could be made to grow into normal embryos, the technique could supply fresh stocks of embryonic stem cells.

Unlike adult cells, which have already followed a path to become, say, heart cells or neurons, embryonic stem cells are uniquely poised to become any cell in the



body. By making these stem cells from a patient's own tissues, once-untreatable conditions might be cured by replacing damaged cells with healthy ones.

Until now, the only way to get embryonic stem cells was from leftover embryos made through in vitro fertilization. These cells are useless for personalized medicine because they are not genetically matched to a patient, but they are extremely valuable for laboratory experiments. In 2001, however, President George W. Bush set new regulations that choked off federal funding for embryonic stem cell research. Scientists could use only discarded embryos created for reproductive purposes, and all embryos discarded after 9 p.m. August 9, 2001, were off limits. The rules sent researchers racing to find alternative ways to make embryonic stem cells.

In 2007, one new technique to create the cells dazzled scientists in the field. By dosing human cells with a small cocktail of molecules, researchers pushed a reset button that turned adult cells back into embryonic-like ones called induced pluripotent stem cells, or iPS cells.

"For the last six or seven years, virtually all of us have ended our nuclear transfer efforts and switched over to iPS cells," Daley says.

But a team led by Shoukhrat Mitalipov of the Oregon National Primate Research Center in Beaverton kept plugging away at nuclear transfer, first using rhesus macaques, and then human cells.

Using cloning to create embryonic stem cells in humans has proven tricky, says Kathrin Plath, a stem cell biologist at UCLA. No one knew why the technique worked in some other mammals but not humans.

Researchers had to figure out the best way to ease out an egg's DNA, slip in a new nucleus and then cue the egg to divide and grow. In 2011, scientists came close, but the egg stalled out after three divisions, producing just eight cells.

A key change to the protocol was adding caffeine to the eggs before DNA transfer, says stem cell biologist James Byrne of UCLA, who was not involved in the new work. Caffeine acts like a set

TACHIBANA

OF M.

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of chemical reins, holding back the egg's development until researchers inject a new nucleus. The new protocol also features other tweaks such as examining the eggs under polarized instead of ultraviolet light, which can be more damaging to the egg.

Using the new method, researchers made embryonic stem cells from a donor egg and the nucleus of a young boy's skin cell. The new cells can grow and divide to form a mass of embryonic stem cells just like those derived from fertilized embryos, Mitalipov said in a press briefing May 14.

Since then, questions have been raised about image duplications and manipulations in the Mitalipov group's Cell paper. In the past, such discoveries have led to charges of scientific misconduct and even fraud, but so far there has been no evidence that the research is invalid and the journal stands by the paper.

When the researchers ground the cells up and compared the genetic bits with those in embryonic stem cells, they didn't see much of a difference. Virtually all of the new cells' genes were reset to their embryonic states.

What's more, Byrne says, the approach is much more efficient than traditional methods of producing embryonic stem cells. Instead of burning through thousands of eggs to make a single embryonic stem cell line, Mitalipov's group

"Most

scientists

who practice

nuclear

transfer think

it's unethical

and unsafe

to try human

reproductive

cloning."

GEORGE DALEY

succeeded with as few as two eggs.

The new cells may have advantages over iPS cells in treating some genetic flaws that lurk in mitochondria. little cellular power plants that carry their own DNA. By putting the nucleus of a patient's skin cell into a fresh egg with healthy mitochondria, scientists could conceivably make a customized therapy that erases the defects, Mitalipov said.

The work "is certainly impressive," says developmental biologist John Gurdon, who shared the 2012 Nobel Prize in physiology or medicine for pioneering the nuclear transfer technique to clone a frog.

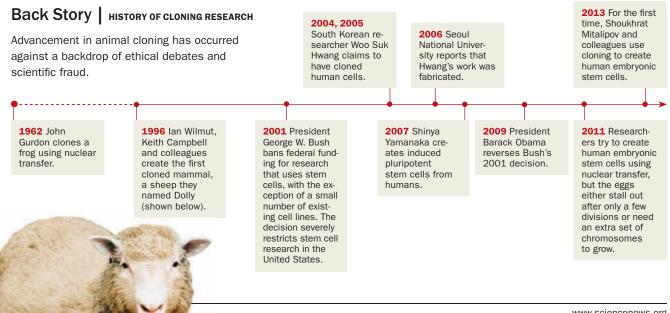
Next, Gurdon says, researchers ought to compare the new embryonic stem cells with iPS cells. A side-by-side look might provide clues to how resetting adult cells actually works. If they can figure out why Mitalipov's nuclear transfer method is so successful, researchers might be able to improve the technique to make iPS cells and avoid having to retrieve eggs from volunteer donors.

> Improving iPS cells could also help scientists skirt the ethical issues of human cloning. One of the biggest issues with nuclear transfer is the possibility that it could be misused for human fertility treatments, says Daley.

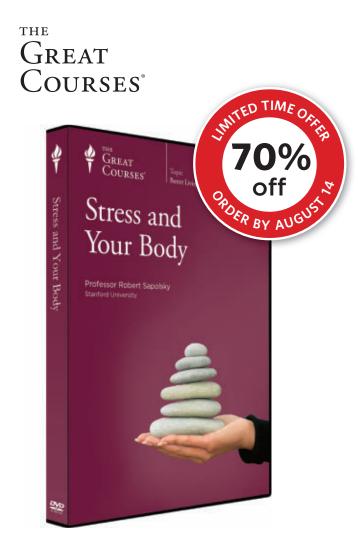
> "The animals produced by cloning are abnormal," he says. "Most scientists who practice nuclear transfer think it's unethical and unsafe to try human reproductive cloning."

But, he says, used for research, the technique could address many important scientific questions.

Embryonic stem cells made using this method also have the potential to treat spinal cord injuries and diseases such as diabetes or Parkinson's, says Dietrich Egli, a stem cell biologist at the New York Stem Cell Foundation. "I'm very confident that such cells will be used for therapies in humans in the future."



GETTY IMAGES



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Genes & Cells

"What's really surprising is just how closely related Europeans — and likely all people in the world—are." – graнам соор

Europeans are one big family

DNA finds common ancestry about 30 generations back

By Meghan Rosen

The branches of Europe's family tree converge remarkably recently in the continent's history — around the time of the Norman conquest and the Vikings' transatlantic voyages.

Virtually every person living in Europe today shares a common set of ancestors that lived about 1,000 years ago, Peter Ralph and Graham Coop of the University of California, Davis report May 7 in *PLOS Biology*.

"What's really surprising is just how closely related Europeans – and likely all people in the world – are," Coop says.

In the past, mathematical analyses have concluded that everyone on the globe shares not just a single ancestor, but a complete set of ancestors who lived about 3,000 years ago. In other words, all of the people living then who have any modern descendants are ancestors of everyone living today.

Ralph and Coop set out to test this idea in Europe using genetic data. The pair scanned a dataset containing the genomes of 2,257 Europeans, looking for shared signatures sprinkled throughout people's DNA. Because long shared chunks tend to come from recent ancestors and short chunks from ancient ones, the researchers could estimate how long ago two people shared a relative.

Then the researchers calculated how many ancestors various pairs of Europeans shared to determine how closely they were related. The researchers' genetic calculations supported the earlier theoretical work: The DNA data show that everyone living in Europe 1,000 years ago who left any descendants is an ancestor of every European living today.

Next, Ralph and Coop compared genetic details about local populations with historical information.

Eastern Europeans tended to be slightly more related to each other than to people from other regions, Ralph and Coop found. These close family ties support the historical and linguistic evidence that Eastern Europeans largely descend from Huns and Slavs who migrated from the East during the fourth through the ninth centuries.

Unlike Eastern Europeans, Italians shared fewer ancestors with each other and with other Europeans. Their lack of common ancient relatives meshes with the idea that Italy had a large and stable population that was fed by a diverse assortment of people and not overwhelmed by any single group of migrants.

The work is "a real advance," says population geneticist John Novembre of the University of Chicago. "We've never had the resolution to see these kinds of historical events before."

Because population genetic data can tease apart the details of people's ancestry, Coop says the information can help flesh out human history. Next, he'd like to analyze genetic data from people all around the world.

"We're really excited to think about doing this for larger collections of human populations," Coop says.

What the DNA evidence shows for Europeans' common ancestry is bound to be true in other groups of people too, he says. Studying larger groups can also help researchers learn about historical events across the globe over the past few thousand years, he says. (i)

How a sea anemone grows its tentacles

Making a sea anemone tentacle takes a bit of stretching, researchers report in the May 15 Development. Little is known about how the largely sedentary creatures form their multiple appendages. "What I expected to find were stem cells at the base of the tentacle," says developmental biologist Matthew Gibson of the Stowers Institute for Medical Research in Kansas City, Mo. Those cells, he figured, would then produce other cells to build the protrusions. By examining growing larvae under a microscope, Gibson and his colleagues instead found that starlet sea anemones (Nematostella vectensis) form tentacles from thick patches of cells called placodes. Rows of tall, thin cells at the edges of these disks gradually flatten and become short and squat, then pancakelike. Flattening the ring of cells causes the interior of the placode to telescope outward, forming a tentacle that the sea anemone will use to catch food. The researchers don't yet know whether other animals produce tentacles this way. - Tina Hesman Saey

Life

Fossils reveal primate history

Jaws and teeth shed light on ape-monkey split

By Bruce Bower

The oldest known fossils of an ape and a monkey have been uncovered, providing an intriguing glimpse of a crucial time in primate evolution.

The discoveries are controversial but suggest that by 25 million years ago, two major primate groups were distinct: one that today includes apes and humans and another that encompasses Old World monkeys such as baboons and macaques. Previous studies using living primates' DNA suggested that ancient apes and Old World monkeys parted from a common ancestor between 25 million and 30 million years ago.

The new fossils, from Tanzania's Rukwa Rift Basin, suggest that the evolutionary split between these primate lines must have occurred close to 30 million years ago, or perhaps even earlier, anthropologist Nancy Stevens of Ohio University in Athens and her colleagues conclude May 15 in *Nature*.

Fossil finds since the 1800s have revealed that dozens of ape species inhabited Africa, Asia and Europe between 22 million and 5.5 million years ago. Fewer fossils of Old World monkeys have been found, but a handful of monkey species are known to have inhabited Africa around 20 million years ago.

"The period from 25 million to 30 million years ago is the least-sampled interval in primate evolutionary history, with only three fossil primates known before our discoveries and five known now," Stevens says.

Her team assigns a tooth-bearing lower right jaw to a new ape genus and species, *Rukwapithecus fleaglei*. The scientists classify a second find, a jaw fragment containing a tooth, as a new monkey genus and species, *Nsungwepithecus*

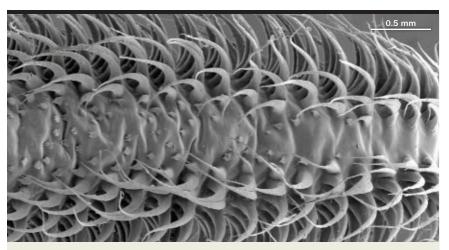
gunnelli. These animals lived 25.2 million years ago, based on age estimates of volcanic ash layers that sandwiched the Tanzanian fossils.

The new report "makes a strong case that Old World monkeys and apes had already diverged 25 million years ago," says K. Christopher Beard of the Carnegie Museum of Natural History in Pittsburgh.

But New York University anthropologist Terry Harrison disagrees. The new A tooth-bearing lower right jaw found in Tanzania may come from the oldest known ape, which lived 25 million years ago.

Rukwapithecus jaw joins a cluster of fossils from African primates that probably did not evolve into apes, he says.

The tooth-and-jaw piece attributed to a monkey may instead come from an ancient form of pig or peccary, Harrison adds. In his view, the researchers need more fossils to tell whether the animal is even a primate. (i)



Tongue bristles help bats slurp

A rush of blood to the tongue helps some bats slurp up their food. Erect bristles that spring from the tongue tip of a nectar-feeding bat, Glossophaga soricina, help the bat snag sweetness from flowers, a new study finds. As a bat stretches its tongue deep into a flower (or a manmade feeder), muscles extend out, forcing blood from the middle of the tongue down into the hairlike nubs (shown) in the tip, biomechanist Cally Harper and her colleagues at Brown University in Providence, R.I., report May 6 in the Proceedings of the National Academy of Sciences. Like water balloons that fill up when the bat feeds, those blood-inflated bristles grab lots of nectar quickly, making it easier for the mammal to snatch food on the fly. To see the bristles in action, Harper and colleagues stuck a high-speed video camera on a clear acrylic feeder filled with sugar water and rigged up fiber optics to shine bright lights on bats' tongues. When the animals lapped up the sweet water, the sides of their glistening pink tongues turned bright red and blood-engorged bristles swelled into spikes. Like a multipronged soup ladle, the swollen spikes each pull in some nectar, Harper says. The findings suggest that the honey possum, a mammal with a brush-shaped tongue tip, might also use the inflate-a-bristle technique to gather its treats. — Meghan Rosen

Atom & Cosmos

Kepler honored, not mourned

Even without telescope, scientists will hunt planets

By Andrew Grant

When scientists at the Harvard-Smithsonian Center for Astrophysics scheduled a conference called "Exoplanets in the Post-Kepler Era" for May 2013, they figured that era would still be several years off when the meeting happened. But after May's malfunction of a crucial piece of equipment on NASA's planet-hunting Kepler space telescope, the gathering of more than 100 astronomers in Cambridge, Mass., proved all too timely.

As astronomers presented new planetary measurements and observation techniques, Kepler engineers in California were strategizing about how to remotely repair one of two broken reaction wheels that precisely point the telescope. They planned to beam commands up to the \$600-million telescope, but admit that a fix is a long shot.

Kepler is shut down and probably out of service for good (*SN Online: 5/15/13*). But its discoveries have revolutionized scientists' understanding of planets beyond the solar system and are steering the course of existing and future missions. Though astronomers would have liked to have gotten a few more years out of the instrument, it already has planet hunters more confident than ever that they will detect an Earthlike world with the ingredients and conditions for life.

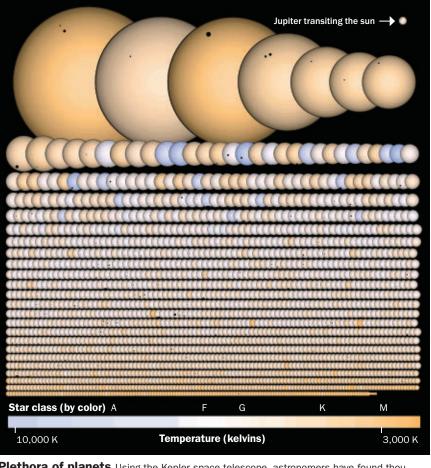
"This is still an upbeat, exciting field," says David Latham, a Harvard-Smithsonian astronomer and member of the Kepler team. "Kepler contributed enormously, and now we're excited to go on to the next steps."

Kepler has become so synonymous with exoplanets that it can be hard to remember the state of the science before

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Plethora of planets Using the Kepler space telescope, astronomers have found thousands of planet candidates outside the solar system. The illustration shows the silhouetted planets against their stars, each to scale.

the telescope launched. When a Delta II rocket carried Kepler into space on March 6, 2009, astronomers knew that the galaxy contained at least 350 exoplanets, nearly all of them the size of Jupiter or larger.

After four years detecting the shadows of stars' orbiting worlds, Kepler has added nearly 3,000 planets to that census. And because of Kepler, astronomers are convinced that the Milky Way contains hundreds of billions of planets, roughly one for every star, with at least 17 billion of them Earth-sized.

Those numbers boosted the case for funding NASA's next exoplanet-hunting mission, the Transiting Exoplanet Survey Satellite, which is scheduled for a 2017 launch. Whereas Kepler has fixed its gaze on distant stars, TESS will focus on nearby stars so that powerful instruments like the upcoming James Webb Space Telescope will be able to probe the atmospheres of planets that TESS discovers. Kepler's planet haul has TESS scientists optimistic that their modest \$200-million telescope, while less sensitive than Kepler, will nonetheless uncover plenty of planets in our neighborhood, including a handful of Earth-sized worlds.

Kepler has also exposed an intriguing new class of potentially habitable planets larger than the Earth-sized realms astronomers have traditionally targeted. Kepler's database includes nearly 700 worlds that are between 25 and 100 percent larger in diameter than Earth. Some orbit stars far cooler than the sun but sit close enough to have liquid water on their surfaces. These worlds are not Earthlike, and there is no planet comparable to them in our solar system, but that doesn't mean that they are inhospitable to life.

A key to understanding these super-Earths, as well as other planets seemingly ripe for life, is to determine their composition. Astronomers hope to pair size measurements of planets observed by telescopes such as TESS with mass readings from ground-based scopes that look for subtle wobbles in stars' motion caused by planets' gravitational pull.

Several years ago this technique, known as radial velocity, could pick out only hulking planets that delivered a hard yank to their stars. But lately the technology has improved so drastically that in October 2012, the High Accuracy Radial Velocity Planet Searcher instrument, which is affixed to a 3.6-meter telescope in Chile, spotted what appears to be a planet only slightly heavier than Earth tightly orbiting Alpha Centauri B, a sunlike star a mere 4.4 light-years away (*SN*: *11/3/12*, *p*. *5*).

Other radial velocity instruments are popping up at observatories throughout the United States, Europe and South America. By 2016, the European Southern Observatory plans to install one with unprecedented precision, called ESPRESSO, which will be able to pick out tiny stellar quivers caused by Earthmass planets around nearby stars.

ESPRESSO will be able to pull off that feat only if there is a healthy population of such planets. Kepler's main goal was to determine the frequency of Earthlike planets in the galaxy, but achieving that is in jeopardy due to the telescope's mechanical failure. "Right now we have enough data to make an intelligent extrapolation about what that number is, but that is not the same as actually determining that number," says Alan Boss, an astronomer and Kepler team member at the Carnegie Institution for Science in Washington, D.C.

Other astronomers share his frustration, but they are still optimistic. They have a year of data from the telescope left to analyze, which should yield some exciting finds, quite possibly including an Earth-sized planet orbiting a sunlike star at a distance suitable for life. "We can't feel sad, because we have a beautiful dataset that we're going to work on for years," Latham says.

Combine those data with upcoming missions, plus 16 bottles of wine uncorked after the meeting presentations, and Latham says astronomers at the post-Kepler conference were upbeat about the future.

"In a way," he says, "everyone was toasting Kepler." ■



Mind & Brain

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Memory training questioned

Brain workout may not improve intelligence or multitasking

By Bruce Bower

Provocative evidence that certain memory exercises make people smarter has sparked the rise of commercial braintraining programs such as Lumosity. But at least one type of brain training may not work as advertised, a study finds.

Practicing did improve volunteers' performance on tests of memory and the ability to locate items in busy scenes, say psychologist Thomas Redick of Indiana University Purdue University Columbus and his colleagues. That improvement did not, however, generate higher scores on tests of intelligence and multitasking, the researchers report in the May Journal of Experimental Psychology: General.

Redick's investigation is part of a growing scientific debate about brain training's claimed wide-ranging effects. The dispute feeds into a long-standing scientific controversy about whether enriched environments can increase intelligence as measured on IQ tests.

What's not up for debate is that many people feel smarter after brain training.

In the new study, 10 of 23 individuals who completed memory sessions said that the program helped them to think, multitask and focus better in daily life. But the sci-

entists say that even if some participants performed daily tasks better after memory training, they may simply have tried harder or felt better about their efforts.

Redick's team studied 73 adults, split into three groups. One group completed 20 training sessions over about six weeks on a task aimed at boosting working memory, the ability to keep in mind and compare several pieces of information.

In this task, volunteers watch blocks pop up at various spots on a computer screen. With each block presentation, volunteers hear a spoken consonant. Participants are instructed to press a computer key if a block's location and the accompanying consonant match the

The dispute feeds into a long-standing scientific controversy about whether enriched environments can increase intelligence as measured on IQ tests.

pair encountered before. If an individual performs well, the task becomes harder, requiring the identification of matching pairs shown two to four instances earlier. Psychologist Susanne Jaeggi of the University of Maryland in College Park reported in 2008 that this form of working memory training upped volunteers'

reasoning and problemsolving skills.

A second group in the new study received training aimed at improving the ability to pick out novel shapes from large arrays of similarlooking shapes. A third group received no training.

In the two training groups, volunteers showed no increases on tests of intelligence and of the total amount of information that could be held in working memory.

Participants in the new study didn't receive enough instruction and practice to benefit from the training, Jaeggi says.

But until larger studies with longer follow-ups are completed, Redick cautions against assuming that memory training smartens people up. (i)

Body clock tied to depression

Brain's gene activity reflects off-kilter circadian rhythms

By Rachel Ehrenberg

The disruption of sleep and other bodily rhythms that often accompanies clinical depression may leave a mark on gene activity in the brain. The study appears May 13 in the *Proceedings of the National Academy of Sciences*.

In mammals, daily rhythms such as sleep, hormone cycles and eating patterns are guided by a master clock in the brain whose rhythms are maintained in part by genes and patterns of light and darkness. The master clock can get out of sync with clocks elsewhere in the brain and body. It's this discord that produces the out-of-sorts feeling of jet lag.

People with depression also often have off-kilter body rhythms. But the molecular and cellular mechanisms behind these disrupted cycles have been hard to pin down. Jun Li, a statistical geneticist at the University of Michigan in Ann Arbor, and his colleagues took an ambitious approach with an unusual set of samples: the brains, removed just after death, of 34 people with depression and 55 people without.

After determining how long after

sunrise each person's death took place, the team looked at which genes were turned on in six brain regions, gathering 12,000 records of gene activity. Among nondepressed people, patterns were pretty predictable. One gene's activity, for example, peaked at sunrise, another's at midday, Li says. But in the depressed brains, gene activity was less predictable and uncoupled from time of day.

The research doesn't demonstrate whether depression causes the circadian disruption or vice versa, but it confirms a link and might lead to investigations of the physiological processes that are affected, says Ying-Hui Fu, a molecular biologist and geneticist at the University of California, San Francisco. (a)

Earth

Forests once covered Arctic

Warm era had greenhouse gas levels like today's

By Erin Wayman

The Arctic wasn't always frozen. About 3.6 million years ago, the far north was blanketed in boreal forests and summers were 8 degrees Celsius warmer than today, geologists report May 9 in *Science*.

Researchers pieced together that picture from sediments buried beneath Lake El'gygytgyn, north of the Arctic Circle in northeastern Russia (*SN: 11/20/10, p. 13*). The sediments preserve the most complete history of Arctic climate on land over the last 3.6 million years.

The sediments depict the end of the Pliocene epoch, which lasted from 5.3 million to 2.6 million years ago. The Pliocene was the last time the atmospheric carbon dioxide concentration was roughly



Summer

temperature in

0

Summer

temperature

Sediments from Lake El'gygytgyn in Russia reveal that 3.6 million years ago, the Arctic's summers were 8 degrees Celsius warmer.

400 parts per million — a benchmark reached in the Arctic in spring 2012. The Pliocene may be the best analog for the future, says geologist Gifford Miller of the University of Colorado Boulder.

Previous geologic evidence had indicated the Pliocene Arctic was warm, but these terrestrial records are spotty, providing only isolated snapshots of time. To get a more comprehensive look, Julie Brigham-Grette, a geologist at the University of Massachusetts Amherst, and colleagues drilled a 318-meter-long core into the lake's bottom. From 3.6 million to 3.4 million years ago, average summer temperatures were about 15°, the team determined through analyses of the sediments' chemistry and trapped pollen. The region also received three times as much precipitation as it does today.

ppm

Atmospheric

carbon dioxide

level, both eras

From 3.26 million to 2.2 million years ago, temperatures gradually cooled in a series of steps that coincided with the beginnings of a glacial period. Forests gave way to shrubby environments, and the Arctic became more arid.

Despite the cooling, Arctic summers generally stayed 3 to 6 degrees warmer than today, until about 2.2 million years ago. Even during periods when Earth's orbit should have made the Arctic cold, warm summers persisted. "We didn't expect it to be so consistently warm," Brigham-Grette says.

These findings hint that the switch to a glacial period may be complicated. Comparisons with other climate records from the oceans and the tropics may help researchers identify the mechanisms that drove the Earth's transition from warm to cool, Brigham-Grette says.



The Arctic's stockpile of carbon may be more secure than scientists previously thought. In a 20-year experiment that warmed patches of chilly ground, tundra soil kept its stored carbon, researchers report.

Almost half of the world's soil carbon is stored at high latitude, in the form of dead and decaying organisms. Some scientists worry that rising temperatures could accelerate decomposition, which unleashes carbon dioxide.

In 1989, ecologists set up greenhouses (seen here in fall) on plots of tundra in northern Alaska. Air temperature inside was on average 2 degrees Celsius warmer than outside. Over two decades, the team found, mosses and lichens gave way to woody shrubs. Decomposition slowed in surface soil, while it sped up deeper underground. Warmer soils may have allowed roots and plant litter to penetrate farther into the ground, increasing both the deep soil's carbon stocks and its rates of decomposition, the researchers suggest. Overall, though, there was no difference in total soil carbon in the greenhouse plots compared with plots that had no greenhouses.

Seeta Sistla of the University of California, Santa Barbara and colleagues report May 15 in *Nature* that they don't know whether the study's results can be extrapolated over longer periods of time. — *Erin Wayman*

Matter & Energy

Atom's core gets pear-shaped

Tapering asymmetry of some nuclei confirms predictions

By Andrew Grant

Atomic nuclei come in many shapes and sizes, and scientists have now obtained precise measurements of an elusive form: pear-shaped. Studying these exotic nuclei, described in the May 9 *Nature*, could allow physicists to better understand subatomic structure and to find new particles and forces.

Diagrams in middle school textbooks depict atomic nuclei as spherical, but reality is more complex. Protons and neutrons are jam-packed into a space just 10⁻¹⁵ meters wide. The subatomic particles constantly move, shifting around and sometimes warping the nucleus into the shape of a football or even a flattened disk — shapes that are symmetrical vertically and horizontally.

Physicists want to find asymmetrical nuclei because some theories predict that such deformed nuclei could exhibit strange properties.

For the new study, physicist Peter Butler of the University of Liverpool in England and an international team probed two potentially pear-shaped nuclei: radon-220, which is made up of 86 protons and 134 neutrons, and radium-224, with 88 protons and 136 neutrons. Scientists can determine the shapes of nuclei by measuring the pattern of radiation they emit.

At the On-Line Isotope Mass Separator facility at CERN outside Geneva, Butler's team fired protons at a thick slab of uranium carbide. The highenergy protons shattered the atoms in the block, producing a cornucopia of exotic atoms that included radon-220 and radium-224.

The physicists collected the isotopes they wanted and stripped away the atoms' electrons, leaving behind nuclei. Then magnets accelerated the nuclei toward a thin layer of metal foil. The nuclei interacted with atoms in the foil as they passed through, resulting in the emission of a measurable stream of gamma radiation.

The radiation showed that both radon-220 and radium-224 nuclei have an asymmetric pear shape. The radium appears to maintain a rigid pear shape, while the radon is shiftier: Its mass Precise measurements of atomic nuclei showed that the radium-224 nucleus

showed that the radium-224 nucleus (graphical representation at right) is rigid and shaped like a pear. Radon-220 (left) wobbles from side to side.

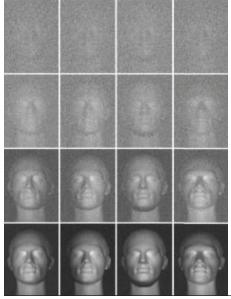
continuously jiggles around so that the fat and narrow ends trade places.

"It oscillates like a ball of jelly," says Matt Dietrich, a physicist at Argonne National Laboratory in Illinois.

Dietrich is impressed that Butler's team achieved such precise measurements of the nuclei's dimensions. In his own work, Dietrich searches for a phenomenon called an electric dipole moment, in which the center of positive charge of an atom lies at a different point than its center of negative charge.

In every atom ever measured, no such dipole moment exists. Dietrich believes that an asymmetrical nucleus would be a good place to find a dipole moment.

The standard model of particle physics predicts that atoms should have virtually nonexistent electric dipole moments, so finding one could mean that an undiscovered particle or force is at work.



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3-D imaging, pixel by pixel

A network of four single-pixel sensors has done what a 20-million-pixel digital camera cannot: create a three-dimensional image. Producing a 3-D image is normally not easy. Filming a 3-D movie, for example, requires two expensive cameras plus complex software that stitches together the cameras' 2-D images. Physicist Baoqing Sun of the University of Glasgow in Scotland and colleagues accomplished the feat with cheap parts and equipment available in many class-rooms. They used a projector to illuminate a mannequin head with a sequence of speckled light patterns. Four single-pixel detectors positioned around the projector tallied the amount of reflected light they collected for each pattern. After collect-ing light readings for thousands of patterns over several minutes, Sun's team was able to construct four vivid, black-and-white 2-D images of the head (shown), one from each detector. A simple algorithm then combined the readings from the four detectors into a 3-D reconstruction of the head, Sun and his team report in the May 17 *Science*. The researchers hope to adapt their system to pick up other kinds of radiation, such as X-rays or infrared. —*Andrew Grant*

Health & Illness

Black women get MS more

Study counters belief that whites have highest rates

By Nathan Seppa

Multiple sclerosis, long considered a disease of white females, has affected more black women in recent years, a new study finds. The results bolster a theory that vitamin D deficiency, which is common in people with dark skin in northern latitudes, contributes to MS.

The debilitating condition, in which the protective coatings on nerves in the central nervous system get damaged, results in a loss of motor control, muscle weakness, vision complications and other problems. The National Multiple Sclerosis Society estimates that

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2.1 million people worldwide have MS.

The researchers scanned medical information from 3.5 million people who were members of the health maintenance organization Kaiser Permanente Southern California and found that 496 of them received diagnoses of MS from 2008 through 2010. Of these patients, women comprised 70 percent, not an unusual fraction for people with MS.

Surprisingly, the researchers report May 7 in Neurology, the patients included 84 black women. That means the annual incidence of MS in black women was 10.2 cases per 100,000 people. That's not a great risk for an individual, but it was higher than the annual rates for white, Hispanic and Asian women, which were 6.9, 2.9 and 1.4 per 100,000 people, respectively.

Among blacks, women had three times the incidence of men: in the other racial and ethnic groups the MS rate in women was roughly double that of men.

"This is a good study, an important study," says George Ebers, a neurologist at the University of Oxford in England. Ebers says other work suggests that MS is on the rise.

The cause of MS is unknown, but it is widely thought to be a combination of genetic predisposition and environmental factors. Women's higher MS frequency might be related to hormones, because the disease rarely strikes females before puberty or after menopause, says study coauthor Annette Langer-Gould, a Kaiser neurologist.

The relative rise in blacks diagnosed with MS raises the specter of vitamin D deficiency. MS could be linked to a lack of sunlight exposure. It's well established that many dark-skinned people in North America and northern Europe don't maintain adequate vitamin D levels in winter (*SN: 7/16/11, p. 22*). 📵

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C. Kenneth Dodd Jr.



Life Support

Studies reveal the placenta's crucial role in healthy pregnancies By Tina Hesman Saey

hantelle, 20 years old and 29 weeks into her third pregnancy, was sitting in John Kingdom's office at Toronto's Mount Sinai Hospital waiting for a prescription. Her blood pressure was high. Her developing baby, a girl, weighed about 500 grams but at this point should have weighed closer to 1,300 grams.

Chantelle's two previous pregnancies had failed for reasons she couldn't fathom, but this time she knew exactly what was wrong. Her baby's placenta was thick, bulky and riddled with holes. "They compare it to Swiss cheese," she said. Blood and nutrients weren't flowing properly, restricting the fetus's growth. And now the pregnancy was taking a toll on Chantelle as well.

"I know already I'm not going to go full term," she said. "My placenta just doesn't deliver all the nutrients she needs."

The baby was born one week later. Chantelle hoped the infant would fare better outside of the womb, and she did—at seven weeks old she was still tiny but rapidly gaining weight. Chantelle also wanted to know why she'd had to go through this again and again. "I don't know if there's any real answer," she said. "That's just the placenta you get and there's nothing you can do about it."

In the future, that might no longer be true. Chantelle's placenta from this pregnancy was collected and stored in a placenta bank in a gleaming glass building across the street from the hospital, to be examined by researchers.

Kingdom and his medical partner, Rory Windrim, started their Placenta Clinic at Mount Sinai in 1999 to care for women who have had late miscarriages, stillbirths, preeclampsia, intrauterine growth restriction and a host of other placenta problems in earlier pregnancies. Now the team has expanded placental care on a research basis to first-time moms, one of the groups at considerable risk for trouble. The researchers hope to screen and track 5,000 first-time mothers (they've already tracked nearly 1,000) to determine whether problems with the placenta can be detected early enough in pregnancy to head off serious complications later.

The pancake-shaped piece of tissue that nourishes a baby in the womb doesn't get the respect it deserves, says Peter Parham, a geneticist and immunologist at Stanford University: "Most of us are used to thinking of the placenta as the afterbirth, this nasty, messy stuff that comes out after the baby. In reality, it's an organ that is every bit as sophisticated as a liver or a heart."

Even so, few researchers have studied the organ, says Susan Fisher, a reproductive biologist at the University of California, San Francisco. Twenty years ago, when she began studying preeclampsia, a complication of pregnancy in which the mother develops high blood pressure and protein in the urine, she couldn't find diagrams in medical texts of how placental cells interact with the uterus. "I was just blown away; these massive tomes of histology and no description of this," she says.

Now a handful of researchers are focusing on this previously overlooked organ, revealing new clues to its role in a variety of pregnancy complications. They are also learning about the intricate biology that, when all goes well, allows it to skillfully mediate between mother and fetus.

The invasion

The placenta isn't mom's property. It is composed mostly of tissue made by the baby beginning four or five days after fertilization. The embryo consists at that time of about 100 cells known as a blastocyst, a hollow ball with a lump of cells clinging to the inside. The cells in the lump grow into the fetus. The blastocyst's outer layer of cells, called the trophoblast, gives rise to the placenta.

The trophoblast forges an aggressively intimate connection with the mother from the start, invading the lining of the uterus and rerouting the mother's blood supply. As the placenta grows, it forms projections called chorionic villi that bathe in maternal blood. Some branches lodge their tips in the uterine wall to anchor the placenta. The umbilical cord plugs into the placenta's center and carries blood to the fetus. By the time the organ is fully grown, the interface between it and the uterus encompasses 12 square meters or more; if all of its branched blood vessels were stretched

flat the placenta would cover three ping-pong tables.

How the placenta maintains a human pregnancy for so long is still one of the fundamental mysteries of biology, Fisher says. By all rights, the mother's immune system should attack the fetus right off the bat because it carries foreign genes; half a baby's genetic makeup comes from the father. "If it were the father's kidney, it would be instant rejection," she says.

But the placenta starts negotiations right away with the mother's immune system by excreting diplomatic packages in the form of tiny membranous spheres called exosomes. Placental cells pack their exosomes

with proteins, information-carrying molecules called microRNAs and other substances that can either shift the mother's immune system toward or away from an inflammatory reaction that might damage the placenta. Nearly every cell in the body uses such packages to communicate, but in pregnancy the propaganda machine is cranked to new heights. "This is the beauty of human reproduction," says Ian Sargent, a reproductive immunologist at the University of Oxford in England. "It's hijacked the immune system and used it for its own purposes."

Researchers are beginning to learn more about how the placenta tweaks the immune response during pregnancy. Fisher and her colleagues have been studying certain immune cells called natural killer cells in the uterine lining. Immunologists often name cells after the proteins that stud their surfaces, but not in this case. "It's one area of immunology where we call the cells exactly what they are; natural killers of foreign cells," says Fisher.

Natural killer cells lurk everywhere in the body, ever vigilant, targeting invaders be they bacteria, viruses or rogue human cells. The assassins can tell the body's own cells from outsiders by asking for ID

percent

Risk of preeclampsia

in first pregnancy

Risk of preeclampsia

in second pregnancy

after experiencing it in first pregnancy

percent

Risk of preeclampsia

in third pregnancy

after experiencing it in

first two pregnancies

SOURCE: S. HERNÁNDEZ-DÍAZ

ET AL/BMJ 2009

in the form of major histocompatibility complex, or MHC, proteins. Every person has his or her own combination of six different MHC proteins. Killer cells pounce on cells that display the wrong combination of MHC proteins (or no MHCs). But that doesn't happen in the uterus, even though, thanks to dad, the implanting embryo is almost certain to carry an MHC combo that is different from mom's.

Researchers originally thought that the natural killers in the uterus had gone a bit soft and lost the ability to kill invading placental cells. But natural killers in the uterus are every bit as lethal as their brethren elsewhere

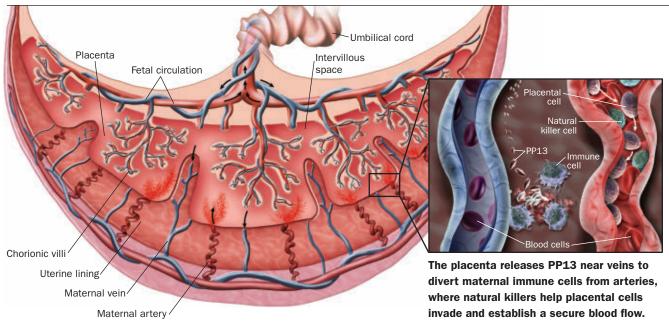
in the body, Fisher's team reports April 3 in *Biology of Reproduction*.

Fisher and colleagues discovered that other maternal immune cells called macrophages secrete a protein called TGF-beta 1 that restrains the natural killers in the uterine lining. Fisher doesn't yet know what motivates the macrophages to produce the chemical, but she thinks the interaction could be important in cementing a foothold for the placenta early in pregnancy.

Right now, there's no way to tell whether a misstep in that preliminary process occurs. But when it does, it can cause big problems later in pregnancy—as Ilanit Genkin found out.

Genkin was 25, healthy and pregnant for the first time. But 26 weeks into her pregnancy she started feeling sick at work and went to the hospital for an emergency ultrasound. Her doctors told her that the fetus was small, but that was to be expected for a diminutive mother

FEATURE | LIFE SUPPORT



Intimate exchange During pregnancy the placenta forges a bond with the inner lining of the uterus. Maternal blood bathes the chorionic villi within the intervillous space, delivering nutrients and oxygen, and removes nutrient-depleted blood via maternal veins. Embryonic blood is carried to the villi by umbilical arteries and, after picking up oxygen in the capillaries of the villi, returns to the fetus via the umbilical vein.

like Genkin. They sent her home to rest.

By week 29, Genkin was vomiting and had severe headaches. Her urine was as brown as leather. Her blood pressure was alarmingly high. Her daughter, now 4, was delivered by emergency Cesarean section. Even with the early delivery, it took months for Genkin to return to normal. The diagnosis was severe preeclampsia, a disorder Genkin had never heard of. "Nobody could give me an answer about what happened to me," she says.

It's impossible to know what went wrong in Genkin's case, in part because her placenta was discarded. But research suggests that in preeclampsia, the placenta fails to dig into the uterus early on, depriving the fetus of nourishment and stressing the mother's body. Genkin's problems started long before her symptoms appeared.

Tactical moves

Grabbing a good hold of the uterus is such a demanding maneuver that only a few fetal cells take on the job. Those special operatives are known as extravillous trophoblast cells; they infiltrate the uterus and open up maternal blood vessels. Success ensures that the placenta will have sufficient blood supply to sustain a full-term pregnancy. Failure can lead to numerous complications.

To get the invading cells past the mother's immune defenses, the placenta stages an early diversion says Harvey Kliman, a physician and scientist at Yale University. Kliman made the discovery while examining healthy placentas ranging in age from six to 18 weeks of gestation. In some parts of the attached maternal uterine lining, he found "total destruction, areas of complete napalm war."

Those zones of destruction crawl with inflammation-producing immune cells and are littered with dead cells and crystals of placental protein 13, which helps regulate the activity of immune cells. Kliman discovered that these areas of wanton cell death occur near uterine veins, away from the sites where placental cells invade maternal blood vessels. The PP13 attacks peak at about seven to eight weeks of gestation. At the same time, the maternal arteries in the uterus undergo remodeling. He deduced that the placenta sets off PP13 explosions to draw immune attention away from mom's spiral arteries, allowing placental cells to sneak in.

Even with the diversion, placental

cells need help to enter arteries. Invading cells send out a protein, called adrenomedullin, to trick natural killer cells in the uterus into helping placental cells infiltrate the maternal arteries, Kathleen Caron, a cardiovascular physiologist at the University of North Carolina in Chapel Hill and colleagues report May 1 in the *Journal of Clinical Investigation*. Baby mouse placentas that don't produce adrenomedullin look pockmarked, very much like those from human babies of preeclamptic mothers, Caron's group discovered.

Levels of adrenomedullin in a human mother's blood generally climb during pregnancy. Studies have shown that women with preeclampsia don't experience that rise. Caron thinks that early monitoring of the protein could provide an important indicator for preeclampsia risk. Clinical tests already measure levels of the protein in heart attack and heart failure patients, so such tests might be adapted to give pregnant women and their doctors early warnings, she says. That could allow future therapies time to correct problems.

Back in Kingdom's lab, scientists investigate other possible signs of early trouble. Dora Baczyk, a molecular biologist on Kingdom's team, perched at a black-topped lab bench and placed a slide under the lens of a microscope. The slide contained dozens of tiny dots of tissue from placentas stored in a placenta bank. Some of the samples were taken from normal placentas. Others came from abnormal placentas from patients with preeclampsia or intrauterinegrowth restriction, the conditions that plagued Chantelle and her tiny baby.

With a microscope, even a novice can see the difference between the lush bushy vessels of a normal placenta and the sparse twigs of a growth-restricted one. Baczyk and her colleagues are hopeful that they can find molecular factors that distinguish a sick placenta from a healthy one when it counts.

One clue comes from a gene called glial cells missing 1, or *GCM1*. The gene, named for a mutation found to block the formation of glial cells in the brain, appears to play an important role in placenta development too, Haibin Wang of the Chinese Academy of Sciences in Beijing and others report April 16 in *PLOS Biology*. The team shows that *GCM1* works with a gene called *Frizzled5* in the earliest stages of placenta development to direct formation of the bushy branches of the chorionic villi.

But the gene's job is far from done once the branches form. Kingdom, Baczyk and others have found that *GCM1* helps the placenta's skin replenish itself. The *GCM1* protein ensures that stem cells divide to make more stem cells and also make mature cells that can replace damaged ones in the placental skin. When *GCM1* doesn't work properly, the surface of the placenta becomes raggedy — either because only stem cells are made, leaving no mature skin cells to replace damaged ones, or because the stem cell supply dries up.

Recently Baczyk, Kingdom and their colleagues discovered that *GCM1*'s activity is controlled by a protein called DREAM. And DREAM is governed by how much calcium is available in cells, the team reported January 3 in *PLOS ONE*. That could help explain why women in developing countries who take calcium supplements have a lower risk of preeclampsia, Kingdom says. But he cautions that this doesn't mean cal-

cium supplements are right for everyone; too much of that good thing can also be bad for the placenta.

Marching on

If early efforts to establish the placenta fail, problems can compound later. In women like Genkin, debris shed by a damaged or dying placenta may send exactly the wrong message to the mother's immune system. Decrepit placental cells, Sargent and colleagues reported February 20 in PLOS ONE, scatter large spheres that act like distress beacons

jettisoned from dying cells. Sargent has some evidence that this debris may actually provoke the mother's immune system to attack the placenta.

Notably, while a vigilant immune reaction may increase the threat to a healthy pregnancy, it also might provide some benefits to the mother. Recent research by Parham and Ashley Moffett of the University of Cambridge reveals that some of the same genetic variants associated with a higher risk of preeclampsia may make it easier for the mother to fight off viral infections such as hepatitis C or Ebola. The researchers make their case for a balance between virus combat and healthy babies in

> the February Nature Reviews Immunology.

In the end, even a wayward immune system can learn to get along with a fetal interloper. Many women who have miscarriages or other pregnancy complications the first time go on to have healthy placentas the next. Perhaps that's because the mother's immune system, after acting up once, learns to tolerate cells with part of the father's MHC profile. By late May, Ilanit Genkin was 38 weeks along with her second daughter. Her blood pressure was nor-

mal with no sign of preeclampsia. Her previous experience gave her a healthy respect for the placenta, she says. "It's this weird thing growing inside of you, but the placenta, it's wonderful."

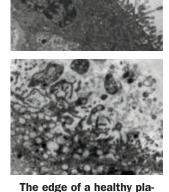
Kingdom agrees. It is also the future of maternal-fetal medicine, he says: "In the 19th century we saved moms. In the last 30 years we saved babies. Placentology is 21st century obstetrics." ■

Explore more

 Placenta clinic: www.mountsinai. on.ca/care/placenta-clinic

Signs in the folds

New research suggests that examining the postbirth placenta could yield clues about a child's risk for developing autism. Placentas with multiple abnormal folds signal higher risk for autism than those that are crease-free, Harvey Kliman of Yale University and colleagues report April 26 in *Biological Psychiatry*. Kliman studied placentas from 117 babies in his search for early indicators of autism. "The structure of the placenta is a microcosm of cellular and developmental biology," Kliman says. The placental defect he discovered may indicate that some of a baby's other tissues also didn't fold properly, a problem for the intricately crinkled brain. Doctors may one day dissect placentas for clues about other developmental problems a child might face. —*Tina Hesman Saey*



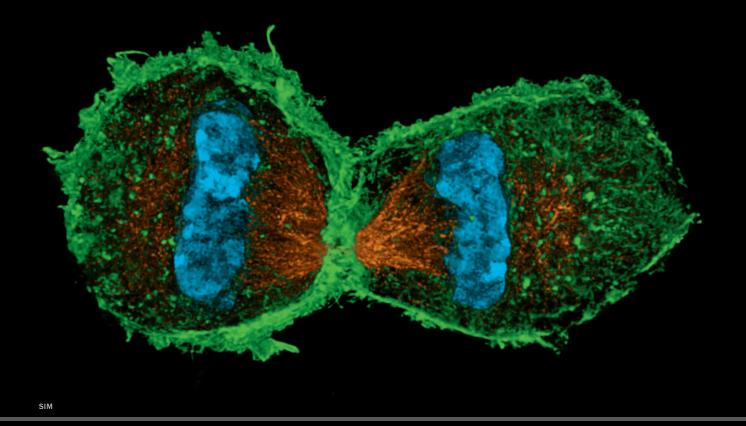
centa (top) is dense with

blood vessels. In preeclamp-

sia, the placenta withers and

sheds dead cells, which may

trigger an immune attack.



MAKING TWINS

Mitosis, the cellular division that produces two genetically identical daughter cells, is perhaps the most fundamental process in biology. Without it, multicellular life wouldn't exist, a broken bone would never heal, tissues would disintegrate. Cancer—essentially mitosis gone rogue—also wouldn't exist. Scientists have been watching mitosis through a microscope for about 150 years, but new views are fleshing out the less-detailed pictures of the past (inset, opposite page). After DNA replicates, the nuclear envelope surrounding it dissolves. Spindle fibers (gold above, red at right) align pairs of chromosomes (blue) and then separate the genetic material into two daughter cells (shown forming, above).



New optics shatter the diffraction barrier, illuminating life within us

By Rachel Ehrenberg

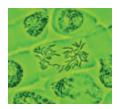
magine if your best knowledge of human anatomy came from viewing the body through binoculars from a mile away. You might make out the shape of a hand, but knuckles and fingernails would elude you. Experiments could tell you there's a pumping heart inside, but to see that heart with any clarity you would have to fix it in formaldehyde or liquid nitrogen, blast it with electrons and add dyes to impart contrast. For a long time, that's what it's been like for biologists trying to observe cells.

English scientist Robert Hooke coined the term *cell* in 1665 after examining a slice of cork through a light microscope. The plant parts he saw reminded him of the cells of a monastery. In the centuries since, we've learned that our bodies comprise some 200 different cell types and a total of several trillion cells, not counting microbes, at any given moment. (As you read this sentence, about 50 million have died and been replaced.) Within a single cell there may be 10,000 different proteins; thousands of the energy factories called mitochondria; and half a billion actin molecules, which provide scaffolding to support the cell and help it move and change shape.

The structures and activities within our cells are a major force in determining the stuff we're made of, even though each of us begins with the humble fusion of just two. Following genetic instructions and taking cues from its environment, each cell realizes its fate — a fate that is inextricably linked to our own.

Until now this internal machinery has remained largely hidden from sight. Viewed through microscopes similar to Hooke's, most cells are see-through and colorless; it's hard to discern fine features. Due to diffraction, the bending of light, objects smaller than about 250 nanometers — the size of the smallest bacteria — are fuzzy when viewed through an optical microscope, if they can be seen at all. (Consider that most proteins are merely a few nanometers across.) This diffraction barrier, explicitly defined by German physicist Ernst Abbe in 1873, makes a smeared blur of much that happens in and on a cell.

That's all changed in the last few decades. Scientists have developed a suite of new optical techniques that circumvent

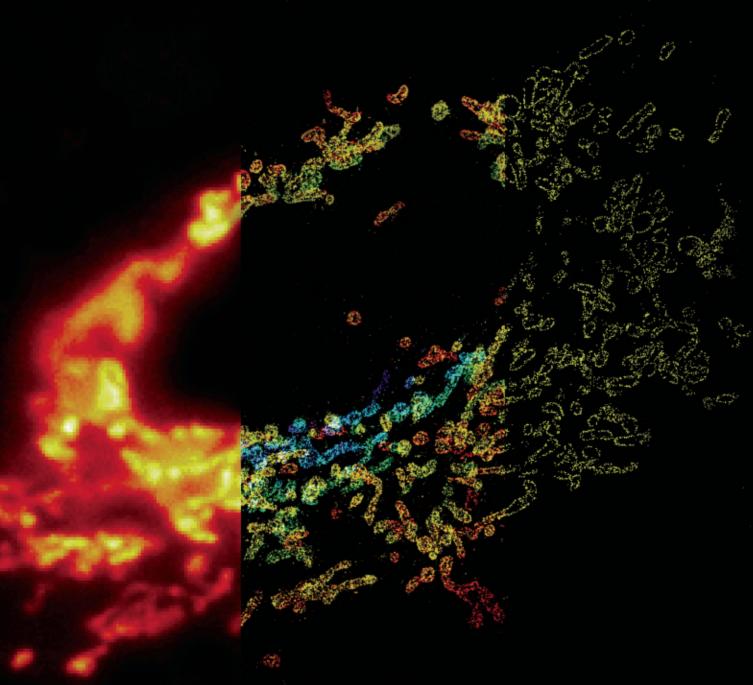


the diffraction barrier and show us a cell's full guts and glory. With new fluorescent tags that light up structures in the dense darkness inside a cell, these new optical approaches produce detailed images of what was once invisible. In the pages that follow,

some of the most striking images are highlighted, all from animal cells that scientists use to understand basic cellular processes and disease.

By capturing the inner workings of a cell and interactions between cellular neighbors, scientists can now connect knowledge gleaned from genetic experiments to actual structures and activities they can see. Discoveries will lead to new hypotheses and experiments that will further our understanding of animal development and function — and how both can go awry.

Some of these super-resolution techniques are still so new and challenging that many scientists think the major breakthroughs they will yield are yet to come. But for now, we can all enjoy stunning, unprecedented views of the cellular world.

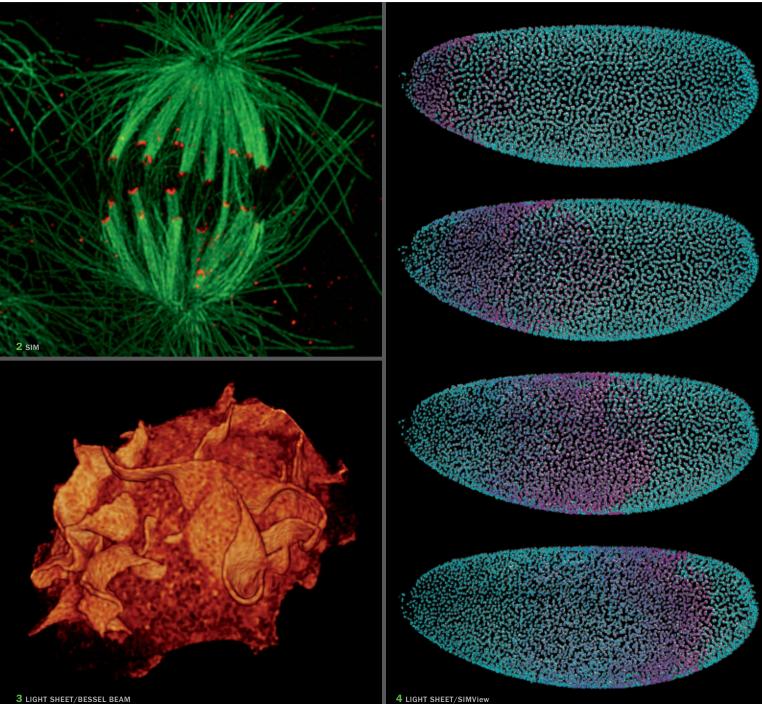


1 CONVENTIONAL/DSTORM/STORM

1. POWERHOUSES Scientists are expanding their view of mitochondria, long known for their energy-producing role and quintessential kidney bean shape. It turns out that mitochondria are at the center of numerous biological processes, including regulating cell death. Mitochondria are also highly dynamic, traveling through cells on tracks, elongating into slender tubes, condensing, dividing and fusing (becoming, for example, one giant network to power energy-sucking DNA replication). Blurred by conventional techniques (left), mitochondria's details are revealed through super-resolution microscopy (shown color-coded by depth, center, and in cross section at right). ZHUANG LAB/HARVARD/HHMI

2. HEALTHY DAUGHTERS Protein structures called kinetochores (red) are largely responsible for a crucial task: ensuring that each daughter cell produced when a cell divides in two ends up with a complete set of chromosomes. These protein structures assemble on chromosomes (not visible). Kinetochores attach to hollow rods called microtubules (green) and pull the chromosomes into each daughter cell. If kinetochores don't attach properly, daughter cells can end up with extra or missing chromosomes, a condition called aneuploidy that can cause miscarriages and birth defects, including Down syndrome.

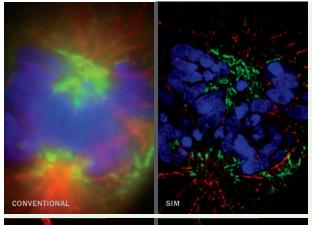
K. DELUCA/COLORADO STATE UNIV.

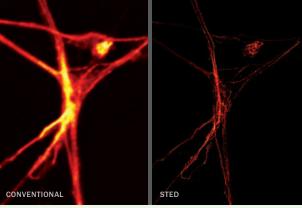


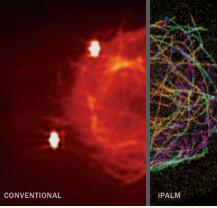
3 LIGHT SHEET/BESSEL BEAM

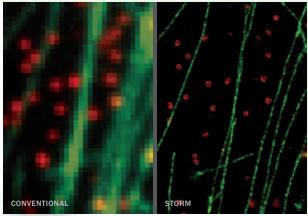
3. PACKING IT IN The ruffles decorating this monkey kidney cell aren't as dainty as they look. They will fold in on the cell, enabling it to gulp a considerable amount of fluid and solid cargo. Vigorous cell ruffling is a defining feature of macropinocytosis, one of several ways that cells bring in dissolved molecules and fluid from the environment. At times the process also allows entry of viruses and bacteria: salmonella and *E. coli*, for example, have tricks that induce cell ruffling, allowing entry of toxins or the microbes themselves. Scientists also have a growing interest in ruffling as a vehicle for drug delivery. BETZIG LAB/JANELIA FARM RESEARCH CAMPUS/HHMI

4. A FLY IS BORN Around two hours after fertilization, a fruit fly embryo has grown from one cell to about 3,500 (top). This nascent fly is still a single layer of cells, sitting atop the egg's yolk within a shell. Using an approach that looks at the embryo from four different perspectives at once, scientists can witness a wave of cell division (purple) pass through (top to bottom), nearly doubling the number of cells to about 6,000. The cells do not yet have membranes; they exist as tiny islands of cytoplasm and nuclei. A few minutes after this wave of cell division, the cell membranes will form, and within 22 hours the fly larva will hatch. KELLER LAB/JANELIA FARM RESEARCH CAMPUS/HHMI









Then and now

The nitty-gritty of cell biology happens on scales too small to see through a conventional light microscope. But several new imaging techniques at a range of resolutions provide new views—and new understanding—of how cells function.

SIM (~100 nm)

Structured illumination microscopy shines a striped pattern of light onto a sample. That light interacts with light from fluorescent tags on cellular material and generates a pattern of interference called a moiré fringe. Using a series of moiré fringes it's possible to mathematically extract and reconstruct a super-resolution image. SIM is ideal for looking at entire cells in 3-D, ensembles of cells or multiple cellular structures at once.

STED (~30–70 nm)

When a focused light beam hits a fluorescent-tagged specimen, it generates a blurry halo. With stimulated emission depletion microscopy, a second laser shines a doughnut-shaped beam of light that turns off the excited molecules in the halo. This provides a sharper view that, when scanned across the sample, produces a super-resolution image.

PALM (~10–55 nm)

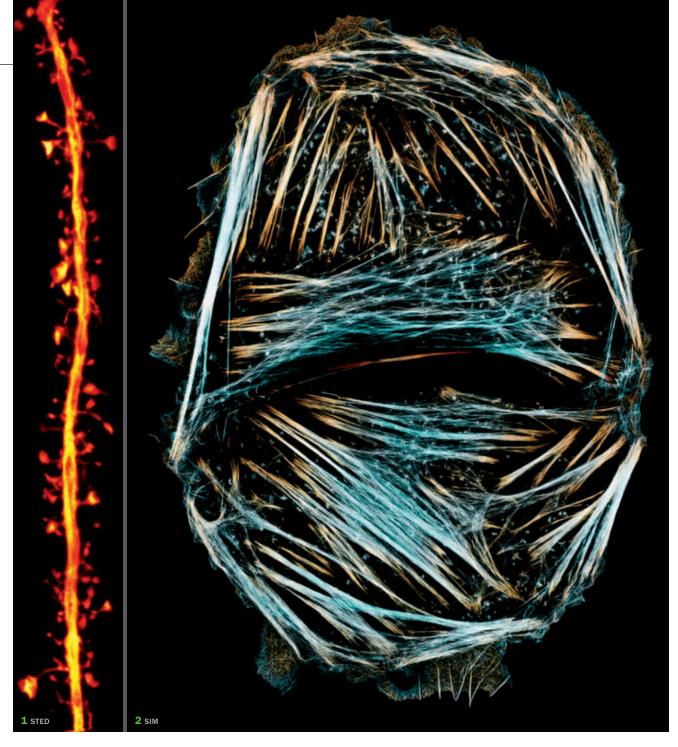
Photoactivated localization microscopy incorporates into a sample special fluorescent proteins that can be toggled between on and off states when hit with a particular wavelength of light. This allows researchers to illuminate a subset of molecules in a sample and eliminate overlapping fluorescence that would blur details if everything in the sample was lit up at once. iPALM (interferometric PALM) provides images in 3-D.

STORM (~20–55 nm)

Stochastic optical reconstruction microscopy, developed around the same time as PALM, also relies on fluorescent tags that can be switched on and off. In STORM's case, the tags can be dyes or proteins. Using dyes may require an extra step, but they can be switched on and off more quickly and don't burn out as fast as fluorescent proteins. Dyes can also be attached to genetic material.

Light sheet

Imaging cells can be a violent process. The heat from light can cook cells, and the tinier the object the more light scientists need to see it (or to "interrogate" it). Light sheet microscopy hits a sample with a thin sheet of light that excites only the molecules in a single plane, minimizing damage. Bessel beam imaging uses superthin sheets of light to image live cells and their innards—in action (Pages 23, 26). Simultaneous multiview light-sheet microscopy (Page 23) uses thicker sheets to track ensembles of cells.

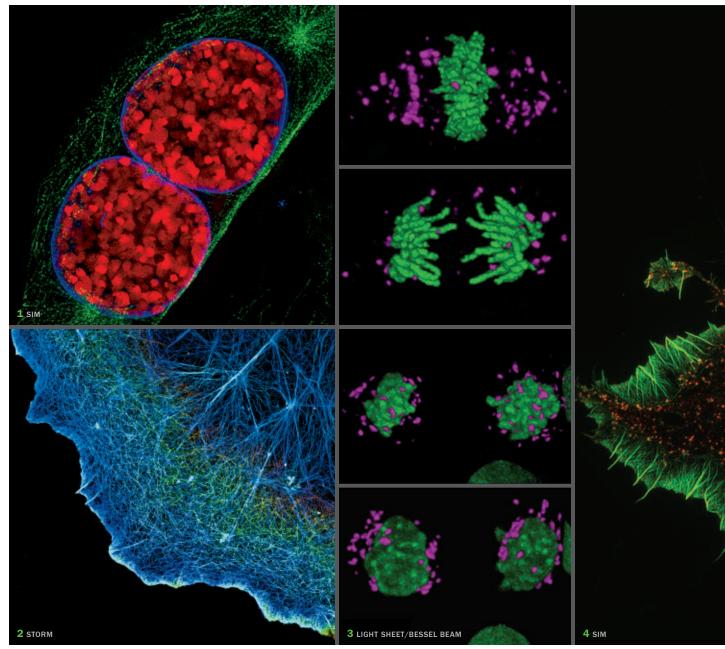


1. BRANCHES IN THE BRAIN Better views of dendritic spines, the leaflike structures that protrude from nerve cells (seen here in live mouse-brain tissue), can elucidate how the human brain functions. Dendritic spines are essential for nerve-to-nerve communication; throughout life they continue to morph, grow and perish. A recent study reveals that dendritic spines in a live adult mouse can undergo shape changes on a timescale of minutes. The spines play a pivotal role in memory formation and learning, and specific changes in dendritic spine size and shape have been implicated in brain disorders including schizophrenia and Alzheimer's disease.

J. TONNESEN AND U.V. NÄGERL/CNRS AND UNIV. OF BORDEAUX

2. GETTING A MOVE ON Cells would go nowhere without actin, the most abundant protein in eukaryotic cells (the sperm cells of some roundworms are thought to be the only ones with absolutely no actin). Actin filaments (color-coded by depth, blue farther away) act as the muscles of cells and are especially prominent in the cellular skeleton, where they constantly re-form and dissolve into stiff networks that are crucial for cell locomotion. "Stress fibers" that enable contraction are made from a combination of actin and motors made of myosin. The fibers are visible in this bottom layer of two cancer cells. Actin can also contort into treadlike spikes (visible on the lower and left edges). The cell can use these as battering rams to push and pull itself into a tissue. When a tumor cell crawls along a blood vessel or an immune system cell rushes to a site of injury or infection, it's actin that's making them move. D. BURNETTE/NICHD/NIH

PHOTO ESSAY | VIEW TO A CELL



1. MAKING MUSCLE Skeletal muscle is unusual: Its cells form from the fusion of precursor cells called myoblasts, and the resulting megacells may have tens to hundreds of nuclei each. In addition to making muscle, myoblasts can also differentiate into bone precursor cells or even be coaxed into becoming fat. This mouse myoblast cell already has two nuclei, but they are preparing for another round of division. While the nuclear envelope (blue) is still intact, the tangled mixture of DNA and proteins have begun to condense into chromosomes (red), which eventually will be divvied up with help from the microtubules (green). L. SCHERMELLEH/UNIV. OF OXFORD

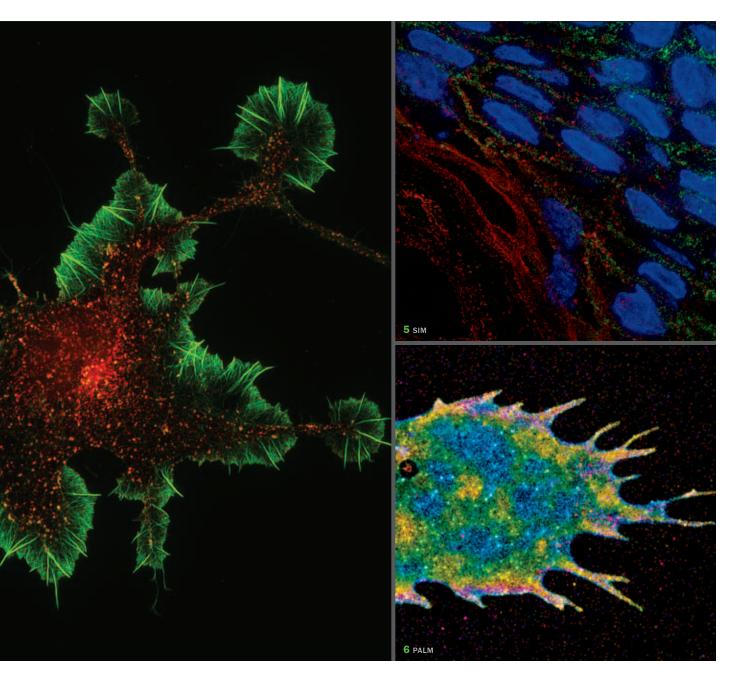
2. TAKING ACTION The tiny diameter and high density of actin filaments are visible in the sheetlike protrusions at this monkey kidney cell's edge (color-coded by depth, red farthest away). Scientists are still trying to figure out precisely how these sheets

form and connect to the cell's interior so they can understand more about how cells travel.

K. XU, H.P. BABCOCK AND X. ZHUANG/NATURE METHODS 2012

3. SIGNED, SEALED, DELIVERED The processing, packaging and shipping of the numerous proteins and other big molecules made within a cell is the purview of the Golgi body (purple), which along with the chromosomes (green), gets divided up during mitosis. This type of pig kidney cell is often used in drug research and is especially good at making a protein that helps break up blood Clots. T.A. PLANCHON ET AL/NATURE METHODS 2012

4. SAFETY WRAP Nerve cells that send electrical signals are coated in a protective sheath of myelin (like the insulation surrounding electrical wires), without which the elaborate, efficient nervous system of vertebrates might never have evolved.



Precisely how myelin sheaths form is still a mystery, and one that scientists would desperately like to solve, since faulty myelin has been implicated in several neurological diseases including multiple sclerosis. This glial cell will extend to wrap a nerve in myelin, a task likely dependent on the actin skeleton (green) and the associated actin proteins (red). B. ZUCHERO AND A. OLSON, BARRES LAB/STANFORD

5. NO TRESPASSING One of the body's primary bulwarks against outside contaminants are epithelial cells, which make up skin and line cavities such as the intestine. These protective cells (human newborn foreskin shown) can exist as sheets of tissue that are held tightly together by several structures including adherens junctions (green, blue shows cell nuclei). Scientists are investigating how HIV, the virus that causes AIDS, manages to get through the adherens junctions and into the body.

6. HAVE FEET, WILL TRAVEL Cancer cells become difficult to eradicate once they spread, and the sheetlike cellular feet called lamellipodia make such locomotion possible. By studying how cells like this bone cancer cell (membrane proteins color-coded by depth) sense tension and crawl and stick themselves in tissue, scientists may identify new potential therapeutic targets. P. KANCHANAWONG AND C. WATERMAN/NIH; M. DAVIDSON/FSU; G. SHTENGEL AND H. HESS/ JANELIA FARM RESEARCH CAMPUS/HIMI

Explore more

- Learn more about optics research at Janelia Farm Research Campus: bit.ly/JaneliaLabs
- C.G. Galbraith and J.A. Galbraith.
 "Super-resolution microscopy at a glance." Journal of Cell Science. May 2011.

Society News

Eesha Khare (left), lonut Budisteanu (center) and Henry Wanjune Lin claimed the top prizes at the 2013 Intel International Science and Engineering Fair.



Intel ISEF honors teens' science

PHOENIX — A self-driving vehicle brought its inventor, a 19-year-old Romanian computer scientist, the top prize — and \$75,000 — last month at the world's premier high school research competition. Ionut Budisteanu, of Râmnicu Vâlcea, Romania, was the big winner at the 2013 Intel International Science and Engineering Fair.

"This competition encourages millions of students worldwide every year to explore their passion for math and science while developing solutions for global challenges," said Wendy Hawkins, the executive director of the Intel Foundation.

Budisteanu received his award for designing software to pilot a low-cost, self-navigating vehicle. His design relies on cameras to detect people, cars and other objects. Onboard 3-D laser radar measures distance to those objects. The software then uses that information to adjust the speed of the vehicle.

Two other young researchers each won \$50,000 awards. Eesha Khare, 18, of Saratoga, Calif., picked up one for designing and building a supercapacitor, a device to store electrical energy. Her novel device can charge up very quickly. It also can store almost three times as much electrical energy as previous capacitors. And unlike previous capacitors, it stores that energy in a tiny volume, one comparable to a battery's. Her new device also holds a charge far longer than batteries do.

The other \$50,000 award went to Henry Wanjune Lin, 17, of Shreveport, La., for modeling the behavior of distant galaxies. Lin compared his mathematical predictions about galaxy clusters with what astronomers have observed using telescopes. He found that the scientists are slightly more likely to find a particular type of cluster: one with galaxies that have cooler-than-usual temperatures at their cores. But overall, the teen confirmed, the way astronomers have been surveying clustered galaxies works well.

Seventeen "best of category" awards, each worth \$5,000, were given out, including to Budisteanu, Khare, and Lin in each of their fields.

"The Intel ISEF inspires students not previously involved in such competitions to see that independent research is both possible and rewarding," said Elizabeth Marincola, president of Society for Science & the Public and publisher of *Science News. — Sid Perkins*



For more Society News, visit **www.societyforscience.org**

Category Winners

In addition to the three top winners, Intel ISEF finalists picked up 14 other "best of category" awards.

Animal sciences Michael Shao, 16, Northville, Mich., for showing how a worm responds to cold temperatures.

Behavioral and social sciences

Zarin Rahman, 16, Brookings, S.D., for showing that stressful experiences impair a teen's mood and memory.

Earth and planetary sciences

rotating wheels.

Gyou Tanaka, 16, Mobara, Japan, for finding that a site southeast of Tokyo was part of the seafloor 300,000 years ago.

Electrical and mechanical engineering Zeyu Liu, 17, Calgary, Canada, for designing a device that minimizes friction in systems used to store energy in large

Environmental sciences Naomi Shah, 17, Portland, Ore., for creating an air filter that includes natural materials such as peat, mulch and live plants.

Mathematical sciences Vinay lyengar, 17, Portland, Ore., for developing new techniques to create secret codes.

Medicine and health Jessie MacAlpine, 17, Woodstock, Canada, for demonstrating that consuming mustard oil inhibits growth of malarial parasites in people.

Microbiology David Zimmerman, 18, Los Angeles, for genetically altering a difficult-to-modify microbe.

Biochemistry Savannah Tobin, 18, Salem, Ore., for developing a method to measure a chemical in cat saliva that can cause allergies in people.

Cellular and molecular biology

Hannah Wastyk, 17, Palmyra, Pa., for developing a promising treatment for melanoma, a particularly deadly form of cancer.

Materials and bioengineering

Samantha Marquez, 17, Midlothian, Va., for creating drug delivery vehicles using bacteria and algae.

Energy and transportation Evie Sobczak, 16, St. Petersburg, Fla., for finding an efficient way to grow algae and then break them down to extract their oil.

Environmental management Shixuan Li, 15, Lynn Haven, Fla., for developing a way to extract an antioxidant from shrimp.

Plant sciences Samantha DiSalvo, Ryan Kenny and Amy Vitha, Hewlett, N.Y., for probing how plants respond to, and sometimes resist, bacterial infections.

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Test and Fitting Required	No
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Friendly Return Policy	60 Days

is small and lightweight enough to hide behind your ear... only you'll know you have it on. It's comfortable and won't make you feel like you have something stuck in your ear. It provides high quality audio so sounds and conversations will be easier to hear and understand.

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Zombie Birds, Astronaut Fish and Other Weird Animals

Becky Crew

Weird Life

David Toomey



Even on bad days, humans don't have their tongues eaten by crustaceans. Fish in the English Channel are not so lucky, reports Crew, a science writer. Neither have human males evolved into little more than mobile genitals that attach to females for life, as have some anglerfish. Putting our own species' vexations in perspective may be a big part of the fun of reading about other life-forms. Whatever drives biodiversity gawking, it's persistent. So is, thank goodness, the stream of books that satisfies it.

Crew's Zombie Birds stands out for

Present Shock: When Everything Happens Now

Douglas Rushkoff

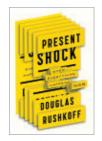
In the 1970 book *Future Shock*, Alvin Toffler popularized a term for the disorientation that people suffer when they can't cope with the pace of change around them. Media theorist Rushkoff makes a good case that this predicament has arrived in a generation struggling to live a modern life that's always on.

He starts by decrying the decline of narrative in Western culture. The recent technology explosion — from television to video games to YouTube — has put stories on life support, Rushkoff argues. Early TV used reminders about plotlines. (Everyone knew where "a threehour tour" was headed.) But cable TV and the remote control now allow viewers to flit from show to show. A generation of viewers lost the narrative thread, reaching rock bottom with reality TV. Technology alters behavior, too. its rowdy zest and fine choice of creatures. As in her acclaimed blog *Running Ponies*, chapters pair brisk explanations of phenomena with fictional interludes. The chapter on pearlfish, for instance, titled "At Home in Someone Else's Anus," ends with gambits to help the parasite through awkward conversations about where it lives.

None of her characters, though, is unusual enough for *Weird Life*, a book that's both the polar opposite of Zombie Birds and its secret twin. Toomey, an English professor, could read his prose in Sunday school without offending. But he sets the standard for oddity even higher than Crew does. Tongue-eating crustaceans, anglerfish and humans at least descend from a common ancestor at the same origin of life, but Toomey chronicles the search for life from some entirely separate event, perhaps with unimagined chemistry. So far no one has found it, but humankind feels the need to keep looking. - Susan Milius Zombie Birds: Adams Media, 2013, 240 p., \$15.95; Weird Life: W.W. Norton & Co., 2013, 268 p., \$25.95

Glued to mobile devices, Rushkoff says, "we tend to exist in a distracted present." It started with call-waiting and has evolved to texting and tweeting.

Rushkoff is no Luddite. But he warns that living in the present has repercussions. Human biology is ill prepared for this lifestyle. Living in present tense,



people take out mortgages they can't pay, governments rack up debt and corporations deplete resources. Such robbing from the future is a losing strategy. Illegally download-

ing music or movies may benefit a scofflaw, but ultimately the industry suffers.

It's hardly clear where all this is going. Present shock, Rushkoff summarizes, is "destabilizing." To be continued. – *Nathan Seppa Current, 2013, 256 p., \$26.95*



Bootstrap Geologist

Gene Shinn In this autobiography, Shinn documents his career spanning nearly 50 years in science, including many adven-

tures in remote and exotic locales. *University Press of Florida, 2013, 297 p., \$34.95.*



The Unpredictable Species

Philip Lieberman A cognitive scientist argues that flexibility and the creative capacities of the

brain—not genes—have made humans unique. *Princeton Univ.*, 2013, 255 p., \$29.95



How Animals Grieve Barbara J. King Through stories of creatures that have lost family members or partners, an anthropol-

is known about grief among animals. Univ. of Chicago, 2013, 193 p., \$25

The Autistic Brain THE Autistic Brain TEMPLE GRADIN IN THE AUTOS

The Autistic Brain

ogist discusses what

Temple Grandin and Richard Panek Grandin, an animal behaviorist diagnosed with autism in 1950, examines the latest

science on the condition. *Houghton Mifflin Harcourt, 2013, 240 p., \$28*

FILE CONTROL

Odd Couples

Daphne J. Fairbairn A biologist explores gender differences among animals, such as female spiders that dwarf their mates.

Princeton Univ., 2013, 300 p., \$27.95

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FEEDBACK

Wet Earth

Erin Wayman's article "Faint young sun" (SN: 5/4/13, p. 30), about how the early Earth stayed warm enough for liquid water, made me wonder about the effect of the temperature of the planet itself. A hotter core, thinner crust, more volcanism — wouldn't those factors in addition to atmospheric influences affect surface temperature? **Virginia Bruce**, via e-mail

"For the present-day climate, internal heat provides only 0.02 percent of the energy input to the climate system," says Georg Feulner of Germany's Potsdam Institute for Climate Impact Research. Scientists estimate that heat flow 3.8 billion years ago was three times as high as today, still negligible compared with energy from the sun. — Erin Wayman

Planet search

Kudos to Eva Emerson for her editorial "Discoveries help reveal our place in the universe" (*SN: 5/18/13, p. 2*). She clearly defines the challenges in identifying a "true" Earthlike planet with current technologies. Too often, articles make claims on the distribution of hot Jupiters and Earthlike planets without considering the prejudicial nature of sampling techniques. This is why I have read *Science News* for over 20 years. **Robert Powell,** Austin, Texas

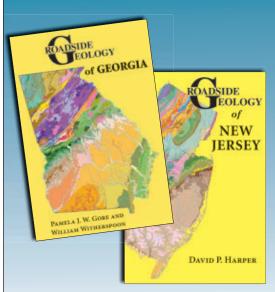
Correction

Richard Marshall and Earl Kooi manipulated the chemical structure of cornstarch at the Corn Products Refining Company, not the Corn Projects Refining Company as misstated in "Sweet confusion" (*SN: 6/1/13, p. 22*).

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Blogger busts dinosaur myths

For Brian Switek, the arrival of warm weather means it's time to grab a case of beer, jump in the car and head out for the first dinosaur dig of the season. As a blogger who writes mainly about dinosaurs, he'll spend days at a time camped out with paleontologists in America's premier dino-hunting territory.

The actual fieldwork isn't always so romantic — "looking for crumbs" is how Switek describes it — but he says there's nothing more rewarding than spotting an interesting bit of bone.

As new finds emerge, scientists continually renovate theories on dino biology. "The pace of discovery is almost impossible to keep up with," says Switek (below). He has spent the last seven years writing about all things paleontological, and the fast-moving field has provided him with plenty of material to work with.



Switek started blogging about science in the fall of 2006 while studying marine science at Rutgers University in his home state of New Jersey. What began as a hobby eventually led to freelance writing, and his blog *Laelaps* has built up a readership of hard-core paleontology fans.

Until recently, Switek balanced writing with an office job at Rutgers' agricultural regulation department. (He finished his first book, *Written in*

Stone, by working nights and weekends.) In 2011 he quit to pursue writing full time, leaving the East Coast for Salt Lake City in the fossil-hunting heartland.

"I accidentally created a sort of career," he jokes, "where I can write like crazy during the winter and go out in the field in summer."

In his early blogging days, Switek volunteered to do fieldwork anywhere he could. Now scientists invite him on field expeditions. He has hunted fossils at well-known sites like Ghost Ranch in New Mexico and Grand Staircase–Escalante National Monument in Utah. One of his favorite places is Dinosaur National Monument, which straddles the border between Utah and Colorado. There, he says, you can climb a ridge "and see over 500 million years of natural history."

Switek's second book, *My Beloved Brontosaurus*, hit bookstores in April (*SN:* 5/4/13, p. 34). In it, he takes on popular misconceptions about dinosaurs (there's no such thing as a *Brontosaurus*, for example) and catches readers up on the latest dino research. For his next project, he might explore what the fossil record reveals about how species respond to climate change and habitat loss. But that's just one option. "I have more ideas than I know what to do with," he says. *—Allison Bohac*

Dinosaurs in flux

Forget one-shot finds of new species. Author and blogger Brian Switek is more interested in discoveries that open up new biological and evolutionary questions about dinosaurs. Here are a few of the discoveries that he finds most intriguing from recent years.

Dinos growing up

A 2010 study proposed that two species of three-horned dinosaurs, *Triceratops* and *Torosaurus*, were actually different life stages of the same animal. Skulls thought to belong to full-grown *Triceratops* (below), the authors noted, might actually be from young adult *Torosaurus*. If true, this would mean the animals endured major physical

changes during their lifetimes; Torosaurus, for instance, sports large holes in its bony frill, but Triceratops doesn't. The find fits with the idea that other dinos that were once considered different species might represent one animal across a lifetime.

A hint of hue

Dinosaur colors have been a longstanding mystery for paleontologists. "As kids, we were told we're never going to know what color they were," Switek notes. But recently, researchers examining fossilized melanosomes — pigment-producing organelles found in feathers — have started reconstructing the hues of the birdlike dinosaurs Archaeopteryx, Sinosauropteryx, Anchiornis and Microraptor.

Mesozoic moms

A broken Tyrannosaurus rex femur reported in 2005 made it easier to determine the gender of some dinosaur fossils. Mary Schweitzer of North Carolina State University in Raleigh and her colleagues noticed that the inner cavity of the bone was lined with a special type of tissue called medullary bone, which stores calcium in egg-laying birds. The team surmised that the tyrannosaur was pregnant when she died. With a reliable way to identify some females in the fossil record, scientists can start studying new facets of dinosaurs' sex lives.

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