Dimensions in Hiding | Bilateral Asymmetry | Bond, Basement Bond

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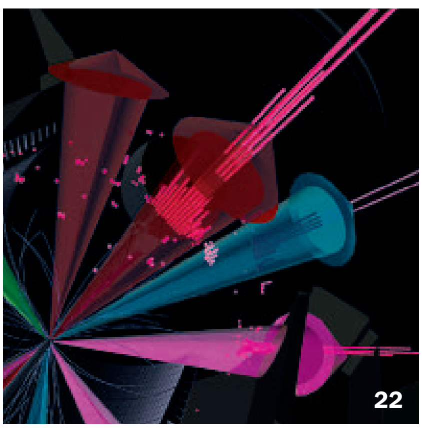

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In The News

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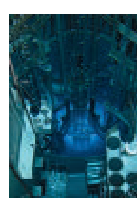

COVER Someday, the University of Missouri Research Reactor could be a source for a medical imaging isotope. *David Nickolaus/ University of Missouri Research Reactor*

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FROM THE EDITOR

Imagining the universe from outside of the plane

Picture a tiny ant (or better yet something smaller, perhaps a bacterium with legs) that lived on a cosmic-sized sheet of paper. For the bug, the universe would seem two dimensional, apparently extending endlessly in all directions but also forever flat. Like the polygons in E.A. Abbott's *Flatland*, the minuscule inhabitant of this paper universe would perceive only two spatial dimensions and would be baffled by proposals that reality possessed extra, invisible "higher" dimensions.

And yet the paper universe does in fact have another dimension — the thickness of the sheet. Our bug could not travel far enough to reach the edge of the paper and so could not see or move in that very thin dimension. In a very similar way, many physicists believe, the three-dimensional space presented to human consciousness does not exhaust the spatial complexity of the cosmos. In one (or possibly several) additional dimensions, the universe may be ultrathin, a realm too tiny to notice or visit. All of known space could fit easily within that extra dimension, just as a full-sized sheet of paper can fit in a file folder only a fraction of an inch thick.

If they really exist, such extra dimensions could help explain some of the strange physics of the ordinary universe. But they aren't good for much else. You can't use them for storing junk or hiding food. Of the known forces, only gravity is free to explore the other dimensions, current theory suggests. Matter and light are trapped in the three ordinary dimensions, as the bug would be if its universe was flypaper. So you can't see them and you can't visit them. Direct contact with the extra dimensions appears to be forbidden.

But wait. There is a way the bug could encounter evidence of the sheet of paper's other dimension — if somebody poked a hole in it. A little less directly, black holes in real space could provide clues to extra-dimensional reality, as freelance writer Diana Steele reports in this issue (Page 22).

Of course, there is danger in such pursuits. In *Flatland*, Abbott's protagonist polygon, a mathematician named A. Square, succeeded in detecting the third dimension's presence, with the help of an extraplanestrial sphere. When A. Square realized the importance of his discovery, he attempted to explain it to all the citizens of Flatland. They threw him in jail.

—Tom Siegfried, Editor in Chief

“TV Ears saved our marriage!”

—Darlene and Jack B., CA

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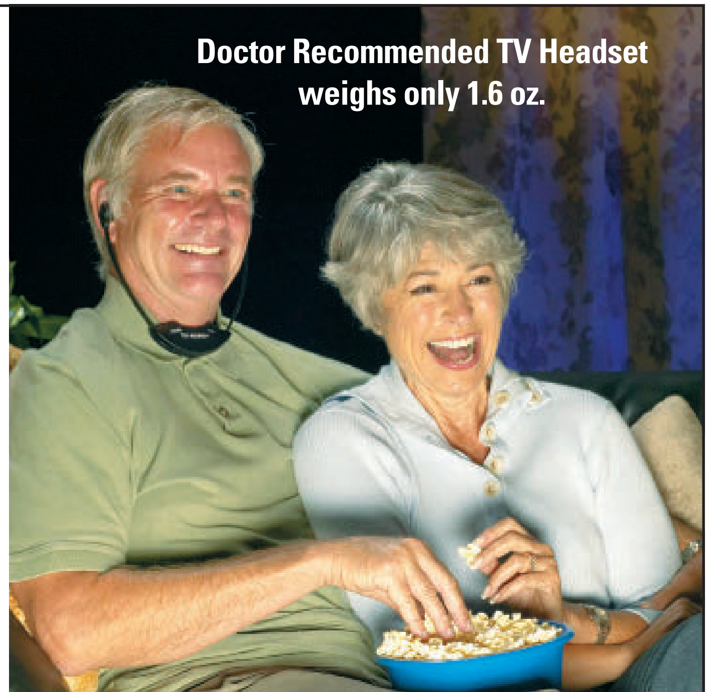

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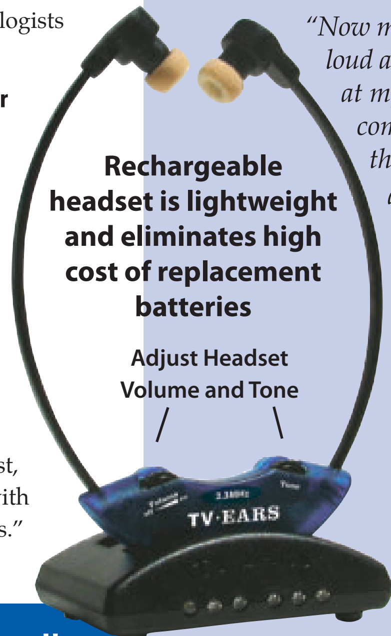

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Scientific Observations

"As a dancer and choreographer I've spent a tremendous amount of my life defending something that's very hard to see. I mean people see dance, they see the dancers, but they have trouble understanding why it's valuable, what you're trying to say. And in some ways I feel that's reflected in what I learned initially from the physicists. It's very abstract, it's hard to see, people have trouble trying to understand it, it has tremendous value to us as a civilization but it's not easy to explain." CHOREOGRAPHER AND MACARTHUR FELLOW LIZ LERMAN IN THE AUGUST *SYMMETRY*. SHE RECENTLY VISITED CERN WITH DANCERS (ONE SHOWN AT CERN) TO DO RESEARCH FOR AN UPCOMING PRODUCTION ON PARTICLE PHYSICS.

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ATOM & COSMOS

Five spacewalks later, the refurbished Hubble Space Telescope can see more clearly than ever before. Visit www.sciencenews.org/Hubble909 for story and slide show of newly released images.

HUMANS

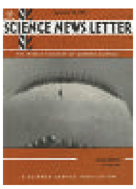
Just three months of playing the computer game Tetris can increase the brain's size and efficiency. Read "Tetris players are not block heads."

SPECIAL ONLINE FEATURE

Quark theory originator Murray Gell-Mann discusses current issues in particle physics and what he's busy investigating now. See "Interview: Murray Gell-Mann."

Science Past | FROM THE ISSUE OF SEPTEMBER 26, 1959

MANY AMERICANS SUFFER "TELEVISION BOTTOM" — Many Americans are suffering from a condition called "television bottom." The medical term for the condition is coccygodynia, pain in the tail of the spine. It arises frequently from spending long periods of time before the television set.... Most patients habitually sit with a poor posture, with the lower portion of the back arched out instead of arched inward.... They slump in a chair and allow the middle portion of the sacrum and coccyx to press against a chair.... There is hope for these people, however. Of 100 patients, 62 were treated by massage only. This treatment was given an average of six times over a period of three to four weeks. Relief came to 50 patients, 80% of that group.



Science Future

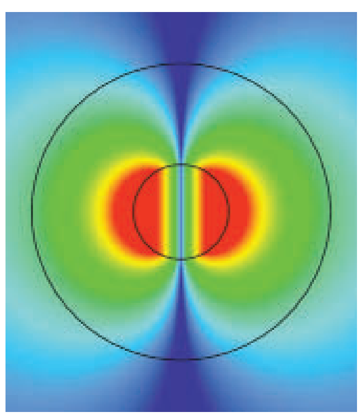
October 5–7
Nobel Committee announces medicine, physics and chemistry awards. Visit nobelprize.org

November 1
Petitions for a chemistry-themed postage stamp are due to the American Chemical Society. See cenblog.org/2009/07/07

November 1–3
"Darwin in the 21st Century: Nature, Humanity and God" at the University of Notre Dame in Indiana. Visit nd.edu/~reilly/darwinconference.html

The (-est)

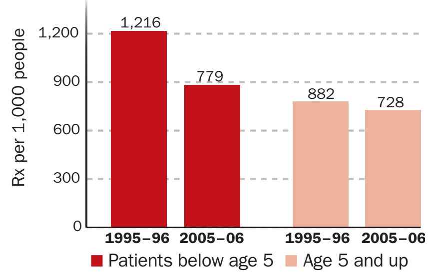
Researchers have devised the world's smallest laser, measuring just 44 nanometers across, a team from Georgia and Virginia reported online August 16 in *Nature*. The laser (shown, with false color) is made up of a gold core and silica shell coated in a special dye. Where a typical laser emits light, the new device emits surface plasmons, produced by oscillations in the density of electrons at a metal's surface. Surface plasmons are grouped more closely than photons so the new device — called a "spaser" — has a tighter focus than traditional lasers.



Science Stats | REDUCING Rx's

U.S. doctors are prescribing fewer antibiotics for respiratory infections, especially in children

Annual U.S. prescriptions for respiratory illness, 1995–96 vs. 2005–06



SOURCE: GRIJALVA *ET AL./JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION* 2009

CLOCKWISE FROM TOP LEFT: AMELIA COX; NASA, ESA, HUBBLE SM4 ERO TEAM; A. NANDY; M. NOGINOV *ET AL./NATURE* 2009

“ Energy does not go from the grass to the lion without going through the zebra. ” — STEFANO ALLESINA, PAGE 10

In the News

STORY ONE

New bond in the basement tethers body’s tissues together

Sulfur-nitrogen link had never been seen in living creature

By Rachel Ehrenberg

The foot bone’s connected to the leg bone, the leg bone’s connected to the knee bone — thanks in part to a chemical bond never before seen in living things, researchers report in the Sept. 4 *Science*.

The bond — a link between sulfur and nitrogen— was found buried in the basement membrane, a tough, structural layer of cells that surrounds most tissues. A greater understanding of the links within this membrane may lead to new approaches for targeting tumors and for treating a number of diseases.

Animals from roundworms to humans have basement membranes, long recognized as important for a body’s structural integrity. The membranes surround tissues, tethering muscle to skin or to cartilage. Basement membranes also play a signaling role, sort of like a thermostat for cell health.

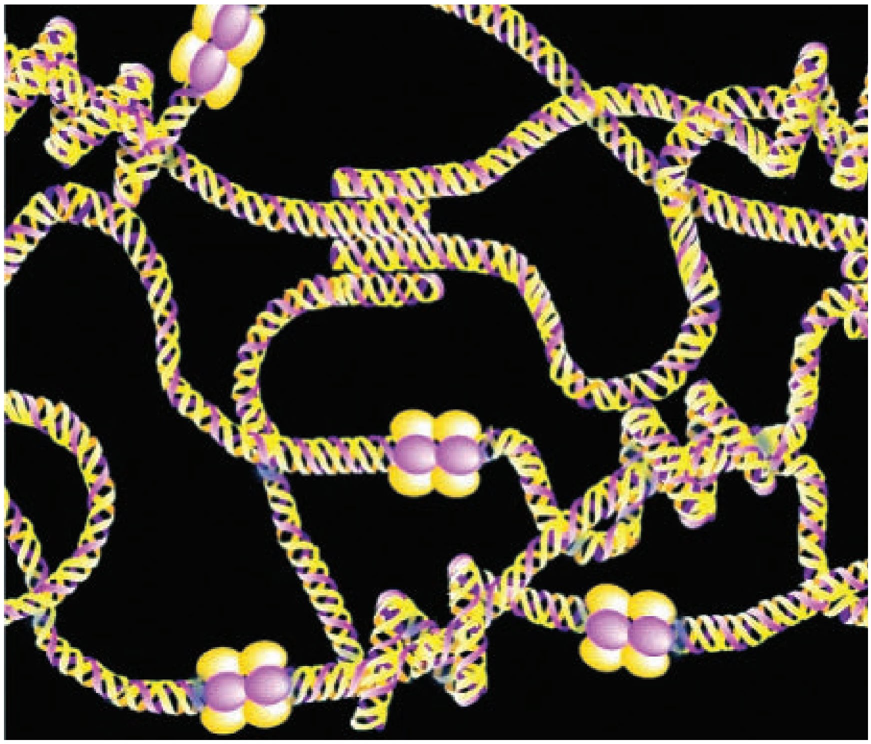
“If the basement membrane misbehaves, then the cell misbehaves,” comments Raghu Kalluri, a matrix biology specialist at Harvard Medical School in Boston.

A major component of basement membranes is type IV collagen, which provides a strong, cross-linked mesh material that lends strong structural support. The collagen molecule is a triple helix, three strands twisted together like rope. One end of each ropelike chain is capped with a globule of amino acid molecules. These amino acids connect to the globule of another collagen chain, helping to form a matrix. Though such matrices are pervasive in animals, the nature of the bonds connecting the globules had eluded scientists.

Initially, researchers thought the bond might be a disulfide bridge, a link between two sulfur atoms. Previous research had hinted that sulfur was involved. And bonds between two sulfurs on amino acids commonly impart 3-D stability in proteins. But X-rays of the globular tips’ crystal structure ruled out the sulfur-sulfur connection, says biochemist Billy Hudson, who led the new research.

Now finer instruments reveal a sulfur-nitrogen bond, a partnership created in organic chemistry labs a handful of times but never detected in an organism.

Today’s super-high-resolution mass spectrometers made the discovery possible, says Hudson, director of the Center for Matrix Biology at Vanderbilt University School of Medicine in Nashville. Previous attempts with less powerful instruments suggested that when the bond formed between the amino acid



A new study shows that the tangles of type IV collagen chains (helices) in the basement membrane connect at globules (spheres) via sulfur-nitrogen bonding.

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SN Today at **www.sciencenews.org**

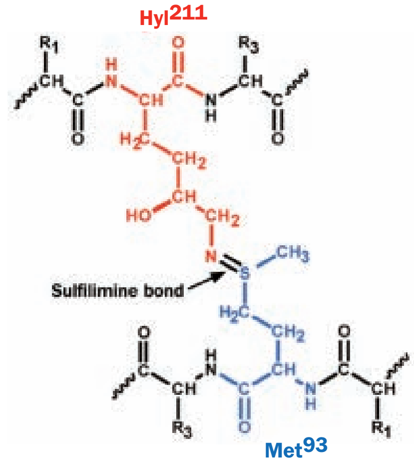
tips, one hydrogen atom departed. But the experimental error was too large to say for sure what was happening. The new analysis reduced the experimental error by a factor of 1,000. The team found that two hydrogen atoms are lost during bond formation and that sulfur and nitrogen atoms link. Covalent sulfur-nitrogen bonds — called sulfilimine bonds — connect the two collagen chains, linking the amino acids methionine and a version of lysine, the team reports.

"The collagen IV network is what cells lay on, no matter if it's an anemone or a human," Hudson says. The bond "is the molecular fastener."

Research by James Kramer of the Northwestern University Feinberg School of Medicine in Chicago and colleagues revealed the crucial role of collagen in holding together the nematode *C. elegans*. Even when collagen IV genes were disabled, the worm developed. But when it moved, its muscles pulled apart and detached from the skin.

The sulfilimine bond is a strong one. Covalent bonds, where atoms share electrons, "really up by an order of magnitude the force that the material can deal with," Kramer says. It isn't clear what advantages a sulfur-nitrogen bond might have over a disulfide bridge, which is known for its strength. There are already disulfide bonds within the globules, Kramer notes, so perhaps using a different bond avoids potential problems in initial globule formation.

Hudson's team first found the bond in cow placenta tissue but has been looking in other creatures. Over the summer, along with several middle school and high school students, he launched a "biochemical expedition through the animal kingdom," he says. The young researchers detected the two connected globules — a telltale sign of the bond — in tissues of all the animals investigated, including monkeys, sea urchins and *C. elegans*.



A sulfilimine bond links two amino acids in collagen IV: a version of lysine (hydroxylysine, top) and methionine (bottom).

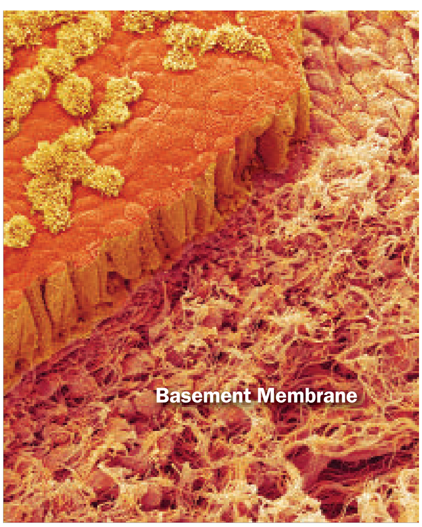
Perhaps the cross-link evolved in response to the mechanical stress of having an elaborate body, the researchers speculate. Their analyses comparing the amino acid sequences of the globular tips from different organisms suggest that the unusual bond may have arisen early in animal evolution, after the sponge and jellyfish lineages diverged.

Regardless of the bond's evolutionary past, disrupting it could help attack tumors, Kalluri says. In some cases, nearly half of a tumor's weight comes from the collagen-basement membrane matrix. Because basement membranes surround all blood vessels, the membranes can act like train tracks that allow tumor cells to spread, he says. Perhaps collapsing those blood vessels by breaking the bonds could halt tumor growth.

The work may also inform research on Alport syndrome, an inherited condition related to collagen IV that involves loss of kidney function, and Goodpasture syndrome, a rare autoimmune disease. Goodpasture syndrome, which affects the lungs and kidneys and can be fatal, is caused in part by the immune system attacking a section of the amino acid tips connected by the newly discovered bond. "This bond is uniquely involved," Hudson says. How, precisely, remains unknown. ■

Back Story | SUPPORT IN THE BASEMENT

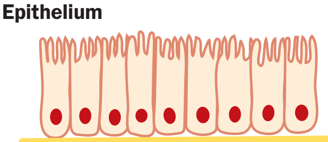
Basement membranes anchor cells, act as barriers and provide a framework for blood vessel development. The membranes also help regulate cell behavior and signaling.



Windpipe lining This scanning electron micrograph image shows how the columnar epithelial cells (left) that line the trachea are supported by their basement membrane (right).

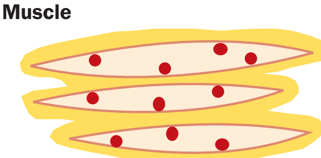
Basement membrane   Cell

Epithelium



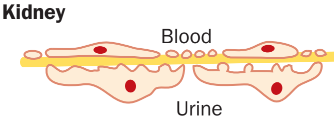
The membranes underlie tissues that act as lining, such as skin, providing support and tethering them together.

Muscle



In addition to their role in healthy cells, membranes act as scaffolding for regeneration of damaged muscle cells.

Kidney



The membrane of a healthy human kidney acts as a barrier and filters nearly 200 liters of blood per day.

TOP: COURTESY OF *SCIENCE*/AAAS; BACK STORY LINE ART: A. NANDY; IMAGE: SUSUMU NISHINAGA/PHOTO RESEARCHERS, INC.

Atom & Cosmos

For a slide show of new Hubble images, visit **www.sciencenews.org/Hubble909**

Decay patterns at B factory could challenge physics' standard model

Tentative evidence hints at new massive elementary particle

By Ron Cowen

In a weak moment, researchers have found an unexpected asymmetry in particle production that could hint at exotic physics. The tentative evidence, announced August 21, could be the fingerprint of a massive elementary particle that would help unify three of the four known forces in nature.

The physicists collected data for nearly a decade at the Belle particle accelerator experiment in Tsukuba, Japan. In the experiment, known as a B factory, beams of electrons and positrons collide to produce millions of pairs of B mesons and anti–B mesons. Such particles live brief but eventful lives, decaying through the weak nuclear force — the same force that powers some radioactivity and helps keep the sun burning.

In a mere 1.5 trillionths of a second, B mesons and their antiparticles disintegrate in any of hundreds of ways. In one of the more unusual decay paths — so rare it happens only about once in every million decays — a B meson turns into a particle called a K* meson and a particle-antiparticle pair. This pair can include an electron and its positively charged partner, the positron, or a heavier cousin to an electron, the muon, and its positively charged partner, the anti-muon.

The Belle team found that the number of positrons or anti-muons released in one direction, the direction of travel of the K* meson, doesn't equal the number released in the opposite direction. The standard model of particle physics predicts such an asymmetry because the weak interaction picks a preferred direction in space. As a result, the mirror image of a physical process involving the weak interaction doesn't look the same as the original process.

However, the researchers found that the directional imbalance was slightly greater than the standard model predicts. That could mean that some type of massive elementary particle, briefly created during the decay process, has enhanced the asymmetry, says Belle collaborator Tom Browder of the University of Hawaii at Manoa. The team presented the findings in Hamburg, Germany, at the International Symposium on Lepton and Photon Interactions at High Energies.

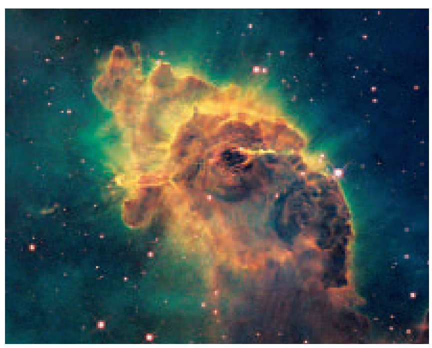
If an additional mystery particle were produced in the decay, it would have to be much heavier than the B meson that decayed in the first place. That seeming contradiction is permitted by the weird laws of quantum theory — as long as the heavy particle lasts for only a brief time. And such a particle could lend credence to the proposed theory of supersymmetry, which holds that every known elementary particle has a heavier partner. One of the proposed supersymmetric particles could be a candidate for dark matter, the elusive, invisible material that keeps galaxies intact.

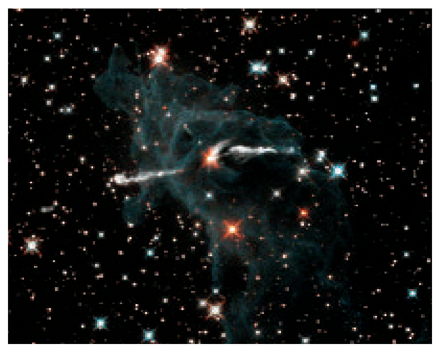
"This is the strongest hint we've had so far" of physics beyond the standard model, Browder says.

But, he adds, with only about 250 of the rare B meson decays generated at Belle so far, the team can't yet reach a firm conclusion.

Physicist Andreas Kronfeld of the Fermi National Accelerator Laboratory in Batavia, Ill., agrees that the finding is intriguing but tentative. He says the Large Hadron Collider accelerator near Geneva, once it's finally operating at full capacity, could look directly for tracks left by the proposed particle.

Seeing again through Hubble's eyes





Five grueling space walks in May have transformed the aging—and ailing—Hubble Space Telescope into a brand new observatory. Images and spectra released by NASA on September 9 confirm that two new instruments and two old, revived instruments are working properly. The Wide Field Camera 3, which has begun peering into the cosmos at wavelengths ranging from the infrared to the ultraviolet, captured these two images of a Milky Way star-birthing region in the Carina nebula. The region is similar to that seen in the iconic Pillars of Creation image taken in 1995 by a visible-light camera on Hubble. Recorded in visible light, the left image shows a dusty cloud—a stellar nursery. In the infrared image, on the right, the hatchlings themselves are revealed because the starlight penetrates the dusty cocoon and the cloud itself all but vanishes. The Wide Field Camera 3 is likely to image galaxies more distant than those imaged by any other detector on the ground or in space. —*Ron Cowen*

BOTH: NASA, ESA, THE HUBBLE SM4 ERO TEAM

Body & Brain

For longer versions of these and other Body & Brain stories, visit **www.sciencenews.org**

Mito (left) and Tracker (right), born on April 24, developed from donor cells with donor mitochondrial DNA.

Four healthy rhesus monkeys born with mitochondrial DNA from donor

Procedure may one day prevent some inherited diseases

By Laura Sanders

Scientists may have found a way to prevent the transfer of serious inherited mitochondrial diseases from mother to child. By shuttling nuclear DNA from an egg cell to a donor cell, the technique enabled the birth of four healthy rhesus macaque monkey males, researchers report online August 26 in *Nature*.

"We consider this a big achievement," study coauthor Shoukhrat Mitalipov of the Oregon National Primate Research Center in Beaverton said in a news briefing August 25. "We believe that the technique can be applied very quickly to humans, and we believe it will work."

Mitochondria, the power-producing organelles in cells, carry their own DNA, distinct from the DNA held in cells' nuclei. Healthy or otherwise, mitochondrial DNA is passed from mother to child. In recent years, researchers have identified more than 150 harmful mutations in mitochondrial DNA, some of which can cause serious diseases (*SN: 2/28/09, p. 20*). There are only preimplantation and prenatal tests for some of these diseases, and most tests are unreliable.

"This whole field of mitochondria medicine is very new," says Douglas Wallace of the University of California, Irvine. "It affects lots of people, but we have very little to offer them." Some estimates report that 1 in 6,000 people may have inherited a mitochondrial DNA disorder.

A single cell can have thousands of copies of mitochondrial DNA. Usually, all of these copies are the same, healthy type. But occasionally a cell can have a mix of normal and mutant mitochondrial DNA, a condition called heteroplasmy.

Heteroplasmy in an egg cell makes it nearly impossible to determine if a baby is going to inherit a severe mitochondrial disease, says Jo Poulton of the University of Oxford in England. "You can get quite a big range of how much mitochondrial DNA is transferred to children."

To get around the guesswork surrounding inherited mitochondrial diseases, the researchers took the mother's mitochondrial DNA completely out of the picture. In the new work, researchers identified nuclear DNA in a mother's egg cell by the DNA's attachment to structures called spindles. Researchers removed the nuclear DNA (leaving the original mitochondrial DNA behind) and then put it into a donor egg cell lacking nuclear DNA but replete with healthy mitochondrial DNA. With the help of an inactive virus, the nuclear DNA fused into the donor cells.

Next, these modified egg cells were fertilized with donor sperm and implanted into rhesus females to develop. Male twins, named Mito and Tracker, were born healthy, followed later by two more individual males, named Spindler and Spindy, from different mothers.

Researchers found no traces of the original egg cell's mitochondrial DNA in the offspring, indicating that the process successfully prevented its transfer.

"I'm very pleased to see that, in nonhuman primates, this paper shows conceptually that this system might work," Wallace comments.

Mitalipov and colleagues plan to monitor the monkeys as they age. "We'd like to see the growth and development of the offspring, to see if they have any abnormalities," he says. Seeing how the mitochondrial DNA fares in subsequent generations will also be important, he adds. Doing that, though, will require female offspring, since mitochondria are passed on maternally. Mitalipov says the team is now trying for a girl.

Many of the techniques used in the experiment are already in use at human fertility clinics, Mitalipov says, though the procedure as a whole will need to gain approval from the Food and Drug Administration. The procedure, he says, "is offering real treatments to real patients."

Others remain cautious. Wallace says that the virus used to integrate the nuclear DNA into a donor cell would need to be scrutinized for safety. And Poulton says that performing techniques like this in animals might not reveal subtle defects. "Doing it in an animal is quite a long way off from doing it in humans," she says.

20,000 Estimated number of people who had bariatric surgery in the United States in 1995

171,000 Estimated number of people who had bariatric surgery in the United States in 2005

Stomach surgery benefits children

Study finds obesity creates unhealthy fetal environment

By Nathan Seppa

Children born to women who have achieved drastic weight loss through stomach surgery are healthier than kids born to severely obese moms, a new study shows. The findings suggest that obesity creates an unhealthy environment for a fetus that has ramifications later, scientists report in the November *Journal of Clinical Endocrinology & Metabolism*.

"This is the first proof that exposure to obesity in utero is associated with long-term effects," says Dana Dabelea, a physician and epidemiologist at the University of Colorado Denver and the Colorado School of Public Health in Aurora.

Severely obese women should be encouraged to lose weight before pregnancy, says study coauthor John Kral of the State University of New York Downstate Medical Center in Brooklyn.

Kral and his colleagues contacted 49 women who had given birth and had undergone biliopancreatic diversion bariatric surgery. On average, the women lost more than one-third of their body weight, going from severely obese to slightly overweight. The surgeries took place from 1984 to 2005. In that time, the women had a combined total of 111 children — 54 before surgery and 57 afterward.

The researchers found that 19 children born before their moms underwent surgery were severely obese, compared with six children born after surgery. Blood tests revealed that those born after surgery had healthier levels of two hormones that regulate appetite. These children also used insulin more efficiently. Measurements of overall HDL cholesterol, the good kind, were higher in post-surgery children, and their total-cholesterol-to-HDL ratio was lower.

These scores reveal a person's risk of cardiovascular disease, stroke and other health risks, Kral says.

Rodents lacking gene feel the burn

Study finds mutated mice use energy instead of storing fat

By Tina Hesman Saey

Mice with a mutation in an immune system gene don't get fat, they burn it.

A gene that helps regulate inflammation also stops fat cells from wasting energy. When the gene, *I kappa B kinase epsilon* or *IKKε*, is missing, mice turn a high-fat diet into heat instead of body fat, a study in the Sept. 4 *Cell* shows.

If the gene works the same way in humans as in mice, it could be a new target for antiobesity drugs.

Scientists know that low-level inflammation produced by obesity can trigger type 2 diabetes, but the details are unclear, says Alan Saltiel of the University of Michigan in Ann Arbor. In the new study, Saltiel and his colleagues found that in mice fed a high-fat diet, levels of the *IKKε* protein were elevated in the liver and fat tissue, compared with mice on a regular chow diet. *IKKε* is involved in regulating inflammation, and the researchers thought the protein might be the link between diet and diabetes.

"What I expected was that if we knocked out this gene we'd get rid of the link between obesity and diabetes," by eliminating inflammation, Saltiel says. He didn't suspect the connection would be severed further up the chain — preventing mice from getting obese to begin with.

Mice lacking the gene increase production of uncoupling protein, or UCP1, an energy-burning protein. It is found in mitochondria, the cell's power plants. Excess UCP1 causes fat cells to burn more energy and release it as heat.

Normally, IKKε "keeps the brakes on the expression of UCP1 in white fat," Saltiel says. "When we knocked out IKKε, we released the brakes."

After three months on a high-fat diet, the mice with the mutation gained an average of 12 grams, while normal mice gained about 20 grams. Although the mutant mice still gained some weight, the researchers say that it wasn't enough to trigger the inflammation and diabetes associated with obesity. When fed a normal diet, both types of mice weighed about 32 grams on average.

A gene deletion protected the mouse on the left against weight gain from a high-fat diet (visible in mouse on the right).

Removing *IKKε* clearly changes the mice's energy balance, says C. Ronald Kahn of Harvard's Joslin Diabetes Center, but the mechanism still isn't understood. He suspects that the mutant mice have more energy-burning brown fat cells, rich in UCP1, mixed in with white fat.

Previous studies have shown that mice lacking the immune gene are more susceptible to deadly viral infections. But Saltiel says that potential drugs inhibiting *IKKε* to fight obesity probably wouldn't turn the gene off completely, leaving enough activity to combat infections. White blood cells from the mutant mice in the new study responded normally to a substance designed to mimic a bacterial infection.

IMAGE: SCOTT GALVIN, UNIVERSITY OF MICHIGAN PHOTO SERVICES; STATS SOURCE: NATIONAL ASSOCIATION FOR WEIGHT LOSS SURGERY, WWW.BARIATRIC-SURGERY.INFO

Life

For audio clips of music based on monkeys' calls, visit **www.sciencenews.org/monkeymusic**

Tamarins sway to their own tune

Call-inspired music can alter primates' emotional states

By Jenny Lauren Lee

When people play their funky music for cotton-top tamarins, the monkeys hardly get their groove on. But playing monkey music does the trick. Cello music that mimics tamarin calls seems to bring forth the same sorts of emotions in the monkeys that the original calls would have elicited, researchers report online September 1 in *Biology Letters*.

People across cultures respond similarly to certain musical characteristics, such as inflection and pitch, says coauthor Charles Snowdon of the University of Wisconsin–Madison. "But we shouldn't expect other species to process it in the same way." Snowdon and David Teie of the University of Maryland School of Music in College Park wanted to know if monkeys' emotional states, like people's, could be manipulated by music.

Cotton-top tamarins seem to change behavior in response to cello music.

Teie, a composer and cellist, used traits from calls that tamarins made in response to both stressful and calming situations to compose cello and voice music designed especially for monkeys. After listening to a 30-second clip inspired by the contented vocalizations, the tamarins acted calmer than usual, moving less and eating more. Threatening music, full of "ch-ch-ch" noises and short staccato notes, made for anxious monkeys. The tamarins moved around from perch to perch and urinated frequently.

Snowdon says even the music that made the monkeys content is not pleasant to the human ear. Tamarin calls are higher pitched than human voices and use faster tempos. Likewise, the monkeys showed no response to human music, except for an unexpected "calm" reaction to a piece by the heavy metal band Metallica.

Even though it sounds different, the music tamarins and people find relaxing or stressful shares some common elements. Long legato notes and certain jumps in pitch, such as the leap from do to mi in Western music, calm monkeys and people. Clashing chords and short staccato bursts seem to have menacing associations. Snowdon says the similarities suggest that tamarins and people may share evolutionary roots for music.

But Joshua McDermott of New York University says: "Although I don't see that these initial results tell us a whole lot about the origins of human music, I think there are extensions of [the study] that could."

Google works on a different web

Ranking system inspires algorithm for predicting extinctions

By Susan Milius

Ecologists are taking a page, and its ranking, from Google.

A new algorithm inspired by the search engine works well for predicting which species losses will trigger collapse of a food web, says Stefano Allesina of the University of Chicago.

Food webs describe the pattern of what eats what in the neighborhood. If one species disappears, creatures that fed on it would need to find another lunch. If they couldn't, or if alternative entrées went extinct too, then the loss would trigger a cascade of extinctions. In some cases, it would unravel the whole food web.

The food web algorithm works much like PageRank, Google's system for ranking the importance of Web pages. The food web version does a better job of predicting collapse than simply comparing the number of connections each species has with other species in the food web. The method also beats out analyzing the network for hub species, Allesina and Mercedes Pascual of the University of Michigan in Ann Arbor report online September 3 in *PLoS Computational Biology*.

"The problem of how ecosystems are likely to respond to the loss of species is quite important, particularly in light of how many different ways human activities are resulting in the local extinctions of populations," says Jennifer Dunne of the Santa Fe Institute in New Mexico.

Allesina got the idea for treating food webs like the World Wide Web while he was at the National Center for Ecological Analysis and Synthesis in Santa Barbara, Calif., and chanced upon a description of Google's ranking system. In essence, the system calculates a page's importance, or value to searchers, based on the importance of the pages that link to it. In a food web, species draw importance from the importance of the species that eat them.

With some tweaks, the researchers accounted for the fact that anything can't eat just anything. "Energy does not go from the grass to the lion without going through the zebra," Allesina says. The team also added a path to a "detritus pool," so all species can die and become nutrients for primary producers.

BRYCE RICHTER/UNIV. OF WISCONSIN–MADISON

Humans

2.4 percent Men in a Swedish study found to have a snake phobia

8.3 percent Women in a Swedish study found to have a snake phobia

Girls but not boys may be primed for arachnophobia, ophidiophobia

Fear of crawly, slithery things could begin before first birthday

By Bruce Bower

Gut-wrenching fears of snakes and spiders may start early for many women. Before their first birthdays, girls but not boys adeptly learn to link the sight of these creatures to the frightened reactions of others, a new study suggests.

Neither infant girls nor boys link happy faces with snakes and spiders, reports study author David Rakison of Carnegie Mellon University in Pittsburgh in an upcoming *Evolution & Human Behavior*. Youngsters of both sexes also don't tend to associate images of flowers and mushrooms with either fearful or happy faces, he finds.

In Rakison's tests, 11-month-old babies first looked at pairs of images — a happy or fearful cartoon face was paired with a snake, spider, flower or mushroom. After the first brief display, Rakison timed how long each child gazed at new pairs of images. Youngsters who learned to associate two images, say a fearful face with a snake, would gaze longer at a violation of what they expected to see, the researcher reasoned.

Only girls associated the snake or spider that they originally saw with a fearful reaction and then acted on that knowledge, looking longer at the unexpected appearance of a happy face with a new snake or spider, Rakison proposes. No other pair of images elicited longer gazes from girls or boys.

If confirmed in further studies, these findings support the idea that people have evolved a brain mechanism that primes them for learning to pair fearful expressions with threats that would have repeatedly confronted prehistoric populations, Rakison says. In his view, bites from poisonous snakes and spiders presented a special danger to prehistoric women, whose children would have suffered or died without their mothers.

A Swedish survey of adults and children found that 5.5 percent report snake phobias and 3.5 percent report spider phobias. These phobias affect roughly four times more women than men.

"The basis for women's greater incidence of fear and phobias for snakes and spiders may be an evolved fear mechanism that operates during infancy and is especially sensitive in females," says Rakison.

Rakison theorizes that risk-taking personalities offered greater survival value for men in prehistoric times, when they had to hunt, defend their families and occasionally fight other groups.

A simpler form of learning may explain the findings, comments Vanessa LoBue of the University of Virginia in Charlottesville. Infants of both sexes may be equally primed to fear snakes and spiders. But if 11-month-old girls are generally better at recognizing facial expressions than their male peers, that would give infant girls an advantage at pairing fearful faces with snake and spider images.

In an unpublished review of her earlier studies, LoBue concludes that 5-year-old girls recognize threatening and nonthreatening expressions more quickly than boys. But it's not yet known if that difference holds for 11-month-olds. Further research needs to establish whether the sex difference reported by Rakison vanishes as boys become more experienced at decoding faces, LoBue says.

Genes & Cells

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Reptile research tells a tale of four chambers

Scientists find gene that may help regulate heart evolution

By Laura Sanders

Lizards and turtles are not warm and cuddly, but they do have hearts — and interesting ones, at that. A molecular difference in reptile hearts may have divided single ventricles into two, creating four-chambered hearts from three-chambered ones as species evolved, a study published in the Sept. 3 *Nature* finds.

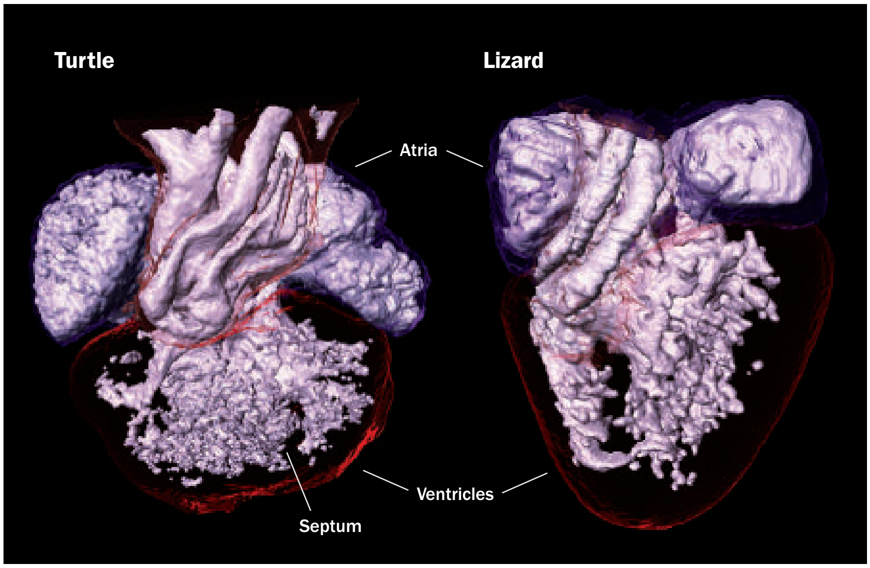
"The major question has been, what drove the evolution of the four-chambered heart?" comments James Hicks, an evolutionary biologist at the University of California, Irvine. Results from the new study "could lead to a deeper understanding of the fundamental factors involved in heart development," he says.

Amphibians have three-chambered hearts with two atria (the top chambers) and one bottom chamber, the ventricle. Mammals and birds have two atria and two ventricles, with ventricles separated by a muscular ridge called a septum.

Reptile hearts, on the other hand, have long been a mystery, says study coauthor Benoit Bruneau of the Gladstone Institute of Cardiovascular Disease in San Francisco. Lizard and turtle hearts appear to be intermediate forms, with two atria and a semiseparated ventricle. Muscular ridges lie in the middle of the ventricular region, but the anatomy didn't reveal whether they were true septa or not. With the new study, "we wanted to lay that uncertainty to rest," Bruneau says.

Researchers already knew that in mammals and birds, a gene called *TBX5* is active during development on the left side of the heart where the left ventricle forms, but not on the right side.

Bruneau and colleagues looked for



A new study may help solve a long-standing mystery by revealing that a turtle heart has two ventricles (separated by a septum) but a lizard heart has just one ventricle.

TBX5 gene activity in the developing hearts of red-eared slider turtles and green anole lizards to see if the segregated pattern of *TBX5* was present in reptiles. Early in development, *TBX5* was active throughout the entire ventricle region in both turtle and lizard hearts. But later, *TBX5* activity was greatly reduced in the right side of the turtle heart, remaining strong in the left side. Such separation suggested that the turtle does have two ventricles, Bruneau says. In the lizard heart, *TBX5* had no separation, suggesting a single ventricle.

"We were able to conclusively say that the large structure found in lizards is not a septum," Bruneau says. Lizards are thought to have evolved before turtles, indicating that *TBX5*'s segregation, and the ensuing ventricle separation, evolved after the two groups' ancestors split.

But just because the *TBX5* pattern correlated with septum formation — or lack thereof — doesn't mean that *TBX5* was actually causing ventricle separation. "We didn't know how important the *TBX5* pattern was," Bruneau says.

So the researchers manipulated the pattern in developing mouse hearts. When researchers shifted levels of the gene's expression, the mouse hearts failed to form two ventricles. Mouse hearts also did not form two ventricles when *TBX5* was expressed everywhere throughout the ventricle region, similar to what happens in lizard hearts.

"We found that the activity of *TBX5* is really important for septation," Bruneau says. "I've always wondered about the evolution of the heart. Being able to pinpoint an important regulator of the heart is exciting."

A four-chambered heart with two ventricular chambers allows for two different blood pressures: low pressure for blood pumped to the lungs and high pressure for the oxygen-rich blood pumped to the rest of the body. This dual pressure system is a requirement for warm-bloodedness, Hicks says. Warm-blooded animals may have higher growth rates, niche expansion and greater competitiveness in an environment. "Now that the tools are there, we can look at a whole variety of reptiles," Hicks says.

The new study not only sheds light on the evolution of the four-chambered heart, but also may improve understanding of congenital heart diseases, some of which are caused by *TBX5* mutations.

BOGAC KAYNAK, B. BRUNEAU

"This is the tip of the iceberg of what we will find when we start looking at all the bacteria in our gut…" — VINCENT YOUNG

Antibiotic resistance resides in gut

New genes transfer defensive trait when inserted into *E. coli*

By Jenny Lauren Lee

The human gut is a reservoir of antibiotic resistance. And bacteria residing there could bequeath that resistance to harmful microbes under the right conditions, a team reports in the Aug. 28 *Science*.

Harvard Medical School researchers have found more resistance genes in indigenous gut bacteria than had been known to exist. So far, the team has identified more than a hundred new genes conferring resistance to up to 13 antibiotics. All of the genes retain that role when inserted into *E. coli* bacteria in the lab, the authors say.

"This is the tip of the iceberg of what we will find when we start looking at all the bacteria in our gut that we mainly just ignore," says Vincent Young of the University of Michigan in Ann Arbor.

Morten Sommer and his colleagues tested bacteria from feces and saliva of two people for genes that would allow the bacteria to grow in the presence of common antibiotics.

Previous tests of antibiotic resistance in human gut bacteria have looked only at bacteria that grow well in a laboratory. But the Harvard group used a recently developed method to insert DNA from bacteria that are difficult to culture directly into more easily grown bacteria. In DNA from lab-friendly and lab-loathing bacteria, the team has identified 215 genes conferring antibiotic resistance so far. More than a hundred of these genes had never been identified before.

"It's a very good study," says Stuart Levy of Tufts University in Boston. However, he says, people should not assume that this resistance is an effect of antibiotic use. It could be a more general, natural reaction to the food and other substances that gut bacteria encounter daily.

Though bacteria are known to transfer genes among themselves, scientists have not yet found direct evidence that gut bacteria have passed antibiotic resistance to pathogens. If bacteria can exchange the newly found genes, then the study's findings suggest to Sommer that the resistance could be transferred too. But it's not clear how often it would happen or whether it would threaten health.

Molecules

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Fruity whiffs can mask the scent of carbon dioxide for flies, mosquitoes

Study suggests new approach to making insect repellents

By Susan Milius

Fruit flies actually have a love-hate thing with the smell of fruit. And a new insight into the chemistry of that relationship could lead to novel repellents for other insects, researchers say.

Carbon dioxide is a known turn-off to fruit flies when it emanates from stressed peers. "*Drosophila* sniff CO_2 and avoid it like crazy," says neurobiologist Anand Ray of the University of California, Riverside. But ripe fruit puffs out the gas and still attracts plenty of the flies. In this case, compounds in the fruit block the flies' CO_2 receptors, Ray and Riverside colleague Stephanie Turner report online August 26 in *Nature*.

Mosquitoes, in contrast, love CO_2. They hunt down blood by following plumes of the exhaled gas. But as in fruit flies, a fruit compound can jam CO_2 receptors in the mosquito *Culex quinquefasciatus*, the researchers say.

This species spreads West Nile fever virus and the parasites that cause the limb swellings of filariasis. Ray proposes that compounds that could keep the mosquito detectors from sensing those plumes might render people hard to find.

The paper looks like a significant contribution toward developing new controls for disease-spreading insects, says Pablo Guerenstein of CONICET, Argentina's research council in Diamante and Entre Rios National University in Oro Verde.

> "*Drosophila* sniff CO_2 and avoid it like crazy.… There was this paradox."
> ANAND RAY

An aversion to CO_2 turned up in fruit flies when researchers stressed some of the insects. Stressed flies released an odor with CO_2 as a key component, and unharmed flies fled from that odor. "There was this paradox," Ray says, because fruit flies avoid stressed flies but crowd around ripe fruit and other CO_2 sources.

To study the seeming contradiction, Ray and Turner looked to the sensory detectors on the insects' antennae. "Each antenna is shaped like a strawberry, with hundreds of tiny hairs on it," Ray says. Inserting minute electrodes into some of the hairs let the researchers check for activity in a neuron bearing the specialized receptor known to detect CO_2. The researchers monitored that neuron's activity while releasing both fruit odors and CO_2. Two of the fruit odors strongly reduced the neuron's reaction to CO_2.

Those two molecules, 1-hexanol and 2,3-butanedione, were quite a surprise, Ray says. Yet, he and Turner note, earlier studies showed that as bananas ripen, concentrations of 1-hexanol increase by 777 percent and 2,3-butanedione by 14,900 percent.

To test the receptor independent of the neuron, Ray says, the team used "the awesome power of fly genetics" to put the receptor in a neuron that normally does not respond to the gas. The new neuron responded to CO_2 and also showed reduced activity when the fruit molecules wafted by.

Mosquito neurons also failed to respond to CO_2 in the presence of 1-hexanol and 1-butanal, a close relative of 2,3-butanedione.

JAQUELINE HO/THE DEMAS LAB/INDIANA UNIVERSITY

Leptin-led hamster boom

Pregnant mommas must make a tough choice: preserve energy for themselves or invest it in their little ones. Now new research reported online August 26 in *Proceedings of the Royal Society B* suggests that higher levels of the hormone leptin may fool a hamster's brain into thinking there is energy to spare. Susannah French of Utah State University in Logan and colleagues fitted Siberian hamsters (one shown) with a pump that kept their leptin levels artificially high. Pregnant hamsters receiving leptin had larger litters than pregnant hamsters without the leptin pumps. And whereas hamsters are known to pick off a newborn pup or two, the leptin-treated hamsters did not eat a single one of their young. But leptin-treated hamsters also paid a price for a larger brood. While pregnant, they could not fend off bacterial attacks as easily as untreated counterparts. And once off the pumps, rodents that had received leptin ate more than untreated hamsters. —*Jenny Lauren Lee*

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Desperately Seeking Moly

Unreliable supplies of feedstock for widely used medical imaging isotope prompt efforts to develop U.S. sources

By Janet Raloff

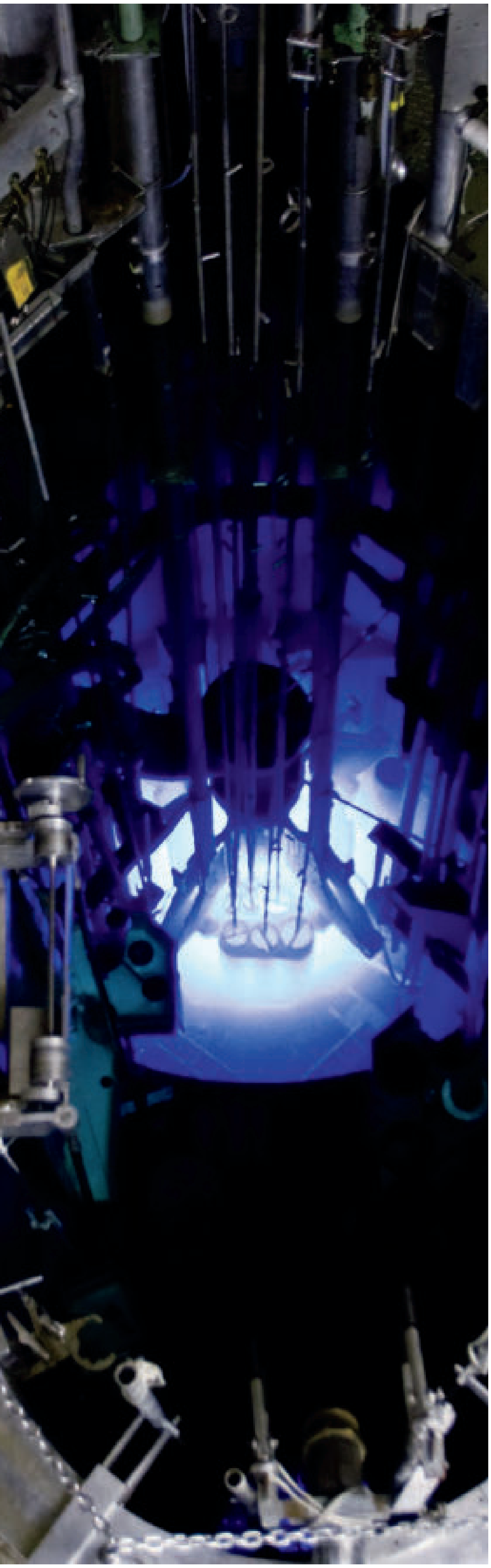
Of all the radioactive isotopes used in medical diagnostics, none plays a more pivotal role than technetium-99m. Each weekday, hospitals and clinics around the world use it to perform about 60,000 diagnostic procedures. Used in about 80 percent of nuclear imaging tests, the isotope is one of modern medicine's major tools for detecting, evaluating and treating cancers, heart disease and other serious illnesses. It helps doctors lengthen patients' lives.

Trouble is, Tc-99m itself has a very short life. Radioactive decay depletes it by half every six hours. The feedstock that supplies it — molybdenum-99 — also has a rather short half-life (66 hours), so neither isotope can be stockpiled. New Mo-99, or "moly," must be made continually and delivered to imaging centers weekly.

But now the system for supplying the feedstock for nuclear imaging's star isotope is in peril. Just five geriatric nuclear reactors in Canada, Europe and South Africa produce roughly 90 percent of the global Mo-99 feedstock. At an average age of 47, those plants frequently shut down for the kinds of repairs commonly needed in reactors operating well past their prime. This summer such shutdowns led to technetium shortages so severe that U.S. officials now say efforts must begin, at long last, to establish American sources of these critical isotopes.

On again, off again

Problems began on May 15, when reactor operators found a small leak at the biggest Mo-99 producer, Canada's 52-year-old National Research Universal reactor near Chalk River, in Ontario. Inspections would eventually turn up widespread corrosion in the reactor's outer wall.



This University of Missouri reactor core could be harnessed to make moly for the short and eventually the long run.

NICHOLAS BENNER/UNIVERSITY OF MISSOURI

Atomic Energy of Canada Limited, which runs the facility, recently announced that the reactor would not restart until well after the first of the year.

Routine maintenance brought down the second biggest Mo-99 producer — the Dutch High Flux Reactor in Petten — for roughly a month this summer. With the Canadian reactor offline as well, worldwide supplies of Mo-99 plummeted to about 30 percent of normal. Although the Petten reactor resumed operation in mid-August, its return to service will be short-lived. By March 2010, the 47-year-old reactor must shut down for an estimated six months to undergo delayed repairs of corrosion damage.

The precarious health of Mo-99–production reactors had already spurred the Society of Nuclear Medicine to petition Congress for help in 2008. Led by Robert Atcher of Los Alamos National Laboratory in New Mexico, then president of the society, these scientists and physicians campaigned for development of new, more reliable — and preferably domestic — sources of Mo-99. Even before this summer's technetium crisis emerged, the White House launched a federal interagency panel to look at developing homemade moly — perhaps, on an emergency basis, as early as spring 2010.

Such developments are fueling optimism, Atcher says, because the erratic availability of Tc-99m and its feedstock are "finally on the radar screen." Many U.S. companies, he adds, are now lining up to help bring moly production home.

Few good alternatives

A Society of Nuclear Medicine survey in August of 710 members found that 80 percent felt the impact of the summer's Tc-99m shortage. Only 31 percent of participants reported having enough isotope to perform at least three-quarters of their normal imaging workload; 5 percent were working at no more than 25 percent capacity. Of the respondents, 16 percent expected to "be down to zero percent capacity within a month."

Since the Canadian reactor's Mo-99 production stopped in May, Tc-99m supplies to Vanderbilt University Medical Center in Nashville have been only about two-thirds of what was requested, and sometimes have been as low as 25 percent of normal, says Jeff Clanton, who runs the radiopharmacy there.

What worries him most: the Petten reactor's long outage beginning next spring — especially if the Canadian reactor isn't back in operation. "I expect we'll be down to 10 or 20 percent of our normal supply," he says. That would be a serious shortfall for a hospital system that had been performing 1,000 Tc-99m tests weekly.

Some hospitals report that by scheduling procedures carefully — say early in the week when supplies haven't decayed as much — they have been managing fine with the limited technetium.

"They may be fine," says Chaitanya Divgi, who heads nuclear medicine at the University of Pennsylvania School of Medicine in Philadelphia, "but in many cases the patient will not be fine."

For instance, imaging centers normally use roughly half of their Tc-99m in procedures to monitor blood perfusion into heart tissue following cardiac stress tests. When technetium — the gold standard for such heart studies — is in critically tight supply, as it now is in Divgi's hospital, physicians have been substituting a much older procedure that uses thallium-201.

Thallium is not as energetic as Tc-99m, "so the diagnostic quality of the image is not as good," explains Dean Broga, a medical physicist at the Medical College of Virginia in Richmond. The test's false negative rate is potentially higher, he says, which means some heart problems might be missed.

Divgi points out another potential problem: "An old dog like me has seen plenty of thallium images. But there's a whole slew of cardiologists and nuclear medicine physicians out there who've never seen a thallium image and could have some trouble reading it."

Switching to thallium also substantially increases how long a patient must lie still on a hard table as the heart scan proceeds following a stress test. Perhaps 4.5 hours with thallium, instead of two with Tc-99m. The patient's radiation dose will roughly double as well.

The trade-off, Divgi and others explain, is that by shifting cardiac–stress test scans to thallium, Tc-99m can be reserved for applications with no good or affordable alternatives. These include scans to measure irreversible damage to heart function by chemotherapy drugs and probes in the emergency room of potentially serious gallbladder inflammation.

About 16 percent of technetium imaging tests scout for cancer in bone. Here, another procedure, sodium-fluoride positron emission tomography, is as good as Tc-99m — and is recommended by the Food and Drug Administration as a suitable alternative during the current isotope crisis. However, Medicare won't cover it. So few hospitals will consider using this PET scan as a substitute.

At the request of five medical societies, Medicare officials are reevaluating their agency's exclusion of coverage for PET bone scans. But officials say they plan no announcement before March.

In a pinch

The White House, meanwhile, has recognized the growing vulnerability of moly imports to the United States. "We decided it was time to move forward, as quickly as we could, on establishing domestic production," says Jean Cottam in the White House Office of Science & Technology Policy.

Even if expedited, new facilities would take some four to 10 years to build, license and put into operation. Since the United States might not be able to wait that long, the White House office set up an interagency group and charged it with finding bridge tactics.

To make moly today, existing reactors bombard targets — essentially metal plates containing 95 percent–pure uranium-235 — with neutrons. This prompts some uranium to fission, or break apart, into fragments that include the sought-after isotope.

The easiest way to spur domestic isotope production, Cottam says, would be to take existing targets from Chalk River, irradiate them in a similar facility and then send those irradiated targets back to Canada to have their moly extracted. Letting the Chalk River facility extract the isotope would avoid having to get FDA licensing of some new facility, which "can take years," Cottam says.

At least a few reactors in the United States, such as the University of Missouri Research Reactor, known as MURR, and the High Flux Isotope Reactor at Oak Ridge National Laboratory in Tennessee, are good candidates for irradiating Canadian targets, Cottam notes.

But licensing those facilities to irradiate targets and to send them to and from Canada might take six months, she says. Chalk River targets contain bomb-grade uranium, albeit in small quantities. So obtaining clearance to transport the targets in large quantities requires permission from the National Nuclear Security Administration, part of the Department of Energy.

Although some scientists worried that this might be a nonstarter, the agency recently jumped on board. "NNSA supports the White House decision to implement any interim solution for the supply of this important medical isotope, including irradiation of highly enriched uranium targets in appropriate and available facilities," says agency spokesman Damien LaVera.

Long-term solutions

As bad as this year's Mo-99 shortages became, Atcher points out that things could get even worse. The Department of Homeland Security "could close our borders at any given time because of some real or perceived threat," he notes. Also, considering the age of the Chalk River reactor, its frequent outages and a summer-long escalation in the recognition of how serious its corrosion problems are, "many are speculating that this reactor will never restart," he observes. It had been providing about one-third of global Mo-99 supplies.

Without any U.S. capacity to process irradiated targets, Atcher notes, either scenario could result in an almost immediate suspension "of all but about 20 percent of the imaging that we do in nuclear medicine." This explains the premium that the White House and the medical community are placing on domestic moly processing as well as its production.

Any next-generation moly makers in the United States, meanwhile, must adhere to a new federal policy: They can no longer use targets containing more than 20 percent uranium-235 (compared with the current 95 percent). While this alleviates the risk of targets being hijacked by terrorists to make bombs, it could also quintuple the number of targets needed to produce a given amount of Mo-99 and jack up moly extraction costs.

Worldwide Supplies of Moly

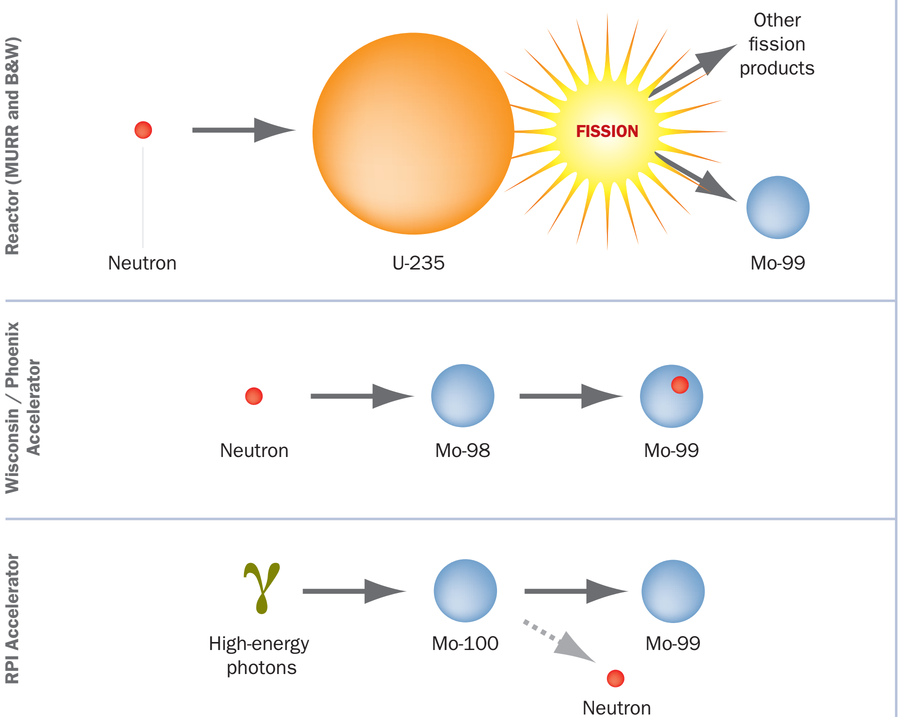
Most molybdenum-99, feedstock for the most-used radioisotope in medical imaging, comes from just five aging reactors. A little is made by newer reactors, such as OPAL. Outages at older reactors have created shortages, prompting calls to make moly in the United States.

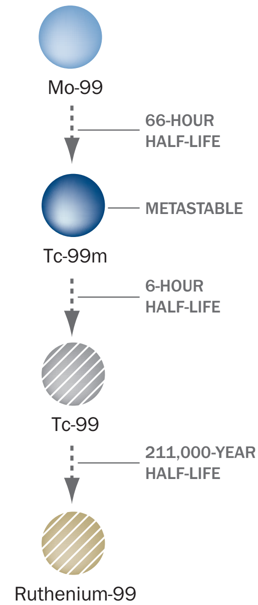
Country	City, Province	Facility Name	Reactor Age (Years)	% World Supply of Moly	Power Output (Megawatts)
Canada	Rolphton, Ontario	NRU Chalk River	52	33%	135
The Netherlands	Petten	HFR	47	33%	45
Belgium	Mol	BR2	47	10%	100
France	Saclay	OSIRIS	42	8%	70
South Africa	Pelindaba	SAFARI	43	3%	20
Australia	Sydney	OPAL	2	N/A	20

TABLE: A. NANDY, SOURCE: SOCIETY OF NUCLEAR MEDICINE

New Routes to U.S. Moly

Currently, the conventional approach to making molybdenum-99 uses neutrons to bombard uranium-235 atoms, which fission, or split, to form Mo-99 and other products (top). An alternative approach being investigated by a Wisconsin team would use an electron-beam accelerator to produce neutrons, which would strike targets containing molybdenum-98 to create Mo-99 (middle). One New York researcher suggests shooting high-energy photons at a target of Mo-100 atoms (bottom). Mo-100 atoms would then shed a neutron, forming Mo-99.





Moly Decays to Technetium

Mo-99 is the feedstock for technetium-99m, the isotope used in 80 percent of diagnostic nuclear medicine. Roughly every three days, half of the Mo-99 will decay into Tc-99m (the m stands for metastable). Every six hours, half of that decays into the long-lived Tc-99 (not useful in medicine), which glacially decays into ruthenium.

A. NANDY

Making the old new again

The top two homegrown candidates for supplying moly are the 43-year-old MURR, in Columbia, Mo., and a reactor still undergoing development by Babcock & Wilcox Co. of Lynchburg, Va. Both rely on designs that are conceptually old.

MURR is a small, conventional reactor that houses highly enriched uranium-oxide fuel in rods that are inserted into a pool of water. The reactor already creates dozens of different isotopes for use in medicine and research and can fairly easily be adapted to produce Mo-99. The first thing MURR needs are uranium targets. The fission — or splitting — of the reactor's fuel releases neutrons. If those neutrons strike a target containing uranium-235, the resulting fission generates a mix of products, including Mo-99. (This is what happens at Canada's Chalk River facility, for instance.)

MURR also lacks Chalk River's ability to chemically dissolve uranium from those targets, extract the moly and enrich that isotope into a clean, medical-grade product. The University of Missouri is, however, planning to develop such onsite processing capabilities for this isotope.

Once initial federal approval comes through, "it's probably going to take us three years to design and construct the processing facility, and another six months to do the commissioning and testing," says MURR director Ralph Butler. "We're very optimistic that we could supply at least half of the United States' [Mo-99] needs."

Production could begin by 2013, he says — especially if DOE helps fund the processing facility's construction.

The Babcock & Wilcox reactor employs a totally different design — a pool of water seeded with uranium, which serves as both the fuel and molybdenum-producing target. More than 30 of these homogenous aqueous-phase reactors have been operated around the world, notes Bob Cochran, president of B&W's Technical Services Group. His company has patented elements of the design that would make it suitable for Mo-99 production.

Part of this reactor's appeal — what could satisfy critics worried about nuclear safety — is that "this is what we refer to as an inherently safe reactor," Cochran says. It's not pressurized. To shut it down, he says, "just pull the plug" and drain the water into tubing or tubs that alter the geometry of the fuel.

That's also how any moly would be retrieved. The aqueous fuel would be drained from the reactor's core and passed through separation columns, now under design. Following moly retrieval, the uranium-laced water would return to the reactor, where unfissioned atoms would become the fuel again.

This reactor should produce very little waste compared with conventional reactors and can be quite small — probably smaller than a 55-gallon drum. Its design, Atcher says, also makes it difficult to extract weapons-grade material, "thus providing a reactor design that can be safely installed around the world."

How soon? "In the best case," Cochran says, "probably the end of 2013. But no later than 2015."

Slower, but accelerated

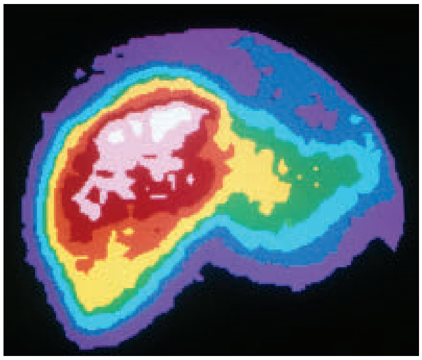
Although it will take them appreciably longer to get isotopes to market, at least three teams are looking to sidestep reactors and make moly using accelerators.

Researchers at Rensselaer Polytechnic Institute in Troy, N.Y., use accelerators that create a beam of high-energy electrons. As these particles slam into a metal target, they create high-energy photons, similar to gamma rays, called bremsstrahlung, or braking radiation, explains nuclear engineer Yaron Danon. The trick is to put a batch of stable, or nonradioactive, molybdenum — Mo-100 — into the path of those bremsstrahlung photons. The energy they deposit when they hit the isotope can knock a neutron from its nucleus. The result: Mo-99.

After extracting this new isotope, the stable moly that is left over would get recycled back for another encounter with the beam. One batch of Mo-100 should last a long time, he says.

This process generates far fewer waste products than fission-based Mo-99 production, Danon says, and yields almost no radioactive waste. The primary radioactive material is the commercial product.

Advanced Medical Isotope Corp. of Kennewick, Wash., hopes to commercialize a somewhat related concept, one developed by researchers at the University of Missouri and which was the subject of a patent filing earlier this year. Robert Schenter, the company's chief science officer, envisions the system as a squat, meter-long vessel containing heavy water (deuterium oxide) and uranium. Shooting a beam of high-energy electrons at a tungsten target produces bremsstrahlung. The bremsstrahlung photons then rip apart deuterium, releasing neutrons. As these neutrons hit uranium, they'll cause it to fission, producing some Mo-99.



A healthy liver as viewed with nuclear imaging. Scans like this one, produced using a radioactive isotope of technetium labeled with a sulfur compound, assist doctors in assessments of organ function and in diagnoses.

To boost the efficiency of this system, Schenter came up with the idea of blanketing the vessel with a material that acts like a neutron mirror; it should reflect any unreacted neutrons back and forth within the vessel, thereby increasing their chance of hitting a uranium atom. A blanket of polyethylene would work well, his calculations indicate, potentially increasing the effective flux of neutrons more than a thousandfold. On August 18, Schenter filed for patent protection on this blanket reflector.

Tests in August confirmed that the accelerator could make neutrons in heavy water, as predicted, but this system did not include uranium. A full prototype is probably a couple of years away, Schenter says.

Meanwhile, for the past six months researchers in Madison, Wis., have been investigating the idea of turning an electron beam loose in an ionized gas, thereby producing neutrons to direct into a pool of heavy water seeded with molybdenum-98. Some of the neutrons would merge with Mo-98 nuclei, creating Mo-99, explains Paul DeLuca Jr., the University of Wisconsin–Madison's provost and a codeveloper of the idea.

So far, there's been no construction or design development. The idea "is purely on paper," DeLuca says, although based on neutron studies performed in his lab. Phoenix Nuclear Labs in Middleton, Wis., hopes to commercialize the concept.

What lies ahead

Right now, the Office of Science & Technology Policy and DOE are trying to figure out "exactly which research groups are the most technically mature and have the highest production capability," Cottam says. "Then we will work with them to assist bringing them online," providing money for nonproprietary research and technical assistance on design issues.

Legislation supporting the development of domestic moly production has also emerged in Congress this summer, suggesting the isotope's precarious supplies are on lawmakers' radar screens.

As encouraging as the developments are, Atcher says, what the medical community needs is action. After all, no blueprint yet exists for ensuring stable supplies of Mo-99, the federal government has yet to give any financial support to domestic companies and a host of regulatory obstacles must still be hurdled.

Meanwhile, Broga noted in August, "I was in a hospital this morning, and I could only schedule two patients [for Tc-99m imaging]. Normally we'd do eight to 10." He suspects a lot of elective procedures — such as for cardiac stress tests — are being postponed. Undoubtedly, he adds, some emergency room scans for pulmonary embolisms, inflamed gallbladders or heart blockages are being shifted to less sensitive screening technologies, "which represents a severe in-hospital risk."

Divgi concurs. "In most instances," he says, "these compromises can make a difference in the quality of patient care." ■

Explore more

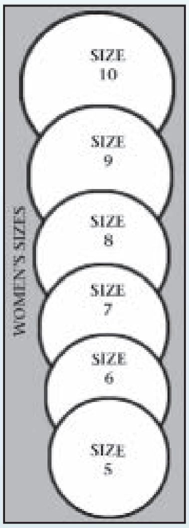
- Nuclear and Radiation Studies Board. *Medical isotope production without highly enriched uranium*. National Academies Press, 2009.
- Society of Nuclear Medicine www.snm.org
- H.R. 3276 (American Medical Isotope Production Act of 2009). July 21, 2009. http://bit.ly/7uW2S

Sabatini's Big Mistake

*Top luxury designer gets desperate, offers masterpieces for Better Than FREE!**

Timing is everything in the jewelry business. Some of the most gifted designers in the world learned that lesson the hard way after scores of high-end luxury houses filed Chapter 11 during the economic meltdown and retail boutiques shut their doors. Luckily, more than a few of them held on to my business card.

The call from Sabatini's brought mixed emotions. I felt terrible for my colleagues, but excited by what I knew was a once-in-a-lifetime opportunity. Some big-name clients had to cancel their orders and the designers were looking to sell.



USING THE RING SIZE CHART
Place one of her rings on top of one of the circle diagrams. Her ring size is the circle that matches the inside diameter of the ring diagram. If her ring falls between sizes, order the next larger size.

A masterpiece that's "Better Than Free". I tried not to sound too eager, and immediately made an offer on this spectacular 3-stone ring setting. The exquisite, handcrafted detail of the .925 sterling silver elevates each piece to the level of fine art. I'm in awe of the technique that involves placing each delicate bead of granulation one-at-a-time, up on the ring's shoulders and along the band. Even before setting a single stone, the ring took my breath away. Their price to Stauer was so reasonable that we can present to you our **"Better Than Free"** offer. Priced at only $195, you get $200 in Stauer **Gift Coupons** with the purchase of this ring. **Basically, we're paying you to shop Stauer.**


Gaze over the fine sterling silver details embellishing the Sabatini Ring

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HUNTING HIDD

Black hole blast

The creation of black holes in the Large Hadron Collider, which will smash protons together at nearly the speed of light, would indicate the existence of extra dimensions. A simulation of one possible fingerprint of a black hole (above) in the collider's Compact Muon Solenoid detector shows colored cones to represent different particle types, and bar lengths indicate particles' energy intensity.

In many ways, black holes are science's answer to science fiction. As strange as anything from a novelist's imagination, black holes warp the fabric of spacetime and imprison light and matter in a gravitational death grip. Their bizarre properties make black holes ideal candidates for fictional villainy. But now black holes are up for a different role: heroes helping physicists assess the real-world existence of another science fiction favorite — hidden extra dimensions of space.

Astrophysical giants several times the mass of the sun and midget black holes smaller than a subatomic particle could provide glimpses of an extra-dimensional existence.

Out in space, astrophysicists are looking hard to see if large black holes are

EN DIMENSIONS

Black holes, giant and tiny, may reveal new realms of space

By Diana Steele

shrinking on a time scale that might be detected by modern telescopes. If so, it might mean the black holes are evaporating into extra dimensions.

In the laboratory, black holes far smaller than anything that could be seen with a microscope might be produced in Europe's Large Hadron Collider after it starts running again in November (*SN: 7/19/08, p. 16*). The detection of such a black hole, which would evaporate in a hail of subatomic particles in a tiny fraction of a second, would provide evidence that unseen dimensions of space exist.

What makes either of these ideas even plausible is a bold theory put forth just over 10 years ago that purports to explain the weakness of gravity by supposing that some of it is leaking out into extra dimensions.

Gravity feels strong to humans because it makes climbing hills hard. But one of the fundamental paradoxes about gravity is demonstrated by the fact that an ordinary refrigerator magnet can pick up a paperclip — counteracting the entire mass of the Earth pulling down on the clip.

Physicists call this the "hierarchy problem," referring to the fact that all the other forces of nature are more than 30 orders of magnitude stronger than gravity.

"It's hard to explain such a huge number from any mathematical postulate or any physical principle," says Greg Landsberg, a theoretical physicist at Brown University in Providence, R.I. "It's a bit of an embarrassment for our field, because what it really means is, we don't seem to understand gravity."

Measuring extra dimensions

Isaac Newton declared in the 17th century that gravity gets weaker by the square of the distance between two objects. If the moon were twice as far from Earth, it would feel one-quarter the gravity.

But in 1998, theoretical physicists Nima Arkani-Hamed, Savas Dimopoulos and Gia Dvali pointed out that gravity had never been measured below a distance of about a millimeter. Suppose, they suggested, that gravity differs from Newtonian expectations at distances smaller than a millimeter.

That could happen if there are extra dimensions of space that gravity leaks into. These hidden dimensions might be shaped, for example, like the circumference of a hose. From a distance, the hose looks like a one-dimensional line, but seen up close, it has a curled-up second dimension. Arkani-Hamed, Dimopoulos and Dvali — whose model is known as ADD, short for their names — suggest that there could be extra dimensions as large as a millimeter in diameter.

"In principle, the extra dimensions can be so small, like trillions and trillions of times smaller than a millimeter, and that's what string theory predicts," says theoretical astrophysicist Dimitrios Psaltis of the University of Arizona in Tucson. But "if you introduce those large extra dimensions, then gravity can get diluted in some way."

Gravity may spread into the extra dimensions while the other known forces and particles are confined to the three familiar spatial dimensions. So gravity could be just as strong as the other forces — but only felt strongly at short distances.

Tiny curled extra dimensions aren't the only possibility. In 1999, theoretical physicists Lisa Randall and Raman Sundrum proposed that one extra dimension might stretch out to infinity. If either theory is true, it would also mean that at very small distances, gravity would be much stronger than Newton's prediction.

The idea of "large" extra dimensions sent experimental physicists scrambling.

So far, physicists using sensitive small-scale experiments have measured the force of gravity at distances just under 50 micrometers and haven't found any deviation from Newton's law yet. But they keep looking.

Shrinking black holes

Black holes, as the most gravitationally dense objects in the universe, might provide another way of testing the extra-dimension hypotheses. Black holes know a thing or two about gravity; the trick is getting them to reveal their secrets.

In the 1970s, theoretical physicist Stephen Hawking calculated that black holes actually lose mass. That mass vanishes over time in the form of what's now called Hawking radiation. "Over time" generally means over billions of years, like the age of the universe. The larger

THE CMS COLLABORATION

the black hole is, the more slowly it shrinks. But as it gets smaller, the evaporation rate accelerates.

And if there are extra dimensions of the Randall-Sundrum type, astrophysical black holes might emit gravity waves into these other dimensions and shrink faster than otherwise expected. So, Psaltis thought, finding a small black hole that's really old would limit the size of the extra dimensions. "If you notice that a black hole lived, for example, a hundred million years," Psaltis says, "that means that it couldn't have evaporated, couldn't have lost its mass really, really fast."

But finding out the age and weight of a black hole is about as tricky as discovering that of a vain movie star. So Psaltis tried to find a way to get the black hole to reveal a little bit more about itself.

He found a black hole that looked like it had been kicked out of the plane of the Milky Way galaxy following a violent supernova explosion, like a fastball hit over the wall at Fenway Park. Since the black hole would have been born in the explosion, Psaltis could estimate its age by measuring how fast it and its companion star were zooming away from the galaxy, then backtracking to find out how long ago it had been ejected.

He calculated that this particular black hole, J1118+480, was a minimum of 11 million years old. Using that age and an estimated mass, Psaltis put an upper limit of 80 micrometers on the size of any extra dimensions, as he reported in *Physical Review Letters* in 2007.

Tim Johanssen, Psaltis' graduate student, came up with another idea for measuring whether black holes are losing weight, one that doesn't depend on knowing their ages. Most black holes a few times the mass of the sun have been detected because they orbit a companion star. The masses of the star and the black hole, as well as the distance between them, determine how fast the two rotate around each other, like Olympic pair skaters spinning around each other in a death spiral. If the mass of the black hole is changing, the rate at which it and its companion orbit each other, called the orbital period, changes as well.

Johanssen calculated how quickly a black hole would have to lose mass in order to see a noticeable difference in the orbital period. "Just from normal astrophysical mechanisms, we would expect [the period] to halve or double at a timescale on the order of the age of the universe, billions of years," says Psaltis. "If extra dimensions exist, and they are as large as, say, a tenth of a millimeter, then that time scale goes down to about several millions of years. Which means that if you make an observation over a year, you expect a change in the orbital period of a few parts per million. This is tiny, but this is something that modern observations of binary systems can actually do."

Johanssen, Psaltis and astronomer Jeffrey McClintock of the Harvard-Smithsonian Center for Astrophysics looked closely at the best-studied black hole binary, A0620-00, which has been observed for about a decade. So far, they found, there has been no observable change in its orbital period. That let them constrain the size of the extra dimension to less than 161 micrometers. Their results appeared in February 2009 in the *Astrophysical Journal*.

Another researcher, Oleg Gnedin of the University of Michigan in Ann Arbor, extrapolated from Psaltis' work. Gnedin learned of a recently discovered black hole in a globular cluster, one of the oldest groups of stars in the universe. Black holes in globular clusters are on the order of 10 billion years old. The mere existence of a black hole this old puts a very tight constraint — less than 3 micrometers — on the size of the Randall-Sundrum extra dimensions, Psaltis says. That work was published online at arXiv.org in June (*SN: 8/1/09, p. 7*).

Although the globular cluster work sets the tightest constraint on extra-dimension size so far, the researchers admit that it relies on a lot of assumptions.

Psaltis is pinning his hopes on observations of binary systems because, he says, they're "a measurement of what is happening right now to the black hole that we are seeing. It does not depend on the history." He says that even though the researchers haven't seen any changes in orbital periods so far doesn't mean the extra dimensions don't exist, just that they haven't been found yet. Any change in orbital period, he says, would challenge physicists' current theory of forces and particles in the universe — called the standard model.

But even if the extra-dimension theories are correct, observers still may never find evidence of such dimensions in the astrophysical black holes. One reason may be that the extra dimensions are of the ADD variety, small and curled up, in which case these tiny dimensions make no difference to the massive black holes in outer space.

The other reason may be that black holes don't really evaporate faster into other dimensions even if they do exist, says Randall, the Harvard theoretical physicist who coauthored two of the popular extra-dimension models. "People have suggested that the decay rates of black holes might be a way of distinguishing" between the models, she says, "but it's not fully resolved."

Micro black holes

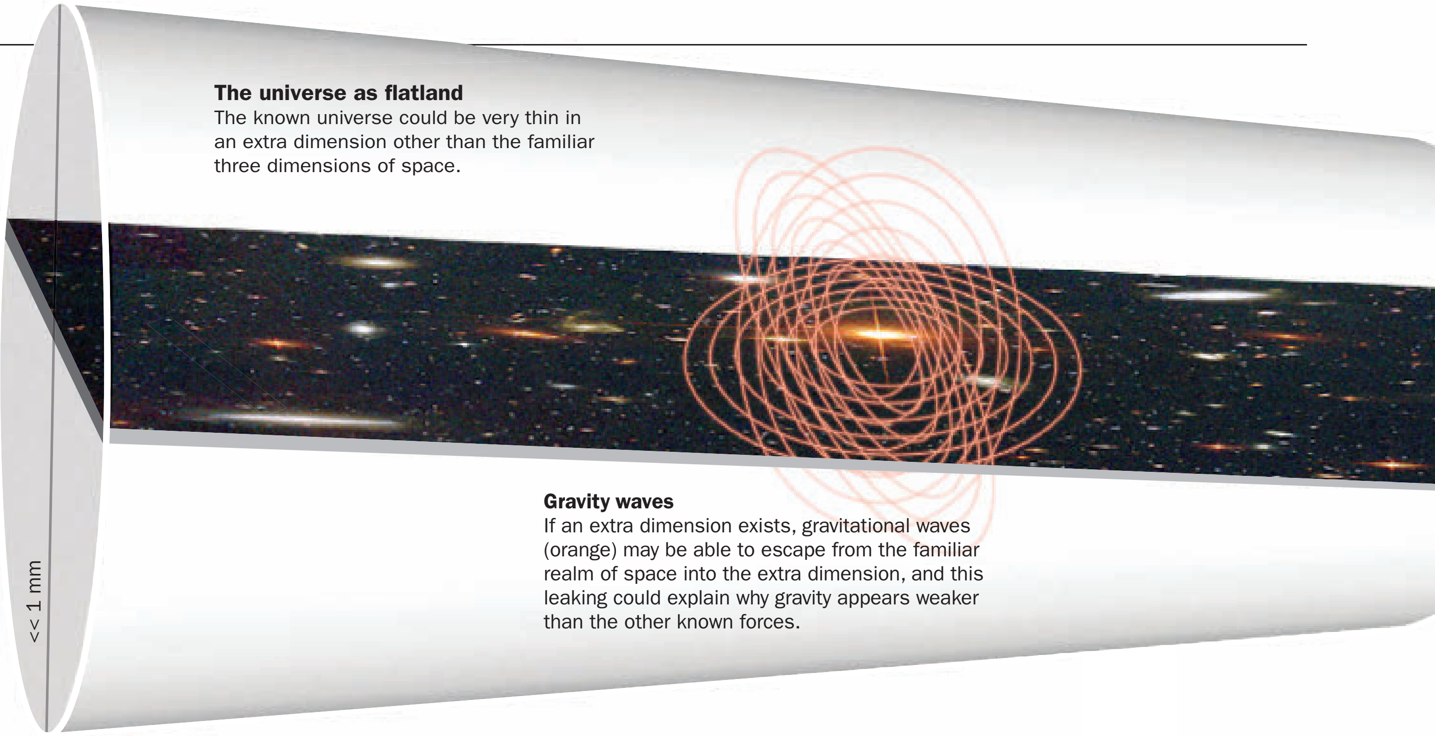
It will become pretty clear that large extra dimensions exist if a micro-sized black hole happens to appear in the Large Hadron Collider, or LHC, near Geneva. That's because if gravity really is much stronger than expected at distances around a few micrometers or so, the LHC may be able to pack enough matter and energy into a small enough space that the system will automatically collapse into a black hole.

But before anyone starts worrying about Geneva disappearing into a black hole, know that this gravitationally dense midget wouldn't even cross the diameter of an atomic nucleus before disintegrating (*SN Online: 6/24/08*).

"In this sense, these black holes are completely organic," says Landsberg. "You could put them in your salad, and you wouldn't notice that they exist because they immediately evaporate."

But they might make their presence known to the LHC's detectors.

That's the province of a number of theoretical physicists, including



Glenn Starkman of Case Western Reserve University in Cleveland. Starkman led a team that developed a computer program, called BlackMax, that tells researchers what subatomic debris a black hole might leave behind as evidence.

Inside the LHC, two beams of protons will stream at speeds close to the speed of light in opposite directions around a circular tunnel. Protons are actually somewhat spread out, says Starkman, and mostly made up of subatomic particles called quarks and gluons. It's extremely unlikely that any two of these particles will hit each other exactly head-on. But if two quarks or two gluons, or one of each, get close enough to each other as they are flying in opposite directions, there could be enough energy in a small enough space that a black hole would form — if, and only if, gravity is strong enough to start playing a role. "For that to happen," says Starkman, "there have to be more than three dimensions."

The black hole would evaporate almost instantaneously, perhaps in a hail of subatomic particles shooting forth in all directions, like a cherry bomb firecracker. Or perhaps researchers would see a signature event in which some of the energy disappears, carried away into other dimensions by gravitons — the invisible gravitational counterpart to the photon.

The good thing, from a theoretical physics point of view, is that if the LHC makes any black holes at all, it will make a lot of them — as many as one per second, or 30 million a year. "Now, 30 million a year may involve optimistic assumptions, but perhaps a million or a hundred thousand or even ten thousand is not impossible," says Stanford University's Savas Dimopoulos, the middle "D" of the ADD extra-dimension hypothesis. "Even if you have 10,000 black holes, that is a lot of events to do statistics with and to start testing in detail both the existence of the black hole and the framework of large dimensions."

Randall, like many, is skeptical. "It's a cute idea," she says. But with coauthor Patrick Meade, then at Harvard and now at the Institute for Advanced Study in Princeton, N.J., she argues that the scenario is highly unlikely. Their work was published in May 2008 in the *Journal of High Energy Physics*.

"It's virtually impossible that you're going to make genuine black holes at the LHC because the energy isn't really high enough," she says. "You could see some evidence of interesting gravitational effects in higher dimensions in terms of how things would scatter off each other ... but it seems very unlikely that you would actually have anything that is really a genuine black hole."

Still, there are a lot of uncertainties, and until the LHC is up and running, no one will really know.

Dimopoulos, for one, remains optimistic, but he has hedged his bets. In addition to large extra dimensions, he has a stake in two other leading candidates for solving the hierarchy problem. These theories, called technicolor and supersymmetry, don't rely on extra dimensions — and they both might show their colors at the LHC.

But chances are "that nature may choose a completely different route, and it may be that the solutions to the hierarchy problem will be something that nobody ever thought about," he says. "And that may be the most exciting scenario for what we will discover." ■

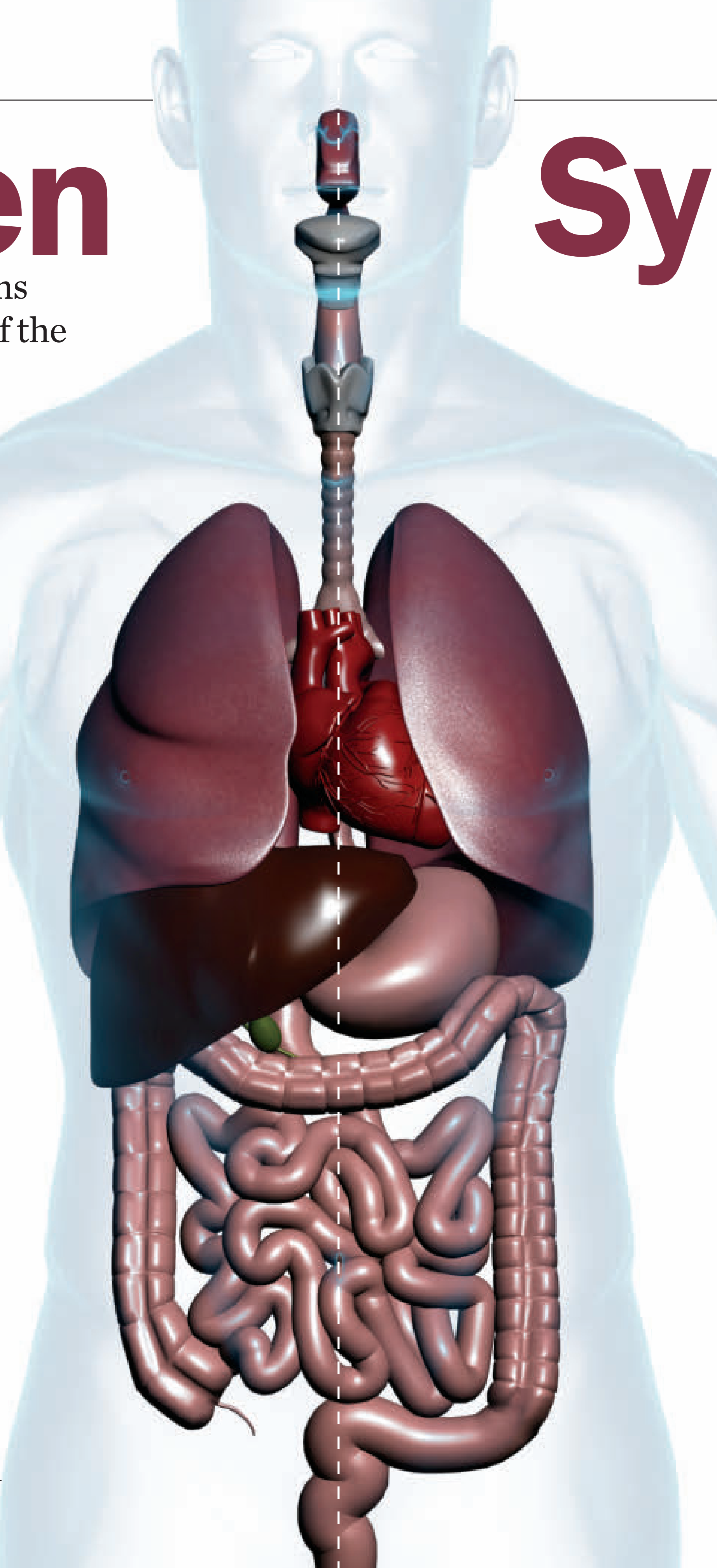
Diana Steele is a freelance science writer based in Oberlin, Ohio.

Explore more

- Read about micro black holes in the blog BackRe(Action) by physicists Sabine Hossenfelder and Stefan Scherer at http://bit.ly/11bDq4

J. KORENBLAT, NASA

Broken Sy



Scientists seek mechanisms explaining development of the body's left-right pattern

By Jenny Lauren Lee

On the outside, people's right and left sides look pretty much the same. On the inside, though, such superficial symmetry gives way to an imbalanced array of organs: The heart, spleen and stomach sit on the left side of the body, while the liver and pancreas take up the right. Even organs that at first glance appear as perfect mirror images of each other, such as the kidneys, lungs and testicles, turn out to have telltale left-right differences.

Figuring out how a body with such internal asymmetry develops from an egg (and later an embryo) with near-perfect symmetry has long stymied developmental biologists. But in recent years, scientists have identified a structure that seems to explain how mice — and possibly humans — break left-right symmetry early in development. In an 8-day-old mouse embryo, researchers discovered a short-lived, shallow pit covered with cilia. The whiplike protrusions paddle through the surrounding embryonic fluid, creating a microcurrent that flows over the pit from right to left. This leftward flow may send a signal that starts the body on its journey to an asymmetrical destination.

Many researchers believe that this cilia-powered flow is the left-right symmetry breaker in mice, and probably in fish, too. But while some other animal embryos have been shown to develop these pitlike structures, accumulating evidence suggests that frogs, rabbits and perhaps other animals have asymmetric concentrations of certain molecules long before any cilia form in the pits. Chickens don't show any

mmetry

directional flow at all in their equivalent of this structure. And neither do pigs, a recent paper in *Science* reports. With so many inconsistencies, some scientists question whether the cilia model alone can explain symmetry breaking.

Another area of intense investigation is how this leftward flow might tell organs such as the heart and lungs which way to grow. In this year's *Annual Review of Fluid Mechanics*, published in January, Nobutaka Hirokawa and colleagues at the University of Tokyo discuss one way in which left-side–determining chemicals might be transported leftward with the flow, to accumulate on one side of the embryo and begin a cascade of development. Other recent reviews have discussed different possible mechanisms.

Showing how left-right patterning emerges in human embryos is critical to understanding not just human development, but also what goes wrong in the thousands of people born each year with asymmetry disorders. These little-known diseases have a wide range of effects — some prove lethal in the first few hours of a child's life, while other forms are harmless.

Mystery of the frozen cilia

Forty years ago, a baby girl was born blue. Doctors looking for the cause of her poor blood circulation found the answer in her heart: She had two left heart halves, pumping blood at a dangerously inefficient level. The rest of her body was symmetrical, too — with two left lungs, two left kidneys and spleens on either side of her abdomen.

Humans, like many animals, are built with an asymmetrical body plan, visible in the placement of the heart and other organs. Recent work hints at when and how such asymmetry may first develop.

ANGELHELL/ISTOCKPHOTO

Disorders in asymmetry of a single organ can cause serious health problems. Pediatric cardiologist Martina Brueckner of Yale University School of Medicine estimates that one in every 25 patients at heart clinics nationwide has some problem with asymmetry. Yet a totally reversed body asymmetry, called situs inversus, is not a problem in itself. Flipping an entire jigsaw puzzle upside down does not affect the function of each piece, but flipping a single piece certainly affects how the puzzle fits together. Those whose hearts are flipped in relation to the rest of their bodies face serious health problems. But people with situs inversus can live for years without realizing that their hearts and other organs are on the wrong side of their bodies.

In fact, it was people with situs inversus who first gave researchers the idea that cilia and fluid flow could function as symmetry breakers in an embryo.

In 1933, a Swiss doctor reported on several patients with a bizarre collection of symptoms: frequent infections in the lungs, ears and nose; in men, an inability to have children; and, in many patients, situs inversus. Named Kartagener syndrome after the doctor, the disorder affects about 1 in every 10,000 people.

In the mid-1970s, Swedish doctor Björn Afzelius made an intriguing discovery while examining four men diagnosed with Kartagener syndrome. Normally, the beating motion of the cilia that line people's throats and ear canals pushes bacteria and debris out of these passageways. But the cilia of these men were stiff and unmoving. Afzelius and colleagues showed that in people with Kartagener syndrome, certain cilia are missing protein structures called the dynein arms, which make up the motor that allows the cilia to move. The static cilia explained the patients' chest and ear infections, as well as the immotile sperm. But no one could figure out what cilia had to do with body asymmetry.

A biology graduate student in Hirokawa's lab stumbled across the connection in the late 1990s, when his mutant mouse embryos died in utero. The genetically engineered mice lacked a gene key to normal cilia development. The researchers were forced to dissect the embryos at an earlier developmental stage than planned.

"It was kind of a lucky accident," says Shigenori Nonaka, now at the National Institute for Basic Biology in Okazaki, Japan. At this time in development — 9 ½ days after fertilization — the heart is just beginning to form, visible inside a transparent envelope in the embryo.

"That's when I noticed that some of the mutant mice had an inverted heart," Nonaka says. In fact, nearly half of the mutant mouse embryos showed reversed asymmetry. This was, strangely enough, about the same percentage of cases of reversed asymmetry seen in people with Kartagener syndrome. In the mice, no functional cilia seemed to randomize the chance of the proper body pattern developing, the team reported in 1998 in *Cell*.

Nonaka and colleagues turned their attention to a triangular pit in the side of the embryo that eventually morphs into the beginnings of the spinal cord. In mice, this structure, called the ventral node, is covered with several hundred cilia, each rotating clockwise like a jump rope twirled overhead by a child. The researchers found that these twirling cilia were somehow pushing the surrounding fluid neatly from right to left.

The clincher came when the team artificially reversed the direction of the flow across the ciliated pit, forcing the fluid to move from left to right. In a seminal 2002 paper in *Nature*, Nonaka, Hiroshi Hamada of Osaka University and colleagues showed that the left side of a mouse goes with the flow. When the flow moved toward the right instead of the left, the mice developed reversed asymmetry.

"That was the big breakthrough," says physicist Julyan Cartwright of the

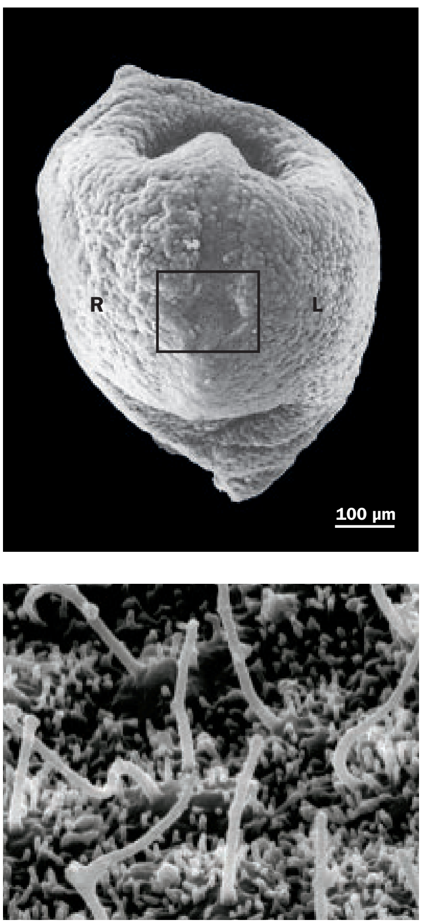
University of Granada in Spain. "It showed that it was fluid mechanics that was driving the process."

The role of the cilia explained why patients with Kartagener syndrome had about a 50-50 chance of situs inversus. In the patients with frozen cilia, the fluid in the node would have had nothing to guide its flow; sometimes the flow went the "right" way, and sometimes it didn't.

Mystery of the leftward flow

But it wasn't clear how twirling cilia could produce a uniform leftward flow. Technically the cilia should have moved the fluid around in a vortex, the way an eggbeater creates whirlpools in a bowl of whipping cream. Instead, somehow these eggbeaters were pushing the fluid from one side of the bowl (as it were) to the other.

A key step in establishing left-right asymmetry occurs in the ventral node (box) of a week-old mouse embryo (top). A close-up of the node floor (bottom) shows whip-like cilia that push fluid from right to left.



FROM TOP: N. HIROKAWA *ET AL.*/*ANNUAL REVIEW OF FLUID MECHANICS*; COURTESY OF H. HAMADA

Cartwright, who has worked on fluid mechanics problems in a variety of biological systems, hypothesized that the orderly leftward flow could be produced if the cilia were positioned at an angle instead of straight up and down.

Consider the rotaries of an eggbeater: "If you have them vertically in a bowl of some liquid you're mixing, it gives you a vortex, a whirlpool," Cartwright says. "But if you tilt them over, you get flow along the surface. And that's exactly what nodal flow is like."

Some fluid would still flow to the right, Cartwright reasoned in a 2004 paper in the *Proceedings of the National Academy of Sciences*. But the rightward flow would come in contact with the walls of the pit, and the friction from this contact would slow it down. Leftward flow would be the stronger of the two.

Nonaka and Hamada confirmed Cartwright's theory when their team caught the tilt of the cilia in action using a high-speed microscope, publishing their results in *PLoS Biology* in 2005.

But deciphering the first steps of asymmetry is not the same as understanding how the body develops its full asymmetry. Researchers now want to know how fluid flowing leftward in a divot on an embryo tells the body which way to grow.

Some scientists think the leftward flow may carry chemicals that turn on a sequence of left-side–producing genes. Hirokawa's group at the University of Tokyo suggested that such chemicals could be encased in a lipid envelope, what he calls a nodal vesicular parcel, that could be carried leftward with the flow and then break upon impact with the node's floor, spilling its chemical contents. In *Nature* in 2005, the researchers reported finding evidence of these parcels using time-lapse microscopy.

But others note that in such a small-scale system, where the thickness of the fluid is great compared with its volume, the impact of hitting the node floor would not provide enough force to break open such a package. To spill the chemicals in the appropriate place would require an active parcel-breaking mechanism.

"If you stop stirring, everything stops," Cartwright says. "The parcel can't break as if it were a ripe tomato that's being squashed on the floor."

Other researchers prefer the idea that some cilia are sensors that communicate a signal based on the direction of the flow. In 2003, Yale's Brueckner and colleagues showed that the cilia at the periphery of the node are missing a dynein structure needed for movement. That suggests that outlying cilia may play a role other than generating the leftward flow and might respond passively to flow produced by their neighbors, sending signals when the cilia bend like trees in a storm.

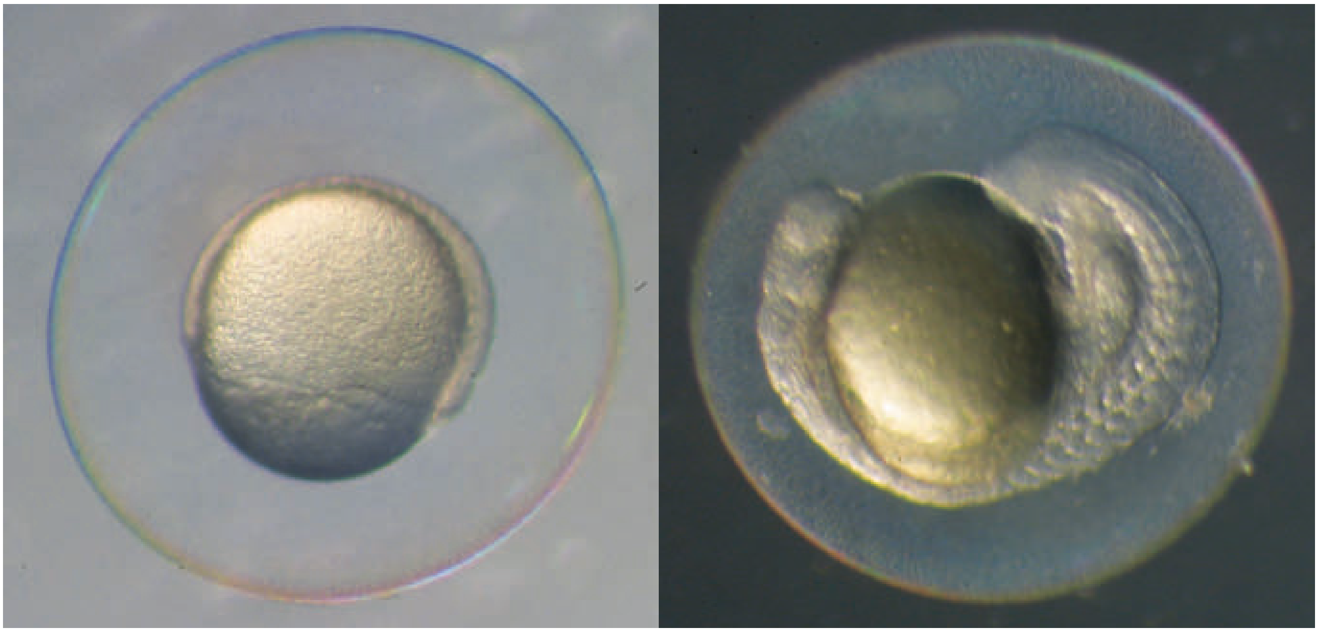
Not by mouse alone

Scientists have found strong evidence that nodal pit fluid flow determines left from right — in a mouse. Work with zebrafish also suggests that similar flow plays a part in breaking symmetry.

But some animals, like frogs and rabbits, appear to break symmetry well before their equivalent of the nodal pit appears. Biologist Michael Levin of Tufts University in Boston and colleagues discovered in 2005 that in frogs, symmetry may be broken as early as the first few hours after the egg is fertilized. In the May 15 *Science*, Harvard's Clifford Tabin and colleagues in Germany reported that pigs do not have cilia in their nodal pits, yet still are asymmetric, so perhaps humans and other mammals rely on other early symmetry-breaking events, too.

Meanwhile, scientists have uncovered other potential mechanisms for left-right patterning. Individual cells can create a left-right axis using their own intrinsic sense of left and right, given to them by the inherently biased structure of their protein skeletons, researchers from the University of California, San Francisco and the University of California, Irvine showed in 2007. The team, led by Henry Bourne of UCSF, claimed that this mechanism could work in the absence of any external cues.

Some experts wonder if there really are distinct symmetry-breaking mechanisms that differ from animal to animal.



Before and after: An 8-hour-old zebrafish embryo (left) appears symmetrical. At 24 hours, the embryo's symmetry is broken, probably by a mechanism similar to one first described in mice. How the process works in human embryos is unclear.

COURTESY OF STEVEN J. BASKAUF (HTTP://BIOIMAGES.VANDERBILT.EDU)

"My own view is that the origin of left-right asymmetry is really fundamental, and has been with us from the single-cell level," Levin says.

While a universal symmetry breaker for all animals remains to be found, one thing almost all animals share is two genes — appropriately named *Nodal* and *Lefty*. Wherever *Nodal* expression is concentrated, there the left side grows, with *Lefty* apparently keeping *Nodal* in check. The presence of the genes in animals as diverse as snails, sea urchins, frogs, mice and people indicates to many that these two genes play a fundamental role in the process of telling left from right, regardless of the initial symmetry-breaking process.

"The most important event is the ability of *Nodal* to take slight asymmetries set up by a variety of means and translate them into a robust asymmetry," Tabin says.

Even if fluid flow is not the first symmetry-breaking event, it may amplify an initial asymmetry, or even be a backup mechanism — what Cartwright calls a "belt-and-braces" design, with two mechanisms designed for the same purpose (such as holding up trousers). Nevertheless, many scientists agree that nodal flow plays an important role in the process of breaking symmetry at least in some animals — and given the connections between cilia and asymmetry in human disorders such as Kartagener syndrome, probably in people, too.

"It would be extraordinarily unlikely in my view that humans don't use the same mechanism as in mice," Tabin says.

Left-left and right-right

In people, some birth defects involving asymmetry can kill a person within the first minutes of life. Other kinds allow a somewhat normal life. And these conditions occur so early in development that it is impossible to repair the defects except through surgery. As Tabin says, doctors can't return an individual to an embryonic state as a therapy.

But some researchers hope that understanding more about how asymmetry is produced will help physicians to tailor treatments to individuals.

The girl born blue was lucky. She survived to her teen years, had life-prolonging heart surgery and grew up to hold a regular job and even have children. But only about 60 percent of children born with two left sides survive their first five years, Brueckner says. Children with two right halves survive to the age of 5 in only about 30 percent of cases.

Brueckner and colleagues are now collecting genetic information from patients with asymmetry disorders to find out why some people survive to adulthood while others die within hours of birth. The gene library may help explain why people develop the wrong asymmetries or fail to develop asymmetry at all, she says.

Many related mysteries persist. Scientists still don't know how an organ like the heart forms the correct way rather than in reverse, Tabin says. And though Kartagener syndrome patients with situs inversus have reversed brain hemispheres, the patients still have the same tendency to right-handedness as the rest of the population — a ratio of about 9-to-1. To Tabin, this forces biologists to ask themselves to what extent form in the brain determines function.

"We're piecing it together in very broad strokes," Tabin says. "I don't worry about running out of things to do for the next two decades." ■

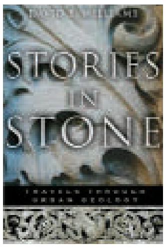
Explore more

- H. Hamada. "Breakthroughs and future challenges in left-right patterning." *Development, Growth & Differentiation*, 2008.

Stories in Stone: Travels Through Urban Geology

David B. Williams

Cities may seem like the most artificial places on Earth, yet a close look at massive buildings can reveal troves of natural geological glory. In chapter after fascinating chapter of *Stories in Stone*, Williams, a geologist, deftly describes the mineralogy and history of some of the world's most common building materials.



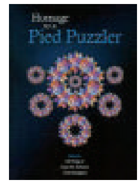
The porosity of marble often renders the stone useless for architecture in cold climates, for example, but many of the world's most recognizable edifices — including the Parthenon and the Taj Mahal — are made of this luxurious material. Marble's luminosity contrasts sharply with the chocolate color of brownstone, a sandstone derided by one critic as "the most hideous stone ever quarried." Still, the material was fashionable: In 1880, 96 percent of Brooklyn stone structures were clad with it.

The age of the metamorphic gneiss quarried near Morton, Minn. — 3.5 billion years old — sets that stone apart from the geological youth of a conglomeration of shells and shell fragments called coquina. Some coquina deposits formed as recently as 110,000 years ago, just before the last ice age began.

Williams repeatedly shows that building stones hold more than just geological history: When hunks of 450-million-year-old granite were hauled to Boston in the mid-1820s to build a monument commemorating the Battle of Bunker Hill, they arrived via the nation's first commercial railroad.

Each chapter showcases a different stone. By describing how the stones formed and how they are used, this book reveals that natural and cultural history may lie no farther than the building next door. *— Sid Perkins*

Walker & Company, 2009, 261 p., $26.



Homage to a Pied Puzzler

Ed Pegg Jr., Alan H. Schoen and Tom Rodgers, eds.

A collection of math problems and stories pays tribute to math popularizer and *Scientific American* columnist Martin Gardner.

AK Peters, 2009, 285 p., $49.

Theo Gray's Mad Science: Experiments You Can Do at Home— But Probably Shouldn't

Theodore Gray

Dramatic experiments, captured in color photography with step-by-step instructions, demonstrate scientific principles from the everyday world.

Black Dog & Leventhal, 2009, 239 p., $24.95.

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FEEDBACK

'Black hole' origins

"Black hole theory and discovery" (Back Story, *SN: 7/4/09, p. 6*) credits John Archibald Wheeler for inventing the term black hole in 1967. This is a very widespread choice, but it cannot be right. In January 1964, your ancestral publication, *Science News Letter*, carried a short article titled "'Black holes' in space," which reported on a session at the AAAS meeting in Cleveland. Hong-Yee Chiu, who organized and chaired that session, remembers hearing the phrase from the late Robert Dicke in about 1960–61.

Virginia Trimble, Irvine, Calif.

Trimble, an astronomer at the University of California, Irvine, is correct, and we are gratified to be credited with the first use in print of "black hole" as an astrophysical object (see the original story on the Science News *website at http://bit.ly/1dkgEg). But apparently Wheeler, who popularized that name, did not learn of it from* Science News Letter. *By his account, it was suggested by an unknown questioner in the audience during a 1967 lecture given by Wheeler, who then used it in a later lecture that was published in the Spring 1968 issue of* American Scientist. *— Tom Siegfried*

Bog iron

It is unfortunate that "The iron record of Earth's oxygen" (*SN: 6/20/09, p. 24*) didn't at least mention bog iron, which was the major source of iron ore during the Iron Age, at least in the Northern Hemisphere. I understand that it was, and is still, found in bogs left behind after the last ice age. It sounds like the same mechanism of formation.

John O. Kopf, Cupertino, Calif.

The chemistry is similar, but banded iron formations arose when dissolved iron and dissolved oxygen reacted underwater. Bog iron forms when iron-rich waters seeping from a bog are exposed to oxygenated air. — Sid Perkins

Squished skull

The skull photo with "Ancient Andean civilization likely spurred by maize" (*SN: 8/1/09, p. 16*) looked odd. Did the Wari have different shaped heads than other modern humans?

Henry Jones, Baton Rouge, La.

No. Inhabitants of the ancient site studied by archaeologist Brian Finucane took skulls such as the one shown from enemies killed during raids and modified them with various tools, giving them an odd shape — a fact that should have been mentioned in the caption. — Eva Emerson

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Andrew Meltzoff

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From baby scientists to a science of social learning

Developmental psychologist Andrew Meltzoff codirects the Institute for Learning and Brain Sciences at the University of Washington in Seattle. In the July 17 Science*, Meltzoff and his colleagues published a paper titled "Foundations for a New Science of Learning." Meltzoff recently spoke with* Science News *writer Bruce Bower.*

What does the science of learning tell us about the nature of intelligence?
People sometimes think of intelligence as a reflection of individual problem-solving skills. But we're increasingly realizing that humans have special brain and cognitive mechanisms for social interaction. A powerful aspect of intelligence is the ability to solve problems collaboratively.

Individuals and groups incorporate knowledge passed along from others into new problem solutions and innovations. Computers and other modern technologies have greatly increased the impact of this type of intelligence. In business and science, innovative breakthroughs now come from those who leverage the intellectual power of groups. These advances aren't going to come from a lone genius in a garret.

Do findings about learning have any practical implications for education?
More and more kids come to school as bilingual speakers or speaking a language other than English. Second-language learning, whether of English or another language, can potentially be improved by integrating social interactions into teaching methods.

Research shows that individual, face-to-face tutoring is the most effective form of school instruction. Learning researchers are now trying to develop intelligent tutoring systems that provide key elements of human tutoring while avoiding its extraordinary financial cost.

In one approach, adults learn a second language by interacting with a simulated tutor on a computer screen.

Are educational videos and scheduled activities preferable to free play for young children?
We now know that early learning sculpts the brain in important ways. This has led to an industry of selling products that promise to increase babies' IQs and learning abilities. But there is no scientific evidence that any product on the market does that. This situation has led to much confusion among parents and much frustration among developmental scientists.

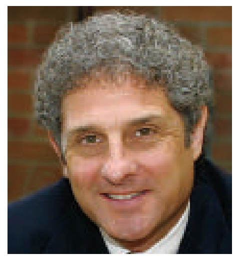
There is no dichotomy between early educational activities and free play. In the first three years of life, free play *is* an educational activity. Driven by their own natural curiosity, infants solve problems for the pure joy of learning about the physical and social world. If you watch babies' faces as they build block towers and see gravity in action, it's obvious that they're learning.

People are the favorite playthings of young children, who are drawn to faces, voices, colors and movement. Through play, kids learn about others' goals and intentions — what makes people tick.

A baby is like a little scientist running experiments. And babies love to replicate their experiments. An infant will drop a block from one angle, then from another and then try a third approach, to see what happens in each case. It's like running pilot studies on the world.

Is it worthwhile to identify gifted children in kindergarten or earlier?
Testing for exceptional abilities can level the playing field and identify promising students who might not otherwise get noticed, such as those from poor neighborhoods. On the other hand, if a child does poorly on a test at one age, he or she can get labeled as a slow learner.... A self-fulfilling prophecy then occurs, with the child meeting teachers' low expectations.

Society's desire to help every child succeed is running ahead of scientists' ability to design tests that identify specific talents early on. Children with special talents often pop out at us by virtue of what they do, not by what they score on a test. For now, that may be the more humane way to identify them.



INSTITUTE FOR LEARNING AND BRAIN SCIENCES/UNIV. OF WASHINGTON

Having a mentor can change a child's, and an adult's, social identity.

What question about the nature of learning would you most like to answer?
What makes social interaction such a powerful catalyst for learning? This is the key that will unlock more effective educational practices. Also, how do we design learning environments that capitalize on ... social interaction rather than having kids work alone at desks?

One element of social learning involves having a mentor, someone you identify with who frames important issues and provides an example that can be imitated and emulated. Having a mentor can change a child's, and an adult's, social identity.

Lucky scientists have kind and supportive mentors.... My mentor was Jerome Bruner, a psychologist who inspired me by connecting cognitive science to education. Scientists who have effective mentors learn to learn for the joy of it. They go back to being like baby scientists in the crib. ■

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