ENDING PAIN WITHOUT SIDE EFFECTS • THE MOUNTAINS THAT SANK

SCIENTIFIC AMERICAN

JANUARY 2007 WWW.SCIAM.COM

If This Is a **PLANET,** Then Why Isn't Pluto?

DAWN OF THE AGE OF ROBOTS

Bill Gates writes that every home will soon have smart mobile devices

Evolution and **Cancer**

Can **Ethanol** Replace Gasoline?

Secret **Controls** for Genes

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On the Cover:

The gleaming metallic figure appearing on the cover resembles the android robots of classic science fiction but is really a posable sculpture by the artist Mark Ho of Amsterdam. *Artform No. 1* stands 43 centimeters high from head to toe, weighs six kilograms and consists of 920 separate parts, each of which Ho crafted from solid bronze or stainless steel with a lathe and a milling machine. Its 85 mobile parts give the figure human mobility; an accompanying magnetic base allows it to stand even in precariously unbalanced poses (*as seen on page 3*). More images of this sculpture and Ho's other work can be seen on his Web site (www.zoho.nl).

Cover and page 3: photograph by Louis Lemaire and sculpture by Mark Ho; cover illustration of protoplanet by Ron Miller; photograph at left by Mike Simmons.

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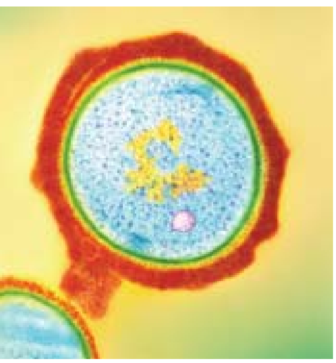
SA Perspectives

Meet Resistance Head-On

Finding traces of pollution in a supposedly pristine mountain brook is sadly no longer surprising. But when the contaminants are genes for antibiotic resistance, the implications should still raise concern. With resistance to antibiotics growing at an alarming pace among pathogenic bacteria, humans must become more aggressive. In keeping with the "ounce of prevention" principle, early intervention in the processes that foster resistance would be a very good start.



DRUG-RESISTANT staph bacteria are killers.

KARI LOUNATMAA *Photo Researchers, Inc.*

A news story beginning on page 22 describes work by Colorado scientists who make a case for monitoring and mitigating the dangerous DNA as one would any other environmental pollutant. The researchers sampled the variety and concentrations of resistance DNA in and near Colorado's Cache la Poudre River. They found the genes inside living microbes and even as free-floating DNA. Predictably, the intensity of the problem increased nearer to human and agricultural waste sources, peaking in the bovine cesspools known as dairy lagoons.

One need only return to last summer's contaminated spinach scare to understand how we are literally breeding the bugs that come back to bite us. The *Escherichia coli* strain involved in that deadly outbreak, O157:H7, gained its virulence in the antibiotic-saturated world of large-scale cattle processing. Inside the cows and their effluent, the surviving bacteria engage in a frenetic swap meet, trading genes for both pathogenicity and drug resistance. Then they make their way into hamburger patties, foul the water supply or dirty the spinach crop of a nearby farm.

In January 2006 Europe forbade all nontherapeutic use of antibiotics in animals to stanch this flow of superbugs from farms to people. A total ban on agricultural use of avoparcin, a derivative of the antibiotic vancomycin—currently the last-hope treatment for deadly, resilient pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA)—was already in place. Liberal use of avoparcin to promote animal growth had been conclusively linked to increasing vancomycin resistance in human gut pathogens and from there to resistant staph strains ravaging hospital patients.

Parts of Europe are also pioneering ways to fight MRSA in hospitals. In the Netherlands and Denmark, rather than waiting for staph symptoms to appear, hospitals preemptively isolate all incoming high-risk patients (such as those who have been on catheters or who have lived in nursing homes) until tests show them to be MRSA-free. This step prevents carriers of MRSA from passing the infection to other patients and hospital workers. As a result, less than 1 percent of staph infections in Dutch hospitals are MRSA; the comparable U.S. figure is 64 percent.

In the U.S., where MRSA kills 13,000 annually, hospitals are reluctant to adopt this search-and-destroy strategy in part because of its cost. That may be a false economy: an MRSA infection can add tens of thousands of dollars to a patient's hospital bill. The Centers for Disease Control and Prevention did not back search-and-destroy methods in its most recent guidelines to hospitals but rather preached traditional hygiene-based prevention. To be sure, doctors and nurses are still woefully noncompliant with recommendations that they wash their hands more often between patients, and that simple measure can dramatically lower infection rates. Nevertheless, the ongoing rise in antibiotic-resistant infections suggests that the old standbys are not enough.

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SCIENCE IN PICTURES

Close Encounters of the Microbial Kind

NASA/JPL/SPACE SCIENCE INSTITUTE

Are we alone? Although tales of alien abduction and SETI's extrasolar search for intelligent life fuel the imagination, astrobiologists know that the first positive proof that we are not alone is likely to be found in our own solar system. And rather than being a bug-eyed humanoid, when we finally meet E.T. he will probably most resemble extremophile microbes living here on Earth. With every new microbe discovered thriving in a place formerly thought to be uninhabited, more extraterrestrial environments are realized to have the potential to support life.

NEWS

High IQs May Help Thwart Post-Traumatic Stress

Those who have had a hard life may not be truly hardened to its most traumatic moments. A new study of more than 700 children born in the mid-1980s finds that those with higher IQs were less likely to have been exposed to traumatic events in their youth and therefore less likely to have experienced post-traumatic stress disorder (PTSD). Children who exhibited anxiety or poor conduct at young ages and those who grew up in inner cities were both more likely to encounter trauma and suffer from PTSD.

PODCAST

Visit www.sciam.com/podcast to download our free daily and weekly audio programs, *60-Second Science* and *Science Talk*. Recent topics include electroshock therapy, mega-earthquakes in the Himalayas, and the physics of synthetic basketballs.

ASK THE EXPERTS

Why do veins pop out when exercising, and is that good or bad?

Mark A. W. Andrews, professor of physiology at the Lake Erie College of Osteopathic Medicine, explains.

Letters

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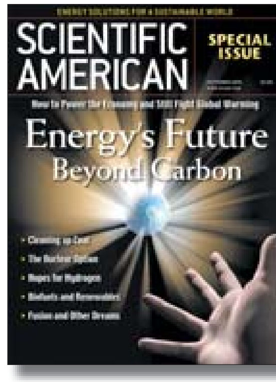


READERS RESPONDED to September's special issue "Energy's Future: Beyond Carbon" like there was no tomorrow—with critiques, alternatives and prescriptions to help assure that there will be. Critical letters ranged from global warming deniers to cautious skeptics, many of whom felt it was unscientific for Gary Stix to pronounce in the introduction, "A Climate Repair Manual," that "the debate on global warming is over." Vern Porter of Elk Grove, Calif., begged to differ: "It seems potency of water vapor as a greenhouse gas is largely ignored and its capacity to moderate temperatures unappreciated."

Then there were readers who concluded that if global warming is upon us, we should strive to adapt to it rather than to reverse its effects. Others felt achieving sustainability would require humanity to surmount not only technological but also cultural hurdles, including the willingness to control population growth. The largest volume of responses, however, offered options that were not covered, from harvesting lightning to white rooftops to underground homes lit with LEDs as well as a low-tech return to using clotheslines, more rail transport and the 55-mph national speed limit.

ENERGY'S FUTURE: BEYOND CARBON

Thank you for the special issue "Energy's Future: Beyond Carbon." Sustainable living is a topic close to my heart. I am a science teacher and try to positively influence how my students think about their impact on our planet. This issue was so relevant and informative that I purchased more copies and mailed them to my state and federal representatives. I only hope that they will read it and make informed decisions.

Susan Niederberger
Columbia, Mo.

I was very disappointed that you did not mention geothermal energy. The earth has an inexhaustible supply of heat; one merely has to dig a well deep enough and pump the water to a heat exchanger or recirculate water from the surface. Why omit this perfectly clean source of energy that is abundant everywhere?

Daniel P. Christopher
Patchogue, N.Y.

Extensive climate changes, including ice ages and global warming, have been taking place for almost 4.6 billion years, and it is not clear whether human activity in the past century has had a significant impact on these natural cycles. I therefore find unfounded your assertion that we are on the verge of a climatic apocalypse because of man-made greenhouse gases. Before we decide how to spend scarce resources, we should focus on getting a better understanding of climate change and rational risk. Irrational allocation of limited resources to cap greenhouse gases, under the pretext of the imminent crisis, would inevitably lead to increased taxation, higher energy and food costs, with a corresponding deterioration in health care, education and defense. This would cripple our economy and cause waste and human misery. More important, such resources may be better used to prepare for the next major climate change that may be unavoidable.

Arnon Rosenthal
Woodside, Calif.

CARBON NATION

In "Cooling Our Heels" [SA Perspectives], the editors spoke of the "consumerist way of life that Americans have come to accept as a birthright" and of having an energy consumption "10 times that of a Chinese," as if we should apologize to the world for the fruits of our forebears' hard work. Whereas it seems you would like to see all of us in matching gray surrounded by happy butterflies, I would have us avoid the fate of the *Imperium Romanum* by winning economic as well

as military battles. By paying twice as much for every Btu, we could not "lead by example," because we would no longer be leaders. Moreover, to think China could be influenced by example is laughable. (Human rights, anyone?)

Alternative fuels will become economical much sooner than the world will be destroyed by our carbon footprints. I would advise patience in lieu of risking my ability to wear red, white and blue. Stick to printing otherwise well-reasoned articles. Think of all the huggable trees you would save!

John A. Gragg
Wichita, Kan.

Why do Americans think they have to lead? Yes, the U.S. is in many aspects comparable to the *Imperium Romanum,* but I think that their leadership has not included energy conservation and the environment. You mention that 2003 statistics show that a western European consumes half the energy an American does. Yet as a frequent visitor to the U.S., I never thought your living standard was higher than ours in Belgium. So there must be another way to lead by example: in western Europe energy conservation is a mind-set and a driving force in all industry. My work, for example, focuses on enhancing the efficiency of lighting systems, at times by advocating leaps into completely new technologies. You do not have to lead; you just have to do it. The rest—respect and admiration—comes easily, as I have experienced from my U.S. and Japanese counterparts.

Jos Peeters
Oud-Turnhout, Belgium

ANSWERS to the December 2006 crossword.

BLUE SKY TECHNOLOGY

Congratulations to W. Wayt Gibbs in "Plan B for Energy" for putting together what our governments have failed to: a framework to understand and solve the carbon emissions problem. Some comments: he mentions both high concentrator solar power and thermochemical separation of water (albeit nuclear-based) to generate hydrogen, but not together. There is some activity in direct solar hydrogen generation that deserves serious funding, as it just might power the hydrogen economy with renewable energy. Also, dismissing cold fusion and sonofusion as "entertainment" closes the door on what could possibly be a silver bullet. Good science is being done in the field—and even if the chances are slim, the rewards would be great. Last, thanks for presenting wind power not tied to massive towers.

Rand Wrobel
Alameda, Calif.

NUCLEAR REACTION

In "The Nuclear Option," by John M. Deutch and Ernest J. Moniz, does the cost of fission power include a "radiation tax"? That is, the cost of waste disposal and the number of Yucca Mountain–size facilities that would be needed to store the spent fuel produced by their proposed tripling of nuclear capacity?

Margaret E. Venable
Lincolnton, N.C.

Deutch and Moniz mention the establishment of an international system of fuel-supplier and fuel-user countries as a means of avoiding proliferation as nuclear energy use expands. But if the right to produce reactor-grade enriched uranium is limited to a handful of countries (such as the U.S., Russia, France and the U.K.), even with compensatory measures the supply of nuclear fuel will be ultimately tied to the state of the relations between the suppliers and their users and, therefore, to the former's internal politics.

Insofar as nuclear energy becomes an increasingly strategic part of domestic agendas, fuel-user nations will be suspicious of any attempt by the nuclear powers to control the supply of fissile materials. Closely monitored, transparent and accountable multilateral arrangements are more politically viable than that proposed by Deutch and Moniz.

Juan Pablo Pardo-Guerra
University of Edinburgh

THE EDITORS REPLY: When Deutch and Moniz wrote "all the costs of a plant," they included allowances for waste disposal and plant decommissioning. The details on this and other questions can be found in the full M.I.T. report at http://web.mit.edu/nuclearpower/

ERRATA In "A Plan to Keep Carbon in Check," by Robert H. Socolow and Stephen W. Pacala, on page 56 in the box "Rich World, Poor World" three percentages on the map showing the share of carbon dioxide emissions in 2002 should have read: Europe: 16 percent; Former Soviet Bloc: 10 percent; West Asia: 5 percent.

"Plan B for Energy," by W. Wayt Gibbs, incorrectly stated that the U.S., China and India did not sign the Kyoto Protocol. China and India signed it and have ratified the treaty. Though major polluters, both are classified under its provisions as developing countries and therefore not required to make emissions reductions—a reason cited by the U.S. for its decision not to ratify the treaty after signing the agreement.

50, 100 & 150 Years Ago

FROM *SCIENTIFIC AMERICAN*

The Modern Condition ▪ Utility of Flight ▪ News from Africa

JANUARY 1957

BOREDOM—"In this age of semi-automation, when not only military personnel but also many industrial workers have little to do but keep a constant watch on instruments, the problem of human behavior in monotonous situations is becoming acute. In 1951 McGill University psychologist Donald O. Hebb obtained a grant from the Defense Research Board of Canada to make a systematic study. Prolonged exposure to a monotonous environment has definitely deleterious effects. The individual's thinking is impaired; he shows childish emotional responses; his visual perception becomes disturbed; he suffers from hallucinations; his brain-wave pattern changes."

ANXIETY—"In the past year and a half prescription sales of the tranquilizing drug meprobamate, better known as Miltown and Equanil, have jumped to the rate of $32.5 million a year. More than a billion tablets have been sold, and the monthly production of 50 tons falls far short of the demand. Some California druggists herald each new shipment with colored window streamers reading, 'Yes, we have Miltown today!'"

JANUARY 1907

AUTO CHIC—"The improved appearance of this year's cars is largely aided by the considerable increase in the wheel base which, in the case of some of the heavier machines, is now as great as 123 inches. Furthermore, the use of six-cylinder motors has brought with it a considerable increase in the length of the bonnet, and this also adds to the generally rakish and smart appearance of the up-to-date machine. By a judicious attention to these principles, the builders of even the low-powered and low-priced machines have succeeded in giving to their output a style which was altogether lacking in the earlier models."

FLYING FOR SPORT AND WAR—"With mechanical aeroplane flight an accomplished fact, we may now look for a diversion of interest from the dirigible balloon to the aeroplane proper. Its field of usefulness will be found chiefly in military service, where it will be invaluable for reconnoitering purposes and for the conveyance of swift dispatches. In all probability its chief development ultimately will be in the field of sport, where it should enjoy a popularity equal to that of the automobile."

TEA MONEY—"The queerest use to which brick-tea (tea leaves compressed into a block) has ever been put in the Orient is in the capacity of money. It is still in circulation as a medium of exchange in the far-inland Chinese towns and central Asian marts and bazaars. Between the Mongolian town of Urga and the Siberian town of Kiakta, there is as much as half a million taels (say $600,000) of this money in circulation. At the latter place it ceases to be used as currency, and enters into the regular brick-tea trade of Siberia and Russia, where it is largely used in the Russian army, by surveying engineers, touring theatrical companies, and tourists in general."

THE LATEST AUTOMOBILES, January 1907

JANUARY 1857

REALITY THEATER—"A severe test of the strength of the suspension bridge at Niagara Falls was afforded by the gale on the evening of the 13th of last month, when the toll gatherers deserted their posts at either end, and crowds assembled to see it fall, but it stood like a rock."

DR. LIVINGSTONE'S TALES—"The celebrated traveler Dr. Livingstone has been lecturing since his return to England. During his unprecedented march, alone among savages, to whom a white face was a miracle, Dr. Livingstone was compelled to struggle through indescribable hardships—he conquered the hostility of the natives by his intimate knowledge of their character and the Bechuana tongue. He waded rivers and slept in the sponge and ooze of marshes, being often so drenched as to be compelled to turn his arm-pit into a watch-pocket. Lions were numerous, being worshiped by many of the tribes as the receptacles of the departed souls of their chiefs; however, he thinks the fear of African wild beasts greater in England than in Africa."

The full version of the Dr. Livingstone story is available at **www.sciam.com/ontheweb**

NORTH KOREA'S NUCLEAR TEST, 1

Kim's Big Fizzle

THE PHYSICS BEHIND A NUCLEAR DUD **BY GRAHAM P. COLLINS**

FISSILE FIZZLE: North Korea's leader, Kim Jong Il, had his country test a nuclear device underground near P'unggye, in the northeastern part of the country.

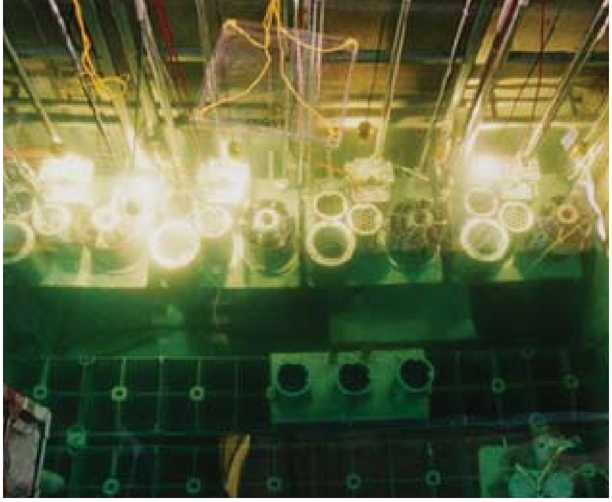
KATSUMI KASAHARA *AP Photo*

Soon after the news broke that North Korea claimed to have conducted a nuclear test, experts realized that the blast had been much smaller than is usual for a first device. Nuclear explosions are measured in kilotons, an energy release equivalent to that of thousands of tons of TNT. Most countries' first tests range from five to 25 kilotons. For example, the U.S.'s 1945 "Trinity" test had a yield of about 20 kilotons. Yet estimates of the North Korean test clustered around half a kiloton. Reportedly, North Korean officials had told China to expect a blast of four kilotons.

Some commentators immediately speculated that the explosion had not been nuclear, but air samples collected two days after the explosion confirmed the nuclear nature of the explosion. One such signal is the detection of radioactive isotopes of the element xenon, a chemically inert gas produced by the atom splitting that takes place in these blasts, which readily seeps out even from underground tests.

Clearly, then, the North Koreans produced some kind of a nuclear damp squib. What could have gone wrong depends on the nuclear fuel used. Apparently, the device relied on plutonium (like Trinity and the Nagasaki bomb) and not uranium (like Hiroshima), a conclusion that is supported by the nature of the air samples, according to U.S. officials. Indeed, North Korea has ample quantities of plutonium, but outside that country no one knows its progress in enriching significant quantities of uranium to weapons-grade levels.

Plutonium weapons have several ways of misfiring. The first depends on the triggering of the plutonium by an implosion pro-



SPENT FUEL RODS from the Yongbyon nuclear reactor probably provided the plutonium 239 needed for North Korea's test.

YONHAP/AP PHOTO

cess. The implosion must be extremely symmetrical to be fully successful. Typically a combination of fast and slow conventional explosives surrounds a sphere of plutonium (the "core" or "pit"). Engineers must carefully machine all the pieces that make up this explosive shell into shapes that, when detonated simultaneously, produce a precisely spherical shock wave that compresses the plutonium to two to five times its normal density (the more compression, the greater the explosive yield). At the higher density, what was a subcritical mass of plutonium becomes supercritical—that is, one in which a sustained chain reaction takes place, producing the blast.

If the shock wave fails to be completely symmetrical—for example, if a detonator goes off 100 nanoseconds later than the rest—the compression will be less efficient because the core will tend to squirt out in the directions where the shock wave is weaker or arrives late. Another potential troublemaker is the initiator, a small device at the center of the core that emits a burst of neutrons to start the chain reaction reliably at a precise stage of the implosion. An initiator going off early or late—or not at all—reduces the yield.

Early triggering of the explosion, a kind of fizzle called a predetonation, can also occur when too much of the isotope plutonium 240 is present. The fuel rods of nuclear reactors produce the desired isotope, plutonium 239, but the longer it remains in the reactor, the more of it becomes plutonium 240. Plutonium 240 constantly emits tens of thousands of times more neutrons a second than plutonium 239. Although neutrons are the key particles in producing a nuclear chain reaction, an excess of them early in the implosion is a recipe for predetonation.

Whatever happened near P'unggye on October 9, probably only Kim Jong Il's scientists know. In any case, the technological shortcomings of the blast have not significantly altered the political implications.

MAKING THE BOMB GRADE

North Korea may have had enough plutonium for a nuclear weapon as long ago as 1989, when it shut down its small nuclear reactor at Yongbyon for a few months and could have removed the fuel rods for extraction and reprocessing of the plutonium. In 1994 the Clinton administration negotiated the "Agreed Framework" with North Korea, which brought a halt to plutonium reprocessing and instituted a regime of on-site monitoring. Although North Korea embarked on a program of enriching uranium for weapons sometime around 1998, most experts think that no fresh plutonium was produced until 2002, when the Agreed Framework collapsed and North Korea recommenced activities with fuel rods at Yongbyon.

NORTH KOREA'S NUCLEAR TEST, 2

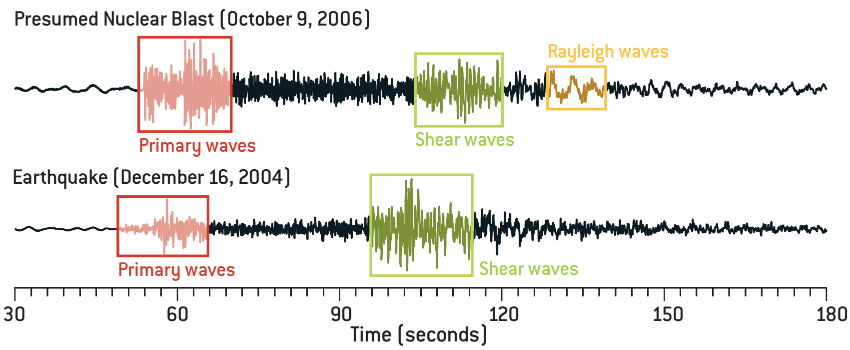
Seismic Sentries

WHY UNDERGROUND NUCLEAR TESTS ARE SO HARD TO HIDE **BY SARAH SIMPSON**

On October 9, 2006, seismometers around the world picked up a magnitude 4.2 event located in northeastern North Korea. Considering that an average of 20 earthquakes that size or larger occur every day, seismologists might not have immediately singled out this incident had not North Korea's leader, Kim Jong Il, promised an underground nuclear test.

Although seismometers could not conclusively confirm the nature or size of the explosion, they did indicate that the bomb was more fizzle than blast. Perhaps more important, they showed that as long as the geology of the region is well known, local sensors can accurately distinguish even small detonations from earthquakes.

Explosions produce a notably different mix of waves than earthquakes do. A detonation projects an instantaneous pulse of pressure outward in all directions. These push-pull, or P, waves are the first to jiggle seis-



BLAST VS. QUAKE: The seismic signature of detonation differs from that of a typical earthquake in the size of the primary waves (push-pull activity) and shear waves (side-to-side motion). Rayleigh waves indicate an event no more than three kilometers deep.

PAUL G. RICHARDS AND WON-YOUNG KIM *Lamont-Doherty Earth Observatory, Columbia University*

mometer needles, so the textbook seismogram starts off with a series of intense spikes and dips and then quiets down.

In contrast, classic earthquake recordings begin with a barely perceptible bump of P waves, followed a few seconds or minutes later by an increasingly strong batch of squiggles representing slower shear, or S, waves. Earthquakes produce this side-to-side energy as two sides of a fault slip past each other.

The real world is not that simple, of course. By itself, a bomb would generate no S waves at all. But underground detonations can twist the surrounding rock and release some of the same energy an earthquake would—especially in shock-prone areas where stress has already built up in the crust, says Francis T. Wu of Binghamton University.

Geology can play other tricks. Explosive P waves can turn into S waves as they impinge on a fault surface, say, or when they cross from sediment into hard rock. Some geologic materials, such as volcanic tuff or partially molten rock, can muffle or even block a temblor's normally intense S waves as they travel through the earth's crust. By the time the P and S waves reach a seismometer, their sizes—and thus their creator—may be less distinguishable, Wu explains. Hence, observers must consult seismic stations along multiple paths from the event. "You also have to build up experience about how each station records a particular seismic source," says Paul G. Richards of the Lamont-Doherty Earth Observatory of Columbia University.

To verify North Korea's purported test, many experts consulted a station in Mudanjiang, China. About 370 kilometers north of the epicenter, that sensor captured the clearest signal of the 128 stations in the Global Seismographic Network. By comparing the October 9 blast and other nearby explosions with local earthquakes of similar size, Richards and fellow Lamont seismologist Won-Young Kim noted systematic differences in the seismograms from the two types of events. The analysis suggests that a single seismometer within a few hundred kilometers of an event in North Korea can be used to identify an explosion. Before the nuclear test, that hypothesis was "nothing but conjecture," Richards says. "Now we have a direct example."

Using seismograms to determine the explosive yield is tougher, however. The actual yield could vary by a factor of 10 or more, depending on the geology. A magnitude 4.2 detonation at the former Soviet test site in Central Asia would correspond to a yield of approximately half a kiloton. But the fault-riddled rocks of the western U.S. tend to attenuate waves quickly. As a result, a magnitude 4.2 explosion at the former test site in Nevada corresponds to about 2.2 kilotons.

Richards remains confident, though, that the yield of the North Korean blast was less than a kiloton because geologists have established the nature of the material that lies under much of that country—namely, hard rocks such as granite gneiss, which readily transmits seismic waves.

Nuclear-seeking Iran is a different case. Like the western U.S., Iran is tectonically active, and seismic waves do not propagate as efficiently there as they do in North Korea, Richards points out. And because the Middle East experiences many more tremors than the Korean peninsula does, sorting signals would be a much more complicated task should Iran ever develop and test a bomb.

During the cold war, the U.S. missed 26 of the Soviet Union's 366 underground tests in Central Asia, mostly because the yields were less than one kiloton and could only be assessed by regional stations. Such detection failures appear unlikely in the Middle East today, because an extensive network of seismometers maintains a watch for earthquakes there. Moreover, the Comprehensive Nuclear Test Ban Treaty Organization operates 170 stations worldwide. All this vigilance may not deter Iran or other suspected nuclear aspirants, but it makes any surreptitious test highly unlikely.

ENVIRONMENT

Pollution in Solution

DRUG-RESISTANCE DNA AS THE LATEST FRESHWATER THREAT **BY CHARLES Q. CHOI**

DNA that makes germs resistant against medicines may increasingly be polluting water, from rivers all the way to the faucet. Scientists caution these contaminants, if not cleansed, could exacerbate the growing problem of drug resistance among potentially harmful microbes. The genes join a long list of contaminants being found in water, posing a challenge for devising an effective means of treatment.

COW FARMS could promote the spread of antibiotic-resistance genes if farmers dose the bovines with the bacteria-beating compounds.

Currently the World Health Organization reports that drug-resistant germs infect more than two million people in the U.S. every year and that 14,000 die as a result. The rise of drug resistance among germs is tied to the widespread use of pharmaceuticals in humans and animals. Up to 95 percent of antibiotics are excreted unaltered, seeping into the environment and possibly encouraging antibiotic resistance there.

Instead of focusing on the presence of antibiotics in the surroundings, environmental engineer Amy Pruden of Colorado State University searched for the presence of genes that help to confer drug resistance to germs in the first place. Microbes regularly swap DNA with one another, and the fear is that antibiotic-resistance genes can persist and spread long after the drugs they target have dissipated.

Pruden and her colleagues looked for genes bestowing resistance against tetracycline and sulfonamide, two antibiotics linked to urban and farm activity, in northern Colorado waters. They analyzed DNA extracted from bacteria collected from relatively pristine river sediments and drinking water from treatment plants to effluents from a wastewater recycling plant and samples from irrigation ditches and dairy lagoons, where microbes decompose cow excrement.

The levels of antibiotic-resistance genes ran hundreds to thousands of times higher in waters directly affected by urban or farm activity than in relatively pristine bodies. Still, the researchers found the genes everywhere they investigated, including drinking water. "It is very important to emphasize that although this study was conducted in Colorado, by no means are antibiotic-resistance genes localized to this region," says Pruden, whose findings appear in a special December 1 issue of *Environmental Science & Technology Briefs*.

These genes have become the latest in an increasing menagerie of pollutants not yet commonly monitored in the environment. These emerging contaminants include antibiotics and other pharmaceuticals, hormones, detergent by-products, fragrances and other personal care products. "A lot of times these contaminants may actually have been in the environment for years, but we only now have the analytical tools to detect them well," explains research hydrologist Dana Kolpin, coordinator of the U.S. Geological Survey emerging contaminants project.

Conventionally, water treatment plants go after pollutants such as bacteria and toxic metals as well as nutrients such as nitrates and phosphates, which can create algal blooms deadly to other aquatic life. Emerging contaminants such as DNA, however, slip through "because water treatment plants are generally designed to inactivate bacteria, not to destroy the DNA inside them," Pruden explains.

Designing treatment systems against emerging contaminants is tricky. "You have to make sure that by removing one compound through, say, chlorination or ozonation, you're not generating by-products you're not seeing that could have an impact. You don't want to swap one problem for another," Kolpin says.

Still, researchers are seeking a good solution. For instance, activated sludge systems containing high concentrations of bacteria can remove 60 to 70 percent of at least 100 trace contaminants from liquid streams, notes wastewater treatment specialist Beverley Stinson of the Laurel, Md., office of environmental engineering firm Metcalf & Eddy. "Many municipalities are now going through very expensive upgrades to such systems—not to target those contaminants but primar-

GRANT JEFFRIES *Bradenton Herald*

NEW AND LASTING THREATS

Emerging contaminants can exert a wide range of effects. For instance, alkylphenols, which are surfactants found in many detergents, wreak havoc on the balance of hormones in animals. Any number of emerging contaminants could act as such endocrine disruptors, explains U.S. Geological Survey fish pathologist Vicki Blazer. With her colleagues, she has discovered that more than half the male smallmouth bass sampled at several sites in the Potomac and Shenandoah rivers are "intersex"—that is, males bearing immature eggs.

What is more, these new pollutants could persist. Scientists at the Europa University of Applied Sciences Fresenius in Idstein, Germany, found significant concentrations of barbiturate drugs in a tributary of the river Elbe near a landfill, even though Valium and other modern tranquilizers replaced barbiturates 30 years ago.

ily to remove nutrients from wastewater. So these systems will have a nice double benefit," she states.

Meanwhile Pruden is working with her colleagues on experimental water treatment systems that degrade genes using ultraviolet light, perhaps in combination with peroxide. They plan to test pilot systems within the year. "Those should almost certainly disrupt DNA sequences," Stinson says.

Charles Q. Choi is a frequent contributor.

TELESCOPES

Seeing Stars in Iraq

RESTORING WRECKED OBSERVATORY MAY BOOST IRAQI SCIENCE BY MIKE SIMMONS

Erbil, Iraq—High in the mountains of northern Iraq's Kurdistan Autonomous Region stands the empty shell of what would have been a world-class astronomical observatory. In 1973 President Ahmed Hassan al-Bakr ordered the construction of the $160-million observatory of three telescopes. Once completed, it would have been the only major observatory in the Middle East. But positioned on a strategic mountaintop less than 50 kilometers from the border with Iran, the observatory's radio telescope dish and optical telescope domes became targets, first in 1985 by Iranian missiles and then in 1991 by U.S.-led forces in the Persian Gulf War.

Atop the 2,127-meter-high Mount Korek, the observatory elicits a mix of emotions. The setting is spectacular, with expansive vistas of mountains and valleys. The facilities, however, show the effects of battle and 20 years of neglect. Debris and the detritus of war litter the buildings; several mortar rounds lie unused in the smaller telescope's dome. Still, the structures appear to be readily repairable.

Unlike the ruins of ancient observatories that dot this region—reminders of an era when Islamic science led the world—the Iraqi National Astronomical Observatory may have a second chance. Isolated from the war-ravaged areas to the south—and with international sanctions, internal strife and the constant threat of Saddam Hussein's army now in the past—the three peaceful provinces in the Kurdistan region are enjoying something of a renaissance.

Cognizant of the importance of science and education in rebuilding their society—and of the prestige a respected scientific institution could bring—Kurdistan's leaders are considering proposals aimed at rebuilding the observatory. Nawzad Hadi Mawlood, the governor of Erbil province, worked on Mount Korek as a broadcast engineer before entering politics. (Broadcasters take advantage of Mount Korek's lofty position to transmit radio and television signals.) Mawlood sees restoration of the observatory as a priority. "It will be a famous place," he says, adding that "as an engineer it's very important for me to renovate it." Athem Alsabti, who was charged with founding the observatory by al-Bakr, is now at the University of London Observatory and has worked toward the Iraqi facility's renovation since the fall of Saddam's government. Alsabti believes a renewed facility will be "a center for the whole Middle East."

SHELLED: Observatory dome shows the effects of war and 20 years of neglect inside and out. A plan could restore the telescopes and revive science in Iraq.

MIKE SIMMONS

As originally conceived, the observatory would have consisted of a 30-meter-diameter radio telescope for millimeter-wave observations and 1.25- and 3.5-meter-diameter optical telescopes. At the time of the first attack, the radio telescope and the 1.25-meter optical telescope were installed and undergoing tests. Three missile strikes heavily damaged the radio telescope's dish and concrete supporting structure. Little of the 1.25-meter telescope remains because of looting.

The 3.5-meter telescope lay packed in shipping crates elsewhere on the mountain when missiles ripped through the huge dome's skin. Hurriedly moved to Baghdad for safekeeping, the telescope—among the

world's largest at the time—has probably escaped harm, but a survey of the crates' contents is considered too dangerous within the beleaguered city. Trucking the crates to Erbil along the treacherous highway may be the only way to determine its condition.

An alternative could be an entirely new instrument. Peter Wehinger, an astronomer at Steward Observatory at the University of Arizona, notes that current technologies can construct far wider telescopes in more compact packages; he recommends placing a 6.5-meter telescope in the existing large dome. This instrument would collect three times the light of its predecessor, and if based on designs of existing telescopes of similar size, it would have a relatively modest cost, estimated at $30 million. A repaired observatory "could excite people in the Middle East to support such projects," Wehinger says.

Alsabti expects that such a facility could lure back Iraqi astronomers from abroad—no more than a dozen remain in the country. Wehinger agrees and anticipates enthusiasm from neighboring countries as well. "It just builds a much greater sense of ownership and purpose" than traveling to distant facilities, he says.

The Kurdistan region could also couple the observatory to a proposed center for astrophysics and space science at Salahaddin University in Erbil, which would most likely draw astronomers from throughout the area and function as a regional scientific facility. The observatory's fate might well foreshadow the future of Iraq's reemerging scientific community as it struggles to regain its place within a country in transition.

Mike Simmons, an astronomy writer based near Los Angeles, visited Iraq for the second time in October 2006.

GENETICS

Here Come the X-Mice

A MUTANT MOUSE ARMY TO BATTLE DISEASE BY CHRISTINE SOARES

Wanted for long-term occupancy: clean, secure home, must have ample freezer space, 20,000 bedrooms, starting July 2007. An ambitious plan getting under way to learn the function of every gene in the classic lab mouse *Mus musculus* will require the manufacture of a large living "database" of mutant mice over the next five years, with the ultimate goal of understanding comparable genes in humans.

MAGGIE BARTLETT *National Human Genome Research Institute*

MUTANT MOUSE (*left*) has a gene affecting hair growth knocked out, giving it a thinner coat than a normal mouse (*right*).

The U.S. component of the multinational effort, the Knockout Mouse Project (KOMP), will target some 10,000 mouse genes, half the rodent's estimated complement. (Canadian and European researchers will tackle most of the rest.) Project investigators will have to make a lot of mice—or, more precisely, a lot of mouse embryos. Those will be used to derive embryonic stem cell lines, which can be turned back into embryos to make litters of live mice when they are needed for study. Grants issued last summer totaling nearly $50 million will go toward producing the first 8,500 or so of the cell lines, each carrying one disabled, or "knocked out," gene.

Realistically, litters of pups representing every mouse gene will probably never reside in the same place at the same time, according to Colin Fletcher,

program director at the National Human Genome Research Institute. Instead most will be stored as cell lines, which KOMP participants can withdraw to make batches of mice. Over time, researchers will systematically screen animals representing each gene to assess the knockout effects.

Nevertheless, the National Institutes of Health has set aside $4.8 million to cover four years' room and board, starting in July, for the project's output. Perhaps half a dozen sites in the U.S. are already equipped to handle the job of official KOMP repository, Fletcher says. The lucky facility will be chosen in May.

Candidate sites would include the Jackson Laboratory in Bar Harbor, Me., which creates some two million designer mice every year. The Oak Ridge National Laboratory in Tennessee also boasts a new, superclean, 36,000-square-foot mouse house with room for 60,000 furry residents. Upward of 40 liquid-nitrogen tanks there could hold at least 1,500 frozen embryo lines as well, according to technical manager Darla R. Miller. At full capacity, the Oak Ridge facility would be serving up about 20,000 pounds of mouse chow a month and employing at least 10 full-time technicians just for cage-cleaning duty, Miller says. So the facility has plenty of vacancies for the KOMP family if they're interested.

CHEMISTRY

Real Stinkers Reformed

MALODOROUS BUT USEFUL CHEMICALS NOW SMELL SWEET BY STEVEN ASHLEY

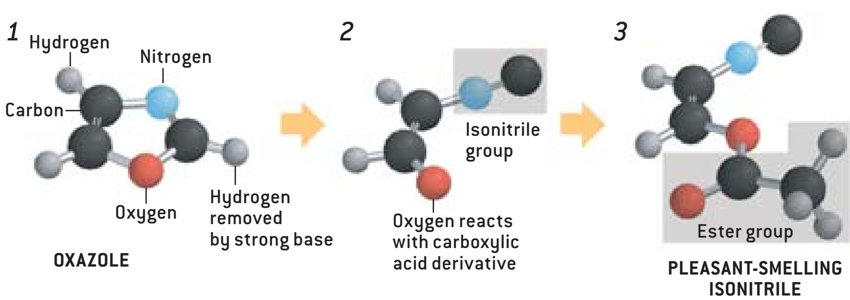
Name the world's most offensive odor: Rotting fish? Refinery fumes? Skunk spray? For many organic chemists, top honors go to a family of carbon-nitrogen-based compounds called isonitriles. This chemical group is "the Godzilla of smells ... they make you vomit your guts out instantly," declared Luca Turin, a leading olfaction theorist and protagonist of Chandler Burr's 2003 biography, *The Emperor of Scent*. Add the fact that a prime ingredient for isonitriles is phosgene gas—a notorious chemical warfare agent from World War I, and it is little surprise that many investigators shun these noxious and unstable substances despite their acknowledged utility in drug discovery, polymer manufacture and elsewhere.

That situation is apt to change soon, however. Two researchers at the University of California, Riverside, have recently synthesized fragrant isonitriles that not only work just as well as their foul-smelling cousins but are safer to formulate. The aromas of the new substances include soy, malt, old wood, cherry and even taffy, report chemist Michael C. Pirrung and his postdoctoral student Subir Ghorai in the *Journal of the American Chemical Society*. "These compounds are so versatile and easy to make that I think that many people will use them for many purposes," Pirrung predicts.

"Isonitrile molecules are interesting to organic chemists because they can stitch together three or more other functional groups—specific ensembles of atoms that display a characteristic reactivity," explains chemist Bruce Ganem of Cornell University. Most other substances used for this purpose can link up only two reactants at a time. Isonitriles' rare capability, Ganem points out, is especially valuable for combinatorial chemistry, a staple in pharmaceutical development, which seeks to create many different compounds quickly to offset the vanishingly low odds of discovering a useful drug. "Researchers mix variants of several reactants in ma-

SWEET MYSTERY

Chemists at the University of California, Riverside, have found a way to make isonitriles—ordinarily noxious, malodorous compounds—smell nice. But just why the modified isonitriles have such scents is not known. The new method places an ester functional group—a class of molecules responsible for the agreeable fragrances of fruits and flowers—in the molecules. But esters may not be responsible for the pleasing smell, as one of the isonitriles already known to have a nasty odor contains an ester.



ODOR-EATING: Chemists can make an isonitrile compound by first removing a hydrogen atom from oxazole, an organic ring molecule (*1*). The ring breaks open to yield a molecule with an isonitrile group and an oxygen atom that reacts with a carboxylic acid derivative (*2*). The reaction forms an ester functional group (*3*), which may impart pleasant odors to isonitriles.

DANIELA NAOMI MOLNAR

trix fashion to produce large libraries of new compounds that are then screened for efficacy against disease," he notes.

Ideally, pharmaceutical scientists would prefer a single procedure in which several starting materials react to form a product and all or most of the atoms contribute to the creation. Unusually, Ganem says, an isonitrile can make possible a "'shake and bake'-type reaction" in which the chemist merely mixes a few compounds and the isonitrile directs an orderly sequence of the necessary reactions. "Dominolike," he says, "it first releases a functional group from ingredient A, which reacts and triggers the release of another functional group in ingredient B, and so forth, each one waiting for just the right moment to join the dance."

Isonitriles in particular make possible two well-known organic reactions, the Ugi and Passerini reactions, which yield biomorphic molecules with bonds that resemble those of peptides, the building blocks of proteins. The resultant compounds can thus often mimic the functions of natural peptides.

Pirrung and Ghorai chanced on the new versions of isonitriles by accident. "From the literature," Pirrung recounts, "I knew of another method to make isonitriles," one that did not involve phosgene gas. Instead they used oxazole (C_3H_3NO) and benzoxazole (C_7H_5NO), which were not easily obtainable until long after isonitriles were first developed. These ring compounds (specifically, heterocyclic molecules) feature one particular hydrogen atom located between the nitrogen and the oxygen that is far more easily removed than the others. This hydrogen allows the rings to be broken up relatively easily using very strong organic bases that were unavailable to early isonitrile chemists.

"After we made several isonitriles, I asked my postdoc what they smelled like," Pirrung recalls. "When he told me that they didn't smell bad, my curiosity was piqued." The pair then went on to synthesize several isonitrile variants, whose differing but relatively pleasant odors were then characterized by an ad hoc panel of Pirrung's students.

"The notion that effective isonitriles could be made to smell good really knocks my socks off," Ganem enthuses. "This innovation should open up a whole panoply of useful reactants for combinatorial chemistry, which is likely to capture the imagination of the pharma industry, among others." After decades as a distasteful research backwater, isonitriles may finally fulfill their potential as important tools in organic chemistry.

DATA POINTS: STOVE SOOT

Traditional cookstoves, fueled by wood and crop waste, emit smoke containing particles. Depending on their makeup, these particles can absorb or reflect solar energy, thereby heating or cooling the atmosphere. A recent field study in Honduras characterized the smoke released from stoves and measured the amount of global warming–related soot within the emissions. It found that traditional cookstoves may contribute to atmospheric warming more than previously thought.—*Alison Snyder*

Number of cookstoves in use worldwide every day: 400 million

Grams of soot emitted per kilogram of firewood based on:

Previous lab estimate: 0.75

Current field estimate: 1.5

Kilograms of firewood burned per stove per day, worldwide: 7.5

Minimum percent of light absorbed by particles that warm the atmosphere: 15

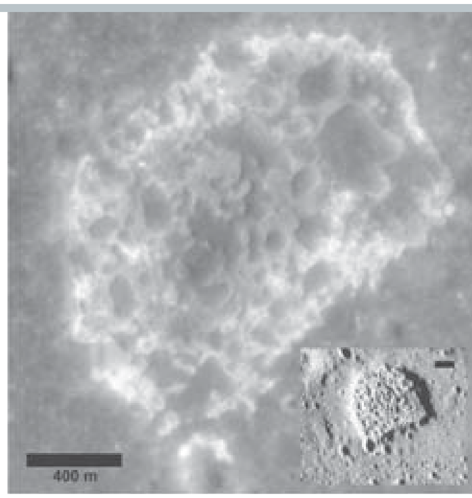
Percent absorbed by Honduran stove smoke: 65

SOURCE: Environmental Science & Technology Briefs, *December 1, 2006*

ASTRONOMY

Moon Gas

The moon's reputation as a cold, inactive orb may be undeserved. A new look at *Apollo 15* photographs revealed crisp features inside the Ina structure that suggest relative youth. A general absence of asteroid impact craters on the structure's floor also indicates that it is no more than 10 million years old. Satellite spectral data show reflective mineral bands deep in one of Ina's craters that would typically dull over time. A rapid release of gases sometime in the past one million to 10 million years evidently blew dust from the surface and revealed the young features in Ina. Study author Peter Schultz of Brown University says that even if volcanism on the orb has ceased, its by-products are still bubbling up to the surface. The report appeared in the November 9 *Nature*. —*Nikhil Swaminathan*



D-SHAPED Ina structure has few impacts, suggesting surface gassing from volcanic activity reshaped it. Bright areas are scarps and rubble. Low-angled light reveals Ina's depression (*inset*).

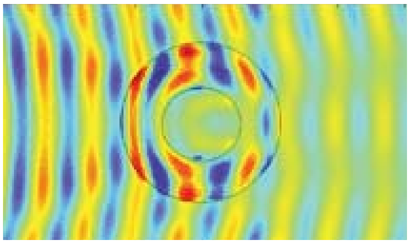
FROM "LUNAR ACTIVITY FROM RECENT GAS RELEASE," BY PETER H. SCHULTZ ET AL., IN *NATURE*, VOL. 444; NOVEMBER 9, 2006; ILLUSTRATION BY MATT COLLINS

PHYSICS

I Don't See the Light

Mere months after making a technologically feasible proposal, researchers have demonstrated a rudimentary example of an invisibility cloak. The device consists of a composite of metal and wires embedded in fiberglass and structured so as to make light behave in weird ways. David Schurig and David Smith of Duke University, along with their colleagues, designed concentric rings of this so-called metamaterial that bend microwave radiation around the innermost ring, like water flowing around a stone. The central ring absorbed and reflected microwaves less than it normally would have. "We've reduced both the reflection and the shadow generated by the object, and those are the two essential features of the invisibility cloaking," Schurig says of their proof-of-concept, published in the November 10 *Science*. Getting the technology up and running was easier than they anticipated, the researchers say, but don't expect Harry Potter's cloak anytime soon.

—JR Minkel



VANISHED: A ring-shaped cloaking material absorbs direct microwaves (*blue*), produces weak reflections (*red*) and creates minimal shadows.

LONGEVITY

Being Cool for a Longer Life

Warm-blooded animals on calorie-restricted diets live longer—but also feel chilly. Now researchers find lowering the core body temperature alone can extend the lives of mice. Tamas Bartfai, Bruno Conti and their colleagues at the Scripps Research Institute in La Jolla, Calif., tricked the brains of transgenic mice into thinking the ambient temperature was too hot so that they lowered their body temperature a few fractions of a degree. All the mice could then consume whatever they pleased. The cooler, transgenic mice lived about three months longer than the control mice, an extension about one third as long as that of calorie-restricted diets, according to the study that appears in the November 3 *Science*. Bartfai says a number of high-tech firms have approached his team with an interest in developing a small, inductive device that could be put in people's brains to govern the neural region regulating body temperature.

—Nikhil Swaminathan

NEUROPSYCHOLOGY

Language Trumps Innate Spatial Cognition

Language seems to override an innate ability to understand spatial relations. Researchers compared Dutch adults and children, who describe a spatial relation from the point of view of the speaker, with a group of adults and children from a hunter-gatherer community in Namibia, who rely on a viewer-independent description of a space. Researchers hid a block under one of five cups in front of them and asked the subjects to find a similar block under their own set of five cups in front of them. The Dutch could locate the block more easily when it was placed in relation to the researcher (they may describe it as "the block to the left of the researcher"). The group from Namibia, however, fared better under absolute geocentric conditions ("the block is north of the researcher"). When four-year-old German children and great apes were tested, both preferred environment-centered processing. The difference between the German children and the eight-year-old Dutch kids who preferred egocentric directions suggests that language alters an innate preference, according to the study that appeared online October 30 in the *Proceedings of the National Academy of Sciences USA*.

—David Biello

BRIEF POINTS

- **Scientists have sequenced the genome of the honeybee, *Apis mellifera*, and hope to learn the genetic basis behind its traits, such as sociability and aggression.**

  Nature, October 26, 2006

- **The U.S. can meet its need for iron via recycling of scrap alone. It would both eliminate mining and the most energy-intensive step in steelmaking—the conversion of iron ore into iron.**

  Proceedings of the National Academy of Sciences USA, October 31, 2006

- **Tim Berners-Lee and other Web heavyweights have launched a field called the science of the Web. Among other tasks, the subject will formally explore how the network can grow productively and in socially responsible ways.**

  World Wide Web Consortium announcement, November 2, 2006

- **Researchers resurrected a five-million-year-old retrovirus, dubbed Phoenix. It could infect cells only weakly, although some scientists questioned the safety level of the resuscitation, noting that no one could have predicted the infectivity.**

  Genome Research, published online October 31, 2006

Extended coverage of these News Scan briefs can be found at ***www.sciam.com/ontheweb***

TARANTULA VENOM is peppery, in a way.

SENSES

Partners in Pain

Three molecules discovered in spider venom may provide a new tool to probe how the receptors on sensory neurons work to produce pain. When researchers injected the purified toxins into the paws of mice, their limbs became inflamed and the animals reacted by licking them and flinching. Mice genetically engineered not to express the receptor, however, did not react when the toxin was administered, according to the study in the November 9 *Nature*. The peptides isolated from the tarantulas target the same receptor as capsaicin, the fiery compound in hot chili peppers. But unlike capsaicin, the tarantula toxins target the outside of sensory neurons and could be used to study neurons without destroying them. —*Alison Snyder*

MEMORY

Brain Gain

Running a weak electric current through the brains of sleeping student volunteers improved their performance on a word-recall task. Prior to sleep, the students memorized 46 word pairs and, on average, recalled 36.5 of them. After the electrically stimulated sleep, they improved their recall to 41.2 words, compared with just 39.5 words for the group that did not receive the jolt. The findings suggest that electrically stimulating the brain can exert a synchronizing effect on individual neurons and produce beneficial results. The researchers, who published their work online November 5 in *Nature*, are now investigating just how long the improvement might last and how deep sleep affects memory—for some reason, humans begin to lose the ability to sleep deeply around 40 years of age, at about the same time that memory begins to decline. —*David Biello*

GERRY ELLIS *Minden Pictures*

BY THE NUMBERS

Teen Sex in America

VIRGINITY INTO THE THIRD MILLENNIUM TAKES AN UPTICK BY RODGER DOYLE

Teen sex was rarely talked about in the 19th century, but that changed in the 20th with the coming of new sexual mores and the growth of public high schools, which brought girls and boys together in an institutional setting that fostered greater contact and intimacy than ever before. In 1900 probably less than 10 percent of Americans ages 15 to 18 were in public high schools, but by 1940 the proportion had grown to about two thirds.

Not surprisingly, in the 21st-century U.S. many teenagers admit to loss of virginity. This behavior becomes problematic when young people fail to use contraception. A quarter of 15- to 16-year-old girls, for example, had unprotected sex during their first intercourse. (This statistic, however, marks an improvement over the pre-1980s level of 57 percent.) Only half the parents of girls younger than 18 counsel their daughters on how to say no to boys, and only about half talk to them about birth control. Teenage girls from intact homes are less likely to have had sexual intercourse.

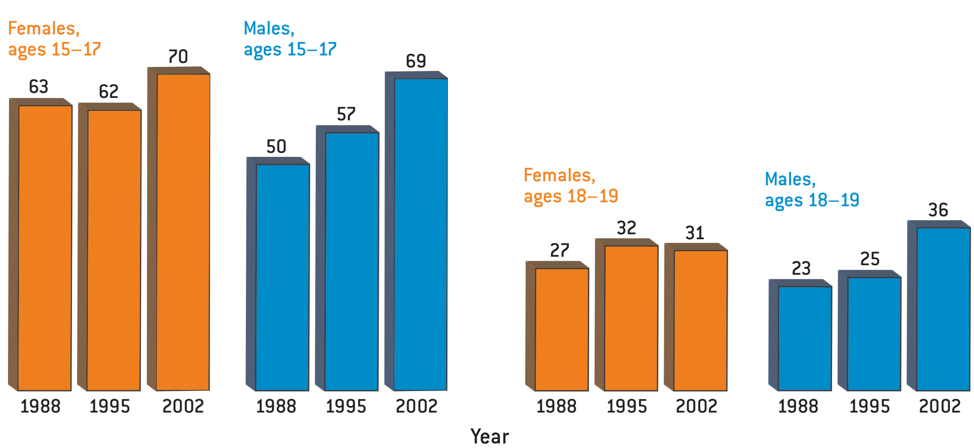
As the chart shows, the popularity of virginity has grown somewhat among all groups except for 18- to 19-year-old females. Vital statistics tabulations show strong and consistent declines in birth rates for both groups since 1991 and continuing into 2004, the latest year for which information is available. The timing of this decline is consistent with the notion that fear of HIV was spreading throughout high schools beginning in the early 1990s.

Virginity pledges, such as that promoted by the Southern Baptist Convention, may have also prompted some of the decline. Since the early 1990s at least 2.5 million adolescents have taken the pledges, which are unaccompanied by information on contraceptives. Teenagers who pledge are one third less likely to engage in intercourse than nonpledgers, but those who break the pledge are less likely to use contraception during their first intercourse than nonpledgers and also are less likely to be tested for sexually transmitted diseases. As a result, virginity pledgers have the same rates of sexually transmitted disease as nonpledgers.

Health professionals probably deserve some of the credit for the decline in teenage sex, because they have put considerable effort into improving sex education for adolescents in recent years. Evidence suggests that the declining trend in teenage births also stems from the same broad historical tendency that has reduced crime, depressed divorce rates and brought "family values" to the forefront of politics over recent decades.

Rodger Doyle can be reached at rodgerpdoyle@verizon.net

PERCENT OF TEENAGERS WHO CLAIM TO BE VIRGINS



RODGER DOYLE; SOURCES: *TEENAGERS IN THE UNITED STATES: SEXUAL ACTIVITY, CONTRACEPTIVE USE, AND CHILDBEARING 2002*, BY JOYCE C. ABMA ET AL., NATIONAL CENTER FOR HEALTH STATISTICS, DECEMBER 2004

FAST FACTS: TEENAGE MOMS

Estimated number of U.S. women in 2002 ages 15 to 19 who:

Had intercourse: 4.6 million

Became pregnant: 747,000

Miscarried: 107,000

Had abortions: 215,000

Carried to term: 425,000

SOURCES: Guttmacher Institute and Joyce C. Abma et al.

FURTHER READING

Parents' Beliefs about Condoms and Oral Contraceptives: Are They Medically Accurate? Marla E. Eisenberg et al. in *Perspectives on Sexual and Reproductive Health*, Vol. 36, No. 2, pages 50–57; March–April 2004. www.guttmacher.org/pubs/journals/3605004.html

Teenagers in the United States: Sexual Activity, Contraceptive Use, and Childbearing 2002. Joyce C. Abma et al. National Center for Health Statistics, Vital and Health Statistics, Series 23, No. 24; December 2004. www.cdc.gov/nchs

After the Promise: The STD Consequences of Adolescent Virginity Pledges. Hannah Brückner and Peter Bearman in *Journal of Adolescent Health*, Vol. 36, No. 4, pages 271–278; April 2005. www.jahonline.org

What Works: Curriculum-Based Programs That Prevent Teen Pregnancy. National Campaign to Prevent Teen Pregnancy. www.teenpregnancy.org

The first principle is that you must not fool yourself—
and you are the easiest person to fool.
—Richard Feynman, California Institute of Technology physicist and Nobel laureate

Airborne Baloney

The latest fad in cold remedies is full of hot air By MICHAEL SHERMER

I violated Feynman's first principle during a recent book tour. I traveled daily through congested airports, crowded jets and crammed bookstores amid sneezing, coughing, germ-infested multitudes. One day, while squeezed into the sardine section of coach, with the guy behind me obeying the command of the germs in his lungs to go forth and multiply, I cursed myself for having forgotten my Airborne tablets, an orange-flavored effervescent concoction of herbs, antioxidants, electrolytes and amino acids that fizzles into action in a glass of water.

In the logic-tight compartments of my brain, my magic module had trumped my skeptic module. I had not given this product any thought until, much to my chagrin, the host for one of my tour stops, a Menlo Park, Calif., Internet venture capitalist and science blogger named David Cowan, mentioned that recently he had debunked Airborne on his blog (http://whohastimeforthis.blogspot.com). A science-savvy investor, Cowan was quick to spot the clever marketing technique of suggesting that Airborne prevents or cures colds without actually saying so. "Take at the FIRST sign of a cold symptom or before entering crowded environments," the instructions say. Then "repeat every three hours as necessary." In the (really) fine print, however, is this: "These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

Annual sales of $100 million are all the data the lab needs.

Even more troublesome is how the company turned a liability into an asset. Most drugs are developed by Big Pharma—Brobdingnagian corporations with vast teams of scientists who have, to date, failed to cure the common cold. Airborne's creator is "Knight-McDowell Labs"—Victoria Knight-McDowell is a schoolteacher and her husband, Rider McDowell, is a scriptwriter. Instead of hiding their lack of credentials, they boast about them on their Web page (www.airbornehealth.com): CREATED BY A SECOND-GRADE SCHOOL TEACHER! "As any confidence artist knows," Cowan explains in his blog, "disclosing unflattering facts up front wins the target's trust." And $100 million in annual sales is all the data the lab needs.

As for real scientific evidence on Airborne, the Web page used to provide a link to "clinical results" (no longer there). When Cowan wrote to the company for the information, he received this reply: "The 2003 trial was a small study conducted for what was then a small company. While it yielded very strong results, we feel that the methodology (protocol) employed is not consistent with our current product usage recommendations. Therefore, we no longer make it available to the public." Why? The company CEO, Elise Donahue, told ABC News: "We found that it confused consumers. Consumers are really not scientifically minded enough to be able to understand a clinical study."

ABC News looked into the clinical trial and discovered that it was conducted by GNG Pharmaceutical Services, "a two-man operation started up just to do the Airborne study. There was no clinic, no scientists and no doctors. The man who ran things said he had lots of clinical trial experience. He added that he had a degree from Indiana University, but the school says he never graduated."

In one final lunge at product verisimilitude (dang it, that zesty taste feels like it works), I consulted Harriet Hall, a retired U.S. Air Force flight surgeon and family physician who studies alternative medicine. Hall looked up Airborne's ingredients in the Natural Medicines Comprehensive Database and found no evidence that any of the ingredients prevents colds. Worse, vitamin A is unsafe in doses greater than 10,000 units a day, and Airborne contains 5,000 units per tablet and recommends five pills a day or more. The only positive finding was for vitamin C, for which some evidence indicates that taking high doses may shorten the duration of cold symptoms by one to one and a half days in some patients. But the large amounts needed may cause side effects. "There's more evidence for chicken soup than for Airborne," Hall told me. "In the absence of any credible double-blind studies to support the claims for Airborne, I'll stick to hand washing."

Chicken soup for the traveler's soul. SA

Michael Shermer is publisher of Skeptic *(www.skeptic.com). His new book is* Why Darwin Matters.

BRAD HINES

Sustainable Developments

The Neglected Tropical Diseases

For the equivalent of a few days' worth of military spending, devastating illnesses of the global poor could be controlled worldwide By JEFFREY D. SACHS

Our planet is filled with marvelous science-based opportunities for improving human welfare at a tiny cost, but these opportunities are often unrecognized by policymakers and the public. There is no better example than treatment of a group of tropical diseases that maim and kill millions, but which are largely unknown to Americans and Europeans.

Experts formally refer to them as the "neglected tropical diseases," or NTDs. They are hellish infections whose combined impact on disease, disability and death rivals the impacts of AIDS, tuberculosis and malaria, yet they are far less known, partly because they are diseases that afflict only the poor in the tropics.

Seven of the diseases are caused by helminths (worm infections): hookworm, trichuriasis, ascariasis, schistosomiasis and dracunculiasis (guinea worm), onchocerciasis and lymphatic filariasis. Another three are protozoan infections: leishmaniasis, trypanosomiasis and Chagas' disease. Three more are bacterial: leprosy, trachoma and Buruli ulcer.

Of these 13 diseases, nine (the seven helminth infections, plus leprosy and trachoma) have powerful, low-cost preventive or curative interventions that are easy to administer. As President Jimmy Carter has shown through his steadfast personal leadership over 20 years, filtering water through cheesecloth can dramatically reduce the burden of dracunculiasis. Insecticide-treated bed nets, which cost just $5 and last for five years, can break the transmission of lymphatic filariasis and greatly reduce the transmission of malaria.

Medicines can handle all the helminths other than guinea worm by keeping the number of worms infecting an individual at a tolerably low level through routine treatments. For example, where the helminth infections and schistosomiasis are prevalent, all schoolchildren should be treated with deworming medicine up to three times annually. The pharmaceutical companies have stepped up to do their part. Merck & Co., GlaxoSmithKline, Johnson & Johnson, Pfizer, Novartis and Sanofi-Pasteur have donated medicines and made other contributions to the fight against various illnesses. All these companies eagerly support the expansion of control programs.

It is time for governments to join in, too. The U.S. has recently committed $15 million to the fight against NTDs—a start but still less than one tenth of the $250 million or so a year needed for a comprehensive campaign for Africa. The best strategy would be to link the control of the NTDs with malaria control. The same bed nets and community health workers can attend to both malaria and the NTDs, which have a very high geographic overlap throughout the tropical countries. Moreover, millions of children in Africa are "polyparasitized," infected with both malaria and combinations of the NTDs. These multiple infections seem to be especially injurious.

The best strategy would be to link control of NTDs and malaria.

Our policymakers should ponder that effective disease control does more to promote global stability and goodwill, via economic development, than do vastly larger outlays for military approaches after instability has broken out. Targeted disease-control measures have been highly effective in the past, even in the poorest countries. Smallpox was eradicated, and polio has been brought down 1,000-fold worldwide by vaccine efforts, led notably by Rotary International.

Comprehensive, Africa-wide control of malaria and NTDs together would probably cost no more than $3 billion a year, or just two days of Pentagon spending. If each of the billion people in the rich world devoted the equivalent of one $3 coffee a year to the cause, several million children every year would be spared death and debility, and the world would be spared the grave risks when disease and despair run unchecked. A new Global Network for Neglected Tropical Disease Control (see www.gnntdc.org) is helping to make this opportunity a reality. SA

Jeffrey D. Sachs is director of the Earth Institute at Columbia University.

An expanded version of this essay is available at **www.sciam.com/ontheweb**

BRUCE GILBERT/EARTH INSTITUTE

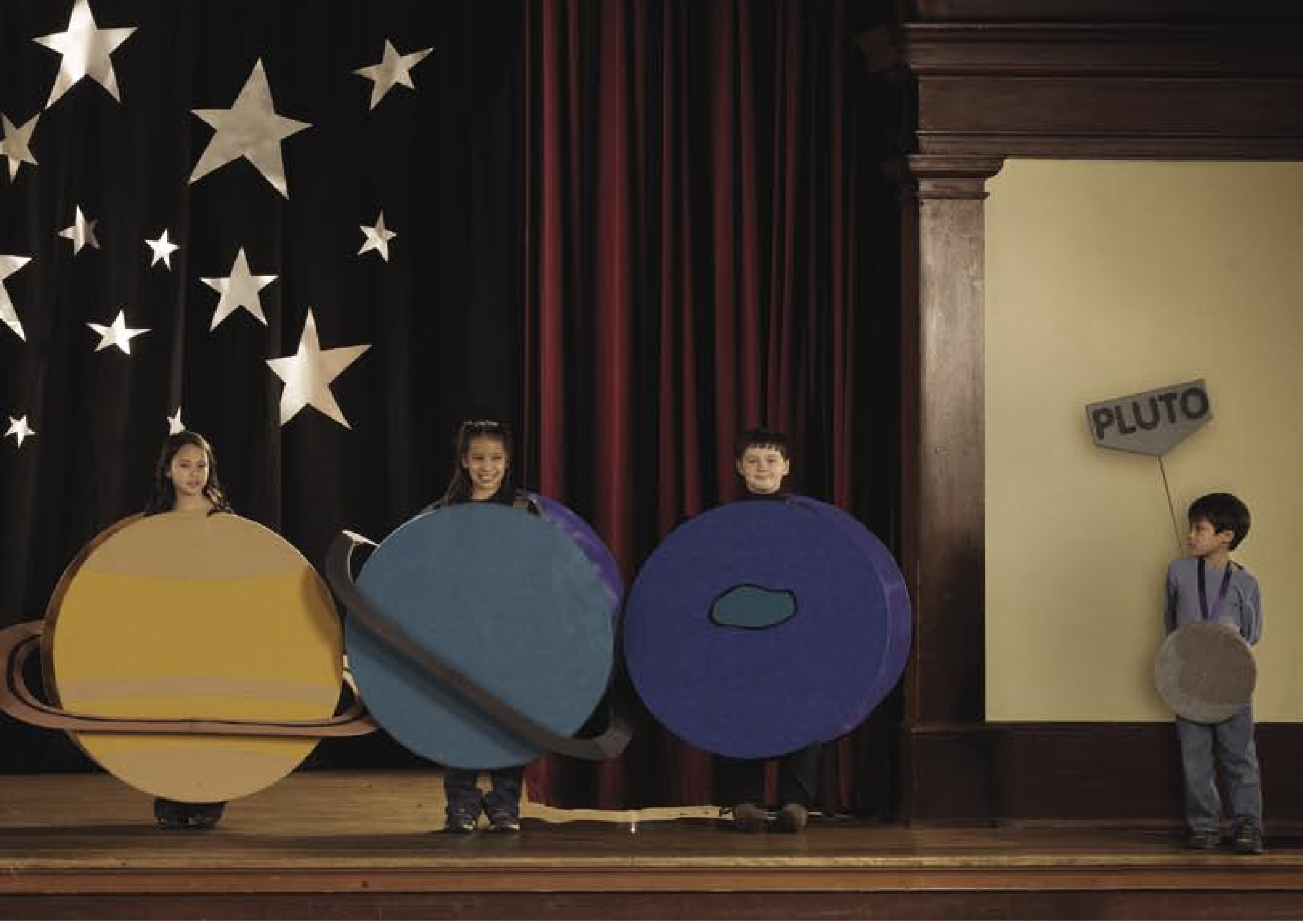
WHAT IS A PLANET?

By Steven Soter

The controversial new official definition of "planet," which banished Pluto, has its flaws but by and large captures essential scientific principles

Most of us grew up with the conventional definition of a planet as a body that orbits a star, shines by reflecting the star's light and is larger than an asteroid. Although the definition may not have been very precise, it clearly categorized the bodies we knew at the time. In the 1990s, however, a remarkable series of discoveries made it untenable. Beyond the orbit of Neptune, astronomers found hundreds of icy worlds, some quite large, occupying a doughnut-shaped region called the Kuiper belt. Around scores of other stars, they found other planets, many of whose orbits

DAVID EMMITE PHOTOGRAPHY



look nothing like those in our solar system. They discovered brown dwarfs, which blur the distinction between planet and star. And they found planetlike objects drifting alone in the darkness of interstellar space.

These findings ignited a debate about what a planet really is and led to the decision last August by the International Astronomical Union (IAU), astronomers' main professional society, to define a planet as an object that orbits a star, is large enough to have settled into a round shape and, crucially, "has cleared the neighborhood around its orbit." Controversially, the new definition removes Pluto from the list of planets. Some astronomers said they would refuse to use it and organized a protest petition.

This is not just a debate about words. The question is an important one scientifically. The new definition of a planet reflects advances in our understanding of the architecture of our solar system and others. These systems formed by accretion within rotating disks: small grains clump together to form bigger ones, which draw themselves together to form still bigger ones, and so on. This process eventually produces a small

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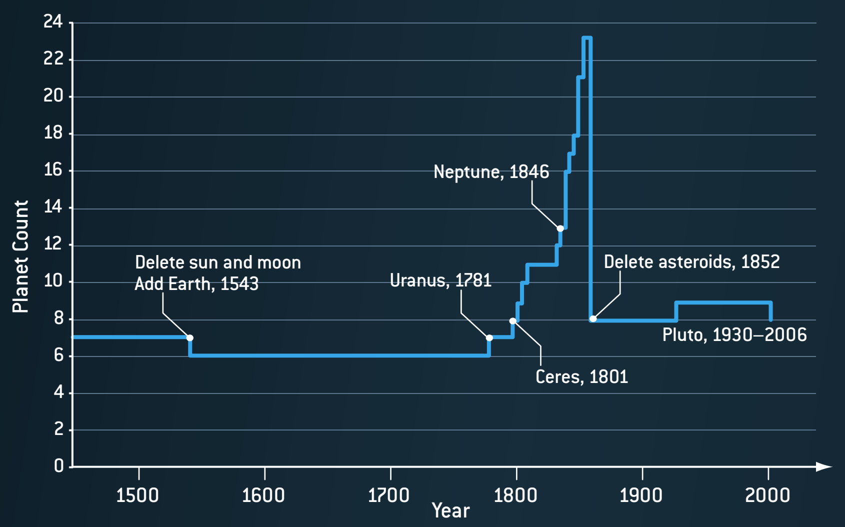
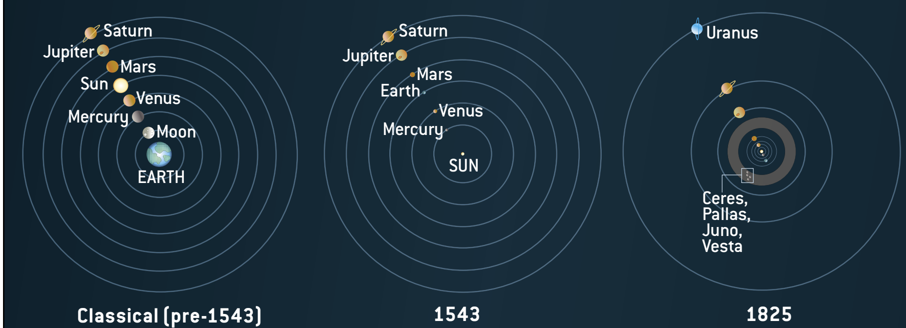
HISTORICAL COUNT OF PLANETS

Planets come, planets go as a result of new discoveries and changing conceptions of what a "planet" is. The decision to recategorize Pluto is simply another step in this historical progression.





DATE	PLANETS
Pre-1543	Mercury, Venus, Mars, Jupiter, Saturn, sun, moon
1543	Earth added sun, moon deleted
1781	Uranus
1801	Ceres
1802	Pallas
1804	Juno
1807	Vesta
1845	Astraea
1846	Neptune
1847	Hebe, Iris, Flora
1848	Metis
1849	Hygiea
1850	Parthenope, Victoria, Egeria
1851	Irene, Eunomia
1852	Asteroids deleted
1930	Pluto
2006	Pluto deleted

LUCY READING-IKKANDA

number of massive bodies—the planets—and a large number of much smaller bodies—the asteroids and comets, which represent the debris left over from planet formation. In short, "planet" is not an arbitrary category but an objective class of celestial bodies.

When Earth Became a Planet

ASTRONOMERS' reevaluation of the nature of planets has deep historical roots. The ancient Greeks recognized seven lights in the sky that moved against the background pattern of stars: the sun, the moon, Mercury, Venus, Mars, Jupiter and Saturn. They called them *planetes*, or wanderers. Note that Earth is not on this list. For most of human history, Earth was regarded not as a planet but as the center—or foundation—of the universe. After Nicolaus Copernicus persuaded astronomers that the sun rather than Earth lies at the center, they redefined planets as objects orbiting the sun, thereby putting Earth on the list and deleting the sun and moon. Telescope observers added Uranus in 1781 and Neptune in 1846.

Ceres, discovered in 1801, was initially welcomed as the missing planet that filled the gap between Mars and Jupiter. But astronomers began to have doubts when they found Pallas in a similar orbit the following year. Unlike the classical planets, which telescopes revealed as little disks, both these bodies

Overview/*Planet Definition*

- Last August members of the International Astronomical Union voted to define a planet as a body that orbits a star, is large enough to be round, and has cleared other bodies out of its neighborhood. The definition was intended to bring closure to a long-standing debate but instead seems to have poured fuel on the fire.
- Critics have called the definition arbitrary and imprecise, but the charge is unfounded. The solar system divides cleanly into eight bodies massive enough to dominate their orbital zones and swarms of smaller ones that occupy intersecting orbits. This pattern appears to reflect the way the solar system formed and evolved.

appeared as mere pinpricks of light. English astronomer William Herschel proposed naming them "asteroids." By 1851 their number had increased to 15, and it was becoming unwieldy to consider them all planets. Astronomers then decided to list asteroids by their order of discovery rather than by distance from the sun, as for planets—the de facto acceptance of the asteroids as members of a distinct population. If we still counted asteroids as planets, schoolchildren studying the solar system would now have to cope with more than 135,000 planets.

Pluto has a similar story. When Clyde Tombaugh discovered it in 1930, astronomers welcomed Pluto as the long-sought "Planet X" whose gravity would account for unexplained peculiarities in the orbit of Neptune. Pluto turned out to be smaller not only than the other eight planets but also than seven of their satellites, including Earth's moon. Further analysis showed the peculiarities in Neptune's orbit to be illusory. For six decades, Pluto was a unique anomaly at the outer edge of the planetary system.

Just as Ceres began to make sense only when it was recognized as one of a vast population of asteroids, Pluto fell into place only when astronomers found it was one of a vast population of Kuiper belt objects (KBOs) [see "The Kuiper Belt," by Jane X. Luu and David C. Jewitt; SCIENTIFIC AMERICAN, May 1996, and "Migrating Planets," by Renu Malhotra; SCIENTIFIC AMERICAN, September 1999]. Astronomers began to reconsider whether it should still be called a planet. Historically, revoking the planetary status of Pluto would not be unprecedented; the ranks of ex-planets include the sun, moon and asteroids. Nevertheless, many people have argued for continuing to call Pluto a planet, because almost everyone has grown quite accustomed to thinking of it as one.

The discovery in 2005 of Eris (formerly known as 2003 UB313 or Xena), a KBO even larger than Pluto, brought the issue to a head. If Pluto is a planet, then Eris must also be one, together with scores of other large KBOs; conversely, if Pluto is not a planet, neither are the other KBOs. On what objective grounds could astronomers decide?

Clearing the Air

TO AVOID an open-ended proliferation of planets, Alan Stern and Harold Levison of the Southwest Research Institute suggested in 2000 that a planet could be defined as a body less massive than a star but large enough for its gravity to overcome its structural rigidity and pull it into a round shape. Most bodies larger than several hundred kilometers in radius satisfy the latter criterion. Smaller ones often have a craggy shape; many of them are basically giant boulders.

This definition was the one advocated in early August by the IAU Planet Definition Committee, chaired by Owen Gingerich of Harvard University. It would have retained Pluto as a planet, but at the expense of admitting potentially dozens of KBOs and restoring the planetary status of Ceres, the largest asteroid and the only one known to be spherical.

Many astronomers argued that the roundness criterion is inadequate. In practical terms, it is very difficult to observe the shapes of distant KBOs, so their status would remain ambiguous. Furthermore, asteroids and KBOs span an almost continuous spectrum of sizes and shapes. How are we to quantify the degree of roundness that distinguishes a planet? Does gravity dominate such a body if its shape deviates from a spheroid by 10 percent or by 1 percent? Nature provides no unoccupied gap between round and nonround shapes, so any boundary would be an arbitrary choice.

Stern and Levison proposed another criterion that does, however, lead to a nonarbitrary way to classify objects. They remarked that some bodies in the solar system are massive enough to have swept up or scattered away most of their immediate neighbors. Lesser bodies, unable to do so, occupy transient, unstable orbits or have a heavyweight guardian that stabilizes their orbits. For

FREQUENTLY ASKED QUESTIONS

Q Isn't the definition of a planet really arbitrary?

A Scientists need precise definitions to communicate effectively. Careful definitions reflect our understanding of basic relationships in nature. If new discoveries render an old definition misleading or obsolete, we need to revise it accordingly.

Q What's wrong with the old definition of a planet as a nonluminous body orbiting a star and larger than an asteroid?

A It makes no distinction between planets and Kuiper belt objects, even though they are clearly different.

Q The definition approved by the International Astronomical Union says that a planet "has cleared the neighborhood around its orbit." But many asteroids and comets cross Earth's orbit, so why is it still called a planet? Or, for that matter, why is even Jupiter a planet? The Trojan asteroids share Jupiter's orbit, so Jupiter hasn't "cleared" its neighborhood.

A The clearing is never perfect because asteroids, comets and meteoroids continue to stray into the neighborhoods of the planets. Yet the amount of this debris is negligible compared with each planet's mass. A more precise definition would say that a planet "dominates" its orbital zone. Jupiter's gravity controls the orbits of the Trojan asteroids. The IAU definition has the right idea, but its unqualified use of the word "cleared" has inadvertently caused some confusion.

Questions continued on page 40

instance, Earth is big enough that it eventually sweeps up or flings away any body that strays too close, such as a near-Earth asteroid. At the same time, Earth protects its moon from being swept up or scattered away. Each of the four giant planets rules over a sizable brood of orbiting satellites. Jupiter and Neptune also maintain their own families of asteroids and KBOs (called Trojans and Plutinos, respectively) in special orbits known as stable resonances, where an orbital synchrony prevents collisions with the planets.

These dynamical effects suggest a practical way to define a planet. That is, a planet is a body massive enough to dominate its orbital zone by flinging smaller bodies away, sweeping them up in direct collisions, or holding them in stable orbits. According to basic orbital physics, the likelihood that a massive body will deflect a smaller one from its neighborhood within the age of the solar system is roughly proportional to the square of its mass (which determines the gravitational reach of the massive body for a given amount of deflection) and inversely proportional to its orbital period (which governs the rate at which the encounters occur).

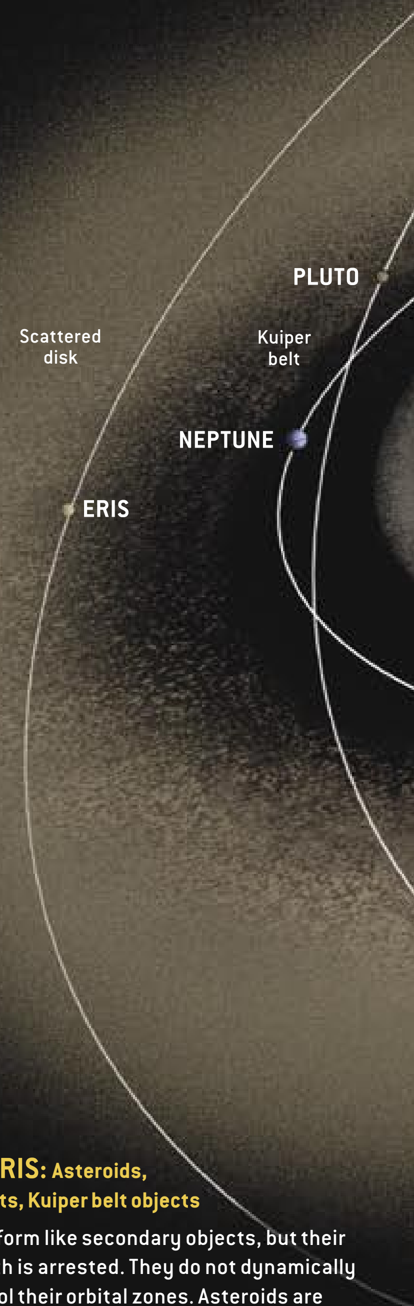
The eight planets from Mercury through Neptune are thousands of times more likely to sweep up or deflect small neighboring bodies than are even the largest asteroids and KBOs, which include Ceres, Pluto and Eris. Mercury and Mars by themselves are not massive enough to scatter away all the bodies in their vicinities. But Mercury is still large enough to sweep up most of the nearby small objects that cross its orbit, and Mars has sufficient gravitational influence to deflect passing objects into nearby unstable orbits, including some with periods exactly one-third or one-quarter that of Jupiter. The gravity of the giant planet then completes the task of ejecting those objects from the vicinity of Mars.

The ability of a body to clear its neighborhood depends on its dynamical context; it is not an intrinsic property of the body. Nevertheless, the large gap in dynamical power provides a clear way to

DON DIXON (*solar system*); LUCY READING-IKKANDA (*graph and orbits*)

THE "NEW" SOLAR SYSTEM

The planet definition approved by the International Astronomical Union is based on the observed architecture of the solar system, in which a small number of dominant bodies, the eight planets, have well-separated orbits, in contrast to the swarms of smaller asteroids, comets and Kuiper belt objects. Ceres and Pluto, once considered planets, are (along with Eris) swarm dwellers. Trojan asteroids share the orbit of Jupiter and are dynamically controlled by it. Centaurs are comets orbiting between Jupiter and Neptune.



TAXONOMY OF CELESTIAL BODIES

PRIMARY OBJECTS: Stars, brown dwarfs, sub-brown dwarfs

They form when an interstellar cloud collapses under its own gravity. Those with at least 80 times the mass of Jupiter undergo stable nuclear fusion of hydrogen and are called stars. Those in the range of 13 to 80 Jupiter masses undergo a brief period of nuclear fusion of deuterium, a rare isotope of hydrogen, and are called brown dwarfs. Less massive ones may be termed sub-brown dwarfs.

SECONDARY OBJECTS: Planets

They form when dust grains clump together in the rotating disk of material around a primary object. They undergo a period of runaway growth in which the larger ones sweep up most of the rest of the material. A planet that reaches a certain critical size can also pull in a thick envelope of gas.

TERTIARY OBJECTS: Satellites

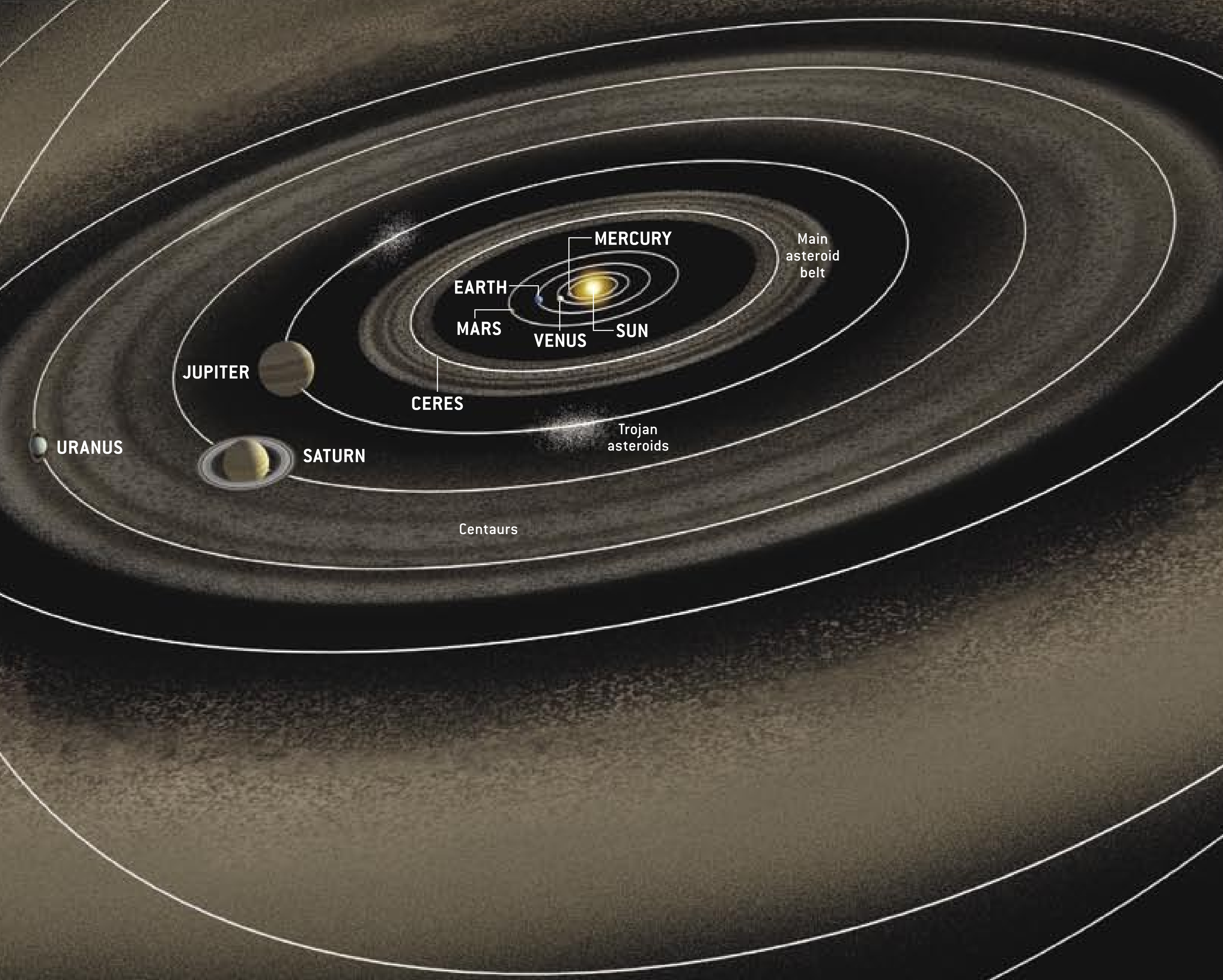
They orbit secondary objects, either having been formed in place or captured from independent orbits.

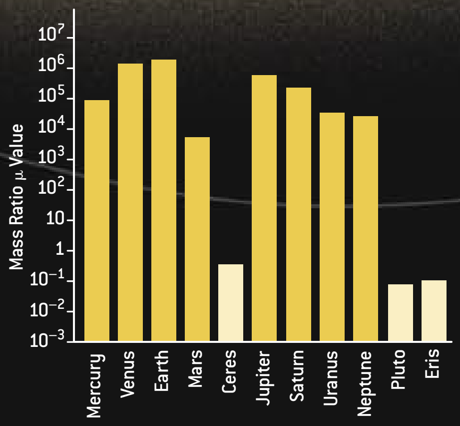
DEBRIS: Asteroids, comets, Kuiper belt objects

They form like secondary objects, but their growth is arrested. They do not dynamically control their orbital zones. Asteroids are small rocky worlds, most of which reside in a belt between the orbits of Mars and Jupiter. Kuiper belt objects are small icy bodies that orbit in a belt beyond Neptune; the belt appears to be the source of most periodic comets. The distinction between asteroids and comets is sometimes ambiguous: comets are typically more volatile-rich and form farther from the sun.

ROGUE PLANETS

They form as secondary objects but have been ejected to interstellar space. Simulations suggest that such objects may outnumber the stars in our galaxy. Observationally, though, they will be difficult to detect, let alone distinguish from free-floating sub-brown dwarfs that formed as primary objects.

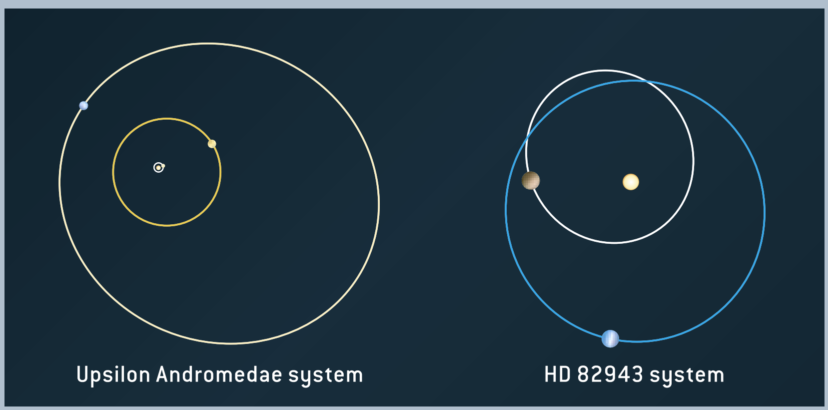




CLEAR DIVISION between planets (*gold*) and lesser bodies (*cream*) is evident in their mass ratio μ—the mass of a body divided by the total mass of all other bodies that share its orbital zone. All eight planets have a μ value of at least 5,000, whereas Pluto's is less than 1. A μ value of 100 serves as a convenient dividing line between planets and nonplanets in our solar system.

PLANETS ELSEWHERE IN THE GALAXY

ORBITAL DOMINANCE by a few bodies appears to be a property of other known planetary systems, too. In most, the planets' orbits do not overlap (*left*), so they are unable to collide. Even in those few cases where the orbits do overlap (*right*), an orbital synchrony prevents them from colliding.



MORE QUESTIONS

Q **Pluto's orbit crosses that of Neptune, so why is Neptune called a planet but not Pluto?**

A Neptune is more than 8,000 times as massive as Pluto and dominates its neighborhood gravitationally. Neptune long ago locked Pluto's orbit into a resonance with its own, making a collision between the two bodies impossible. Pluto is too small to dominate anything beyond its own satellites (one of which, Charon, is almost half as big as it is).

Q **Doesn't having a satellite qualify a celestial body to be a planet?**

A No. Many asteroids and Kuiper belt objects have satellites, but Mercury and Venus do not, and no one would deny that they are planets.

Q **If we discovered a Mars-size body in the outer Kuiper belt or even a Neptune-size body in the distant Oort cloud, would we call it a planet?**

A Not according to the new definition, because such a body would not dominate its neighborhood. We might need to coin a new term for it.

Q **Isn't it more practical to classify celestial bodies based only on their intrinsic features rather than on their orbital context?**

A Not necessarily. We already classify many objects as "moons" based on their orbital context. Some are as large as planets, and others are simply captured asteroids or comets, but we classify them by the shared dynamical characteristic of orbiting a planet.

Ask more questions at www.sciam.com/ontheweb

distinguish the planets from other bodies. We do not need to make an arbitrary distinction because, at least in our own solar system, nature does it for us.

Kings of Their Kingdoms

A CLOSELY RELATED criterion was proposed by astronomer Michael Brown of the California Institute of Technology in 2004. He defined a planet as "any body in the solar system that is more massive than the total mass of all of the other bodies in a similar orbit." To make this more precise, I have suggested replacing "similar orbit" with the concept of an orbital zone. Two bodies share such a zone if their orbits ever cross each other, if their orbital periods differ by less than a factor of 10, and if they are not in a stable resonance. To apply this definition, I undertook a census of the known small bodies that orbit the sun.

Earth, for example, shares its orbital zone with an estimated 1,000 asteroids larger than one kilometer in diameter, most of which are relatively recent arrivals from the main asteroid belt between Mars and Jupiter. They add up to less than 0.0001 percent of the mass of our planet. The ratio between the mass of a body and the mass of all other bodies that share its orbital zone can be abbreviated μ. For Earth, μ is about 1.7 million. In fact, Earth appears to have the highest μ value in the solar system. Jupiter is 318 times more massive but shares its orbital zone with a larger swarm of bodies. Mars has the lowest μ value for any of the planets (5,100), but even that is far greater than the value for Ceres (0.33) or Pluto (0.07) [*see box on preceding page*]. The result is striking: the planets are in a different league from the asteroids and KBOs, and Pluto is clearly a KBO.

Such arguments persuaded the IAU to define a planet in terms of "clearing" its orbital neighborhood. The IAU may need to amend the definition to specify what degree of clearing qualifies a body as a planet. I have suggested setting the cutoff at a μ value of 100. That is, a body in our solar system is a planet if it accounts for more than 99 percent of the mass in its orbital zone. But the exact value of this cutoff is not critical. Any value between about 10 and 1,000 would have the same effect.

A planet is thus a body that has swept up or scattered away most of the mass from its orbital zone. The clean division of bodies into planets and nonplanets reveals important aspects of the process that formed the solar system. All these bodies grew from a flattened disk of gas and dust orbiting the primordial sun. In the competition for the limited amount of raw material, some bodies won out. Their growth became self-reinforcing, so instead of a continuous spectrum of bodies of all sizes, the result was a single large body that dominated each orbital zone. The smaller bodies were swept up by the larger ones, ejected from the solar system or swallowed by the sun, and the survivors became the planets we see today. The asteroids and comets, including the KBOs, are the leftover debris.

Our solar system is now in the final cleanup phase of accretion. The asteroids have intersecting orbits that allow them to collide with one another and with the planets. The Kuiper belt is a remnant of the outer part of the original accretion disk, where the material was too sparse to form another planet. The planets of our solar system have orbits that do not intersect and so are unable to collide. As the dynamically dominant bodies, they must be few in number. If another planet tried to squeeze in between the existing ones, gravitational perturbations would eventually destabilize its orbit.

A similar situation appears to be true of other planetary systems as well. So far observers have found about 20 systems with more than one planet. In most, the planets have orbits that do not intersect, and in the three exceptions, the overlapping orbits appear to be resonant, allowing the planets to survive without colliding. All the known nonstellar companions of sunlike stars are massive enough to deflect nearby small bodies. They would probably qualify as planets by the criterion of dynamical dominance.

Endgame

A PLANET is, in effect, the end product of accretion from a disk around a star. This definition applies only to mature systems, such as ours, in which accretion has run effectively to completion. For younger systems, where accretion is still important, the largest bodies are not strictly planets but are called planetary embryos, and the smaller bodies are called planetesimals.

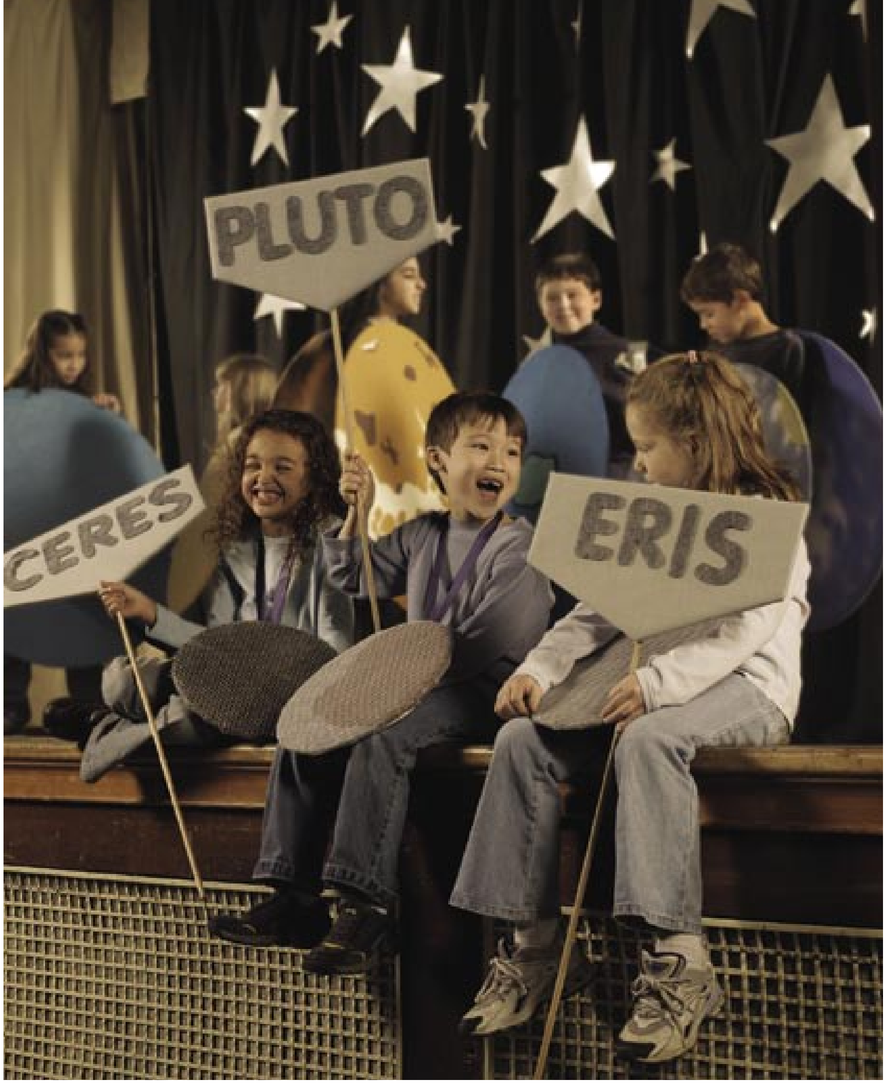
The IAU definition still includes roundness as a criterion for a planet, though strictly speaking, that is unnecessary. The orbital-clearance criterion already distinguishes planets from asteroids and comets. The definition also removes the need for an upper mass limit to distinguish planets from stars and brown dwarfs. The relatively rare brown dwarf companions orbiting close to stars can be classified as planets; unlike brown dwarfs in wider orbits, they are thought to have formed by disk accretion.

In short, the difference between planets and nonplanets is quantifiable, both in theory and by observation. All the planets in our solar system have enough mass to have swept up or scattered away most of the original planetesimals from their orbital zones. Today each planet contains at least 5,000 times more mass than all the debris in its vicinity. In contrast, the asteroids, comets and KBOs, including Pluto, live amid swarms of comparable bodies.

A prominent objection to any definition of this kind is the contention that astronomical objects should be classified only by their intrinsic properties, such as size, shape or composition, and not by their location or dynamical context. This argument overlooks the fact that astronomers classify all objects that orbit planets as "moons," although two of them are larger than the planet Mercury and many are captured asteroids and comets. Context and location are clearly important. In fact, distance from the sun determined that close-in bodies became small rocky planets and farther ones became giant planets rich in volatile ices and gases. The new definition distinguishes planets, which dynamically dominate a large volume of orbital space, from asteroids, KBOs and ejected planetary embryos, which do not. The eight planets are the dominant end products of disk accretion and differ recognizably from the vast populations of asteroids and KBOs.

The historical definition of nine planets no doubt retains a strong sentimental attraction. But ad hoc definitions devised to grandfather in Pluto tend to conceal from the public the profound changes that have occurred since the early 1990s in our understanding of the origin and architecture of the solar system.

For 76 years, our schools taught that Pluto was a planet. Some argue that culture and tradition are sufficient grounds to leave it that way. But science cannot remain bound by the misconceptions of the past. To be useful, a scientific definition should be derived from, and draw attention to, the structure of the natural world. We can revise our definitions when necessary to reflect the better understanding that arises from new discoveries. The debate on the definition of a planet will provide educators with a textbook example to show how scientific concepts are not graven in stone but continue to evolve. SA



DAVID EMMITE PHOTOGRAPHY

MORE TO EXPLORE

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Is Ethanol

By Matthew L. Wald

The airport terminal in Sioux Falls, S.D., could be anywhere, until you reach the baggage claim area. Between the carousels is a green and white Indy-style race car, covered with decals that indicate it runs on ethanol. Approach the rent-a-car booths, and you will see a sign taped to the countertop reminding customers *not* to pump E85, the ultraethanol blend sold locally, into the rental cars because they are not designed for it and it will ruin their engines.

This is ethanol country, the center of the national push to turn carbohydrates into hydrocarbons.

The U.S. has gone on an ethanol binge, anticipating a fuel transition unrivaled since electric utilities set out 40 years ago to build hundreds of nuclear power plants. In August 2005 Congress passed a major energy bill

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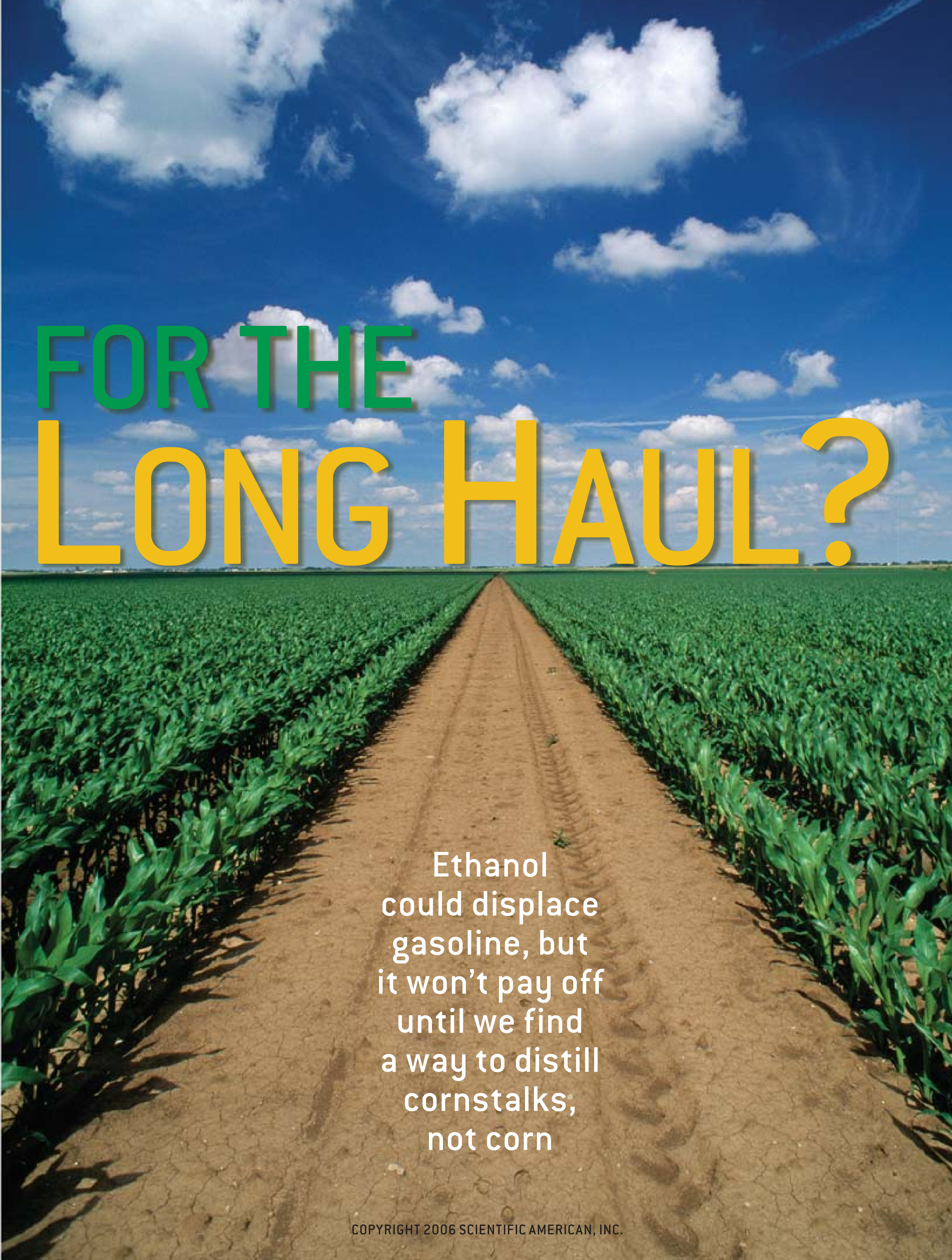


FOR THE LONG HAUL?

Ethanol could displace gasoline, but it won't pay off until we find a way to distill cornstalks, not corn

calling for production of 7.5 billion gallons of ethanol a year by 2012, up from about four billion gallons at the time, to help displace imported fuel. Industry analysts say the nation will be burning that much ethanol long before the deadline, thanks to government tax rules and subsidies—and especially if oil prices stay high—because the cost to convert plant matter into ethanol is far below the $2.50 a gallon that gasoline was fetching last fall.

Indeed, according to the Renewable Fuels Association, domestic ethanol production was more than five billion gallons in 2006. That quantity is small compared with gasoline and diesel consumption of about 140 billion gallons annually, but it is up 50 percent in one year. Andy Karsner, the assistant secretary of energy for efficiency and renewable energy at the DOE, says that because of the market pull exerted by the high price of oil, developers are scrambling to build ethanol plants. There is an ethanol boom, he says, "a little like the Pennsylvania oil rush in the 1850s."

But is the rush worth it? Not the way we generate ethanol now. All the fuel ethanol sold commercially in the U.S. comes from corn kernels, and it is energy-intensive to produce. Some studies indicate that refining a gallon of ethanol takes more energy than it provides when combusted. Even the positive studies demonstrate only a slight net energy gain. Other research shows that the ethanol-from-corn cycle reduces greenhouse gases marginally or not at all compared with gasoline from crude.

Ethanol will not make economic or environmental sense until refiners perfect methods to derive the fuel from cellulose, not corn. Cellulose is the woody material that forms the stalk of a corn plant and the bodies of trees and other plants such as grasses, which require less energy to tend and harvest. But although scientists understand the biology-based processes that convert the sugars tied up in cellulose, companies trying to make ethanol from these materials have so far not reached commercial viability. Sugarcane is the ultimate plant source, far richer than cornstalks and grasses in the sugars that are distilled into ethanol, but the U.S. does not have the climate or cheap labor to exploit that crop the way Brazil has.

Ironically, to make "domestic" corn ethanol, the U.S. will have to increase imports of natural gas.

Making ethanol production from cellulose practical will require agricultural advances and major improvements in industrial processing. Without those steps, ethanol will remain a cumbersome product with little net benefit, and the country will remain dependent on foreign oil.

Overview/*Myth and Reality*

- Although politicians are aggressively pushing ethanol from homegrown corn as a substitute for foreign oil, the conversion makes little energy sense. It requires copious amounts of fossil fuels, and even if 100 percent of the U.S. corn supply was distilled into ethanol it would supply only a small fraction of the fuel consumed by the nation's vehicles.
- Studies show that producing ethanol from corn creates almost the same amount of greenhouse gases as gasoline production does. Burning ethanol in vehicles offers little if any pollution reduction.
- Deriving ethanol from cellulose—cornstalks and the straw of grains and grasses—consumes far less fossil fuel than ethanol from corn kernels. But companies have had trouble coaxing the natural enzymes needed for conversion to multiply and work inside the large bioreactors required for volume production. More promising organisms are being discovered; ethanol's long-term viability depends on their success.

Renewable? Not Really

MOST ETHANOL PRODUCED in the U.S. is sold as a kind of Hamburger Helper for gasoline. It may constitute up to 10 percent of the blend, the most that conventional engines can handle without damage. In some locales, primarily the farm belt, drivers can find the E85 blend—85 percent ethanol and 15 percent unleaded regular gasoline. This mix requires specially equipped "flexible fuel" engines designed to tolerate it. Otherwise the ethanol—the same form of alcohol as in distilled liquor—eats away at the seals in the engine and fuel system. Several million vehicles are so equipped (although many owners do not know it), but there are only a few hundred places that sell E85, and the fuel supply chain is expanding slowly.

Nevertheless, ethanol from corn is surging in part because it has a strong bipartisan constituency of farm-state senators and representatives in Washington, D.C. It also has support from people outside agriculture who believe the country

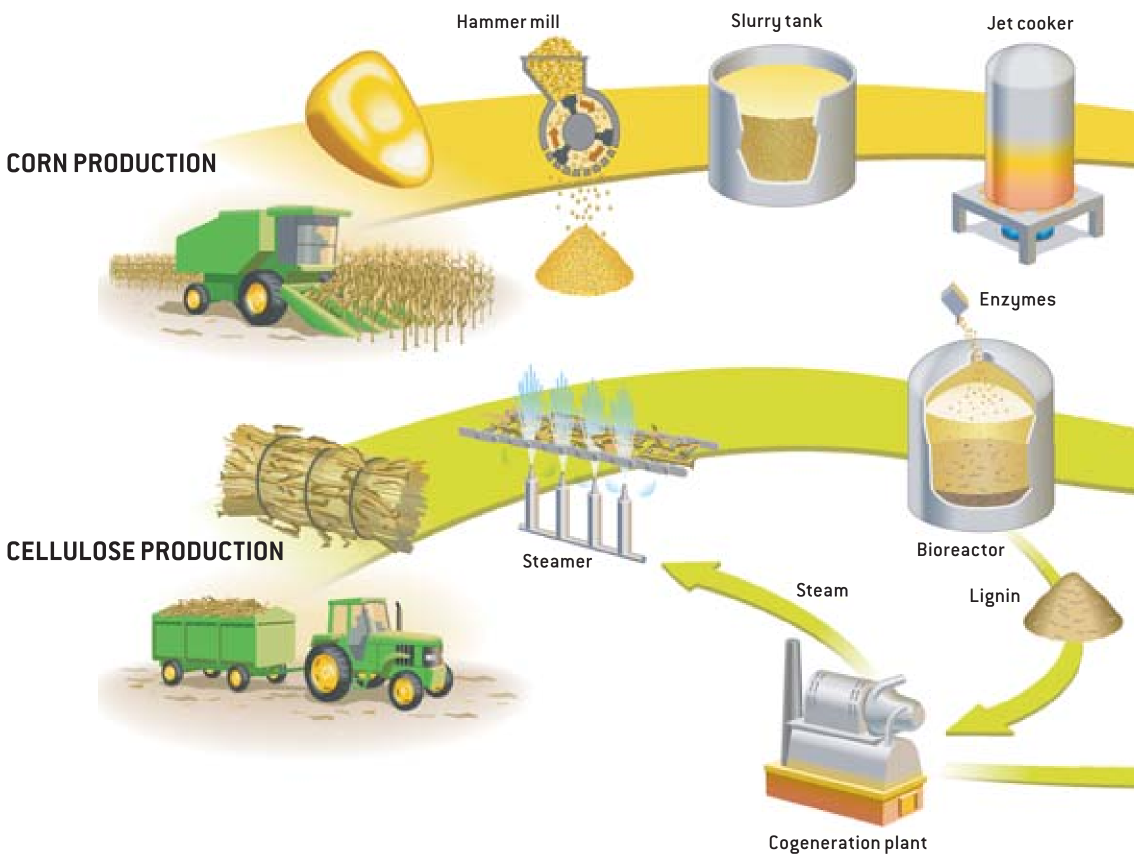
DON FOLEY (*opposite page*)

FROM WELL TO WHEEL: HOW FUEL IS MADE

Many steps are required to convert oil into gasoline and corn into ethanol and to deliver them to the local pump. Some stages are energy-intensive, consuming volumes of fossil fuels.

ETHANOL FROM KERNELS OR STALKS

The initial steps in converting corn or cellulose into ethanol differ significantly. Corn is ground, cooked and mashed before entering a fermenter. Cellulose is steamed to expose fibers that enzymes then convert into sugars in a bioreactor. Companies are still looking for bioreactions that are efficient on a large scale, but one payoff is the lignin that remains behind, which can be burned to cogenerate steam and electricity. The distillation of either raw material creates stillage, a valuable by-product that can be processed into animal feed.



should be less dependent on imported oil. Advocates argue that ethanol is a renewable fuel, because the corn can be grown year after year. The Renewable Fuels Association has a slick pamphlet that implies that consuming 7.5 billion gallons a year means 179 million fewer barrels of foreign oil. That level would equal about 15 days of imports—a start, if not a cure-all.

But there is less to ethanol than meets the eye. The first problem is that a standard barrel (42 gallons) of ethanol is worth about 28 gallons of gasoline because it contains only 80,000 British thermal units (Btu) of energy, versus about 119,000 for unleaded regular. If you fill your tank with E85, you will run dry about 33 percent sooner. Even if a gallon of ethanol were cheaper at the pump, drivers would have to buy many more gallons to go the same distance.

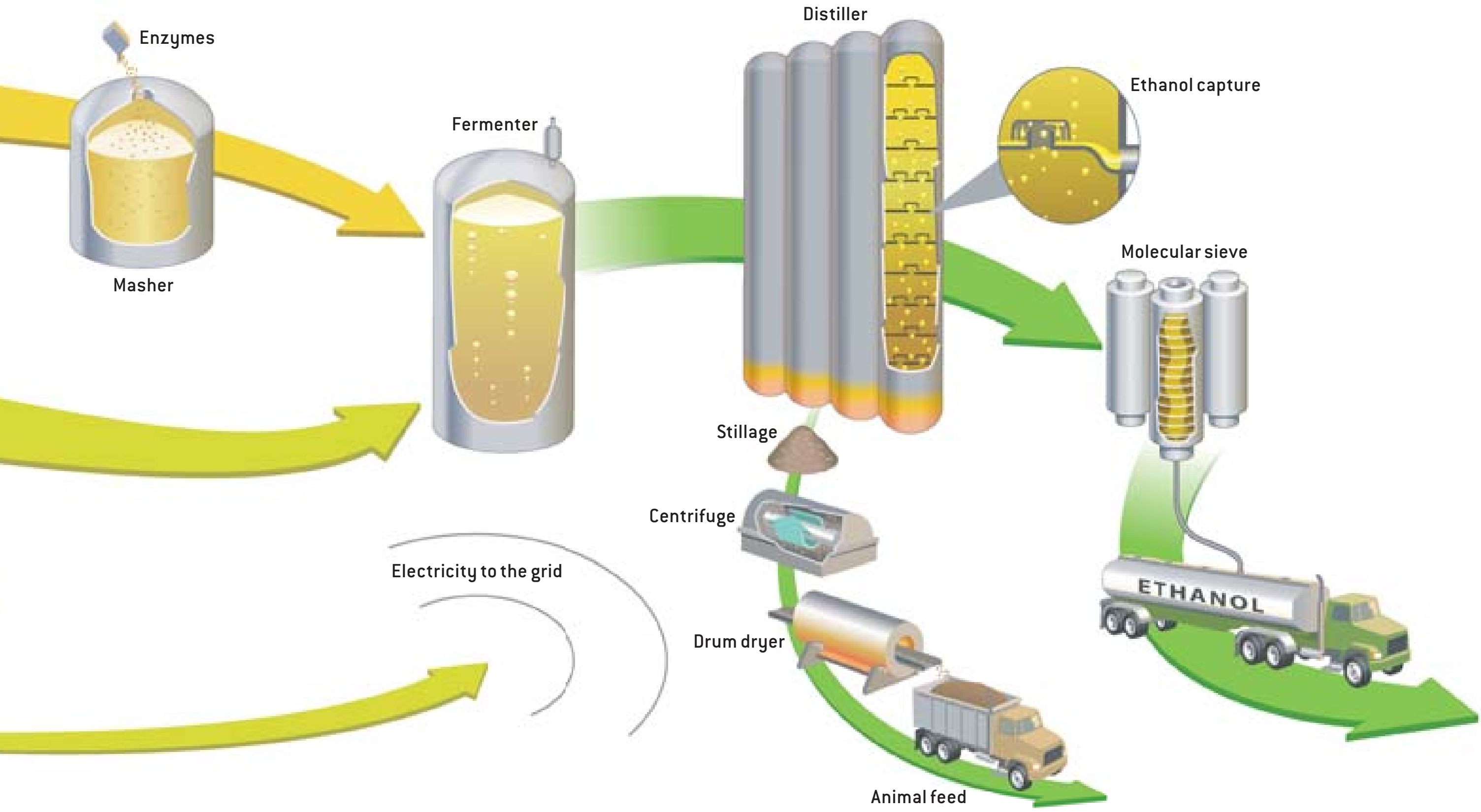
The other earworm in the ointment is that the U.S. lacks some of the resources to produce ethanol. The country has corn in abundance, spreading out in all directions from the Sioux Falls airport. But manufacturing ethanol requires copious amounts of natural gas. Basically, ethanol for fuel is produced the same way that ethanol for liquor is made. Yeast eats sugar and gives off alcohol and carbon dioxide. The output is distilled, vaporizing the alcohol, then capturing and recondensing it. Natural gas is used for heating at various steps. Producing a gallon of ethanol, with its 80,000 Btu of energy, currently requires about 36,000 Btu of natural gas.

In the 1990s, when Congress tried to prop up farm-state economies with laws that encouraged refiners to make more ethanol, natural gas was cheap, averaging around $3 per million Btu. Last winter the price hit $14. Furthermore, high demand pushes natural gas prices up for everyone. Although ethanol backers say their fuel is part of a sustainable energy future, using so much natural gas may not be sustainable, even in the present. American production is falling, and Canadian production is not sufficient to match consumption. Ironically, to make "domestic" ethanol, the U.S. will have to increase natural gas imports from outside North America.

As an alternative, some ethanol producers are burning coal, which fits nobody's definition of clean and renewable. Using coal releases so much carbon dioxide that driving a mile on that ethanol is worse for climate change than driving a mile on plain old gasoline. In theory, a distillery could produce heat with electricity purchased from a power company, but for many U.S. utilities, that would mean burning more coal and natural gas to supply the demand.

Ethanol requires other forms of energy, too. The obvious

GEORGE RETSECK



one is diesel fuel for trucks that haul it to market—and it is sometimes a very long haul, because ethanol is not shipped in pipelines like gasoline and diesel are. Pipelines are readily contaminated with water, which does not mix with gasoline or diesel but does bind with ethanol, ruining its fuel value. Diesel fuel also runs the combines that harvest the corn. And the corn is usually fertilized with chemicals made with natural gas.

These considerations are key to the calculation of a "net energy balance" for ethanol. The figure is the subject of lively debate. David Pimentel, a professor of agriculture at Cornell University, asserted in 2005 that it takes more energy to make a gallon of ethanol than the fuel produces when burned. Critics argued he had assigned too little value to by-products, some of which can be fed to livestock (displacing the need to grow some corn), and that he had billed ethanol for extraneous energy costs, including the value of the food eaten by workers at ethanol plants. But the consensus among the analysts is that even if the net energy value of ethanol is positive, the margin is small. That same year a large study by the American Institute of Biological Sciences concluded that ethanol from corn yielded only about 10 percent more energy than was required to produce it. That finding compared with a 370 percent energy yield from sugarcane as harvested in Brazil.

Michael Wang, an environmental scientist at Argonne National Laboratory's Center for Transportation Research, has calculated that making a million Btu of ethanol requires 740,000 Btu of fossil fuels, when considering all the steps in the chain—fertilizing fields, harvesting the corn, distilling its starch into alcohol, and so on. Ethanol is promoted as a farm product, but it is largely a product of fossil fuels.

The greenhouse benefit of ethanol is even smaller. Writing in *Science* in January 2006, Alexander E. Farrell, an assistant professor of energy and resources at the University of California, Berkeley, declared that the effect on greenhouse gases was "ambiguous." After reviewing various studies, Farrell and his co-authors concluded that ethanol made with natural gas is marginally better than gasoline production for global warming pollutants, but ethanol made with coal is worse. Burning

THE AUTHOR

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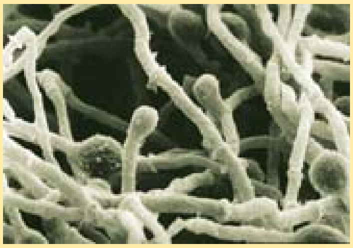
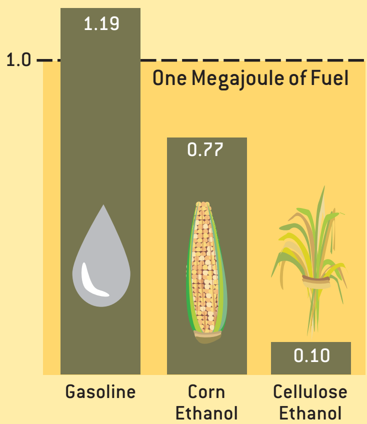
TAKES FUEL TO MAKE FUEL

Vastly different amounts of fossil fuel (natural gas, oil and coal) are burned to produce gasoline and ethanol, considering all the steps from drilling or farming to final delivery. The numbers below are averages derived from six studies by California Institute of Technology researchers.



JUNGLE ROT from Guam (the fungus *Trichoderma reesei*) helps to break down cellulose into sugars that can be readily distilled into ethanol.



Megajoules of Fossil Energy to Produce One Megajoule of Fuel

a gallon of gasoline releases about 20 pounds of carbon dioxide, counting the contributions from the car engine as well as the refinery. The comparable figure for ethanol is a matter of some dispute, but it varies from slightly better to slightly worse, depending on how the ethanol is made. Promoting a switch to ethanol on the basis of limiting emissions of climate-changing gases is deceptive.

Life Cycle or Political Cycle?

UNFORTUNATELY, net energy and pollution considerations may not have played much of a role in the federal government's 2005 setting of a "renewable fuel standard" for 2012 or in giving ethanol a 51-cent-per-gallon tax break. "Congress didn't do a life-cycle analysis; it did an ADM analysis," says one federal official with long-term experience in energy and pollution. He is referring to Archer Daniels Midland, the agricultural products giant, which has for years been a driving force behind ethanol policy.

Life-cycle analysis of fuels does seem to be a new idea to the people who set energy policy. For the first time, instead of assessing the payoff of converting low-value Btu to high-value Btu (such as coal to electricity or crude oil to gasoline) simply on the basis of price, analysts are starting to regard the energy losses and pollution releases along the way.

Whether such assessments will inform policy is another question, however. For example, a broad-based coalition of biofuels, wind and solar power advocates has formed an umbrella group calling itself "25 × '25." They want 25 percent of the nation's energy to come from renewable sources by 2025. Dozens of members of Congress are endorsing the group, yet at a news conference last spring in Washington, D.C., held to introduce the organization, its leaders could not even say whether wind, solar, ethanol or direct combustion of biomass would be the largest source. There was little desire to blemish the concept with arithmetic.

Some of the sudden interest in ethanol is actually an unintended consequence of a failed policy effort to tinker with the recipe for gasoline. In the 1980s some states began requiring certain oxygen levels in gasoline, an ill-advised attempt to make cars burn cleaner. In response, most refiners added methyl tertiary butyl ether (MTBE)—and not ethanol—to gasoline. (Critics said the politicians' hidden motivation was to help farm states by boosting ethanol use.) Over the ensuing years, inspectors found that whenever gasoline leaked into the dirt, MTBE—a possible carcinogen—readily migrated into local drinking water.

In the 2005 Energy Act, Congress eliminated the rule that encouraged MTBE, and refiners dropped the stuff because of potential liability problems. But the refiners needed another high-octane substitute and feared new initiatives calling for oxygen levels, so they rushed to ethanol. American oil refineries also happen to be short on capacity, so adding ethanol would stretch the volume of gasoline they produce, forestalling the need to build costly new plants.

The Stalk, Not the Ear

ONE OTHER fundamental problem plagues the current scheme for ethanol: corn. The crop is in surplus right now, but even that is not nearly enough to quench a significant portion of the country's thirst for fuel.

Pimentel wrote in a letter to Senator John McCain of Arizona in February 2005 that making 3.4 billion gallons of ethanol was consuming about 14 percent of America's corn crop. At that rate, he pointed out, 100 percent of the nation's corn crop would supply only 7 percent of the fuel consumed by its vehicles. Even if the corn crop grew much bigger somehow, U.S. farmers could never grow anywhere near the amount of corn needed to fuel the nation. And critics say any acceleration in agriculture should be used to raise crop exports or feed the world's starving people.

DANIELA NAOMI MOLNAR; SOURCE: CALIFORNIA INSTITUTE OF TECHNOLOGY (*graph*); VTT TECHNICAL RESEARCH CENTER OF FINLAND (*micrograph*)

A solution would be to derive ethanol from cellulose. Cellulose forms the stalk of a corn plant, the straw of grains, and the body of other plants not typically thought of as crops, such as some fast-growing grasses. Much more cellulose exists than corn kernels; according to the Department of Agriculture and others, massive harvesting of cellulose across the nation could generate enough ethanol to replace one third of the gasoline the U.S. consumes.

In energy terms, distilling ethanol from the sugar in cellulose instead of corn is a double play. For corn, the cellulose itself can be thought of as nearly "free"—it takes very little more work to harvest the stalk and requires no extra fertilizer. Farmers say they must plow under some of the stalks, cobs and leaves to reinvigorate the soil but can harvest most of this plant matter. Switchgrass, the favored grass for ethanol, requires minimal fertilizer.

Second, when the sugar is removed the remaining material, lignin, burns well. The North American research leader in cellulose ethanol, Iogen Corporation in Ottawa, Ontario, predicts that when it builds a commercial-scale plant, energy from burning the lignin will provide enough surplus heat to boil water to generate electricity. Rather than robbing food crops to make fuel, cellulose ethanol begins with agricultural waste and ends with two marketable products: transportation fuel and electric power. Net emissions of carbon dioxide per mile driven from cellulose ethanol are near zero—or perhaps below zero, if the co-produced electricity displaces coal or natural gas at a power station. The lignin does give off carbon dioxide when burned, but growing new corn or switchgrass consumes gases. Optimists, including scientists at Iogen, foresee adapting their process to progressively lower-value feedstock, including converting the cellulose in paper such as that used in this magazine (after you have finished reading it).

Problems remain, though. Chief among them is taming one of the natural processes that break down cellulose; the sugars locked in the fiber cannot be distilled into ethanol until they are liberated from the lignin. Bacteria or fungi must produce enzymes to do the job. Those bacteria live in inconvenient locations, such as the underbrush of a distant jungle or the gut of a termite, and they turn out to be harder to domesticate than yeast was. Convincing them to multiply inside the unfamiliar confines of a 2,000-gallon stainless-steel tank is tricky, as is controlling their activity in the industrial-scale quantities needed to sustain conversion to ethanol inside such a space.

Several companies have made their proprietary processes work, but it does not appear that any has done so with enough consistency to persuade lenders. Although they have not been explicit about their technical problems, at a seminar at the House of Representatives last September companies complained that they could not convince a design firm to guarantee to a bank that the finished plant would work.

Certain organisms being tried may improve the odds. Iogen, whose process exploits a fungus from Guam that company scientists refer to as "jungle rot," has tinkered with the organism's DNA so it produces more of the needed enzyme. Other investigators are using enzymes made by mushrooms. Last fall Honda said it might have found a new bug for the job. Agrivida in Cambridge, Mass., is trying to bioengineer corn that contains enzymes that make it break down more readily to ethanol.

If companies can spawn enzymes in sufficient amounts, cellulose ethanol could extensively displace gasoline.

Nevertheless, U.S. Energy Secretary Samuel Bodman said at a September roundtable with reporters that the technology might be commercially viable within five years. More companies should be lured in part by generous government incentives, even though no one seems quite ready to build on a commercial scale.

In the meantime, relying on ethanol from corn is an unsustainable strategy: agriculture will never be able to supply nearly enough crop, converting it does not combat global warming, and socially it can be seen as taking food off people's plates. Backers defend corn ethanol as a bridge technology to cellulose ethanol, but for the moment it is a bridge to nowhere. SA

MORE TO EXPLORE

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25 × '25 Vision on renewable energy: **www.25x25.org/**

The POWER of Riboswitches

Discovering relics from a lost world run by RNA molecules may lead to modern tools for fighting disease

By Jeffrey E. Barrick and Ronald R. Breaker

A mystery surrounding the way bacteria manage their vitamins piqued our interest in the fall of 2000. Together with growing evidence in support of a tantalizing theory about the earliest life on earth and our own efforts to build switches from biological molecules, the bacterial conundrum set our laboratory group at Yale University in search of an answer. What we found was a far bigger revelation than we were expecting: it was a new form of cellular self-control based on one of the oldest types of molecule around—ribonucleic acid, or RNA.

Long viewed as mostly a lowly messenger, RNA could have considerable authority, as it turned out, and sophisticated mechanisms for asserting it. Although the workings of this newfound class of RNA molecules that we dubbed riboswitches are still being characterized, it is already clear that they may also provide novel ways of fighting human diseases. Many pathogenic bacteria rely on riboswitches to control aspects of their own fundamental metabolism, for instance.

That this ancient form of self-regulation persists in modern organisms attests to its importance. Bacterial cells are astonishingly adaptive and self-reliant chemical factories dedicated to making one final product: endless copies of themselves. But only strains that have been able to maintain this hurried chain of descent in the face of cutthroat competition for resources in changing environments have survived this long.

Inventory Control

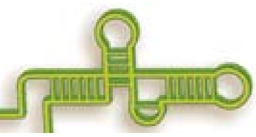
A BACTERIUM'S ABILITY to craft the hundreds of elaborate molecules required to replicate itself in as little as 20 minutes starts with the double-stranded DNA genome that every living organism faithfully copies from generation to generation. This operating manual is written in the four-nucleotide DNA alphabet of the nitrogenous bases adenine, thymine, cytosine and guanine, which are strung onto an alternating sugar-phosphate backbone. As much as 90 percent of the DNA in a typical bacterium is dedicated to coded instructions for assembling the protein machinery that accelerates and organizes the chemical steps of metabolism neces-

SLIM FILMS

sary to build a new cell from scratch.

On the cellular factory floor, that process begins when RNA polymerase enzymes latch onto the genomic DNA and start copying portions of its text into the chemically similar form of messenger RNA (mRNA) molecules. Bacterial cells are in such a hurry that after one polymerase has scarcely begun reading the DNA message and transcribing it, another polymerase is pressing eagerly against it to begin the next mRNA copy. Most messages encode a single protein, although some, known as operons, describe how to make an entire suite of operationally related proteins. RNA is less chemically stable than DNA, and the bacterial cell treats these multiple mRNA transcripts like paper photocopies. Unused mRNAs are rapidly shredded and recycled so that only fresh work orders get distributed to ribosomes, the factory's protein-building machinists.

Ribosomes, too, are in a rush, typically lining up like boxcars of a train to start reading and executing the mRNA instructions even before the polymerase enzyme has completely finished the transcript. They chug along the mRNA track, decoding each successive triplet of nucleotides into a specific amino acid and adding that to a growing chain. As this protein emerges from the ribosome, it wraps around itself into a complicated three-dimensional structure, and a new piece of machinery is now ready to float off and begin work.



These photocopies were folding like possessed origami and CHOOSING THEIR OWN FATES.

The cell relies in particular on two categories of protein to keep its chemical production humming smoothly: transporters, which shuttle raw materials, and enzymes, which accelerate their transformation through successive steps in the dizzying cycles and pathways of metabolism. Bacteria are careful not to waste resources by making superfluous infrastructure, however, so they have evolved control mechanisms that can short-circuit the transfer of work orders for this equipment in response to changes in nutrient needs and availability. Scientists' understanding of how those cellular supervisors function first raised the mystery of vitamin management.

Bacteria typically employ a number of proteins that constantly check the current stocks of various raw materials and adjust the number of transporters and enzymes allocated to different production lines. The Lac repressor in the gut bacterium *Escherichia coli,* for example, is a protein complex that blocks access to DNA blueprints, both for a transporter that pumps the sugar lactose into the cell and for an enzyme that cleaves lactose apart so that it can be used as fuel, until they are needed. When lactose concentration rises above a certain threshold, the Lac complex lets go of the DNA template, allowing transcription of the genes to commence.

A similar regulatory mechanism relies on protein supervisors that decide what to do with mRNA strands as they are being copied from genomic DNA. In the soil bacterium *Bacillus subtilis,* a protein complex with the acronym TRAP controls one operon encoding enzymes for synthesizing the amino acid tryptophan and another describing a tryptophan transporter. When TRAP senses that these proteins are not needed, it wraps the leading end of their mRNA instructions tightly around itself. This prevents a ribosome from recognizing a valid site on the transporter transcript to start translation. Sequestration of its leader causes the synthesis mRNA strand to fold into a hairpin shape, held together by nucleotides binding to one another, that prematurely terminates transcription of the message [*see box on opposite page*].

In addition to such equipment for regulating the manufacture of basic cellular protein machinery, bacteria carry around a large toolbox for making more exotic chemicals. We humans must obtain the nutrients we call vitamins from what we eat, for example, whereas bacteria know how to assemble them from scratch. Many of the more complex vitamins are actually versions of "coenzymes," which, as the name hints, are small molecules that cooperate with protein enzymes. They are specialty tools, akin to pneumatic nail guns and diamond drill bits, with powerful chemical functions. Epic metabolic pathways are involved in constructing coenzymes from raw materials, and naturally thrifty bacteria strictly control this expensive synthesis by shutting it down when coenzymes are not in demand.

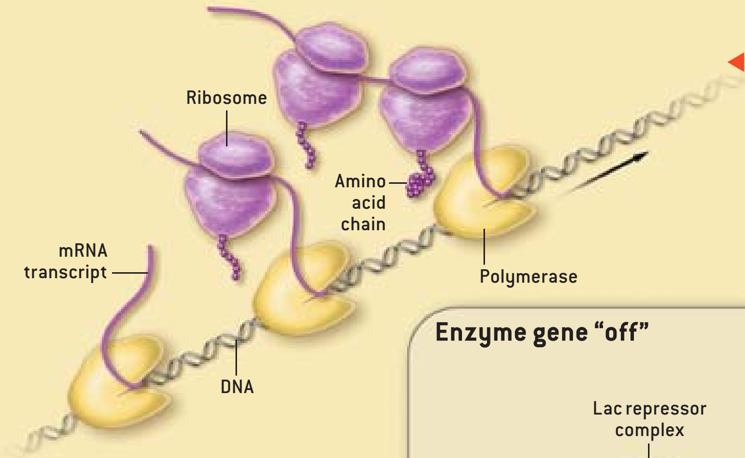
By the late 1990s scientists investigating exactly how manufacture of certain coenzymes was regulated in bacteria recognized a molecular pattern reminiscent of the TRAP and Lac repressor

Overview/*Flipping Ancient Switches*

- Regulation of gene activity in cells is usually the job of protein supervisors, but certain bacteria employ RNA messengers to oversee some valuable cellular infrastructure.
- Forms of RNA with proteinlike powers lend support to the idea of a primordial world ruled by RNA.
- Newly discovered riboswitches are a group of RNA molecules that carry messages transcribed from DNA while also making supervisory decisions about whether those instructions should be executed.
- Riboswitches regulate many fundamental processes in microbes, making them potential targets for new antimicrobial drugs.

PROTEIN SUPERVISORS IN THE CELLULAR FACTORY

To coordinate and optimize manufacture of the parts bacteria need to survive and replicate, the cells typically employ protein supervisors. These can repress production of equipment until they sense it is needed and the raw materials for making it are available. Knowledge of their mechanisms helped to reveal the existence of riboswitches.

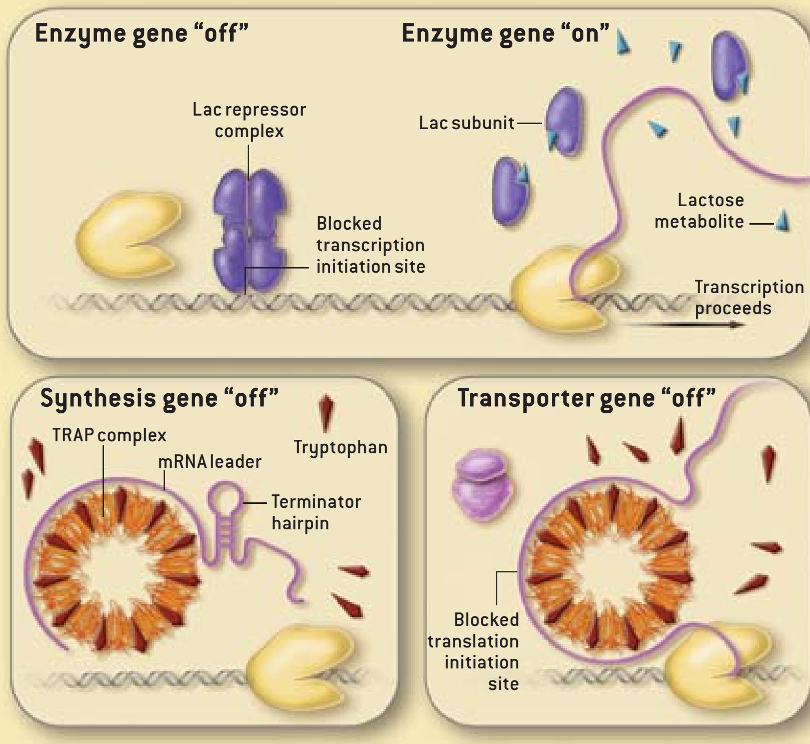


THE FACTORY FLOOR
Fast-moving assembly lines turn out cellular equipment based on instructions encoded in DNA genes (*left*). Polymerase enzymes move along the DNA strand, transcribing a gene into a messenger RNA (mRNA) copy. Ribosomes latch onto the mRNA as it emerges and begin translating its message into an amino acid chain that will fold itself into a finished protein.

INVENTORY MANAGEMENT
Supervisor proteins regulate a bacterium's manufacture of basic parts through a variety of mechanisms (*right*).

The Lac repressor complex (*top*) turns "off" a gene encoding a lactose-cleaving enzyme by blocking polymerase from accessing the DNA when lactose is absent. When lactose is high, one of its metabolites binds to clefts in Lac subunits, causing them to let go of the DNA and turning the gene "on."

A TRAP complex regulates genes involved in the synthesis and transport of the amino acid tryptophan by interfering with their mRNA copies in two ways. When tryptophan is present, TRAP wraps the leading end of a tryptophan-synthesis mRNA around itself, causing part of the message strand to assume a hairpin shape that prematurely terminates transcription (*bottom left*). TRAP also sequesters the leader of mRNA for a tryptophan transporter, blocking ribosomes from accessing a translation initiation site (*bottom right*).



systems. Yet as their attempts to identify the supervisory proteins responsible for sensing each coenzyme and controlling mRNA transcription or translation in response drew a blank, a deepening mystery emerged: if not through hypothetical protein supervisors, how was the cell's machinery measuring the levels of these nutrients? The unexpected answer arose from the work of researchers studying apparently unrelated applications for RNA molecules. To understand how, one must briefly revisit the ribosome.

RNA World Legacy

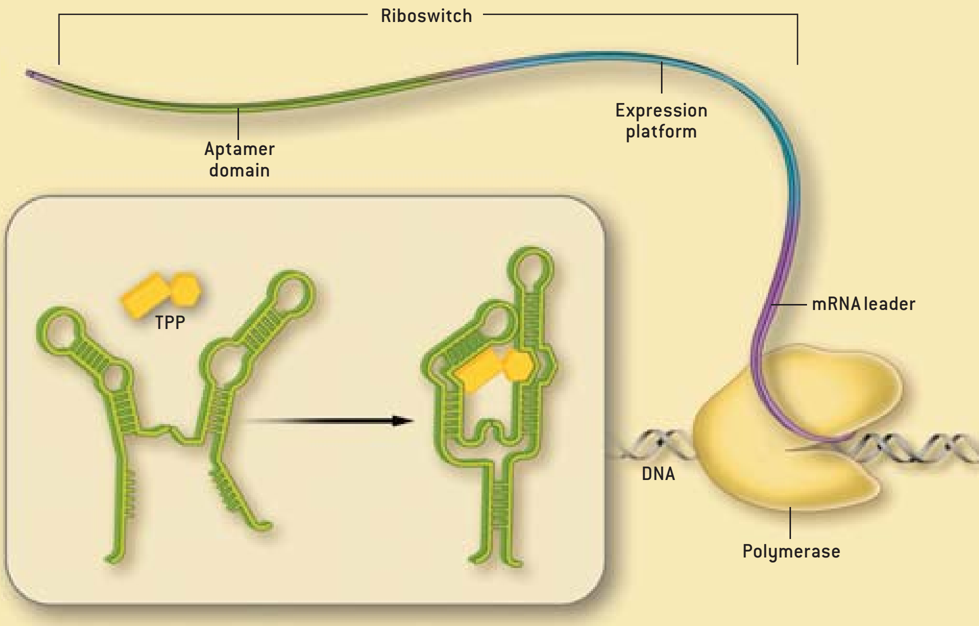
PROTEINS MAY BE the wheels, cogs, chutes and conveyor belts that transport and transform raw materials into new cells, but not all of the factory's essential equipment is made of protein. Most notably, the ribosome has a core consisting of the very same nucleotides that make up the mRNA messages it reads. But although ribosomal RNA (rRNA) starts out as a ticker-tape transcript of a DNA blueprint, unlike mRNA it contains no instructions for making something else. Instead the rRNA immediately crumples itself into a defined shape, within which certain nucleotide bases bind to one another, much like a terminator hairpin.

Ribosomal RNA folds on a much grander scale, involving several subunits that are further hardened in places by subtle chemical modifications. Protein staples and struts reinforce its crevices and coat its surface. But atomic-resolution structure studies have revealed that the core of the ribosome, responsible for catalyzing the formation of new bonds between amino acids, is made exclusively of RNA.

TAMI TOLPA

SELF-DETERMINING SWITCHES

A newfound form of cellular regulation relies on certain RNA copies of genes to supervise themselves. Riboswitches are segments within the leading end of a messenger RNA transcript that are able to gauge the cell's need for the protein encoded by the rest of their message, then rearrange their own shape to control whether that protein is manufactured. Riboswitches therefore have two important domains: an aptamer that senses a specific metabolite (*below*) and an expression platform that affects the mRNA's fate by undergoing one of many possible structural reconfigurations (*right*).



METABOLITE SENSING
An aptamer for the coenzyme thiamine pyrophosphate (TPP) assumes a defined shape (*left*) as it exits the polymerase. When TPP is present, the aptamer binds to it, grasping the molecule tightly (*right*).

TAMI TOLPA

This recent confirmation of an RNA structure with the powers of a protein catalyst was exciting to anyone familiar with a theory about early life advanced in the late 1970s by Harold White III of the University of Delaware. He had observed that many important coenzymes have curious RNA components within their chemical structures. Adenosylcobalamin (coenzyme B_{12}), for example, contains an entire RNA nucleotide, and thiamine pyrophosphate (coenzyme B_1) carries around a piece of sugar-phosphate backbone. These nucleotide bits seem to act as handles for proteins to grasp, and White theorized that they could be vestigial traces from a primordial time when protocells had not yet evolved modern DNA storage or protein synthesis. Instead RNA performed double duty as the information storage molecule and the biopolymer capable of folding into metabolic machines and performing the complex work that today is generally the province of proteins.

By the early 1980s two "living" examples of such ancient RNA elements had been discovered. One of them, RNase P, is an RNA molecule in bacteria that is able to cleave raw RNA transcripts. Another breakthrough identified fascinating RNA sequences that edit themselves out of a longer mRNA transcript, achieving their self-cleavages through a series of chemical bond exchanges. Sidney Altman of Yale University and Thomas R. Cech of the University of Colorado at Boulder received the 1989 Nobel Prize in Chemistry for these separate findings, which demonstrated that RNA molecules—previously seen as only passive messages—could fold into complex three-dimensional structures and accelerate chemical reactions, just like protein enzymes. Collectively, such RNA enzymes, including ribosomes, are termed ribozymes.

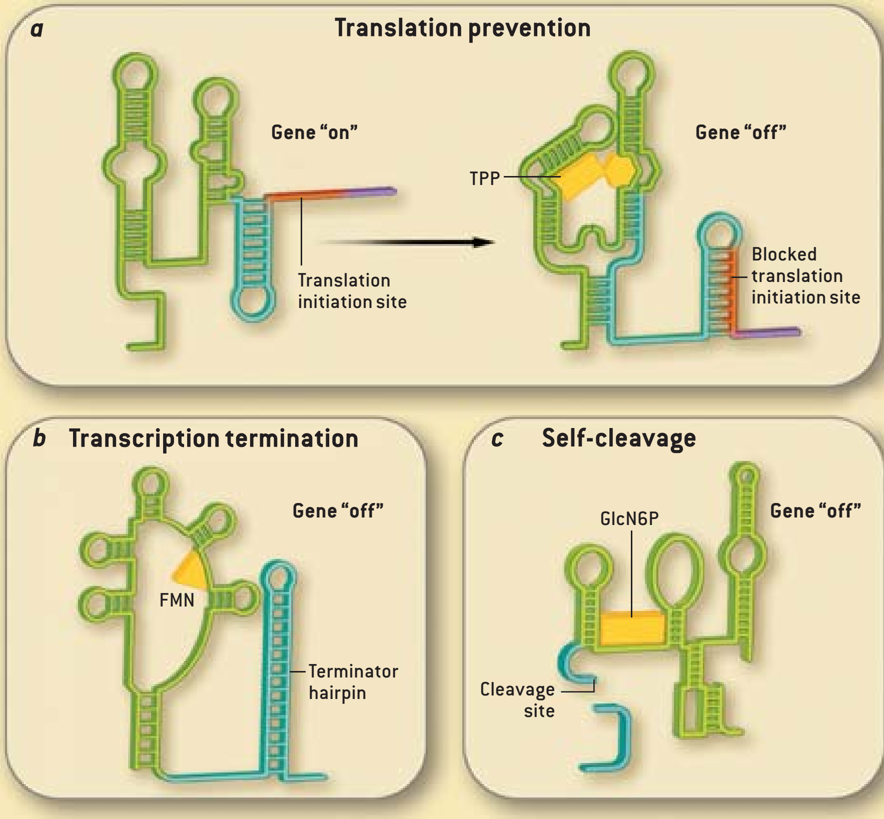
In the early 1990s research tools for manipulating biomolecules outside of living cells had matured enough for investigators to experiment with creative uses of RNA's newfound ability to fold itself into complex and functional shapes. In part, scientists were seeking to test the versatility of RNA and thus the plausibility of the "RNA world" hypothesis; they were also looking for new biotechnology applications for ribozymes. Our own group's participation in these pursuits is what eventually led us to look beyond proteins for the mysterious regulators of bacterial coenzyme production.

Natural Sensors

THE LABORATORIES of Larry Gold at U.C. Boulder, Gerald Joyce of the Scripps Research Institute and Jack W. Szostak of Massachusetts General Hospital developed a method of test-tube evolution that enabled them to subject trillions of synthetic RNA sequences to a Darwinian test that the "fittest" molecules would pass. Using this test-tube evolution, Szostak's group quickly discovered a variety of short RNA structures that could bind tightly to adenosine triphosphate (ATP), as well as many organic dyes, amino acids and antibiotics.

Szostak christened all these RNA molecules born in laboratories "aptamers," a term derived from the Latin *aptus*, meaning "fitted." And despite their unnatural origins, many aptamers possessed a quality that is more important in a biological context than just binding their target molecule tightly: they reject molecules with closely related structures.

Our laboratory set out to exploit this high selectivity by designing a sensor made of RNA. The plan was to create an aptamer capable of recognizing a target molecule by binding to it and to join



RIBOSWITCH RESPONSES
Riboswitches employ a variety of strategies to control protein manufacture. When TPP is absent, for example, the expression platform can leave a translation initiation site open to ribosomes, allowing expression of the gene's instructions to remain "on" (*a, left*). When TPP is bound by the aptamer, the expression platform can form a hairpin that blocks translation, turning the gene "off" (*a, right*). A riboswitch sensing the coenzyme flavin mononucleotide (FMN) forms a terminator hairpin that halts transcription of its message by polymerase (*b*). An unusual ribozyme triggered by glucosamine-6-phosphate (GlcN6P) self-destructs by cleaving itself (*c*).

that to a second RNA segment that could signal the event with a visible readout. For the latter role, we chose the "hammerhead" ribozyme. Named for its distinctive-looking structure, it is one of the simplest and most effective natural self-cleaving ribozymes known. We could, for example, attach a fluorescent tag to one end of the hammerhead strand and a so-called quencher group that dampens the fluorescence in close proximity to each other within the RNA's folded structure. Once the aptamer end of our apparatus found and bound the target molecule, self-cleavage by the hammerhead would separate the quencher group from the fluorescent tag, and the molecule would light up as if a lampshade had been removed.

RNA proved so adept at this sensor function that we were later able to develop aptamer-coupled ribozymes capable of sensing and reporting the presence of a wide variety of molecules. Our collection of sensors could be arrayed on a tiny chip and used to accurately detect many different chemical compounds simultaneously, even in a complicated mixture.

Indeed, the ease with which we could create RNAs that sensed small molecules and transduced that binding into a purposeful rearrangement of their own structures made us wonder whether natural evolution had created similar RNAs. Ribozymes from the RNA world were clearly still performing critical tasks in modern organisms. Might there be undiscovered sequences for other important RNA machines hiding in modern genomes?

We started scouring the scientific literature for hints pointing to natural aptamers and found only tantalizing references to noncoding RNA sequences known to be somehow important for cellular regulation. Then our search brought us to the mystery of bacteria and their vitamins. We came across mentions of a protein, BtuB, which is a part of the apparatus for importing coenzyme B_{12} into the *E. coli* bacterium. The mRNA transcript that encodes the BtuB protein begins with a massive leader of 240 noncoding nucleotides, and its extraordinary length was our first clue that it might have an unusual function. Another research group had also already shown that production of BtuB protein was inhibited when B_{12} concentrations in the cell were high. Yet no protein sentry that sensed B_{12} had been discovered.

From the previously published work of others, we knew that the presence of B_{12} somehow prevented ribosomes from binding to BtuB mRNA. One experiment had also hinted that some kind of structural change in the mRNA leader sequence was occurring in the presence of B_{12}. Could it be that the long BtuB RNA leader contained a natural B_{12}-binding aptamer that acted to regulate expression of the instructions encoded in its own gene?

We used a technique called in-line probing to map the parts of the BtuB RNA message that were becoming more structured or more flexible in the pres-

THE AUTHORS

JEFFREY E. BARRICK and *RONALD R. BREAKER* investigated the diversity and importance of riboswitches together in Breaker's laboratory at Yale University. Barrick is now a postdoctoral fellow at Michigan State University, where he is studying the evolution of bacteria as well as self-replicating computer programs. Breaker's group is continuing to explore the nature and uses of nucleic acids, in part by creating designer gene-control elements made of RNA and developing antibiotics to target natural riboswitches.

ence of B_{12} and found, most notably, that a new twist was formed near the beginning of the BtuB mRNA coding region. This structure could explain the inhibition of ribosome binding. The RNA itself seemed to be sensing B_{12} and regulating its transport in the same manner that TRAP regulates the tryptophan transporter message in *B. subtilis*—by preventing the ribosome from translating it. We therefore named this RNA molecule that was able to toggle gene expression from on to off a "riboswitch."

As we were investigating the BtuB leader, another case of unexplained regulation also caught our attention. Previous research had determined that the mRNAs encoding synthesis enzymes and transporters for coenzyme B_1 in diverse groups of bacteria all contained a common stretch of RNA sequence and that mutations in this sequence disrupted the normal repression of these genes in cells that had accumulated sufficient B_1. In *E. coli,* the mRNA of an operon for two synthesis enzymes has a leader containing the sequence near the site where translation of the first protein starts. We were able to show that B_1 induced a structural change in this mRNA such that the ribosome binding site was tightly zippered up. We then determined that a smaller 91-nucleotide domain within the leader could bind to B_1. Like our artificial sensors, this natural riboswitch consisted of a separate aptamer domain linked to a functional "response" sequence that allowed it to regulate whether B_1 would be produced.

Thus, we had found at least two messenger RNAs with the remarkable ability to monitor cellular conditions and make their own decisions about whether the protein machines they encoded were necessary, without intervention by protein supervisors. These paper photocopies were not passive messages; they were folding like possessed origami and choosing their own fates. And those two proved to be more than curiosities. Natural RNA switches that responded to a variety of other fundamental cellular metabolites were latent in the scientific literature and quickly identified by members of our labs and other research groups.

A sequence common to relatives of *B. subtilis* turned out to be a riboswitch that recognizes the coenzyme *S*-adenosylmethionine (SAM). An RNA element known to occur in messages directing the synthesis and transport of the coenzyme flavin mononucleotide (B_2) was another riboswitch. A section of mRNA thought to encode a protein monitor for lysine in *E. coli* was in fact a piece of a complex lysine aptamer that regulated synthesis of this amino acid in a broad range of bacteria. Riboswitches were a widespread form of genetic control.

Reverse-Engineering Riboswitches

A DOZEN CLASSES of riboswitches, defined by their aptamer structures, have been identified so far, and although they vary in certain features and mechanisms, a few general principles have emerged. Riboswitches are messenger RNA transcripts capable of regulating their own gene's expression by controlling whether the message they contain is translated into a protein or destroyed without ever being read by a ribosome. The riboswitch makes this call by monitoring the cell's need for the protein it encodes through its ability to sense a target metabolite and then altering its own structural configuration in response. A riboswitch thus contains two important segments: its metabolite-sensing aptamer domain and its regulatory "expression platform" sequence.

The aptamer serves as a complex receptor for one specific small-molecule metabolite, and in all members of a class the core aptamer structure is the same, even in evolutionarily distant organisms. Riboswitch expression platforms, which can include part of the aptamer domain, contain the sequences that rearrange their own structure to affect gene expression [*see box on pages 54 and 55*]. The B_{12} and B_1 riboswitches we first discovered both have expression

Tempting Targets

Many bacteria, including the human pathogens listed here, employ riboswitches to control the activity of their own genes. Agents that trigger those riboswitches might therefore serve as new antibiotics, particularly if the drugs disrupt the function of genes essential to an organism's virulence or survival. The number of riboswitch classes found in each organism and the number of genes known to be regulated by riboswitches are shown below. Asterisks indicate that at least one vital gene is regulated by a riboswitch.

Human Bacterial Pathogen	Riboswitch Classes	Genes Regulated
Acinetobacter baumannii	4	6
Bacillus anthracis	9	82
Brucella melitensis	5	21*
Enterococcus faecalis	7	17
Escherichia coli	4	15*
Francisella tularensis	4	8
Hemophilius influenzae	5	15*
Helicobacter pylori	1	2
Listeria monocytogenes	9	49
Mycobacterium tuberculosis	3	13
Pseudomonas aeruginosa	3	27
Salmonella enterica	3	34*
Staphylococcus aureus	8	30*
Streptococcus pneumoniae	5	19
Vibrio cholerae	5	13
Yersinia pestis	3	11

SOURCE: KENNETH F. BLOUNT AND RONALD R. BREAKER *Yale University*

platforms that prevent translation initiation by configuring themselves to hide sequences the ribosome needs to recognize a valid work order, for example. Other instances of riboswitches containing these same aptamers have expression platforms that cause premature termination of mRNA transcription by forming a terminator hairpin.

As our group learned more about riboswitches, we began to appreciate how carefully evolution has balanced the gears and springs that animate their mechanisms. For example, metabolite recognition in the cells must occur within the mere seconds that it takes polymerase to stream out an mRNA leader and ribosomes to bind to it and begin translation. Thus, the speed of metabolite binding, not necessarily the strength, is critical for determining whether a riboswitch can sense its target. Timing sequences between the aptamer and expression platform, which cause polymerase to briefly stall, are sometimes necessary to introduce delays that give the aptamer enough time to capture a metabolite and properly rearrange its expression platform.

When we started scanning bacterial genomes looking for new examples of riboswitches, we found still more surprises. In the *B. subtilis* genome alone, we identified eight new sequences with the hallmarks of riboswitches. One of these was a riboswitch with a double aptamer that acted to turn gene expression on rather than off. Another, as it turned out, was not just a riboswitch but a metabolite-triggered ribozyme. Rather than undergoing a structural reconfiguration, this molecule's expression platform self-cleaved—in essence, self-destructing before its message could be translated.

Just one of the riboswitch classes discovered to date has been seen in multicellular organisms; the rest, as far as we know, are found only in bacteria. The genomes of higher organisms have more complicated genetic regulation than bacteria, and the route from blueprints to protein is also more circuitous. Instead of tidy mRNA photocopies, first-draft gene transcripts often have huge chunks of noncoding text, known as introns, which must be spliced out before the message is translated into protein. We found a riboswitch on the cutting-room floor.

The coenzyme B_1 aptamer occurs in the sequences of introns within thiamine synthesis operons in many fungi and plants, including rice. When bound to B_1, these riboswitches appear to cause the RNA structure around the intron junctions to be rearranged, preventing splicing from proceeding. Although the details are not clear, this may target the entire message for the rubbish bin or prevent it from being moved to the correct part of the cell to be translated.

Intriguingly, a known antifungal drug has also been found to bind the B_1 riboswitch. Evidence suggests that it thereby tricks a fungus into thinking that it has enough B_1, repressing synthesis of more. Because the fungus does not actually have this important nutrient, its growth is slowed and eventually it can die from the deficiency. As this example illustrates, riboswitches are such vital regulators of critical nutrient supplies in a range of microbes that they also make tempting targets for new antibiotics.

More than a dozen human pathogens are now known to rely on riboswitch regulation of several important metabolites [*see box on opposite page*]. Many researchers are working to find molecules that can fool bacterial riboswitch aptamers into mistaking them for a natural metabolite and thereby trigger a gene regulatory response that would be deleterious to the cells.

Some research groups are also exploring the idea of using artificial riboswitches to control genes inside living cells—for example, in the context of gene therapy. The goal is to design an on-off switch triggered by a benign druglike molecule and incorporate that into a therapeutic gene. The construct could then be inserted into a patient's cells and regulated by having the person take a pill containing the molecule that activates the designer riboswitch. As with antibiotic applications, this use of riboswitches is still in early stages of investigation.

The general feeling of surprise and excitement that was inspired by ribozymes and the efforts to apply those ancient molecules to modern uses is renewed by the very existence of riboswitches. Only bits and pieces of the lost RNA world seem to be with us today, but these RNA devices with complex mechanisms and regulatory roles have tenaciously hung on in modern organisms. We cannot help but wonder whether riboswitches are the last vestiges of the RNA world that will be revealed or if other primordial molecules are still employed by the metabolic factories or administrative offices in modern cells—perhaps even our own human cells—and awaiting discovery. SA

Only bits and pieces of the LOST RNA WORLD seem to be with us today.

MORE TO EXPLORE

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A ROBOT IN EVERY HOME

The leader of the PC revolution predicts that the next hot field will be robotics

By Bill Gates

Imagine being present at the birth of a new industry. It is an industry based on groundbreaking new technologies, wherein a handful of well-established corporations sell highly specialized devices for business use and a fast-growing number of start-up companies produce innovative toys, gadgets for hobbyists and other interesting niche products. But it is also a highly fragmented industry with few common standards or platforms. Projects are complex, progress is slow, and practical applications are relatively rare. In fact, for all the excitement and promise, no one can say with any certainty when—or even if—this industry will achieve critical mass. If it does, though, it may well change the world.

Of course, the paragraph above could be a description of the computer industry during the mid-1970s, around the time that Paul Allen and I launched Microsoft. Back then, big, expensive mainframe computers ran the back-office operations for major companies, governmental departments and other institutions. Researchers at leading universities and industrial laboratories were creating the basic building blocks that would make the information age possible. Intel had just introduced the 8080 microprocessor, and Atari was selling the popular electronic game Pong. At homegrown computer clubs, enthusiasts struggled to figure out exactly what this new technology was good for.

But what I really have in mind is something much more contemporary: the emergence of the robotics industry, which is developing

AMERICAN ROBOTIC: Although a few of the domestic robots of tomorrow may resemble the anthropomorphic machines of science fiction, a greater number are likely to be mobile peripheral devices that perform specific household tasks.


GRANT
WOOD

in much the same way that the computer business did 30 years ago. Think of the manufacturing robots currently used on automobile assembly lines as the equivalent of yesterday's mainframes. The industry's niche products include robotic arms that perform surgery, surveillance robots deployed in Iraq and Afghanistan that dispose of roadside bombs, and domestic robots that vacuum the floor. Electronics companies have made robotic toys that can imitate people or dogs or dinosaurs, and hobbyists are anxious to get their hands on the latest version of the Lego robotics system.

Meanwhile some of the world's best minds are trying to solve the toughest problems of robotics, such as visual recognition, navigation and machine learning. And they are succeeding. At the 2004 Defense Advanced Research Projects Agency (DARPA) Grand Challenge, a competition to produce the first robotic vehicle capable of navigating autonomously over a rugged 142-mile course through the Mojave Desert, the top competitor managed to travel just 7.4 miles before breaking down. In 2005, though, five vehicles covered the complete distance, and the race's winner did it at an average speed of 19.1 miles an hour. (In another intriguing parallel between the robotics and computer industries, DARPA also funded the work that led to the creation of Arpanet, the precursor to the Internet.)

What is more, the challenges facing the robotics industry are similar to those we tackled in computing three decades ago. Robotics companies have no standard operating software that could allow popular application programs to run in a variety of devices. The standardization of robotic processors and other hardware is limited, and very little of the programming code used in one machine can be applied to another. Whenever somebody wants to build a new robot, they usually have to start from square one.

Despite these difficulties, when I talk to people involved in robotics—from university researchers to entrepreneurs, hobbyists and high school students—the level of excitement and expectation reminds me so much of that time when Paul Allen and I looked at the convergence of new technologies and

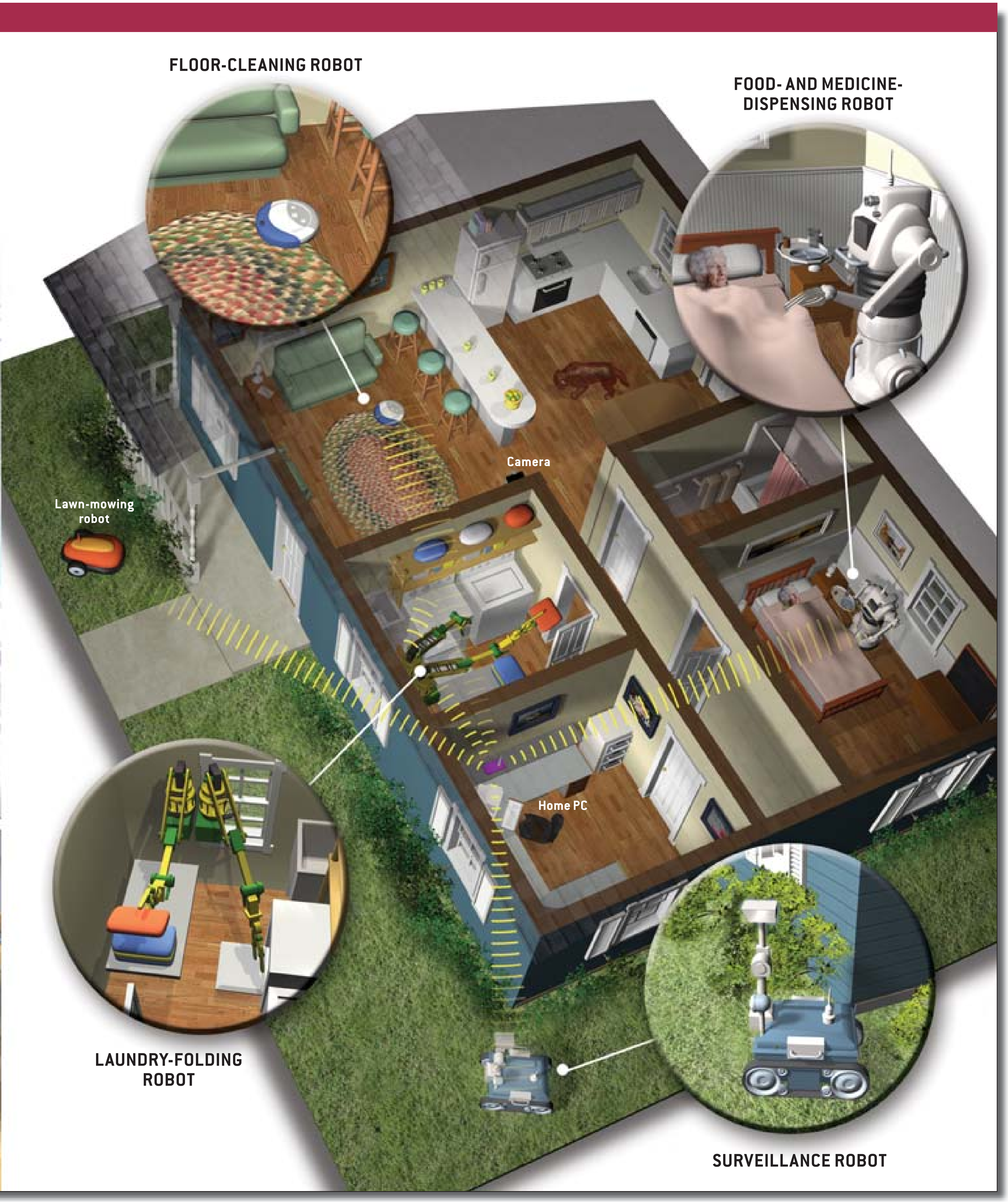
THE ROBOT AND THE PC CAN BE FRIENDS

Linking domestic robots to PCs could provide many benefits. An office worker, for example, could keep tabs on the security of his home, the cleaning of his floors, the folding of his laundry, and the care of his bedridden mother by monitoring a network of household robots on his desktop PC. The machines could communicate wirelessly with one another and with a home PC.

DON FOLEY

Overview/*The Robotic Future*

- The robotics industry faces many of the same challenges that the personal computer business faced 30 years ago. Because of a lack of common standards and platforms, designers usually have to start from scratch when building their machines.
- Another challenge is enabling robots to quickly sense and react to their environments. Recent decreases in the cost of processing power and sensors are allowing researchers to tackle these problems.
- Robot builders can also take advantage of new software tools that make it easier to write programs that work with different kinds of hardware. Networks of wireless robots can tap into the power of desktop PCs to handle tasks such as visual recognition and navigation.


FLOOR-CLEANING ROBOT
FOOD- AND MEDICINE-DISPENSING ROBOT
Camera
Lawn-mowing robot
Home PC
LAUNDRY-FOLDING ROBOT
SURVEILLANCE ROBOT

dreamed of the day when a computer would be on every desk and in every home. And as I look at the trends that are now starting to converge, I can envision a future in which robotic devices will become a nearly ubiquitous part of our day-to-day lives. I believe that technologies such as distributed computing, voice and visual recognition, and wireless broadband connectivity will open the door to a new generation of autonomous devices that enable computers to perform tasks in the physical world on our behalf. We may be on the verge of a new era, when the PC will get up off the desktop and allow us to see, hear, touch and manipulate objects in places where we are not physically present.

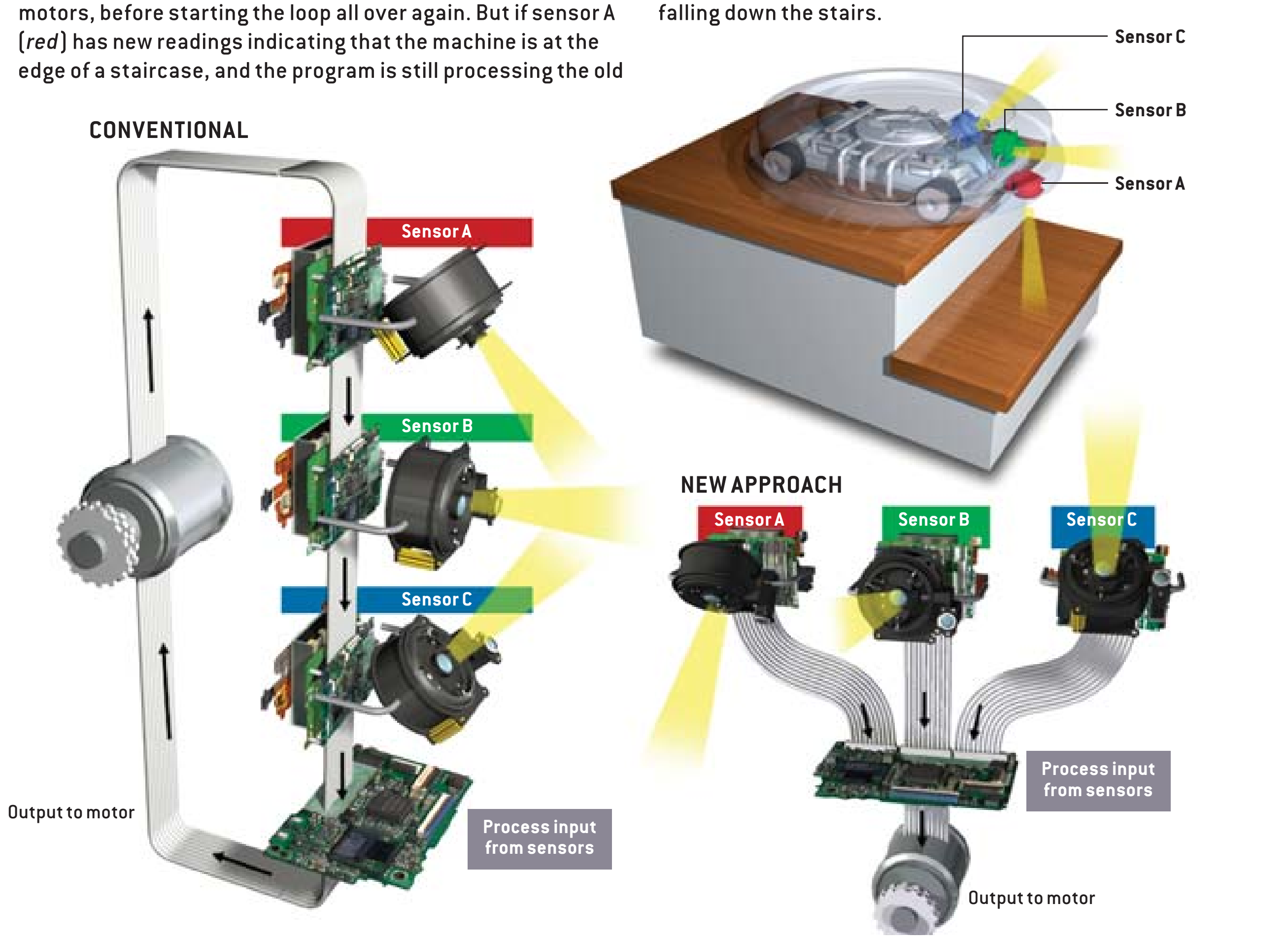
From Science Fiction to Reality

THE WORD "ROBOT" was popularized in 1921 by Czech playwright Karel Čapek, but people have envisioned creating robotlike devices for thousands of years. In Greek and Roman mythology, the gods of metalwork built mechanical servants made from gold. In the first century A.D., Heron of Alexandria—the great engineer credited with inventing the first steam engine—designed intriguing automatons, including one said to have the ability to talk. Leonardo da Vinci's 1495 sketch of a mechanical knight, which could sit up and move its arms and legs, is considered to be the first plan for a humanoid robot.

Over the past century, anthropomorphic machines have become familiar figures in popular culture through books such as Isaac Asimov's *I, Robot*, movies such as *Star Wars* and television shows such as *Star Trek*. The popularity of robots in fiction indicates that people are receptive to the idea that these machines will one day walk among us as helpers and even as companions. Nevertheless, although robots play a vital role in industries such as automobile manufacturing—where there is about one robot for every 10 workers—the fact

BETTER PROGRAMMING MEANS FEWER TUMBLES

Handling data from multiple sensors—for example, the three infrared sensors pictured on the robot at the right—can pose a dilemma. Under the conventional approach (*below*), the program first reads the data from all the sensors, then processes the input and delivers commands to the robot's motors, before starting the loop all over again. But if sensor A (*red*) has new readings indicating that the machine is at the edge of a staircase, and the program is still processing the old sensor data, the robot may take a nasty fall. A better approach to dealing with this problem of concurrency is to write a program with separate data paths for each sensor (*bottom right*). In this design, new readings are processed immediately, enabling the robot to hit the brakes before falling down the stairs.



DON FOLEY

is that we have a long way to go before real robots catch up with their science-fiction counterparts.

One reason for this gap is that it has been much harder than expected to enable computers and robots to sense their surrounding environment and to react quickly and accurately. It has proved extremely difficult to give robots the capabilities that humans take for granted—for example, the abilities to orient themselves with respect to the objects in a room, to respond to sounds and interpret speech, and to grasp objects of varying sizes, textures and fragility. Even something as simple as telling the difference between an open door and a window can be devilishly tricky for a robot.

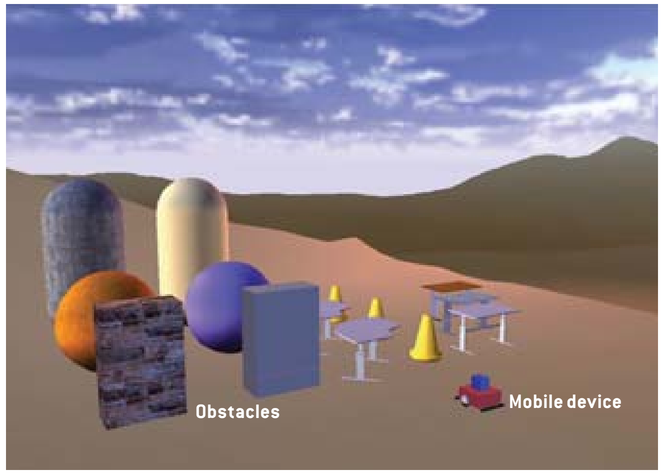
But researchers are starting to find the answers. One trend that has helped them is the increasing availability of tremendous amounts of computer power. One megahertz of processing power, which cost more than $7,000 in 1970, can now be purchased for just pennies. The price of a megabit of storage has seen a similar decline. The access to cheap computing power has permitted scientists to work on many of the hard problems that are fundamental to making robots practical. Today, for example, voice-recognition programs can identify words quite well, but a far greater challenge will be building machines that can understand what those words mean in context. As computing capacity continues to expand, robot designers will have the processing power they need to tackle issues of ever greater complexity.

Another barrier to the development of robots has been the high cost of hardware, such as sensors that enable a robot to determine the distance to an object as well as motors and servos that allow the robot to manipulate an object with both strength and delicacy. But prices are dropping fast. Laser range finders that are used in robotics to measure distance with precision cost about $10,000 a few years ago; today they can be purchased for about $2,000. And new, more accurate sensors based on ultrawideband radar are available for even less.

Now robot builders can also add Global Positioning System chips, video cameras, array microphones (which are better than conventional microphones at distinguishing a voice from background noise) and a host of additional sensors for a reasonable expense. The resulting enhancement of capabilities, combined with expanded processing power and storage, allows today's robots to do things such as vacuum a room or help to defuse a roadside bomb—tasks that would have been impossible for commercially produced machines just a few years ago.

A BASIC Approach

IN FEBRUARY 2004 I visited a number of leading universities, including Carnegie Mellon University, the Massachusetts Institute of Technology, Harvard University, Cornell University and the University of Illinois, to talk about the powerful role that computers can play in solving some of society's most pressing problems. My goal was to help students understand how exciting and important computer science can be, and I hoped to encourage a few of them to think about careers in technology. At each university, after delivering my speech, I had the opportunity to get a firsthand look at some of the most interesting research projects in the school's computer science department. Almost without exception, I was shown at least one project that involved robotics.



COMPUTER TEST-DRIVE of a mobile device in a three-dimensional virtual environment helps robot builders analyze and adjust the capabilities of their designs before trying them out in the real world. Part of the Microsoft Robotics Studio software development kit, this tool simulates the effects of forces such as gravity and friction.

At that time, my colleagues at Microsoft were also hearing from people in academia and at commercial robotics firms who wondered if our company was doing any work in robotics that might help them with their own development efforts. We were not, so we decided to take a closer look. I asked Tandy Trower, a member of my strategic staff and a 25-year Microsoft veteran, to go on an extended fact-finding mission and to speak with people across the robotics community. What he found was universal enthusiasm for the potential of robotics, along with an industry-wide desire for tools that would make development easier. "Many see the robotics industry at a technological turning point where a move to PC architecture makes more and more sense," Tandy wrote in his report to me after his fact-finding mission. "As Red Whittaker, leader of [Carnegie Mellon's] entry in the DARPA Grand Challenge, recently indicated, the hardware capability is mostly there; now the issue is getting the software right."

Back in the early days of the personal computer, we realized that we needed an ingredient that would allow all of the pioneering work to achieve critical mass, to coalesce into a

THE AUTHOR

BILL GATES is co-founder and chairman of Microsoft, the world's largest software company. While attending Harvard University in the 1970s, Gates developed a version of the programming language BASIC for the first microcomputer, the MITS Altair. In his junior year, Gates left Harvard to devote his energies to Microsoft, the company he had begun in 1975 with his childhood friend Paul Allen. In 2000 Gates and his wife, Melinda, established the Bill & Melinda Gates Foundation, which focuses on improving health, reducing poverty and increasing access to technology around the world.

BIRTH OF AN INDUSTRY: Robot makers have so far introduced a variety of useful machines, but the designs are wildly different. Stanley (*above*), an autonomous vehicle built by the Stanford Racing Team, won the 2005 DARPA Grand Challenge, traversing more than 130 miles of desert without the aid of a human driver. iRobot, a company based in Burlington, Mass., manufactures the Packbot EOD (*opposite page*), which assists with bomb disposal in Iraq, as well as the Roomba (*right*), which vacuums hardwood floors and carpets. And Lego Mindstorms (*this page, far right*), a tool set for building and programming robots, has become the best-selling product in the history of the Lego Group, the Danish toy maker.

real industry capable of producing truly useful products on a commercial scale. What was needed, it turned out, was Microsoft BASIC. When we created this programming language in the 1970s, we provided the common foundation that enabled programs developed for one set of hardware to run on another. BASIC also made computer programming much easier, which brought more and more people into the industry. Although a great many individuals made essential contributions to the development of the personal computer, Microsoft BASIC was one of the key catalysts for the software and hardware innovations that made the PC revolution possible.

After reading Tandy's report, it seemed clear to me that before the robotics industry could make the same kind of quantum leap that the PC industry made 30 years ago, it, too, needed to find that missing ingredient. So I asked him to assemble a small team that would work with people in the robotics field to create a set of programming tools that would provide the essential plumbing so that anybody interested in robots with even the most basic understanding of computer programming could easily write robotic applications that would work with different kinds of hardware. The goal was to see if it was possible to provide the same kind of common, low-level foundation for integrating hardware and software into robot designs that Microsoft BASIC provided for computer programmers.

Tandy's robotics group has been able to draw on a number of advanced technologies developed by a team working under the direction of Craig Mundie, Microsoft's chief research and strategy officer. One such technology will help solve one of the most difficult problems facing robot designers: how to simultaneously handle all the data coming in from multiple sensors and send the appropriate commands to the robot's motors, a challenge known as concurrency. A conventional approach is to write a traditional, single-threaded program—a long loop that first reads all the data from the sensors, then processes this input and finally delivers output that determines the robot's behavior, before starting the loop all over again. The shortcomings are obvious: if your robot has fresh sensor data indicating that the machine is at the edge of a precipice, but the program is still at the bottom of the loop calculating trajectory and telling the wheels to turn faster based on previous sensor input, there is a good chance the robot will fall down the stairs before it can process the new information.

Concurrency is a challenge that extends beyond robotics. Today as more and more applications are written for distributed networks of computers, programmers have struggled to figure out how to efficiently orchestrate code running on many different servers at the same time. And as computers with a single processor are replaced by machines with multiple processors and "multicore" processors—integrated circuits with two or more processors joined together for enhanced performance—software designers will need a new way to program desktop applications and operating systems. To fully exploit the power of processors working in parallel, the new software must deal with the problem of concurrency.

One approach to handling concurrency is to write multithreaded programs that allow data to travel along many paths. But as any developer who has written multithreaded code can tell you, this is one of the hardest tasks in programming. The answer that Craig's team has devised to the concurrency problem is something called the concurrency and coordination runtime (CCR). The CCR is a library of functions—sequences of software code that perform specific tasks—that makes it easy

GENE BLEVINS *L.A. Daily News/Corbis* (*Stanley*); ©2006 iROBOT CORPORATION (*Packbot EOD* and *Roomba*); ©2004 THE LEGO GROUP (*Lego Mindstorms*)

to write multithreaded applications that can coordinate a number of simultaneous activities. Designed to help programmers take advantage of the power of multicore and multiprocessor systems, the CCR turns out to be ideal for robotics as well. By drawing on this library to write their programs, robot designers can dramatically reduce the chances that one of their creations will run into a wall because its software is too busy sending output to its wheels to read input from its sensors.

In addition to tackling the problem of concurrency, the work that Craig's team has done will also simplify the writing of distributed robotic applications through a technology called decentralized software services (DSS). DSS enables developers to create applications in which the services—the parts of the program that read a sensor, say, or control a motor—operate as separate processes that can be orchestrated in much the same way that text, images and information from several servers are aggregated on a Web page. Because DSS allows software components to run in isolation from one another, if an individual component of a robot fails, it can be shut down and restarted—or even replaced—without having to reboot the machine. Combined with broadband wireless technology, this architecture makes it easy to monitor and adjust a robot from a remote location using a Web browser.

What is more, a DSS application controlling a robotic device does not have to reside entirely on the robot itself but can be distributed across more than one computer. As a result, the robot can be a relatively inexpensive device that delegates complex processing tasks to the high-performance hardware found on today's home PCs. I believe this advance will pave the way for an entirely new class of robots that are essentially mobile, wireless peripheral devices that tap into the power of desktop PCs to handle processing-intensive tasks such as visual recognition and navigation. And because these devices can be networked together, we can expect to see the emergence of groups of robots that can work in concert to achieve goals such as mapping the seafloor or planting crops.

These technologies are a key part of Microsoft Robotics Studio, a new software development kit built by Tandy's team. Microsoft Robotics Studio also includes tools that make it easier to create robotic applications using a wide range of programming languages. One example is a simulation tool that lets robot builders test their applications in a three-dimensional virtual environment before trying them out in the real world. Our goal for this release is to create an affordable, open platform that allows robot developers to readily integrate hardware and software into their designs.

Should We Call Them Robots?

HOW SOON WILL ROBOTS become part of our day-to-day lives? According to the International Federation of Robotics, about two million personal robots were in use around the world in 2004, and another seven million will be installed by 2008. In South Korea the Ministry of Information and Communication hopes to put a robot in every home there by 2013. The Japanese Robot Association predicts that by 2025, the personal robot industry will be worth more than $50 billion a year worldwide, compared with about $5 billion today.

As with the PC industry in the 1970s, it is impossible to predict exactly what applications will drive this new industry. It seems quite likely, however, that robots will play an important role in providing physical assistance and even companionship for the elderly. Robotic devices will probably help people with disabilities get around and extend the strength and endurance of soldiers, construction workers and medical professionals. Robots will maintain dangerous industrial machines, handle hazardous materials and monitor remote oil pipelines. They will enable health care workers to diagnose and treat patients who may be thousands of miles away, and they will be a central feature of security systems and search-and-rescue operations.

Although a few of the robots of tomorrow may resemble the anthropomorphic devices seen in *Star Wars,* most will look nothing like the humanoid C-3PO. In fact, as mobile peripheral devices become more and more common, it may be increasingly difficult to say exactly what a robot is. Because the new machines will be so specialized and ubiquitous—and look so little like the two-legged automatons of science fiction—we probably will not even call them robots. But as these devices become affordable to consumers, they could have just as profound an impact on the way we work, communicate, learn and entertain ourselves as the PC has had over the past 30 years. SA

MORE TO EXPLORE

More information about robotics in general is available at:

Center for Innovative Robotics: **www.cir.ri.cmu.edu**

DARPA Grand Challenge: **www.darpa.mil/grandchallenge/**

International Federation of Robotics: **www.ifr.org**

The Robotics Alliance Project: **www.robotics.nasa.gov**

Robotics Industries Association: **www.roboticsonline.com**

The Robotics Institute: **www.ri.cmu.edu**

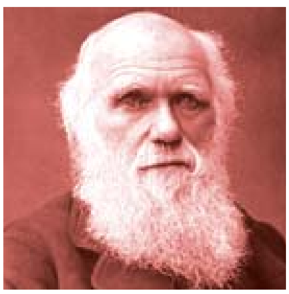
The Tech Museum: Robotics: **www.thetech.org/robotics/**

Technical details and other information about Microsoft Robotics Studio can be found at **msdn.microsoft.com/robotics**

EVOLVED FOR CANCER?

BY CARL ZIMMER

Natural selection lacks the power to erase cancer from our species and, some scientists argue, may even have provided tools that help tumors grow



Charles Darwin, 1881

RICHARD MILNER ARCHIVES

NATURAL SELECTION IS NOT NATURAL PERFECTION. Living creatures have evolved some remarkably complex adaptations, but we are still very vulnerable to disease. Among the most tragic of those ills—and perhaps most enigmatic—is cancer. A cancerous tumor is exquisitely well adapted for survival in its own grotesque way. Its cells continue to divide long after ordinary cells would stop. They destroy surrounding tissues to make room for themselves, and they trick the body into supplying them with energy to grow even larger. But the tumors that afflict us are not foreign parasites that have acquired sophisticated strategies for attacking our bodies. They are made of our own cells, turned against us. Nor is cancer some bizarre rarity: a woman in the U.S. has a 39 percent chance of being diagnosed with some type of cancer in her lifetime. A man has a 45 percent chance.

These facts make cancer a grim yet fascinating puzzle for evolutionary biologists. If natural selection is powerful enough to produce complex adaptations, from the eye to the immune system, why has it been unable to wipe out cancer? The answer, these investigators argue, lies in the evolutionary process itself. Natural selection has favored certain defenses against cancer but cannot eliminate it altogether. Ironically, natural selection may even inadvertently provide some of the tools that cancer cells can use to grow.

NATURAL SELECTION HAS FAVORED CERTAIN DEFENSES AGAINST CANCER BUT CANNOT ELIMINATE IT ALTOGETHER.

The study of cancer evolution is still in its infancy, with much debate about the mechanisms involved and much testing of hypotheses left to carry out. Some medical researchers remain skeptical that the work will affect the way they fight the disease. Evolutionary biologists agree that they are not about to discover a cure for cancer, but they argue that understanding cancer's history could reveal clues that would otherwise remain hidden. "Obviously, we always have that in the back of our minds in everything we do," says Judith Campisi of Lawrence Berkeley National Laboratory.

The Dawn of Cancer

AT ITS ROOT, cancer is a disease of multicellularity. Our single-celled ancestors reproduced by dividing in two. After animals emerged, about 700 million years ago, the cells inside their bodies continued to reproduce by dividing, using the molecular machinery they inherited from their progenitors. The cells also began to specialize as they divided, forming different tissues. The complex, multicellular bodies animals have today were made possible by the emergence of new genes that could control how cells divided—such as by stopping the cells' reproduction once an organ reached its adult size. The millions of animal species are evidence of the great evolutionary success that came with acquiring a body. But bodies also present a profound risk. Whenever a cell inside a body divides, its DNA has a small chance of acquiring a cancer-causing mutation. "Every time a cell divides, it's going to be at risk of developing into cancer," Campisi says.

Rare mutations, for instance, may cause a cell to lose restraint and begin to multiply uncontrollably. Other mutations can add to the problem: They may allow deranged cells to invade surrounding tissues and spread through the body. Or they may allow tumor cells to evade the immune system or attract blood vessels that can supply fresh oxygen.

Cancer, in other words, re-creates within our own bodies the evolutionary process that enables animals to adapt to their environment. At the level of organisms, natural selection operates when genetic mutations cause some organisms to have more reproductive success than others; the mutations get "selected" in the sense that they persist and become more common in future generations. In cancer, cells play the role of organisms. Cancer-causing changes to DNA cause some cells to reproduce more effectively than ordinary ones. And even within a single tumor, more adapted cells may outcompete less successful ones. "It's like Darwinian evolution, except that it happens within one organ," explains Natalia Komarova of the University of California, Irvine.

Limits to Defenses

ALTHOUGH OUR BODIES may be vulnerable to cancer, they also have many ways to halt it. These strategies probably resulted from natural selection, because mutations that made our ancestors less likely to die of cancer in their prime could have raised their reproductive success. But given the many millions of people who get cancer every year, it is obvious that these defenses have not eradicated the disease. By studying the evolution of these defenses, biologists are trying to understand why they fall short.

Tumor suppressor proteins are among the most effective defenses against cancer. Studies suggest that some of these proteins prevent cancer by monitoring how a cell reproduces. If the cell multiplies in an abnormal way, the proteins induce it to die or to slip into senescence, a kind of early retirement. The cell survives, but it can no longer divide. Tumor sup-

Overview/*Cancer Evolution*

- Natural selection has only a limited ability to prevent cancer. It has provided some defenses, but these tend to delay the disease until late in life rather than eliminating it entirely.
- In addition, evolutionary forces have apparently favored some genes that can contribute to cancer's development or aggressiveness.
- An understanding of cancer's evolutionary history—and how individual tumors evolve in the body—could suggest fresh angles of attack on the disorder.

pressor proteins play a vital role in our survival, but scientists have recently discovered something strange about them: in some respects, we would be better off without them.

Norman E. Sharpless of the University of North Carolina at Chapel Hill genetically engineered mice to study the effect of one of these proteins, called p16 (or, more properly, p16-Ink4a). He and his colleagues created a line of mice that lacked a functional gene for p16 and thus could not produce the protein. In September 2006 the group published three studies on the mice. As expected, the animals were more prone to cancer, which could arise when they were only a year old.

But losing the p16 gene had an upside. When the mice got old, their cells still behaved as if they were young. In one experiment, the scientists studied older mice, some of which had working p16 genes and some of which did not. They destroyed insulin-producing cells in the pancreases of the animals. The normal rodents could no longer produce insulin and developed fatal diabetes. But the ones without the p16 protein developed only mild diabetes and survived. The progenitors of their insulin-producing cells could still multiply quickly, and they repopulated the pancreas with new cells. The scientists found similar results when they examined cells in the blood and brains of the mice: p16 protected them against cancer but also made them old.

These results support a hypothesis Campisi has developed over the past few years. Natural selection favors anticancer proteins such as p16, but only in moderation. If these proteins become too aggressive, they can create their own threats to health by making bodies age too quickly. "It's still a working hypothesis," Campisi admits, "but the data are looking stronger and stronger."

Delaying the Inevitable

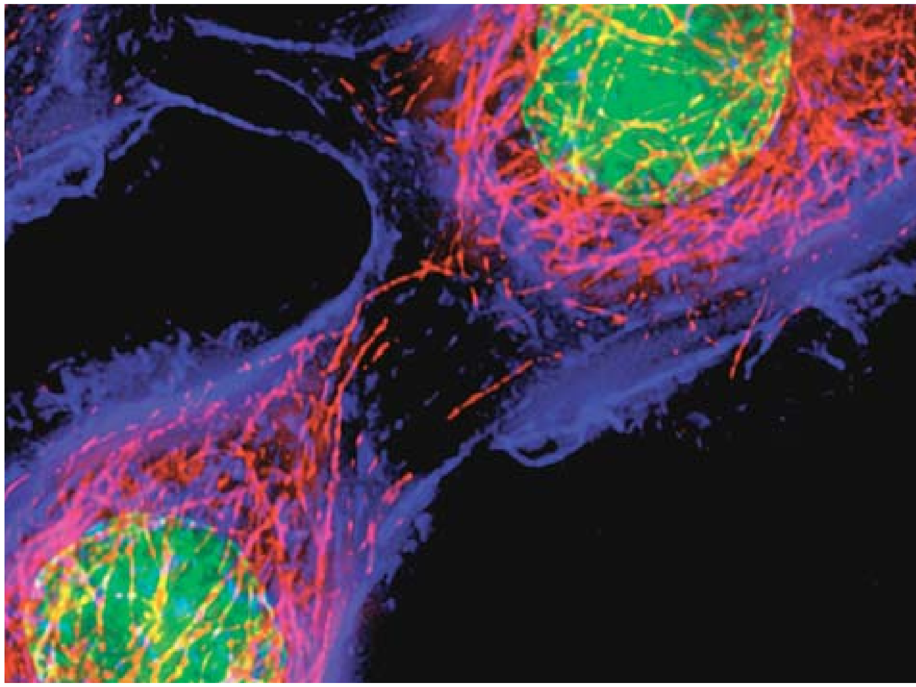
A DEFENSE AGAINST CANCER does not have to eradicate the disease completely to be favored by natural selection. If it can just delay tumors until old age, it may allow people to have more children, on average, than others who lack the defense. It may seem cruel for evolution to stick old people with cancer, but as Jarle Breivik of the University of Oslo points out, "natural selection does not favor genes because they let us live long and happy lives. They are selected for their ability to propagate their information through the generations."

Anticancer proteins such as p16 may favor the young over the old. When p16 pushes a cell into senescence, the cell does not just stop multiplying. It also begins producing an odd balance of proteins. Among the proteins it makes is vascular endothelial growth factor (VEGF), which triggers the growth of more blood vessels. VEGF fosters the growth of tumors by supplying them with extra nutrients. In young people, p16's main effect may be to suppress cancerous cells. But over time, it may create a growing population of senescent cells, which could make people more vulnerable to cancer in old age.

Another way to delay cancer is to set up several lines of defense. Studies on colon cancer, for example, show that cells in the colon must acquire mutations to several genes before they turn cancerous. These defense lines do not prevent people from getting colon cancer—in fact, it is the third most common form of the disease. But the need for multiple mutations to occur in a cell may reduce the chances that colon cancer will arise in young individuals. The average age of people diagnosed with colon cancer is 70.

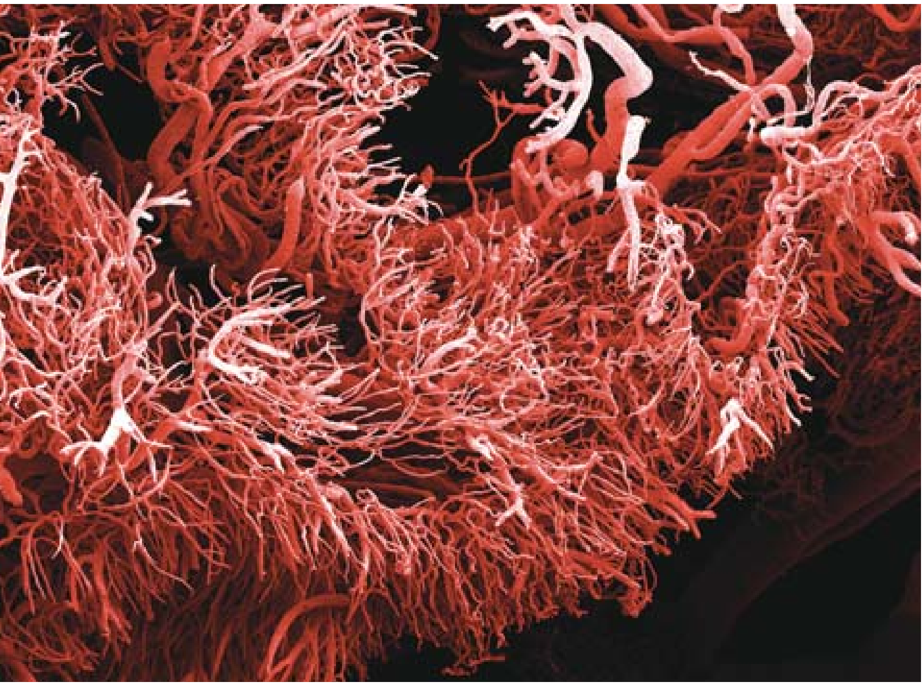
Not all cancers strike the old, of course. Most victims of a cancer of the retina called retinoblastoma, for example, are children. But Leonard Nunney of the University of California, Riverside, argues that evolution is responsible for that difference between the

Cell in the final stage of division



PAUL ANDREWS *University of Dundee/Photo Researchers, Inc.*

"EVERY TIME A CELL DIVIDES, IT'S GOING TO BE AT RISK OF DEVELOPING INTO CANCER."
—Judith Campisi



Resin cast of blood vessels in a tumor

THE ABILITY TO STIMULATE NEW BLOOD VESSEL FORMATION SERVES A TUMOR JUST AS IT DOES A PLACENTA.

two cancers. Nunney points out that colon cells have many more opportunities for acquiring dangerous mutations than retinal cells do. The colon is a large organ made of many cells, which continue replicating throughout a person's life as old cells slough off and new ones take their place. That risk puts a big evolutionary premium on defenses that can prevent colon cells from turning cancerous.

The retina, on the other hand, is "the smallest bit of tissue you can imagine," as Nunney puts it. That small set of retinal cells also stops multiplying by the time a child turns five. With fewer cell divisions occurring, the retina has far fewer opportunities to turn cancerous. As a result, retinoblastoma is extremely rare, striking only four people in a million. Because the risk is so much lower, Nunney argues, natural selection cannot drive the spread of new defenses against retinoblastoma. A defense against cancer in the retina would make very little difference to the average reproductive success of a population.

Making Tools for Tumors

RECENT RESEARCH SUGGESTS that natural selection may have altered genes in ways that make cancer cells more dangerous. Evolutionary biologists discovered this disturbing possibility as they searched for the changes that have made us uniquely human. After our ancestors diverged from other apes about six million years ago, they experienced natural selection as they adapted to a new way of life as a toolmaking, savanna-walking hominid. Scientists can distinguish between genes that have not changed significantly since the origin of hominids and those that have undergone major alteration as a result of selection pressures. It turns out that among the genes that have changed most dramatically are some that play important roles in cancer.

Scientists suspect that the adaptive advantages brought by these genes outweigh the harm they may cause. One of these highly evolved cancer genes makes a protein called fatty acid synthase (FAS). Normal cells use the protein encoded by this gene to make some of their fatty acids, which are used for many functions, such as building membranes and storing energy. In tumors, however, cancer cells produce FAS protein at a much higher rate. The protein is so important to them that blocking the activity of the gene can kill cancer cells. By comparing the sequence of the FAS gene in humans and other mammals, Mary J. O'Connell of Dublin City University and James McInerney of the National University of Ireland found that the gene has undergone strong natural selection in humans. "This gene has really changed in our lineage," McInerney says.

McInerney cannot say what FAS does differently in humans, but he is intrigued by a hypothesis put forward by the late psychiatrist David Horrobin in the 1990s. Horrobin argued that the dramatic increase in the size and power of the human brain was made possible by the advent of new kinds of fatty acids. Neurons need fatty acids to build membranes and make connections. "One of the things that might allow a larger brain size was our ability to synthesize fats," McInerney speculates. But with that new ability may have come a new tool that cancer cells could borrow for their own ends. Cancer cells may, for

THE AUTHOR

CARL ZIMMER writes frequently about evolution for the *New York Times*, *National Geographic* and other publications. He is the author of five books, including *Parasite Rex* and *Soul Made Flesh*. He is now working on a book about *Escherichia coli* and the meaning of life. His blog, The Loom (www.scienceblogs.com/loom), is a winner of *Scientific American*'s Science and Technology Web Awards. Zimmer wrote about the neurobiology of the self in the November 2005 issue of *Scientific American*.

CLOUDS HILL IMAGING LTD. *Photo Researchers, Inc.*

example, use FAS as an extra source of energy.

Many fast-evolving cancer genes normally produce proteins in tissues involved in reproduction—in the placenta, for example. Bernard Crespi of Simon Fraser University in British Columbia and Kyle Summers of East Carolina University argue that these genes are part of an evolutionary struggle between children and their mothers.

Natural selection favors genes that allow children to draw as much nourishment from their mothers as possible. A fetus produces the placenta, which grows aggressively into the mother's tissue and extracts nutrients. That demand puts the fetus in conflict with its mother. Natural selection also favors genes that allow mothers to give birth to healthy children. If a mother sacrifices too much in the pregnancy of one child, she may be less likely to have healthy children afterward. So mothers produce compounds that slow down the flow of nutrients into the fetus.

Each time mothers evolve new strategies to restrain their fetuses, natural selection favors mutations that allow the fetuses to overcome those strategies. "It's a restrained conflict. There's a tug-of-war about how much the fetus is going to take from the mother," Crespi says.

Genes that allow cells to build a better placenta, Crespi and Summers argue, can get hijacked by cancer cells—turned on when they would normally be silent. The ability to stimulate new blood vessel formation and aggressive growth serves a tumor just as it does a placenta. "It's something naturally liable to be co-opted by cancer cell lineages," Summers says. "It sets up the opportunity for mutations to create tools for cancer cells to use to take over the body."

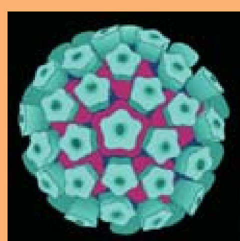
Yet even though activation of these usually quiet genes may make cancers more potent, natural selection may still have favored them because they helped fetuses grow. "You may get selection for a gene variant that helps the fetus get a little more from mom," Crespi says. "But then, when that kid is 60, it might increase the odds of cancer by a few percent. It's still going to be selected for because of the strong positive early effects."

Sperm are another kind of cell that multiplies rapidly. But whereas placental cells proliferate for a few months, sperm-making cells function for a lifetime. "For decades, human males are producing an enormous amount of sperm all the time," says Andrew Simpson of the Ludwig Institute for Cancer Research in New York City. Genes that operate specifically in such cells are also among the fastest evolving in the human genome. A gene that allows a progenitor sperm cell to divide faster than other cells will become more common in a man's population of sperm. That means it will be more likely to get into a fertilized egg and be passed down to future generations.

Evolution of a Cancer-Causing Virus

The American Cancer Society estimates that 17 percent of all cancer cases—more than 1.8 million a year—are caused by viruses and other infectious agents. Scientists are studying the evolution of these cancer-causing pathogens to find hints for fighting them. One such pathogen is the human papillomavirus, responsible for most of the half a million cases of cervical cancer diagnosed annually. The virus can cause host cells to divide long after normal cells would stop and also prevents them from repairing mutations to their DNA.

Scientists have reconstructed some of the virus's evolutionary history by sequencing and comparing the genomes of hundreds of different types of viruses. Papillomaviruses, which form a large family, are found in most vertebrates, in whom they typically engender only warts and other benign growths. Yet when *Homo sapiens* first emerged—about 200,000 years ago in Africa—our ancestors already carried a number of strains that could infect our species and no other animal, and these included cancer-causing types.



HUMAN PAPILLOMAVIRUS is shown in a computer-generated rendering.

LINDA M. STANNARD *University of Cape Town/Photo Researchers, Inc.*

After about 100,000 years, *H. sapiens* expanded out of Africa to other continents, bringing the viruses with them. As human populations became isolated from one another, their papillomaviruses did as well. Consequently, the genealogy of human papillomaviruses reflects human genealogy. The oldest lineage of the viruses is most common in living Africans, for example. Native Americans descended from Asians, and their viruses share that kinship.

This coevolution may be medically relevant, because the viruses appear to have adapted to their hosts. In August 2006 scientists published a report in the *Journal of the National Cancer Institute* on the persistence of various virus types in different ethnic groups. A woman who becomes infected by a virus having an ancient association with her ethnic group will carry the virus for a longer time than if she were infected by another type.

Scientists are also investigating how certain benign papillomaviruses evolved to cause cancer. Their discoveries will become all the more important as vaccines are introduced against the viruses. The FDA has approved a vaccine against the most dangerous human papillomavirus strain, known as H16. But evolutionary studies indicate that on rare occasions, human papillomavirus types have traded genes involved in triggering cancer. The global HIV epidemic might raise the risk of this gene swapping. As HIV weakens a person's immune system, more types of human papillomaviruses can invade and coexist. This mingling could conceivably give rise to a new cancer-causing strain for which today's vaccines would be less protective. *—C.Z.*

Unfortunately for us, genes that make for fast-breeding sperm cells can make for fast-breeding cancer cells. Normally, nonsperm cells prevent these genes from making proteins. "These are genes that need to be firmly silenced, because they are dangerous genes," Simpson says. It appears that in cancer cells, mutations can unlock these sperm genes, allowing the cells to multiply quickly.

How vs. Why

EVOLUTIONARY BIOLOGISTS hope that their research can help in the fight against cancer. In addition to clarifying why evolution has not eradicated cancer, evolutionary biology may shed light on one of the most daunting challenges faced by oncologists: the emergence of drug-resistant tumors.

Chemotherapy drugs often lose their effectiveness against cancer cells. The process has many parallels to the evolution of resistance to antiviral drugs in HIV. Mutations that allow cancer cells to survive exposure to chemotherapy drugs enable the tumor cells to outcompete more vulnerable cells. Understanding the evolution of HIV and other pathogens has helped scientists to come up with new strategies for avoiding resistance. Now scientists are investigating how understanding the evolution within tumors could lead to better ways of using chemotherapy.

The concepts evolutionary biologists have been exploring are relatively new for most cancer biologists. Some are reacting with great enthusiasm. Simpson believes, for instance, that deciphering the rapid evolution of sperm-related genes could help in the fight against tumors that borrow them. "I think it's absolutely crucial to understand exactly why there is such strong selection on these genes," Simpson says. "Understanding that will give us a real insight into cancer."

Bert Vogelstein of the Howard Hughes Medical Institute also finds it useful to view cancer through an evolutionary lens. "Thinking about cancer in evolutionary terms jibes perfectly with the views of cancer molecular geneticists," he says. "In one sense, cancer is a side effect of evolution."

But Vogelstein is not yet persuaded by the significance of fast-evolving cancer genes. "One has to be a little cautious. The first question I would ask is, Are they looking at the whole genome in a wholly unbiased way?" McInerney acknowledges that such systematic studies have not yet been conducted, but the early results have prompted him and other scientists to begin them.

Some cancer specialists are leery of the entire approach. Christopher Benz of the Buck Institute for Age Research says that any insights from evolution should not be accepted until they are put to an experimental test the way any other hypothesis would be. "Call me skeptical," he says.

Crespi is familiar with this skepticism, and he thinks that it may emerge from the different kinds of questions evolutionary biologists and cancer biologists ask. "The peo-

The Surprising History of a Dog Cancer

A canine cancer called Sticker's sarcoma can be transmitted both through sex and by licking or touching a tumor. Once established in a new host, it can produce tumors that grow to the size of grapefruits before gradually disappearing. Many scientists once thought that the disease, like cervical cancer, was spread by viruses. Now they know that the cancer cells themselves move from dog to dog and have been spreading this way for centuries.

A team of scientists from University College London and the University of Chicago recently analyzed the genes of Sticker's sarcoma cells collected from dogs around the world. They found that the tumors are much more genetically similar to one another than they are to the dogs in which they grew. Additional research confirmed that the tumors belong to a single lineage of cancer cells.

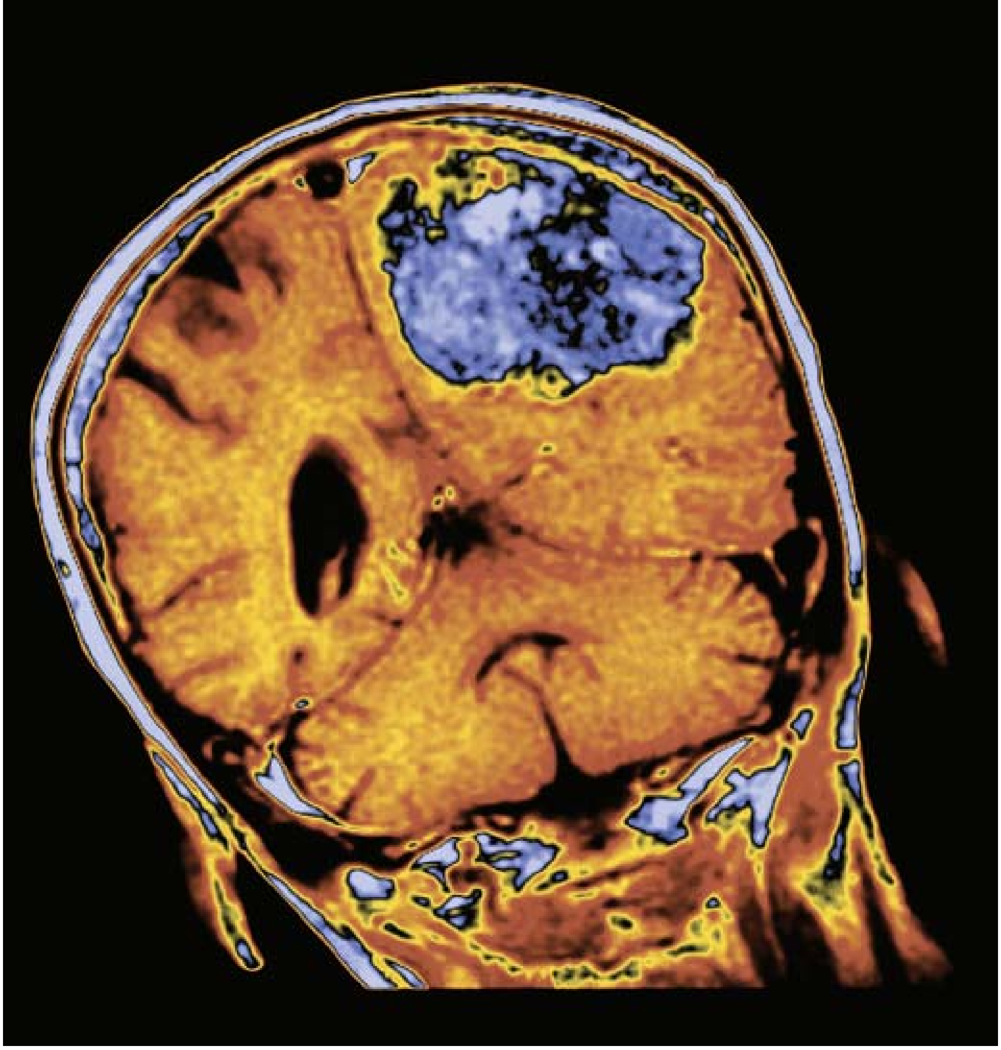
"It represents the evolution of a cancer cell into a successful parasite of worldwide distribution," the scientists wrote last year in the journal *Cell*.

Investigators have identified only a few other possible examples of parasitic cancer. Tasmanian devils, for example, can spread a facial tumor by biting one another. Why aren't there more parasitic cancers? Organ transplantation may offer a clue. One of the biggest dangers in organ transplantation is rejection, in which a patient's immune system violently attacks the organ. All vertebrates reject grafts of foreign tissue with this kind of ferocity. It is possible that this rejection response evolved hundreds of millions of years ago as a defense against parasitic cancers.

Sticker's sarcoma appears to have evolved its way around this ancient defense. The cells in the tumor make very few of the surface proteins that vertebrates use to distinguish self from nonself—allowing them to evade an all-out attack from the dog's immune system. Instead the immune system erodes the tumor slowly over the course of several months, and individual cancer cells can survive even after the tumor is gone. Rather than being just an ordinary cancer that dies with its host, it has become a cancer that can live for centuries. —*C.Z.*

SOME HUSKY might have started the spread of Sticker's sarcoma cells among dogs hundreds of years ago.

DANIEL BOSCHUNG *zefa/Corbis*



Large brain tumor, highlighted in blue

ple working on cancer are working on the how question, and the evolution people are working on the why," he says.

Perhaps by asking different questions, evolutionary biologists will be able to contribute to some of the debates among cancer biologists. One long-standing argument focuses on whether mice are good models for cancer in humans. Some evolutionary biologists argue that they are not, because of their separate history. Rodents inherited the same set of genes as we did from our common ancestor some 100 million years ago, but then many of those genes underwent more change in the two lineages. Cancer-related genes such as FAS may have experienced intense evolutionary change in humans in just the past few million years, making them significantly different from their counterparts in mice.

Mice may also be a poor choice for a cancer model because of the way they reproduce. Scientists have bred lab mice to produce more pups at a faster rate than their wild cousins. Such manipulation may have altered the evolutionary trade-off faced by mice, so that they are rewarded for investing energy into growing quickly and reproducing young. At the same time, this artificial selection may be selecting against cancer defenses. "We have changed their life histories by selecting on their timing of reproduction," Crespi says.

Ultimately, the study of the evolution of cancer may reveal why eradicating the disease has proved so difficult. "There is no real solution to the problem," Breivik says. "Cancer is a fundamental consequence of the way we are made. We are temporary colonies made by our genes to propagate them to the next generation. The ultimate solution to cancer is that we would have to start reproducing ourselves in a different way." SA

ULTIMATELY, STUDY OF THE EVOLUTION OF CANCER MAY REVEAL WHY ERADICATING THE DISEASE HAS PROVED SO DIFFICULT.

MORE TO EXPLORE

Evolutionary Biology of Cancer. Bernard J. Crespi and Kyle Summers in *Trends in Ecology and Evolution,* Vol. 20, pages 545–552; 2005.

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Positive Selection in the Evolution of Cancer. Bernard J. Crespi and Kyle Summers in *Biological Reviews,* Vol. 81, pages 407–424; 2006.

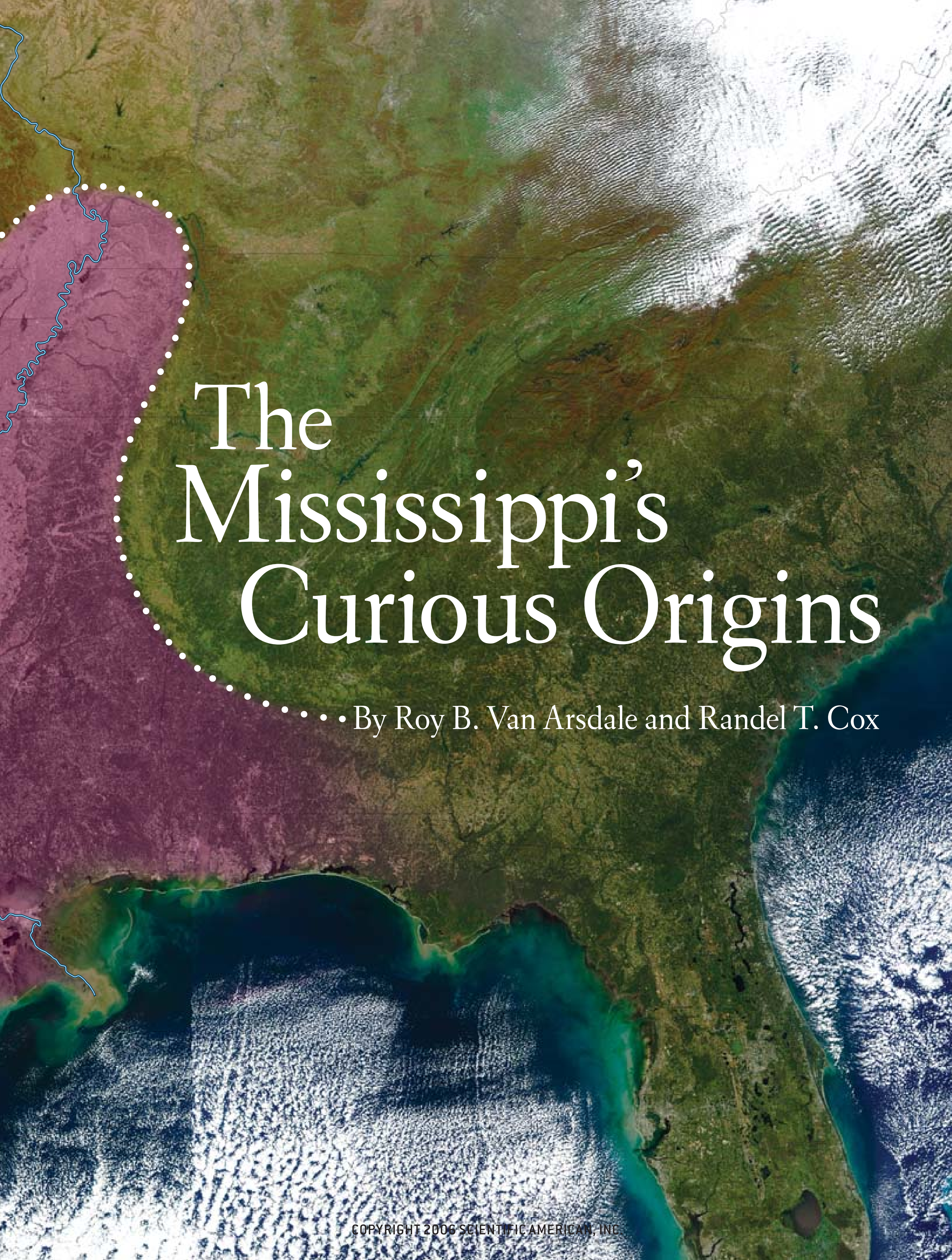
SIMON FRASER/RNC, NEWCASTLE UPON TYNE *Photo Researchers, Inc.*

A mountain range once separated the continental interior of the U.S. from the Gulf of Mexico. Some clever geologic sleuthing has revealed how that barrier was breached, allowing the river to reach the Gulf

On examining a map of the world, many schoolchildren notice that the continents surrounding the Atlantic Ocean can be neatly fit together like pieces of a gigantic jigsaw puzzle. Just snug West Africa up against the East Coast of the U.S. and shove the northern end of South America into the Gulf Coast. That is indeed how these continents were arranged a few hundred million years ago, a fact geologists know, in part, because the plate tectonic movements that created this great landmass left their marks.

In the eastern U.S., the collision with Africa raised the Appalachian Mountains to heights that probably once rivaled the Rockies. Similarly, the impact of South America created the Ouachita (pronounced "WAH-shi-TAH") Mountains, which run west to east across Oklahoma and Arkansas and formerly blended smoothly into the southern Appalachians. Yet somehow the once continuous Ouachita-Appalachian range was cleaved in two, leaving room for the

SOUTHERN PORTION of the Mississippi River (*blue*) flows within a tongue-shaped region of low-lying land (*purple*) that separates the Ouachita Mountains to the west from the Appalachians to the east. This distinctive feature, called the Mississippi Embayment, owes its existence to the passage of North America over a geologic "hot spot"—a concentrated source of heat located, most probably, close to the earth's core.



The Mississippi's Curious Origins

By Roy B. Van Arsdale and Randel T. Cox

The Mississippi Embayment constitutes one of the largest and least understood landforms in the central U.S.

Mississippi River to flow into the Gulf of Mexico. The explanation for the split, which the two of us have been investigating for most of the past decade, touches on many other mysteries of North American geology, too—such as why you can find diamonds in Arkansas and why the largest earthquake that was ever recorded in the contiguous U.S. occurred not in California or Washington but in Missouri, of all places.

The break that now separates the Ouachita Mountains from the Appalachians, a feature known as the Mississippi Embayment, constitutes one of the largest and least understood landforms of the central U.S. This huge horseshoe-shaped lowland is underlain by massive quantities of sand, silt and mud deposited within a bay of the ancestral Gulf of Mexico, which first washed over this region some 85 million years ago (during the late Cretaceous, when dinosaurs still roamed the earth), and did not recede until tens of millions of years later.

It is tempting to imagine that the deposits formed because Gulf waters flooded a slightly low-lying area of the continent, leaving behind a veneer of sediment when they receded. But such a conclusion would be incorrect. As geologists have known for quite a while, the base of these sediments sits as much as 2.6 kilometers below current sea level. Clearly, this part of the midcontinent must have dropped down considerably, allowing whatever river had previously drained the vast continental interior toward the north or west to turn around and flow south, thus becoming the familiar Mississippi. But why did the land there sink?

The Earth Moved

THE ANSWER to this particular geologic riddle begins with some well-understood events that took place while trilobites were still scurrying around and long before the Mississippi Embayment formed. Throughout most of the Paleozoic era (545 million to 245 million years ago), the region destined to become the U.S. was surrounded by ocean. But 300 million years ago (about when the first reptiles evolved), the landmasses that would later turn into North America, South America, Africa and Eurasia came together to form the supercontinent that geologists call Pangaea. These titanic collisions raised several mountain ranges, including the Ouachita-Appalachian chain. For the next 70 million years or so, this east-west-trending mountain range divided the interior of one vast continent. Rivers that began as tiny streams in these mountains flowed either to the south, onto the future South American continent, or to the north, onto what would become North America.

About 230 million years ago (which happens to be when the first dinosaurs appeared), Pangaea started to break up. Not surprisingly, it ripped apart where it had previously been sutured together: just outside the arc of the Ouachita-Appalachian mountains. This opening formed both the Atlantic Ocean and the Gulf of Mexico. The Atlantic is still expanding today, but the Gulf continued to widen only until about 145 million years ago (about when the first birds evolved).

For tens of millions of years, the Ouachita-Appalachian mountains stood as a continuous range along the northern border of the Gulf of Mexico. While such a barrier was in place, the continental interior could not have drained southward into the Gulf. The geology of the Gulf of Mexico indicates as much. Over this lengthy interval, the northern fringes of the Gulf hosted a bank of coral reefs, which later became the thick petroleum-bearing limestone deposits that geologists have traced in the subsurface all the way from Florida to northern Mexico. Corals cannot tolerate being smothered by silt and clay; hence, a major river such as the Mississippi could not have been dumping sediment into the northern Gulf during that era.

For this great breadth of time, the Gulf Coast remained geologically stable, with no continents plowing into it or rifting away. But the calm was broken about 95 million years ago: beginning then, and continuing for the next 10 million years, the crust warped upward over a large area, from southern Louisiana north into southeastern Missouri and from the present-day Tennessee River west to Little Rock, Ark.—the footprint of what is now the Mississippi Embayment.

The result was a broad, northeast-trending arch, which rose to an impos-

Overview/*Making Way for a River*

- The Ouachita Mountains of Arkansas and Oklahoma once connected with the southern end of the Appalachians, forming a continuous range that forced rivers draining the continental interior to flow north or west into the sea.
- Passage of North America over a temporarily reinvigorated mantle hot spot caused uplift of a section of this mountain range just north of the Gulf of Mexico in the mid-Cretaceous, forming an arch. Weathering soon eroded the newly formed highlands, reducing them to the level of adjacent lands.
- As this region moved away from the hot spot, the land subsided, allowing the ocean to flood a large tongue-shaped area into which rivers draining the continent could then flow. The modern Mississippi continues to meander south through sediments that fill this depression.
- Passage of North America over mantle hot spots also accounts for the earthquakes that have struck some areas of the midcontinent.

NASA/THE VISIBLE EARTH (*base satellite image*) (*preceding pages*); CHRISTOPHER R. SCOTESE *PALEOMAP Project* (*paleogeographic globes for Triassic, early Cretaceous and late Cretaceous*) (*opposite page*)

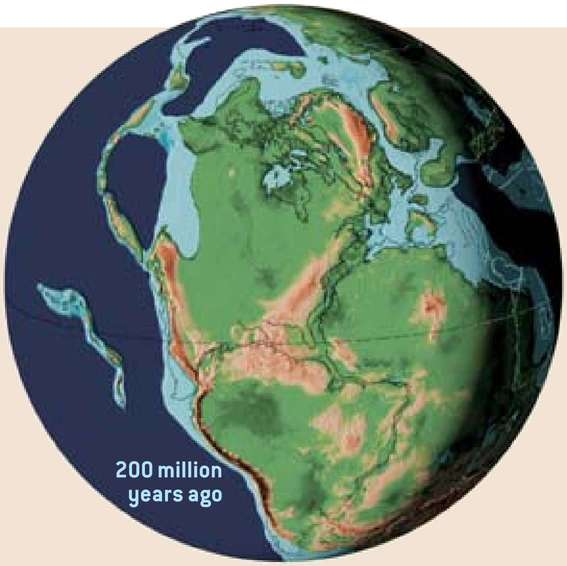
ing altitude, perhaps two or three kilometers above sea level. (In comparison, the Himalayan Plateau currently stands about five kilometers high.) Evidence that such a vast uplifted region once existed over the Mississippi Embayment is indirect—but quite solid. For example, geologists have found telltale gravels at various sites to the east. Detailed studies of these deposits indicate that energetic streams flowed at this time out of the newly created highlands, carrying gravel with them as they cascaded eastward.

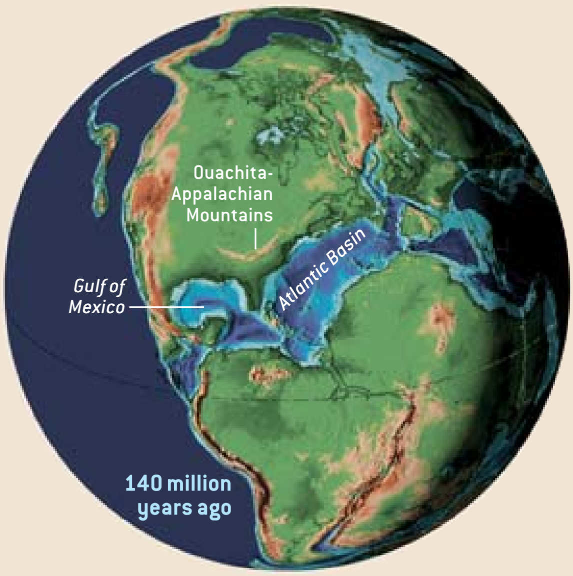
Even more compelling proof of widespread uplift comes from what is *not* found in the Mississippi Embayment: up to three kilometers of rock formed before the late Cretaceous. That pile of rock is conspicuously missing along the axis of the embayment. We would expect the missing strata to have been eroded away if they were raised far above sea level during this 10-million-year period—high-standing terrain being especially susceptible to the ever present influence of weathering, which over geologic time tends to grind even great mountains down to near nothingness.

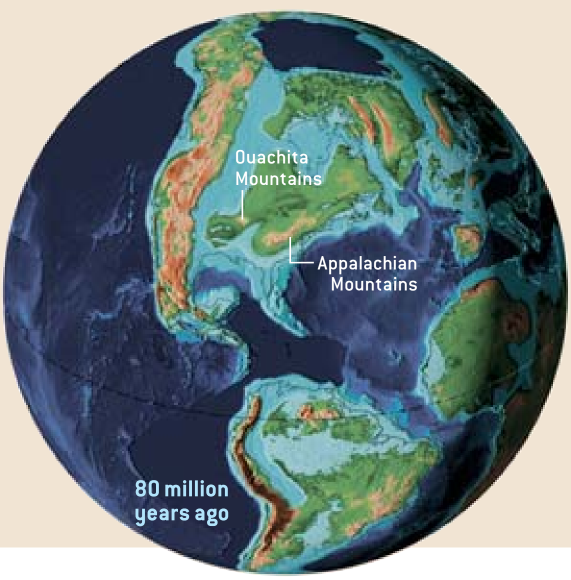
The next major event was the subsidence of the embayment, which geologists have determined must have taken place from 85 million to 24 million years ago. During this interval, the area that had previously been lifted two to three kilometers into the air headed in the other direction, dropping below sea level by about the same amount. Thus, what had formerly been the crest of a high, arched mountain range became inundated with seawater and was eventually buried by as much as 2.6 kilometers of marine sediment.

Hot-Spot Roller Coaster

WHAT PROCESS could have raised an immense area of the planet's crust and then caused it to start sinking, all within a geologically short period? The answer that the two of us have slowly put together is that the Mississippi Embayment passed over a mantle hot spot—a deep-seated source of exceptionally great heat situated, most likely, near the base of the earth's mantle (the thick zone







Snapshots from the Past

Plate tectonic reconstructions show the evolution of the mountainous barrier that long prevented the rivers draining the interior of North America from flowing south to the sea, as the Mississippi does today.

About 200 million years ago (*top*) the continents of the world abutted one another, forming a giant supercontinent, which geologists call Pangaea. The collisions that brought the continents into this configuration raised various mountain ranges, including what was then a continuous line of mountains that ran along the southern and eastern flanks of the North American plate. Rivers draining the interior of North America could not have crossed this formidable barrier and thus must have flowed northward or westward into the sea.

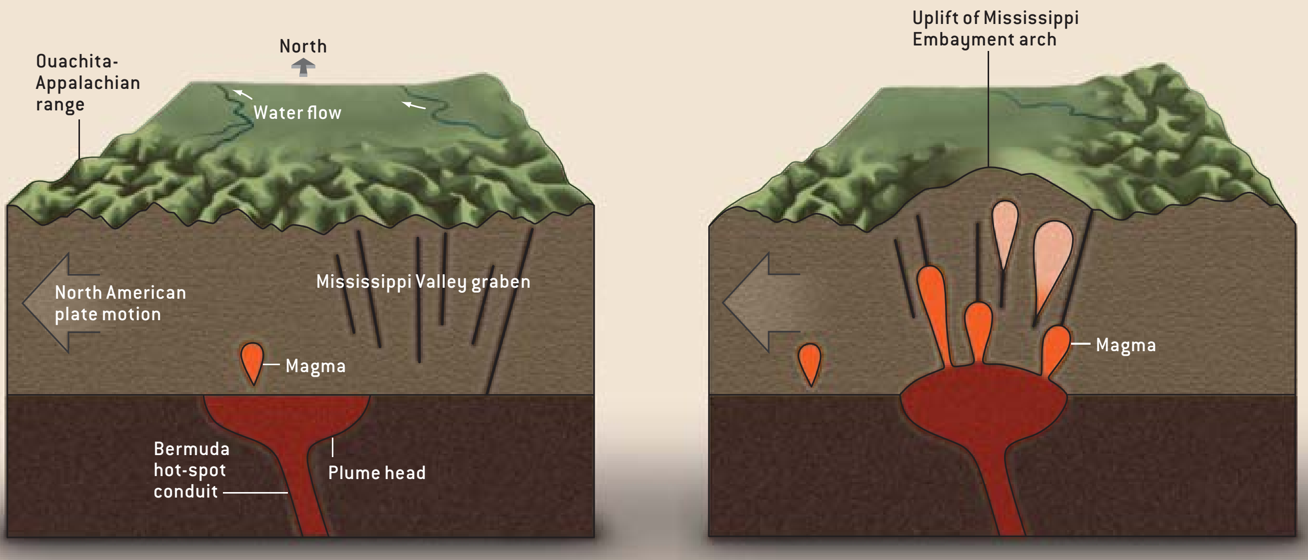
The Ouachita-Appalachian mountains remained a continuous barrier even after the Yucatán block shifted southward and the African plate separated from North America, plate tectonic motions that by the early Cretaceous (about 140 million years ago) created, respectively, the Gulf of Mexico and much of the modern Atlantic Basin (*middle*).

By the late Cretaceous (some 80 million years ago), a large depression divided this mountain range north of the Gulf of Mexico, forming a huge bay. This was a time of globally high sea level, when the ocean flooded low-lying continental areas all over the world (*bottom*).

—R.B.V.A. and R.T.C.

HOW TO DIVIDE A MOUNTAIN RANGE

The once continuous Ouachita-Appalachian range was cleaved in two by the Mississippi Embayment, created after this area of the continent



1 In the early Cretaceous, the plume of hot, rising rock engendered by the Bermuda hot spot was located west of the Mississippi Valley graben, a zone containing ancient, steeply inclined faults. The presence of the high-standing Ouachita-Appalachian range forced the rivers that drained the interior of the continent to flow north or west to the sea.

2 Plate tectonic motion brought the Mississippi Valley graben over the Bermuda hot spot in the mid-Cretaceous, when the activity of such deep-seated heat sources was heightened worldwide. Magma flowed up along the faults, inflating this region with added material, while simultaneously causing the upper part of the plate here to expand thermally. The result was a broad zone of uplift—the Mississippi Embayment arch.

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within the earth between the crust and the core). Above such heat sources, hot rock rises through nearly 3,000 kilometers of mantle and crust before reaching the surface.

When a plate passes over such a deep source of heat, the motion often creates a distinctive line of volcanoes on the surface (for example, the Hawaiian Island chain). They can be arrayed one after the other, or they can blend together into one continuous ridge. These hot-spot-induced volcanic features can be likened to the line of burn marks you might see if you moved a plate of steel horizontally above a stationary welder's torch.

We began to think that a hot spot was involved when we reviewed plate motion models for North America. They revealed that the central and eastern U.S. moved over the Bermuda hot spot (so named because it later created the volcanic edifice that underlies Bermuda). This motion occurred during the very time that the area of the Mississippi Embayment was rising upward. Such passage would neatly explain the uplift, because the hot, rising magma engendered by the Bermuda hot spot would have buoyed the crust and caused it to expand thermally.

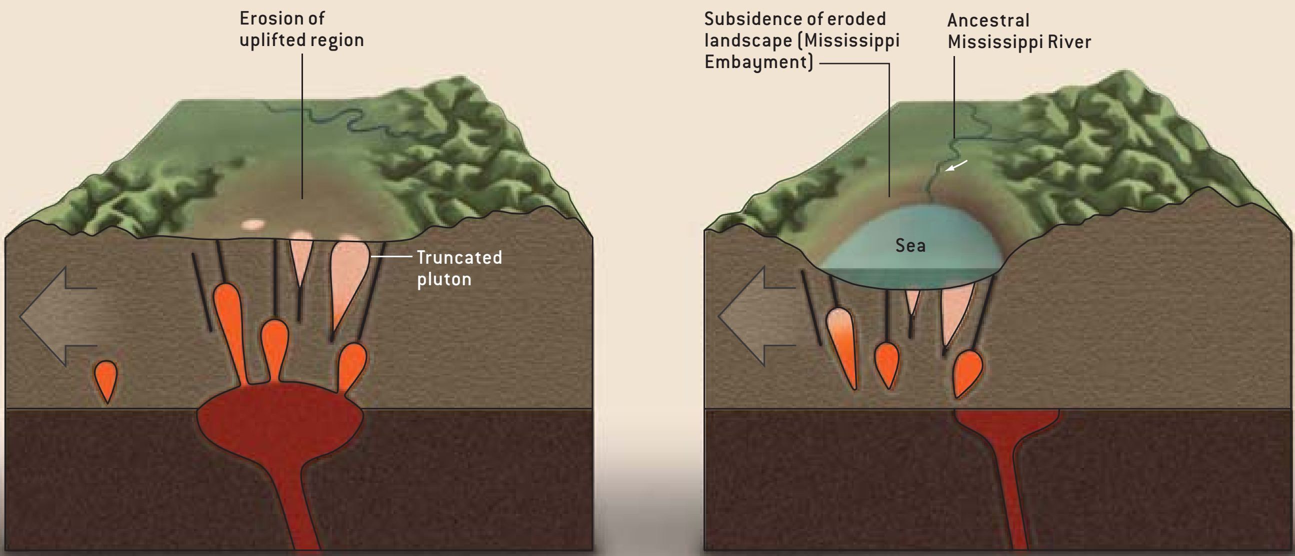
Direct evidence for this phenomenon includes some rather special volcanic features called kimberlite pipes, in which a few fortunate people have found diamonds. (Those wishing to try their luck should head for Crater of Diamonds State Park near Hot Springs, Ark.) Indeed, igneous rocks, the kind formed by the cooling of magma, can be found intermittently at many points that once passed over the Bermuda hot spot. These igneous rocks stretch from central Kansas, where they are 115 million years old, to central Mississippi, where they are 70 million years old—an age progression that fits well with the east-to-west motion of North America over the hot spot.

Having come to this realization, we saw clearly what had caused the Mississippi Embayment not only to rise but also to fall back down later. The uplift created a high arch whose crest extended along a line that approximately follows where the Mississippi River is today. But within 10 million years, weathering caused those highlands to erode down to sea level or thereabouts. Then, as the Mississippi Embayment drifted off the

THE AUTHORS

ROY B. VAN ARSDALE and *RANDEL T. COX* share a keen interest in the causes of earthquakes that occur in the interiors of tectonic plates. Van Arsdale earned a Ph.D. in geology from the University of Utah in 1979 and is now a professor at the University of Memphis. He has studied the geology of the New Madrid seismic zone in particular for the past 15 years. Cox received a doctorate from the University of Missouri–Columbia in 1995 and is currently a professor at Memphis. His research interests include the evolution of the Mississippi Valley and surrounding regions, documentation of prehistoric earthquakes in the central U.S. and Central America, and the geologic effects of volcanic hot spots.

passed over a mantle hot spot. The four panels illustrate the mechanism by which the embayment formed.



3 The ever present forces of weathering soon eroded the newly uplifted terrain. This lowering of what had been a high-standing, mountainous arch truncated the tops of some igneous “plutons.” These bodies of crystalline rock were formed earlier by magma that rose from great depths but cooled and solidified before reaching the surface. Their truncation is one sign that erosion occurred.

4 In the late Cretaceous, after the Mississippi Valley graben moved away from the Bermuda hot spot, the region that had been uplifted cooled and subsided, allowing the sea, which stood relatively high at the time, to flood the area. Rivers draining the continental interior, including the ancestral Mississippi, could now flow southward, into the new embayment, which gradually filled with sediment.

Bermuda hot spot, the crust there cooled, contracted and subsided to a maximum depth of 2.6 kilometers below sea level.

It might seem surprising that the land sank so low. But remember that the area was raised to a height somewhere between two and three kilometers above sea level and then erosionally beveled off. So after the crust cooled and subsided, it did not return to its original configuration because it was missing between two and three kilometers’ worth of rock at the top. Hence, a trough formed and was inundated with water from the Gulf of Mexico.

A closer look at the Arkansas diamond-bearing rocks supports our notion of how the crust lifted upward and then sank. The character of the rocks that gave rise to those diamonds implies that their parent magmas rose from the mantle to shallow depths in the crust, about a kilometer or so below the surface, where they solidified. Yet geologic investigations reveal that along the axis of the embayment many of these great masses of rock were deeply eroded at their tops and later buried under late Cretaceous deposits—just what you would expect to see if uplift and erosion accompanied the injection of magma before the crust subsided below sea level, allowing the ocean to flow in and cover everything with marine sediments.

Flies in the Ointment?

TWO FEATURES of our scenario may seem problematic at first blush. The first is that the crest of the arch that once occupied the embayment ran from southwest to northeast, at nearly right angles to the trace of the Bermuda hot spot, the line marking places that at one time sat directly above this long-lasting heat source. If you accept that the hot spot caused the arch to form, you might well wonder why this trace is not aligned with the crest.

This incongruity is not as troubling as it might seem. On the floor of the Atlantic Ocean near the current location of the Bermuda hot spot is the Bermuda rise, a northeast-trending feature where the seafloor is arched upward. And it, too, is essentially perpendicular to the trace of the hot spot. The standard explanation for the orientation of the rise hinges on the observation that the seafloor in this area has a steeply inclined set of faults that trend northeast to southwest and cut through the entire crust. The upwelling of magma that

The crust subsided below sea level, allowing the ocean to flow in and cover everything with marine sediments.

Hot-Spot Signatures

The motion of North America over the Bermuda hot spot and over a second one—the Great Meteor hot spot—is illustrated by a plot of the hot spots' "tracks," lines delineating locations on the surface that have passed over these deep-seated sources of heat (*orange lines*). These hot spots affected the North American plate in various ways. The elongation of the embayment to the northeast results from the channeling of hot-spot-derived magma along preexisting faults (*yellow lines in embayment region*)—as does the northeast-southwest elongation of the Bermuda rise on the ocean floor. The New England seamounts are a product of the plate's travel over the Great Meteor hot spot. And passage of North America over these two hot spots reactivated ancient faults in the central North American, Mississippi Valley and St. Lawrence rift systems, accounting for the earthquakes that have taken place near the southern end of the central North American rift system, in New Madrid, Mo., in Charleston, S.C., and around the St. Lawrence River in Canada. —*R.B.V.A. and R.T.C.*

JEN CHRISTIANSEN

built the rise was presumably channeled along these lines of weakness, raising the seafloor in places that are relatively far from the hot spot. If this conclusion is correct, the first difficulty with our theory disappears, because ancient northeast-trending rift faults can also be found under the Mississippi Embayment. These fractures in the crust could have similarly channeled magma engendered by the Bermuda hot spot, creating an uplifted landscape that was elongated from southwest to northeast.

The second potential fly in the ointment is the obvious question of why the Bermuda hot spot had such a profound effect in the area of the Mississippi Embayment, given that it left so little signature elsewhere on the North American continent. But we think we have an explanation for this observation as well, one that revolves around the fact that the Bermuda hot spot was underneath the Mississippi Embayment precisely during a period in the earth's history when hot spots were pouring out enormous volumes of magma all over the world. Geologists call this interval of enhanced magmatism and heat production a "superplume" event [see "The Mid-Cretaceous Superplume Episode," by Roger L. Larson; Scientific American, February 1995]. (Among other manifestations of this distinctive occurrence, many diamond-bearing kimberlite pipes formed.) Thus, the solution to this second concern may be that the faulted crust of the Mississippi Embayment just happened to be in the right place at the right time, when the usually docile Bermuda hot spot kicked into high gear.

So it seems that the passage of the North American tectonic plate over the temporarily reinvigorated Bermuda hot spot accounts for how a part of the crust that was once covered by mountains could be turned into a trough. This change was sufficient to reverse the

On February 7, 1812, the largest earthquake ever recorded in the contiguous U.S. struck the town of New Madrid, Mo.

drainage of the continental interior, sending water that once must have flowed far to the north or west instead to the Gulf of Mexico.

Whole Lot of Shakin' Going On

FURTHER SUPPORT for our model comes from a geologic event of much younger vintage—it took place less than two centuries ago. On February 7, 1812, the largest earthquake ever recorded in the contiguous U.S. struck the town of New Madrid, Mo. The temblor, which seismologists estimate would have measured 8.0 on the Richter scale, was even powerful enough to change the course of the Mississippi in one spot.

It might appear strange that such a calamity should strike the typically quiet center of the continent, far from all the grinding and slipping that goes on at plate boundaries, where earthquakes are relatively common. Yet such interior quakes can occur in places that contain old, faulted crust, and New Madrid sits above an ancient fractured structure called the Mississippi Valley (or "Reelfoot") rift system. Most areas with ancient faults do not experience earthquakes. Indeed, the entire East Coast is underlain by rifted crust but is largely without earthquakes.

A hint to what makes the rifted crust below the Mississippi Embayment prone to earthquakes comes from Charleston, S.C., which is also a seismic zone (the big one having struck there in 1886). Like New Madrid, Charleston lies over ancient rifted crust. What the New Madrid and Charleston seismic zones also have in common is that they once passed over the Bermuda hot spot. To the west, the anomalously seismic southern end of the central North American rift system near Manhattan, Kan., lies close to the trace of the Bermuda hot spot as well. The trace of a hot spot also coincides with the most seismically active area in eastern Canada, the St. Lawrence rift: during the Cretaceous period, this part of Canada passed over the Great Meteor hot spot, named for the Great Meteor seamount in the Atlantic Ocean, where subsea volcanism has taken place during geologically recent times.

It thus appears that passage of a tectonic plate over a hot spot can reactivate ancient faults, causing slippage to occur on them from time to time, even many millions of years later, presumably because the crust takes a long while to settle down after being heated and uplifted. So the picture we have put together not only accounts for creation of the Mississippi Embayment—it also explains why significant seismicity occurs in parts of eastern North America far from the boundaries of tectonic plates.

That such different things as earthquakes in Canada and diamonds in Arkansas fit well with our explanation for the formation of the Mississippi Embayment gives us confidence in the validity of our ideas. And it is quite interesting to think that the course of the mighty Mississippi was fundamentally controlled by goings-on a full 2,900 kilometers away—and straight downward, at the boundary between the earth's core and mantle. This surprising conclusion provides a close-to-home reminder of the connectedness of the different parts of our fascinating planet. SA

EARTHQUAKE rocked Charleston, S.C., in 1886. The cause was slippage along ancient faults, a delayed response to the passage of the area over the Bermuda hot spot some 60 million years ago.

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MORE TO EXPLORE

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Improved understanding of the chemical pathway on which aspirin and Vioxx act may lead to analgesics with fewer side effects

Better Ways

By Gary Stix

Bengt Samuelsson won the Nobel Prize in Physiology or Medicine in 1982 for his work on providing an exacting picture of how the body generates prostaglandins. These hormonelike substances play a role in regulating various biological processes, including the pain induction, fever and inflammation that are blocked by aspirin, ibuprofen and related drugs. Samuelsson did his research, along with Sune Bergström, another of that year's co-winners, on the red-brick campus of Sweden's Karolinska Institute, which also selects the annual Nobel medicine prize.

Karolinska has a long history with prostaglandins, one that dates back to the discovery of these fatty acid derivatives in 1935 and extends up to the present day. In recent years Samuelsson and his collaborators have further elucidated prostaglandin biochemistry—research that is now being exploited in an attempt to develop painkillers and anti-inflammatory drugs that are safer than existing agents, including the now tarnished group known as COX-2 inhibitors. "There's an enormous demand for anti-

to Target PAIN

inflammatory drugs," Samuelsson notes. "And if we can develop a drug that's as effective as previous drugs with fewer side effects, that's very important."

The Tree and Its Branches

THE KAROLINSKA'S 1982 press release applauding Samuelsson's Nobel credits the scientist for "our present knowledge of the prostaglandin tree with all its branches." Samuelsson had shown that prostaglandins are manufactured when arachidonic acid in the cell membrane is processed by enzymes through a series of steps [*see box on next page*]. These steps eventually result in compounds that supply a variety of regulatory functions within the body—ensuring, for instance, that the kidneys receive sufficient blood flow, controlling the contraction of the uterus during birth and menstruation, or invoking inflammation (marked by redness and swelling) as a protective response to infection and injury.

Aspirin and other nonsteroidal anti-inflammatory drugs, such as ibuprofen, function by blocking the action of two enzymes that act early in the prostaglandin-making pathway: cyclooxygenase 1 and 2 (COX-1 and COX-2). By inhibiting the COX enzymes, the medicines shut down production of the full suite of prostaglandins.

By hitting the off switch so hard, however, aspirin and its relatives sometimes cause problems of their own. When aspirin damps production of prostaglandins responsible for inflammation, it also does the same for one or more of the arachidonic acid derivatives that protect the stomach lining from the hydrochloric acid in digestive juices. Drug companies came up with a fix in the 1990s when they developed Vioxx, Celebrex and other drugs that specifically block COX-2, a move that leaves intact some of the stomach-protective prostaglandins produced in response to COX-1 activity.

Interrupting COX-2, however, soon turned out to have its own drawbacks. The disruption apparently upsets a series of complex interactions among prostaglandins. Although blocking the enzyme decreases manufacture of prostaglandin E_2 (PGE_2), thought to play a major role in inducing pain and inflammation, it also reduces synthesis of prostacyclin (PGI_2), a heart-protective prostaglandin that dilates blood

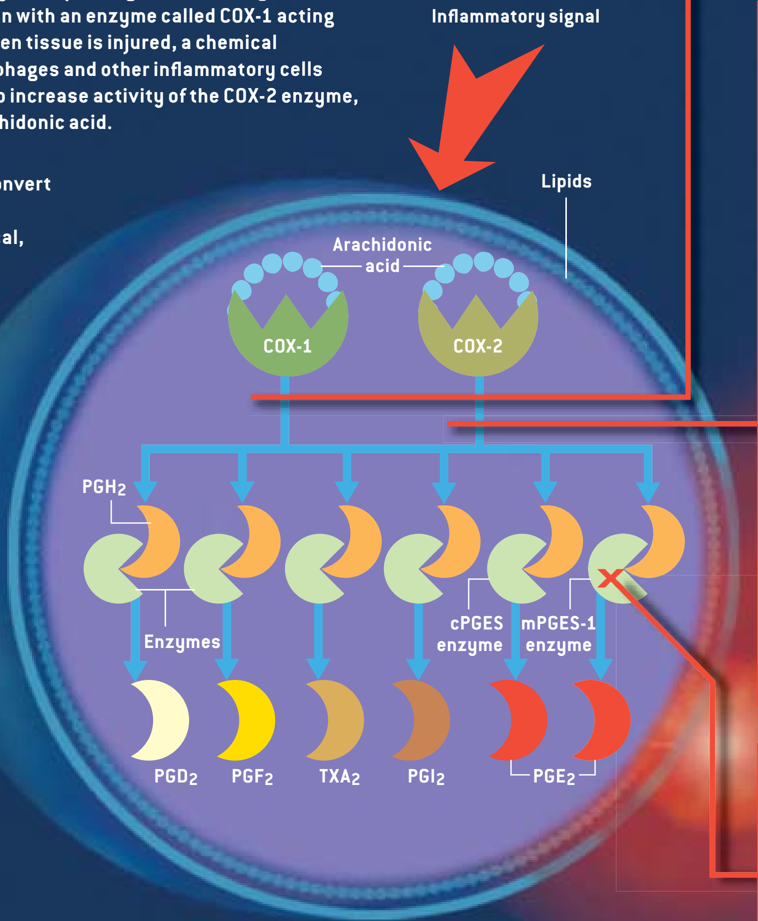
IMPROVING ON ASPIRIN AND VIOXX

One cause of pain, inflammation and fever in the body is production of large amounts of a molecule called prostaglandin E_2 (PGE_2) (*steps 1–3 in diagram*) by cells involved in inflammation. Aspirin, Vioxx and various other painkillers work by inhibiting enzymes that catalyze prostaglandin synthesis (*top two boxes*). But some prostaglandins and other substances produced by the enzymes are beneficial, and interrupting their production can cause side effects. Drug developers are therefore studying agents, such as mPGES-1 inhibitors, that block only the synthesis of excessive PGE_2 and thereby allow the beneficial substances to be made (*bottom box*).

1 Most cells routinely make prostaglandins through reactions that begin with an enzyme called COX-1 acting on arachidonic acid. When tissue is injured, a chemical signal instructs macrophages and other inflammatory cells in the injury's vicinity to increase activity of the COX-2 enzyme, which also acts on arachidonic acid.

2 COX-1 and COX-2 convert arachidonic acid to an intermediate chemical, prostaglandin$_2$ (PGH_2).

3 Additional enzymes subsequently convert PGH_2 into other prostaglandins and thromboxane, each with a different function (*below*). All prostaglandins—including the pain-producing PGE_2—are ultimately released to act on other cells.



HOW ASPIRIN WORKS

Aspirin and other nonsteroidal anti-inflammatory drugs block both COX-1 and COX-2 enzymes, which stymies production of all prostaglandins, including beneficial ones.

HOW COX-2 INHIBITORS WORK

COX-2 causes pain and inflammation by pumping up PGE_2 levels through a pathway involving an enzyme called mPGES-1. By blocking COX-2, Vioxx, Celebrex, Bextra and other inhibitors halt this rise in PGE_2. The agents pose less of a threat of stomach damage, presumably because normal levels of PGE_2 continue to be made under the direction of COX-1 and an enzyme named cPGES. The COX-2 inhibitors, though, also diminish PGI_2, which has protective effects on the vascular system. Attenuated PGI_2 may explain the higher incidence of heart attacks and strokes among those taking these drugs.

HOW mPGES-1 INHIBITORS WORK

These agents, still under development, specifically block mPGES-1, which is made in large amounts at the behest of COX-2 in cells responding to an inflammatory insult. Curtailing mPGES-1 but not the enzymes that make normal levels of prostaglandins may thus control PGE_2 levels and provide pain relief without harming the heart and gastric system.

PROSTAGLANDINS AND THEIR VARIED EFFECTS

Prostaglandin D_2 (PGD_2)
Involved in sleep regulation and allergic reactions

Prostaglandin F_2 (PGF_2)
Controls the contraction of the uterus during birth and menstruation

Thromboxane A_2 (TXA_2)
Stimulates constriction of blood vessels and induces platelet aggregation (clotting)

Prostacyclin (PGI_2)
Dilates blood vessels and inhibits platelet aggregation (clotting) and may protect against atherosclerosis and damage to the stomach lining

Prostaglandin E_2 (PGE_2)
Involved with pain, inflammation and fever and protects against harm to the stomach

DAVE CUTLER (*preceding pages*); DANIELA NAOMI MOLNAR (*this page*)

vessels and prevents blood platelets from aggregating. And that diminution has potentially dangerous consequences.

In 1999 Garrett A. FitzGerald of the University of Pennsylvania Medical Center reported in the *Proceedings of the National Academy of Sciences USA* on a small clinical trial that demonstrated the PGI_2 inhibition. FitzGerald also showed that when PGI_2 diminishes after ingestion of a COX-2 inhibitor, thromboxane, another prostaglandin produced in the arachidonic acid pathway still functions, exerting vessel-constricting and platelet-clumping properties normally opposed by PGI_2. The imbalance, the report observed, could encourage formation of clotting (thrombosis) that could provoke heart attacks and strokes, a conclusion lawyers for plaintiffs in much publicized suits against makers of COX-2 inhibitors have duly noted in recent years. FitzGerald had begun reporting his findings at conferences in 1997, a year before approval of the first COX-2 inhibitor, Celebrex.

When FitzGerald's group was uncovering the early-warning sign of dangers to come, Samuelsson's research group was laboring away on putting a new leaf on one of the branches of the prostaglandin tree. A postdoctoral fellow in the lab, Per-Johan Jakobsson, led a project that discovered the human version of an enzyme that produces PGE_2. The abstract of a 1999 paper co-authored by Jakobsson, Samuelsson and two collaborators ends on an upbeat note, saying that the enzyme "is a potential novel target for drug development."

A small company started by two Karolinska scientists took notice of both publications. Biolipox opened its doors in 2000 to develop anti-inflammatory drugs for respiratory diseases by tweaking a newly discovered class of biochemicals, called eoxins, that are also generated from arachidonic acid. A year later the company decided to diversify. It licensed from Karolinska the intellectual property for the enzyme, called microsomal prostaglandin E synthase (mPGES-1). A drug that could selectively block the enzyme's making of PGE_2 might quell pain and inflammation without gastrointestinal or cardiovascular side effects because it would not diminish PGI_2 levels. "We realized that this might be interesting as a third-generation nonsteroidal anti-inflammatory," says Charlotte Edenius, Biolipox's chief scientific officer.

Unleashing Inhibitors

BIOLIPOX is now installed in a nondescript building that also houses the scientific library and the bioinformatics and teaching departments on the Karolinska campus. Samuelsson has signed on as a scientific adviser and member of the board of directors. And Boehringer Ingelheim, the manufacturer of the COX-2 inhibitor Mobic, inked an agreement with Biolipox in 2005 to fund research on mPGES-1 and then license inhibitors for final development and marketing.

The more than $10-billion annual U.S. market for nonnarcotic painkillers—combined with the COX-2 debacle—has meant that other companies have also devoted keen attention to the enzyme. Merck has published a study on inhibitors of mPGES-1. Pfizer has filed for a patent for a mouse with the gene for mPGES-1 eliminated so that the effects of blocking the enzyme can be examined. Other major drug firms have also filed for mPGES-1-related patents. "Tectonic plates are shifting," FitzGerald remarks. "It's currently a huge market with a lot of insecurity around the current repertoire of drugs." He adds that one company, whose name he is unable to disclose, plans to enter clinical trials with an mPGES-1 inhibitor in 2007. (Separately, other makers are trying to develop drugs that would bind to PGE_2 receptors and directly block them from functioning.)

The Vioxx trials may deter any new anti-inflammatory drug from being rushed to market. The doubters, in fact, have already come forward. An article published in 2006 in *Trends in Pharmacological Sciences* entitled "Is mPGES-1 a Promising Target for Pain Therapy?" raises the issue of whether the complexity of prostaglandin metabolism will foil prospects for a new drug. Turning off mPGES-1 may result in less production of PGE_2 but more of another prostaglandin, with unknown physiological consequences, the article observes. Moreover, most other prostaglandins, not just PGE_2, play some role in triggering pain.

Only clinical trials for safety and effectiveness in humans will resolve any disputes. But early studies in knockout mice with mPGES-1 removed lend some hope. In one report from FitzGerald's group in 2006, mPGES-1 knockouts had increased levels of the heart-sparing PGI_2, while the detrimental thromboxane remained stable. At the same time, both clotting and blood pressure remained normal. A subsequent study by FitzGerald's team demonstrated that an mPGES-1 knockout experienced certain cardiovascular benefits, perhaps from elevated PGI_2.

The search continues for compounds that can replicate the effects of silencing mPGES-1. And preparations have begun to take the delicate next step of moving from mouse to human. SA

MORE TO EXPLORE

Identification of Human Prostaglandin E Synthase: A Microsomal, Glutathione-Dependent, Inducible Enzyme, Constituting a Potential Novel Drug Target. Per-Johan Jakobsson, Staffan Thorén, Ralf Morgenstern and Bengt Samuelsson in *Proceedings of the National Academy of Sciences USA,* Vol. 96, No. 13, pages 7220–7225; June 22, 1999.

Is mPGES-1 a Promising Target for Pain Therapy? Klaus Scholich and Gerd Geisslinger in *Trends in Pharmacological Sciences,* Vol. 27, No. 8, pages 399–401; August 2006.

Deletion of Microsomal Prostaglandin E Synthase-1 Augments Prostacyclin and Retards Atherogenesis. Miao Wang, Alicia M. Zukas, Yiqun Hui, Emanuela Ricciotti, Ellen Puré and Garret A. FitzGerald in *Proceedings of the National Academy of Sciences USA,* Vol. 103, No. 39, pages 14507–14512; September 26, 2006.

STADIUM TURF

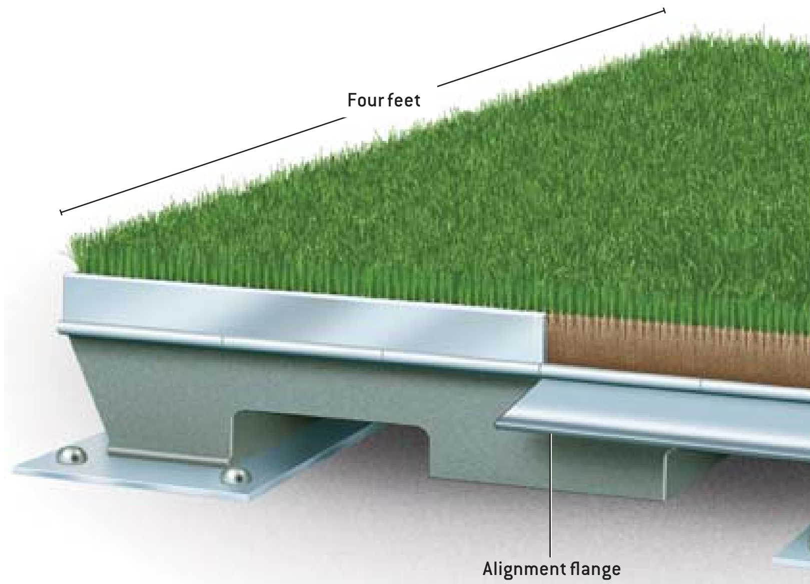
Grass vs. Plastic

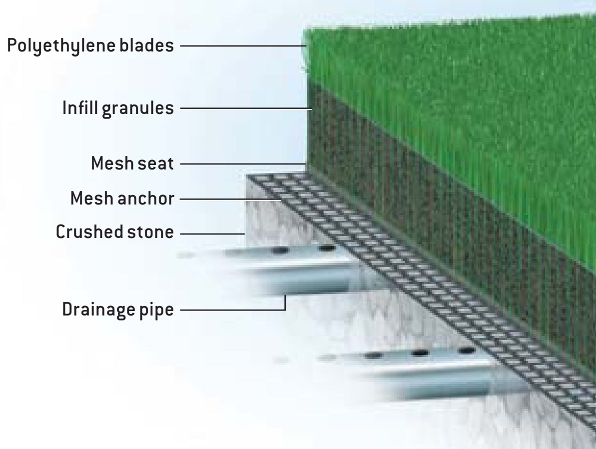
Tough competition is under way in sports stadiums—between grass fields and artificial turf.

Athletes have always torn up grass fields, especially during rainy, cold or dry spells. To fight back, installers have devised substructures that quickly drain excess water to keep soil firm and even pump in warm air to help roots thrive [*see illustration, top left*]. Synthetics sprouted in the late 1960s after installation in the Houston Astrodome. The AstroTurf brand, named for the venue, remained synonymous with "artificial turf" for 30 years, even though players said it felt hard underfoot and complained of rug burns when they hit the deck. In the past decade a new generation of products from companies such as FieldTurf has overtaken the brand and been adopted widely. These products boast softer tufts and more consistent footing from "infills" of rubber granules or rubber and sand between the "grass" blades [*see illustration, bottom left*].

Debate continues over which surface is preferable. Last summer Purdue University renovated its football field with a new strain of Bermuda grass bred to withstand colder temperatures. "The new synthetics are great," admits Al Capitos, sports turf manager at the school, "but there's still nothing better than grass." Stadium managers acknowledge that most players prefer grass—if it is in pristine condition. But drought makes it hard, and rain makes it slick or uneven. In northern states, "all you need is a mud game after September when grass stops growing, and you've lost your field for the season," says Joe Frandina, head of stadium operations for the Buffalo Bills in Orchard Park, N.Y. His snowy facility has relied on synthetic turf for years.

Money matters, too. An average synthetic installation can cost $500,000 to $800,000 or more. Grass may range from $250,000 to $500,000 or higher, but it requires fertilizing, watering and cutting. Personal preference may clinch the choice. In 2002 Michigan State University replaced its artificial turf with interlocking grass modules from GreenTech in Roswell, Ga. Company founder Chris Scott says, "Michigan State has a renowned turf department … grass just seemed right." Last year, when the Bills updated their synthetic surface, Frandina chose a different supplier whose product "just felt better underfoot." —*Mark Fischetti*





SYNTHETIC TURF, made in swaths or on trays, lies on a crushed stone base. An infill of rubber granules or rubber and sand in suspension keeps blades upright. The backing layers lock the blades in place and allow drainage.

KENT SNODGRASS *Precision Graphics*

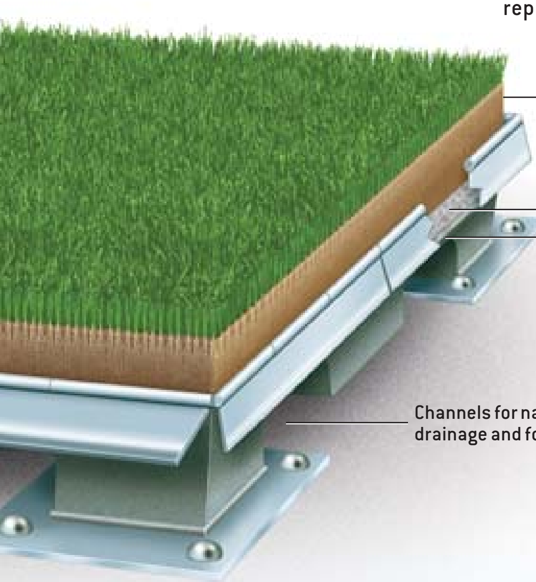
DID YOU KNOW...

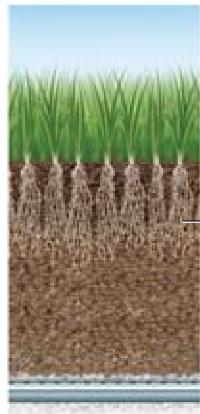
TIRE DRILL: The rubber granules that fill in synthetic turf come primarily from old tires. So-called ambient rubber is ground to the size of small beads. "Cryogenic rubber" is kept frozen while it is ground so it can be reduced to the size of sand particles; producers claim that the granules are more uniformly round, resulting in tighter, more stable fill.

RETRACTABLE GRASS: Last August the University of Phoenix opened a new stadium (also home to the Arizona Cardinals pro football team) that sports the first retractable turf in the U.S. Modeled after several European venues, the grass field lies on a single tray, 234 feet wide and 403 feet long, that sits on steel rails set in the concrete floor. The 17-million-pound expanse is rolled inside on game days and returned to the parking lot all other days so it can grow and so conventions, concerts and rodeos can take place inside. The translucent-fabric roof retracts, too. The stadium will host the college football championship game this January.

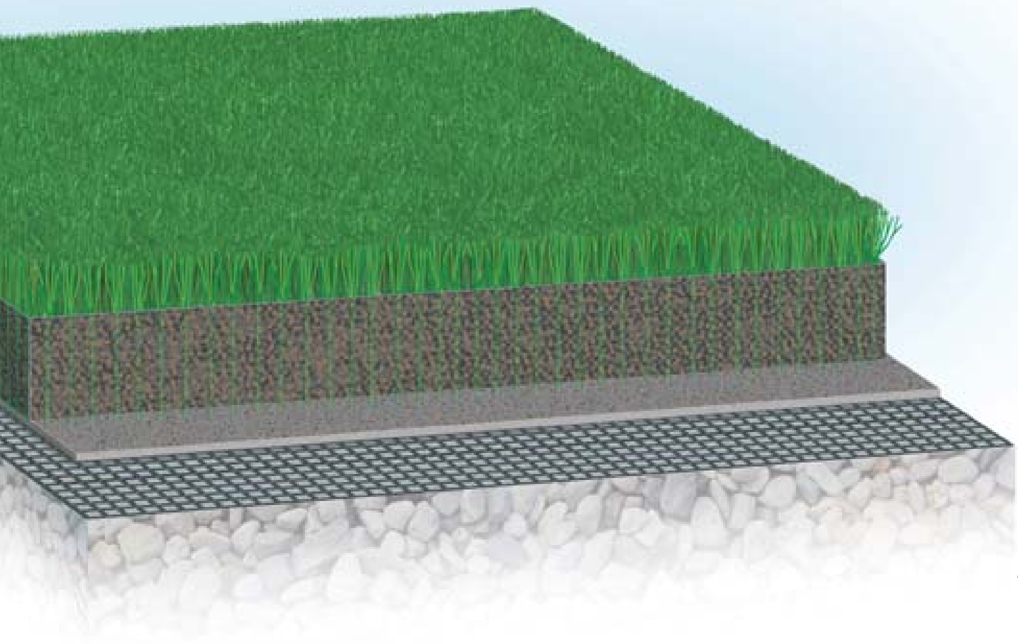
INJURY AND ILLNESS: Athletic trainers for the Buffalo Bills (this writer's brother among them) say they do not see more injuries to players on new artificial surfaces, a criticism sometimes made of earlier products. New synthetic surfaces may be associated with different kinds of foot or leg traumas than grass is but not necessarily with more injuries overall.

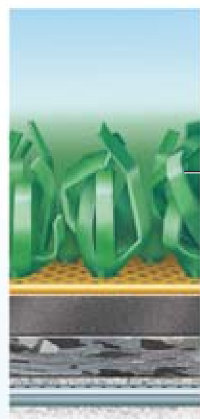
NATURAL GRASS can grow on replaceable trays that lock together.





PLAIN GRASS is laid above drainage for quick drying.





ARTIFICIAL SURFACES without infills rely on nylon fibers sewn into a mesh backing that is fixed to an energy-absorbing pad. The pad is bound to an aggregate base of rubber, polyurethane and minerals.

Have a topic idea?
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Sweet and Soiled Science

LIMBS AND HANDS FROM THE NORTHEAST TO THE SOUTHWEST **BY STEVE MIRSKY**

What makes the sap run? Because he or she wants to serve in Congress. Well, that's the first answer that springs to mind this autumn day just after the November elections, and we'll get back to that subject later. But a better answer deals with a better interpretation of the question—regarding maple syrup. That subject was also on my mind, I having recently returned from a trip to the Proctor Maple Research Center in Underhill Center, Vt., while attending the annual meeting of the Society of Environmental Journalists in Burlington.

Turns out that what makes *that* sap run is devilishly complex. It's so complicated, in fact, that the only way I may ever really understand it is to have the scientists who research this question write a feature article for *Scientific American* so I can read it.

The key point, though, is that sugar maple trees have the unusual property of producing positive internal pressure after freezing and thawing. That internal pressure can tap, I mean top, that of a car tire, reaching about 40 pounds per square inch. In order to top, I mean tap, the tree, makers of maple syrup rely on the tree tap, I mean top—the branches are really where the action takes place that ultimately brings you your favorite pancake tapping. I mean topping.

Most trees have fibers filled with water, but sugar maples have air-filled fibers. "So," explains top tap (works either way) researcher Timothy Wilmot, "instead of getting the conditions you'd expect—where freezing would cause an expansion and something would come out of the tap hole when it froze—because of the physiology of the maple wood, water is actually sucked up during the freezing period. And during the thawing period, it's pushed out."

Because making the sap run—we're still talking maple trees here—requires a series of freezes and thaws, the entire industry is dependent on temperatures oscillating between a narrow range just below and just above freezing. A growing fear in the northeastern U.S. is that sustained warming will push both that temperature range and the sugar maple range north of the freezing point and border, respectively. Indeed, the sugaring season is getting shorter in Vermont but not in Canada. Yet.

By the way, I took a break in the middle of writing this story to have pancakes and Vermont maple syrup. While eating, I read a short item in the publication *Funny Times* that concerned a visit to a grade school by a firefighter. He showed the students a smoke alarm and asked if they could identify it. One kid responded, "That's how Mommy knows supper is ready." Just minutes earlier I had shut off a smoke alarm to prevent the hearing damage that ordinarily accompanies my pancake cooking.

Speaking of smoke-filled rooms, back to the election. The week before the voting, a story circulated about the practice among many politicians of using liberal—even among conservatives—dollops of those syrupy hand sanitizers when they're meeting and greeting hundreds of strangers. Seemed like a good and innocuous idea, and one of the few on which George W. Bush and Al Gore publicly agree.

But New Mexico governor Bill Richardson said he found it "condescending to the voters," according to the *New York Times*. "I'm not afraid to get my hands dirty," Richardson said. Two stats: Richardson holds the world record for most hands shaken—13,392 in eight hours at his state fair and at the University of New Mexico in 2002; a 2005 American Society for Microbiology study of more than 6,000 subjects found that 18 percent did not wash their hands after using a public restroom. So, unless New Mexicans are unusually clean or the venues had no facilities, Richardson probably shook hands with about 2,400 could-be contaminated constituents. And he may have passed along their microbes to the washed masses. Syrupticiously. SA

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

ASK THE EXPERTS

How do researchers trace mitochondrial DNA over centuries?

—M. Sivak, Irvington, N.Y.

Bert Ely, a biologist at the University of South Carolina, offers this explanation:

Mitochondrial DNA (mtDNA) does not change very much, if at all, from generation to generation. The mtDNA passes only from a mother to her children; fathers cannot impart their mtDNA.

Mutations (changes) do occur in mtDNA but not often—less frequently than once per 100 descendants. Therefore, a person's mtDNA is probably identical to that of his or her direct maternal ancestor a dozen generations back, and this shared inheritance can be used to connect people across large spans of time. For example, if a particular type of mtDNA were found primarily in Africa, then we could conclude that people from elsewhere in the world who had that type of mtDNA had a maternal ancestor from Africa.

Unlike most DNA, mitochondrial DNA is not found in our chromosomes or even in the nucleus (the central enclosure that contains all the chromosomes) of our cells. Small membrane-bound structures present in all plant and animal cells, mitochondria are responsible for generating most of the energy needed for cell function. Each mitochondrion contains its own DNA and its own protein-synthesizing machinery.

Before people started to travel around the world, the rare changes that occurred in mtDNA resulted in unique types of mtDNA on every continent. Therefore, scientists can assign most contemporary mitochondrial DNAs to a continent of origin based on the region of the mtDNA—the so-called HvrI—where mutations are most likely to occur. Scientists can analyze the HvrI to find a record of all the past mutations as the mtDNA was transmitted from mother to daughter from one generation to another. These accumulated mutations are the basis for distinctive mitochondrial DNAs found on every continent.

Within continents, regional mtDNA variation exists as well. Because a woman's descendants are likely to settle nearby, mutations originating in her mtDNA generally will be confined to the local area where she lived. Whenever people moved from one place to another, of course, they took their mtDNA with them. People have moved extensively over time in sub-Saharan Africa, for example. As a result, a recent study has shown that approximately half of all African mtDNAs are shared among people from multiple countries in Africa.

How are seashells or snail shells formed?

Francis Horne, a biologist at Texas State University, provides an answer:

Shells, which are the exoskeletons of mollusks such as clams, oysters, snails and many others, are not made up of cells like typical animal structures. They are composed mostly of calcium carbonate with a small quantity of protein—usually less than 2 percent.

Mantle tissue located under and in contact with the shell secretes proteins and minerals to form the shell. First, an uncalcified layer of conchiolin—protein and chitin, a strengthening, naturally produced polymer—forms. Then comes the highly calcified prismatic layer, followed by the final pearly layer, or nacre. The process is analogous to laying down steel (protein) and pouring concrete (mineral) over it.

Whereas the bones of land animals such as humans grow with them, snails and clams have to gradually enlarge and extend their shells by adding new material at the margins. The newest part of a snail's shell, for example, is located around the cavity where the animal pokes out. The outer edge of its mantle continuously adds new shell at this opening. SA

For a complete text of these and other answers from scientists in diverse fields, visit www.sciam.com/askexpert

MATT COLLINS