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JANUARY 11, 2014

Twin Prime Gap Shrinking

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SPECIAL REPORT

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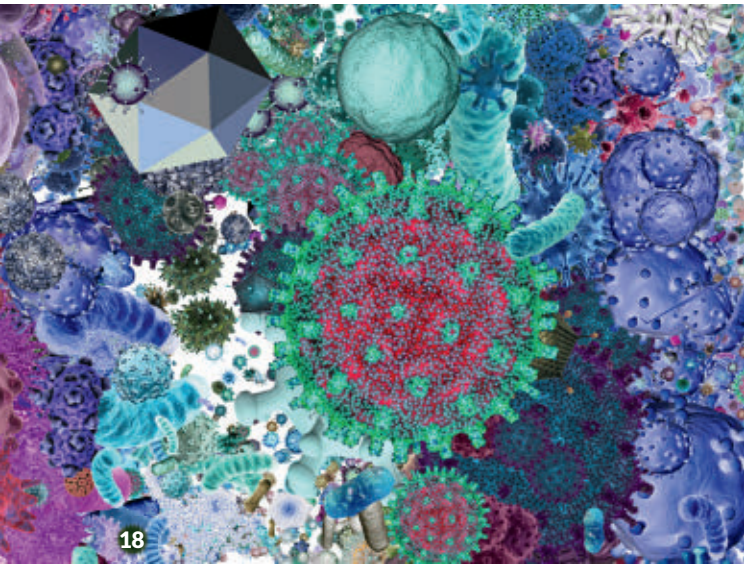
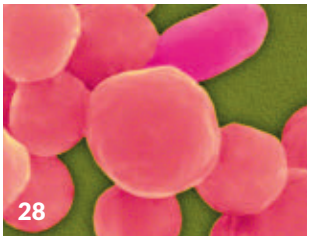


Special Report

BEYOND THE MICROBIOME

News

FROM TOP: CHARIS TSEVIS; DENNIS KUNKEL MICROSCOPY; KELVIN AITKEN/VWPICS/ASSOCIATED PRESS



Departments

COVER Researchers are only beginning to reveal how intimately bacteria, viruses, fungi and archaea intertwine with multicellular life. *Charis Tsevis*

A newfound respect for the microbial world

Many years ago, I heard the scientist and writer Stephen Jay Gould speak eloquently and convincingly about bacterial dominance. Despite what many people think about humans' place in the scheme of things, he said, we live in a world of microbes. "The most outstanding feature of life's history is that through 3.5 billion years this has remained, really, a bacterial planet," he said in a 1997 interview with *Mother Jones*. "Most creatures are what they've always been: They're bacteria and they rule the world. And we need to be nice to them." (If it has been awhile since you've indulged in Gould's wonderful prose, I highly recommend his 1996 essay "Planet of the bacteria," available at bit.ly/SN_Gould.)

Gould would not be surprised to learn, I think, of all the rich details coming out about just how bacteria and other small-scale creatures (the archaea, fungi and viruses) exert dominance on other living things, including us. Thanks to technical advances in genetic sequencing that have made it relatively affordable and easy to take microbial censuses, scientists have been able to explore the microscopic denizens of the soil, oceans, Earth's crust and, increasingly, the human body. Last issue, Tina Hesman Saey offered a wrap-up of some of 2013's most exciting findings about the human microbiome (*SN: 12/28/13, p. 18*), the collection of all the microbial creatures that live in and on the body. In this issue, *Science News* considers the next frontiers of microbiome research.

New insights into how microbes influence the lives and evolution of animal species are front and center in Susan Milius' story on Page 14. Saey, beginning on Page 18, considers scientists' emerging appreciation of how viruses that call humans home affect health and disease. Diet's influence on the microbiome is examined on Page 32. On Page 22, former intern Jessica Shugart provides a detailed look at a consequence of humans' intimate relationship with microbes: Many sugars in human breast milk nourish bacteria, not babies. It turns out that these sugars also tweak the baby's immune system to help beneficial microbes colonize the gut, fend off possibly dangerous bacteria and even trigger changes in gene activity that help protect cells from pathogens. With growing evidence of such benefits, scientists are looking for ways to mass-produce these oligosaccharides.

Gould was right: The microbial world dominates our existence in ways we are just beginning to appreciate. And it will be to our benefit if we can use our growing understanding to foster a healthy relationship with the microscopic inhabitants whose turf we share. — *Eva Emerson, Editor in Chief*

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Excerpt from the January 11, 1964, issue of *Science News Letter*

50 YEARS AGO

Flightless Birds Face Extinction

The government of New Zealand is desperately trying to save what is left of its world-famous flightless birds. The man-sized moa has been extinct for two centuries, and the flightless huia for one. Other species, including the remaining varieties of huia, the kiwi, the flightless rail, the takahe and the kakapo are all on the verge of disappearance. Of these, the kiwi is perhaps the best known, but it is the takahe and the kakapo that are in the greatest danger of extinction. These two birds live in the still-wild Fiordland in the southwest of the South Island. Both are virtually defenseless against predators.

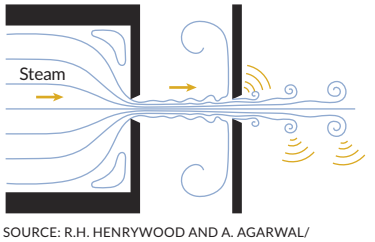
UPDATE: New Zealand's flightless birds have limped through the last few decades, but conservation efforts have had some success. After transplantation to a predator-free island, the kakapo population increased from a low of 50 in the 1990s to about 125 today. Likewise, there are now more than 250 transplanted takahe. Many are successfully breeding in their new homes.

SAY WHAT?

Kleptoplast *KLEP-toh-plahst*\ *n.*

A cellular part such as a light-harvesting chloroplast that an organism takes from algae it has eaten. Some sea slugs hold on to these stolen chloroplasts for months. Scientists thought the slugs (one shown) might get extra food from the photosynthetic organelles (*SN: 2/13/10, p. 10*). But now it appears that two of the four species known to steal chloroplasts don't use them. The slugs lack genes needed to help chloroplasts function, and without food they starve at the same rate in the light as in the dark, where the chloroplasts can't work, researchers report November 20 in the *Proceedings of the Royal Society B*. — *Sarah Zielinski*

Steam movement in kettle



SOURCE: R.H. HENRYWOOD AND A. AGARWAL/ *PHYSICS OF FLUIDS* 2013

Pressurized steam moving past the plates (black) in a tea kettle's spout produces vortices that split off and generate acoustic waves (orange), creating a whistling sound.

MYSTERY SOLVED

Tea time

Leave it to the English to solve the mystery of a tea kettle's whistle. English physicist Lord Rayleigh proposed in 1877 that water molecules bouncing back and forth in the spout produce the whistle, but new experiments show that little swirls of steam are responsible. University of Cambridge engineers mimicked a tea kettle in the laboratory using tubing and a series of pressure sensors and microphones. The researchers found a two-step process; steam lazily rising from water that is just starting to boil vibrates within the spout to produce a faint tone, much the way a bottle neck hums when you blow across its mouth. Then, as pressure builds and a strong jet of steam escapes through the lid's opening, small vortices of steam break off and create pressure waves in the air that we hear as a high-pitched whistle, Ross Henrywood and Anurag Agarwal report in the October *Physics of Fluids*. The whistle rises in pitch as the speed of the jet grows. In addition to satisfying the curiosity of tea drinkers, Henrywood says the research could help engineers reduce pesky noises caused by fluid rushing through household plumbing and industrial pipelines. — *Andrew Grant*

FROM TOP: SVEN GOULD AND JAN DE VRIES/HHU DÜSSELDORF, CENTER FOR ADVANCED IMAGING; SILVER-JOHN/SHUTTERSTOCK; ADAPTED BY S. EGTS

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ATOM & COSMOS

Moon dust gathers surprisingly fast

Data from Apollo missions stir debate about the lunar surface

Moon dust, the fine grains that coat the lunar surface and stuck to Apollo astronauts and their equipment, may accumulate more rapidly than researchers once thought.

EUGENE CERNAN/NASA

BY MEGHAN ROSEN

Beware of lunar dust bunnies. Moon dust may pile up far more quickly than scientists thought, and the claim is churning up some controversy. Powdery particles resting on the moon's surface could form a layer up to 1 millimeter thick every 1,000 years, according to a new analysis.

The estimate relies on data dug up from the Apollo missions of the 1960s and 1970s.

"It's pretty remarkable that we're still getting results out of 40-year-old data," says physicist James Gaier of NASA's Glenn Research Center in Cleveland. Other researchers have used computers to simulate lunar dust, he says, "but we haven't really had any data."

Apollo 11 gave astronauts and scientists their first taste of moon dust. When the spacecraft descended, the rocket's engines kicked up dust clouds that made a clear moon landing tricky. And when the astronauts ventured outside, dust slicked the ladders, stuck to their suits and fouled experiments.

The gritty substance filled in bolt holes, made vacuum seals leak and dulled shiny surfaces intended to protect instruments from overheating by reflecting sunlight. Moon dust is finer than flour but sharp, says study coauthor Brian O'Brien of the University of Western Australia in Crawley. "Think of shards of a broken bottle," he says.

In 1966, O'Brien invented the first device to measure moon dust. His matchbox-sized gadget housed solar cells and thermometers, and journeyed to the moon with Apollo 11 in 1969.

In sunlight the solar cells generated an electrical current and beamed voltage data to Earth. The device could detect dust because particles sticking to the cells' surfaces blocked incoming sunlight, making the voltage drop.

Later Apollo missions carried more dust detectors to the moon, and for six years, the gizmos sent data home every 54 seconds. NASA copied the information onto 7-track tapes but later lost them.

"Back then, nobody gave a darn about dust," says Lawrence Taylor, a geochemist at the University of Tennessee at Knoxville who worked on the Apollo missions. NASA had so much other data coming in that the dust detector data "sort of fell by the wayside," he says.

When NASA announced in 2006 that it had misplaced the tapes, O'Brien scrambled to recover the lost data. His personal files held some of the information and he tracked down other researchers to complete the dataset.

In the new analysis, O'Brien and University of Western Australia colleague Monique Hollick wanted to measure moon dust's natural accumulation rate. So they analyzed only measurements collected hundreds of hours after astronauts left the moon.

To estimate just how much dust had caused the solar cells' voltage drop, the researchers used results from previous experiments with fake moon dust. Scientists had sprinkled dust on solar cells and measured changes in output. The high rate of dust accumulation that Hollick and O'Brien report November 19 in *Space Weather* has stirred up wildly different opinions among other scientists.

"It's just too much dust," Taylor says. "Nobody will believe it." He says the estimate is flawed because the simulated dust doesn't really mimic moon dust. What's more, other aspects of lunar weather could have perturbed the solar cells, causing similar voltage drops, adds planetary scientist David Williams of the NASA Goddard Space Flight Center in Greenbelt, Md.

Though the estimate is larger than previous calculations, the rate of dust accumulation is small relative to that on Earth. "This is telling us that if you set something down on the moon, it's going to stay pretty clean," Gaier says.

He thinks the findings could give researchers clues about dust transport over the lunar surface, a topic that's been controversial. Some scientists think electrostatic forces gently sputter dust over the moon; others believe dust swirls around in sweeping storms. The new results suggest that dust isn't moving all that much. But, he adds, "the jury is still way out on this." ■

Snake DNA offers clues to the evolution of venom, binge eating

Python and cobra genes changed quickly as new hunting adaptations arose

BY TINA HESMAN SAEY

Snake genes are in high evolutionary gear. The first two complete snake genomes ever assembled, of a Burmese python and king cobra, reveal that many snake genes have changed more rapidly than those of other vertebrates, researchers report December 2 in two studies in the *Proceedings of the National Academy of Sciences*.

Snakes have evolved some extreme survival strategies. Cobras and pythons represent some of the most out-there examples, says David Pollock, a coauthor of both studies who is an evolutionary biologist and genomicist at the University of Colorado School of Medicine in Aurora.

Burmese pythons (*Python molurus bivittatus*) are ambush predators that seldom find meals. When they do, they gorge. Adult pythons can swallow an adult pig whole. Within four days of consuming such a feast, the snake's organs expand by at least 35 percent, with some even doubling in size.

"The change in metabolic activity is greater than a racehorse going from standing still to running a quarter-mile race," Pollock says. After the meal is digested, the organs shrink back to size within days. Pollock and his colleagues determined that this extreme metabolism is coordinated by hundreds of genes.

King cobras, in contrast, rely on venom to take down prey. They are one of the deadliest species of venomous snakes, says Jimmy McGuire, an evolutionary biologist at the University of California, Berkeley. "One is almost certainly toast if bitten by an adult king cobra in a setting where there is no immediate access to antivenin." Studying how snake venom evolved may lead to better treatments, he suggests.

The king cobra (*Ophiophagus hannah*) preys on other snakes and is ideal for studying venom evolution because it must evolve new toxins to take down its victims as prey develop defenses against old toxins.

Michael Richardson, a developmental biologist at Leiden University in the Netherlands, and his colleagues discovered that cobras' venom glands produce a small RNA known as *miR-375*, which in other animals is found in the pancreas and the pituitary gland. MicroRNAs help regulate where and when proteins are made. Finding the microRNA in the venom gland may revive an out-of-favor theory that venom glands evolved from the pancreas, though Richardson cautions that the result does not prove evolutionary connection. He thinks that organs such as the pancreas and venom gland both produce *miR-375* because they need to secrete proteins.

As for venom components, the researchers discovered that king cobras produce 20 different categories of toxins. Many are altered versions of proteins produced elsewhere in the body. The team found that many venom genes started out as duplications of "normal, old, innocent housekeeping genes," Richardson says. During cobra evolution, those genes in the venom glands rapidly shifted and took on new, deadly properties.

King cobras evolved deadly venom from ordinary proteins. Duplicated genes and mutations altered the proteins' functions, turning them into toxins.

The quick change of nontoxic proteins into venom surprised Scott Edwards, an evolutionary biologist at Harvard University. "Proteins tend to evolve in a very conservative manner," he says. The rapid change probably reflects strong evolutionary pressure to keep up with and override prey defenses.

The researchers also found a genetic explanation for snakes' limbless bodies: a missing gene. Snakes have a nearly complete set of *Hox* genes, which lay out the body plans of a variety of animals. Even though snakes have almost all the genes required to build legs, they lack one called *Hoxd12*, which scientists previously showed to be important for limb development in four-legged creatures. The gene probably went missing in an early snake ancestor. ■

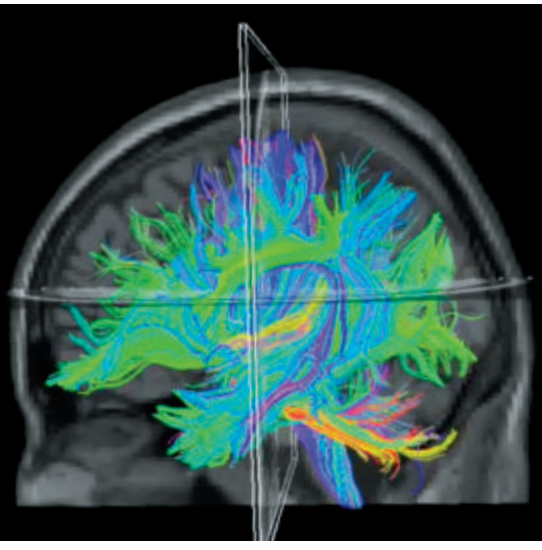
Scientists have discovered that coordinated efforts of hundreds of genes allow the Burmese python's organs to grow after a big meal and then rapidly shrink once digestion is complete.

FROM TOP: ERIC ISSELEE/SHUTTERSTOCK; FIVESPOTS/SHUTTERSTOCK

BODY & BRAIN

Faulty brain wiring may contribute to dyslexia

Adults with disorder showed difficulty relaying information among language areas



Connections between language-processing regions of the brain (shown here as colored links in a diffusion magnetic resonance image) may be impaired in people with dyslexia.

BY BETH MOLE

Hampered connections between brain regions that decipher spoken sounds may partly explain why people with dyslexia have trouble reading and spelling, researchers report in the Dec. 6 *Science*. Both activities require the ability to translate the sounds of language into meaning, which is an obstacle for people with dyslexia.

The new results provide some of the first support for an underdog hypothesis that broken bridges in the brain thwart these mental interpretations of sound information. Neuroscientists have traditionally held — and previous data have supported — the competing hypothesis that the learning disorder arises from trouble properly distinguishing the sounds of language before they're interpreted by the brain.

In the study, Bart Boets of Katholieke Universiteit Leuven in Belgium and colleagues investigated brain activity using functional magnetic resonance imaging. The researchers compared patterns of brain activity in 23 adults with dyslexia with those of 22 adults without the disorder after both groups listened to fragments of words.

The two groups had similar activity in the speech-processing regions of their brains, suggesting that adults with dyslexia can distinguish the sounds of speech just as well as, if not better than, adults without the disorder.

But those with the disorder had more trouble transmitting a sound's repre-

GENES & CELLS

Autism may be linked to chemicals produced by microbes in the gut

Mice with altered intestines were less social, more anxious

BY TINA HESMAN SAEY

Leaky intestines and an abnormal mix of gut microbes may contribute to autism symptoms, a study of mice suggests.

Mice with autism-like behaviors have a skewed mixture of intestinal microbes that results in high levels of certain chemicals, including one similar to a compound found in the urine of some children with autism. These mice also have leaky intestines, which allows the chemicals to build up in the animals' blood, researchers report in the Dec. 19 *Cell*.

Giving the mice beneficial bacteria reduced gut leakiness and improved some abnormal behaviors, suggesting that some children with autism might benefit from probiotic treatments.

The study "really connects the dots on some scattered observations about kids with autism spectrum disorders," says Alessio Fasano, a gut biologist at Massachusetts General Hospital in Boston. While previous studies have also linked changes in intestinal microbes to autism, none has offered a plausible mechanism for how gut bacteria might contribute to the disorder, he says. Although the new work may explain a possible cause of autism in a fraction of children, Fasano cautions that "this is not going to be the solution for everybody."

Many people believe that children with autism are prone to digestive problems, but that connection has been hotly debated. This study is likely to provoke more controversy, says Caltech microbiologist Sarkis Mazmanian, who teamed up with Caltech neuroscientist Paul Patterson to lead the work.

The researchers knew that pregnant women who develop severe infections or high fevers have a greater risk than normal of having children with autism. So Patterson, Mazmanian and colleagues stimulated the immune systems of pregnant mice to mimic severe infections. Those mice had young with characteristics of autism such as problems socializing, including a tendency to squeak less when with other mice. The offspring were also more anxious, startled more readily at noises and repeated behaviors such as burying a marble again and again.

Mice born to immune-stimulated moms also had leaky intestines, the researchers found. These mice had an altered mix of gut microbes, carrying more bacteria called *Lachnospiraceae* and related microbes than normally behaving mice did.

The autistic-like mice had high levels of

COURTESY OF KU LEUVEN

sentation to other parts of the brain that decipher meaning in language.

The authors also calculated that those disconnections account for 35 percent of reading and spelling difficulty seen in the group with dyslexia.

The new evidence that connectivity plays a role in dyslexia is important, says neuroscientist Daniel Brandeis of the University of Zurich. But the results also suggest that less than half of the observed differences in reading and spelling ability are explained by this connectivity, he says. Brandeis also cautions that the authors did not specifically study brain activity while people were reading and spelling, which are the troubled skills that define dyslexia.

Franck Ramus of École Normale Supérieure in Paris, who in 2008 first suggested that people with dyslexia have poor brain connectivity, agrees that the finding is important but inconclusive: "This study will not put an end to this debate, but it is the best piece of evidence in five years." ■

some bacterially produced chemicals in their blood. One of those chemicals, called 4-ethylphenylsulfate, was 46 times as abundant in the mice with autism symptoms as in normal mice. Injecting the chemical into the blood of normal mice led to anxious behavior. Previous studies had found a similar molecule, known as p-cresol or 4-methylphenol, in high levels in the urine of some children with autism.

When the researchers gave a helpful bacterium called *Bacteroides fragilis* to mice with autism-like behavior, many of their symptoms improved, although the mice were still less social than normal mice. The bacterial treatment also helped seal the mice's leaky guts and reduced blood levels of the autism-linked chemicals.

Though the study is "fascinating and important," says microbiologist Brent Williams of Columbia University, much more research is needed to establish whether people with autism have similar microbe-related problems. ■

BODY & BRAIN

Thalidomide treats Crohn's disease

Study of children with disorder finds new use for tainted drug

BY NATHAN SEPPA

The ongoing repurposing of the infamous drug thalidomide may include treatment of Crohn's disease, an incurable bowel condition.

Thalidomide was banned or never approved in many countries because it caused thousands of severe birth defects when pregnant women took it for nausea in the late 1950s and early 1960s. But researchers have now shown it can knock out symptoms in pediatric Crohn's patients, sending the disease into remission in most cases.

Crohn's is an inflammatory bowel disease marked by diarrhea, abdominal pain, weight loss and vomiting. One-fourth of cases show up in childhood. Crohn's affects roughly 500,000 people in the United States and 1.2 million in Europe.

25 percent
Fraction of Crohn's disease cases that begin in childhood

Starting in 2008, Marzia Lazzerini of the Institute for Maternal and Child Health in Trieste, Italy, and her colleagues randomly assigned 54 children with Crohn's to get daily thalidomide or a placebo. Many of the children were also taking steroids to reduce inflammation. All had failed to improve on other medications. Their average age was in the mid-teens.

After the eight-week trial, 13 of 28 kids taking thalidomide were in remission and five others had substantially fewer symptoms. Three of 26 children getting the placebo also went into remission, and two others needed surgery. The researchers then offered thalidomide to the other 21 placebo recipients, 11 of whom went into remission within eight weeks.

The researchers then extended the trial, offering thalidomide long-term to patients who had shown some benefit and hadn't experienced any severe side effects. Overall, 31 of 49 children taking thalidomide achieved remission. After one year, 30 were still free of disease. Sixteen weeks into the extended phase, all children still taking the drug had stopped using steroids. During the trial extension, doctors gradually decreased the daily thalidomide dose.

The average time in remission for these patients has been 3.5 years, the scientists report in the Nov. 27 *JAMA*. One patient has been taking thalidomide for five years, Lazzerini says.

"This is a well-designed study, no doubt about that," says W. Douglas Figg, a pharmacologist at the National Cancer Institute in Bethesda, Md., who has investigated thalidomide use against cancer. "I'm glad to see the activity it has shown here. There's very little out there for [treatment of] Crohn's disease."

Thalidomide was effective in many children who had failed to improve while taking infliximab (Remicade), a front-line drug against Crohn's. Both drugs neutralize an inflammatory protein called tumor necrosis factor-alpha, or TNF-alpha, but thalidomide also thwarts the formation of new blood vessels. Scientists think that action is what caused the birth defects.

Thalidomide also exerts many other effects in the body, Figg says, and that has scientists intrigued. Hundreds of clinical studies testing the drug are under way. Thalidomide is approved by the U.S. Food and Drug Administration for treatment of a complication of leprosy and a blood cancer called multiple myeloma, but its history remains a red flag.

"There is clearly a concern that's always there," Figg says.

In nine instances, a child in the new study experienced a side effect severe enough to require the patient to stop taking thalidomide. The most common problem was peripheral neuropathy, damage to nerves away from the brain and spinal column. ■

LIFE & EVOLUTION

Fly form of sexual frustration takes toll

Whiff of female but no mating causes males to die young

BY SUSAN MILIUS

Smelling female fruit flies but not mating with them can actually shorten males' lives.

Drosophila melanogaster males not allowed to mate despite receiving tantalizing chemical sex messages lose about 35 to 40 percent of their normal life span, says molecular geneticist Scott Pletcher of the University of Michigan in Ann Arbor. These males' fat stores also dwindle, and the flies prove less able to cope with starvation, Pletcher and his colleagues report November 29 in *Science*.

Creating the reciprocal situation of celibate females sniffing but not mating with males wasn't as easy, he says. But so far, experiments show female life span declining 15 to 20 percent too.

This marks the second time Pletcher and colleagues have linked premature demise with frustrated expectations. Fruit flies on a low-calorie diet, which normally would lengthen lives and sustain health, lost some of the diet's benefits if the flies lived with the smell of food they couldn't eat, he and colleagues reported in 2007.

Like a person salivating at the odor of a pie baking, flies pick up cues to likely events and start to prepare physically. Their brains may be monitoring the expected events as well as what the flies actually experience, Pletcher speculates, and "bad things happen when they don't match up."

To see whether odors of inaccessible mates would affect aging, Pletcher and his colleagues housed normal flies for two days or more with members of their own sex engineered to give off the distinctive signaling scents of the opposite sex. That deception let researchers look at the effects of the odor alone without any confounding behavioral or visual cues from the opposite sex.

Males escaped much of the damage of the frustrating experience if they could mate with females afterward, the researchers found.

Fruit flies have their own version of anticipation, and failure to mate as expected turns out to have physiological costs.

Rescuing the expectation-denied males, however, required an unusually high 5-to-1 female-to-male ratio, notes Jennifer Perry of the University of Oxford. She points out that in Pletcher's experiments, routine 1-to-1 mating opportunities didn't much affect the premature demise of frustrated males.

The males, however, had been set up to have unusually high expectations: The researchers had surrounded five males with 25 female-scented brethren.

The detectors for the sex-signaling compounds are particular molecules in male fruit fly forelegs, Pletcher and his colleagues determined. Fruit flies have abundant ways of sniffing and tasting their environment. When Pletcher and his team sabotaged a molecular sensor in the legs, scent-exposed flies had normal life spans.

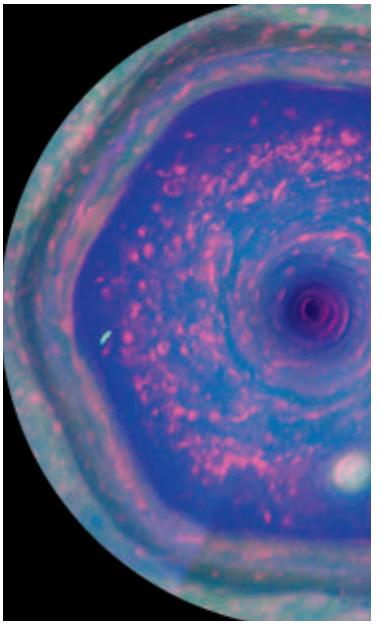
The experiments may help explain why male animals of many species have shorter life spans than females, says Urban Friberg of Uppsala University in Sweden. Males often face "harsh" competition for mates, he says, and he thinks unfulfilled mating expectations may turn out to be less of a problem for females.

A nugget of support for the idea that many animals could experience frustration effects, Pletcher says, comes from a paper on longevity in nematodes also appearing in *Science*. Hermaphrodite nematodes that wriggle around on lab dishes where males once congregated have shortened life spans, report Anne Brunet of Stanford University and her colleagues. There's no mating between the males and the hermaphrodites — again, the mere perception of secretions from a different sex triggers physiological consequences. ■

ATOM & COSMOS

Saturn's hexagon

A six-sided cloud pattern on Saturn has gotten its day in the sun. The Cassini spacecraft snapped high-resolution images of the hexagonal jet stream at the planet's north pole (center right). Using colored filters, the Cassini team identified large particles, shown in pink, swirling in the planet's lower atmosphere. Large particles at higher altitudes appear green, and tiny particles even higher in the atmosphere appear blue. Those tiny particles define the sharp boundary of the hexagonal jet stream, which fuels the clouds. The roughly 30,000-kilometer-wide cloud structure has been there for decades or even centuries. — *Ashley Yeager*



FROM TOP: COURTESY OF CHRISTI GENDRON; HAMPTON, SSI, JPL-CALTECH/NASA

ATOM & COSMOS

Huge plasma loops drive sun's rotation

Giant structures support theory of heat transport mechanism

BY GABRIEL POPKIN

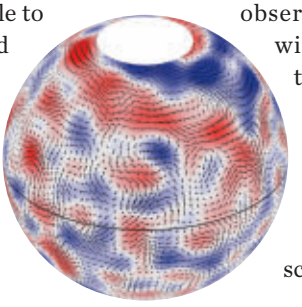
Massive, long-lasting plasma flows 15 times the diameter of Earth move heat from the sun's depths to its surface, according to a study in the Dec. 6 *Science*. The finding supports a decades-old explanation of why the sun rotates fastest at its equator.

In the outermost 30 percent of the sun, known as the convective zone, rising plasma carries heat generated by nuclear fusion in the sun's guts. Once at the surface, much of the plasma's energy radiates into space; the cooler, denser plasma then sinks, driving further convection and creating circulating loops called convection cells. Some especially massive convective structures, called supergranules, can last up to 24 hours and have diameters greater than Earth's.

In 1968, scientists theorized that even longer-lived and larger convection cells, big enough to span the entire convective zone, maintain the fast rotation researchers had long observed around the sun's equator; without such cells, the poles should rotate faster than the equator. Since then, scientists have sought observations of such giant cells.

A team led by David Hathaway of NASA's Marshall Space Flight Center in Huntsville, Ala., looked for these elusive convection cells using the agency's most sophisticated sun watcher, the Solar Dynamics Observatory. The researchers measured shifts in the wavelengths of light radiating from the sun's plasma as it flowed toward or away from Earth, and used the shifts to compute plasma velocities over the solar surface. These velocities revealed the positions of supergranules, a feat Hathaway had already accomplished with data from other observatories.

This time, however, Hathaway and his colleagues were able to use many closely timed observations to see that supergranules traveling across the solar surface were pushed by even larger plasma flows.



The sun's giant convective cells are illustrated (westerly flows in red, easterly flows in blue).

Many of these flows reappeared roughly once every 27 days, the time it takes for a spot on the sun's equator to rotate and reappear in view from Earth. That these flows lasted for multiple rotations strongly suggests that they are the predicted giant convection cells, Hathaway says. His team also found that giant cells appeared to transport fast-rotating plasma toward the equator and slow-rotating plasma toward the poles, confirming other predictions.

The study is the most compelling claim anyone has made about detecting giant convection cells, says Mark Miesch, an astrophysicist at the National Center for Atmospheric Research in Boulder, Colo., who has built computer simulations of solar convection. But, he adds, "I wouldn't call it a slam dunk."

Hathaway acknowledges that the observations don't entirely agree with leading theories. Simulations predict longer-lived cells near the equator and shorter-lived ones near the poles; Hathaway's team found the opposite. Theorists who have read his paper, he says, are "still scratching their heads a bit." ■

COURTESY OF D. HATHAWAY/NASA

GENES & CELLS

To cook up life, just add citrate

Theory that RNA spawned first organisms gets boost

BY SAM LEMONICK

A common biochemical may help forge a missing link in a popular but unproven theory about how life got started.

A leading idea of how loose molecules evolved to become self-replicating cells begins with the hereditary molecule ribonucleic acid. Any RNA-based origin-of-life theory has to include a way for RNA to copy itself. Harvard biologist Jack Szostak and colleagues had previously shown that primitive RNA replication happens best when contained in protocells. These containers have porous walls made of simple fat molecules.

Magnesium ions are also crucial to RNA replication. Without them, the reaction is impractically slow. However, Szostak has found that magnesium ions destroy the walls of his protocells.

In the Nov. 29 *Science*, Szostak and Katarzyna Adamala, also at Harvard, show that citrate, a chemical cousin of the citric acid in lemons and limes, protects protocell walls and allows RNA copying to proceed at a reasonable pace. Citrate latches onto three of the six available attachment points on the magnesium ion, leaving it open enough to assist the RNA reaction but too enclosed to interfere with the protocell walls.

Szostak, though, seems far from declaring victory. "Our goal is finding some reasonable and continuous pathway from small molecules up to more complicated building blocks, then to cells that can start to evolve," he says.

He's already experimenting with alternatives to magnesium and citrate because those substances may not have been readily available on the early Earth. Iron might be able to take the place of magnesium. Instead of citrate, Szostak is thinking of using a protein fragment.

John Sutherland, a chemist at the Medical Research Council in Cambridge, England, thinks Szostak's theory is gathering steam. When a plausible path emerges with many similarities to modern biochemistry, he says, "it's difficult to escape the conclusion that it is actually the way things happened." ■

MATH & TECHNOLOGY

Prime clusters may go all the way

Major advance made toward proving legendary conjectures

BY DANA MACKENZIE

A famous conjecture in number theory has stood unproven for more than 150 years, but for the second time this year mathematicians have gotten dramatically closer to proving it. With a strategy others had abandoned, a young mathematician has narrowed the gap between primes, in hopes of ultimately proving the twin prime conjecture.

His work has also shown that prime numbers bunch together in clusters as well as in pairs.

The twin prime conjecture asserts that infinitely many pairs of prime numbers are separated by only two, as are 3 and 5 or 1,997 and 1,999. Prime numbers are divisible only by themselves and 1. Number theorists know that as numbers get larger, primes gradually get sparser. Nonetheless, if the twin prime conjecture is true, pairs of primes separated by two continue to pop up forever.

Number theorists have been revved up since May, when Yitang "Tom" Zhang, a University of New Hampshire mathematician, announced a partial solution to the twin prime problem, which will appear in *Annals of Mathematics*. Researchers have since been refining his methods, getting closer to solving the problem (*SN: 12/28/13, p. 32*).

In October, James Maynard, a postdoctoral researcher at the University of Montreal, announced at a workshop in Germany that he had improved Zhang's estimate for prime pairs. In doing so, he had also resuscitated a previously discarded technique to prove that primes also occur in clusters. Maynard posted his results November 19 at arXiv.org.

Zhang had shown that pairs of primes with gaps no larger than 70 million keep occurring forever. He was the first to demonstrate a finite cap on the minimum gaps between primes.

Even though 70 million is a long way from 2, it's an even longer way from infinity. "He didn't waste time trying to get a smaller number," says John Friedlander of the University of Toronto. Zhang knew that just getting any finite number would be a sensational result.

But other mathematicians enthusiastically pounced on the problem. In June, hardly a day passed without a new world record for the smallest prime gap that repeats infinitely. By the end of July, the record stood at 4,680. The researchers made these gains using tweaks and refinements of Zhang's argument, not by breaking new mathematical ground.

Meanwhile, as he was finishing up his doctorate at the University of Oxford, Maynard pondered a related question: Do primes occur infinitely only in pairs like cherries or also in bunches like grapes?

2
Gap between primes that appears infinitely, according to conjecture

600
Smallest prime gap now proven to appear infinitely

In addition to twin primes with their gaps of 2, triplets may occur in baskets of width 6. Such a basket catches 7, 11 and 13 or 2,707, 2,711 and 2,713, and the harvest presumably continues forever. This statement is the prime triplets conjecture, and there is an analogous conjecture for prime quadruplets and larger.

Zhang's work says nothing about prime triplets or other multiples. It uses a prime detection tool called the one-dimensional Selberg sieve that, for reasons not completely understood, can detect only pairs of primes. The sieve is a theoretical function (not an actual device or program) that weights numbers roughly according to their probability of being prime.

The original multidimensional Selberg sieve, discovered in the 1940s by the Norwegian mathematician Atle Selberg, does not have the pair limitation. Zhang had borrowed the simpler one-dimensional version from 2005 work on prime gaps by mathematicians Daniel Goldston, János Pintz and Cem Yıldırım.

That paper was itself a modification of an argument from a 2003 paper by Goldston and Yıldırım, which had used the multidimensional sieve to address the twin prime conjecture but had to be retracted because of a fatal error.

Because of this history, many number theorists considered the multidimensional sieve inherently flawed. "I think the issue was perhaps more psychological than technical," says Terence Tao of UCLA.

But Maynard, who had nothing to lose because he was essentially done with his doctoral dissertation, decided to play around with the discredited sieve. Nearly on the eve of his dissertation defense, he figured out how to make it work.

Using the sieve, Maynard found a list of 105 numbers (0, 10, 12, 24, ... 594, 598, 600) that serves as a template for prime pairs. This means that infinitely many numbers, when added to the numbers in the template, produce at least two primes. (For example, 3 works because 3+0 and 3+10 are both prime.) The template produces pairs of primes that are separated by 600 at most — a major improvement over the record of 4,680.

Even more important, Maynard showed that longer templates exist for prime triplets, quadruplets and higher-order prime multiples, thereby establishing world records that had not even existed for prime bunches of varying size. (Tao independently used the same ideas to reach a similar but slightly weaker result.)

"Maynard's proof is much shorter than Zhang's and much more elementary, and it produces stronger results," Friedlander says. "But the proofs are quite different, so at some point in time Zhang's ideas and Maynard's could be incorporated together to get results stronger than either one got alone. It's a wonderful situation." ■

KELVIN AITKEN/VWPICS/ASSOCIATED PRESS

LIFE & EVOLUTION

How the ghost shark lost its stomach

Animals from lungfish and ghost sharks (one shown) to platypuses have lost acid-making stomachs over evolutionary time, and researchers have now traced the genetic changes behind these stomach upsets. True stomachs with digestive glands that concentrate acid and release protein-cutting enzymes evolved with vertebrates. The gastric glands have dwindled away at least 15 separate times across the animal tree of life, explains Filipe Castro of the University of Porto in Portugal. After scrutinizing genes of 14 vertebrates with and without stomachs, Castro and his colleagues determined that none of the stomach losers has genes for maintaining a highly acidic zone in their digestive tracts. The animals also lack or have low-functioning genes for secreting the enzymes that slice up proteins under acidic conditions, the researchers report December 4 in the *Proceedings of the Royal Society B*. Other parts of the animals' digestive systems are thought to break down food into nutrients. — *Susan Milius*

BODY & BRAIN

Fear can be inherited

Along with eye color, height and dimples, parents' fears may pass down to children, scientists report December 1 in *Nature Neuroscience*. The results, from experiments with mice, suggest how fallout from a person's experiences might ripple through generations. Mouse parents learned to associate the scent of orange blossoms with a shock. Their children and their grandchildren startled in response to the scent even though they had never smelled it before. Offspring also had more neurons that detect the orange blossom scent than mice whose parents weren't exposed to the scent. Sperm cells alone can deliver this fear message, study authors Brian Dias and Kerry Ressler of Emory University found. DNA in the sperm cells was epigenetically imprinted with this fearful association: A gene that codes for the molecule that detects the orange blossom odor carried a chemical stamp that may have changed the gene's behavior. — *Laura Sanders*

Cell counts provide a read on ovarian cancer

A new test that tallies up useful immune cells in cancerous tissue could clarify a patient's prognosis and possibly guide treatment. The technology counts immune cells that infiltrate and attack tumors. Jason Bielas and his colleagues at the Fred Hutchinson Cancer Research Center in Seattle devised a procedure that identifies gene signatures specific to these immune cells and applied it to ovarian tumors that had been removed from 30 patients and stored. After surgery, the patients' survival ranged from one month to more than 10 years. Tumors removed from patients who had survived for more than five years had 2.5 times as many of the immune cells as those taken from patients who had lived less than two years. The researchers report the findings in the Dec. 4 *Science Translational Medicine*. The researchers suggest the technology might work in various cancers. — *Nathan Seppa*

EARTH & ENVIRONMENT

Earth's plate boundaries may nurture diamond formation

Boundaries between tectonic plates may make ideal diamond nurseries, according to an experiment that mimics conditions deep in the Earth. Scientists have long thought diamonds might form in subduction zones, where one tectonic plate plunges under another and sinks hundreds of kilometers into the mantle. To simulate this extreme environment, scientists led by Yuri Palyanov of the Russian Academy of Sciences in Novosibirsk put minerals that are common in Earth's crust into a chamber where the researchers could apply intense pressures and temperatures. The team found that at around 74,000 times atmospheric pressure and above 1,200° Celsius, diamonds crystallized. The exact makeup of the diamonds depended on which mineral the carbon came from. The team reports its findings December 2 in the *Proceedings of the National Academy of Sciences*. — *Gabriel Popkin*

HUMANS & SOCIETY

Fossils reveal a strong-armed, dead-end hominid

A first look at the strapping arms and legs of an unusual member of the human evolutionary family has arisen from new fossil finds at Tanzania's famous Olduvai Gorge site. A team led by paleoanthropologist Manuel Domínguez-Rodrigo of Complutense University of Madrid unearthed nine teeth and large parts of two arm bones and two leg bones from an adult male *Paranthropus boisei*. This hominid lived alongside early *Homo* species in eastern Africa for about 1 million years before dying out. Age determinations for volcanic ash layers that border fossil-bearing sediment indicate that this Stone Age hominid lived 1.34 million years ago. Large, powerful limbs enabled *P. boisei* to both walk upright and at least occasionally spend time in the trees, the scientists report December 5 in *PLOS ONE*. The individual stood just over 5 feet tall and weighed about 136 pounds, the team estimates. — *Bruce Bower*

MICROSCOPIC Menagerie

New view of microbes forces rethinking of what it means to be an organism

By Susan Milius

"What is a wasp?" might seem like an overly simple question for a Ph.D. biologist to be asking. "What is a human?" Even more so.

But these are strange times in the life sciences. Seth Bordenstein of Vanderbilt University in Nashville now embraces the notion that each wasp he studies, each squirrel darting around campus — not to mention himself, every reader of science magazines and every other representative of see-it-without-a-microscope life on Earth — is really a blend of one big organism and a lot of little ones.

In recent years, research has shown that what people commonly

NICOLLE RAGER FULLER

think of as "their" bodies contain roughly 10 microbial cells for each genetically human one. The microbial mass in and on a person may amount to just a few pounds, but in terms of genetic diversity these fellow travelers overwhelm their hosts, with 400 genes for every human one. And a decent share of the metabolites sluicing through human veins originates from some microbe. By these measures, humanity *is* microbial.

But numbers are just the beginning. The evolutionary impact of animals' microbial denizens can be substantial. Adult wasps of the genus *Nasonia* are only about 30 percent microbial, Bordenstein estimates. But those microbes keep two species apart that could otherwise interbreed.

Some researchers think of these microbes as just another part of a plant or animal's environment, like a mountain range that keeps two related species separate. But, with a squint and a slap to the worldview, researchers like Bordenstein are exploring whether a body's microbes are so intimate that they're part of the organism itself. Or, if you prefer, the metaorganism.

"Ecosystem" is the word that 26 scientists used in a call for new thinking about animal-bacteria interactions that was published in February by the *Proceedings of the National Academy of Sciences*. The recent accumulation of knowledge about bacteria vis à vis their animal hosts "is fundamentally altering our understanding of animal biology," the group declared.

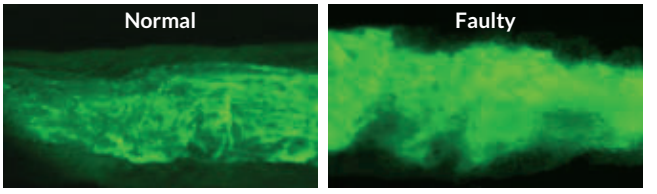
Why would biologists get so excited about teeming microorganisms now? Even someone who missed the earliest fiddling with magnifying lenses has had 330 years to catch up on volume 14 of the Royal Society's *Philosophical Transactions*, wherein merchant microscopist Antonie van Leeuwenhoek reported "to my great surprise," that watered-down scrapings from his teeth revealed "very many small living Animals, which moved themselves very extravagantly."

For more than three centuries after van Leeuwenhoek's discovery, anyone interested in studying the microbial world was limited by the frustrations of "growing fuzzy things in Petri dishes," as Corrie Moreau of the Field Museum in Chicago puts it. A fascinating microorganism might thrive in the gills of deep-ocean clams, in groundwater seeping through porous rock or in the gonads of mosquitoes. But if you couldn't culture it in a lab dish you had no way of knowing about it. Even with clever technical advances, an estimated 99 percent of microbial life can't be cultured, Moreau says. And what does grow may be misleading. A marginal freak may look like the dominant member of a community only because it's the one that flourishes in the lab.

Recent genomic innovations have changed all that. In the last few years, automated systems have been developed to quickly and affordably determine the genetic signatures of thousands of individual microbes in a sample.

What a world the new technology reveals: In just 19 samples from four colonies of turtle ants, Moreau says, 445 kinds of bacteria showed up that cultures and clunkier genetic techniques had missed. Eight kinds of bacteria consistently show up in the guts of honeybees and a few other bees, but so far, nowhere else. Bedbugs need *Wolbachia* bacteria inside their cells to survive.

Gut buster Tsetse flies must be infected during gestation with a particular bacterium in order to develop a normal gut lining (left). Lab-raised larvae that were bacteria-free developed faulty guts (right) and weak immune systems that made them much more vulnerable to infection by the parasite that causes sleeping sickness.



B.L. WEISS *ET AL*/*PLOS PATHOGENS* 2013

And bacteria may at last explain how the giant panda, a bamboo-eating member of the mammalian order Carnivora without a grass-grazer's capacious fermenting gut or specialist digestive enzymes, can live on 12.5 kilograms of highly fibrous plant material a day. The bear's puzzling digestive system turns out to gurgle with bacteria that apparently belong to groups that include competent digesters of cellulose.

Born with it

Bacteria start shaping their hosts' lives right from the beginning. In tsetse flies, for example, inheriting genes from mom isn't enough; larvae that don't also inherit the right kind of bacteria don't grow properly.

10

Microbial cells for each human cell in body

400

Microbial genes for each human gene in body

The way tsetse flies start their lives "is eerily similar to what happens in mammals," says Brian L. Weiss of Yale University. In most insects, "the female will just lay a bunch of eggs and fly away." Tsetse females, however, gestate one fertilized egg at a time inside what amounts to a uterus. Glands inside the uterus produce a white milklike liquid rich in fats and proteins. After suckling for its first three larval stages, the youngster weighs about as much as its mother. Then she gives birth.

Gorging on mother's milk doses the infant with a *Wigglesworthia* bacterium, which Weiss describes as looking like a hot dog. *Wigglesworthia* can live only inside a tsetse fly, and flies deprived of it don't give birth.

Weiss was able to deduce what *Wigglesworthia* does in development by dosing moms with B vitamins to artificially keep their bacteria-free larvae alive. The larvae grew up but never formed a decent immune system. Flies deprived of bacteria as larvae also failed to form a real gut lining, Weiss and his colleagues reported in April in *PLOS Pathogens*.

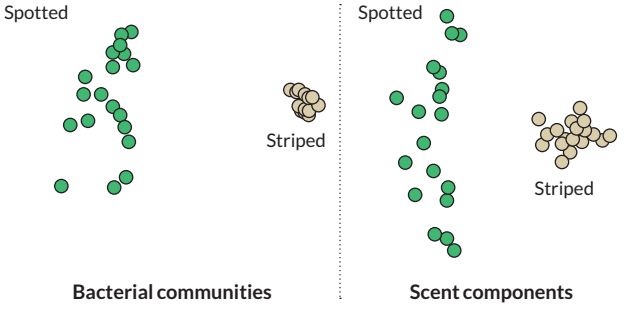
A faulty gut lining in a tsetse fly is a serious problem, and not just for the flies. Even though they're famous for

spreading the trypanosome parasite that causes sleeping sickness, only 1 to 5 percent of normal tsetse flies become carriers when feeding on infected blood. With faulty guts, though, more than 50 percent of bacterially starved, skimpy-gut flies turn into carriers.

Other studies have turned up similar examples of microbial power in animal development. Females of the parasitic wasp *Asobara tabida* need a *Wolbachia* bacterial strain in order to form wasp eggs. Developing mice can't form normal capillaries in their guts without a standard set of microbes being present. And young lab mice may even need their gut bacteria for proper brain development, a research team in Sweden reported in 2011. Mice raised without normal gut microbes were unusually active and bold in tests, as if their brains weren't wired the same way as those of regular shadow-loving, skittish mice. Returning gut bacteria to germfree mice re-created normal caution in their offspring. But it failed in adults with brains that were already mature.

Moms of a variety of species appear to microbially prep their young, says Bordenstein. Vesicomyid clams that need microbial help to survive at deep-sea vents, some sponges and cockroaches release eggs already loaded with bacteria. When stinkbugs lay eggs, the capsules get smeared with mom's bacteria-rich excrement. When the youngsters hatch, they gobble the egg case, smear and all.

Reports of mother-to-child bacterial transmission appear to be so widespread among animals, Bordenstein argues, that it's time to consider them the norm. He and Vanderbilt colleague Lisa Funkhouser published a manifesto in August in *PLOS Biology* calling for an end to "the sterile-womb paradigm."



Say it with scent Striped and spotted hyenas (shown, top) both use a smelly paste exuded from pouches under their tails to mark territory and communicate with one another. A two-dimensional statistical plot showing variation among bacterial communities hosted by individual hyenas of the two species (bottom left) looks very much like one showing variation in chemical components of their scents (bottom right). SOURCE: K. THEIS *ET AL*/PNAS 2013

Bacterial billboards

Other paradigms are drawing strength from microbiologists' recently developed ability to genetically probe bacterial communities. Since the mid-1970s, biologists have suspected that in many mammals a microbial community ferments various sweats, oozes and excretions into distinctive scents that reveal age, health and much more to knowing noses in a select social circle.

The notion sounds plausible, but attempts to test it have stalled for years. Culturing bacteria from various mammal scent glands has generally yielded only one or two, or sometimes five, kinds. This paltry haul seemed too limited to convey all the information that biologists think is wafting around.

With modern genetic tools to identify bacteria, Kevin Theis of Michigan State University in East Lansing and his colleagues are revisiting the classic hypothesis of messaging by fermentation. His scent-marking research subjects are spotted and striped hyenas.

"Pretty robust," is how Theis rates the funk wafting off hyena scent marks. Both species evert a pouch just under the tail and dab a pungent paste produced by sebaceous glands onto a grass stem or other convenient landmark. The paste smells to Theis like pine mulch fermenting after a rain. It could encode territorial information as well as olfactory gossip such as who's growing eager for a mate, already pregnant or perhaps ill.

Hyenas have a lot to smear and sniff about. Spotted hyenas live in hierarchical clans of dozens of animals. "It's like watching a soap opera," says Theis. Striped hyenas spend more time alone and form smaller groups, but still need to keep up with their kind while they forage, rest and travel.

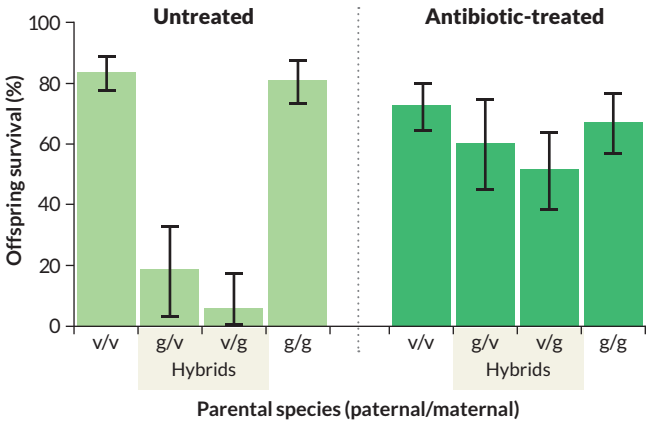
So far, Theis says, he's found more bacterial genera just in the scent paste of adult female spotted hyenas than researchers had discovered in 15 earlier studies of any mammalian scent gland.

The blends of stinky volatile compounds that striped and spotted hyenas use to communicate are distinct enough that biologists can distinguish the two species by their scent marks. And, as would be predicted if microbes were making the scents, the two species likewise have distinctive microbial communities that align with those scent differences, Theis and his colleagues report November 11 in the *Proceedings of the National Academy of Sciences*. The link between odor difference and community difference supports a main pillar of the hypothesis that the microbes are the message.

SAM DCRUZ/SHUTTERSTOCK

A breed apart When two related species of *Nasonia* wasp mate (left), their hybrid male offspring (g/v and v/g) usually don't survive. With a dose of antibiotics, however, hybrid males are almost as viable as nonhybrids (right). SOURCE: R. BRUCKER AND S. BORDENSTEIN/*SCIENCE* 2013

v = *N. vitripennis* g = *N. girault*



The researchers also detected some patterns within species suggesting that the communities shifted with events such as pregnancy. This paper marks the closest anyone has come to demonstrating the whole fermented-message idea, Theis says.

Choice microbes

Microbial residents do more than broadcast scented status updates. Bacteria also appear to steer their hosts away from some mates.

One startling example, described in 2010, grew out of a peculiar side effect of rearing fruit flies on different diets. In earlier experiments, researchers had noticed that lineages of fruit flies fed for 25 generations on different diets became less likely to mate with each other.

Follow-up tests at Tel Aviv University found that *Drosophila melanogaster* flies rejected opposite-diet flies as potential mates after just one generation of eating molasses rather than starch. At Tel Aviv, Eugene Rosenberg and Ilana Zilber-Rosenberg had been formulating ideas on the importance of what they called the hologenome, the sum of genetic information in a host species and its microbial residents. To test this comprehensive view of the fruit fly, researchers fed the flies antibiotics to kill the insects' microbial communities. Without microbial influence, the lineages took to mating with each other again.

Microbial incompatibility appears to render hybrid male wasp larvae of two *Nasonia* species much less viable than purebreds.

Inoculating reconciled fly lineages with different microbial communities resurrected the mating barrier. What made the difference, researchers proposed, were diet-based shifts in gut microbes that in turn influenced sex pheromones.

Observing a microbial effect on mate choice makes it sensible to ask a very big question: Could these teeming microscopic masses control the evolutionary fate of whole species?

In jewel wasps, for example, a genetic barrier that keeps two species apart turns out to have a previously overlooked microbial aspect (*SN: 8/10/13, p. 13*), Bordenstein and Vanderbilt colleague Robert Brucker reported in the Aug. 9 *Science*.

Two kinds of jewel wasp, *Nasonia girault* and *Nasonia vitripennis*, split off from a common ancestor about a million years ago. If the two species happen to mate now, the second-generation male larvae develop a dark splotch and die. Geneticists have traced this lethal incompatibility in detail, finding genetic differences between the species that appear to influence hybrid survival.

To test for a possible missing microbial something, Brucker dosed doomed hybrids with an antibiotic. Their resident microbes died, but many of the hybrid wasps lived. A mismatch between their parents' differing microbes and their genes seemed to be killing hybrids.

As a further test, Brucker gave the unexpectedly alive germ-free hybrids some of the gut bacteria that hybrids normally have. No longer germ-free, the hybrids died.

The experiment supports Bordenstein's view that evolutionary forces act not just on an animal's DNA but on the sum of its own genome and those of its microbial residents.

Of course microbes matter, says Tadashi Fukami of Stanford University. But he isn't ready to declare them and their hosts a single evolutionary entity. He studies the microbial communities living in flowers' nectar, and applauds increased attention to microbial influences. Yet he says that he would expect the hologenome theory of evolution to apply only in specialized, albeit interesting, cases. The discussion reminds him of debates over what's called group selection. The idea that evolution acts on groups of organisms caused excitement and controversy when first proposed. But now Fukami and a fair number of other evolutionary biologists don't find many cases in which it applies.

Still, appreciating microbes' evolutionary significance could upend some fundamental ideas taught in introductory biology, says developmental biologist Scott Gilbert of Swarthmore College in Pennsylvania. Learning that a normal set of mouse genes isn't sufficient to grow a healthy mouse body "set off all kinds of gongs and whistles," he remembers. "All this stuff about 'you are who you are depending on your nuclear genes' was demonstrably not true," he says, if microbes living symbiotically in the body amount to a second mode of inheritance.

He's embracing the idea of animals as composite beings. On occasion he finishes scientific presentations with a closing PowerPoint slide that credits the talk not to him alone, but to "Team Scott Gilbert." ■

Explore more

- Margaret McFall-Ngai *et al.* "Animals in a bacterial world, a new imperative for the life sciences." *Proceedings of the National Academy of Sciences*. February 26, 2013.

R. BRUCKER AND S. BORDENSTEIN/*SCIENCE* 2013

THE VAST VI

Studying complex diseases is like trying to solve a massive jigsaw puzzle with a blank box cover and who knows how many missing pieces. Scientists now realize that human genes form the borders of many disorders. But it turns out that the picture can't be filled in without considering microbes, especially the bacteria and viruses that make the human body home.

Four years ago, evolutionary geneticist Vicente Pérez-Brocal found himself trying to complete the Crohn's disease puzzle. As a member of a research group headed by Andrés Moya at the University of Valencia in Spain, Pérez-Brocal was tasked with determining if viruses fit into the picture.

Crohn's disease is an inflammatory bowel disease thought to result when the immune system goes into overdrive, causing chronic inflammation that can damage the intestines and raise the risk of colon cancer. Genes and personal habits, such as diet and smoking, play a role, but there are still gaps. Scientists think infectious organisms could be involved, but still debate where those pieces belong.

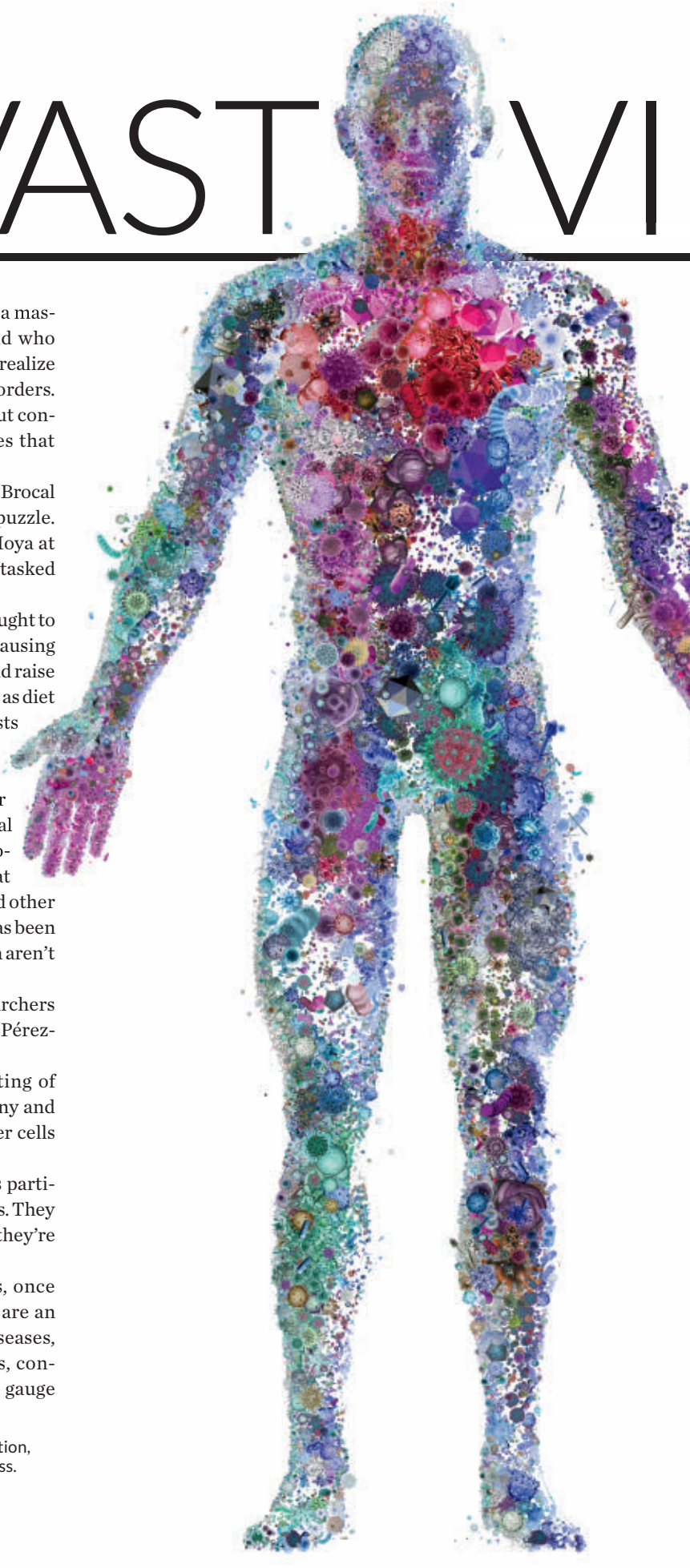
Bacteria are obvious gap-fillers; they outnumber human cells 10-to-1 and influence nearly every biological process in the body. Some promote disease, others protect against it (*SN: 6/18/11, p. 26*). The microbiome — what scientists refer to as the collection of bacteria, fungi and other single-celled organisms that live in and on the body — has been a hot research topic for more than a decade. But bacteria aren't the only microbes with which we humans share space.

The most abundant inhabitants of what many researchers are calling "the human ecosystem" are the viruses. So Pérez-Brocal reasoned they were worth a closer look.

Viruses are deceptively simple organisms consisting of genetic material packed in a protein shell. They are tiny and can't replicate on their own, relying on human or other cells to reproduce.

And yet, scientists estimate that 10 quintillion virus particles populate the planet. That's a one followed by 31 zeros. They outnumber bacteria 10-to-1 in most ecosystems. And they're ubiquitous in and on humans.

Pérez-Brocal and others are learning that viruses, once seen only as foreign invaders that make people sick, are an integral part of human biology. Some cause major diseases, including influenza, AIDS and some cancers. Others, conversely, may promote health. Some may even help us gauge



The human body is mostly microbes. Bacteria get a lot of attention, but viruses also turn out to be important in both health and illness.

ROME

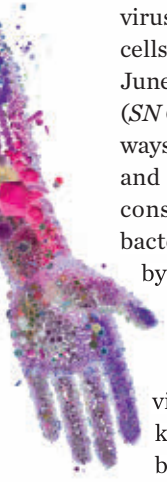
Scientists are just beginning to get a handle on the many roles of viruses in the human ecosystem

By Tina Hesman Saey

how well the human immune system works.

The study of people's resident viruses, known collectively as the human virome, is "a whole new frontier in the understanding of humans," and could become important for the future of medicine, says Forest Rohwer, an environmental microbiologist at San Diego State University.

Rohwer's research indicates that viruses are part of the human defense system. Mucus studded with bacteria-infecting viruses called bacteriophage, or phage, may help protect host cells from invasive microbes, he and his colleagues reported June 25 in the *Proceedings of the National Academy of Sciences* (*SN Online: 5/20/13*). Within the mucus barrier that lines airways and intestines and coats the mouth and other orifices, the host and phage conspire to control the movement of bacteria. Anchored to sugars produced by host cells, phage infect and blow up invading bacteria that try to cross the mucus barrier.



As scientists take a census of the virome, they've begun to reveal these kinds of unexpected partnerships, but the work lags far behind that of the rest of the microbiome.

"We know a lot about the bacteria that inhabit humans," says David Pride, an infectious disease doctor at the University of California, San Diego. In comparison, "we know absolutely nothing about the viruses."

ID tags

Not that scientists haven't been interested in viruses. Until recently there was just no good way to identify them, an important first step toward understanding the biology of health and disease. As a consequence, virome research is in its infancy.

Researchers have gotten a head start on cataloging bacterial denizens of the body because all bacterial cells contain a version of the 16S ribosomal RNA gene. That gene encodes an RNA component of protein-building machines called ribosomes. The 16S rRNA gene clearly flags bacteria because humans and other eukaryotes build their ribosomes with a different set of RNAs. Each bacterial species has a slightly different version of the gene, which researchers use to identify who's who among microbial citizens of the human body.

Virus hunters aren't so lucky. There is no analogous virus-identification tag. Instead, to look for viruses, researchers must sequence hundreds of thousands of bits of DNA from a sample — skin swabs, saliva, feces or mucus, for example. Scientists have gotten really good at generating these DNA sequences; the trick is figuring out what they are.

Some of these DNA bits come from human cells, some from bacteria and other microbes that occupy the body, such as archaea and fungi. Some bits may come from viruses, but it is hard to tell for sure, says Pérez-Brocal, because scientists have a limited set of characterized viruses to use as a guide for spotting new ones.

In their search for a viral cause of Crohn's disease, Pérez-Brocal's team examined the DNA in stool samples from eight healthy people and 10 people with the condition. After tossing out DNA that clearly came from humans and bacteria, the team was left with one pool of DNA that matched sequences from a database of viral DNA and another pool of unknown origin.

The researchers found less viral diversity in the Crohn's disease patients. Only retroviruses appeared to be more abundant in people with Crohn's disease than in healthy people, the team reported June 13 in *Clinical and Translational Gastroenterology*.

Retroviruses, including HIV, the virus that causes AIDS, insert copies of themselves into the host's genome. Sometimes that insertion disrupts host genes, leading to cancer or other diseases.

To be fair, Pérez-Brocal and his colleagues have nothing more than guilt-by-association to link retroviruses and Crohn's disease. They don't yet know if a retroviral infection sparks the disease

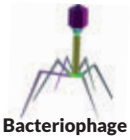
Cast of characters Many of the viruses that inhabit humans remain unidentified. But plenty are well-known, and they are with us even when we're not sick.

Pepper mild mottle virus
This virus may grow on plant material passing through the intestines.

Polyomavirus
Varieties of this virus infect humans; one may cause skin cancer.

Papillomavirus
Some strains cause cervical cancer, others live on the skin of healthy people.

Anellovirus
This virus may be a bellwether for the immune system's health.



Bacteriophage
Viruses that infect bacteria may help shape bacterial communities in our bodies.

Adenovirus
This respiratory virus is detected in kids with fevers, but also in the noses of healthy children.

Retroviruses
These viruses insert themselves into human DNA and may play a role in Crohn's disease.

Marseillevirus-like virus
Found in healthy people, this virus resembles giant viruses common in amoeba.

ALL: CHARIS TSEVIS

or if having an inflamed bowel makes it easier for retroviruses to gain a foothold. "We cannot say if this is cause or consequence," Pérez-Brocal says. "At this point we're just describing what we observe."

Early virome studies indicate that there's still much more to observe.

Every time Frederic Bushman samples a new person's virome, he says, he finds new viruses. A microbiologist at the University of Pennsylvania Perelman School of Medicine in Philadelphia, Bushman has shown that no two people's gut viruses are exactly alike (*SN Online: 7/14/10*). But once a person has picked up a community of bacteria-infecting phage, it tends to stick around. Fully 80 percent of the viruses present when the researchers first started tracking one man's virome were still there more than two years later.

10 quintillion
Number of virus particles that populate the planet

That's not to say things stagnated, viromewise. The viruses themselves mutated rapidly; some changed up to 4 percent of their DNA over the course of the experiment, Bushman and his colleagues reported July 23 in the *Proceedings of the National Academy of Sciences*. That amount of mutation is similar to the degree of DNA difference between two viral species, he says, and could account for why people's gut viruses are so individual.

Pride and his colleagues at Stanford, the University of California, San Diego and elsewhere tracked viruses from the mouths of four volunteers to get a sense of their viral history. The researchers used tags known as CRISPRs to observe the changing viral landscape. CRISPRs are bits of phage DNA that bacteria have chopped up and incorporated into their own chromosomes. When bacteria encounter a new phage, they check its DNA profile against this internal dossier and destroy those that have caused trouble before.

Those CRISPR tags help researchers determine which phage that the bacteria — and therefore the human host — have encountered in the past.

In Pride's study, volunteers spit into tubes four times over 11 months. In each person, a small number of tags — between 3 and 18 percent — were present in all the saliva samples, Pride's team reported in the September 2012 *Environmental Microbiology*. But in every sample between 25 and 75 percent of the CRISPRs were new, indicating that bacteria are constantly facing fresh phage assaults.

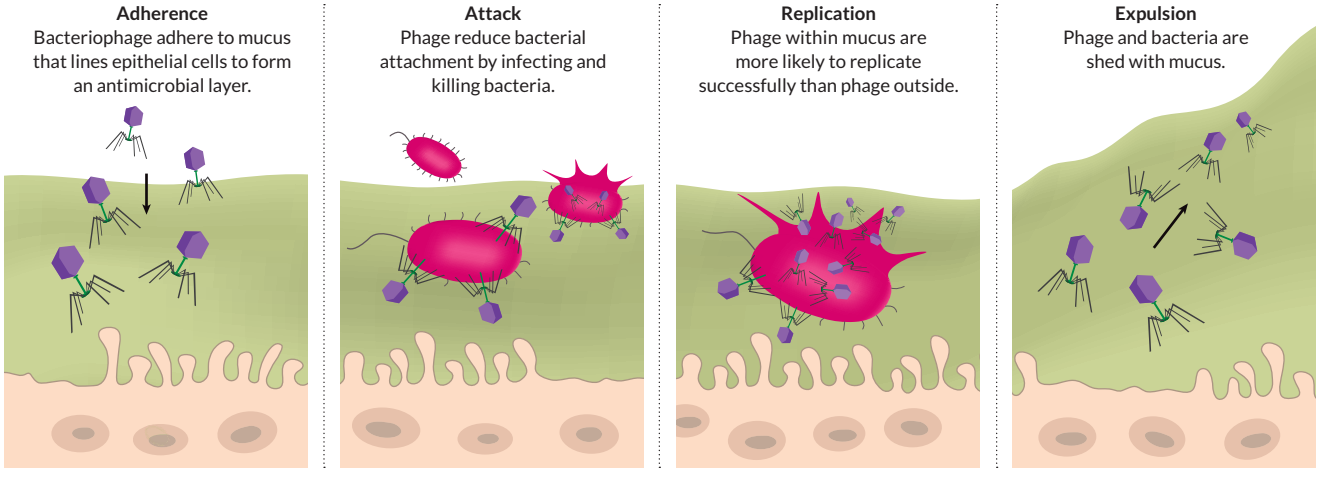
Paradoxically, bacteriophage may play a crucial part in strengthening bacteria's attacks on their human hosts. Phage may deposit genes for resisting antibiotics or for making toxins into the bacteria they infect, potentially producing virulent infections that can withstand antibiotic treatment.

Some bacteria use bacteriophage as a weapon against other bacteria, says Howard Hughes Medical Institute investigator Lora Hooper, a microbiologist and immunologist at the University of Texas Southwestern Medical Center in Dallas. Under certain conditions, a common intestinal bacterium called *Enterococcus faecalis* unleashes a Frankenstein bacteriophage composed of two different phages, she and her colleagues reported in the *Proceedings of the National Academy of Sciences* in October 2012. In experiments with mice, Hooper's group showed that the composite phage gives *E. faecalis* strains an advantage over the competition when settling into the intestines.

Maybe researchers can use bacteriophage to shape the human microbiome in healthier ways. Using phage to control bacteria is a resurgence of an old idea. In the 1920s, doctors in the former Soviet Union and other Eastern European countries began using phage to treat specific bacterial infections. Unlike antibiotics, which kill bacteria indiscriminately, phage target only certain microbes for destruction.

Reviving this strategy will depend on finding or designing bacteriophage that will take out specific "bad bugs," while somehow avoiding the bacteria's ability to ward off attackers

Danger zone Bacteria-slaying viruses called bacteriophage team up with cells in the human host that produce mucus. They form a protective layer that is deadly to microbes that try to cross it. SOURCE: J.J. BARR *ET AL*/*PNAS* 2013



M. ATAROD

with CRISPRs. Researchers admit this type of microbial manipulation is still far in the future.

Immune system sentry

That doesn't mean viruses, and viral surveys, can't be useful in the near term.

Some viruses may act as bellwethers for the health of the immune system.

Stephen Quake, a geneticist and Howard Hughes Medical Institute investigator at Stanford University, and his colleagues were studying recipients of heart or lung transplants to learn why some people reject the organs. They collected blood from 96 transplant patients and examined bits of DNA floating in the samples. "We realized some of the DNA wasn't human," Quake says.

Of the nonhuman component of the patients' blood, 73 percent came from viruses. The majority — 68 percent — of the viruses they found were anelloviruses, mysterious germs that don't cause specific illness but have been linked to fevers in toddlers. Some of the transplant recipients had high levels of the viruses in their blood. It may sound counterintuitive, but "that's good news if you have an organ transplant," Quake says.

It means that immune-suppressing drugs are doing their job of weakening the immune system to prevent organ rejection, a very real danger for people who get hearts or lungs from unrelated strangers. People with lower levels of anelloviruses in their blood were more likely to reject their transplanted organs, Quake and his colleagues reported in the Nov. 21 *Cell*. Because the very immune reactions that keep the viruses in check can also turn against the foreign organ, measuring transplant patients' load of anelloviruses may help predict who is likely to face organ rejection.

Even beyond transplants, doctors may be able to monitor anelloviruses to learn about the health of their patients' immune systems. For example, people with HIV develop escalating levels of anelloviruses in their blood as their immune systems weaken, says Quake's coauthor, Kiran Khush, a cardiac transplant surgeon at Stanford University.

"This is another big, red sign that these things [viruses] should be getting more attention," Quake says.

Friend or foe?

In organ rejection, the anelloviruses are not the cause; they're sentinels. But other maladies may have viral instigators. Figuring out which viruses are the culprits is a difficult task, says Kristine Wylie, a virologist at Washington University School of Medicine in St. Louis.

Wylie and her colleagues took blood samples and nasal swabs from infants and toddlers, some of whom had unexplained fevers. They wanted to see if DNA technology could quickly identify why the kids were sick.

The researchers found 25 different major categories of viruses, including many associated with illness, they reported in *PLOS ONE* in June 2012. Children with fevers tended to carry a heavier viral burden, both in the number and type of viruses. But even healthy kids had plenty of viruses in their noses and in their blood.

"Healthy subjects are just loaded with viruses," Wylie says. Even viruses known to cause diseases such as the common cold were found in healthy kids. That makes it difficult to determine whether a particular virus is really making someone sick.

Some viruses previously thought innocent may cause harm. Rohwer was part of a team that found in 2005 that plant viruses, particularly the pepper mild mottle virus and other pathogens that affect fruit, grain and vegetable crops, are some of the most abundant viruses in human feces. Since plant viruses don't infect human cells, researchers assumed that they were harmlessly passing through the digestive system. But in a 2010 study, the pepper virus was associated with fever, abdominal pain and itching in some people. The virus may accidently set off the immune system's viral sensors and lead to inappropriate inflammation, or the symptoms may be an indirect result of eating spicy food, the researchers speculate.

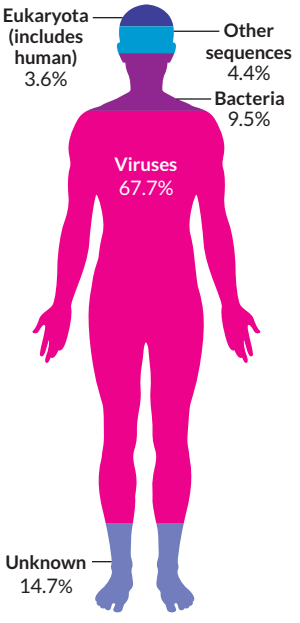
To figure out which viruses are friends, foes or neutral passengers on the human body, scientists first need to identify them. Researchers still aren't very good at recognizing new viruses, says Brian Jones, a molecular biologist at the University of Brighton in England. Hence the large pool of unknown samples in Pérez-Brocal's and other researchers' virome studies. But even if scientists improve their identification skills, it may take a long time to figure out what the viruses are doing in the body.

Based on what researchers have learned so far about the virome, Jones is convinced that viruses and other microbes "should be viewed as a part of us rather than something that lives in or on us." They are part of the puzzle, the intricate ecosystem composed of human and microbial cells, all pushing and pulling at one another and subject to local conditions, such as diet and environment.

If he's right, then knowing our viruses might help us know ourselves. ■

The human ecosystem

Most identified DNA sequences floating in our blood plasma belong to viruses. Some unknown sequences may also be viral. SOURCE: N. POPGEORGIEV *ET AL/JOURNAL OF INFECTIOUS DISEASES* 2013



M. ATAROD

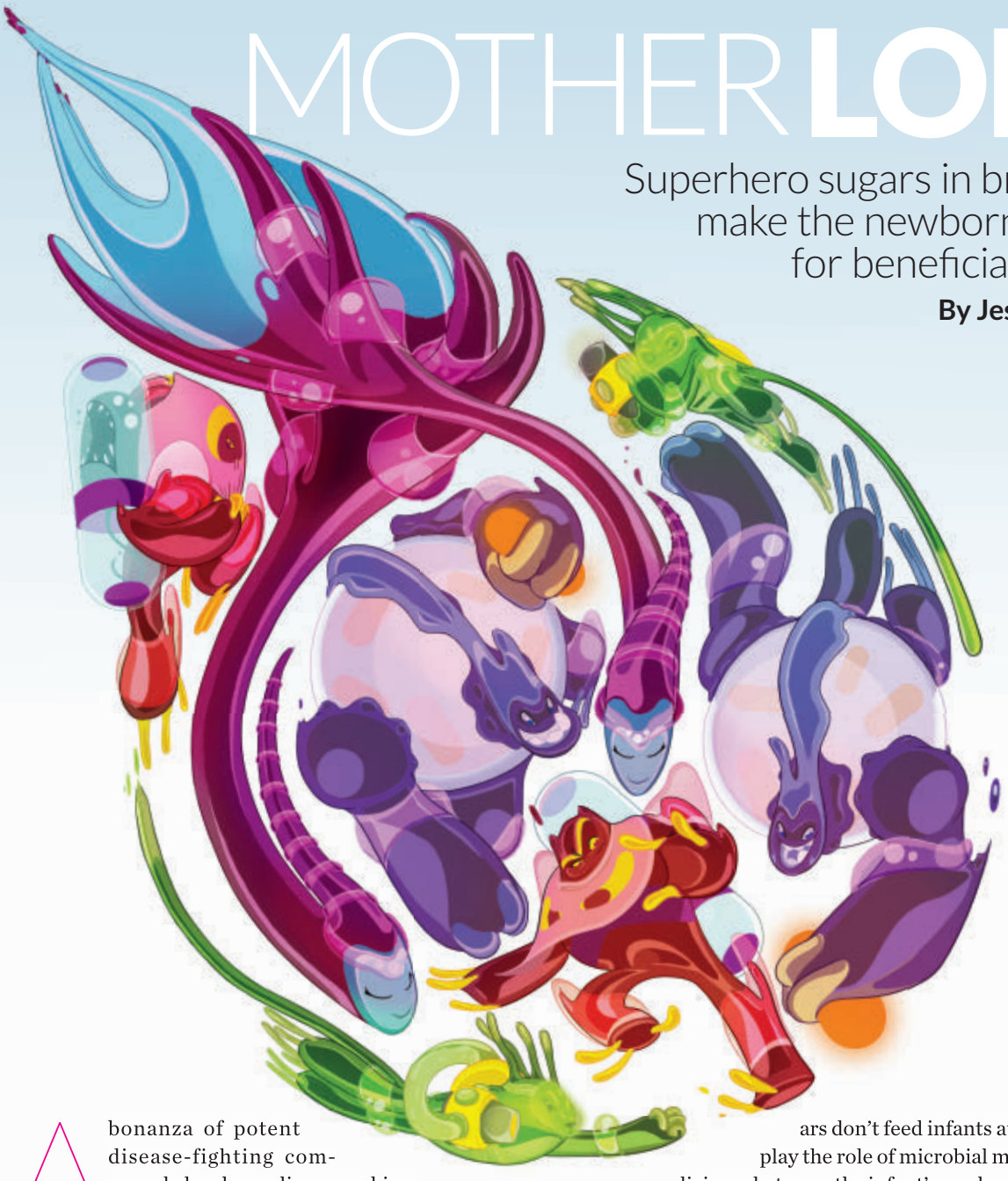
Explore more

- B.A. Duerkop and L.V. Hooper. "Resident viruses and their interactions with the immune system." *Nature Immunology*. July 2013.

MOTHER LODE

Superhero sugars in breast milk make the newborn gut safe for beneficial bacteria

By Jessica Shugart



TODD CHURN

A bonanza of potent disease-fighting compounds has been discovered in a surprisingly common source — the breasts of every nursing mother on the planet. Human milk, the only substance that evolved to feed and protect us, seems to contain a trove of medicines just now being unlocked by scientists.

"We go down to the bottom of the ocean to find new compounds and test them out against diseases," says nutritional scientist Lars Bode of the University of California, San Diego. "But if we just look at the natural compounds in human milk, we'll be surprised at what we find."

At the forefront of breast milk's potential lies a diverse set of sugar molecules called human milk oligosaccharides. Although sculpted by 200 million years of mammalian evolution, the sugars don't feed infants at all. Instead, they play the role of microbial managers, acting as liaisons between the infant's newly available intestinal real estate and the throngs of microbes that seek to call it home.

These oligosaccharides serve as sustenance for an elite class of microbes known to promote a healthy gut, while less desirable bacteria lack the machinery needed to digest them. And recent research has shown that the sugars act as discerning bouncers as well: The molecules prevent pathogens from latching onto healthy cells, routing troublemakers into a dirty diaper instead. The oligosaccharides also defuse bombs by calming an infant's emerging immune system so it doesn't overreact against friendly bacteria.

Oligosaccharides found in human milk might even hold keys to staving off disease in vulnerable children, a notion that

keeps Boston College biochemist David Newburg toiling in the lab late at night. In some scenarios, he suggests, the sugars might even supplant the use of antibiotics.

Newburg and others hope to extract knowledge from breast milk components to thwart disease in babies not receiving this superfood. High on the list are premature infants clinging to life in neonatal intensive care units without access to breast milk and toddlers in developing countries who are susceptible to deadly diarrheal diseases after weaning. Even adults undergoing gut-stripping chemotherapy or antibiotic treatments might stand to benefit from the protective sugars.

But extracting or producing human milk oligosaccharides on an affordable, industrial scale won't be easy. Synthesizing the sugars is an expensive headache because the molecules — about 200 of which have been identified so far — are put together in a dizzying array of configurations. Some scientists are placing their bets on pulling oligosaccharides out of cow's milk, although the sugars found there are less abundant and qualitatively different from their human counterparts. Others are turning to genetic engineering with hopes of designing microbes that can mass-produce the most useful oligosaccharides.

Along with major players such as the Gates Foundation and the formula and dairy industries, researchers and clinicians are striving to understand and in some ways re-create the health-promoting powers of a tailor-made substance that nature has had millennia to perfect. They have big shoes to fill.

Feeding the troops
Many oligosaccharides provide ready-to-eat meals for favorable microbes, giving beneficial species a leg up over less appealing ones. Newborns with healthy microbes are apt to thrive.

Complex sugar supercrew

The train of milk oligosaccharide discovery started rolling in 1900, when microbiologists noticed that the feces of breast-fed infants contained different amounts of some bacterial species than those of bottle-fed infants. Around the same time, chemists discovered a novel carbohydrate component in human milk, later revealed as the oligosaccharides. By 1954, scientists had dubbed these sugars the "bifidus factor," as they fueled the growth of *Bifidobacterium* species abundant in the feces of breast-fed infants.

Fast-forward to 2013, and researchers are still trying to identify the sugars and unravel all their capabilities. The collection of different oligosaccharides in human milk is a ball-and-stick modeler's dream (or nightmare), but the ingredient list for the oligosaccharides' recipe is deceptively simple: Only five simple sugars (called monosaccharides) serve as building blocks.

When two of these monosaccharides — glucose and galactose — get together, they form lactose, which people can digest and use for energy. From there, more and more monosaccharides jump on, forming a conga line of sugars. But the real complexity comes into play when new branches diverge from the line, producing a dazzling array of chemical structures.

Unlike the linear, orderly synthesis of DNA or protein molecules, oligosaccharides assemble Wild West–style. "For all we know, the linkages could be totally random," says milk biochemist Daniela Barile of the University of California, Davis. "They're very unpredictable and there are hundreds of possible structures."

Although a smorgasbord of oligosaccharides have already been spotted using an ultrasensitive detection technique called mass spectrometry, Bode expects newer techniques to uncover still more. Harder will be figuring out all of the sugars' roles and which are most important for health.

Breast-fed bacteria

The growing list of jobs the oligosaccharides perform mirrors the burgeoning diversity of their structures. At UC Davis, researchers focus on the sugars' primary function — feeding and nurturing the beneficial bacteria that live in the infant gut.

To sniff out which oligosaccharides the various species of bacteria consume, microbiologist David Mills' team extracts *Bifidobacterium* from infant feces and feeds the bacteria different oligosaccharides.

Healthy, full-term, breast-fed infants tend to have a gut microbiota dominated by various species of the oligosaccharide-consumer *Bifidobacterium*. But premature infants typically harbor fewer bifidobacteria and more potentially pathogenic microbes such as *Escherichia coli* and *Clostridium difficile*. Of preterm infants, 3 to 7 percent will develop a potentially life-threatening illness called necrotizing enterocolitis, an inflammatory disease that destroys the intestinal lining and exposes the infant bloodstream to hordes of bacteria normally cordoned off in the gut. Ten to 50 percent of babies with NEC ultimately succumb to the disease, with the lowest birth weight infants at most risk.

Breast-feeding halves an infant's chances of getting NEC. While scientists don't yet know whether a preemie's distorted microbiota causes NEC, observational studies have shown that changes in the microbiota precede disease onset.

UC Davis neonatologist Mark Underwood recently teamed up with Mills to conduct a small clinical trial in premature infants in the neonatal ICU that were being fed either their mother's milk or infant formula (a decision made independently of the trial). The researchers spiked the formula or the breast milk with one of two *Bifidobacterium* strains: one that consumes oligosaccharides and one that does not.

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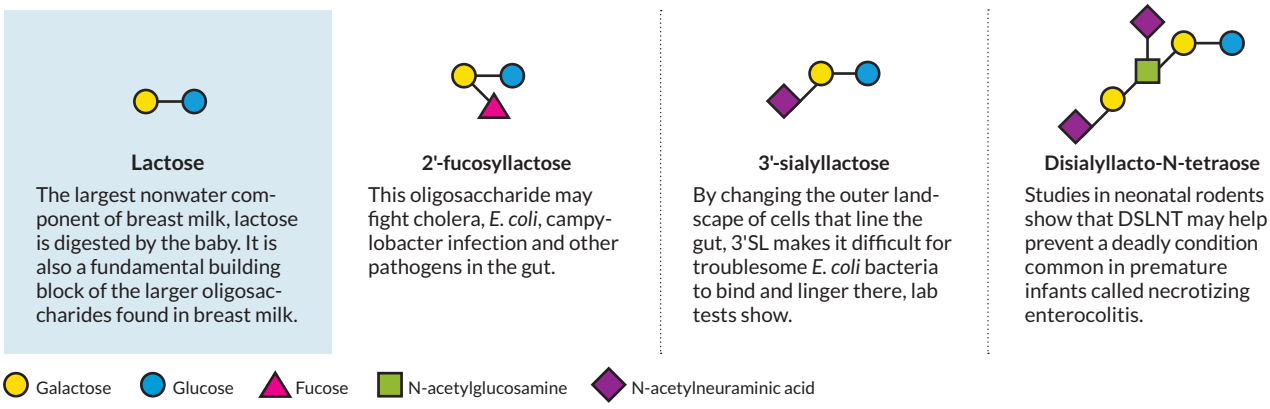
Simply indigestible In addition to nourishing a baby with fats, proteins and ordinary sugars such as lactose, breast milk harbors complex sugars that a newborn largely cannot digest. Some 200 types of oligosaccharides, formed by five simple sugars joined in various structures, help cultivate an infant's microbial garden and provide many indirect benefits. SOURCE: L. BODE/*GLYCOBIOLOGY* 2012



Fecal analysis revealed that the babies who were fed breast milk plus an oligosaccharide-consuming strain of bacteria, *Bifidobacterium longum ssp. infantis*, had more beneficial microbes. "When you put in the breast milk and the *B. infantis* together, then you get *B. infantis* colonization," says Underwood. But when *B. infantis* don't get nourished by the oligosaccharides in breast milk, Underwood hypothesizes, "they fade away quickly and don't get established."

While the study wasn't large enough to establish protection against NEC, Underwood hopes that the trial will pave the way for larger tests. Especially in infants whose mothers produce little or no breast milk, bolstering formula with a combination of oligosaccharides and probiotics could help prevent NEC in the most vulnerable infants.

Depending on blood type, the stage of lactation and other factors, the milk oligosaccharide profile varies from woman to woman. This could explain why some infants develop NEC in spite of being breast-fed, Bode says. Reporting in *Gut* in 2012, his team showed that a specific human milk oligosaccharide helps prevent NEC in rats. In the study, only one oligosaccharide, a branched beauty called disialyllacto-N-tetraose, dampened the disease. And research by Mills and Underwood showed that the milk oligosaccharide content from women delivering at preterm differed from those giving birth at full term. Bode envisions one day mixing NEC-busting oligosaccharides into the breast milk of mothers who lack them and boosting premature infants' chances of getting out of the neonatal ICU alive.

The bouncers Certain oligosaccharides block pathogens seeking to commandeer cells in the intestines. Some microbes mistakenly latch on to oligosaccharides instead of cells and earn a free ride out of the body.

Immune tuners

Beyond feeding bacteria in the gut, the milk oligosaccharides might cultivate a healthy microbiota by dialing down the immune system. Bode argues that a toned-down immune response is crucial for successful colonization of the gut by microbes. The sugars were discovered as "food for bugs," Bode says, "but I believe they're so much more than that."

A tiny fraction of the sugars appear to find their way into a newborn's bloodstream. Bode and others have detected oligosaccharides in the urine of infants, suggesting that the sugars and their influence could extend well beyond the gut. "Milk oligosaccharides may be able to reduce inflammation throughout the body," he says. In one study, oligosaccharides reduced interactions between inflammatory immune cells and cells that line blood vessels. "The oligosaccharides," Bode says, "are able to keep the immune system in check."

Bode's team has also produced a slew of studies that demonstrate human milk oligosaccharides' most provocative power — flushing pathogens out of an infant's body before they get a chance to wreak havoc. The researchers reported on September 16 in the *Journal of Pediatric Gastroenterology and Nutrition* that the sugars block the attachment of a nasty strain of *E. coli* to the cells that line the intestine, thwarting the pathogen's ability to infect neonatal mice. The microbe is responsible for deadly diarrheal diseases that plague infants and children, especially in developing countries where access to clean food and water is lacking.

Milk oligosaccharides that reach the bloodstream may even usher bladder-infecting *E. coli* right out of the urinary tract, the research team has also found.

For more than two decades, Newburg's group has been compiling a hit list of pathogens that fall prey to milk oligosaccharides, starting with the discovery that the sugars could disarm a toxin secreted by some forms of *E. coli*. "Then we tested the oligosaccharides against various pathogen models — and this

TODD CHURN

is my favorite story — it worked against all of them," Newburg recalls. "We thought we'd made a mistake." He and others have since discovered, mostly through cell culture studies, that the sugars may dash the diarrhea pipe dreams of such microbial villains as salmonella, cholera, rotavirus, norovirus, a campylobacter-caused gastroenteritis and multiple strains of *E. coli*.

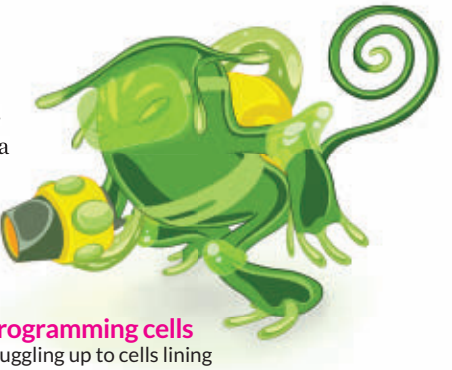
Newburg envisions one day giving toddlers oligosaccharide supplements to stave off diseases that tend to creep in following weaning, especially in poor countries where diarrheal diseases abound. But the hunt for potential sources of the sugars has proved challenging.

A better milk mimic

Milk oligosaccharides possess a seemingly endless spectrum of complexity, and researchers are just starting to understand which structures do what. Synthesizing them in the lab is a tedious and expensive process, Bode says. "If you wanted to synthesize and add oligosaccharides to infant formula at the supermarket," he says, "the price would be ridiculous."

But for premature infants, caregivers may be willing to invest in the costly sugars to help prevent diseases such as NEC, he says. Because synthesis is still cost-prohibitive, Bode suggests using donor breast milk in cases when the mother's milk is unavailable. Frozen, pasteurized donor milk from breast-milk banks is far superior to infant formula for such a use, provided processing leaves the oligosaccharides intact.

Neonatologist Underwood agrees, but says, "the truth is, there's probably not enough donor human milk to go around." While Europe has more than 200 milk banks and Brazil has a similar number, the United States has only 13. Though donor milk is becoming more common in neonatal ICUs around the country, Underwood says, general availability, especially for full-term infants, seems a long way off. "There's a tremendous amount of capacity in the world," Underwood says, "but the U.S. and Canada are very slow to develop milk banks. They're expensive, and the regulations are tremendous."



Reprogramming cells By snuggling up to cells lining the gut and modifying which genes are switched on or off, oligosaccharides can induce cells to make proteins that form a nonstick coating for some pathogens. With nothing to cling to, many bad guys get flushed.

Formula companies already sell an easy-to-synthesize oligosaccharide called galacto-oligosaccharide as an additive to infant formula, a product scientists once thought similar to the oligosaccharides found in human milk. But now they know better, Bode says. "The oligosaccharides that are currently in formula are structurally very different from those in human milk," he says. While the synthesized oligosaccharide has been shown to promote the growth of some beneficial bacteria and to offer protection against certain pathogens, the additive falls short when compared with the benefits of the full spectrum of oligosaccharides found in breast milk.

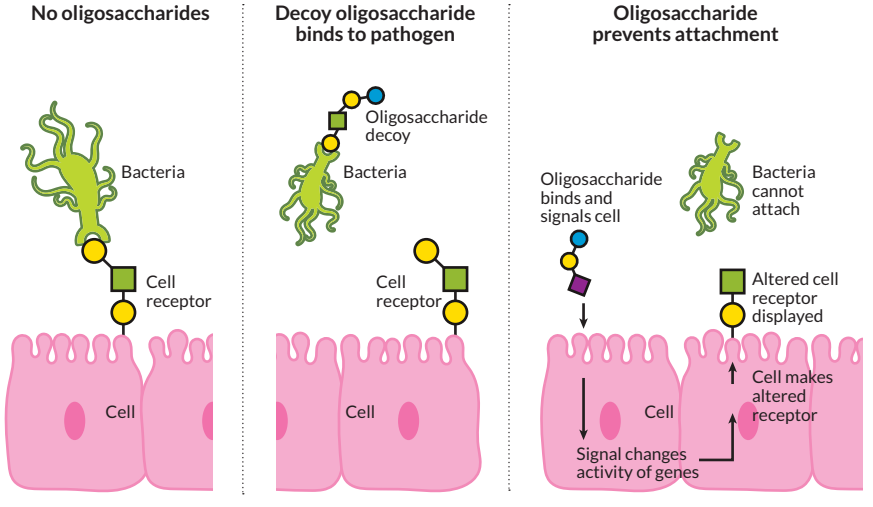
Bode is working to help companies develop better oligosaccharides to add to infant formulas. Although breast-feeding is always the best option, he says, certain circumstances such as low milk supply, illness or the stresses of returning to work may prevent some mothers from breast-feeding. "It's a little bit romantic to think that formula will disappear from the surface of the planet at some point," Bode says. "I'd rather help make something better if it's going to be used anyway."

While Bode hopes that new synthesis techniques or increased donor milk supply will one day meet the demand for oligosaccharides, at least in the neonatal ICU, Mills and his colleagues at UC Davis are betting on dairy cows.

With easy access to a barn full of cows, these scientists have a ready supply of bovine milk at their disposal. The researchers also have a partnership with a cheese producer that sends them regular shipments of various dairy by-products such as whey — a source of oligosaccharides.

Mills and colleagues are hoping to convince the dairy industry to siphon off "waste products" for the production of oligosaccharides. The sugars are at least 20 times more abundant in human milk than in bovine milk, and many of the oligosaccharide

Sweet defenders Undesirable microbes can latch onto cells that line a newborn's intestines by binding to sugar-rich receptors that stud the cell (left). Once tethered, the pathogens can colonize and infect the tissues. But oligosaccharides found in breast milk (center) can act as decoys, snagging undesirables and tagging them for removal. Another defense (right) involves oligosaccharides inducing cells to populate their surfaces with unwelcoming receptors by modifying which genes get switched on in the cell nucleus. This thwarts pathogen binding. SOURCE: L. BODE/*GLYCOBIOLOGY* 2012



FROM TOP: TODD CHURN; S. EGTS

structures in human milk are absent or exist in only trace amounts in bovine milk. "On the other hand," says Mills, processors go through 13 million gallons of cow's milk per day, "so you could have truckloads of it."

That helps motivate Barile to keep digging through dairy products in search of more sugars. In 2009, she reported finding 15 distinct oligosaccharides in whey permeate, a substance Barile calls "a by-product of a by-product." The discovery was initially exciting, Barile says. But the bovine oligosaccharides lack fucose, a monosaccharide that in human milk adorns up to 70 percent of oligosaccharides, tending to lend them pathogen-blocking powers.

Convinced that the fucosylated sugars must exist in bovine milk, even if in trace amounts, Barile's team refined its separation techniques. As reported in the June *Glycobiology*, the team eventually identified 50 different oligosaccharides in bovine milk, including structures with fucose. A disease-busting sugar called 2′-fucosyllactose, or 2′FL, that represents more than 20 percent of the oligosaccharides in human milk, comprised just 0.3 percent of the bovine oligosaccharides. The concentration may be low, Barile says, but at least "now we know it's there."

Barile, Mills and colleagues just completed a study in which 12 healthy people were given a mixture of purified bovine milk oligosaccharides at escalating doses. Everyone tolerated the treatment well, and the team is in the process of screening the participants' fecal samples for leftover oligosaccharides as well as changes in gut microbiota.

The cow oligosaccharides "aren't yet ready for kids in Malawi," Barile says, but the study is the first step in a Gates Foundation–funded effort to treat diarrheal disease in developing countries.

Not every known human milk oligosaccharide is represented in bovine milk, Barile acknowledges, but the diversity of structures there is far superior to anything that the biotech industry can currently produce, she says. "Maybe in 20 years, technology will catch up, and we'll have a better understanding of which structures are important." Until then, she thinks that relying on the natural diversity of structures in bovine milk is a safer bet than cherry-picking some human ones for industrial production.

Newburg's approach couldn't be more different. Rather than milking cows (or humans), he manipulates microbes. By adding just the right mix of genes to bacteria or yeast, he hopes to produce oligosaccharides in huge batches through fermentation. In 2002, Newburg cofounded a small company, Glycosyn, with the goal of designing microbes that produce the sugars.

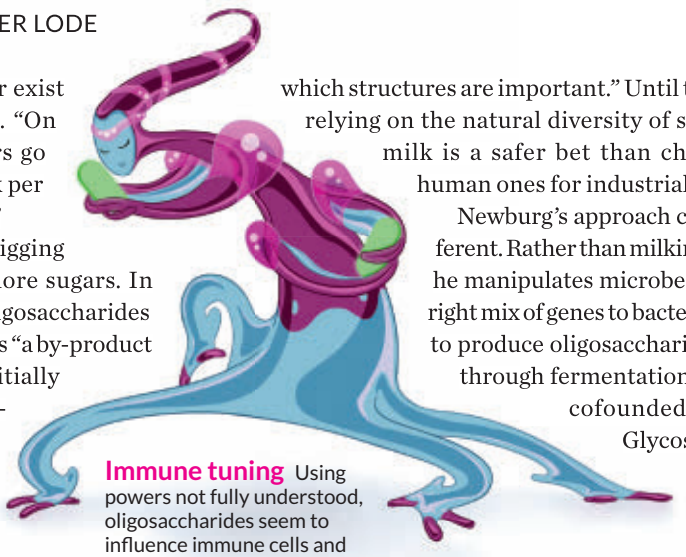
"That's the way to make it most cheaply," Newburg says. "Fermentation technology is something you find in every country, no matter how poor it is." After designing strains of microbes that pump out the oligosaccharides, Newburg envisions inexpensively making oligosaccharides in the countries that need them most.

But before that can happen, Newburg's team must get the microbes on board. "It's actually quite difficult," he says. "You try something, and then you fiddle with it and try it again."

Newburg has set his sights on none other than 2′FL. The molecule holds promise against cholera, campylobacter gastroenteritis and certain *E. coli* infections. "So it's an obvious first target," he says. He expects his team to produce a 2′FL-producing microbe fit for distribution within the next few years, and microbes that make other oligosaccharides are also in the works.

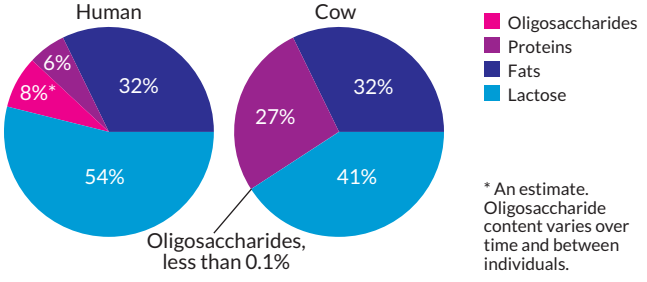
Newburg imagines milk oligosaccharides supplanting the use of antibiotics in some cases. Unlike antibiotics, which breed resistant strains of bacteria, "human milk oligosaccharides have been 'used' for millions of years without resistance," he says. "It could be a game changer."

Whether derived from a chemistry lab, donor's milk, dairy products or microbes, scientists hope to deliver the benefits of milk oligosaccharides to children living on life's vulnerable edges: those born too early and those freshly weaned. Even adults who have had their gut microbiota ravaged by antibiotics or their immune systems pummeled by chemotherapy may, like infants, benefit from the nurturing effects of the oligosaccharides. But researchers will likely never fully re-create nature's potent elixir or unlock all of its mysteries. Breast, so the saying goes, may always be best. ■



Immune tuning Using powers not fully understood, oligosaccharides seem to influence immune cells and modulate their responses to gut bacteria. The result is an immune system that's quick to dispatch pathogens but more tolerant of beneficial microbes.

Breast milk vs. cow's milk On average, oligosaccharides make up a much greater percentage of the nutrient portion of human breast milk than of cow's milk, making it difficult to use cows as a source of the protective sugars. SOURCE L. BODE/*GLYCOBIOLOGY* 2012



* An estimate. Oligosaccharide content varies over time and between individuals.

Explore more

- Lars Bode. "Human milk oligosaccharides: Every baby needs a sugar mama." *Glycobiology*. September 2012.

Former Science News *intern Jessica Shugart is a freelance science writer living in California.*

TODD CHURN

Breakthrough technology converts phone calls to captions.

New amplified phone lets you hear AND see the conversation.

The Captioning Telephone converts phone conversations to easy-to-read captions for individuals with hearing loss.

Do you get discouraged when you hear your telephone ring? Do you avoid using your phone because hearing difficulties make it hard to understand the person on the other end of the line? For many Americans the telephone conversation – once an important part of everyday life – has become a thing of the past. Because they can't understand what is said to them on the phone, they're often cut off from friends, family, doctors and caregivers. Now, thanks to innovative technology there is finally a better way.

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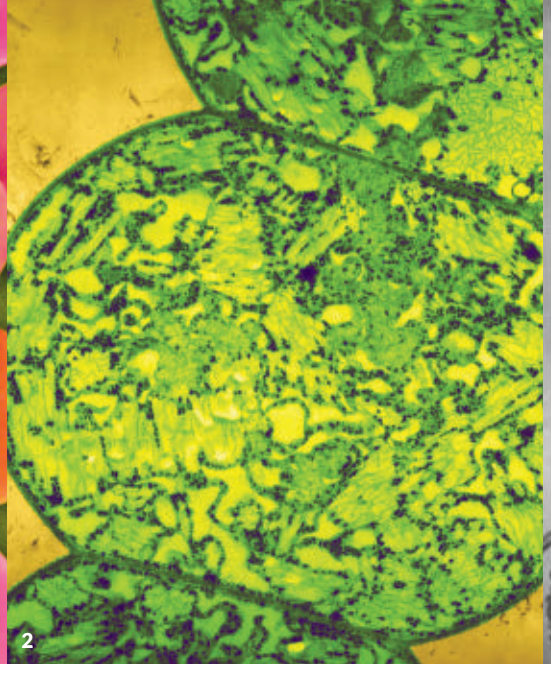
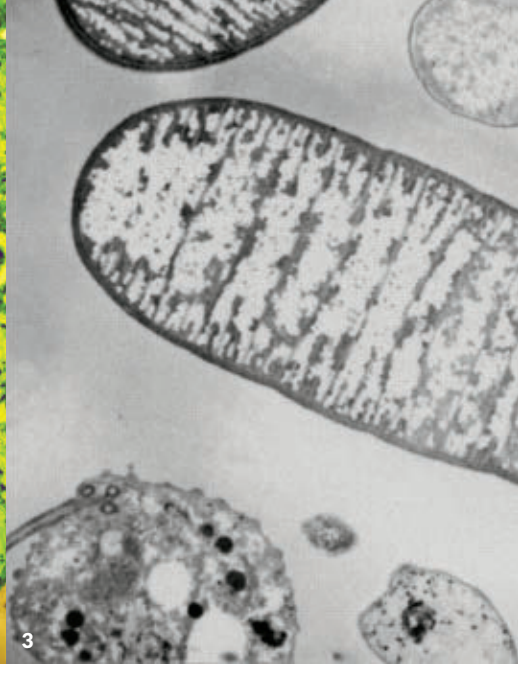




FROM LEFT: DENNIS KUNKEL MICROSCOPY; BIOPHOTO ASSOCIATES/SCIENCE SOURCE; K. YANAGITA *ET AL*./*JSEM* 2003

EXPERIENCES

Me and my microbiome

Tina Hesman Saey tries out new services offering clients a peek at their own bacteria

I first suspected I might be inhabited by traitors when I read a research paper linking gut bacteria to obesity. I was a newspaper reporter in St. Louis in 2006 when local researchers in Jeffrey Gordon's lab at Washington University found that the mix of bacteria in the gut can help determine whether a mouse is lean or obese. I've been writing about the microbiome — the microbes that inhabit the body — ever since.

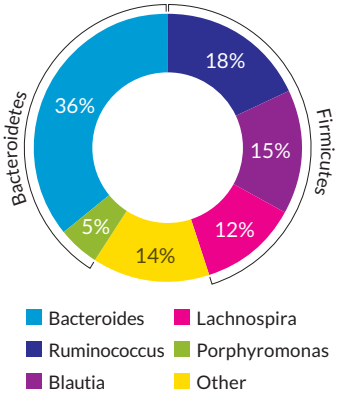
As an obese person, I've always suspected that I have fat microbes. But it's also possible that my bacteria are lean and my genetics, diet and lack of exercise are holding them back from revealing my inner skinny person.

Until last year, I could only speculate about the bacteria that might affect my health. You would have had to be part of a scientific study to get your microbiome analyzed, and not always with personalized results. Then last February, two microbiome sequencing services launched through the crowdsourcing website Indiegogo. Finally, I had a chance to find out how my microbes stack up against everyone else's.

I ordered sampling kits from American Gut — a research project at the University of Colorado Boulder — and from San Francisco startup company μBiome (pronounced "you-biome"). Both services give clients personal information about their own microbiomes while collecting data for further research (although μBiome users can elect not to share their data).

My preliminary results from μBiome cover bacteria from my mouth — specifically my inner right cheek — and my gut (based on a fecal sample). The company expects to release full results in February so that its first batch of customers can see how they compare microbially with other μBiome clients and with people in other research studies, says company spokesman Nigel Tunnacliffe.

For now, my results are what a person who opts out of participating in research will get. It's a list, and not all that revealing. I can see the top five residents of each body site, and an interactive online display allows me to drill deeper, sometimes showing a species but more often stopping at the genus or family level. It has been both fascinating and frustrating to read the Latin names of my bac-



Saey's gut microbes
The top bacteria in the writer's microbiome place her as similar to the average American, who has a nearly even mix of Bacteroidetes and Firmicutes.

Personal microbiome testing services

Service	American Gut	μBiome
Cost	$99 for one sample; $15,000 gene activity analysis showing microbial functions	$89 for one body site; $159 for two body sites; $399 for five body sites
Body sites tested	Gut, mouth, skin, pet's gut	Gut, nose, mouth, genitals, skin
Data you provide	One week of detailed food logs	Two days of detailed food logs
Results	Certificate listing your top microbes and how you compare with others. An upcoming online tool will allow you to see more microbes in your sample.	Interactive online tool showing bacteria present, with links to limited information about them. Upcoming tool will compare your results to others'.

Learn more about personal microbiomes at **bit.ly/SNmybiome**

Reporter Tina Hesman Saey's microbiome sequence revealed these and other bacteria in her mouth and gut: **1.** *Haemophilus* bacteria, some of which are known respiratory pathogens (*H. influenzae* shown). **2.** Unknown species of cyanobacteria, which are photosynthetic (*Anabaena* shown). **3.** *Oscillospira*, typically found in the rumens of herbivores.

teria but not know what they do or why they're there. It's a bit like looking at a stranger's yearbook; you can put names with faces but have no idea what the people are like or why you should care.

A few things did jump out at me. My mouth is full of *Haemophilus*, for instance, a group that includes known respiratory pathogens. So when I went to the doctor for a recurring case of bronchitis, I brought my microbe profile with me and asked if he thought those bacteria could be causing the lung infection and sinus infections I routinely struggle with. He said he didn't know enough about the microbiome to make a judgment. *Haemophilus* could be a normal mouth resident, and anyway the antibiotics he prescribed to knock out the bronchitis would probably kill them too.

Another mystery: I have cyanobacteria in my guts. Yes, a photosynthetic organism in a place where, as they say, the sun doesn't shine. David Relman, a microbiologist at Stanford University, assures me that I'm not alone in harboring cyanobacteria, but he doesn't know if the organisms are just passing through or actually live in the intestines.

Nor am I the only person whose guts house *Oscillospira*, bacteria previously found only in herbivorous animals, says Daniel McDonald, a CU Boulder graduate student who donates time to the American Gut project. When I asked him if my mix of microbes is normal, he said, "We don't know what normal is." I also can't tell based on my preliminary results whether my microbes tend toward fat or lean.

> "We don't know what normal is."
>
> **DANIEL MCDONALD**

At press time I didn't yet have results from American Gut, which is processing samples in batches, but when they arrive I will have a microbial profile of myself suitable for framing. It will show the most abundant bacterial residents of my gut and my skin (sampled by swabbing my forehead). I'll see how my microbes compare with others of my age and gender, or with a similar diet and body mass index. I'll also get to compare myself with others in the American Gut project and around the world.

For now, I'm left wondering what my microbiome means. I'll have more insight once I can access data from both services, and running another test now that I've finished my antibiotics could show whether the *Haemophilus* in my mouth are gone and how the drugs affected my gut microbes. But ultimately, my questions and others' about what microbes mean to weight and health can be answered only if more people are willing to be research subjects and build the databases. We need more swabs for science. — *Tina Hesman Saey*

NOVEMBER 16, 2013

NOVEMBER 30, 2013

Stitch in prime

In its debut, Science Visualized illustrated the distribution of twin primes — prime numbers that are separated by two (*SN: 10/19/13, p. 38*). In an unusual request, reader **John Keebaugh** asked for permission to "reprint" the illustration as a cross-stich. We accepted, and after about 30 hours of work, Keebaugh sent us the piece (below), which is now displayed in our editor in chief's office.

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Sometimes science is political

In "Science slowdown" (*SN: 11/30/13, p. 14*), **Beth Mole** reported on how the recent U.S. government shutdown affected science and on the long-term decline in federal research funding. In the same issue's editor's note, **Eva Emerson** expressed concern that efforts to foster scientific curiosity and talent among students will be wasted if there aren't enough research career options open to brilliant and motivated young people.

Many readers shared our concern, sharing personal stories about the excitement of doing research in the decades after Sputnik, when the United States became a mecca for aspiring scientists from around the world. Others lamented a culture that rewards college football coaches with astronomical salaries while scientific superstars struggle to pay for their work.

But we've also received complaints recently that *Science News* is becoming too political. These readers argue that there's a plethora of political coverage out there, but that our consistent coverage of pure research is what makes us special. "I want news about science, research and discoveries. If I want political news and spin I have plenty of sources for that," wrote **Richie Crutcher**, who warned us that we risked morphing into *Political Science News*.

Such comments always induce a round of soul-searching here: Have we strayed from our primary mission? On balance, we don't think so. We run explicit science policy stories very rarely, and only when it seems that an issue is significant enough to affect the nature and pace of research. By that standard, a many-year downturn in federal research funding is worth exploring.

And looking back, this magazine actually has a long history of reporting on science in the political arena. Psychology and sociology stories in the 1960s explicitly discussed race and civil rights. Back in the 1920s, our then-parent-organization Science Service not only wrote about the debates around the teaching of evolution, it directly aided Clarence Darrow's defense team in the Scopes trial by gathering scientists to testify and distributing articles defending evolution. Since then, controversies over genetic engineering, abortion, climate change and funding have all played out in our pages. If anything, the last few years have seen a decrease in our coverage of the intersection between politics and science.

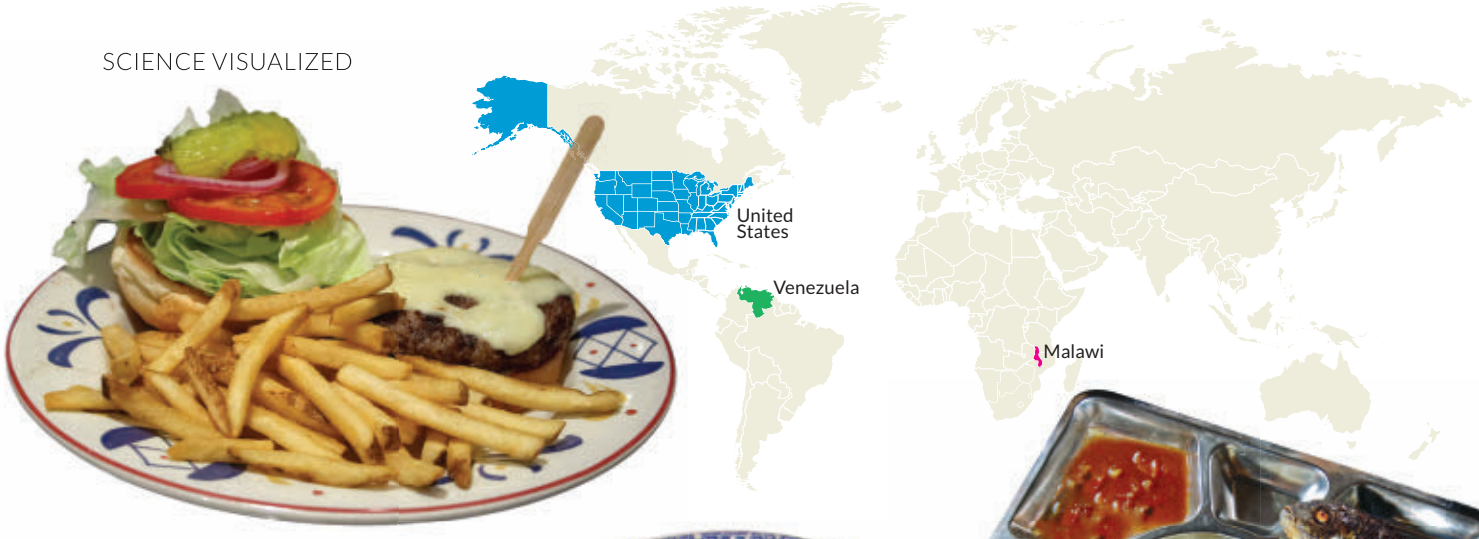
The editors of *Science News* will continue to focus on bringing you the latest research findings, but we will not shy away from the political dimensions of important science nor from examining how scientific discoveries shape society and are in turn shaped by it. That would not be in our tradition.

Brain washing

Tina Hesman Saey wrote about a new idea for sleep's function in "Sleep allows brain to wash out junk" (*SN: 11/16/13, p. 7*).

Sleep — or the lack of it — is clearly an issue that many struggle with. "I've been interested in sleep deprivation for 40 years, since a week when I didn't sleep for six days," **Nancy Sutter Axford** e-mailed. "It took almost three weeks for my brain to return to normal." If sleep is required to cleanse the brain, Axford wonders if insomniacs might tend to develop dementia at earlier ages than good sleepers. And **Mark Pottenger** asks whether the population as a whole may be affected: "Could increasing sleep deprivation in modern society be a causal factor in increasing dementia?"

Saey responds: "Insomnia is a feature of Alzheimer's disease, but whether it is a cause or consequence isn't clear. A study in mice suggests that lack of sleep increases the rate of Alzheimer's disease plaque formation (*SN: 10/24/09, p. 11*), and studies in people have hinted that sleep deprivation increases the risk of Alzheimer's and other neurological disorders. But regardless of the neurological risk, there's plenty of evidence that lack of sleep is detrimental to overall health (*SN: 10/24/09, p. 28*)."



United States

Americans eat more meat than anyone else in the world except Luxembourgers, more than 120 kilograms per person annually. Other widely consumed foods include:

- Bread
- Lettuce and tomatoes
- Potatoes
- Pasta
- Milk and dairy products

SOURCE: USDA

Venezuela

Indigenous Guahibo people only occasionally eat meat, so a meal including stewed fish (on plate, left) might constitute a special occasion. The Guahibo diet is high in starch, and processed foods are not unknown. Some typical foods:

- Corn arepas (shown, bottom)
- Cassava
- Coffee and milk
- Sugar
- Cheese

SOURCE: T. YATSUNENKO *ET AL/NATURE* 2012

Malawi

Meals here are also heavy on starch. One staple is cornmeal porridge or cakes (center) eaten with ndiwo (top left), a sauce or relish made with beans, meat or vegetables. Among the most frequently eaten Malawian dishes:

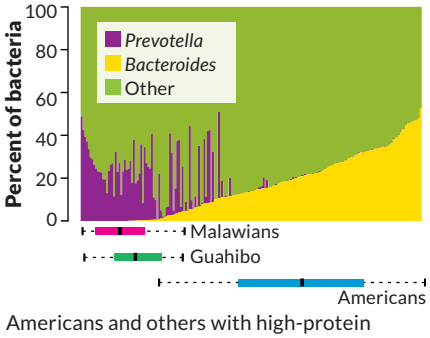
- Cornmeal porridge or cake
- Leafy greens
- Matemba, a small fish
- Pigeon peas
- Pumpkin leaves

SOURCE: T. YATSUNENKO *ET AL/NATURE* 2012

Gut bacteria respect diets, not borders

They live on opposite sides of the planet, but people in Malawi and Venezuela have similar microbes in their guts. Americans, on the other hand, have a distinctive microbiome with about 25 percent less diversity than indigenous Venezuelans'. It comes down largely to diet, researchers determined after comparing more than 500 people from rural Malawi, the United States and the Guahibo society in Venezuela. Malawian and Guahibo diets are rich in corn and cassava, with meat an occasional treat. Gut microbes of the three groups reflected that (see chart, right), the team reported in 2012. Overall, Malawian and Guahibo gut microbiomes resembled those of herbivorous mammals, while American guts were more similar to carnivores'. A more recent study found that major diet shifts can change the mix of gut microbes noticeably in just a day. Omnivores switching to a diet of all animal products saw the biggest change, as some bacteria boomed and others declined. Microbes settled back to their previous profiles a day or two after subjects returned to their usual diets, researchers report December 11 in *Nature*. — *Erika Engelhaupt*

Gut bacteria of three populations



Americans and others with high-protein fatty diets have guts loaded with *Bacteroides* bacteria, which can withstand bile produced after eating fat. *Prevotella* bacteria, which help digest fiber, are more dominant in the guts of people on low-meat, grain-based diets.

MAP: REDMAL/ISTOCKPHOTO; FOOD (FROM LEFT): JON SULLIVAN/WIKIMEDIA COMMONS; WILFREDOR/WIKIMEDIA COMMONS; GEOFF GALLICE/FLICKR; CHART: T. YATSUNENKO *ET AL/NATURE* 2012

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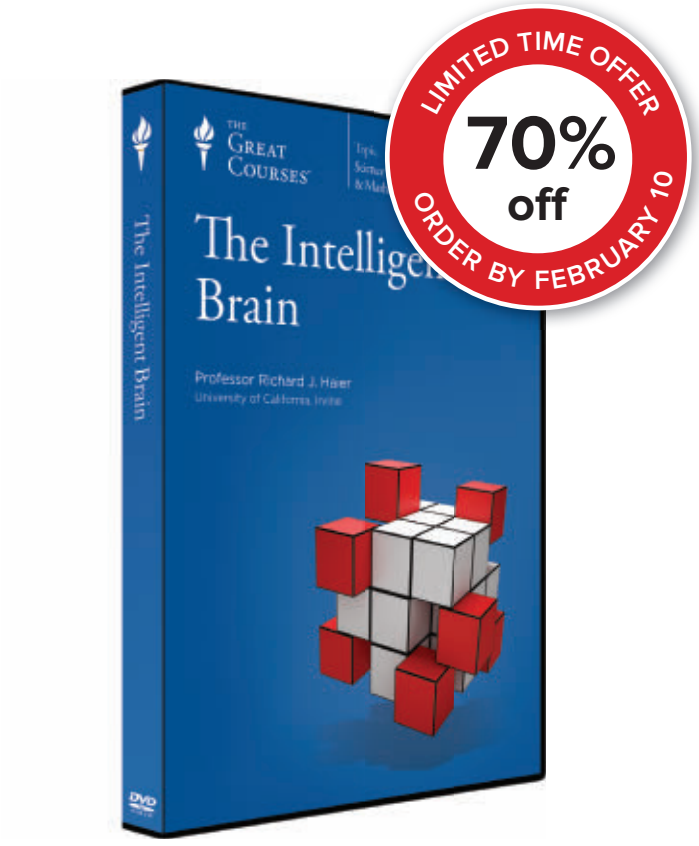

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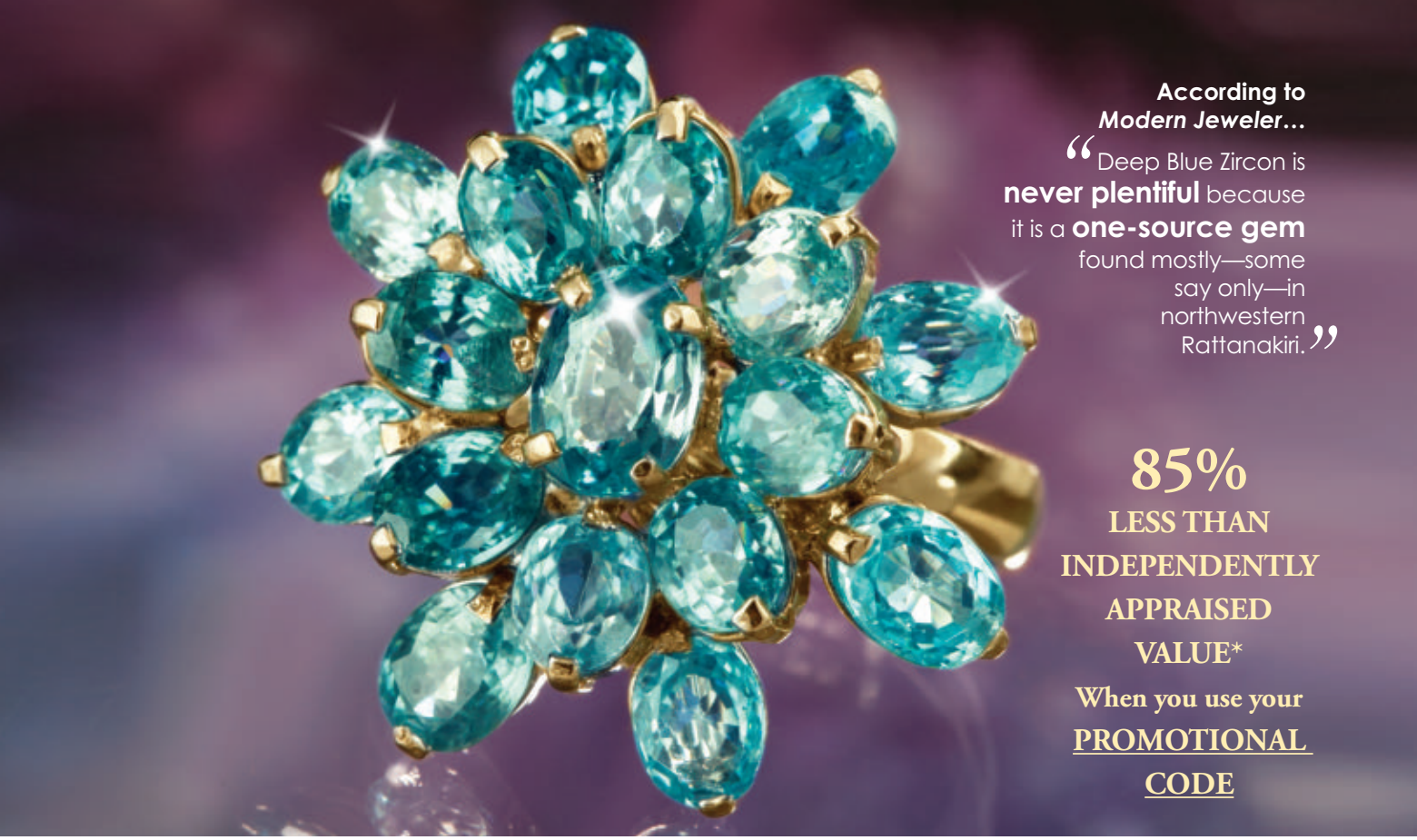

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It is undoubtedly the most brilliant rare blue stone that we've ever seen in the world and the trek to find it took us to the ends of the Earth. In deep northwestern Cambodia, it was 14 hours on a rickety bus from the capital to Rattanakiri's only town. Unpaved roads that could barely be called roads at all, across rivers that weren't even on our map, and finally driving past the ancient love huts that are the romantic traditions of the Kreung people.

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