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August 2011 ScientificAmerican.com

Energy
Biofuels' False Promise

Neuroscience
The Science of Better Learning

Evolution
The Rise of Longevity

Questions about the Multiverse

What lies beyond the cosmic horizon of 42 billion light-years

spread worldwide. See wine as an element of religions, socio-economies, cuisines, and pharmacopoeias of the ancient world.

Ancient Beer: A Global Perspective

Beer powered the ancient world from Africa's millet and sorghum beers, to the Middle East where barley and wheat beers were kings, to east Asia's rice beers. Join Patrick McGovern and discover the significant role beer played in societies worldwide, and the laboratory science that confirms and ties together historical aspects of beer.

BOTANY

Speaker: Spencer C.H. Barrett, Ph.D.

Plant Sex Made Easy

Flowering plants display spectacular floral diversity and complex sex lives. Knowledge of plant reproduction is crucial for understanding plant breeding and biotechnology, conservation biology, and genetically modified crops. Plant sex is fascinating — learn its evolution, details and implications for daily life.

Darwin's Legacy: the Form and Function of Flowers

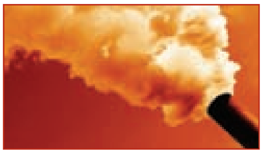
Charles Darwin studied floral biology for over 40 years. Many of Darwin's insights, gained from careful observations and experiments on diverse species, remain remarkably relevant and have stimulated current research on floral function and the evolution of mating systems.Discover a key yet lesser know aspect of Darwin's studies, updated.

Plant Evolution on Islands

Why do islands provide such a rich source of biological novelty for evolutionary enquiry? Learn the answers when we look at characteristic features of plant species on islands and compare the reproductive biology and genetics of island and mainland plant populations. Find out about the problems that are faced by plants that colonize and persist on islands.

Plant Invasions — More Than Just a Nuisance

Biological invasions cause huge economic losses and are also a major threat to biodiversity and ecosystem function. Where do plant invaders come from, what are their characteristic features and how best can we control them? Hear how the latest research is making progress toward protecting the environment and containing the risks of plant invasion.



ENVIRONMENTAL SCIENCE

Speaker: Richard Wolfson, Ph.D.

Global Warming: State of the Science

The first decade of the 21st century was the warmest since record keeping began in the mid-nineteenth century — and probably of the past two millennia. Observations and modeling suggest the dominant cause of this warming is human activity. Get the latest evidence for human-induced global warming, explore the science behind our changing climate, and learn scenarios for possible climate futures.

Energy Futures

Most of humankind's energy comes from fossil fuels — which are running out and which damage our planet. We face the monumental task of reshaping our energy system to run on sustainable sources that inflict less environmental harm. We'll assess current patterns of energy use and how we got here, and then take a realistic look at sustainable energy futures.

SCIENTIFIC AMERICAN Travel HIGHLIGHTS

ARECIBO OBSERVATORY

Explore the contributions and potential of radio astronomy at the celebrated Arecibo Observatory. Get an unparalleled behind-the-scenes tour of the iconic facility, and absorb an in-depth look at the unique contributions derived from Arecibo research and development.

Join us as we wind through the rainforest-blanketed karst terrain of Northern Puerto Rico. We'll get a sense of the massive physical scope of the Arecibo radio telescope. We'll boldly go where ordinary visitors are not permitted. NAIC scientists will update us about the radio astronomy, planetary radar discoveries, and climatology research at the observatory. From the monitoring of near-earth objects to cosmology, astrophysics, and global warming research, you'll gain insight into the vital activities at Arecibo. This $275 optional six-hour tour includes transportation, lunch, and entrance fees.

NASA'S KENNEDY SPACE (KSC) CENTER

NASA's launch headquarters, on the Space Coast, is the only place on Earth where you can tour launch areas, meet a veteran astronaut, and grasp the true enormity of the Space Program. Experience fun and wonder with Bright Horizons companions in this private pre-cruise, custom, full-day tour. Get ready to walk among and beneath giant rockets, discover what it takes to launch the Space Shuttle from preparation to liftoff, and soak in Kennedy Space Center's "The Right Stuff" vibe.

The KSC excursion is $575 pp and includes all of the above plus breakfast, lunch, and dinner; one-night hotel; and transportation to/from the KSC to our hotels in Ft. Lauderdale.

SCIENTIFIC AMERICAN

August 2011 Volume 305, Number 2

ON THE COVER

Cosmologists talk about parallel universes so often and with such conviction that you might be forgiven for thinking their existence is unquestioned. Not so. Many cosmologists remain deeply skeptical. While acknowledging the appeal of the multiverse concept, they think it is unproved—and probably unprovable. Illustration by Kenn Brown, Mondolithic Studios.

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FEATURES

Photograph by Andrew Hetherington

Accelerating Software Modernization with Artificial Intelligence

AI is radically transforming the way organizations evolve their software assets to achieve competitive advantage.

Artificial Intelligence (AI) is the quest to achieve comuters that equal or exceed human performance on complex intellectual tasks. A phenomenal development in AI is the recent emergence of automated computer language translation programs, driven by the need to modernize the nearly half trillion lines of legacy software developed during the latter half of the 20th century.

Just as chess programs routinely outperform grandmasters, leveraging AI technologies that evolved from the 1980s era USAF's Knowledge Based Software Assistant Program & emerging standards, computers can now understand and translate software applications with levels of proficiency that vastly exceed human performance. This technology is revolutionizing the way industries, such as finance, insurance, manufacturing, and healthcare as well as military and governments are modernizing their legacy systems.

Leading this field is The Software Revolution, Inc. (TSRI), a Kirkland, Washington-based company. Building upon 32 years of continuous R&D, TSRI's robust *JANUS* Studio® tool suite provides large-scale, error-free legacy system modernizations at 100% levels of automation. By applying AI to abstract software models, TSRI delivers automated code conversion with unprecedented target code quality, economies of scale, and schedule compression, accomplishing with small teams in months what would take years by other means. The following list of brief case studies represents five recent TSRI legacy system modernization projects.

European Air Traffic Management System (EATMS), Thales Air Systems: This real-time system manages over 100 million passenger flights annually. Thales engaged TSRI to transform EUROCAT's 2 million lines of legacy Ada into Java. On Monday, April 18th, 2011, the system went online for Air Traffic Control (ATC) use at the Shannon Center, in Ireland. This marked a milestone that is expected to lead to the use of the modernized ATC system at the 280 airports in Europe, Asia and Australia, where EUROCAT is currently in use. TSRIs 100% automation eliminated the risk of a manual rewrite of this safety critical system.

Patriot Missile, Fire Platoon Simulation & Battalion Simulation Support Systems, Raytheon: TSRI used the *JANUS* Studio® tool suite to modernize four different Patriot systems, including Patriot Japan. These modernizations included the transformation of nearly 200 thousand source lines of Fortran code to C++, re-factoring and documentation.

Major Healthcare Insurance Company: This system consisted of over 180 thousand source lines of PowerBuilder and nearly 3 million lines of COBOL. In modernizing this system, TSRI provided transformation, re-factoring, and supported system integration. This project was completed in only 15 months.

Major US Bank: This legacy application contained over 3 million source lines of Fortran and over 160 thousand lines of DCL. TSRI automatically generated a *Transformation Blueprint*™ to assist in the systems design architecture, performed the code documentation and provided and engineering support.

Advanced Field Artillery Tactical Data System (AFATDS), Stanley and Associates (Now CGI Federal): A version of their US Army's legacy AFATDS system consisting of over 5 million source lines of ADA-83. TSRI employed the *JANUS* Studio® tool suite to transform this system into Java in only 10 months. TSRI delivered the modern system to Stanley in August 2010.

Information Systems Transformation: *Architecture-Driven Modernization Case Studies* provides more detailed information on some of these case studies.

For more information, visit **www.tsri.com**.

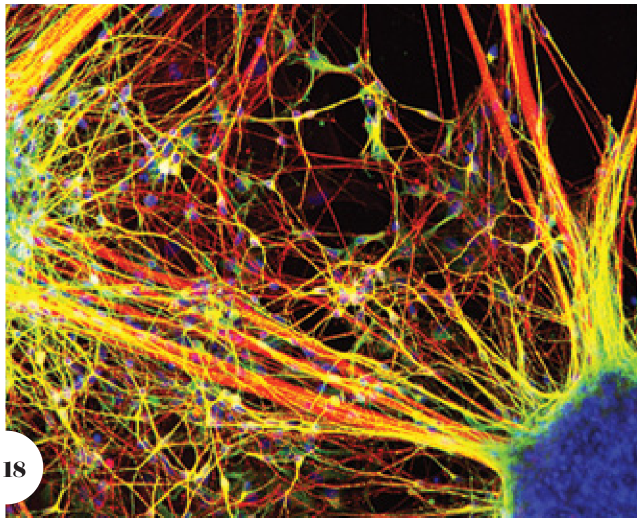
Information Systems Transformation:
Architecture-Driven Modernization Case Studies
By William M. Ulrich and Philip Newcomb
ISBN: 978-0123749130

About the book:
Architecture-Driven Modernization (ADM) gives you everything you need to know to update costly obsolete systems, transform data, and save millions of dollars.

Philip Newcomb
Founder and CEO of TSRI

Mr. Newcomb is an internationally recognized expert in the application of AI and formal methods to software engineering. After leaving Boeing he led a team of software engineers to develop TSRI's *JANUS* Studio® tool suite. Mr. Newcomb is the author of numerous papers, books and industry standards.

TSRI is a Platform Member of the OMG and leading contributor to the ADM Task Force (ADMTF) standards. TSRI's services and *JANUS* Studio® tool suite have served as the leading exemplar for the OMG's emerging ADMTF standards.



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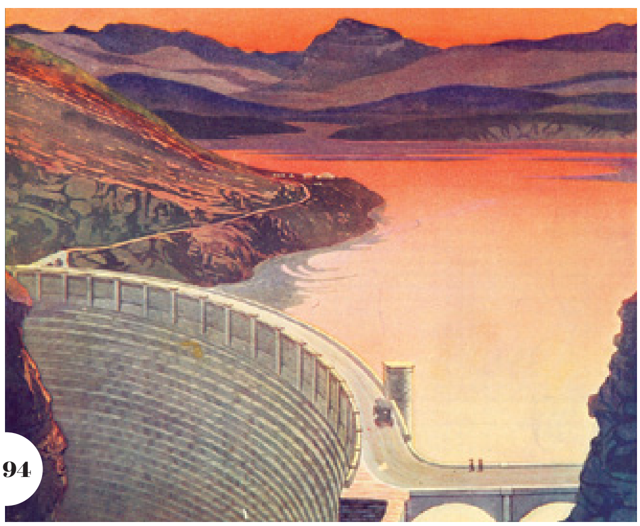

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SCIENTIFIC AMERICAN

DEPARTMENTS

ON THE WEB

Nobelists Greet the Next Generation

The annual Lindau meeting in Germany brings together Nobel laureates with young researchers from around the world. This year's meeting focused on physiology and medicine. *Go to www.ScientificAmerican.com/aug2011/lindau*

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Mariette DiChristina is editor in chief of *Scientific American*. Find her on Twitter @SAeditorinchief

A Future with Science

A DECADE AFTER THE FALL OF THE SOVIET UNION IN 1991, modernization is the watchword in Russia—with science as a vital means to that end. During the spring meeting of the 14 international editions of *Scientific American,* we gathered in Moscow, and our hosts introduced us to many of the surrounding issues.

Scientific American has had a long history in this country, where it has been available in translation for 28 years. The edition's head, Sergei Kapitza, is a beloved researcher, science popularizer and TV personality—the Carl Sagan of Russia. When the Soviet system unraveled, however, science took a backseat to other domestic matters. Researchers lost funding and social status, crippling the former science powerhouse. Up to 35,000 scientists emigrated—a loss that the government is now trying to rectify with targeted programs.

The state-owned venture capital company Russian Corporation of Nanotechnologies, or Rusnano, will spend some 318 billion rubles (around $11 billion) in public-private partnerships aimed at creating a self-sustaining nanotech industry by 2015. (Today Russia's nanotech products account for just 2 percent of the global market.) "Our role is to build this bridge [between science and business] and to start up the Russian nanotechnology industry," Anatoly Chubais, CEO of Rusnano, told the *Scientific American* visitors. Of some 2,000 applicants, Rusnano has so far chosen to help fund 111 companies to build manufacturing facilities.

In an initiative to entice expatriates and foreign scientists to conduct basic research in Russia, the government recently set up a system of "mega grants" totaling 12 billion rubles (about $433 million). The money will help, but Russian science still suffers from the challenges of low pay and stifling bureaucracy, as Vladimir E. Fortov, academician of the Russian Academy of Sciences, explained to me. Scientists need to fill out multiple forms to get basic tools, hindering progress, and technology transfer is difficult.

Despite the problems, Russia has rightly realized that future prosperity will come from fostering science in the present, and it is devoting significant funds toward that goal. It is a lesson that the budget-sensitive U.S., which has long benefited from earlier investment in basic research, should reflect on as well. SA

Members of *Scientific American*'s 14 international editions came together this spring in Russia.

COURTESY OF RICHARD ZINKEN *Spektrum der Wissenschaft*

Illustration by Nick Higgins

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April 2011

RED PLANET MARS LIFE

Lawrence M. Krauss's "Rethinking the Dream" [Forum] rightly points out that the benefits of flying humans in space have not been commensurate with the cost, especially when human flight is compared with advanced robotic or automatic systems that can do many of the same tasks at one tenth of the cost and with no risk to humans. I think this is a result of NASA's focus on dramatic, exciting exploration and failure to create an economical, durable infrastructure. I disagree with Krauss only where he advocates one-way missions to Mars. I believe that keeping humans alive on the planet for more than a few weeks will be extremely costly.

The Martian atmosphere is very thin and contains essentially no oxygen. The average surface temperature is about –60 degrees Celsius. Humans must always be in a pressurized enclosure, with a suitable atmosphere and adequate temperature and humidity control. Unlike Earth, Mars does not have a protective magnetic field, and the thin atmosphere provides little shielding from cosmic rays. I suspect some rather heavy shielding will have to be included in any habitats, rovers, and so on.

Living off the land is, I think, absolutely ruled out on Mars, where there is no free water and what water ice there is seems to lie below the surface. To be of

"Keeping humans alive on Mars for more than a few weeks will be extremely costly."

DON PETERSON *RETIRED NASA ASTRONAUT*

use, it would have to be collected, thawed and purified.

NASA has learned that an average human will require about five kilograms of food, water and oxygen each day and will produce an equal amount of waste. Of course, water can be recycled, oxygen can be extracted from CO_2 and solid waste can be treated, but all that requires power and equipment. Solar arrays on Mars must be twice the size of Earth arrays because solar radiation is weaker (the planet is farther away from the sun). And the arrays will likely require cleaning from Martian dust. For safety reasons, there must also be redundant equipment, plus tools and spare parts for repair. Solid food cannot be recycled, and growing food would require a large, totally enclosed "hothouse."

The habitat must have air locks to enable humans and their rovers to get in and out without depressurizing the entire living environment. Surface excursions must not go so far from the habitat that participants will not be able to walk back in case their rover breaks down. Furthermore, if a sortie lasts longer than a few hours, the rover must provide food, water and toilet facilities.

Finally, there are human considerations that do not factor directly into costs but that I think make the whole idea unfeasible. Will the colonial-nauts include a doctor? Will the habitat include clinical/hospital facilities? What about recreation? What about normal family life? What happens when the colonial-nauts age and die?

Most of all, why would anyone go?

Don Peterson
Retired U.S. Air Force pilot and NASA astronaut
El Lago, Tex.

COCKTAIL PARTY CHATTER

I am deaf in one ear, and even though my hearing is much better than most, I experience the issues described in Graham P. Collins's "Solving the Cocktail Party Problem" every day. For me, it is only when a room is very noisy and I am struggling to comprehend the conversation that I notice the process I use to solve the cocktail party problem. My technique seems to be a combination of those mentioned in the article. As in spread-spectrum signal processing, once I know what a person sounds like, I listen for the sounds he or she is making. Second, I take in the sounds and try to reconstruct the words based on the expected probability of sounds surrounding each one. Finally, I use the probability of words surrounding each one based on the context to fill in the sentence. I knit the sounds into words and the words into a sentence.

This procedure is imprecise and adds a time delay. It is very common for me to knit a sentence together several seconds after everyone else heard it. Everyone laughs, and seconds later I get to "hear" the punch line in my head. Having to do all this processing does have an upside. Sometimes the combination of words that my mind has rejected sounds like what was said and has a message that is related to the topic but creates an absurd vision in my head. Periodically the incorrect interpretation of the sounds is more entertaining than what was actually said.

Kee Nethery
Berkeley, Calif.

BIOTECH FOOD AND DRUGS

Both Brendan Borrell's interview with agro-research czar Roger Beachy ["Food Fight"] and Mary McKenna's "The Enemy Within" point to a serious disconnect between research, learning and hopes for applications of that research. Beachy says that crops with permanent resistance to pests are "almost unheard of," and McKenna shows us how scary the future of infection may be with antibiotic-resistant bacteria winning over the development of new medicines. There is no difference between the loss of valuable antibiotics to ever more resistant bacteria and the fight with pests through ge-

JAMES WEBB SPACE TELESCOPE

As the successor to the Hubble Space Telescope, NASA's James Webb Space Telescope will allow astronomers to examine the Universe in its early years. The Webb's sophisticated high resolution and sensitive infrared technology will enable observations that extend the reach of science. So whether it's looking at the farthest galaxies, examining the birth of stars, or studying planets that might harbor life, the James Webb Space Telescope will find answers to life's greatest questions—and answer the questions we haven't even thought of yet.

netic engineering. In only a few years, with the planet's food-production capability more strained by population demands, major crop harvests may well follow the same hazardous, on-the-edge life we humans are walking ourselves into as a result of not learning our lessons from history nor from one another.

Scott C. Reuman
Nederland, Colo.

FAMILY ALBUMS OF THE FUTURE

David Pogue laments in "Seeing Forever" [TechnoFiles] that current digital media may not last long. And it is good that in 100 years 99.9 percent of all images, video and audio recordings will be gone. Who cares about Uncle Joe's photos from his 2005 vacation in Florida or Italy? Future generations need their own memories plus the very best from past generations. Nobody in the year 2100 will have the time to look at pictures from their forebears of the past 100 years. They need to build their own memories.

Marc Tomaszewski
Friedrichshafen, Germany

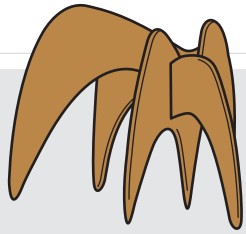
LIVING DREAM

Eitan Haddok's "Can the Dead Sea Live?" shows how pragmatism can give hope. A project involving salvation of an extraordinary body of water brings together three politically disparate regions: Israel, Jordan and the Palestinian Authority. It is a rare example of cooperation in the midst of a bitter area of human conflict. An organization that has been monitoring the project, Friends of the Earth Middle East, consists of participants from each of those regions. The organization, and specifically its undertaking to save the Dead Sea, is a wonderful example of how the effort to save a precious resource can raise people above endless, vicious political squabbling.

Stanley P. Santire
Houston

ERRATUM

"Can the Dead Sea Live?" by Eitan Haddok, described a plan that would inject 1.1 million cubic meters of briny water into the Dead Sea; in fact, the amount would be 1.1 billion cubic meters.



Winner of the 2011 National Magazine Award for General Excellence

LETTERS TO THE EDITOR

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Letters may be edited for length and clarity. We regret that we cannot answer each one. Post a comment on any article at ScientificAmerican.com/aug2011

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Stand and Deliver

Reenergizing science and math education in the U.S. has to begin with the teachers

Jaime Escalante, renowned math teacher

CALCULUS DOES NOT HAVE TO BE MADE EASY—IT IS EASY ALREADY. That banner used to grace the Los Angeles classroom of someone once called the best teacher in America. Jaime Escalante, the unconventional calculus teacher who was depicted by Edward James Olmos in the 1988 film *Stand and Deliver,* died last year of cancer at the age of 79. The year before the film, more students from Garfield High School took the AP calculus exam than at all but three other public schools in the country, with two thirds passing.

Half a year after his death the Obama administration weighed in on the state of science, technology, engineering and mathematics (STEM) education in this country. The report, "Prepare and Inspire," reviewed the sobering statistics about how our K–12 schools suffer by comparison to their counterparts in other developed nations. It called for recruiting and training 100,000 STEM teachers. President Barack Obama mentioned STEM as a priority in his State of the Union address this year, and advocates for science education have been pressing to get student science performance incorporated into the No Child Left Behind law.

But achieving these goals is not going to be easy. The report noted that 25,000 STEM teachers leave the workforce every year, mostly because of disgruntlement with their jobs and lack of professional support. To attract and retain enough science and math teachers will require an elevation in their status and a thorough revamping of attitudes toward the entire profession.

Escalante's career illustrates why. From a job mopping floors after he arrived in the 1960s from his native Bolivia, Escalante procured much better paying work as a technician at an electronics company. From there he went on to get a teaching credential to pursue a passion that dated back to his early years in Bolivia. In 1974, at the age of 43, Escalante decided to take a lower salary as a math teacher at Garfield. He made academic successes of many of his poor Hispanic charges, but first, he had to overcome the system's built-in inertia. Garfield initially assigned him to teach what would have been the equivalent of fifth-grade math in Bolivia, and he had to convince school administrators that students there were capable of learning math at a higher level.

Few teachers are willing to run a similar professional gauntlet—nor should they. The onus to improve schools should be on federal, state and local educational strategists. The first step should be to tap the strengths of the existing teaching pool. We must identify today's Escalantes—the top 5 percent of the nation's STEM teachers—and, as recommended in the administration report, induct them into a STEM master teachers corps that would receive salary supplements and federal funding to support their activities.

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Second, we need to give all teachers the tools they need. Escalante brought toys to class: a plastic monkey climbing up and down a pole illustrated the inverse function. Teachers shouldn't have to rely on homemade props. We should form the equivalent of an Advanced Research Projects Agency to help develop educational technologies, including "deeply digital" instructional materials that encourage active participation. At the same time, we should recognize that new technology isn't a solution in itself and shouldn't come at the expense of other needs. Many schools get grants and donations for the latest computers and software yet can't buy books for their libraries or beakers for their science labs.

Finally, we should shift our emphasis from standards to implementation. Developing new standards does have a role, but the problem for most schools is not a lack of good curriculum options. It is the difficulty of putting them into practice, given the day-to-day pressures that teachers are under. If anything, new standards and tests often get in the way by forcing educators to teach to the test, rather than encouraging critical thinking.

To meet all the goals set by the White House report would require an extra $1 billion each year. Against the nearly $600 billion spent annually for public education, it is not a huge sum. Still, with local districts faced with declining tax revenues and unfunded mandates, some of the money will have to come from the federal government.

That goes against the grain during a time when teachers' salaries and benefits are being cut. Yet the costs of doing nothing are a matter of simple calculus. If we do not improve STEM education, the U.S. will continue a decades-long slide from the middle of the pack in student achievement toward the very bottom. SA

DAVID BUTOW *Corbis*

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Commentary on science in the news from the experts

Kenneth I. Kaitin is director of the Tufts Center for the Study of Drug Development and a research professor at the Tufts University School of Medicine.

Christopher P. Milne is associate director of the Tufts Center for the Study of Drug Development and a research assistant professor at the Tufts University School of Medicine.

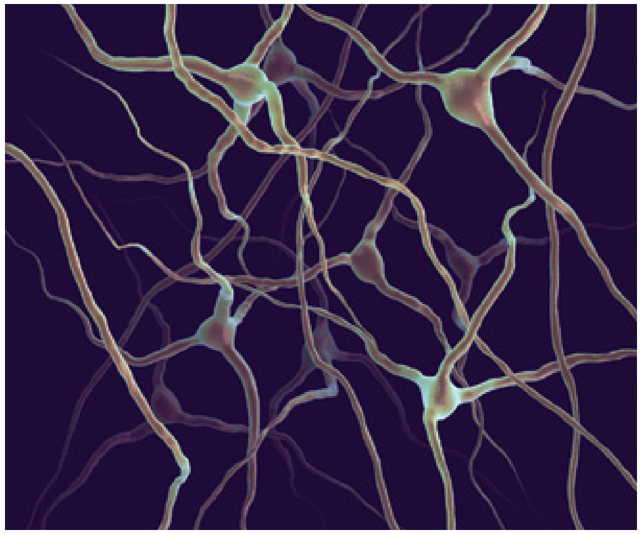
A Dearth of New Meds

Drugs to treat neuropsychiatric disorders have become too risky for big pharma

Schizophrenia, depression, addiction and other mental disorders cause suffering and cost billions of dollars every year in lost productivity. Neurological and psychiatric conditions account for 13 percent of the global burden of disease, a measure of years of life lost because of premature mortality and living in a state of less than full health, according to the World Health Organization.

Despite the critical need for newer and better medications to treat a range of psychiatric and neurodegenerative diseases, including Alzheimer's and Parkinson's, drugs to treat these diseases are just too complex and costly for big pharmaceutical companies to develop. The risk of spending millions on new drugs only to have them fail in the pipeline is too great. That's why many big drug companies are pulling the plug on R&D for neuropsychiatric and other central nervous system (CNS) medicines.

Our team at the Tufts Center for the Study of Drug Development has arrived at this conclusion after conducting surveys of pharmaceutical and biotechnology companies about the drug development process. These surveys allow us to generate reliable estimates of the time, cost and risk of designing new drugs. Our analyses show that central nervous system agents are far more difficult to develop than most other types.



Central nervous system is hard to treat: a new neuropsychiatric drug typically takes 18 years to go from lab bench to patient.

GARY CARLSON *Photo Researchers, Inc.*

One of the problems with neuropsychiatric drugs is that they take so long to develop. A CNS drug, we have found, will spend 8.1 years in human testing—more than two years longer than the average for all agents. It also takes more time to get regulatory approval—1.9 years, compared with an average of 1.2 years for all drugs. Counting the six to 10 years typically spent in preclinical research and testing, CNS drugs take about 18 years to go from laboratory bench to patient.

Few compounds survive this gauntlet. Only 8.2 percent of CNS drug candidates that begin human testing will reach the marketplace, compared with 15 percent for drugs overall. Failures also tend to occur later in the clinical development process, when resource demands and costs are at a peak. Only 46 percent of CNS candidates succeed in late-stage (phase III) trials, compared with 66 percent on average for all drugs. As a result, the cost of developing a CNS drug is among the highest of any therapeutic area.

What makes these drugs so risky? Assessing whether or not a candidate for, say, a new antibiotic works is relatively straightforward—either it kills the bacterium or it doesn't—and a course of treatment typically lasts a few days, which obviates the need for long-term testing for safety and efficacy. CNS compounds, in contrast, have it a lot tougher. It is difficult to judge if a reduction of schizophrenic episodes or a cognitive improvement in Alzheimer's patients is the result of a drug or a random fluctuation in the patient's condition. Treatment periods can last as long as a patient's lifetime. It is no wonder success rates are low.

Some help is on the way. The Coalition Against Major Diseases, made up of government agencies, drug companies and patient advocacy groups, has developed a standardized clinical trials database that will allow researchers to design more efficient studies of new treatments, initially for Alzheimer's and Parkinson's. President Barack Obama's health reform law also contains several provisions that could provide incentives for innovation in areas of unmet medical need. One is the Cures Acceleration Network, which authorizes the National Institutes of Health to help academic researchers screen for promising compounds. Ultimately, making new CNS medicines may depend on a networked approach to innovation, in which many organizations share in the risks and the rewards. It is clear that the challenges of developing new neuropsychiatric medicines are greater than any one company, institution or organization can bear alone. SA

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Disclosure: *The Tufts Center for the Study of Drug Development is funded in part by unrestricted grants from pharmaceutical and biotechnology firms.*

Neurons derived from a patient with schizophrenia.

NEUROSCIENCE

Mental Illness in a Dish

A new technique offers scientists an unprecedented window into complex psychiatric disorders

No organ in the human body is as resistant to study as the brain. Whereas researchers can examine living cells from the liver, lung and heart, taking a biopsy of the brain is, for many reasons, more problematic.

The inability to watch living human brain cells in action has hampered scientists in their efforts to understand psychiatric disorders. But researchers have identified a promising new approach that may revolutionize the study and treatment of conditions such as schizophrenia, autism and bipolar disorder. A team led by researchers at the Salk Institute for Biological Studies in La Jolla, Calif., took skin cells from a patient with schizophrenia, turned them into adult stem cells and then grew those stem cells into neurons. The resulting tangle of brain cells gave neuroscientists their first real-time glimpse of human schizophrenia at the cellular level. Another team, from Stanford University, converted human skin cells directly into neurons without first stopping at the stem cell stage, potentially making the process more efficient. The groups published their results recently in *Nature* (*Scientific American* is part of Nature Publishing Group).

Scientists have used the disease-in-a-dish strategy to gain insight into sickle-cell anemia and heart arrhythmias. But the Salk team, led by neuroscientist Fred H. Gage, is the first to apply the approach to a genetically complex neuropsychiatric disorder. The group found that neurons derived from patients with schizophrenia formed fewer connections with one another than those derived from healthy patients; they also linked the deficit to the altered expression of nearly 600 genes, four times as many as had been previously implicated. The approach may eventually improve therapy, allowing psychiatrists to screen a variety of drugs to find the one that would be most effective for each patient, Gage says.

Whereas the research is still preliminary, many neuroscientists are excited by it. "This study opens up a whole new area of work," says Daniel Weinberger, director of the Genes, Cognition and Psychosis Program at the National Institute of Mental Health. It is unclear what answers the stem cells approach can provide, but by making the inaccessible accessible, it opens up questions that until now could not have been asked. —*Tim Requarth*

"MODELLING SCHIZOPHRENIA USING HUMAN INDUCED PLURIPOTENT STEM CELLS," BY KRISTEN J. BRENNAND ET AL., IN *NATURE*, VOL. 473; MAY 12, 2011

FURTHER READINGS AND CITATIONS ScientificAmerican.com/aug2011/advances

BIOLOGY

A Skill Better than Rudolph's

Reindeer can spot predators and food against a snowy backdrop thanks to an unusual ability to see UV light

To humans, ultraviolet (UV) radiation is a menace: we cannot see it, yet it is all around us, increasing our risks of melanoma, cataracts and other ills. It is especially harmful in the upper latitudes, where a thinning ozone layer has become less and less effective at blocking the sun's UV rays, and ice and snow reflect them back up at us. All these facts have caused biologists to wonder: How have Arctic mammals adapted to handle acute UV exposure—not only tolerating the intense light conditions at the poles, but even using it as an evolutionary advantage?

A study of reindeer has shed some light on this question. Glen Jeffrey and his colleagues at University College London and the University of Tromsø in Norway report evidence that this iconic Arctic species is not only resistant to eye damage from the intense UV rays but is also able to perceive UV light, which is invisible to all but a few mammals, such as some species of rodents, bats and marsupials. They published their findings recently in the *Journal of Experimental Biology.*

Being able to see UV light confers some rich benefits on the reindeer. Its primary winter food source, lichens, and the fur of its main predator, the wolf, both absorb UV light, which makes them stand out against the UV-reflecting snowy landscape.

UV vision actually has deep roots in the mammalian family tree: hundreds of millions of years ago early mammals had a short-wave-sensitive visual receptor, called SWS1, that could detect UV rays. That sensitivity is thought to have shifted toward longer waves—away from short UV wavelengths—because mammals were mainly nocturnal and UV vision was of little use to them at night. This shared ancestral UV sensitivity may explain why a small yet diverse set of mammals has regained the ability to see UV light. If scientists can figure out how the reindeer prevent UV rays from damaging their eyes, it could lead to new ways of treating vision loss in people. The average person loses 20 to 30 percent of central photoreceptors over the course of a life, mostly attributable to light exposure. "We might be able to better deal with age-related cell loss in the retina and perhaps age-related macular degeneration," Jeffrey says.

In the meantime, the revelation that reindeer are able to perceive UV light while also resisting damage from these powerful rays will open a new door to understanding how Arctic animals have adapted to survive in one of the earth's most extreme habitats.

—Anne-Marie Hodge

ASTRONOMY

Ageless. No Plastic Surgery Required

A new study may help scientists determine when stars were born

Stars of the sky play a bit coy with their ages—an ancient star can often pass for a much younger one. That is a problem for astronomers seeking out habitable planets orbiting distant stars because a star's age correlates with the life-forms it could support.

"We know from studying our own planet that if the star and the planet [are] about one billion years old, only the most primitive microbial life might exist," said Søren Meibom of the Harvard-Smithsonian Center for Astrophysics at the May American Astronomical Society meeting in Boston. "Is it perhaps 4.6 billion years old? Well, all of a sudden we know we could have a planet teeming with complex and intelligent life."

But, as Meibom put it, "stars do not have birth certificates." And many visual attributes remain the same for most of a star's life. One feature, though, does change: stars spin more slowly as they grow old. "And so we can use the spin rate, the rotation rate of a star, as a clock to measure its age," Meibom said.

But first someone has to paint the numbers on the face of that clock. Researchers have already pinned down the relation between rotation and age for very young stars. So Meibom and his colleagues are measuring the rotation rates of older stars. If they can figure out the relation between age and rotation for many vintages of stars, a star's age will be much easier to estimate. No birth certificate required.

—John Matson

PAUL NICKLEN *National Geographic/Getty Images (reindeer)*; COURTESY OF NASA, ESA AND AURA/CALTECH *(stars)*

COMPUTER SCIENCE

Parsing the Twitterverse

Smarter language processors are helping experts analyze millions of short-text messages from across the Internet

Researchers have been trolling Twitter for insights into the human condition since shortly after the site launched in 2006. In aggregate, the service provides a vast database of what people are doing, thinking and feeling. But the research tools at scientists' disposal are highly imperfect. Keyword searches, for example, return many hits but offer a poor sense of overall trends.

When computer scientist James H. Martin of the University of Colorado at Boulder searched for tweets about the 2010 earthquake in Haiti, he found 14 million. "You can't hire grad students to read them all," he says. Researchers need a more automated approach.

One promising method is to develop programs that label words in tweets with parts of speech—such as subject, verb and object—and then use those tags to determine what each tweet is about. This method, called natural-language processing, is not a new idea, but applying it to short social text is new and growing. "That is just a huge area right now," Martin says.

Scientists at the Xerox-owned Palo Alto Research Center recently developed one such program. It relies on text processors, called parsers, which are typically tested on news articles. Parsers can distinguish between words and punctuation, label parts of speech and analyze a sentence's grammatical structure. But "they don't do as well on Twitter," says Kyle Dent, one of the Palo Alto researchers. He and his co-author wrote hundreds of rules to account for hash tags, repeated letters (as in "pleaaaaaase") and other linguistic features perhaps not common in the *Wall Street Journal*. They will present their work on August 8 at an Association for the Advancement of Artificial Intelligence conference in San Francisco.

Dent and his colleagues also tried to use their program to distinguish between rhetorical questions and those that require a response. Businesses could use such a program to find what people are asking about their products. In a recent trial, their program classified 68 percent of 2,304 tweets correctly. "For a brand-new field, that sounds like a decent first attempt," says Jeffrey Ellen of the Space and Naval Warfare Systems Command, which provides intelligence technology to the U.S. Navy.

Although Twitter-trawling technology is not yet ready to deploy, as a field, "it's getting there pretty quickly," Martin says. Once it matures, researchers should have access to an unprecedented trove of data about human behavior. For the first time in history, "water-cooler talk" is recorded and publicly available, Ellen says. "A hundred years ago we just didn't know what everybody was thinking."

—Francie Diep

WHAT IS IT?

Exploding with lightning: The eruption at the Puyehue-Cordón Caulle Volcanic Complex, a chain of volcanoes in Chile, spewed ash clouds up to 45,000 feet into the air in early June. Volcanic ash consists of pieces of rock, glass and other minerals. A plume also carries static electricity—the separation of positive and negative charges—so "these large ash clouds from eruptions like Puyehue-Cordón Caulle can generate their own lightning," says Erik Klemetti, assistant professor of geosciences at Denison University. The plume from the eruption—the volcanoes' first in more than two decades—was so great it was seen from space and spread as far as Tasmania.

—Ann Chin

CARLOS GUTIERREZ *Reuters*

Illustrations by Thomas Fuchs


THEY JUST SCORED HUGE
ENERGY SAVINGS. WANT THEIR SECRET?
NAME: Carolina Watt-Busters, Morrison Residence Hall, UNC Chapel Hill
WINNERS OF: EPA's first-ever National Building Competition
SAVINGS: 36% reduction in energy use | $250K in one year
CAROLINA

INFECTIOUS DISEASE

Anatomy of an Outbreak

Researchers untangle the genetics of how a crippling virus mutated and spread via mosquito from Africa to Asia

Chikungunya is a scary-sounding virus with some scary symptoms: joint pain so excruciating that patients often can't stand or even sit upright for months. The mosquito-borne virus got its start thousands of years ago in southeastern Africa, where it generally caused a slow but steady stream of cases. About 50 years ago a mild strain of the virus spread to Asia. Then, following a drought in Kenya in 2004, cases of chikungunya in Africa soared and spread eastward across the Indian Ocean, causing severe disease and affecting hundreds of thousands of people across Asia.

This new strain of chikungunya is apparently replacing the older, milder strains that previously circulated in Asia. But how? In a study published in the *Proceedings of the National Academy of Sciences USA,* researchers have figured out that as it traveled, the virus picked up a single mutation that allowed it to be transmitted much more efficiently by Asian mosquitoes.

Scott Weaver, an infectious disease specialist at the University of Texas Medical Branch in Galveston, compared the preoutbreak African and Asian strains with the newer outbreak strain. He and his colleagues found two mutations that made it possible for the bug to hitch its fortunes to the Asian tiger mosquito (*Aedes albopictus*)—a ubiquitous insect that transmits the virus 100 times better than its previous host, the rarer *A. aegypti.* Some of the older African strains contained one of these variations, whereas the older Asian strains did not. That made it difficult for the strain that traveled to Asia 50 years ago to adapt to the Asian tiger mosquito. When the recent outbreak started in Africa, the virus needed only one mutation to adapt to the Asian tiger mosquito and become more virulent. "It's an elegant and very convincing study," says Peter Palese, a virologist at the Mount Sinai School of Medicine who was not involved in the research.

Understanding how genetic mutations increase or decrease a virus's ability to be passed on by mosquitoes may one day help public health officials take action to prevent an outbreak before it starts, Weaver says.

—*Carrie Arnold*

Asian tiger mosquito

RESEARCH

All Together Now

Scientists take peer review public

Highly technical scientific debates are usually hashed out behind closed doors—in labs, in subscription-based journals, in the hallways at conferences attended only by a few specialized researchers. But in May the rest of us saw three real academic arguments playing out in public, largely via Twitter, blogs and wikis. The episodes have cheered supporters of the open-science movement, but some critics worry that the debates might descend into cacophony. Either way, the stories illustrate one clear fact: science is not usually a series of eureka moments so much as a messy, human process.

First, there was "#arseniclife," which began with a controversial study, first published in the online version of *Science,* suggesting that some bacteria could build DNA with arsenate in place of phosphate. Scientists quickly tried to poke holes in the researchers' methods via blogs and Twitter (hence the controversy's nickname, taken from the practice of categorizing tweets with hash tags), and the debate bounced back into the print version of *Science,* which took the unusual step of publishing eight sharp critiques of its own paper in May. Meanwhile at *Nature* standard peer review had also taken an unusually public turn. Reviewers almost always keep their identities under wraps, but one outed himself online, saying he had been "desperately upset" when the journal published a paper about extinction rates that he had criticized.

Also in May, *Nature Genetics* published online the results of its own experiment in open scientific debate. A team of researchers writing a paper on best practices for following up on new biological hypotheses coming out of genomics solicited opinions in an online forum. The scientists also threw the writing process open on WikiGenes, a collaborative Web site. Did the experiment succeed? *Nature Genetics* seemed pleased: it published an editorial noting that the conversation had been so thorough that publication could proceed "without further need for supervised peer review." But one contributor, a graduate student named Giovanni Marco Dall'Olio, had a quibble: "They did not include almost anything from what has been contributed in the wiki." He wrote that criticism, of course, on his blog.

—*Mary Carmichael*

ALEX WILD *Corbis*

COMMENT AT ScientificAmerican.com/aug2011

MICROBIOLOGY

E. coli on the March

Toxic strains of a common gut microbe are multiplying

If the full name of any germ could be a household word, it would be *Escherichia coli* O157:H7, a bacterium that has in the past caused severe food poisoning linked to Jack in the Box hamburgers, Taco Bell lettuce and prepackaged spinach. Now *E. coli* O157:H7 is being overshadowed by more virulent strains of what is normally a benign gut microbe. This spring a recently identified strain of *E. coli,* O104:H4, killed dozens of people in Europe and landed hundreds more in the hospital. The U.S. Centers for Disease Control and Prevention is now following at least six types of so-called Shiga toxin *E. coli,* which, like O104:H4 and O157:H7, cause bloody diarrhea and, in extreme cases, fatal kidney failure. Below are some surprising facts you may have missed in this spring's headlines.

1 Antibiotics can worsen an *E. coli* infection. Giving antibiotics, including fluoroquinolones such as Cipro, can kill a patient who has been sickened by any strain of Shiga toxin *E. coli.* The reason: when the bacteria die, they release the toxin in massive amounts. Fortunately, one particular group of drugs, called carbapenems, seems to not trigger a major toxin release, but these drugs are generally prescribed only in special circumstances. This explains why travelers who bring antibiotics with them as a precautionary measure should not take them if they develop bloody diarrhea.

2 *E. coli* O104:H4 is resistant to at least 14 antibiotics. Why this is so remains a mystery, particularly because many of these drugs are not usually used to treat *E. coli* infections. Somewhere along the line, either these bacteria or other bacteria with which they exchanged genetic material must have developed in an environment that was awash in antibiotics—possibly a hospital or a farm.

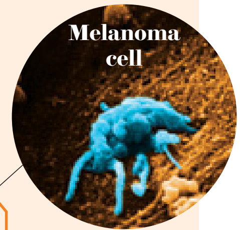
3 *E. coli* O104:H4 may eventually show up in the U.S. The CDC has already confirmed a few cases in U.S. residents who had recently traveled to Germany. Whereas health officials do not believe the current outbreak will spread in the U.S., a similar strain of *E. coli* could evolve here independently at some point.

4 *E. coli* O157:H7 is becoming less of a threat. That is because the government has made it mandatory for food producers to report its presence to health authorities. But the number of ailments caused by the other Shiga toxin *E. coli* strains is growing rapidly. Many food-safety specialists believe that requiring food producers to report more *E. coli* strains to the government would help reduce the incidence of illness.

—Christine Gorman

NEWS SCAN

Genius



Cloud-borne bacteria may be to blame for rain, snow and hail because they affect the way water molecules bind. Does that mean snowballs are germ warfare?

Trials of two different drugs show promise in treating advanced melanoma, which is usually fatal.

NASA finds "a significant amount" of water on the moon, heightening the practicality of a future lunar base just as the space shuttle program draws to a close.

The Milky Way may contain many billions of stray, Jupiter-size planets that were kicked out of their solar systems and left to wander space on their own. This would mean there are many, many more planets than stars, making earthlings even more insignificant.

The World Health Organization issues a finding that cell phones are "possibly carcinogenic." An informal visual survey in New York City shows no apparent reduction in use.

—George Hackett

Folly

CORBIS (*sprouts*); PHOTO RESEARCHERS, INC./COLORIZATION BY JESSICA WILSON (*melanoma*); COURTESY OF R. HURT/SSC, JPL/CALTECH AND NASA (*Milky Way*); COURTESY OF NASA/JPL/USGS (*moon*); ÖZGÜR DONMAZ *iStockphoto* (*cell phones*)

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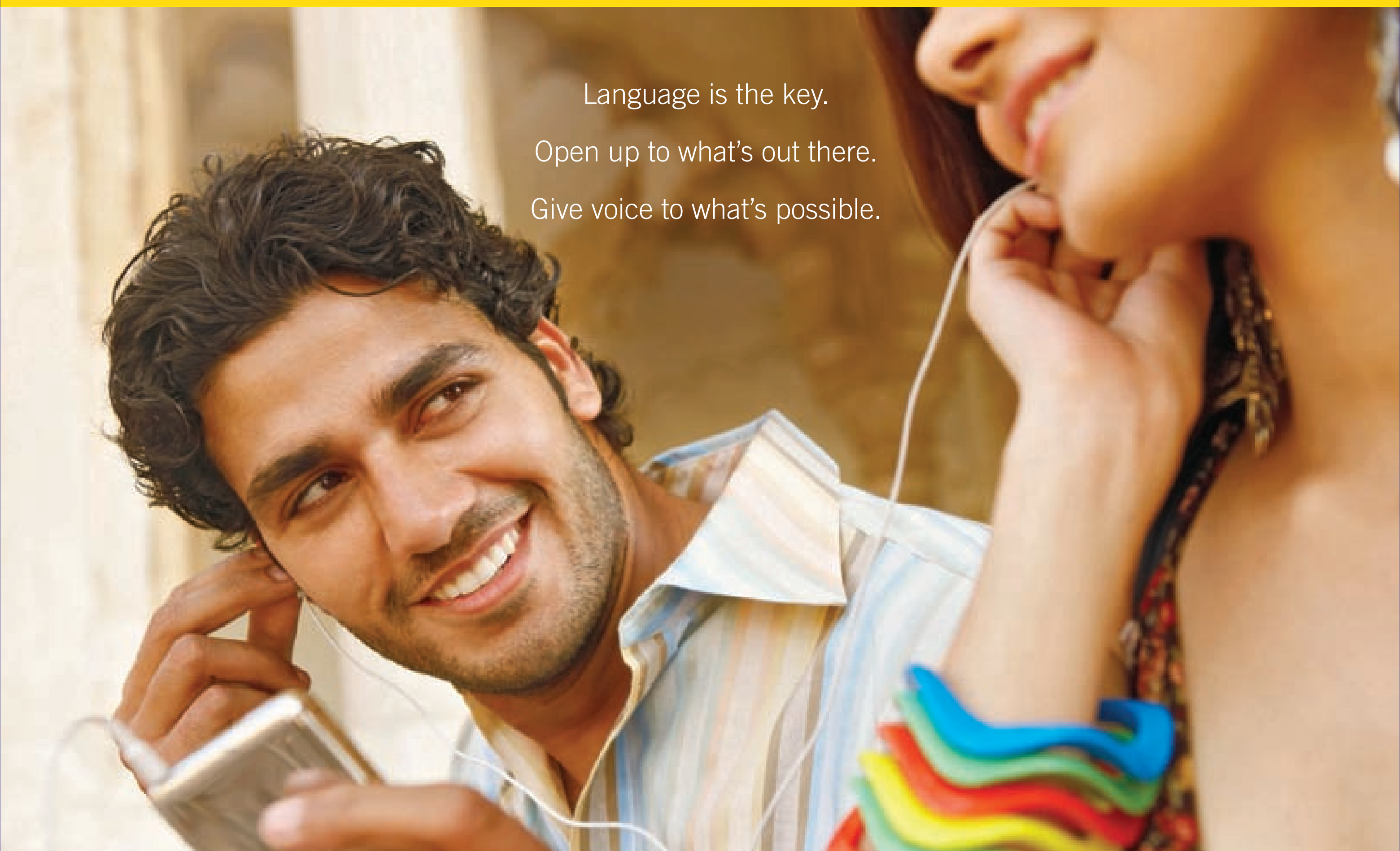
Possibilities.



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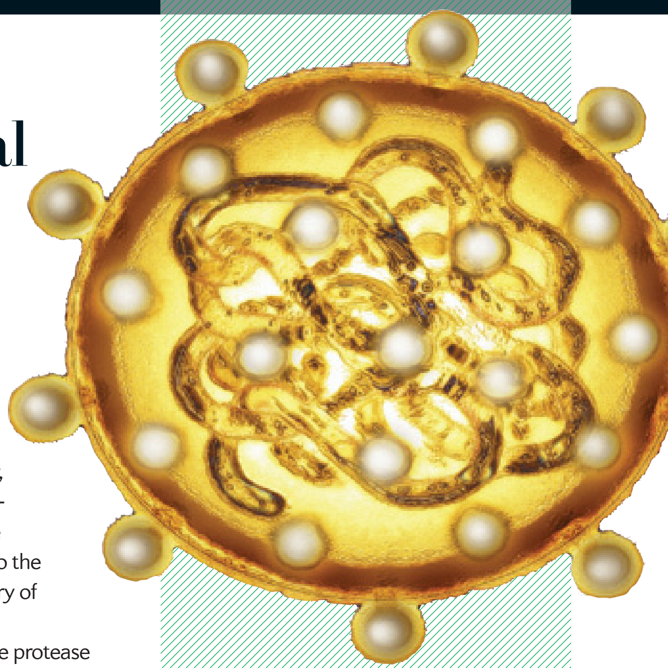
MEDICINE

Going Viral

New hepatitis C drugs owe their success to HIV



The treatment of hepatitis C virus infections has taken a major step forward with the U.S. Food and Drug Administration's approval of two new drugs, telaprevir and boceprevir, for managing the disease. Blocking the same viral protein as the first anti-HIV drugs, they are also the latest chapter in an ongoing story of medical success.

Telaprevir and boceprevir are protease inhibitors, thwarting the activity of key viral enzymes. The first in this class of drugs was saquinavir, available since 1995 for the treatment of HIV. Several protease inhibitors have subsequently been developed for HIV, but the new hepatitis C drugs are the first to tackle other viruses.

The protease targeted by the anti-HIV and anti–hepatitis C drugs is involved in a process called cleavage. These viruses insert their RNA into the host cell. That genetic information is then used to create a single, long strand of proteins, called a polyprotein, that must be chopped up, or cleaved, into its distinct components for the virus to replicate. Protease enzymes perform that job. Protease inhibitors bind to the active part of a key protease, rendering it unable to cleave the polyprotein.

After the success of protease inhibitors in HIV, research groups around the world began investigating whether the same mechanism would work for hepatitis C. In 1997 Charles M. Rice, now head of the laboratory of virology and infectious disease at the Rockefeller University, showed that mutating the viral protease in hepatitis C–infected chimpanzees stopped the virus, the first clue about the enzyme's importance. Subsequently, molecular virologist Ralf Bartenschlager of the University of Heidelberg in Germany confirmed the vital role of the protease in hepatitis C replication. Many studies later protease inhibitors were ready for commercial hepatitis C drug developers. In trials, telaprevir and boceprevir elicited response rates that were 20 to 30 percent higher than those seen with the older regimen—pegylated interferon plus ribavirin—by itself, an encouraging result.

Second-generation inhibitors are already in development, and the enzyme will likely be a target for other infectious diseases. Protease inhibitors may also be tested against cancer, particularly considering their earlier efficacy in HIV-related Kaposi's sarcoma. —*Jessica Wapner*

EXPLAINER

HOW DID HEPATITIS C EMERGE IN HUMANS?

Although it has existed for centuries, hepatitis C was identified just over 20 years ago, and scientists have been puzzling about its origins ever since. In May, Columbia University Medical Center pathologist W. Ian Lipkin and his colleagues identified a hepatitis C–like virus in dogs for the first time, suggesting the disease may have jumped to humans through contact with man's best friend 500 to 1,000 years ago, long after dogs were first domesticated.

JAMES CAVALLINI *Photo Researchers, Inc.*

QUOTABLE

"I never thought I'd work for the hamster, but the job came up."

—A conservation worker speaking about the Great Hamster of Alsace to the *Wall Street Journal.* In June the European Union's highest court fined France for not taking proper care of this wild species.

COMMENT AT ScientificAmerican.com/aug2011

FIELD NOTES

Mouth Wide Open

An aquatic scientist describes the challenges of studying creatures that live deep under the sea

Loosejaw dragonfish

I work on deepwater fishes—species that live anywhere below 200 to 3,000 meters deep in the ocean. The ones that I study, loosejaw dragonfishes, dwell about a kilometer down, in an area called the midwater zone. They have no skin between the two bones that form their lower jaw. This is unique to vertebrates. You might look at this animal and think, “How on earth could it possibly consume anything?” Say you had a natural history museum specimen in your hand, and you put a little tiny food fish in its mouth. You would watch it fall right out.

The deep sea is the largest ecosystem on earth, but we know very little about it. Dragonfishes are the dominant predators of this ecosystem, and they have features similar to those of most predatory fishes in the deep sea: they have long jaws and huge fangs. We hope to learn how predators of the earth’s largest ecosystem feed.

The interesting question is, Why have this loosejaw morphology? I’m working on how these jaws perform using computer models. In January I’ll begin a postdoctoral research fellowship at Harvard, where I’ll be transitioning from the theoretical to building robots of these jaws. We’ll start with micro CT data from museum specimens. The micro CT machine hits the specimen with radiation, taking x-ray images in very thin slices—smaller than the micron level—that software can stack into a 3-D computer model. We’ll send that model to a 3-D printer that works much like the software does, printing thin slices of composite material to make a plastic model of the fish’s skull. We can then add material that will act as muscles, skin and tendons.

We could study dragonfishes in a lab if we could reproduce the conditions in which these fishes live: the pressure, the temperature and the low light. But to maintain these conditions in a lab is very, very difficult.

Perhaps the most challenging proposition to an animal living in the deep sea is the scarcity of available food. I hope this work will uncover how predators cope with scarcity and what physical features and behaviors are important in capturing prey in this barren seascape.

—As told to Francie Diep

PROFILE

NAME
Christopher P. Kenaley

TITLE
Postdoctoral research associate, University of Washington

LOCATION
Seattle

STAT

62%

Share of adults in North, Central and South America who are overweight, the highest rate of any global region

14% Share of adults in Southeast Asia who are overweight, the lowest rate of any global region

EDITH WIDDER *Ocean Research & Conservation Association, Inc.*

DO THE MATH

The Mind-Reading Salmon

The true meaning of statistical significance

If you want to convince the world that a fish can sense your emotions, only one statistical measure will suffice: the *p*-value.

The *p*-value is an all-purpose measure that scientists often use to determine whether or not an experimental result is "statistically significant." Unfortunately, sometimes the test does not work as advertised, and researchers imbue an observation with great significance when in fact it might be a worthless fluke.

Say you've performed a scientific experiment testing a new heart attack drug against a placebo. At the end of the trial, you compare the two groups. Lo and behold, the patients who took the drug had fewer heart attacks than those who took the placebo. Success! The drug works!

Well, maybe not. There is a 50 percent chance that even if the drug is completely ineffective, patients taking it will do better than those taking the placebo. (After all, one group has to do better than the other; it's a toss-up whether the drug group or placebo group will come up on top.)

The *p*-value puts a number on the effects of randomness. It is the probability of seeing a positive experimental outcome even if your hypothesis is wrong. A long-standing convention in many scientific fields is that any result with a *p*-value below 0.05 is deemed statistically significant. An arbitrary convention, it is often the wrong one. When you make a comparison of an ineffective drug to a placebo, you will typically get a statistically significant result one time out of 20. And if you make 20 such comparisons in a scientific paper, on average, you will get one significant result with a *p*-value less than 0.05—even when the drug does not work.

Many scientific papers make 20 or 40 or even hundreds of comparisons. In such cases, researchers who do not adjust the standard *p*-value threshold of 0.05 are virtually guaranteed to find statistical significance in results that are meaningless statistical flukes. A study that ran in the February issue of the *American Journal of Clinical Nutrition* tested dozens of compounds and concluded that those found in blueberries lower the risk of high blood pressure, with a *p*-value of 0.03. But the researchers looked at so many compounds and made so many comparisons (more than 50), that it was almost a sure thing that some of the *p*-values in the paper would be less than 0.05 just by chance.

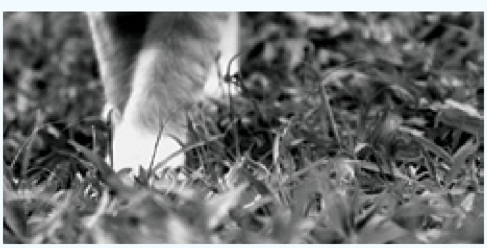
The same applies to a well-publicized study that a team of neuroscientists once conducted on a salmon. When they presented the fish with pictures of people expressing emotions, regions of the salmon's brain lit up. The result was statistically significant with a *p*-value of less than 0.001; however, as the researchers argued, there are so many possible patterns that a statistically significant result was virtually guaranteed, so the result was totally worthless. *P*-value notwithstanding, there was no way that the fish could have reacted to human emotions. The salmon in the fMRI happened to be dead. —*Charles Seife*

Seife is a professor of journalism at New York University.

WILDLIFE

Where House Cats Roam

Researchers compare the mysterious wanderings of pet and stray felines



FAHMI SANI PHOTOGRAPHY *Getty Images*

Anyone who has ever owned an outdoor cat knows that it tends to disappear for hours, sometimes days, at a time. Where do cats go when they are lurking out of sight? The question is of interest not just to pet owners but also to conservation scientists who study the impact of free-roaming cats on wildlife populations. Scientists at the University of Illinois and the Illinois Natural History Survey recently attached radio transmitters to the adjustable collars of 18 pet and 24 feral cats in southeastern Champaign-Urbana and tracked the animals by truck and on foot for more than one year. The research, published in the *Journal of Wildlife Management,* shows that pet cats maintain a rather lazy existence: they spent 80 percent of their time resting. They devoted another 17 percent to low-activity pursuits such as grooming and only 3 percent to high-activity pursuits such as hunting. Unowned cats rested just 62 percent of the time and spent 14 percent, mostly at night, being highly active. Feral cats roamed far more widely than researchers had expected: up to 1,351 acres. In contrast, pet cats stayed within an average of about five acres of home.

The small cats' behavior is similar to that of their larger cousins. "Maintaining a ranging area is a very intrinsic behavior to cats," says Alan Rabinowitz, CEO of the conservation organization Panthera. Like small cats, wild cats like to stay close to humans for easier access to food. Jaguars in Latin America, for example, slink quietly through massive stretches of human land. It's part of a cat's nature to live on the interface of wild and human-inhabited land. —*Madhumita Venkataramanan*

COMMENT AT ScientificAmerican.com/aug2011

FOOD

Cryogenic Cooking

Liquid nitrogen can transform oil, berries and even hamburgers

Since man's discovery of fire, cooking has been mainly a process of subjecting food to high temperatures that chemically alter its color, taste and texture. But the invention of cryogenic technology has handed chefs an exciting new tool—liquid nitrogen—for transforming food in fun and surprising ways. In our culinary research laboratory, we use this ultracold liquid to cryopoach oils, cryoshatter cheese, cryopowder herbs and cryograte meat. It is great for making instant ice cream and perfectly cooked hamburgers.

For many years the coldest substance chefs had ready access to was dry ice (frozen carbon dioxide), which sublimates directly to CO_2 gas at –109 degrees Fahrenheit. Although dry ice has some interesting culinary uses, its solid form limits its utility. Nitrogen boils at a far colder temperature: –321 degrees F, about as many degrees below zero as hot fryer oil is above zero. And because nitrogen melts before it vaporizes, unlike carbon dioxide, it is relatively easy to store as a liquid and pour over food or into a bowl. Because its viscosity is about one-fifth that of water and it has relatively low surface tension, liquid nitrogen flows rapidly into nooks and crannies in foods, such as hamburger patties, that have rough or irregular surfaces. The cooks at our lab use it to make fantastic burgers that are first slow-cooked to medium rare, then dunked briefly in liquid nitrogen to freeze a thin layer of the exterior and, finally, deep-fried. The deep-frying creates a perfect brown crust and thaws the frozen layer but does not overcook the interior.

Liquid nitrogen also makes hard freezing fast and convenient. Spanish chef Quique Dacosta uses it to solidify Parmesan foam, which he then dusts with powdered, flash-frozen mushrooms to make faux truffles. The stuff also makes quick work of disassembling blackberries into individual drupelets and shattering dollops of oil into tiny shards that thaw in minutes.

Speed is crucial for freezing foods without damaging their texture. In general, the faster the freezing process, the smaller the ice crystals and the less they disrupt the cellular structure of the food. Since the 1970s chefs have used liquid nitrogen to make supersmooth ice cream. More recently, chefs have started using it to flash-freeze delicate foods such as foie gras. Because liquid nitrogen is a relatively new addition to the kitchen, many other applications of this versatile fluid still await discovery.

—W. Wayt Gibbs and Nathan Myhrvold

Myhrvold is author and Gibbs is editor of Modernist Cuisine: The Art and Science of Cooking *(The Cooking Lab, 2011).*

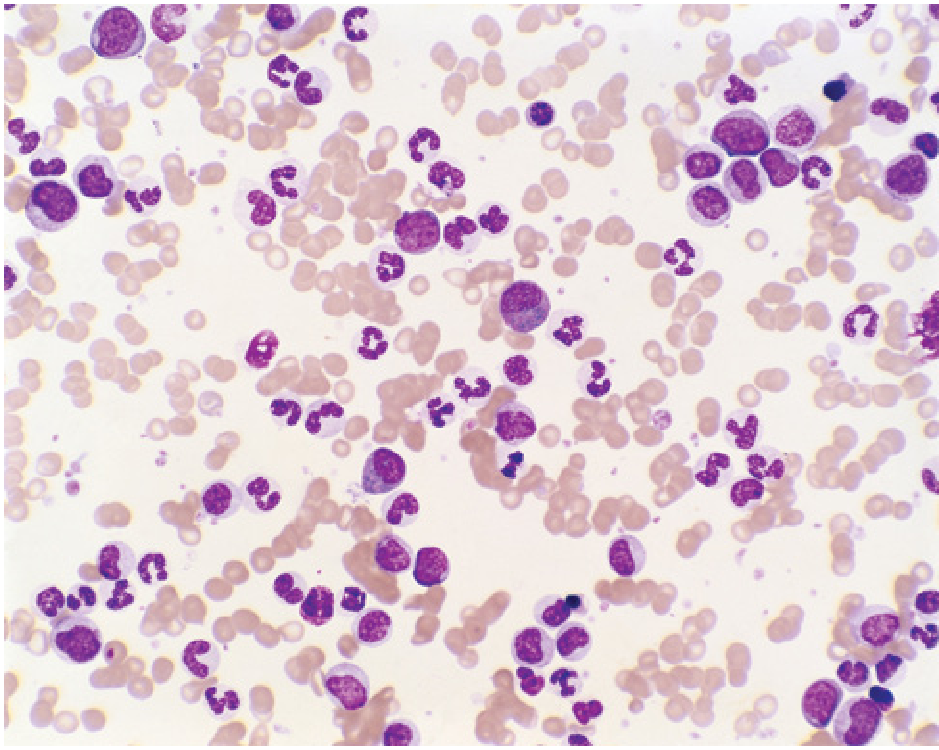
RYAN MATTHEW SMITH *Modernist Cuisine LLC*

Cassandra Willyard is a New York–based science writer with a passion for medicine. Her articles have appeared in *Nature*, *Science*Now and *The Scientist*.

How Do Tumors Grow?

An alternative explanation for cancer's origins could lead to better therapies

On a sweltering August evening in 2009 Pat Elliott noticed that her feet seemed swollen. Because she had been standing for hours while teaching a workshop in Phoenix, she was not surprised. "I thought it was the heat," she says. But her feet hurt, too, so Elliott decided to play it safe and called her doctor, who suggested she come in for some tests. Days later the marketing professional learned that she had developed an uncommon form of blood cancer called chronic myelogenous leukemia (CML).



Lethal signals: Physicians know abnormal stem cells can give rise to cancer cells (*stained purple*) in leukemia patients. But how common is this phenomenon?

JOAQUIN CARRILLO-FARGA *Photo Researchers, Inc.*

Elliott's cancer is the result of a genetic change that arose in one or more stem cells in her bone marrow. (Normally these stem cells give rise to various blood cells in the body.) The defect caused the stem cells and their progeny to produce an abnormal enzyme known as Bcr-Abl. This enzyme signals the marrow to produce too many immature white blood cells and allows them to persist longer than they should. The proliferating blood cells then crowd out healthy cells, damage the bone marrow and allow infections to take hold. Once these abnormal cells enter the bloodstream, they can also cause the spleen to swell and damage other organs. The pain and swelling in Elliott's feet most likely resulted from kidney problems caused by her disease. CML usually starts off being fairly innocuous, especially if treated. It can, however, become aggressive and lethal if left untreated.

To keep her disease in check, Elliott takes a bright yellow pill daily. The medication, called imatinib (sold under the brand name Gleevec), binds to the abnormal enzyme and shuts off the proliferation signal. Without this enzyme, the extra white blood cells mature normally and die as they should. Indeed, a recent study suggests that CML patients who live at least two years after starting imatinib treatment can look forward to a normal life span. But the pill is not a cure. A small number of long-lived cancer cells persist inside Elliott's body. If she stops taking her medication, the cancer will return.

Although imatinib keeps Elliott—and some 22,000 other CML patients in the U.S.—alive and healthy, the drug's inability to eradicate the cancer suggests that perhaps the standard model that most researchers use to visualize how tumors grow—and the treatments that have arisen from that model—is flawed. An alternative hypothesis has recently gained traction; if it proves to be more accurate, physicians may need to adjust their therapeutic approaches, targeting their treatments to destroy particular subsets of cells within the tumor.

TWO MODELS

Oncologists have long worked under the assumption that most tumors develop from a single cell. After a series of genetic mutations, which occur as a result of exposure to radiation, cigarette smoke, dietary choices or a genetic predisposition, this single cell begins to divide uncontrollably into more cells. Each succeeding generation of cells accumulates more genetic mistakes that make the tumor grow bigger, invade local tissues and eventually spread (metastasize) to other parts of the body. Under the standard model of cancer growth, once a tumor has gained the ability to spread, any one of the founding cell's descendants can

break off and form a new mass—which is why health authorities emphasize early diagnosis and the need to destroy all tumor cells to prevent a recurrence.

The alternative view proposes that only a handful of the cells in a tumor—known as cancer stem cells—have the ability to grow uncontrollably and spread. These cells renew themselves indefinitely (essentially making close duplicates of themselves) and also give rise to a mix of cells having different properties and a finite life span. In this way, cancer stem cells resemble the normal stem cells sprinkled throughout the body that replace old or damaged tissues, such as skin or the lining of the intestine. Unlike normal stem cells, however, cancer stem cells ignore any and all chemical signals that tell them to stop dividing. According to this alternative conception, most cells in the tumor will eventually die and so should be less dangerous. The few stem cells in the tumor, however, would be particularly deadly: if even a single cancer stem cell survived the initial therapy, it could give rise to a whole new tumor weeks, months or even years later.

At least four decades of research support the idea that cancer stem cells play a major role in the origin of the so-called liquid tumors of the blood and lymphatic systems. But scientists have only recently begun exploring the possibility that cancer stem cells may be responsible for the development of solid tumors—such as cancers of the lung, breast and liver—as well. The presence of cancer stem cells might also clarify why imatinib does not cure CML. If stem cells uniquely did not need the Bcr-Abl enzyme to survive, no amount of the enzyme-blocking drug would eliminate them. "Those cells can be swimming in a sea of imatinib, but they're not being killed," says John E. Dick of the University of Toronto, a pioneer in cancer stem cell research. Investigators also suspect that cancer stem cells may be the reason relapses can occur years after an apparently successful treatment. Some cancer stem cells seemingly enter a dormant state, allowing them to survive the initial treatment relatively unscathed.

EVIDENCE

The first strong evidence that cancer stem cells might play a role in solid as well as liquid tumors came in 2003 from the study of malignant breast tissue. The study kicked off an era of what Dick calls "breathless excitement." The cancer stem cell idea appealed to many researchers because it seemed to explain so much, not only the variety of cells within tumors but also why traditional cancer therapies often fail. A second study, also of breast tumors, by Jenny C. Chang, who is now an oncologist at Methodist Hospital in Houston, provided compelling evidence that cancer stem cells might be unusually resistant to standard treament.

At the time, Chang was working with patients at Ben Taub General Hospital in Houston, which serves the region's 1.5 million uninsured residents. Because so many Ben Taub patients have limited access to health care, they tend to delay going to the doctor, so their cancers are more advanced when they receive a diagnosis. In fact, the tumors are often so big that they require a dose of chemotherapy to shrink the growths before surgery can even be attempted. These circumstances afforded Chang a unique opportunity to look at drug resistance.

Chang began taking biopsies of the tumors before and after chemotherapy. When she, along with Jeffrey M. Rosen of Baylor College of Medicine, and colleagues compared these biopsies, they found that the samples taken after treatment contained a greater proportion of what appeared to be cancer stem cells, as determined by the presence of certain proteins on their surface. Before the treatment, the putative cancer stem cells accounted for about 4.7 percent of the tumor, on average. After 12 weeks of chemotherapy, the ratio had risen to 13.6 percent, suggesting that the cancer stem cells were better able to survive chemotherapy than other cells in the tumor. In addition, when the cells from the postchemotherapy biopsies were grown in suspension, they formed more multicellular balls than the prechemotherapy ones, something only stem cells typically do.

CONTROVERSY

To date, researchers have reported finding evidence of cancer stem cells in tumors of the breast, brain, skin, colon, prostate, pancreas and liver, among others. But as more and more scientists have joined the field—and tried to replicate one another's work—the picture has gotten a lot more complicated. In 2008, for example, Sean J. Morrison, director of the University of Michigan Center for Stem Cell Biology, found that if he tweaked a test, or assay, in mice that is used to detect cancer stem cells, he could dramatically change the results. A previous study had suggested that only one cell out of every million was a melanoma stem cell. Morrison found one in four cells could form a tumor. "If you make changes in the assay and you get huge changes in the spectrum of human cancer cells that can form a tumor, then that makes you really worry about drawing conclusions," he says.

Today the field is divided. Although it seems clear that at least some cancers follow the stem cell model, researchers disagree over which tumors belong in that category. And no one yet knows whether therapies that specifically target cancer stem cells will save lives or how best to identify cancer stem cells. Nor do researchers understand how cancer stem cells originate, how often they derive from normal stem cells or whether each tumor has just a few or many of the cells. Some of the latest study results suggest that a complex mix of both the standard model and the cancer stem cell idea comes closest to elucidating how cancers form.

Despite the controversy, the research is prompting scientists to pay closer attention to the diverse subsets of cells found within all tumors. Ravindra Majeti, a cancer researcher at Stanford University, is working to develop diagnostic tools that indicate how aggressive a particular cancer will be—and therefore what type of treatment is needed—based on which genes are most active in the tumor cells. The hope is that this approach would be a more accurate way to gauge a tumor's degree of malignancy than the standard method, which involves examining the cells under a microscope and grading them based on their how abnormal they appear.

For now Elliott will continue to take her yellow pills and try to stay positive. "We appreciate everything we do have," she says, speaking for herself and her fellow patients. "But what we really want is a cure for this and to live a normal life." SA

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If you suspect your teen is using a cell phone to connect to drugs, go to drugfree.org for help.

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David Pogue is the personal-technology columnist for the *New York Times* and an Emmy Award–winning correspondent for *CBS News.*

The Perils of Copy Protection

Tech companies handcuff our files to protect against digital pirates. The strategy isn't just annoying for customers—it could be hurting sales

Years ago *Saturday Night Live* featured a hilarious sketch—a talk show called *Ruining It for Everyone.* The guests were all people whose stupid, destructive acts wound up changing society forever, adding bureaucracy and rules and making life less convenient for the rest of the world.

There was the guy who poisoned a Tylenol bottle, which led to the new world of tamper-proof seals; the woman who first drove off without paying for self-serve gas, triggering the era of having to prepay; and the guy who first befouled a restaurant bathroom, so now only paying customers are allowed to use them.

They should have had the guy who first pirated music. He, after all, launched the modern age of copy protection—our current crazy world where the honest are penalized and the pirates go free.

When the iTunes store opened, every song was copy-protected. You could play the tracks on a computer or an iPod—but not on your cell phone or on any non-Apple music player.

Internet movies are also ridiculously protected. For example, once you rent a movie, you generally have 24 hours to finish watching it. That's idiotic. What if it gets to be bedtime, and you want to finish the movie tomorrow night? Don't these movie executives have children? And why 24 hours? Does it take 25 for a hacker to remove the copy protection?

No, of course not. Nonpaying movie buffs don't have to strip off the copy protection; they never even see it. They use BitTorrent and get their movies for free.

Similarly, the proprietary e-book copy-protection schemes of

Amazon, Sony and Barnes & Noble ensure that each company's titles can't be read on rivals' machines. It's an attempt to stop book pirates, of course—but those people are off happily downloading their books from free piracy sites.

The biggest problem is that all of this inconvenience is based on a gut feeling. In a world without copy protection, would the e-book, music and movie industries collapse? Instinct—or at least media company executives' instinct—certainly says so. But without some kind of test, nobody can say for sure.

Actually there have been such tests—at least three of them.

I make most of my income writing computer books. To my great distress, I discovered that they are widely available online as PDF files. But when I griped on my blog, my readers challenged the assumption that I was losing sales.

"First of all," they said, "you're counting a lot of people who never would have bought the book in the first place. Those don't represent lost sales. And you're not counting the people who like the PDF so much, they go buy the print edition or discover from the PDF sample that they like your writing." One reader challenged me to a test: make one book available both on paper and as an unprotected PDF file. Report the effect of sales after one year.

I did that. The results were clear: Piracy was rampant. The book was everywhere online. But weirdly, my readers were also proved right. Sales of the printed edition did not suffer; in fact, they rose slightly year over year.

COPY PROTECTION MAKES LIFE MISERABLE for the honest customers while doing absolutely nothing to stop the pirates.

A recent satirical children's book showed how piracy can actually boost sales. Months before the book came out, a PDF of the story was leaked online and promptly went viral. Yet the leak generated so much interest in the book that eager readers soon pushed it to the top of Amazon's best-seller list.

Even the music industry came to realize that copy protection makes life miserable for the honest customers while doing absolutely nothing to stop the pirates. Today virtually no music files sold online are copy-protected.

Sure, the online stores still lose sales to music pirates—but not measurably more than before. Meanwhile music copy protection is no longer inconveniencing everybody else.

Until that lesson sinks in with the other industries—e-books, movies, television, computer software, maybe even the Transportation Security Administration—I hope *Saturday Night Live* someday remakes that talk-show skit. Can't you just see the list of modern *Ruining It for Everyone* guests? The guy who wrote the first computer virus, the very first spammer, the first person who tried to sneak a bomb through airport security in his shoes.... SA

THE SIX (LEGAL) WAYS TO GET MUSIC ONLINE
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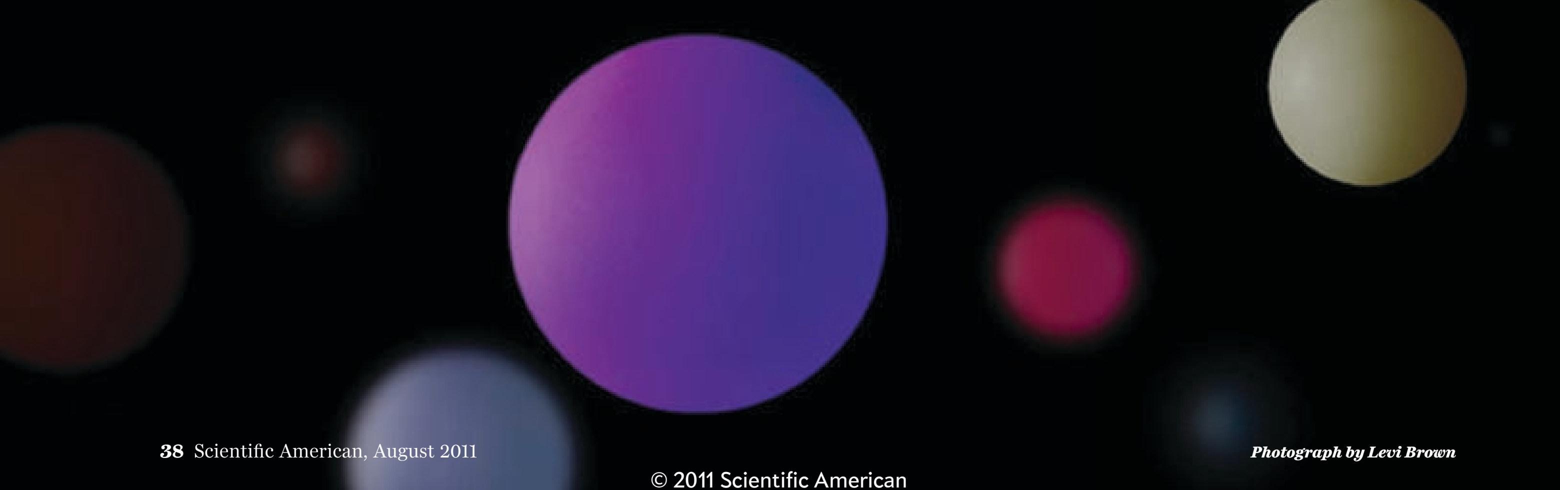
DOES THE MULTIVERSE REALLY EXIST?

Proof of parallel universes radically different from our own may still lie beyond the domain of science

By George F. R. Ellis

IN THE PAST DECADE AN EXTRAORDINARY CLAIM HAS CAPTIVATED COSMOLOGISTS: THAT THE EXPANDING universe we see around us is not the only one; that billions of other universes are out there, too. There is not one universe—there is a multiverse. In *Scientific American* articles and books such as Brian Greene's latest, *The Hidden Reality,* leading scientists have spoken of a super-Copernican revolution. In this view, not only is our planet one among many, but even our entire universe is insignificant on the cosmic scale of things. It is just one of countless universes, each doing its own thing.

The word "multiverse" has different meanings. Astronomers are able to see out to a distance of about 42 billion light-years, our cosmic visual horizon. We have no reason to suspect the universe stops there. Beyond it could be many—even infinitely many—domains much like the one we see. Each has a different initial distribution of matter, but the same laws of physics operate in all. Nearly all cosmologists today (including me) accept this type of multiverse, which Max Tegmark calls "level 1." Yet some go further. They suggest completely different kinds of universes, with different physics, different histories, maybe different numbers of spatial dimensions. Most will be sterile, although some will be teeming with life. A chief proponent of this "level 2"



Photograph by Levi Brown

George F. R. Ellis is a cosmologist and emeritus mathematics professor at the University of Cape Town in South Africa. He is one of the world's leading experts on Einstein's general theory of relativity and co-author, with Stephen Hawking, of the seminal book *The Large Scale Structure of Space-Time* (Cambridge University Press, 1975).

IN BRIEF

The notion of parallel universes leapt out of the pages of fiction into scientific journals in the 1990s. Many scientists claim that megamillions of other universes, each with its own laws of physics, lie out there, beyond our visual horizon. They are collectively known as the multiverse.

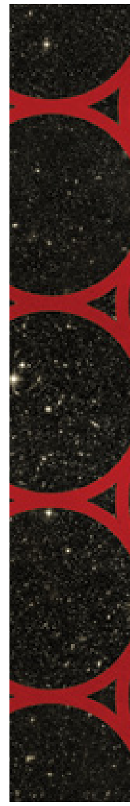
The trouble is that no possible astronomical observations can ever see those other universes. The arguments are indirect at best. And even if the multiverse exists, it leaves the deep mysteries of nature unexplained.

What Lies Beyond?

When astronomers peer into the universe, they see out to a distance of about 42 billion light-years, our cosmic horizon, which represents how far light has been able to travel since the big bang (as well as how much the universe has expanded in size since then). Assuming that space does not just stop there and may well be infinitely big, cosmologists make educated guesses as to what the rest of it looks like.

Level 1 Multiverse: Plausible The most straightforward assumption is that our volume of space is a representative sample of the whole. Distant alien beings see different volumes, but all of these look basically alike, apart from random variations in the distribution of matter. Together these regions, seen and unseen, form a basic type of multiverse.

Level 2 Multiverse: Questionable Many cosmologists go further and speculate that, sufficiently far away, things look quite different from what we see. Our environs may be one of many bubbles floating in an otherwise empty background. The laws of physics would differ from bubble to bubble, leading to an almost inconceivable variety of outcomes. Those other bubbles may be impossible to observe even in principle. The author and other skeptics feel dubious about this type of multiverse.



multiverse is Alexander Vilenkin, who paints a dramatic picture of an infinite set of universes with an infinite number of galaxies, an infinite number of planets and an infinite number of people with your name who are reading this article.

Similar claims have been made since antiquity by many cultures. What is new is the assertion that the multiverse is a scientific theory, with all that implies about being mathematically rigorous and experimentally testable. I am skeptical about this claim. I do not believe the existence of those other universes has been proved—or ever could be. Proponents of the multiverse, as well as greatly enlarging our conception of physical reality, are implicitly redefining what is meant by "science."

OVER THE HORIZON

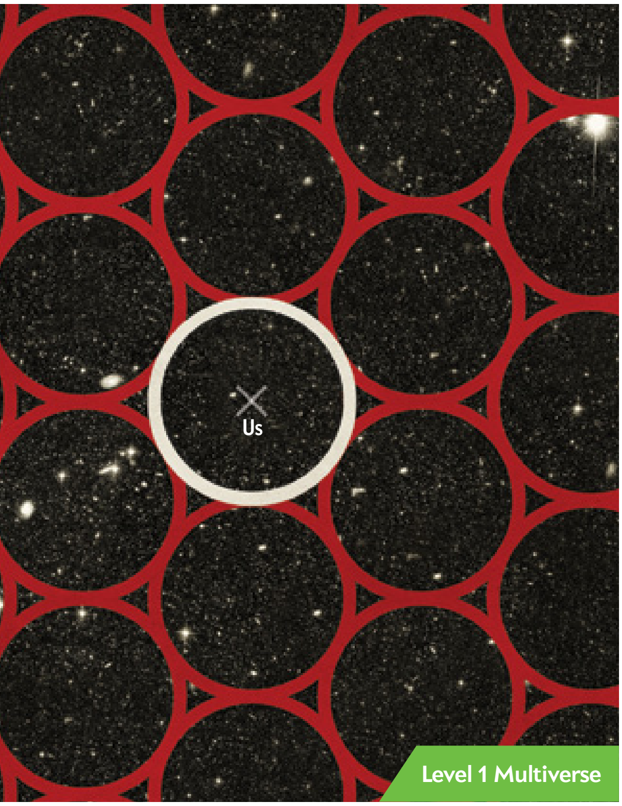
THOSE WHO SUBSCRIBE to a broad conception of the multiverse have various proposals as to how such a proliferation of universes might arise and where they would all reside. They might be sitting in regions of space far beyond our own, as envisaged by the chaotic inflation model of Alan H. Guth, Andrei Linde and others [see "The Self-Reproducing Inflationary Universe," by Andrei Linde; Scientific American, November 1994]. They might exist at different epochs of time, as proposed in the cyclic universe model of Paul J. Steinhardt and Neil Turok [see "The Myth of the Beginning of Time," by Gabriele Veneziano; Scientific American, May 2004]. They might exist in the same space we do but in a different branch of the quantum wave function, as advocated by David Deutsch [see "The Quantum Physics of Time Travel," by David Deutsch and Michael Lockwood; Scientific American, March 1994]. They might not have a location, being completely disconnected from our spacetime, as suggested by Tegmark and Dennis Sciama [see "Parallel Universes," by Max Tegmark; Scientific American, May 2003].

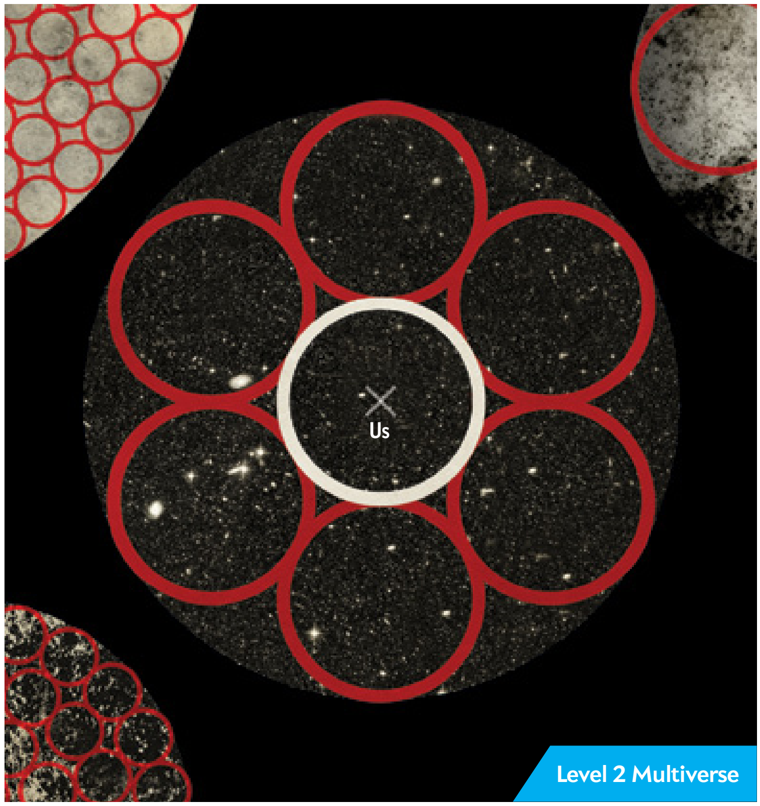
Of these options, the most widely accepted is that of chaotic inflation, and I will concentrate on it; however, most of my remarks apply to all the other proposals as well. The idea is that space at large is an eternally expanding void, within which quantum effects continually spawn new universes like a child blowing bubbles. The concept of inflation goes back to the 1980s, and physicists have elaborated on it based on their most comprehensive theory of nature: string theory. String theory allows bubbles to look very different from one another. In effect, each begins life not only with a random distribution of matter but also with random types of matter. Our universe contains particles such as electrons and quarks interacting through forces such as electromagnetism; other universes may have very different types of particles and forces—which is to say, different local laws of physics. The full set of allowed local laws is known as the landscape. In some interpretations of string theory, the landscape is immense, ensuring a tremendous diversity of universes.

Many physicists who talk about the multiverse, especially advocates of the string landscape, do not care much about parallel universes per se. For them, objections to the multiverse as a concept are unimportant. Their theories live or die based on internal consistency and, one hopes, eventual laboratory testing. They assume a multiverse context for their theories without worrying about how it comes to be—which is what concerns cosmologists.

For a cosmologist, the basic problem with all multiverse proposals is the presence of a cosmic visual horizon. The horizon is the limit to how far away we can see, because signals traveling toward us at the speed of light (which is finite) have not had time

Illustrations by Chad Hagen





since the beginning of the universe to reach us from farther out. All the parallel universes lie outside our horizon and remain beyond our capacity to see, now or ever, no matter how technology evolves. In fact, they are too far away to have had any influence on our universe whatsoever. That is why none of the claims made by multiverse enthusiasts can be directly substantiated.

The proponents are telling us we can state in broad terms what happens 1,000 times as far as our cosmic horizon, 10^{100} times, $10^{1,000,000}$ times, an infinity—all from data we obtain within the horizon. It is an extrapolation of an extraordinary kind. Maybe the universe closes up on a very large scale, and there is no infinity out there. Maybe all the matter in the universe ends somewhere, and there is empty space forever after. Maybe space and time come to an end at a singularity that bounds the universe. We just do not know what actually happens, for we have no information about these regions and never will.

SEVEN QUESTIONABLE ARGUMENTS

MOST MULTIVERSE PROPONENTS are careful scientists who are quite aware of this problem but think we can still make educated guesses about what is going on out there. Their arguments fall into seven broad types, each of which runs into trouble.

Space has no end. Few dispute that space extends beyond our cosmic horizon and that many other domains lie beyond what we see. If this limited type of multiverse exists, we can extrapolate what we see to domains beyond the horizon, with more and more uncertainty as regards the farther-out regions. It is then easy to imagine more elaborate types of variation, including alternative physics occurring out where we cannot see. But the trouble with this type of extrapolation, from the known to the unknown, is that no one can prove you wrong. How can scientists decide whether their picture of an unobservable region of spacetime is a reasonable or an unreasonable extrapolation of what we see? Might other universes have different initial distributions of matter, or might they also have different values of fundamental physical constants, such as those that set the strength of nuclear forces? You could get either, depending on what you assume.

Known physics predicts other domains. Proposed unified theories predict entities such as scalar fields, a hypothesized relative of other space-filling fields such as the magnetic field. Such fields should drive cosmic inflation and create universes ad infinitum. These theories are well grounded theoretically, but the nature of the hypothesized fields is unknown, and experimentalists have yet to demonstrate their existence, let alone measure their supposed properties. Crucially, physicists have not substantiated that the dynamics of these fields would cause different laws of physics to operate in different bubble universes.

The theory that predicts an infinity of universes passes a key observational test. The cosmic microwave background radiation reveals what the universe looked like at the end of its hot early expansion era. Patterns in it suggest that our universe really did undergo a period of inflation. But not all types of inflation go on forever and create an infinite number of bubble universes. Observations do not single out the required type of inflation from other types. Some cosmologists such as Steinhardt even argue that eternal inflation would have led to different patterns in the background radiation than we see [see "The Inflation Debate," by Paul J. Steinhardt; Scientific American, April]. Linde and others disagree. Who is right? It all depends on what you assume about the physics of the inflationary field.

Fundamental constants are finely tuned for life. A remarkable fact about our universe is that physical constants have just the right values needed to allow for complex structures, including living things. Steven Weinberg, Martin Rees, Leonard Susskind and others contend that an exotic multiverse provides a tidy explanation for this apparent coincidence: if all possible values occur in a large enough collection of universes, then viable ones for life will surely be found somewhere. This reasoning has been applied, in particular, to explaining the density of the dark energy that is speeding up the expansion of the universe today. I agree that the multiverse is a possible valid explanation for the value of this density; arguably, it is the only scientifically based option we have right now. But we have no hope of testing it observationally. Additionally, most analyses of the issue assume the basic equations of physics are the same everywhere, with only the constants differing—but if one takes the multiverse seriously, this need not be so [see "Looking for Life in the Multiverse," by Alejandro Jenkins and Gilad Perez; SCIENTIFIC AMERICAN, January 2010].

Fundamental constants match multiverse predictions. This argument refines the previous one by suggesting that the universe is no more finely tuned for life than it strictly needs to be. Proponents have assessed the probabilities of various values of the dark energy density. The higher the value is, the more probable it is, but the more hostile the universe would be to life. The value we observe should be just on the borderline of uninhabitability, and it does appear to be so [*see illustration at right*]. Where the argument stumbles is that we cannot apply a probability argument if there is no multiverse to apply the concept of probability to. This argument thus assumes the desired outcome before it starts; it simply is not applicable if there is only one physically existing universe. Probability is a probe of the consistency of the multiverse proposal, not a proof of its existence.

String theory predicts a diversity of universes. String theory has moved from being a theory that explains everything to a theory where almost anything is possible. In its current form, it predicts that many essential properties of our universe are pure happenstance. If the universe is one of a kind, those properties seem inexplicable. How can we understand, for example, the fact that physics has precisely those highly constrained properties that allow life to exist? If the universe is one of many, those properties make perfect sense. Nothing singled them out; they are simply the ones that arose in our region of space. Had we lived elsewhere, we would have observed different properties, if we could indeed exist there (life would be impossible in most places). But string theory is not a tried-and-tested theory; it is not even a complete theory. If we had proof that string theory is correct, its theoretical predictions could be a legitimate, experimentally based argument for a multiverse. We do not have such proof.

All that can happen, happens. In seeking to explain why nature obeys certain laws and not others, some physicists and philosophers have speculated that nature never made any such choice: all conceivable laws apply somewhere. The idea is inspired in part by quantum mechanics, which, as Murray Gell-Mann memorably put it, holds that everything not forbidden is compulsory. A particle takes all the paths it can, and what we see is the weighted average of all those possibilities. Perhaps the same is true of the entire universe, implying a multiverse. But astronomers have not the slightest chance of observing this multiplicity of possibilities. Indeed, we cannot even know what the possibilities are. We can only make sense of this proposal in the face of some unverifiable organizing principle or framework that decides what is allowed and what is not—for example, that all possible mathematical structures must be realized in some physical domain (as proposed by Tegmark). But we have no idea what kinds of existence this principle entails, apart from the fact that it must, of necessity, include the world we see around us. And we have no way whatsoever to verify the existence or nature of any such organizing principle. It is in some ways an attractive proposition, but its proposed application to reality is pure speculation.

ABSENCE OF EVIDENCE

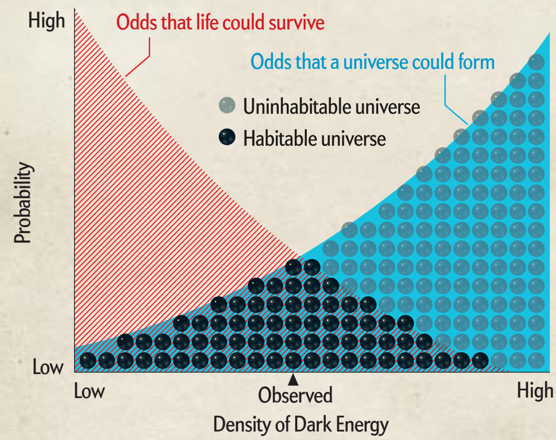
ALTHOUGH THE THEORETICAL ARGUMENTS fall short, cosmologists have also suggested various empirical tests for parallel universes. The cosmic microwave background radiation might bear some traces of other bubble universes if, for example, our universe has ever collided with another bubble of the kind implied by the chaotic inflation scenario. The background radiation might also contain remnants of universes that existed before the big bang in an endless cycle of universes. These are indeed ways one might get real evidence of other universes. Some cosmologists have even claimed to see such remnants. The observational claims are strongly disputed, however, and many of the hypothetically possible multiverses would not lead to such evidence. So observers can test only some specific classes of multiverse models in this way.

A second observational test is to look for variations in one or

DARK ENERGY AND THE MULTIVERSE

Does the Glove Fit?

As evidence for a multiverse, proponents often cite the density of the dark energy that dominates our universe. The process of eternal inflation endows each universe in a multiverse with a random density of dark energy. Relatively few universes have zero or a low value; most have higher values (*blue area*). But too much dark energy tears apart the complex structures needed to sustain life (*red area*). So most habitable universes should have a middling density of dark energy (*peak of overlap region*)—and, lo and behold, our universe does. Multiverse skeptics, though, say this reasoning is circular: it holds only if you assume the multiverse to begin with. It is a consistency test, not a proof.



Graphic by Jen Christiansen

more fundamental constants, which would corroborate the premise that the laws of physics are not so immutable after all. Some astronomers claim to have found such variations [see "Inconstant Constants," by John D. Barrow and John K. Webb; SCIENTIFIC AMERICAN, June 2005]. Most, though, consider the evidence dubious.

A third test is to measure the shape of the observable universe: Is it spherical (positively curved), hyperbolic (negatively curved) or "flat" (uncurved)? Multiverse scenarios generally predict that the universe is not spherical, because a sphere closes up on itself, allowing for only a finite volume. Unfortunately, this test is not a clean one. The universe beyond our horizon could have a different shape from that in the observed part; what is more, not all multiverse theories rule out a spherical geometry.

A better test is the topology of the universe: Does it wrap around like a doughnut or pretzel? If so, it would be finite in size, which would definitely disprove most versions of inflation and, in particular, multiverse scenarios based on chaotic inflation. Such a shape would produce recurring patterns in the sky, such as giant circles in the cosmic microwave background radiation [see "Is Space Finite?" by Jean-Pierre Luminet, Glenn D. Starkman and Jeffrey R. Weeks; SCIENTIFIC AMERICAN, April 1999]. Observers have looked for and failed to find any such patterns. But this null result cannot be taken as a point in favor of the multiverse.

Finally, physicists might hope to prove or disprove some of the theories that predict a multiverse. They might find observational evidence against chaotic versions of inflation or discover a mathematical or empirical inconsistency that forces them to abandon the landscape of string theory. That scenario would undermine much of the motivation for supporting the multiverse idea, although it would not rule the concept out altogether.

TOO MUCH WIGGLE ROOM

ALL IN ALL, the case for the multiverse is inconclusive. The basic reason is the extreme flexibility of the proposal: it is more a concept than a well-defined theory. Most proposals involve a patchwork of different ideas rather than a coherent whole. The basic mechanism for eternal inflation does not itself cause physics to be different in each domain in a multiverse; for that, it needs to be coupled to another speculative theory. Although they can be fitted together, there is nothing inevitable about it.

The key step in justifying a multiverse is extrapolation from the known to the unknown, from the testable to the untestable. You get different answers depending on what you choose to extrapolate. Because theories involving a multiverse can explain almost anything whatsoever, any observation can be accommodated by some multiverse variant. The various "proofs," in effect, propose that we should accept a theoretical explanation instead of insisting on observational testing. But such testing has, up until now, been the central requirement of the scientific endeavor, and we abandon it at our peril. If we weaken the requirement of solid data, we weaken the core reason for the success of science over the past centuries.

Now, it is true that a satisfactory unifying explanation of some range of phenomena carries greater weight than a hodgepodge of separate arguments for the same phenomena. If the unifying explanation assumes the existence of unobservable entities such as parallel universes, we might well feel compelled to accept those entities. But a key issue here is how many unverifiable entities are needed. Specifically, are we hypothesizing more or fewer entities than the number of phenomena to be explained? In the case of the multiverse, we are supposing the existence of a huge number—perhaps even an infinity—of unobservable entities to explain just one existing universe. It hardly fits 14th-century English philosopher William of Ockham's stricture that "entities must not be multiplied beyond necessity."

Proponents of the multiverse make one final argument: that there are no good alternatives. As distasteful as scientists might find the proliferation of parallel worlds, if it is the best explanation, we would be driven to accept it; conversely, if we are to give up the multiverse, we need a viable alternative. This exploration of alternatives depends on what kind of explanation we are prepared to accept. Physicists' hope has always been that the laws of nature are inevitable—that things are the way they are because there is no other way they might have been—but we have been unable to show this is true. Other options exist, too. The universe might be pure happenstance—it just turned out that way. Or things might in some sense be meant to be the way they are—purpose or intent somehow underlies existence. Science cannot determine which is the case, because these are metaphysical issues.

Scientists proposed the multiverse as a way of resolving deep issues about the nature of existence, but the proposal leaves the ultimate issues unresolved. All the same issues that arise in relation to the universe arise again in relation to the multiverse. If the multiverse exists, did it come into existence through necessity, chance or purpose? That is a metaphysical question that no physical theory can answer for either the universe or the multiverse.

To make progress, we need to keep to the idea that empirical testing is the core of science. We need some kind of causal contact with whatever entities we propose; otherwise, there are no limits. The link can be a bit indirect. If an entity is unobservable but absolutely essential for properties of other entities that are indeed verified, it can be taken as verified. But then the onus of proving it is absolutely essential to the web of explanation. The challenge I pose to multiverse proponents is: Can you prove that unseeable parallel universes are vital to explain the world we do see? And is the link essential and inescapable?

As skeptical as I am, I think the contemplation of the multiverse is an excellent opportunity to reflect on the nature of science and on the ultimate nature of existence: why we are here. It leads to new and interesting insights and so is a productive research program. In looking at this concept, we need an open mind, though not too open. It is a delicate path to tread. Parallel universes may or may not exist; the case is unproved. We are going to have to live with that uncertainty. Nothing is wrong with scientifically based philosophical speculation, which is what multiverse proposals are. But we should name it for what it is. SA

MORE TO EXPLORE

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SCIENTIFIC AMERICAN ONLINE
Multiverse: Yay or nay? Read the debate and cast your vote at **ScientificAmerican.com/aug11/multiverse**

Rachel Caspari is a professor of anthropology at Central Michigan University. Her research focuses on Neandertals, the origin of modern humans and the evolution of longevity.

HUMAN ORIGINS

the evolution of grandparents

Senior citizens may have been the secret of our species' success

By Rachel Caspari

IN BRIEF

People today typically live long enough to become grandparents, but this was not always the case.

Recent analyses of fossil teeth indicate that grandparents were rare in ancient populations, such as those of the australopithecines and the Neandertals. They first became common around 30,000 years ago, as evidenced by remains of early modern Europeans.

This surge in the number of seniors may have been a driving force for the explosion of new tool types and art forms that occurred in Europe at around the same time. It also may explain how modern humans outcompeted archaic groups such as the Neandertals.

Illustration by Viktor Deak

During the summer of 1963, when I was six years old, my family traveled from our home in Philadelphia to Los Angeles to visit my maternal relatives. I already knew my grandmother well: she helped my mother care for my twin brothers, who were only 18 months my junior, and me. When she was not with us, my grandmother lived with her mother, whom I met that summer for the first time. I come from a long-lived family. My grandmother was born in 1895, and her mother in the 1860s; both lived almost 100 years. We stayed with the two matriarchs for several weeks. Through their stories, I learned about my roots and where I belonged in a social network spanning four generations. Their reminiscences personally connected me to life at the end of the Civil War and the Reconstruction era and to the challenges my ancestors faced and the ways they persevered.

My story is not unique. Elders play critical roles in human societies around the globe, conveying wisdom and providing social and economic support for the families of their children and larger kin groups. In our modern era, people routinely live long enough to become grandparents. But this was not always the case. When did grandparents become prevalent, and how did their ubiquity affect human evolution?

Research my colleagues and I have been conducting indicates that grandparent-aged individuals became common relatively recently in human prehistory and that this change came at about the same time as cultural shifts toward distinctly modern behaviors—including a dependence on sophisticated symbol-based communication of the kind that underpins art and language. These findings suggest that living to an older age had profound effects on the population sizes, social interactions and genetics of early modern human groups and may explain why they were more successful than archaic humans, such as the Neandertals.

LIVE FAST, DIE YOUNG

The first step in figuring out when grandparents became a fixture in society is assessing the typical age breakdown of past populations—what percent were children, adults of childbearing age and parents of those younger adults? Reconstructing the demography of ancient populations is tricky business, however. For one thing, whole populations are never preserved in the fossil record. Rather paleontologists tend to recover fragments of individuals. For another, early humans did not necessarily mature at the same rate as modern humans. In fact, maturation rates differ even among contemporary human populations. But a handful of sites have yielded high enough numbers of human fossils in the same layers of sediment that scientists can confidently assess the age at death of the remains—which is key to understanding the makeup of a prehistoric group.

A rock-shelter located in the town of Krapina in Croatia, about 40 kilometers northwest of the city of Zagreb, is one such site. More than a century ago Croatian paleontologist Dragutin Gorjanović-Kramberger excavated and described the fragmentary remains of perhaps as many as 70 Neandertal individuals there, most of which came from a layer dated to about 130,000 years ago. The large number of fossils found close to one another, the apparently rapid accumulation of the sediments at the site and the fact that some of the remains share distinctive, genetically determined features all indicate that the Krapina bones approximate the remains of a single population of Neandertals. As often happens in the fossil record, the best-preserved remains at Krapina are teeth because the high mineral content of teeth protects them from degradation. Fortunately, teeth are also one of the best skeletal elements for determining age at death, which is achieved by analyzing surface wear and age-related changes in their internal structure.

In 1979, before I began my research into the evolution of grandparents, Milford H. Wolpoff of the University of Michigan at Ann Arbor published a paper, based on dental remains, that assessed how old the Krapina Neandertals were when they died. Molar teeth erupt sequentially. Using one of the fastest eruption schedules observed in modern-day humans as a guide, Wolpoff estimated that the first, second and third molars of Neandertals erupted at ages that rounded to six, 12 and 15, respectively. Wear from chewing accumulates at a steady pace over an individual's lifetime, so when the second molar emerges, the first already has six years of wear on it, and when the third emerges, the second has three years of wear on it.

Working backward, one can infer, for instance, that a first molar with 15 years of wear on it belonged to a 21-year-old Neandertal, a second molar with 15 years of wear on it belonged to a 27-year-old and a third molar with 15 years of wear on it belonged to a 30-year-old. (These estimates have an uncertainty of plus or minus one year.) This wear-based seriation method for determining age at death, adapted from a technique developed by dental researcher A.E.W. Miles in 1963, works best on samples with large numbers of juveniles, which Krapina has in abundance. The method loses accuracy when applied to the teeth of elderly individuals, whose tooth crowns can be too worn to evaluate reliably and in some cases may even be totally eroded.

Wolpoff's work indicated that the Krapina Neandertals died young. In 2005, a few years after I began researching the evolution of longevity, I decided to take another look at this sample using a novel approach. I wanted to make sure that we were not missing older individuals as a result of the inherent limitations of wear-based seriation. Working with Jakov Radovčić of the Croatian Natural History Museum in Zagreb, Steven A. Goldstein, Jeffrey A. Meganck and Dana L. Begun, all at Michigan, and undergraduate students from Central Michigan University, I developed a new nondestructive method—using high-resolution three-dimensional microcomputed tomography (μCT)—to reassess how old the Krapina individuals were when they died. Specifically, we looked at the degree of development of a type of tissue within the tooth called secondary dentin; the volume of secondary dentin increases with age and provides a way to assess how old an individual was at death when the tooth crown is too worn to be a good indicator.

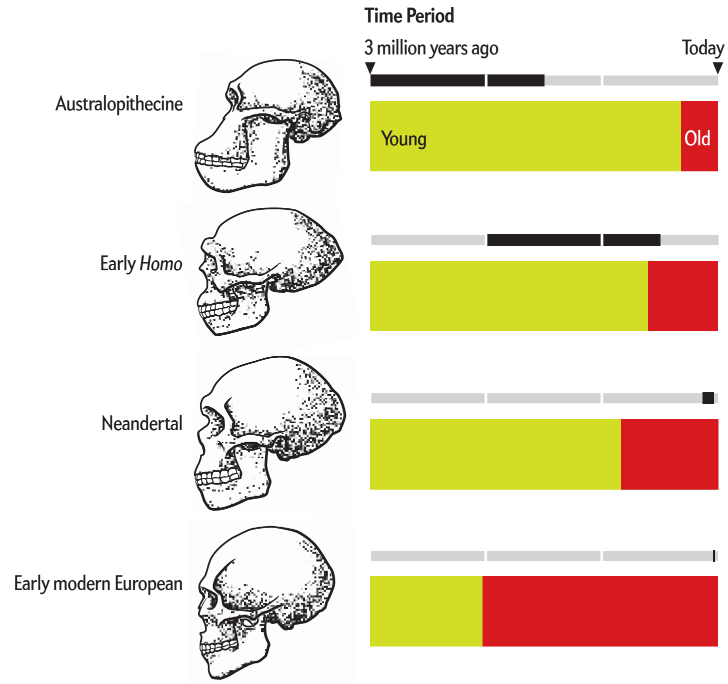
Our initial findings, supplemented with scans provided by the Max Planck Institute for Evolutionary Anthropology in Leipzig, corroborated Wolpoff's results and validated the wear-based seriation method: the Krapina Neandertals had remarkably high mortality rates; no one survived past age 30. (This is not to say that Neandertals across the board never lived beyond 30. A few individuals from sites other than Krapina were around 40 when they died.)

By today's standards, the Krapina death pattern is unimaginable. After all, for most people age 30 is the prime of life. And hunter-gatherers lived beyond 30 in the recent past. Yet the Krapina Neandertals are not unique among early humans. The few other human fossil localities with large numbers of individuals preserved, such as the approximately 600,000-year-old Sima de los Huesos site in Atapuerca, Spain, show similar patterns. The Sima de los Huesos people had very high levels of juvenile and young adult mortality, with no one surviving past 35 and very few living even that long. It is possible that catastrophic events or the particular conditions under which the remains became fossilized somehow selected against the preservation of older individuals at these sites. But the broad surveys of the human fossil record—including the material from these unusually rich sites and other sites containing fewer individuals—that my colleagues and I have conducted indicate that dying young was the rule, not the exception. To paraphrase words attributed to British philosopher Thomas Hobbes, prehistoric life really was nasty, brutish and short.

FINDINGS

Growing Older

Analyses of the fossilized teeth of hundreds of individuals spanning three million years indicate that living long enough to reach grandparenthood became common relatively late in human evolution. The author and her colleague assessed the proportion of older (grandparent-aged) adults relative to younger adults in four groups of human ancestors—australopithecines, early members of the genus *Homo,* Neandertals and early modern Europeans—and found that the ratio increased only modestly over the course of human evolution until around 30,000 years ago, when it skyrocketed.



SOURCE: "OLDER AGE BECOMES COMMON LATE IN HUMAN EVOLUTION," BY RACHEL CASPARI AND SANG-HEE LEE, IN PNAS, VOL. 101, NO. 30; JULY 27, 2004

RISE OF THE GRANDPARENTS

THIS NEW μCT APPROACH has the potential to provide a high-resolution picture of the ages of older individuals in other fossil human populations. But a few years ago, before we hit on this technique, Sang-Hee Lee of the University of California, Riverside, and I were ready to start looking for evidence of changes in longevity over the course of human evolution. We turned to the best approach available at the time: wear-based seriation.

We faced a daunting challenge, though. Most human fossils do not come from sites, such as Krapina, that preserve so many individuals that the remains can be considered reflective of their larger populations. And the smaller the number of contemporaneous individuals found at a site, the more difficult it is to reliably estimate how old members were when they died because of the statistical uncertainties associated with small samples.

But we realized that we could get at the question of when grandparents started becoming common in another way. Instead of asking how long individuals lived, we asked how many of them lived to be old. That is, rather than focusing on absolute ages, we calculated relative ages and asked what proportion of

Illustration by Portia Sloan Rollings, Graphic by Jen Christiansen adults survived to the age at which one could first become a grandparent. Our objective was to evaluate changes over evolutionary time in the ratio of older to younger adults—the so-called OY ratio. Among primates, including humans up until very recently, the third molar erupts at about the same time that an individual becomes an adult and reaches reproductive age. Based on data from Neandertals and contemporary hunter-gatherer populations, we inferred that fossil humans got their third molars and had their first child at around age 15. And we considered double that age to mark the beginning of grandparenthood—just as some women today can potentially give birth at age 15 and those women can become grandmothers when their own children reach age 15 and reproduce.

For our purposes, then, any archaic individual judged to be 30 years old or more qualified as an older adult—one old enough to have become a grandparent. But the beauty of the OY ratio approach is that regardless of whether maturation occurred at 10, 15 or 20 years, the number of older and younger individuals in a sample would be unaffected because the start of older adulthood would change accordingly. And because we were only looking to place the fossils in these two broad categories, we could include large numbers of smaller fossil samples in our analysis without worrying about uncertainties in absolute ages.

We calculated the OY ratios for four large aggregates of fossil samples totaling 768 individuals spanning a period of three million years. One aggregate comprised later australopithecines—those primitive relatives of "Lucy," who lived in East Africa and South Africa from three million to 1.5 million years ago. Another aggregate consisted of early members of our genus, *Homo,* from around the globe who lived between two million and 500,000 years ago. The third group was the European Neandertals from 130,000 to 30,000 years ago. And the last consisted of modern Europeans from the early Upper Paleolithic period, who lived between about 30,000 and 20,000 years ago and left behind sophisticated cultural remains.

Although we expected to find increases in longevity over time, we were unprepared for how striking our results would turn out to be. We observed a small trend of increased longevity over time among all samples, but the difference between earlier humans and the modern humans of the Upper Paleolithic was a dramatic fivefold increase in the OY ratio. Thus, for every 10 young adult Neandertals who died between the ages of 15 and 30, there were only four older adults who survived past age 30; in contrast, for every 10 young adults in the European Upper Paleolithic death distribution, there were 20 potential grandparents. Wondering whether the higher numbers of burials at Upper Paleolithic sites might account for the high number of older adults in that sample, we reanalyzed our Upper Paleolithic sample, using only those remains that had not been buried. But we got similar results. The conclusion was inescapable: adult survivorship soared very late in human evolution.

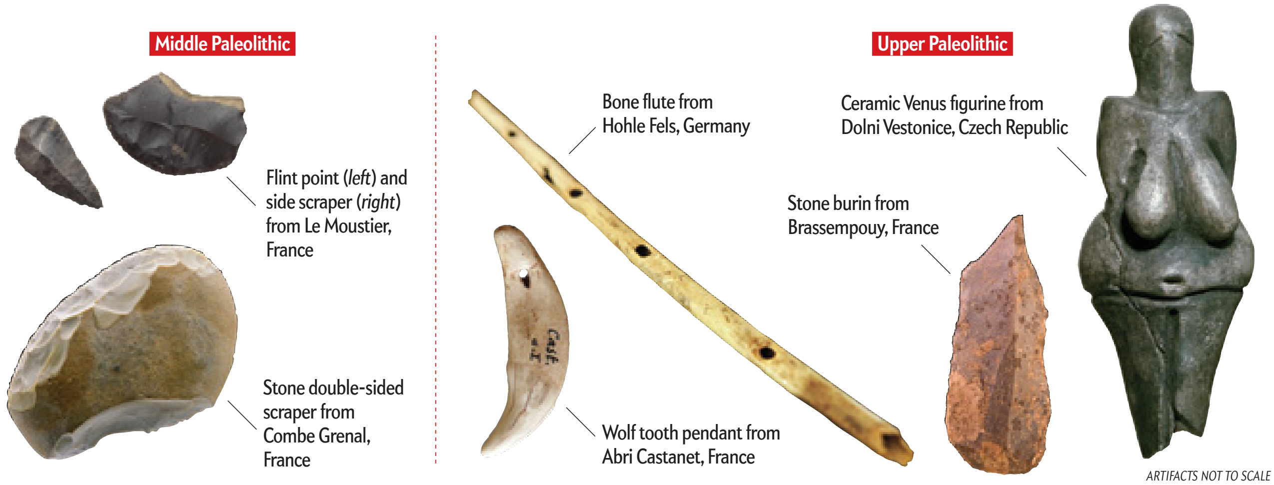
BIOLOGY OR CULTURE?

NOW THAT LEE AND I had established that the number of potential grandparents surged at some point in the evolution of anatomically modern humans, we had another question on our hands: What was it that brought about this change? There were two possibilities. Either longevity was one of the constellations of genetically controlled traits that biologically distinguished anatomically modern humans from their predecessors, or it did not come along with the emergence of modern anatomy and was instead the result of a later shift in behavior. Anatomically modern humans did not burst onto the evolutionary scene making the art and advanced weaponry that define Upper Paleolithic culture. They originated long before those Upper Paleolithic Europeans, more than 100,000 years ago, and for most of that time they and their anatomically

CONSEQUENCES

Culture Comes of Age

A marked increase in adult survivorship starting around 30,000 years ago in Europe may account for the dramatic cultural shift that ensued there as the comparatively simple technology of the Middle Paleolithic gave way to the sophisticated weapons and art of the Upper Paleolithic. Representative artifacts from both cultural traditions are shown here.



NATURAL HISTORY MUSEUM, LONDON (*flint point and side scraper*); DAVID L. BRILL (*double-sided scraper*); RANDALL WHITE *New York University* (*wolf tooth*); GETTY IMAGES (*flute*); DIDIER DESCOUENS *Museum of Toulouse, France* (*burin*); DANITA DELIMONT *Getty Images* (*Venus figurine*) archaic contemporaries the Neandertals used the same, simpler Middle Paleolithic technology. (Members of both groups appear to have dabbled in making art and sophisticated weapons before the Upper Paleolithic, but these traditions were ephemeral compared with the ubiquitous and enduring ones that characterize that later period.) Although our study indicated that a large increase in grandparents was unique to anatomically modern humans, it alone could not distinguish between the biological explanation and the cultural one, because the modern humans we looked at were both anatomically and behaviorally modern. Could we trace longevity back to earlier anatomically modern humans who were not yet behaviorally modern?

To address this question, Lee and I analyzed Middle Paleolithic humans from sites in western Asia dating to between about 110,000 and 40,000 years ago. Our sample included both Neandertals and modern humans, all associated with the same comparatively simple artifacts. This approach allowed us to compare the OY ratios of two biologically distinct groups (many scholars consider them to be separate species) who lived in the same region and had the same cultural complexity. We found that the Neandertals and modern humans from western Asia had statistically identical OY ratios, ruling out the possibility that a biological shift accounted for the increase in adult survivorship seen in Upper Paleolithic Europeans. Both western Asian groups had roughly even proportions of older and younger adults, putting their OY ratios between those of the Neandertals and early modern humans from Europe.

Compared with European Neandertals, a much larger proportion of western Asian Neandertals (and modern humans) lived to be grandparents. This is not unexpected—the more temperate environment of western Asia would have been far easier to survive in than the harsh ecological conditions of Ice Age Europe. Yet if the more temperate environment of western Asia accounts for the elevated adult survivorship seen in the Middle Paleolithic populations there, the longevity of Upper Paleolithic Europeans is even more impressive. Despite living in much harsher conditions, the Upper Paleolithic Europeans had an OY ratio more than double that of the Middle Paleolithic modern humans.

SENIOR MOMENTS

We do not know exactly what those Upper Paleolithic Europeans started doing culturally that allowed so many more of them to live to older age. But there can be no doubt that this increased adult survivorship itself had far-reaching effects. As Kristen Hawkes of the University of Utah, Hillard Kaplan of the University of New Mexico and others have shown in their studies of several modern-day hunter-gatherer groups, grandparents routinely contribute economic and social resources to their descendants, increasing both the number of offspring their children can have and the survivorship of their grandchildren. Grandparents also reinforce complex social connections—like my grandmother did in telling stories of ancestors that linked me to other relatives in my generation. Such information is the foundation on which human social organization is built.

Elders transmit other kinds of cultural knowledge, too—from environmental (what kinds of plants are poisonous or where to find water during times of drought, for example) to technological (how to weave a basket or knap a stone knife, perhaps). Studies led by Pontus Strimling of Stockholm University have shown that repetition is a critical factor in the transmission of the rules and traditions of one's culture. Multigenerational families have more members to hammer home important lessons. Thus, longevity presumably fostered the intergenerational accumulation and transfer of information that encouraged the formation of intricate kinship systems and other social networks that allow us to help and be helped when the going gets tough.

Increases in longevity would also have translated into increases in population size by adding an age group that was not there in the past and that was still fertile. And large populations are major drivers of new behaviors. In 2009 Adam Powell of University College London and his colleagues published a paper in *Science* showing that population density figures importantly in the maintenance of cultural complexity. They and many other researchers argue that larger populations promoted the development of extensive trade networks, complex systems of cooperation, and material expressions of individual and group identity (jewelry, body paint, and so on). Viewed in that light, the hallmark features of the Upper Paleolithic—the explosive increase in the use of symbols, for instance, or the incorporation of exotic materials in tool manufacture—look as though they might well have been consequences of swelling population size.

Growing population size would have affected our forebears another way, too: by accelerating the pace of evolution. As John Hawks of the University of Wisconsin–Madison has emphasized, more people mean more mutations and opportunities for advantageous mutations to sweep through populations as their members reproduce. This trend may have had an even more striking effect on recent humans than on Upper Paleolithic ones, compounding the dramatic population growth that accompanied the domestication of plants 10,000 years ago. In their 2009 book *The 10,000 Year Explosion,* Gregory Cochran and Henry Harpending, both at the University of Utah, describe multiple gene variants—from those influencing skin color to those that determine tolerance of cow milk—that arose and spread swiftly over the past 10,000 years, thanks to the ever larger numbers of breeding individuals.

The relation between adult survivorship and the emergence of sophisticated new cultural traditions, starting with those of the Upper Paleolithic, was almost certainly a positive feedback process. Initially a by-product of some sort of cultural change, longevity became a prerequisite for the unique and complex behaviors that signal modernity. These innovations in turn promoted the importance and survivorship of older adults, which led to the population expansions that had such profound cultural and genetic effects on our predecessors. Older and wiser, indeed. SA

MORE TO EXPLORE

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Is Human Longevity a Consequence of Cultural Change or Modern Human Biology? Rachel Caspari and Sang-Hee Lee in *American Journal of Physical Anthropology,* Vol. 129, pages 512–517; April 2006.

SCIENTIFIC AMERICAN ONLINE
Read about precocious examples of modern human behavior at **ScientificAmerican.com/aug2011/caspari**

NEUROSCIENCE

HOW TO BUILD A BETTER LEARNER

Brain studies suggest new ways to improve reading, writing and arithmetic—and even social skills

By Gary Stix

Thinking cap records electrical signals from the brain of one-year-old Elise Hardwick, who is helping scientists figure out how the youngest children process sounds that make up the building blocks of language.

Photograph by Andrew Hetherington

EIGHT-MONTH-OLD LUCAS KRONMILLER has just had the surface of his largely hairless head fitted with a cap of 128 electrodes. A research assistant in front of him is frantically blowing bubbles to entertain him. But Lucas seems calm and content. He has, after all, come here, to the Infancy Studies Laboratory at Rutgers University, repeatedly since he was just four months old, so today is nothing unusual. He—like more than 1,000 other youngsters over the past 15 years—is helping April A. Benasich and her colleagues to find out whether, even at the earliest age, it is possible to ascertain if a child will go on to experience difficulties in language that will prove a burdensome handicap when first entering elementary school.

Benasich is one of a cadre of researchers employing brain-recording techniques to understand the essential processes that underlie learning. The new science of neuroeducation seeks the answers to questions that have always perplexed cognitive psychologists and pedagogues.

How, for instance, does a newborn's ability to process sounds and images relate to the child's capacity to learn letters and words a few years later? What does a youngster's capacity for staying mentally focused in preschool mean for later academic success? What can educators do to foster children's social skills—also vital in the classroom? Such studies can complement the wealth of knowledge established by psychological and educational research programs.

They also promise to offer new ideas, grounded in brain science, for making better learners and for preparing babies and toddlers for reading, writing, arithmetic, and survival in the complex social network of nursery school and beyond. Much of this work focuses on the first years of life and the early grades of elementary school because some studies show that the brain is most able to change at that time.

THE AHA! INSTANT

BENASICH STUDIES anomalies in the way the brains of the youngest children perceive sound, a cognitive process fundamental to the understanding of language, which, in turn, forms the basis for reading and writing skills. The former nurse, who went on to earn two doctorates, focuses on what she calls the aha! instant—an abrupt transition in electrical activity in the brain that signals that something new has been recognized.

Researchers at Benasich's lab in Newark, N.J., expose Lucas and other infants to tones of a certain frequency and duration. They then record a change in the electrical signals generated in the brain when a different frequency is played. Typically the electroencephalographic (EEG) trace peaks downward in response to the change—indicating that the brain essentially says, "Yes, something has changed"; a delay in the response time to the different tones means that the brain has not detected the new sound quickly enough. The research has found that this pattern of sluggish electrical activity at six months can predict language issues

IN BRIEF

The technology and research methods of the neuroscientist have started to reveal, at the most basic level, what happens in the brain when we learn something new.

As these studies mature, it may become possible for a preschooler or even an infant to engage in simple exercises to ensure that the child is cognitively equipped for school.

If successful, such interventions could potentially have a huge effect on educational practices by dramatically reducing the incidence of various learning disabilities.

Scientists, educators and parents must also beware overstated claims for brain-training methods that purport to help youngsters but have not been proved to work.

at three to five years of age. Differences in activity that persist during the toddler and preschool years can foretell problems in development of the brain circuitry that processes the rapid transitions occurring during perception of the basic units of speech. If children fail to hear or process components of speech—say, a "da" or a "pa"—quickly enough as toddlers, they may lag in "sounding out" written letters or syllables in their head, which could later impede fluency in reading. These recent findings offer more rigorous confirmation of other research by Benasich showing that children who encounter early problems in processing these sounds test poorly on psychological tests of language eight or nine years later.

If Benasich and others can diagnose future language problems in infants, they may be able to correct them by exploiting the inherent plasticity of the developing brain—its capacity to change in response to new experiences. They may even be able to improve basic functioning for an infant whose brain is developing normally. "The easiest time to make sure that the brain is getting set up in a way that's optimal for learning may be in the first part of the first year," she says.

Games, even in the crib, could be one answer. Benasich and her team have devised a game that trains a baby to react to a change in tone by turning the head or shifting the eyes (detected with a tracking sensor). When the movement occurs, a video snippet plays, a reward for good effort. In a preliminary study reported late last year, this brain training for babies, practiced over a period of weeks, enabled a group of 15 healthy infants to react more quickly to tones than a control group did. Benasich hopes that her research will confirm that the game might also assist infants impaired in processing these sounds to respond more quickly. She has started to confer with a toy developer interested in creating a mobile that could be placed on the side of a crib at home to train infants in perception of rapid sound sequences.

THE NUMBER SENSE

FLEXING COGNITIVE MUSCLES early on may also help infants tune rudimentary math skills. Stanislas Dehaene, a neuroscientist at the French National Institute of Health and Medical Research, is a leader

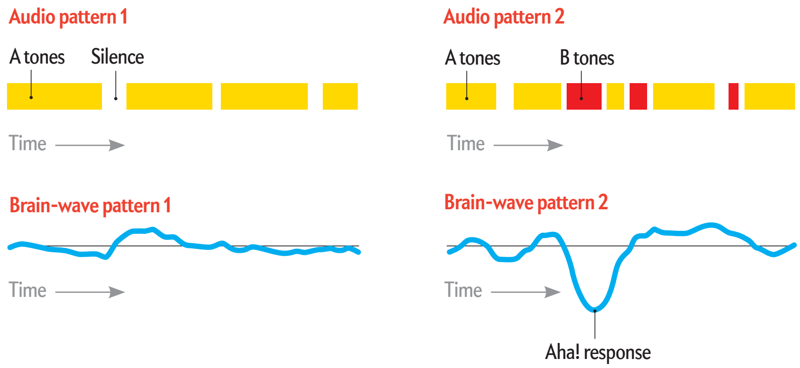
THE YOUNGEST PUPILS

Toning Up for Language: Early Education in the Crib

Scientists at Rutgers University have developed tests to determine whether babies with normal hearing process sound optimally deep within the brain (*top panel*). They are exploring whether a game they are devising (*bottom panel*) might ready the youngest children for speaking, listening, reading and writing.

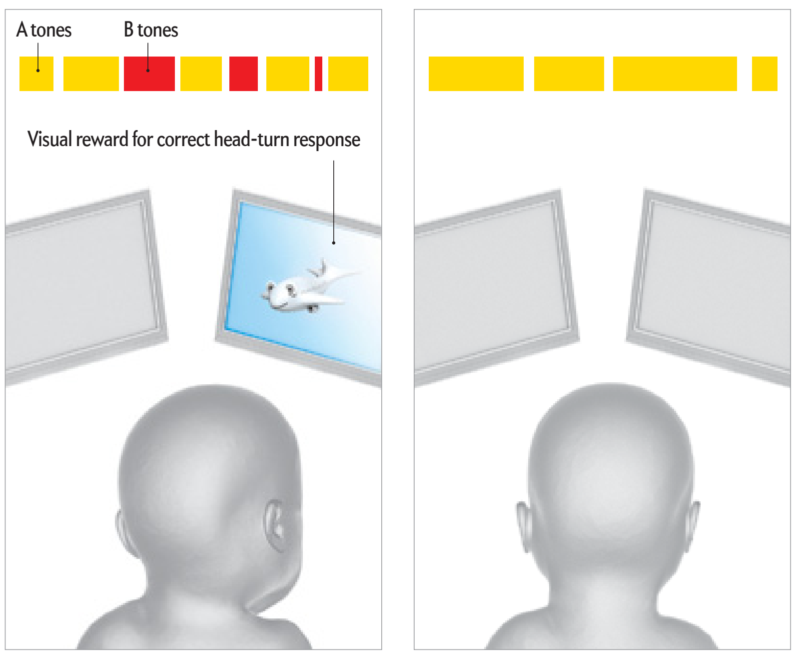
Waiting for "Aha"

The Infancy Studies Laboratory at Rutgers puts an electrode cap on babies to record brain activity while the children listen to different sounds. First, they hear high-frequency tones (*labeled A below*), which elicit a certain brain-wave pattern (*left*). Tones of different pitch (*labeled B*) intersperse with the initial tones and cause a temporary shift in the brain wave (the aha! response) as the brain detects the change (*right*). A slower or weaker response to this sudden alteration in pitch may predict language problems in later life.



A Game for Babies

Infants at Rutgers can learn to process pitch (frequency) more efficiently while also having fun. A child learns to turn the head in response to the B tones (*left*) but not to the A tones (*right*) and is rewarded with a snippet of a video for a correct response. The pace of tone sequences speeds up, and the child learns to respond more and more accurately to this fast tempo.



SOURCES: CYNTHIA ROESLER, APRIL A. BENASICH, TERESA REALPE AND NASEEM CHOUDHURY *Rutgers University*

Illustration by Bryan Christie, Graphics by Jen Christiansen in the field of numerical cognition who has tried to develop ways to help children with early math difficulties. Babies have some capability of recognizing numbers from birth. When the skill is not in place from the beginning, Dehaene says, a child may later have difficulty with arithmetic and higher math. Interventions that build this "number sense," as Dehaene calls it, may help the slow learner avoid years of difficulty in math class.

This line of research contradicts that of famed psychologist Jean Piaget, who contended that the brains of infants are blank slates, or tabula rasa, when it comes to making calculations in the crib. Children, in Piaget's view, have to develop a basic idea of what a number is from years of interacting with blocks, Cheerios or other objects. They eventually learn that when the little oat rings get pushed around a table, the location differs but the number stays the same.

The neuroscience community has amassed a body of research showing that humans and other animals have a basic numerical sense. Babies, of course, do not spring from the womb performing differential equations in their head. But experiments have found that toddlers will routinely reach for the row of M&Ms that has the most candies. And other research has demonstrated that even infants only a few months old comprehend relative size. If they see five objects being hidden behind a screen and then another five added to the first set, they convey surprise if they see only five when the screen is removed. Babies also seem to be born with other innate mathematical abilities. Besides being champion estimators, they can also distinguish exact numbers—but only up to the number three or four. Dehaene was instrumental in pinpointing a brain region—a part of the parietal lobe (the intraparietal sulcus)—where numbers and approximate quantities are represented. (Put a hand on the rear portion of the top of your head to locate the parietal lobe.)

The ability to estimate group size, which also exists in dolphins, rats, pigeons, lions and monkeys, is probably an evolutionary hand-me-down that is required to gauge whether your clan should fight or flee in the face of an enemy and to ascertain which tree bears the most fruit for picking. Dehaene, along with linguist Pierre Pica of the National Center for Scientific Research in France and colleagues, discovered more evidence for this instinctive ability through work with the Mundurukú Indians in the Brazilian Amazon, a tribe that has only an elementary lexicon for numbers. Its adult members can tell whether one array of dots is bigger than another, performing the task almost as well as a French control group did, yet most are unable to answer how many objects remain when four objects are removed from a group of six.

This approximation system is a cornerstone on which more sophisticated mathematics is constructed. Any deficit in these innate capacities can spell trouble later. In the early 1990s Dehaene hypothesized that children build on their internal ballpark estimation system for more sophisticated computations as they get older. Indeed, in the past 10 years a number of studies have found that impaired functioning of the primitive numerical estimation system in youngsters can predict that a child will perform

A NUMBER GAME

Count on It: Born to Estimate

From the time we are born, we have some concept of number. Children with deficits in this innate skill often end up struggling in later life. Stanislas Dehaene and his colleagues have created a game, the Number Race, intended to bolster our natural-born ability to estimate quantity. A preschooler judges which group of gold pieces is larger before the computer's animal avatar can steal the bigger pile (*top left*). A correct guess by the child advances his or her avatar a comparable number of spaces from its previous position; the loser moves ahead by a number equal to the smaller quantity of coins (*bottom right*). The winner is the one to reach the end of the number line first.

MODIFIED FROM "PRINCIPLES UNDERLYING THE DESIGN OF 'THE NUMBER RACE,' AN ADAPTIVE COMPUTER GAME FOR REMEDIATION OF DYSCALCULIA," BY ANNA J. WILSON, STANISLAS DEHAENE, PHILIPPE PINEL, SUSANNAH K. REVKIN, LAURENT COHEN AND DAVID COHEN, IN *BEHAVIORAL AND BRAIN FUNCTIONS*, VOL. 2; 2006

Illustration by QuickHoney

poorly in arithmetic and standard math achievement tests from the elementary years onward. "We realize now that the learning of a domain such as arithmetic has to be founded on certain core knowledge that is available already in infancy," Dehaene says.

It turns out that dyscalculia (the computational equivalent of dyslexia), which is marked by a lag in computational skills, affects 3 to 6 percent of children. Dyscalculia has received much less attention from educators than dyslexia has for reading—yet it may be just as crippling. "They earn less, spend less, are more likely to be sick, are more likely to be in trouble with the law, and need more help in school," notes a review article that appeared in *Science* in late May.

As with language, early intervention may help. Dehaene and his team devised a simple computer game they hope will enhance mathematical ability. Called the Number Race, it exercises these basic abilities in children aged four to eight. In one version, players must choose the larger of two quantities of gold pieces before a computer-controlled opponent steals the biggest pile. The game adapts automatically to the skill of the player, and at the higher levels the child must add or subtract gold before making a comparison to determine the biggest pile. If the child wins, she advances forward a number of steps equal to the gold just won. The first player to get to the last step on the virtual playing board wins.

The open-source software, which has been translated into eight languages, makes no hyperbolic claims about the benefits of brain training. Even so, more than 20,000 teachers have downloaded the software from a government-supported research institute in Finland. Today it is being tested in several controlled studies to see whether it prevents dyscalculia and whether it helps healthy children bolster their basic number sense.

GET AHOLD OF YOURSELF

THE COGNITIVE FOUNDATIONS of good learning depend heavily on what psychologists call executive function, a term encompassing such cognitive attributes as the ability to be attentive, hold what you have just seen or heard in the mental scratch pad of working memory, and delay gratification. These capabilities may predict success in school and even in the working

FACT CHECK

Five Common Myths about the Brain

Some widely held ideas about the way children learn can lead educators and parents to adopt faulty teaching principles.

MYTH: Humans use only 10 percent of their brain.

FACT The 10 percent myth (sometimes elevated to 20) is mere urban legend, one perpetrated recently by the plot of the movie *Limitless,* which pivoted around a wonder drug that endowed the protagonist with prodigious memory and analytical powers. In the classroom, teachers may entreat students to try harder, but doing so will not light up "unused" neural circuits; academic achievement does not improve by simply turning up a neural volume switch.

MYTH: "Left brain" and "right brain" people differ.

FACT The contention that we have a rational left brain and an intuitive, artistic right side is fable: humans use both hemispheres of the brain for all cognitive functions. The left brain/right brain notion originated from the realization that many (though not all) people process language more in the left hemisphere and spatial abilities and emotional expression more in the right. Psychologists have used the idea to explain distinctions between different personality types. In education, programs emerged that advocated less reliance on rational "left brain" activiities. Brain-imaging studies show no evidence of the right hemisphere as a locus of creativity. And the brain recruits both left and right sides for both reading and math.

MYTH: You must speak one language before learning another.

FACT Children who learn English at the same time as they learn French do not confuse one language with the other and so develop more slowly. This idea of interfering languages suggests that different areas of the brain compete for resources. In reality, young children who learn two languages, even at the same time, gain better generalized knowledge of language structure as a whole.

MYTH: Brains of males and females differ in ways that dictate learning abilities.

FACT Differences do exist in the brains of males and females, and the distinctive physiology may result in differences in the way their brains function. No research, though, has demonstrated gender-specific differences in how networks of neurons become connected when we learn new skills. Even if some gender differences do eventually emerge, they will likely be small and based on averages—in other words, they will not necessarily be relevant to any given individual.

MYTH: Each child has a particular learning style.

FACT The notion that a pupil tends to learn better by favoring a particular form of sensory input—a "visual learner" as opposed to one who listens better—has not received much validation in actual studies. For this and other myths, public perceptions appear to have outstripped the science. Uta Frith, a neuroscientist who chaired a British panel that looked at the promise of neuroeducation, urges parents and educators to tread cautiously: "There is huge demand by the general public to have information about neuroscience for education. As a consequence, there's an enormous supply of totally untested, untried and not very scientific methods."

SOURCES: Mind, Brain, and Education Science, by Tracey Tokuhama-Espinosa (W. W. Norton, 2010); *Understanding the Brain: The Birth of a Learning Science* (OECD, 2007); OECD Educational Ministerial Meeting, November 4–5, 2010.

world. In 1972 a famous experiment at Stanford University—"Here's a marshmallow, and I'll give you another if you don't eat this one until I return"—showed the importance of executive function. Children who could wait, no matter how much they wanted the treat, did better in school and later in life.

During the past 10 years experts have warmed to the idea of executive function as a teachable skill. An educational curriculum called Tools of the Mind has had success in some low-income school districts, where children typically do not fare as well academically compared with high-income districts. The program trains children to resist temptations and distractions and to practice tasks designed to enhance working memory and flexible thinking. In one example of a self-regulation task, a child might tell himself aloud what to do. These techniques are potentially so powerful that in centers of higher learning, economists now contemplate public policy measures to improve self-control as a way to "enhance the physical and financial health of the population and reduce the rate of crime," remark the authors of a study that appeared in the February *Proceedings of the National Academy of Sciences USA*.

Findings from neuroscience labs have recently bolstered that view and have revealed that the tedium of practice to resist metaphorical marshmallows may not be necessary. Music training can work as well. Echoing the *Battle Hymn of the Tiger Mother,* they are finding that assiduous practice of musical instruments may yield a payoff in the classroom, similar to the rationale of "tiger mom" author Amy Chua, who insisted that her daughters spend endless hours on the violin and piano. Practicing a musical instrument appears to improve attention, working memory and self-control.

Some of the research providing such findings comes from a group of neuroscientists led by Nina Kraus of Northwestern University. Kraus, head of the Auditory Neuroscience Laboratory there, grew up with a diverse soundscape at home. Her mother, a classical musician, spoke to the future neuroscientist in her native Italian, and Kraus still plays the piano, guitar and drums. "I love it—it's a big part of my life," she says, although she considers herself "just a hack musician."

Kraus has used EEG recordings to measure how the nervous system encodes pitch, timing and timbre of musical compositions—and whether neural changes that result from practicing music improve cognitive faculties. Her lab has found that music training enhances working memory and, perhaps most important, makes students better listeners, allowing them to extract speech from the all-talking-at-once atmosphere that sometimes prevails in the classroom.

Musical training as brain tonic is still in its infancy, and a number of questions remain unanswered about exactly what type of practice enhances executive function: Does it matter whether you play the piano or guitar or whether the music was written by Mozart or the Beatles? Critically, will music classes help students who have learning difficulties or who come from low-income school districts?

But Kraus points to anecdotal evidence suggesting that music training's impact extends even to academic classes. The Harmony Project provides music education to low-income youngsters in Los Angeles. In recent years, dozens of students have graduated high school and gone on to college, usually the first in their family to do so.

Program founder Margaret Martin has invited Kraus to use a mobile version of her EEG sensors and sound-processing software to measure how music affects children in the program. The hack musician is an unabashed advocate of the guitar over brain games. "If students have to choose how to spend their time between a computer game that supposedly boosts memory or a musical instrument, there's no question, in my mind, which one is more beneficial for the nervous system," Kraus says. "If you're trying to copy a guitar lead, you have to keep it in your head and try to reproduce it over and over through painstaking practice."

HYPE ALERT

AS RESEARCH CONTINUES on the brain mechanisms underlying success in the "four Rs," three traditional ones with regulation of one's impulses as the fourth, many scientists involved with neuroeducation are taking pains to avoid overhyping the interventions they are testing. They are eager to translate their findings into practical assistance for children, but they are also well aware that the research still has a long way to go. They know, too, that teachers and parents are already bombarded by a confusing raft of untested products for enhancing learning and that some highly touted tools have proved disappointing.

In one case in point, a small industry developed several years ago around the idea that just listening to a Mozart sonata could make a baby smarter, a contention that failed to withstand additional scrutiny. Kraus's research suggests that to gain any benefit, you have to actually play an instrument, exercising auditory-processing areas of the brain: the more you practice, the more your abilities to distinguish subtleties in sound develop. Listening alone is not sufficient.

Similarly, even some of the brain-training techniques that claim to have solid scientific proof of their effectiveness have been questioned. A meta-analysis that appeared in the March issue of the *Journal of Child Psychology and Psychiatry* reviewed studies of perhaps the best known of all brain-training methods—software called Fast ForWord, developed by Paula A. Tallal of Rutgers, Michael Merzenich of the University of California, San Francisco, and their colleagues. The analysis found no evidence of effectiveness in helping children with language or reading difficulties. As with the methods used by Benasich, a former postdoctoral fellow with Tallal, the software attempts to improve deficits in the processing of sound that can lead to learning problems. The meta-analysis provoked a sharp rebuttal from Scientific Learning, the maker of the software, which claimed that the selection criteria were too restrictive, that most studies in the analysis were poorly implemented and that the software has been improved from the time the studies were conducted.

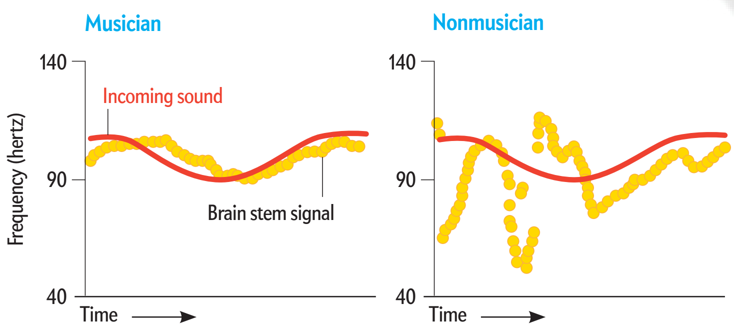
The clichéd refrain—more research is needed—applies broadly to many endeavors in neuroeducation. Dehaene's number game still needs fine adjustments before it receives wide acceptance. One recent controlled study showed that the game helped children compare numbers, although that achievement did not carry over into better counting or arithmetic skills. A new version is being released that the researchers hope will address these problems. Yet another finding has questioned whether music training improves executive function and thereby enhances intelligence.

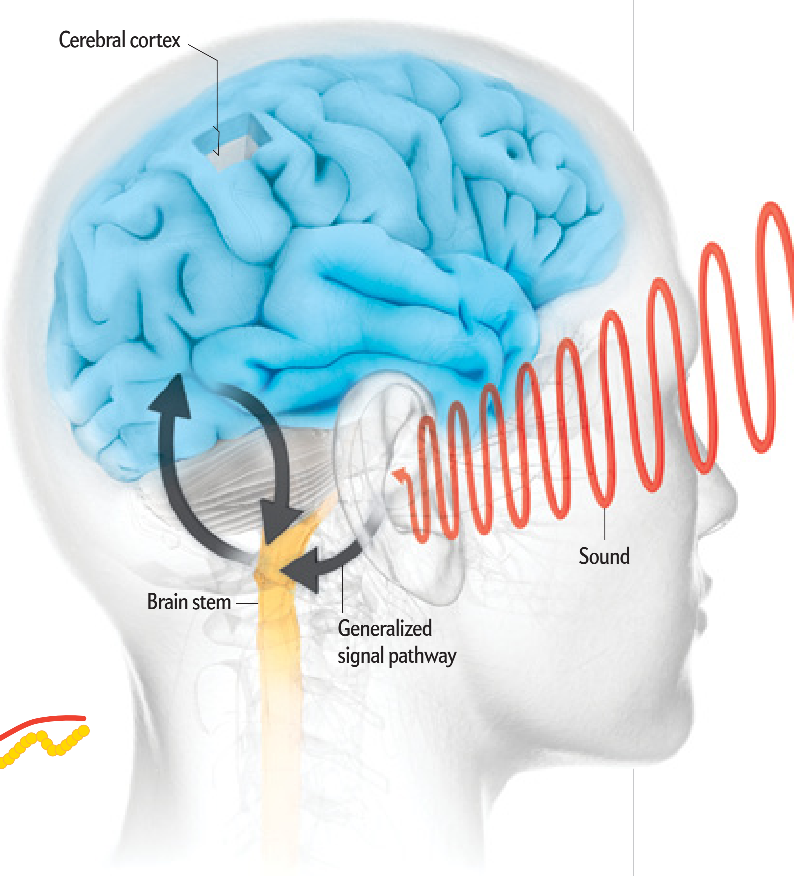
The Best Brain Training: Practice That Violin

Intensive musical training from a young age fosters skills beyond just an ability to play an instrument. The musician's concentration on the fine-grained acoustics of sound helps with language comprehension and promotes cognitive skills: attention, working memory and self-regulation.

Better Listeners

Musicians perceive sound more clearly than nonmusicians because practicing an instrument trains the entire brain. The sounds of an instrument travel from the cochlea in the inner ear to the primitive brain stem before moving to the cortex, a locus of high-level brain functions, and then back again to the brain stem and cochlea. This feedback loop allows the musician to recruit various brain areas to produce, say, the proper pitch for a tune. Monitoring of an electrical signal in the brain stem (*yellow graph line*) reveals the musician's exquisite sensitivity to pitch: the musician tracks an incoming sound wave (*red line*) more accurately than a nonmusician does.





SOURCE: "MUSICAL EXPERIENCE SHAPES HUMAN BRAINSTEM ENCODING OF LINGUISTIC PITCH PATTERNS," BY PATRICK C. M. WONG, ERIKA SKOE, NICOLE M. RUSSO, TASHA DEES AND NINA KRAUS, IN *NATURE NEUROSCIENCE*, VOL. 10, NO. 4; APRIL 2007 *(graphs)*

In a nascent field, one study often contradicts another, only to be followed by a third that disputes the first two. This zigzag trajectory underlies all of science and at times leads to claims that overreach. In neuroeducation, teachers and parents have sometimes become the victims of advertising for "science-based" software and educational programs. "It's confusing. It's bewildering," says Deborah Rebhuhn, a math teacher at the Center School, a special-education institution in Highland Park, N.J., that accepts students from public schools statewide. "I don't know which thing to try. And there's not enough evidence to go to the head of the school and say that something works."

A PRESCHOOL TUNE-UP

SCIENTISTS WHO SPEND their days mulling over EEG wave forms and complex digital patterns in magnetic resonance imaging realize that they cannot yet offer definitive neuroscience-based prescriptions for improving learning. The work, however, is leading to a vision of what is possible, perhaps for Generation Z or its progeny. Consider the viewpoint of John D. E. Gabrieli, a professor of neuroscience participating in a collaborative program between Harvard University and the Massachusetts Institute of Technology. In a review article in *Science* in 2009, Gabrieli conjectured that eventually brain-based evaluation methods, combined with traditional testing, family history and perhaps genetic tests, could detect reading problems by age six and allow for intensive early intervention that might eliminate many dyslexia cases among school-age children.

One study has already found that EEGs in kindergartners predict reading ability in fifth graders better than standard psychological measures. By undergoing brain monitoring combined with standard methods, each child might be evaluated before entering school and, if warranted, be given remedial training based on the findings that are trickling in today from neuroscience laboratories. If Gabrieli's vision comes to pass, brain science may imbue the notion of individualized education with a whole new meaning—one that involves enhancing the ability to learn even before a child steps foot in the classroom. SA

Gary Stix is senior writer at Scientific American.

MORE TO EXPLORE

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Nina Kraus's Auditory Neuroscience Laboratory at Northwestern University: **www.brainvolts.northwestern.edu**

SCIENTIFIC AMERICAN ONLINE
Watch a video of April A. Benasich's research at **ScientificAmerican.com/aug2011/benasich**

Illustration by Bryan Christie, Graphics by Jen Christiansen

ENERGY

THE FALSE PROMISE OF BIOFUELS

The breakthroughs needed to replace oil with plant-based fuels are proving difficult to achieve

By David Biello

Photograph by Levi Brown

RANGE FUELS WAS A RISKY BUT TANTALIZING BET. The high-tech start-up, begun by former Apple executive Mitch Mandich, attracted millions of dollars in private money plus commitments for up to $156 million in grants and loans from the U.S. government. The plan was to build a large biofuels plant in Soperton, Ga. Each day the facility would convert 1,000 tons of wood chips and waste from Georgia's vast pulp and paper industry into 274,000 gallons of ethanol. "We selected Range Fuels as one of our partners in this effort," said Samuel Bodman, then secretary of energy, at the groundbreaking ceremony in November 2007, "because we really believe that they are the cream of the crop."

That crop has spoiled in the ground. Earlier this year Range Fuels closed its newly built biorefinery without selling a drop of ethanol. Turning biomass into a commercially viable, combustible liquid is tougher than anticipated, the company has found. As expensive equipment sits idle, the firm is searching for more funding to try to solve the problem.

Range Fuels is not the only biofuels company to fall short. Cilion in Goshen, Calif., Ethanex Energy in Basehor, Kan., and others have gotten out of the business of making biofuels from plant matter because it is too expensive. Despite the best hopes of scientists, CEOs and government policy makers, hundreds of millions of dollars in government money, more than two dozen U.S. start-ups financed by venture capital and decades of concentrated work, no biofuel that can compete on price and performance with gasoline is yet on the horizon.

This failure is particularly discouraging because only a few years ago biofuels seemed like an ideal solution to two big U.S. problems: dependence on oil and climate change. Terrorism and soaring oil prices had made Middle Eastern oil a particular liability, and rising average global temperatures underscored the need to find alternative fuels for automobiles and airplanes. Because biofuels come from plants, which absorb carbon dioxide from the atmosphere as they grow, burning biofuels in vehicles would in theory slow the buildup of greenhouse gases, compared with burning fossil fuels.

The notion that biofuels technology is not living up to expectations may seem odd, given the rapid expansion in recent years of corn ethanol. U.S. production went from 50 million gallons in 1979 to 13 billion gallons in 2010. A government mandate to supply 10 percent of the country's passenger vehicle fuel drove that enormous growth, however, and the product has been affordable only because of massive federal subsidies. Ethanol yields little if any net savings in carbon dioxide emissions. Furthermore, making those 13 billion gallons consumed roughly 40 percent of the nation's corn crop, cultivated on 32 million acres of farmland, pushing up food prices and feeding an enormous "dead zone" in the Gulf of Mexico, where the Mississippi River dumps all the fertilizer that runs off midwestern cornfields.

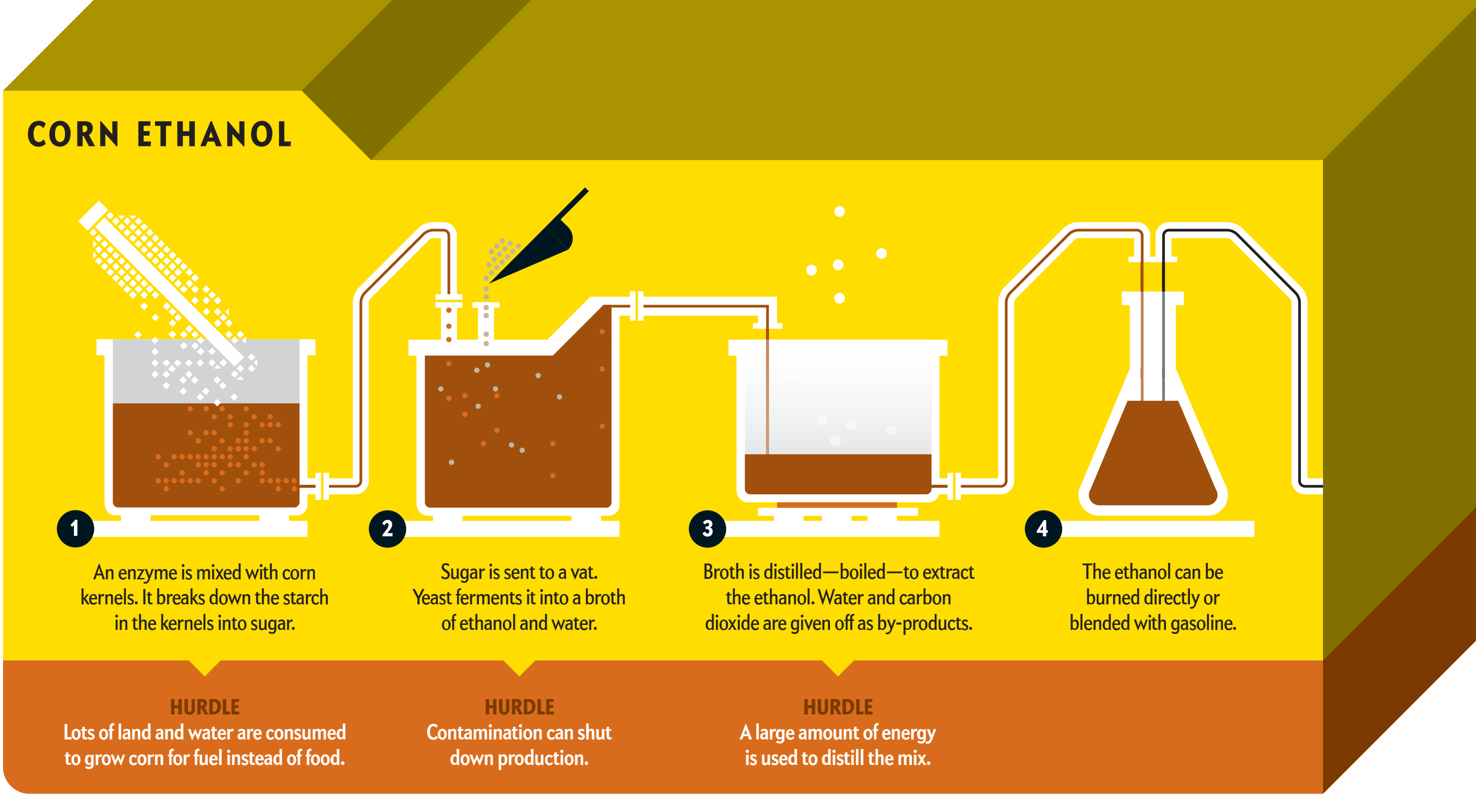
More advanced biofuels made with different processes promised to remedy these flaws. Ethanol could be brewed from sugar derived from the husks and

IN BRIEF

Despite extensive research, biofuels are still not commercially competitive. The breakthroughs needed, revealed by recent science, may be tougher to realize than previously thought.

Corn ethanol is widely produced because of subsidies, and it diverts massive tracts of farmland needed for food. Converting the cellulose in cornstalks, grasses and trees into biofuels is proving difficult and expensive. Algae that produce oils have not been grown at scale. And more advanced genetics are needed to successfully engineer synthetic microorganisms that excrete hydrocarbons.

Some start-up companies are abandoning biofuels and are instead using the same processes to make higher-margin chemicals for products such as plastics or cosmetics.



stalks of the corn plant, rather than the edible kernel, or from similarly fibrous material in grasses or even trees (as in the case of Range Fuels). These plant parts consist of cellulose, which is not used as food for humans nor as feed for animals and therefore would not affect food prices. Liquid fuels could also be harvested from algae, which more efficiently turn water, CO_2 and sunlight into fats that can be converted into hydrocarbons or, more effective still, from genetically engineered microorganisms that could directly excrete hydrocarbons.

None of these advanced biofuels is working at commercially meaningful scales today, however. According to the U.S. Environmental Protection Agency's Renewable Fuel Standard, by 2011 the U.S. was supposed to be producing 100 million gallons of cellulosic ethanol a year. Instead in 2010 the EPA rolled back the 2011 goal to just 6.5 million gallons, and it is unclear whether even that amount will be reached.

Recent experience suggests that the scientific or industrial improvements needed to solve the challenges to making advanced biofuels practical may be extremely difficult to attain. The goal of producing 36 billion gallons of biofuels annually by 2022, set by the U.S. government as a significant solution to energy independence and climate change, looks to be an even more distant prospect. "It's not a simple problem," says microbiologist Timothy Donohue, director of the Great Lakes Bioenergy Research Center in Madison, Wis., one of three Department of Energy labs dedicated to advanced biofuels. "It's no less challenging than doing things with stem cells or other major scientific initiatives this country has embarked on."

CORN ETHANOL: SIMPLY INSUFFICIENT

SO FAR CORN ETHANOL is the only biofuel to reach commercial scale in the U.S., thanks to subsidies that topped $5.68 billion in 2010 alone, according to the White House's Office of Management and Budget. Fermentation is the core technology for making ethanol from corn. Humans have spent the past 9,000 years refining techniques for exploiting enzymes and yeast to ferment sugars derived from corn kernels, sugarcane or other plants into ethanol. To scale up U.S. production over the past decade, an extensive infrastructure of corn mills, stainless-steel fermentation tanks and other equipment has sprung up like mushrooms after rain throughout the Midwest.

Unfortunately, corn ethanol is not very energy-efficient and is therefore not carbon-neutral. Lots of energy is required to distill (basically, boil off) ethanol from the soup of water and yeast in which it has been fermented—energy typically supplied by burning fossil fuels such as natural gas or coal. After all that trouble, a gallon of ethanol supplies a vehicle with only two thirds of the energy in a gallon of gasoline.

Those energy inputs cost money, too, and corn ethanol may never compete on price with gasoline without subsidies. Greater production is also limited by fertile land. In October 2010 the Congressional Research Service reported that if the entire record U.S. corn crop of 2009 was used to make ethanol, it would replace only 18 percent of the country's gasoline consumption. "Expanding corn-based ethanol … to significantly promote U.S. energy security is likely to be infeasible," the researchers concluded.

J. Craig Venter, co-founder of would-be algae producer Synthetic Genomics, puts an even sharper point on the land problem. Replacing all U.S. transportation fuels with corn ethanol, he calculates, would

Lots of energy is required to distill ethanol from the soup of water and yeast in which it has been fermented, energy typically supplied by burning fossil fuels.

Illustrations by Carl DeTorres

require a farm three times the size of the continental U.S.

CELLULOSE: TOUGH TO BREAK DOWN

OF COURSE, using the nation's entire corn crop to make fuel would leave none as food—for people or livestock. That is one reason researchers and policy makers have turned their attention to cellulosic ethanol, produced not from the starchy corn kernel but from the rest of the corn plant—the stover, or "waste"—which would not adversely affect the food supply.

The energy that could be harvested from waste cellulose is potentially huge. According to Oak Ridge National Laboratory, the U.S. could generate 1.4 billion tons of cellulosic material such as corn stover, 80 percent of which could be converted to biofuel, displacing 30 percent of U.S. transportation fuel.

Finding a way to efficiently break down a plant's cell walls is the central challenge. First, there is lignin, the chemical compound that supports a plant's cell wall against gravity and that makes wood indigestible for animals. Then there is the hemicellulose, a long, interlocking complex sugar fiber bonded to the lignin supports that wards off attacking enzymes. Inside these walls is a fibrous core of cellulose—long chains of glucose molecules, simple carbohydrate sugars that hold the energy that will become a biofuel.

One inspiration for breaking through the organic barriers comes from leaf-cutter ants. At the Great Lakes Bioenergy Research Center, leaf-cutter ants mill about in plastic bins, growing fungus caves that turn leaf material into the oils and amino acids that the insects actually eat. Certain microbes in the ants' digestive tract chew up the initial harvest into scraps. Worker ants transfer those scraps into the compost caves. Another set of microbes that the ants deposit converts the scraps, with the addition of water, into lipid droplets. In essence, the ants build an external gut for turning cellulose into fuel—a small model, perhaps, for a biofuels factory.

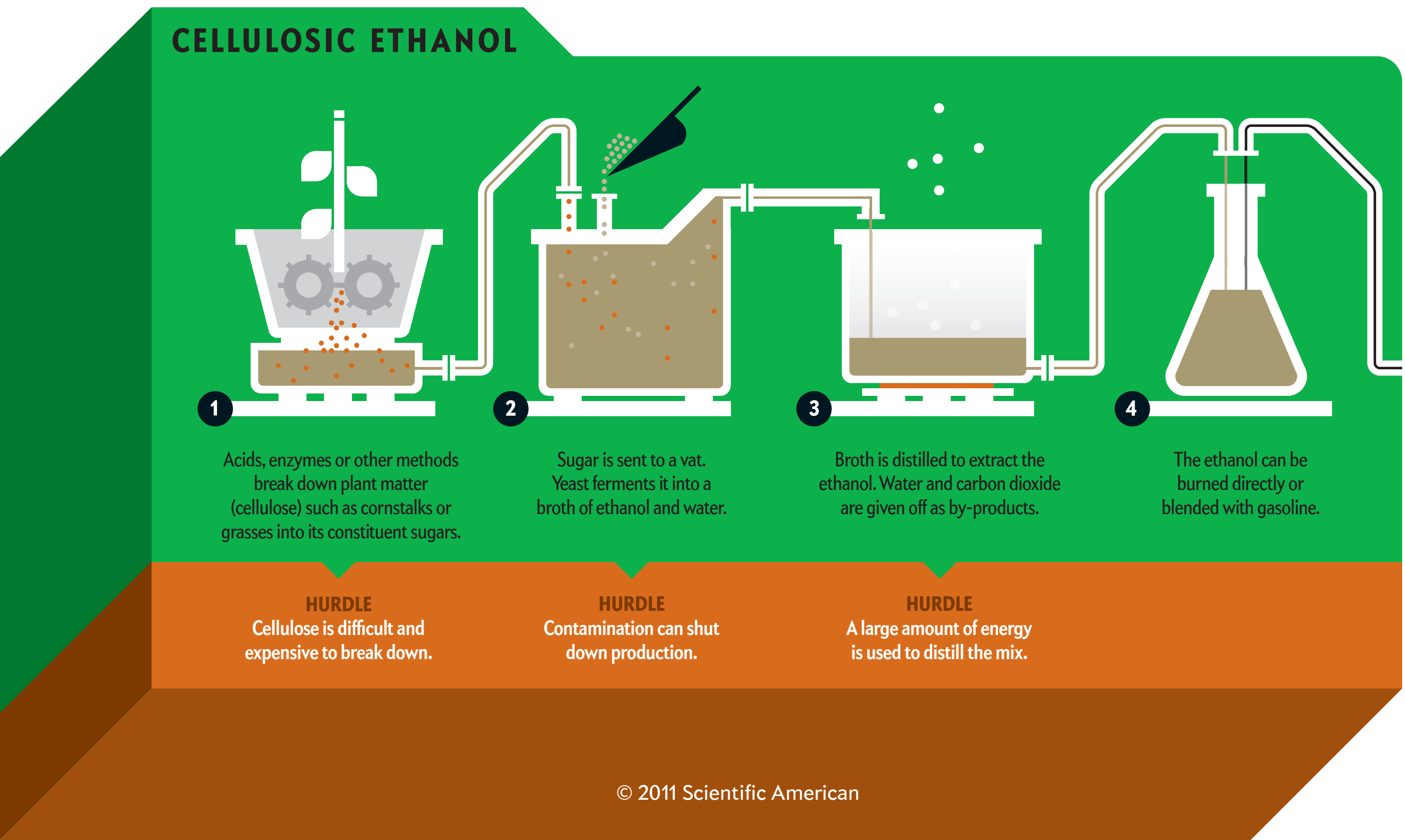
The lab's goal, Donohue says, "is to either use those microbes themselves or isolate the genetic material that encodes their enzymes and use it in an industrial process to take plant cell walls apart."

Inspiration also comes from cows, which break down cells by crushing grass between their powerful teeth and washing it in a bath of saliva. In the cow's gut, a slew of microbes ferment the fibrous cud into lipids—the fatty building blocks of fuels. To mimic a cow's chewing, scientists have tried blasting cell walls with steam or bathing them in liquids made up of charged molecules. HCL Cleantech in Oxford, N.C., dissolves plants in concentrated hydrochloric acid to get at the cellulose inside, then recycles the acid to try to keep costs down.

Yet another approach is to use a family of enzymes known as cellulases, such as the enzyme in a termite's gut that turns wood into food. Only one such enzyme is commercially available—from Danish company Novozymes. It costs roughly 50 cents a gallon—more than 10 times the price of enzymes used in traditional ethanol fermentation. "Enzyme costs have to come down, or there will be no industry," admits Cynthia Bryant, Novozymes's manager for global business development.

Codexis in Redwood City, Calif., is trying to build a more affordable enzyme by screening thousands of natural versions and combining their parts into a hybrid that works better in a factory than in nature. The company is also tweaking the genes that cause living cells to create enzymes, hoping to end up with a superenzyme of sorts.

Even a superenzyme will inevitably be slow to break down cellulose because the biological interactions require time to work, making high-volume production difficult. But what if energy crops such as corn or switchgrass could produce these cellulose-splitting enzymes themselves? The enzymes would hide within the plant cell, waiting for heat or some other industrial trigger to set them off, allowing the cellulose to quickly and easily degrade into its component sugars.



Swiss agribusiness giant Syngenta has already devised a way to embed enzyme-making capabilities into corn kernels, allowing the kernels themselves to convert starch to sugar when exposed to the right temperature, moisture and acidity concocted in a factory. The U.S. Department of Agriculture has approved the process over objections from environmentalists and food producers such as the North American Millers' Association, and Syngenta's seeds containing the enzyme will go on sale this year.

This work proves the principle, but it does not solve the problems of using corn for fuel rather than food. As an alternative, Agrivida in Medford, Mass., hopes to apply its own version of the technology to cellulose from corn stover or dedicated energy crops such as switchgrass.

Inbred enzymes alone may not make cellulosic ethanol affordable. The sugars that are unlocked "better be one-third the cost of a barrel of oil," says chemist Patrick R. Gruber, CEO of biotech company Gevo in Englewood, Colo., given the cost of then refining the sugar into liquid fuel. Indeed, Gevo and other companies, such as Virent in Madison, Wis., have concluded that even with historically high gasoline prices, advanced biofuels cannot compete as a fuel. The companies are de-emphasizing ethanol as a product, and instead they are altering their processes to turn sugars—whether from cellulose or sugarcane—into industrial chemicals such as precursors for plastics in bottles, which now command prices as much as 10 times higher than fossil fuels.

Even if sugar from cellulose somehow became competitive, the approach would impose a significant environmental and agricultural burden. Corn stover is typically left on farmland after harvest, where it improves the soil's fertility as it decomposes. Baling it up and hauling it away may accelerate soil degradation, rendering the soil incapable of growing crops. "I am not convinced that we fully understand the consequences of taking all this biomass out of the system," says Jeffrey Jacobs, vice president of biofuels and hydrogen business for Chevron Technology Ventures in San Ramon, Calif. Some scientists estimate that only 80 million tons of cellulosic material could be safely removed from U.S. fields, which, if converted to ethanol, would supply only 3 percent of U.S. gasoline demand.

Seeking a cheaper feedstock, oil companies such as Royal Dutch Shell in the Netherlands are investing in ethanol fermented from sugarcane rather than from stover. Sugarcane delivers more energy, is easier to grow and has an existing production infrastructure in Brazil thanks to more than 40 years of government effort. That country now supplies roughly seven billion gallons of ethanol from sugarcane annually. Shell has formed a joint venture dubbed Raizen with Brazilian ethanol maker Cosan to produce 581 million gallons of sugarcane ethanol a year, according to Shell's global manager of bioinnovation Jeremy Shears. That much growth in production would exacerbate the leveling of Brazilian natural habitats, which in turn could promote clearing of the Amazon rain forest. "The thing that's going to destroy the planet is not crop-based biofuels, where everybody seems to accept there are limits. It's unlimited cellulosic-based biofuels," notes agricultural expert Timothy D. Searchinger of Princeton University. "We're talking about a gigantic, gigantic effect on world land use and biodiversity."

Even if a superenzyme is found, it will inevitably be slow to break down cellulose because the reactions require time to work, making volume production difficult.

ALGAE: DIE OR BE KILLED

AS AN ALTERNATIVE, some scientists have opted to work with the one photosynthetic organism that does a much more effi-

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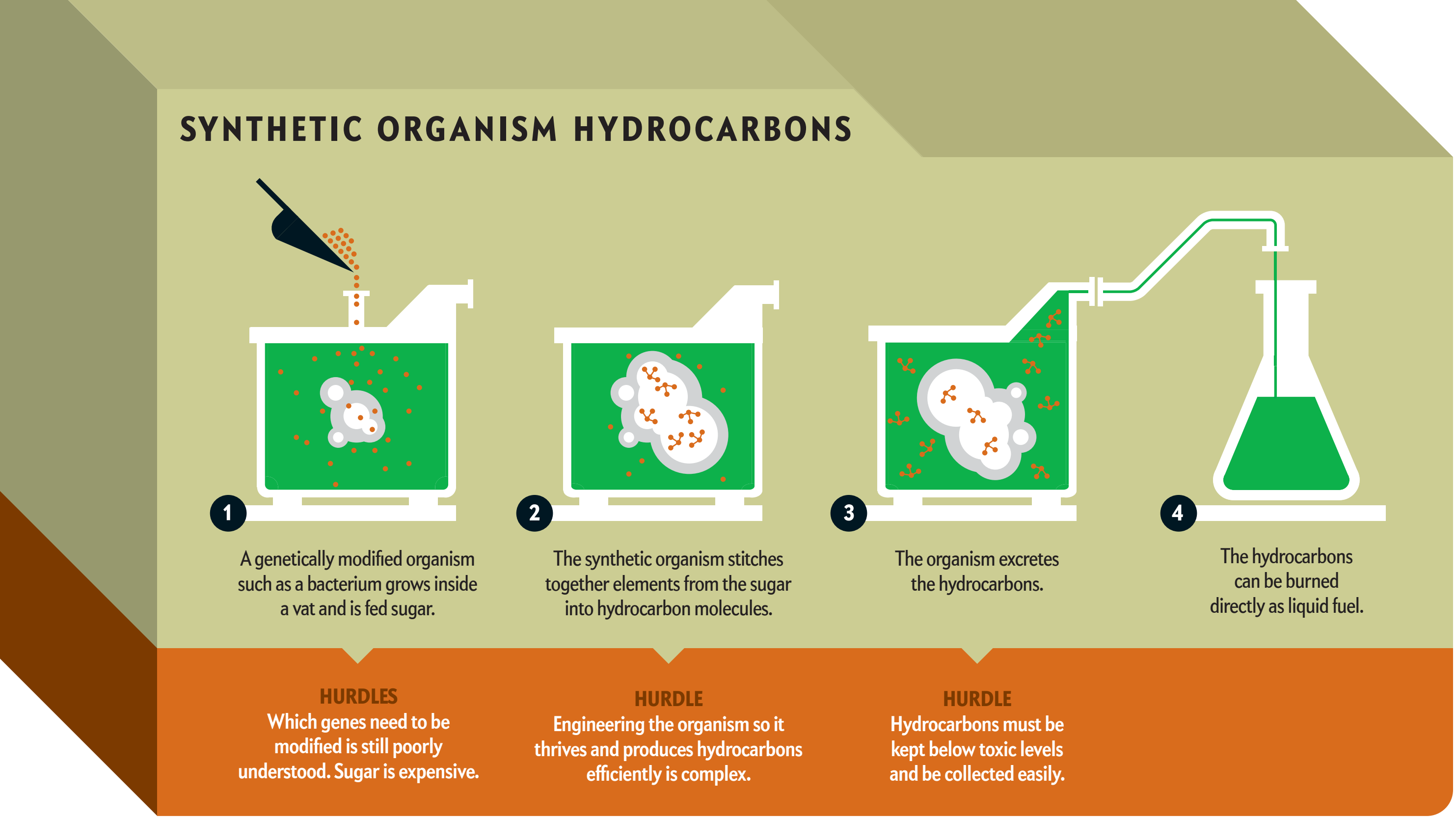

cient job than rooted plants of turning incoming photons into stored chemical energy: pond scum.

Microscopic algae are the titans of photosynthesis. Certain strains can harness 3 percent of the incoming sunlight to make plant matter, as opposed to roughly 1 percent for corn or sugarcane. Their greenish tint comes from chlorophyll, a pigment that captures sunlight to break water into hydrogen and oxygen. The organisms combine the hydrogen with carbon dioxide to make cell walls, food and stockpiled fats—plant oil.

Algae can be grown in the desert instead of on arable land, nourished with undrinkable briny water or even sewage, so the approach does not displace food crops or consume precious freshwater. The efficient process promises as much as 4,270 gallons of oil per acre, depending on conditions. Replacing all U.S. transportation fuels with algal oil "would take a farm roughly the size of Maryland," notes Synthetic Genomics's Venter, compared with his estimate of farmland three times the size of the continental U.S. for corn ethanol. "That's a pretty big difference," Venter quips. "One's doable, and the other's just absurd."

Sapphire Energy in San Diego is testing the algal waters in a series of oval ponds spread across 22 desert acres near Las Cruces, N.M. The company plans to build 300 more acres of ponds near Columbus, N.M. That facility would be the country's first integrated algae production plant, for which Sapphire has secured a $50-million grant from the USDA and a $54.5-million loan guarantee from the DOE. The algae would grow in brine from salt aquifers underneath New Mexico, and the oil would be shipped to a refinery in Louisiana.

The problems facing algal biofuels producers are manifold, however. If they grow algae in open ponds, how do they prevent the organisms from falling prey to predators, disease or contamination by natural strains? If they grow algae inside bioreactors, how do they justify the equipment expense and keep the algae from sticking to the innards? How do they afford nutrients such as the nitrogen and phosphorus required to promote the algae's growth? Ultimately, once they have grown the algae, how do they skim off and tear apart the mature algal cells to get the oil without using as much or more energy than that oil could provide? Few algae companies have produced useful quantities of oil, much less profits.

The biggest challenge may be the fact that producing hydrocarbons is algae's defense against long periods without sunlight or nutrients. When in this stress mode, however, the tiny plants grow slowly. Scientists will have to go against the basic biological mechanisms of these cells to engineer them to respond to stress yet grow quickly.

Sapphire has surveyed 4,000 algal strains and chosen 20 to try to enhance. If all goes well, the Columbus facility would manufacture one million gallons of algal oil a year, which could then be refined into diesel or jet fuel. The dead algal cells would be recycled into the process as nutrients rather than sold as animal meal or other products; that biomass "is expensive, and we need it," says Tim Zenk, vice president for corporate affairs at Sapphire. "You can't add a lot of nutrients to the system and make any money at it."

That fact led the U.S. National Renewable Energy Laboratory to shut down its 18-year-old algal oil research program in 1996, after it consumed $25 million in research funds. The scientists felt their algal oil would never be competitive with fossil oil and lost thousands of strains of characterized algae after the shutdown. The companies making money on algae today do so by harvesting omega-3 fatty acids, sold as a nutritional supplement at a much higher price than crude oil.

The only company to commercially deliver algal fuel did so by avoiding photosynthesis altogether. South San Francisco–based Solazyme has supplied more than 20,055 gallons of oil to the U.S. Navy—at $424 a gallon. Solazyme grows algae inside the kinds of industrial vats typically used to ferment insulin, force-feeding it sugar instead of sunlight and water. Like other advanced biofuels companies, Solazyme will stay in business by making products that are more expensive than fuel; it sells oil for use in cosmetics and is partnering with Dow Chemical to make specialty chemicals such as insulating fluids.

SYNTHETIC ORGANISMS: GENETICS UNCLEAR

THE ALGAE COMPANIES try to overcome obstacles by changing the microorganism's genetic code with chemicals or radiation, but they have not hit on robust combinations yet. Venter sailed the world for a year on his yacht, *Sorcerer II,* sampling the seas for beneficial strains, with no clear winner. "That's why we're not so sanguine about finding the one magic bug out there to do everything," he says.

Maybe it is time to manufacture that magic bug instead.

Researchers have started by tweaking the genes of microorganisms, notably *Escherichia coli,* the common human gut bacterium that can also cause food poisoning. Jay D. Keasling, who directs the DOE's Joint BioEnergy Institute, has turned *E. coli* into an efficient biological factory that converts sunlight, CO_2 and water into different hydrocarbons, including biodiesel. Conveniently, Keasling altered the bacterium to excrete the oil, so it does not have to be killed for harvest. The oils float to the top of a vat, where they can be drawn off. The bacterium grows three times faster than yeast, is happy at tropical temperatures and is hardy, thanks to a heritage of withstanding the often oxygen-free and poisonous conditions of the human digestive tract.

Here again higher-value hydrocarbons will be the first markets, if any, for these biological factories. Amyris in Emeryville, Calif., has tweaked yeast to ferment sugars into farnesene, which can be sold directly or turned into specialty chemicals such as squalane, an emollient in high-end cosmetics. The company is starting with products that have a higher average selling price and will move toward lower prices, "lower being diesel and fuel products," explains chief financial officer Jeryl L. Hilleman. Amyris just opened its first production facility in Brazil as an adjunct to a sugarcane-fermentation plant.

Even a robustly engineered microorganism may find it hard to produce hydrocarbons at a volume or price that can compete with fossil oil. The long-term solution, Venter argues, "is to make the entire genetic code from scratch and control all the parameters." His company has already created a synthetic bacterium cell that secretes oil, as well as the first organism to live entirely on synthesized genetic code. "We're evaluating thousands of strains and large numbers of genetic changes," he notes.

The approach holds enough promise that fossil-fuel giant ExxonMobil has invested $600 million in Venter's firm. But the hurdles come down to basic biology: even the smallest genomes have hundreds of mysterious genes, and scientists have no clue about their function. Biological architects such as Venter can build a genome, but they do not know which genes are needed to make a synthetic microorganism hardy, cheap to keep alive and able to produce oil in abundance. Venter calls the challenge "bigger" than the one he faced when sequencing the human genome.

Biological architects do not know which genes are needed to make a synthetic microorganism hardy, cheap to keep alive and able to produce oil in abundance.

Even if someone produces the magic bug, its viability will depend on the cost of its food. Right now the cheapest source is Brazilian sugarcane, which is what Amyris, LS9 in South San Francisco and others are using, even though it is still too expensive as the starting point for an advanced biofuel. As with algae, infections and other biological mishaps can shut down production vats, a problem that could be even more acute with specialized microbes, ill suited to survival without help from humans. And inevitably, microbes are slower to make biofuels at volume than chemically processing crude oil.

Amyris's own chief technology officer, Neil Renninger, acknowledges that "we are not going to replace petroleum this way. We are going to augment petroleum. It would be great if we could handle [just] the growth in demand for petroleum." That goal places an emphasis on producing a hydrocarbon molecule that will move through today's pipelines, be manageable in today's refineries and burn in today's engines.

FOOL'S ERRAND?

RENNINGER'S POINT of view concurs with that of other experts who argue that our expectations should be lowered. All the energy in crops grown today—along with plants consumed by livestock and trees harvested for pulp, paper and other wood products—comes to roughly 180 exajoules, or about 20 percent of world energy consumption. Increasing that considerably in the near future may not be feasible and would have significant social and ecological consequences. "The goal should be to produce something like the world's supply of airplane fuel," Princeton's Searchinger says.

Breakthroughs remain possible, and the scientific quest for a better biofuel continues, but investors and politicians might be wise not to stake much money or policy on a high-risk bet. As an option, nations could electrify transportation to reduce fossil-fuel use. Until they do, corn and sugarcane will provide the bulk of any alternative to oil, further straining a global agricultural system already struggling to provide food, feed and fiber for seven billion people plus livestock—and counting.

"We can all live with different kinds of transportation," says ecologist G. David Tilman of the University of Minnesota. "We can't live without food." SA

David Biello *is an associate editor for Scientific American Online.*

MORE TO EXPLORE

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SCIENTIFIC AMERICAN ONLINE
For an assessment of biofuels from man-made waste, see ScientificAmerican.com/aug2011/biello

LIFE SCIENCE

TREASURE IN THE TREES

Nests offer clues about natural history, climate change and their owners' mating habits

By Nina Bai

From twigs and grasses to sheep's wool and horsehair, birds weave their world into their nests. The homes they leave behind thus provide clues about their lives and their environment, much as archaeological sites supply glimpses of human history.

The architectural diversity of nests has been used to untangle the complex genealogy of South American songbirds; remnants of prey found in bald eagle nests have revealed the birds' food habits; and carbon dating of feathers and droppings in ancient falcon nests has yielded evidence for the timing of ice-sheet retreats in Greenland. Ongoing research, including a paper published in the journal *Science* earlier this year, shows that birds use nest decor to compete for mates and communicate with one another more often than previously recognized.

Nest collecting was a popular boyhood hobby in the 19th century but is now banned throughout much of the world. Most of the images here come from *Nests: Fifty Nests and the Birds That Built Them* (Chronicle Books, 2011), in which photographer Sharon Beals showcases samples from museums. Lloyd Kiff, a former director of the Western Foundation of Vertebrate Zoology in Los Angeles (which holds the world's largest collection, with 18,000 specimens), says that nests remain a largely untapped scientific resource. They are not just for the birds.

Nina Bai is a science writer based in New York City.

Field notes: 1 House Finch (Arizona, 1965); thread, paper, twist ties. 2 Small Ground Finch (Galápagos Islands, 1906); grass, twigs, wild cotton. 3 Verdin (Mexico, 1961); prickly twigs, spiderweb. 4 Spotted Nightingale Thrush (Mexico, 1968); moss, lichen, leaves. 5 Gray Jay (Colorado, 1938); twigs, cocoons, lichen, bark, fur, feathers. 6 American Dipper (California, 1951); moss, grass, leaves, bark. 7 MacGillivray's Warbler (California, 1920); grass inside bark. 8 Western Tanager (Nevada, 1934); twigs, bark, pine needles, animal hair. 9 House Wren (California, 1974); twigs, fine grass, skeletons of abandoned runt chicks.

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Photographs by Sharon Beals


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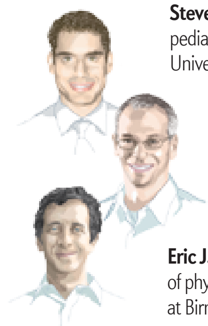

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Eric J. Sorscher is a professor of medicine and a professor of physiology and biophysics at the University of Alabama at Birmingham.

MEDICINE

A BREATH OF FRESH AIR

Fundamental understanding of basic biology has set the stage for new treatments for cystic fibrosis

By Steven M. Rowe, J. P. Clancy and Eric J. Sorscher

Illustration by John Hendrix

I N 1989 WHEN SCIENTISTS DISCOVERED THE DEFECTIVE GENE THAT CAUSES CYSTIC FIBROSIS, a serious hereditary disorder that primarily strikes children of European descent, it seemed as though a long-hoped-for cure might soon follow. After all, tests in many laboratories showed that providing normal copies of the gene should enable patients to make healthy copies of the protein specified by the gene. If successful, that feat would go a long way toward restoring health in the tens of thousands of people around the world who suffered from cystic fibrosis and typically died in their late 20s. (Half of all patients now live to their late 30s or beyond.) The question was whether researchers would be able to reliably insert the correct gene into the proper tissues in patients' bodies to rid them of the illness forever.

That task proved harder than anyone had believed. Although scientists successfully engineered viruses to ferry copies of the correct gene into patients' cells, the viruses did not do the job well. By the late 1990s additional unexpected complications made it increasingly obvious that another approach to addressing the fundamental problem in cystic fibrosis would need to be found.

Meanwhile cell biologists and their colleagues undertook the long, challenging task of determining exactly what the normal protein looked like, how it functioned and how defects led to the symptoms of cystic fibrosis. These efforts included understanding the protein's three-dimensional shape in increasingly fine detail as well as the various ways the abnormal protein failed in its cellular duties. Instead of creating normal proteins by replacing the broken gene with an effective one—as was gene therapy's goal—this group of researchers focused on a different objective: finding a drug that allowed the deficient protein to work better. A fruitful search might give people with cystic fibrosis many additional years of a healthier life.

Today it looks as though the gradual but steady approach is paying off. Several new compounds are in the final stages of being tested for use in the treatment of cystic fibrosis—and one of them looks particularly promising for certain patients. If successful, it would be the first medication that targets the underlying cause of the disease, as opposed to dealing with symptoms. But that is not all. Preliminary studies indicate that these potential new treatments may also work against other, more common conditions, such as bronchitis, chronic sinusitis and pancreatitis, among others.

A PROBLEM WITH SALT

THE STORY OF HOW these drugs were identified begins with a dogged search to understand the basic biology of cystic fibrosis. The disease has long been known to result generally from a failure in the ability of certain body tissues to transport salt (sodium chloride) across the membranes that envelop cells. The cells in these tissues extrude the chloride part of the salt to help maintain the right balance between their fluid-filled interior and the watery exterior environment. As the chloride ions accumulate on the outside of the cell, water molecules follow suit, diffusing across the membrane to the outside. When the cell is finished constructing these tiny chloride channels, it inserts them into the membrane, where each protein forms a passageway that spans the cell border.

The gene that in 1989 was found to cause cystic fibrosis codes for one of these proteins, known as the cystic fibrosis transmembrane conductance regulator, or CFTR. The normal version of this molecule is made of a precise sequence of ap-

IN BRIEF

Cystic fibrosis is a serious hereditary disorder that fills certain organs in the body with a sticky mucus that interferes with the ability to digest food or breathe.

When researchers discovered the gene that causes cystic fibrosis in 1989, a long-hoped-for cure—in the form of gene therapy—seemed possible.

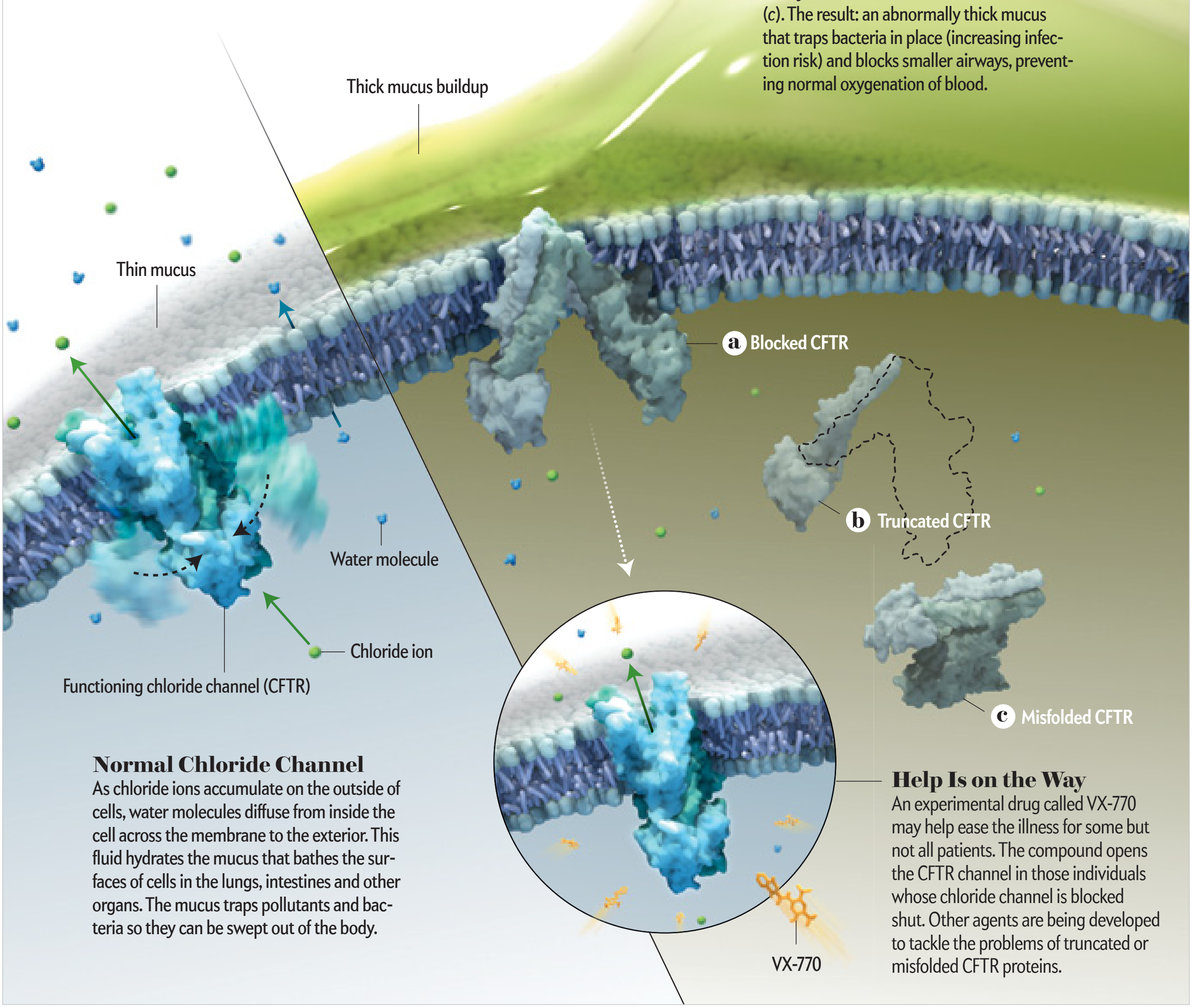
There were setbacks. But a new and different approach is now poised to deliver the first medications that address the fundamental causes of the disorder.

The Food and Drug Administration will probably begin to consider whether to approve a drug based on this latest research this year.

ANATOMY OF GENE DEFECT

Pathways to Trouble

To survive, cells constantly adjust their internal environment, such as by actively moving chloride ions out of the cell through a membrane-spanning protein called the CFTR channel. Mutations in the gene coding for this channel can lead to cystic fibrosis.



Abnormal Chloride Channel
Mutations in the cystic fibrosis gene cause illness in several ways, such as by leading to production of CFTR channels that are permanently blocked (*a*), truncated (*b*) or misfolded (*c*). The result: an abnormally thick mucus that traps bacteria in place (increasing infection risk) and blocks smaller airways, preventing normal oxygenation of blood.

Normal Chloride Channel
As chloride ions accumulate on the outside of cells, water molecules diffuse from inside the cell across the membrane to the exterior. This fluid hydrates the mucus that bathes the surfaces of cells in the lungs, intestines and other organs. The mucus traps pollutants and bacteria so they can be swept out of the body.

Help Is on the Way
An experimental drug called VX-770 may help ease the illness for some but not all patients. The compound opens the CFTR channel in those individuals whose chloride channel is blocked shut. Other agents are being developed to tackle the problems of truncated or misfolded CFTR proteins.

proximately 1,500 amino acids folded intricately and gracefully into a series of three-dimensional loops and sheets that spiral or plunge to form a number of different subsections. The flow of water molecules elicited by the movement of chloride ions through the channel helps to move the mucus that coats the surfaces of the body's airways, as well as the many ducts found in the intestines, pancreas and liver. The CFTR channel can also transport certain other ions, such as bicarbonate.

Here is where the trouble starts. Mutation of the gene results in the body lacking a proper CFTR channel. As a result, people with cystic fibrosis produce a sticky mucus that is so thick it interferes with many physiological processes. In the lungs, the gel-like mucus hampers the diffusion of oxygen into the air sacs and makes the simple act of breathing, as one of our young patients described it, like "trying to breathe with someone's hands over your face." Furthermore, the viscous buildup becomes an ideal breeding ground for serious infections by harmful bacteria, often *Pseudomonas aeruginosa*. In the pancreas, the thick and immobile secretions prevent the passage of digestive enzymes through various ducts into the intestines, interfering with proper digestion and, as a result, frequently causing people with cystic fibrosis to be underweight

Illustration by AXS Biomedical Animation Studio or undernourished. Meanwhile bile becomes trapped in the liver, so fats are not properly processed, and blockages in the intestines lead to constipation and sometimes even a life-threatening shutdown of the entire gastrointestinal tract.

Before the advent of antibiotics to treat recurrent lung infections and the discovery of better nutritional therapy, most children with cystic fibrosis died in infancy. Over the past few decades advances in medical and supportive care have substantially prolonged the lives of individuals with the disease. Some of the treatments can seem rough to the uninitiated: parents or others are taught how to vibrate or pound their children's chest to help move the thick secretions in the lungs and dislodge any mucus plugs. Several drugs have been developed that open the airways, suppress infection or help thin the airway secretions. Supplemental vitamins and enzymes aid the digestive process. It is as a result of these and other measures that half of all cystic fibrosis patients now live to 37 years of age or older. None of these treatments, however, addresses the underlying cause: the insufficient flow of chloride and other ions out of cells.

THREE PATHWAYS

THE FIRST STEP in finding a drug that might restore at least some function to a deficient chloride channel was to better understand on a microscopic level the precise details of what goes wrong. Geneticists have tested DNA samples from cystic fibrosis patients around the world and have so far discovered more than 1,600 different mutations in the CFTR gene that lead to serious illness. The deleterious effects on the resulting CFTR protein can be divided into several groups. In three of the best-studied categories, the channel never gets put in place in the cell membrane, or a truncated channel is synthesized (and the directions for making it are rapidly degraded), or a channel of normal length is made but is unable to open or transport chloride or other ions. A single drug developed to repair one of these problems might not be of much help for the other two. Therefore, it is likely that to help the entire population of cystic fibrosis patients, different drugs will need to be developed—each based on the genetic defect responsible for an individual's condition.

A completely missing chloride channel at the cell surface stems from the most common genetic mutation, which results in the deletion of just one of the channel's 1,500 amino acid building blocks. Because the missing amino acid is phenylalanine (designated "F" in protein parlance) and is the 508th amino acid in the chain, the mutation is referred to as F508del.

The F508del mutation causes disease in a fashion that was at first surprising. Despite the mutation, the cell is able to build a chloride channel, amino acid by amino acid. The final product is equipped to transport chloride ions to a limited extent. But the cell's own molecular quality-control apparatus prevents it from doing so. The cell has several hundred helper proteins and enzymes that ferry the nascent CFTR molecules around the cell, inspect the ways they are being folded and help to insert CFTRs in the cell membrane. Even seemingly minor defects in folding—such as the F508 omission—can be rapidly recognized, leading the cell to quickly destroy the mutant. As a result, the somewhat functional chloride channel never even makes it to the cell membrane.

Because F508del is the most common cause of cystic fibrosis, numerous facilities around the world (including our own) are trying to locate the precise cellular checkpoints at which the F508del CFTR molecule fails to "make the grade" and is routed to the recycling bin. The goal is to aid in the discovery of compounds that will ease cystic fibrosis by helping the protein fold correctly and avoiding its destruction without interfering with the ability of the cells to recognize and eliminate other aberrant amino acid chains.

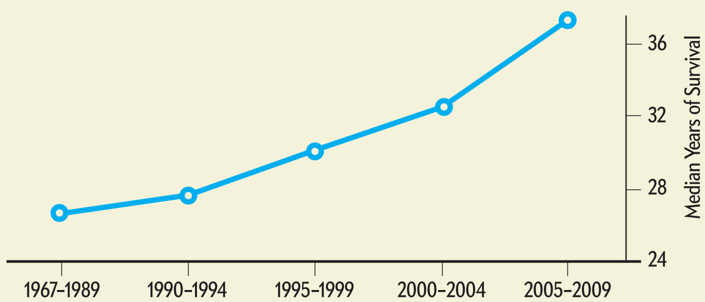
Figuring out how to adjust the cell's quality-control systems could offer benefits beyond treating cystic fibrosis. A number of chronic diseases—such as defects in cholesterol metabolism and some lung disorders (among them, alpha-1-antitrypsin deficiency)—occur because of protein misfolding. In at least certain diseases, evidence is growing that the true culprit is not the altered function of the protein per se but rather the propensity of the quality-control mechanism to degrade the abnormal molecule or deposit it in a tangled clump. It is conceivable that a number of slightly misfolded, mutant proteins would retain significant function if they were spared and allowed to do their intended jobs. Therapies that tackle the quality-control mechanism might therefore provide valuable insight into the biology and treatment of a wide range of diseases.

Mutations that result in abnormally foreshortened CFTR channels account for about 10 percent of cystic fibrosis cases worldwide. One

STEP BY STEP

Steady Progress

People with cystic fibrosis are already living longer thanks to new drugs and new approaches to delivering care. But agents that address the underlying biological cause would also help tremendously.



1994 A drug called dornase alpha improves pulmonary function by breaking down thick mucus in the lungs

1997 Routine spraying of the antibiotic tobramycin into the lungs helps to control infections

2002 The Cystic Fibrosis Foundation launches a quality-improvement program that standardizes treatment of U.S. patients

2009 Mandatory screening of newborns across the U.S. for cystic fibrosis allows for earlier detection and treatment

SOURCE: CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY: ANNUAL DATA REPORT 2009

Graphic by Jen Christiansen

such genetic defect, dubbed W1282X, underlies about 40 percent of cystic fibrosis in Israelis. The protein ends up being truncated because the gene contains misguided instructions telling the protein-synthesizing machinery to stop attaching amino acids to the growing protein molecule at position 1282 in the chain, where the amino acid tryptophan (signified by "W") would normally reside. Such genetic instructions are called nonsense codons and are crucial to the proper manufacture of proteins—provided they occur in the right place. In this case, however, the protein-manufacturing process comes to a premature halt. In addition, the intermediate instructions (known as messenger RNA) that guide the production process are also recognized as abnormal and destroyed so that even if the stop signal could somehow be skipped over, not enough of the now functional protein would be made. Therefore, drug treatments for W1282X may need to attack two problems and not just one.

The last set of mutations we consider here disables the channel's ability to open and accounts for about 5 percent of cystic fibrosis cases worldwide. In effect, these mutations cause the doorway through the membrane to be stuck in the closed configuration, which leaves the channel less able to transport chloride ions to the extracellular environment. One of the mutations that act in this way (called G551D) causes particularly severe symptoms. Although it is generally true that each group of genetic defects may require its own specifically targeted treatment, researchers have shown that compounds designed to prop open a mutant CFTR gate might aid patients who do not have this mutation. For example, take the case of a drug that enabled a small amount of the F508del CFTR to travel to its proper location in the cell membrane. A second drug that braced the channel door open would allow this somewhat sluggish version of the channel to pass more chloride out of the cell.

PROMISING DRUG CANDIDATES

THE NEXT STEP in the long process of drug development was to search for compounds able to alleviate the effects of specific mutations in the CFTR gene. It made sense to start with F508del because of its high prevalence in patients with cystic fibrosis and because the resulting protein retains some residual functionality; if researchers could help F508del CFTR evade premature degradation, the protein could arguably provide partial activity and improve lung function without further prodding.

Knowledge of the ways the F508del CFTR protein misfolds and of how the cell's quality-control machinery detects that folding defect is far from complete. It is, however, reasonably straightforward to determine whether a particular compound can alleviate the effects of the folding error in human cells. By loading fluorescent molecules into a cell, investigators can measure small changes in the concentrations of chloride or other ions moving across the cell membrane. When ions traverse the membrane after exposure to a potentially therapeutic drug, researchers can infer that the impaired CFTR channel has regained some function. If the ions do not make it across, the search continues for a more active compound. By automating and computerizing the drug-screening process, millions of compounds can be analyzed in a relatively short time.

Biotechnology company Vertex Pharmaceuticals identified one compound, known as VX-809, that had encouraging preliminary results but that did not significantly improve lung function in test subjects. Another company, PTC Therapeutics, is directing clinical trials of a drug called ataluren that addresses the less common, CFTR-truncation mutations. This agent causes the protein-making machinery to read through some of the misplaced "stop" instructions, thereby allowing the chloride channel protein to avoid being foreshortened. This agent is also being tested for other hereditary disorders that involve aberrant stop codes, such as Hurler syndrome and Duchenne muscular dystrophy.

Adjusting the cell's quality-control systems could offer benefits beyond treating cystic fibrosis, such as fixing defects in cholesterol metabolism and other disorders.

Scientists have had the best results counteracting the G551D mutation. After testing 228,000 different potential compounds against cells harboring chloride channels that did not open easily, a group of researchers at Vertex discovered a compound that selectively activates the energy switch of the CFTR channel, boosting function to 50 percent of normal levels. The laboratory results were good, and the compound, named VX-770, has now undergone extensive testing. In these trials, the ability to breathe improved substantially in patients with the G551D mutation within weeks, and the benefits were sustained for the length of a one-year study. Just as important, treated individuals were hospitalized less often and gained an average of seven to eight pounds. One of us (Rowe) was the first clinician in the U.S. to administer VX-770 in a patient. Sometime later this year Vertex plans to petition the Food and Drug Administration for the right to bring the drug to market. Further testing to use VX-770 in combination with other agents is also showing some promise in clinical trials. (The University of Alabama at Birmingham is one of the sites for clinical trials of drugs developed by PTC Therapeutics and Vertex; Rowe and Clancy have advised both companies about study design.)

These clinical results are groundbreaking, and the discovery of several drug candidates that take aim at the root cause of cystic fibrosis validates decades of research into its basic biology and funding of such work by the National Institutes of Health and the Cystic Fibrosis Foundation. Although more clinical trials are under way to establish whether the available compounds will be safe and effective in the long term for a larger group of patients, optimism is growing that one day we will finally be able to treat the underlying causes of this difficult disease. SA

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SCIENTIFIC AMERICAN ONLINE
Young people with cystic fibrosis share their lives, philosophies and daily routines on video at **ScientificAmerican.com/aug2011/cf-video**

Franklin E. Zimring is a professor at the University of California, Berkeley, School of Law. He is author or co-author of several books on topics, including capital punishment, the scale of imprisonment, and drug control. Zimring wrote a 1991 *Scientific American* article on firearms and violence.

SOCIOLOGY

How New York Beat Crime

With its judicious use of cops and innovative methods, the Big Apple is a model for how to stem homicides, muggings and other ills

By Franklin E. Zimring

FOR THE PAST TWO DECADES NEW YORKERS HAVE BEEN THE BENEFICIARIES OF the largest and longest sustained drop in street crime ever experienced by a big city in the developed world. In less than a generation, rates of several common crimes that inspire public fear—homicide, robbery and burglary—dropped by more than 80 percent. By 2009 the homicide rate was lower than it had been in 1961. The risk of being robbed was less than one sixth of its 1990 level, and the risk of car theft had declined to one sixteenth.

Twenty years ago most criminologists and sociologists would have doubted that a metropolis could reduce this kind of crime by so much. Although the scale of New York City's success is now well known and documented, most people may not realize that the city's experience showed many of modern America's dominant assumptions con-

IN BRIEF

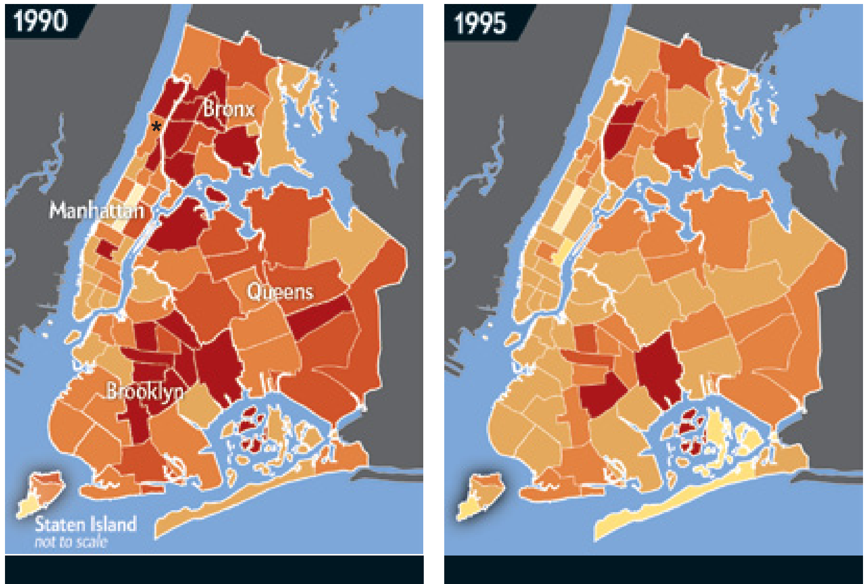
In the 1990s rates of the most common crimes plunged in most of the U.S., but in New York City the drop has lasted twice as long and has gone twice as deep.

New York's successes have defied common assumptions, such as that drug use fosters crime and that locking people up reduces it. **The city's story** shows that people are not hardwired to be criminals and suggests that other cities might achieve similar results by putting more cops on the streets, especially at "hotspots" of crime.

Illustrations by Gary Kelly

A Citywide Cool-Off

Crime rates fell across the U.S. throughout the 1990s, but in New York they kept falling for another decade, and the decline went twice as deep as in most other big cities. Here a combined index of the six most serious crimes (homicide, rape, assault, car theft, burglary and robbery) is displayed by police district. The most dangerous neighborhoods, in Brooklyn and the Bronx, typically showed the biggest improvements. [See details of the calculations, as well as more maps and data, at ScientificAmerican.com/aug2011/crime.]



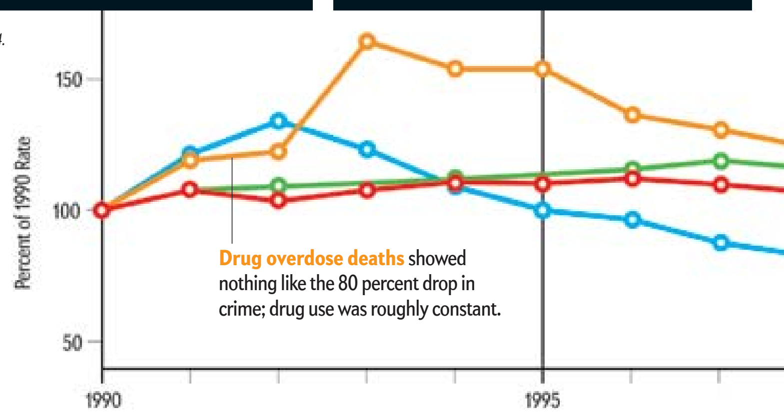
Combined Index of 6 Major Crime Types

High — Low

*The 33rd Precinct was created in 1994. In 1990 it was still a part of the 34th.

Urban Myths, Shattered

Several common assumptions about how best to fight crime—such as lowering drug use, reducing poverty and unemployment or locking more people up—have been proved wrong by New York's numbers: the city cut down crime by 80 percent in the past two decades without making significant changes along those lines. Still, to improve things much further, New York may need to tackle deeper social issues such as income inequalities, racial segregation and the quality of education.



cerning crime to be flat wrong, including that lowering crime requires first tackling poverty, unemployment and drug use and that it requires throwing many people in jail or moving minorities out of city centers. Instead New York made giant strides toward solving its crime problem without major changes in its racial and ethnic profile; it did so without lowering poverty and unemployment more than other cities; and it did so without either winning its war on drugs or participating in the mass incarceration that has taken place throughout the rest of the nation.

To be sure, the city would be even better off, not to mention safer, if it could solve its deeper social problems—improve its schools, reduce income inequalities and enhance living conditions in the worst neighborhoods. But a hopeful message from New York's experience is that most crimes are largely a result of circumstances that can be changed without making expensive structural and social changes. People are not doomed to commit crimes, and communities are not hardwired by their ethnic, genetic or socioeconomic character to be at risk. Moreover, the systematic changes that the city has made in its effort to reduce crime are not extremely expensive and can be adapted to conditions in other metropolises.

A TRUE DECLINE

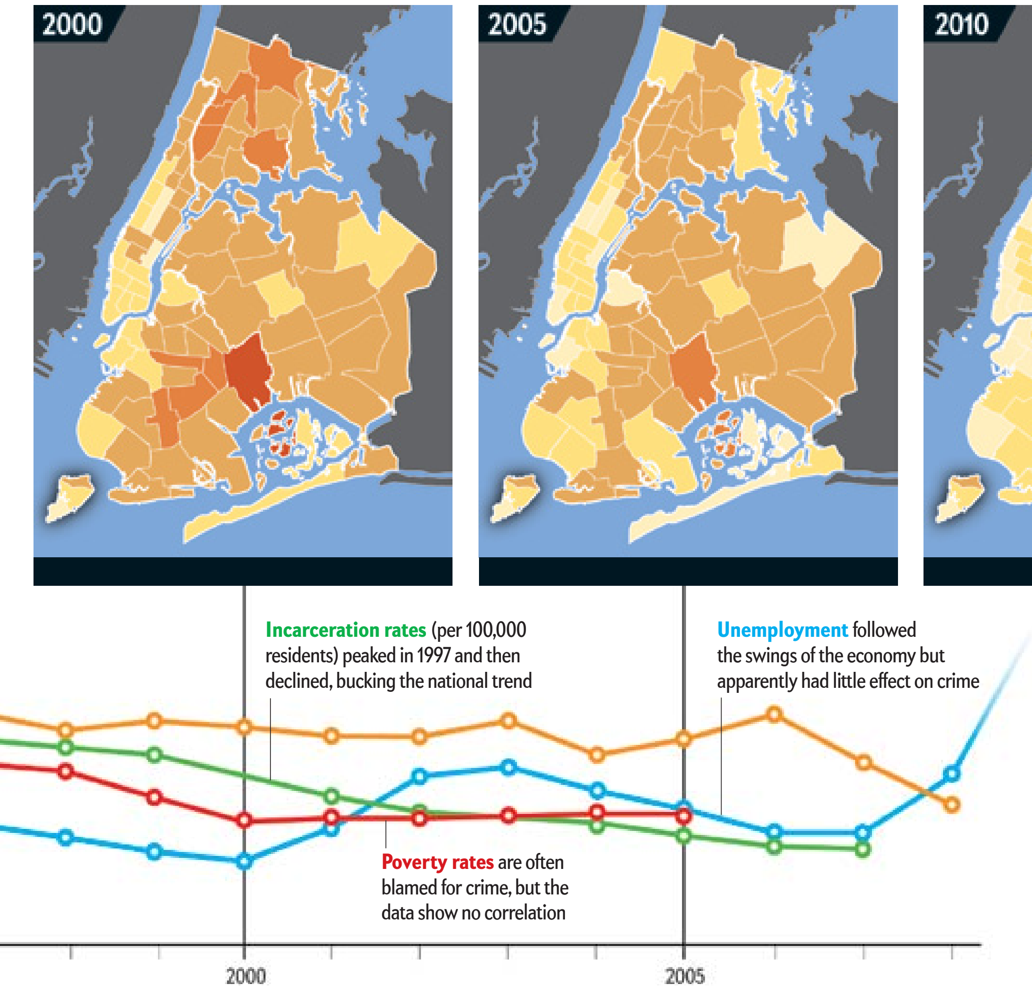
THE FIRST NINE YEARS of New York City's crime decline were part of a much broader national trend, an overall drop of nearly 40 percent that started in the early 1990s and ended in 2000. It was the longest and largest nationwide crime drop in modern history. What sets New York apart from this general pattern is that its decline was twice as large as the national trend and lasted twice as long.

That extraordinary difference—between drops of 40 and 80 percent—can be seen in comparing homicide rates from 1990 and 2009 in the five largest cities in the U.S.: New York, Houston, Philadelphia, Chicago and Los Angeles. The great crime decline of the 1990s reduced homicide in all five cities, in four of those by a substantial amount. But New York went from being dead center in its homicide rates in 1990 to being the lowest of the five—more than 30 percent below the next best city and only 40 percent of the mean rate for the other four places.

Of course, official crime statistics are generated and verified by the same police departments that get credit when crime rates fall and blame when they increase. And indeed, allegations of the New York City Police Department (NYPD) fudging data to make the numbers look pretty have received much media attention. But

SOURCE: NEW YORK CITY POLICE DEPARTMENT (*raw crime data by precinct*)

Maps by XNR Productions, Graphic by Jen Christiansen



How It Happened

What may have made a difference for New York crime was policing and, in particular, a focus on "hotspots." The NYPD compiled detailed crime statistics in real time and used the data to systematically focus its efforts on the most dangerous street corners. (Having more cops on the streets may have also helped in the 1990s, but crime continued to drop even when NYPD rolls fell back somewhat during the 2000s.)

SOURCES: NEW YORK STATE DEPARTMENT OF CORRECTIONS AND COMMUNITY SUPERVISION; NEW YORK CITY DEPARTMENT OF CORRECTION; NEW YORK STATE ARCHIVES; AND BUREAU OF JUSTICE (*incarceration*); CURRENT POPULATION STUDY, U.S. CENSUS BUREAU (*poverty*); BUREAU OF LABOR STATISTICS (*unemployment*); OFFICE OF VITAL STATISTICS, NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE (*drug deaths*)

anecdotal evidence of police misconduct arises frequently in other places as well, including many American cities where the official numbers are not as rosy. Still, how can we be confident that the spectacularly good news reflects the reality of street crime?

The best method to verify trends is with independent data. Fortunately, agencies apart from the police have kept track of two key crime indices, and their findings have corroborated the NYPD's data. First, county health departments keep meticulous records of all deaths and provide specific reports of what the police classify as murder and "nonnegligent" manslaughter. Over the 19 years when the police reported the dramatic decline in most crimes, the agreement between the health and police reports each year was practically perfect. In the second case, auto theft (which went down by a spectacular 94 percent), insurance companies record claims by victims. I obtained reports of theft and loss by year from two separate industry data bureaus. The most complete statistics of insurance claims indicated a decline in theft rates of slightly more than 90 percent.

I also found independent evidence for the big drop in robbery. Whereas simple robberies are reported at the police precinct level, killings from robberies are reported independently by a citywide police office, which also provides data to the FBI—and they are harder to conceal. The rate of killings from robberies fell more than 84 percent in all robberies. Victim surveys also have confirmed the dip in both robberies and burglaries (which are break-ins, usually in which the crime victims are not around, whereas robberies involve a direct encounter with the victim) in the city.

By American standards, then, New York City has become a safe, low-crime urban environment. How did this happen?

GOTHAM CRIME MYTHS

THE PART OF NEW YORK'S crime drop that paralleled the larger national downturn of the 1990s did not seem to have any distinctive local causes. The decline was not easy to tie to specific causes either at the national level or in the city, but the same mix of increased incarceration, higher prosperity, aging population and mysterious cyclical influences probably was responsible in both cases.

What caused the roughly half of New York City's decline that was distinctively a local phenomenon may be easier to single out, as we will see. The answers, however, are not what many people would expect.

For example, very few drastic changes occurred in the ethnic makeup of the population, the economy, schools or housing in the city during the 20 years after 1990. The percentage of the population in the most arrest-prone age bracket, between 15 and 29, declined at essentially the same rate as it did nationally, and economic growth did not reduce either poverty or unemployment in New York significantly below the national average.

A common assumption is that the U.S.'s inner cities became safer because they were "cleaned up," or gentrified—which is when formerly blighted neighborhoods begin to attract people of higher income, and lower-income populations are progressively pushed out by increases in rents and property taxes. During gentrification, so goes the thinking, all the poor people leave, driving down crime rates. And indeed, in Manhattan, the city's wealthiest borough, crime rates dropped along with ethnic and economic diversity. But in the other three most populous boroughs (Queens, Brooklyn and the Bronx), diversity did not drop; if anything, it increased. And yet crime went way down—and at comparable rates—in *all four* of those boroughs.

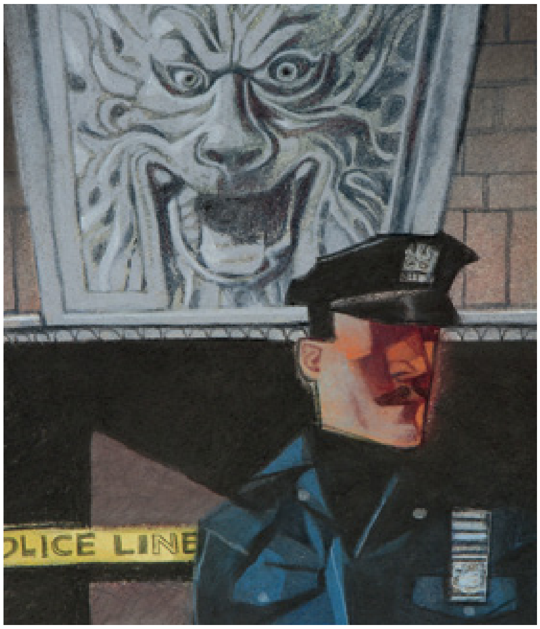
The momentous drop in street crime—especially certain kinds—is surprising in another respect. New York has been the illicit-drug-use capital of North America for at least seven decades. By all accounts, it continues to be. In the 1980s the widespread introduction of crack cocaine was associated with sharp increases in homicide. The perceived close link between drugs and violence was one of the animating theories for the War on Drugs that was declared in the decade after 1985. From the perspective of the late 1980s, a significant reduction in violence without massive reductions in the sale and use of illegal drugs would have been an impossible dream. But that is exactly what seems to have happened in New York.

Drug-related killings (such as dealers shooting one another) dropped 90 percent from peak rates. Meanwhile drug use appears to have stayed relatively stable in the city, whether the indicator is overdose deaths, hospital discharges for drug treatment, or urine tests of criminal suspects. New York seems to be winning the war on crime without winning the war on drugs.

Finally, and perhaps most remarkably, the city's successful crime policies bucked the national trend toward locking up more and more people. The policy tactics that have dominated crime control in the U.S. assume that high-risk youth will become criminal offenders no matter what we do and that criminals will continue to commit crimes unless they are put away. In the mid-1990s proponents of the "supply side" theory of crime were warning that cities such as New York with high numbers of minority youth growing up in single-parent families would require massive new investments in prisons and juvenile facilities. Since 1972 these supply-side theories were the central justification of the sevenfold expansion of imprisonment in the U.S. In the 1980s New York participated in the trend. But in the 1990s, while the U.S. prison and jail population expanded by half, New York went its own way. In the first seven years of the decade its incarceration rate rose only 15 percent, and then it began to fall. By 2008 it was 28 percent below the 1990 rate; nationally, incarceration was up 65 percent.

So where have all the criminals gone?

Many of them just seem to have given up on breaking the law. The rate at which former prisoners from New York were reconvicted because of a felony three years after release—which had increased during the late 1980s—dropped by 64 percent over the years after 1990. The NYPD still catches criminals, and prosecutors and judges still send them to jail. But the city has reduced its most serious crimes by 80 percent without any net increase in prison populations. These numbers disprove the central tenets of supply-side crime control.



As incarceration rates rose 65 percent nationwide, New York's dropped—and serious crime fell by 80 percent.

ESTIMATING POLICE EFFECTS

THE ONE ASPECT of crime policy wherein the municipal government enacted big changes—and the only obvious candidate to take credit for the city's crime decline—was policing. Beginning in 1990, the city added more than 7,000 new uniformed cops and made its police efforts much more aggressive and focused on high-crime settings.

The presence of more police on the street was originally thought to have caused most of the New York decline in the 1990s. But because at that time crime was abating everywhere in the nation, it is hard to know how much of New York's success stemmed from its own policing changes as opposed to the same mysterious set of causes that operated nationally. Moreover, after 2000 the NYPD actually cut its force by more than 4,000 uniformed officers, and yet reported crime kept dropping and doing so faster than in other large cities.

Nevertheless, a close look at the data after 2000 does point to the importance of policing. In spite of the loss of 4,000 officers, the most recent period still has substantially more police on the street compared with 1990. And the number of police relative to the amount of crime kept growing because crime slowed faster than police rolls shrunk. It is also possible that the cumulative effects of increased manpower lasted into the decade when force levels went down. And the impact of cops is reflected in the fact that New York City experienced the largest drops in the crimes that happen on the street or require access from the street—burglary, robbery and auto theft—

and thus are especially deterred by increased police presence.

The police department did not only add more cops on the streets, it also implemented a number of new strategies. It is difficult to determine how much credit, if any, each of the policing changes should get, but some clear indications have appeared.

Once again, the simple explanations are not of much help. Some of the authorities' more prominent campaigns were, in fact, little more than slogans, including "zero tolerance" and the "broken windows" strategy—the theory that measures such as fixing windows, cleaning up graffiti and cracking down on petty crimes prevents a neighborhood from entering into a spiral of dilapidation and decay and ultimately results in fewer serious crimes. For instance, the NYPD did not increase arrests for prostitution and was not consistent over time in its enforcement of gambling or other vice crimes.

But other campaigns seem to have had a significant effect on crime. Had the city followed through on its broken-windows policing, it would have concentrated precious resources in marginal neighborhoods rather than in those with the highest crime. In fact, the police did the opposite: they emphasized "hotspots," a strategy that had been proved effective in other cities and that almost certainly made a substantial contribution in New York. Starting in 1994, the city also adopted a management and data-mapping system called CompStat. At a central office in downtown Manhattan, analysts compile data on serious crimes, including their exact locations, and map them to identify significant concentrations of crime. Patrols then deploy in full force on-site—whether it is a sidewalk, a bar or any other public place—sometimes for weeks at a time, systematically stopping and frisking anyone who looks suspicious and staring down everyone else. Although one might expect that criminals would just move to another street and resume their business as usual, that is not what happened in New York. Thus, crimes prevented one day at a particular location do not ineluctably have to be committed somewhere else the day after.

The biggest and most costly change in police tactics is the aggressive program of street stops and misdemeanor arrests that the police use in almost every patrol operation. In 2009 New York's finest made more than half a million stops and nearly a quarter of a million misdemeanor arrests. The police believe these tactics help to prevent crime. Aggressive patrol, however, has a history almost as long as that of street policing itself, and its effectiveness has not always been clear. Although it could in principle be more effective in New York than in other places, the evidence that it adds distinctive value to the hotspots and CompStat strategies is not strong.

LESSONS LEARNED

TO ESTABLISH CONCLUSIVELY what works and what does not will require scientific field tests measuring the effectiveness of additional manpower and of other techniques from the NYPD's full kitchen sink of tactics. Then there should be trial-and-error adaptations to other urban settings. But even this early in the game, several lessons from New York City should have a significant influence on crime policy elsewhere.

First of all, cops matter. For at least a generation, the conventional wisdom in American criminal justice doubted the ability of urban police to make a significant or sustained dent in urban crime. The details on cost-effectiveness and best tactics have yet to be established, but investments in policing apparently carry at least as much promise as investments in other branches of crime control in the U.S.

Two other important lessons are that reducing crime does not require reducing the use of drugs or sending massive numbers of people to jail. Incidentally, the difference between New York's incarceration trends and those of the rest of the nation—and the money that the city and state governments avoided pouring into the correctional business—has more than paid for the city's expanded police force.

Unfortunately, New York's successes in crime control have come at a cost, and that cost was spread unevenly over the city's neighborhoods and ethnic populations. Police aggressiveness is a very regressive tax: the street stops, bullying and pretext-based arrests fall disproportionately on young men of color in their own neighborhoods, as well as in other parts of the city where they may venture. But the benefits of reduced crime also disproportionately favor the poor—ironically, the same largely dark-skinned young males who suffer most from police aggression now have lower death rates from violence and lower rates of going to prison than in other cities. We do not yet know whether or how much these benefits depend on extra police aggression.

COMING UP

For more articles on how cities are solving their own and the world's problems, see next month's *Scientific American*.

If New York continues on the same path, it may be able to achieve even greater reductions in crime. After all, even after its vast improvements, its homicide rate is still much higher than those of most major European cities and six times higher than Tokyo's. At some point, though, it is possible that rates could reach a hard bottom, beyond which further progress could require solving the deeper social problems, such as economic inequality, racial segregation, or lack of access to quality education.

Perhaps the most optimistic lesson to take from New York's experience is that high rates of homicides and muggings are not hardwired into a city's populations, cultures and institutions. The steady, significant and cumulatively overwhelming crime decline in New York is proof that cities as we know them need not be incubators of robbery, rape and mayhem. Moreover, it demonstrates that the environment in which people are raised does not doom them to a lifetime outside the law—and that neither do their genes. That result is a fundamental surprise to many students of the American city and is the most hopeful insight of criminological science in a century. SA

MORE TO EXPLORE

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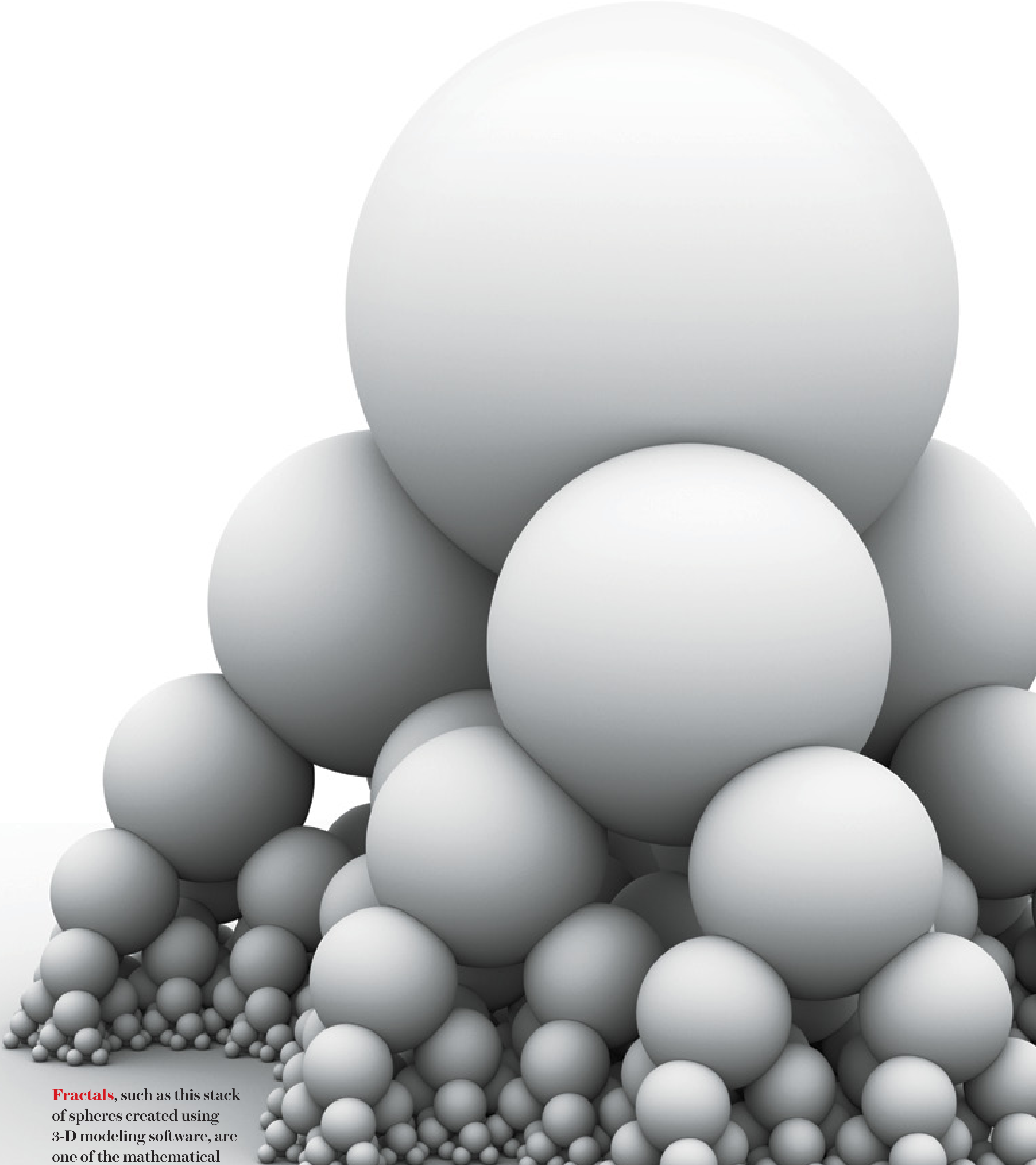
SCIENTIFIC AMERICAN ONLINE
Explore more data and hear an interview with the author at **ScientificAmerican.com/aug2011/crime**



Fractals, such as this stack of spheres created using 3-D modeling software, are one of the mathematical structures that were invented for abstract reasons yet manage to capture reality.

Mario Livio is a theoretical astrophysicist at the Space Telescope Science Institute in Baltimore. He has studied a wide range of cosmic phenomena, ranging from dark energy and supernova explosions to extrasolar planets and accretion onto white dwarfs, neutron stars and black holes.

PHILOSOPHY OF SCIENCE

Why Math Works

Is math invented or discovered? A leading astrophysicist suggests that the answer to the millennia-old question is both

By Mario Livio

MOST OF US TAKE IT FOR GRANTED that math works—that scientists can devise formulas to describe subatomic events or that engineers can calculate paths for spacecraft. We accept the view, initially espoused by Galileo, that mathematics is the language of science and expect that its grammar explains experimental results and even predicts novel phenomena. The power of mathematics, though, is nothing short of astonishing. Consider, for example, Scottish physicist James Clerk Maxwell's famed equations: not only do these four expressions summarize all that was known of electromagnetism in the 1860s, they also anticipated the existence of radio waves two decades before German physicist Heinrich Hertz detected them. Very few languages are as effective, able to articulate volumes' worth of material so succinctly and with such precision. Albert Einstein pondered, "How is it possible that mathematics, a product of human thought that is independent of experience, fits so excellently the objects of physical reality?"

As a working theoretical astrophysicist, I encounter the seemingly "unreasonable effectiveness of mathematics," as Nobel laureate physicist Eugene Wigner called it in 1960, in every step of my job. Whether I am struggling to understand which progenitor systems produce the stellar explosions known as type Ia supernovae or calculating the fate of Earth when our sun ultimately becomes a red giant, the tools I use and the models I develop are mathematical. The uncanny way

IN BRIEF

The deepest mysteries are often the things we take for granted. Most people never think twice about the fact that scientists use mathematics to describe and explain the world. But why should that be the case?

Math concepts developed for purely abstract reasons turn out to explain real phenomena. Their utility, as physicist Eugene Wigner once wrote, "is a wonderful gift which we neither understand nor deserve."

Part of the puzzle is the question of whether mathematics is an invention (a creation of the human mind) or a discovery (something that exists independently of us). The author suggests it is both.

Illustration by Tom Beddard

that math captures the natural world has fascinated me throughout my career, and about 10 years ago I resolved to look into the issue more deeply.

At the core of this mystery lies an argument that mathematicians, physicists, philosophers and cognitive scientists have had for centuries: Is math an invented set of tools, as Einstein believed? Or does it actually exist in some abstract realm, with humans merely discovering its truths? Many great mathematicians—including David Hilbert, Georg Cantor and the group known as Nicolas Bourbaki—have shared Einstein's view, associated with a school of thought called Formalism. But other illustrious thinkers—among them Godfrey Harold Hardy, Roger Penrose and Kurt Gödel—have held the opposite view, Platonism.

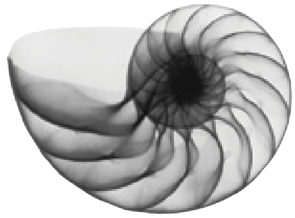
This debate about the nature of mathematics rages on today and seems to elude an answer. I believe that by asking simply whether mathematics is invented or discovered, we ignore the possibility of a more intricate answer: both invention and discovery play a crucial role. I posit that together they account for why math works so well. Although eliminating the dichotomy between invention and discovery does not fully explain the unreasonable effectiveness of mathematics, the problem is so profound that even a partial step toward solving it is progress.

INVENTION *AND* DISCOVERY

MATHEMATICS is unreasonably effective in two distinct ways, one I think of as active and the other as passive. Sometimes scientists create methods specifically for quantifying real-world phenomena. For example, Isaac Newton formulated calculus for the purpose of capturing motion and change, breaking them up into infinitesimally small frame-by-frame sequences. Of course, such active inventions are effective; the tools are, after all, made to order. What is surprising, however, is their stupendous accuracy in some cases. Take, for instance, quantum electrodynamics, the mathematical theory developed to describe how light and matter interact. When scientists use it to calculate the magnetic moment of the electron, the theoretical value agrees with the most recent experimental value—measured at 1.00115965218073 in the appropriate units in 2008—to within a few parts per trillion!

Even more astonishing, perhaps, mathematicians sometimes develop entire fields of study with no application in mind, and yet decades, even centuries, later physicists discover that these very branches make sense of their observations. Examples of this kind of passive effectiveness abound. French mathematician Évariste Galois, for example, developed group theory in the early 1800s for the sole purpose of determining the solvability of polynomial equations. Very broadly, groups are algebraic structures made up of sets of objects (say, the integers) united under some operation (for instance, addition) that obey specific rules (among them the existence of an identity element such as 0, which, when added to any integer, gives back that same integer). In 20th-century physics, this rather abstract field turned out to be the most fruitful way of categorizing elementary particles—the building blocks of matter. In the 1960s physicists Murray Gell-Mann and Yuval Ne'eman independently showed that a specific group, referred to as SU(3), mirrored a behavior of subatomic particles called hadrons—a connection that ultimately laid the foundations for the modern theory of how atomic nuclei are held together.

The study of knots offers another beautiful example of passive effectiveness. Mathematical knots are similar to everyday knots, except that they have no loose ends. In the 1860s Lord Kelvin hoped to describe atoms as knotted tubes of ether. That misguided model failed to connect with reality, but mathematicians continued to analyze knots for many decades merely as an esoteric arm of pure mathematics. Amazingly, knot theory now provides important insights into string theory and loop quantum gravity—our current best attempts at articulating a theory of space-time that reconciles quantum mechanics with general relativity. Similarly, English mathematician Hardy's discoveries in number theory advanced the field of cryptography, despite Hardy's earlier proclamation that "no one has yet discovered any warlike purpose to be served by the theory of numbers." And in 1854 Bernhard Riemann described non-Euclidean geometries—curious spaces in which parallel lines converge or diverge. More than half a century later Einstein invoked those geometries to build his general theory of relativity.



The universe has regularities, known as symmetries, that let physicists describe it mathematically. And no one knows why.

A pattern emerges: humans invent mathematical concepts by way of abstracting elements from the world around them—shapes, lines, sets, groups, and so forth—either for some specific purpose or simply for fun. They then go on to discover the connections among those concepts. Because this process of inventing and discovering is man-made—unlike the kind of discovery to which the Platonists subscribe—our mathematics is ultimately based on our perceptions and the mental pictures we can conjure. For instance, we possess an innate talent, called subitizing, for instantly recognizing quantity, which undoubtedly led to the concept of number. We are very good at perceiving the edges of individual objects and at distinguishing between straight and curved lines and between different shapes, such as circles and ellipses—abilities that probably led to the development of arithmetic and geometry. So, too, the repeated human experience of cause and effect at least partially contributed to the creation of logic and, with it, the notion that certain statements imply the validity of others.

SELECTION AND EVOLUTION

MICHAEL ATIYAH, one of the greatest mathematicians of the 20th century, has presented an elegant thought experiment that reveals just how perception colors which mathematical concepts we embrace—even ones as seemingly fundamental as numbers. German mathematician Leopold Kronecker famously declared, "God created the natural numbers, all else is the work of man." But imagine if the intelligence in our world resided not with humankind but rather with a singular, isolated jellyfish, floating deep in the Pacific Ocean. Everything in its experience would be continuous, from the flow of the surrounding water to its fluctuating temperature and pressure. In such an environment, lacking individual objects or indeed anything discrete, would the concept of number arise? If there were nothing to count, would numbers exist?

Like the jellyfish, we adopt mathematical tools that apply to

EDWARD CHARLES LE GRICE *Getty Images*

our world—a fact that has undoubtedly contributed to the perceived effectiveness of mathematics. Scientists do not choose analytical methods arbitrarily but rather on the basis of how well they predict the results of their experiments. When a tennis ball machine shoots out balls, you can use the natural numbers 1, 2, 3, and so on, to describe the flux of balls. When firefighters use a hose, however, they must invoke other concepts, such as volume or weight, to render a meaningful description of the stream. So, too, when distinct subatomic particles collide in a particle accelerator, physicists turn to measures such as energy and momentum and not to the end number of particles, which would reveal only partial information about how the original particles collided because additional particles can be created in the process.

Over time only the best models survive. Failed models—such as French philosopher René Descartes's attempt to describe the motion of the planets by vortices of cosmic matter—die in their infancy. In contrast, successful models evolve as new information becomes available. For instance, very accurate measurements of the precession of the planet Mercury necessitated an overhaul of Newton's theory of gravity in the form of Einstein's general relativity. All successful mathematical concepts have a long shelf life: the formula for the surface area of a sphere remains as correct today as it was when Archimedes proved it around 250 B.C. As a result, scientists of any era can search through a vast arsenal of formalisms to find the most appropriate methods.

Not only do scientists cherry-pick solutions, they also tend to select problems that are amenable to mathematical treatment. There exists, however, a whole host of phenomena for which no accurate mathematical predictions are possible, sometimes not even in principle. In economics, for example, many variables—the detailed psychology of the masses, to name one—do not easily lend themselves to quantitative analysis. The predictive value of any theory relies on the constancy of the underlying relations among variables. Our analyses also fail to fully capture systems that develop chaos, in which the tiniest change in the initial conditions may produce entirely different end results, prohibiting any long-term predictions. Mathematicians have developed statistics and probability to deal with such shortcomings, but mathematics itself is limited, as Austrian logician Gödel famously proved.

SYMMETRY OF NATURE

THIS CAREFUL SELECTION of problems and solutions only partially accounts for mathematics's success in describing the laws of nature. Such laws must exist in the first place! Luckily for mathematicians and physicists alike, universal laws appear to govern our cosmos: an atom 12 billion light-years away behaves just like an atom on Earth; light in the distant past and light today share the same traits; and the same gravitational forces that shaped the universe's initial structures hold sway over present-day galaxies. Mathematicians and physicists have invented the concept of symmetry to describe this kind of immunity to change.

The laws of physics seem to display symmetry with respect to space and time: They do not depend on where, from which angle, or when we examine them. They are also identical to all observers, irrespective of whether these observers are at rest, moving at constant speeds or accelerating. Consequently, the same laws explain our results, whether the experiments occur in China, Alabama or the Andromeda galaxy—and whether we conduct our experiment today or someone else does a billion years from now. If the universe did not possess these symmetries, any attempt to decipher nature's grand design—any mathematical model built on our observations—would be doomed because we would have to continuously repeat experiments at every point in space and time.

Even more subtle symmetries, called gauge symmetries, prevail within the laws that describe the subatomic world. For instance, because of the fuzziness of the quantum realm, a given particle can be a negatively charged electron or an electrically neutral neutrino, or a mixture of both—until we measure the electric charge that distinguishes between the two. As it turns out, the laws of nature take the same form when we interchange electrons for neutrinos or any mix of the two. The same holds true for interchanges of other fundamental particles. Without such gauge symmetries, it would have been very difficult to provide a theory of the fundamental workings of the cosmos. We would be similarly stuck without locality—the fact that objects in our universe are influenced directly only by their immediate surroundings rather than by distant phenomena. Thanks to locality, we can attempt to assemble a mathematical model of the universe much as we might put together a jigsaw puzzle, starting with a description of the most basic forces among elementary particles and then building on additional pieces of knowledge.

Our current best mathematical attempt at unifying all interactions calls for yet another symmetry, known as supersymmetry. In a universe based on supersymmetry, every known particle must have an as yet undiscovered partner. If such partners are discovered (for instance, once the Large Hadron Collider at CERN near Geneva reaches its full energy), it will be yet another triumph for the effectiveness of mathematics.

I started with two basic, interrelated questions: Is mathematics invented or discovered? And what gives mathematics its explanatory and predictive powers? I believe that we know the answer to the first question. Mathematics is an intricate fusion of inventions and discoveries. Concepts are generally invented, and even though all the correct relations among them existed before their discovery, humans still chose which ones to study. The second question turns out to be even more complex. There is no doubt that the selection of topics we address mathematically has played an important role in math's perceived effectiveness. But mathematics would not work at all were there no universal features to be discovered. You may now ask: Why are there universal laws of nature at all? Or equivalently: Why is our universe governed by certain symmetries and by locality? I truly do not know the answers, except to note that perhaps in a universe without these properties, complexity and life would have never emerged, and we would not be here to ask the question. SA

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SCIENTIFIC AMERICAN ONLINE
Is mathematics invented, discovered, both or neither? See examples of remarkable mathematical structures that invite this question at **ScientificAmerican.com/aug11/livio**

ARCHAEOLOGY

Guardian of the Pharoahs

Egypt had a revolution, but Zahi Hawass, the larger-than-life minister of antiquities, is still calling his own shots and making no apologies

Interview by Jeffrey Bartholet

ONE NIGHT IN THE WEEKS LEADING UP TO THEN PRESIDENT HOSNI MUBARAK'S ouster, looters swarmed the grounds of the Museum of Egyptian Antiquities in Cairo (sometimes called the Cairo museum), and at least one broke into the main building by descending on wires from a skylight. Others rampaged through storerooms at well-known archaeological sites. Panic swept the world of Egyptology.

Ultimately, the looting was not as devastating as some had feared, and many of the country's treasures were recovered. The chaos, though, focused renewed criticism and exacted an emotional toll on Zahi Hawass, the minister of state for antiquities.

IN BRIEF

WHO
ZAHI HAWASS

VOCATION | AVOCATION
Egypt's minister of state for antiquities

RESEARCH FOCUS
Hawass brings a bigger-than-life personality to the quest to find Cleopatra's tomb and other Egyptian treasures.

BIG PICTURE
A consummate marketer and political operator as well as an archaeologist, Hawass was a controversial figure even before the revolution.

Hawass, a celebrity archaeologist known in the West for his larger-than-life persona in such documentaries and television shows as *Chasing Mummies,* provided sometimes confused and contradictory information about what was happening to the ancient relics under his guardianship. Some critics attacked him for being part of the old regime. His enemies saw a chance to get rid of him. Hawass resigned his position in early March, then abruptly returned weeks later. The upheavals raise questions about how secure Egyptian antiquities are now and when visitors will feel safe enough to tour the Nile in large numbers again. Jeffrey Bartholet, who reported from Egypt during the unrest in February, spoke to Hawass recently by phone for *Scientific American*. Excerpts follow.

SCIENTIFIC AMERICAN: The former regime is gone, but there is still a lot of uncertainty. Is Egypt now moving in a clearly positive direction?

HAWASS: I think we are trying. We are doing our best to reach elections for the parliament and a new president.

Photograph by Mikhail Galustov

What are the improvements you are seeing?
Security is starting to come to the streets now. And people are working really hard for democracy and freedom. I don't think Egyptians have had this kind of democracy in 5,000 years. It's the first time that we are really practicing it. I hope that it will not take time to get it right.

You resigned your post in March, then returned. Why?
The reason I resigned was because criminals were looting antiquities at that time, and there was no one to stop them. I was screaming, and no one could help me. At the same time, there were students who needed jobs, and they came in front of my office screaming because they wanted jobs now. All this really made me not want to stay. I came back because I found out that I am a part of antiquities, and antiquities are a part of me.

Was there some specific offer that was made or some suggestion or encouragement that was given?
I found that the government was giving more security, and it was supporting me. The army was supporting me. Now we can see the results of that. Most of the Cairo museum objects that had been looted are back. We are missing only 31 objects from the museum; the rest of the [1,200 or so objects stolen from storerooms and storage vaults] are not really masterpieces.

When the uprising began in Egypt, some feared that we would see a repeat of Iraq—that Egypt's treasures and heritage would be looted and destroyed.
Look: Who protected the Cairo museum? Actually it was the young protesters. In Iraq 15,000 artifacts were stolen from the museum. The Egyptians protected their museum with their bodies. That is something we have to keep in mind.

Tell me about how the underground market for antiquities works. Who are the thieves, who are the middlemen, who are the final buyers?
After the revolution, I don't think there is a market for anything. Before the revolution, there were people who stole objects from Egypt and took them outside of the country. We caught most of them. I returned about 5,000 artifacts from all over the world during the past nine years.

But how does it work? Do foreigners come in and work with criminal rings?
You have to understand that most of modern Egypt is built on top of ancient Egypt. People can do illegal excavations; they dig in their courtyards to find antiquities. But I have put antiquities inspectors in every port and airport to stop people from taking objects outside. And I hired educated guards. And I built 47 storage vaults.

The Hamas government in Gaza sent a delegation recently to return some stolen items, and it turned out the items were fake. Can you tell me about that?
They found two statues, and they brought them to me. I found that they were not genuine, and I gave them back. I thanked them and encouraged them to visit the antiquities of Egypt anytime.

What more can be done internationally to recover items looted since January?
We've gotten back the masterpieces. But I met someone from Interpol a few days ago: we're going to put information about every object out to the whole world. I really think the looters who took the objects were not professional criminals. Therefore, I think the objects will be back. They will not leave Egypt.

You said 31 objects from the Cairo museum are still missing at this point. What are the most significant ones?
The only significant one from the museum is a small head of Queen Nefertiti—a few centimeters high.

The statue of Akhenaton has been returned.
We brought back the statue of Akhenaton holding a stela. And we've brought back most of King Tut's objects that were stolen.

And where were they? Where did you find them?
Those were taken by the looters who entered the museum on the night of January 28. We got the objects of King Tut because there was someone working for the antiquities department who came to me and said that there were looters who wanted to return these objects to me. And the next day he brought a bag with four objects.

Over the years you have carried out a campaign to force international museums to return Egyptian artifacts. In the wake of the revolution and looting, some in the West made the argument that items were safer spread around the globe. The Natural History Museum of Basel became the first to return an artifact since the January revolution. Do you see that as significant?
Very important. It's a relief from the Old Kingdom, about 4,000 years ago.

You had a role in the former government and are now part of the current government. What is different now, in the day-to-day work of your ministry and the way the country is run?
You know, I am a technician. I am not a politician. I have never been in any party, and I did my job beautifully.

You did have a fairly close working relationship with the former first lady, Suzanne Mubarak. Was she an important political patron for the antiquities department?
No, she had nothing to do with any work in antiquities. I collaborated with her to create the children's museum in Cairo. We will be finishing the work on this museum two months from now, and it will be the best museum for children in the Middle East.

As we speak now in May, have you been in touch with the former first lady since her husband relinquished power?
I told you, I'm a technician, not a politician. My relationship with the first lady

Zahi Hawass gives an update on missing artifacts from the Cairo Museum.

PEDRO UGARTE AFP/Getty Images

was just working in this museum. It wasn't really close. Many people think I am from the old regime—my enemies say this. But I'm not. I've never been a politician my whole life.

But still, you must have a personal sensitivity to seeing her get arrested.
This is something that governments do, and I can't interfere. Every Egyptian—85 million—can be connected with the old regime. But when you have a new regime that you like, you connect with it.

Has the unrest interfered with archaeological activity in Egypt?
Things are coming back now. Most of the foreign expeditions have applied to work in September and October. Everyone wants to come back and work.

How is the ongoing quest for Cleopatra's tomb proceeding?
You know, we really did not excavate [in recent months] because of the revolution. But I will continue in September to work in the Valley of the Kings and also continue the excavation to search for the tomb of Cleopatra.

What have you found so far?
We have found statues of Cleopatra and coins of Cleopatra, statues of [Ptolemaic] kings—and all of these discoveries are very important.

Tell me about the Valley of the Kings. What are you looking for there?
I'm looking for the tomb of Ankhesenamun, the wife of King Tut. I don't have evidence for it, but I'm hoping that in the next season something might happen.

Now, you mentioned before your critics and enemies. Tell me about them.
I found out [before the revolution] that some people had a very bad reputation in the antiquities department and had been accused in the past of stealing antiquities and things like that. And I really did punish them. When the revolution happened, they could say anything about me. And they started attacking me. And I really did not care and didn't answer them back. But if you look at these cases, it shows that they are jealous people, and they tried to stop me, but they did not.

You are at the moment appealing a one-year jail sentence for failing to halt bidding by companies interested in running a new gift shop in the museum. Can you tell me about that?
Any government official who tries to protect anything from a civilian, the civilian can take you to court. When the court makes a decision, it's not against you personally, it's against your position. But because my name is big, they made it big.

The case concerns the bookshop in the museum?
This man, who had this old bookshop, did not pay us before. I'm not going to say anything about him. But I made a beautiful new shop, and this man didn't like that.

Some critics say that your governing style is imperious and that you're overly ambitious. They point to a clothing line you started at one point. Can you respond to that?
People don't understand the clothing line. First of all, the photo shoot [for the clothing] did not happen at the Cairo museum, as people say. And second, all the money that comes to me goes to a hospital for children with cancer. I'm very proud that the clothing line became famous and is helping children.

You're well known for your Indiana Jones–style hat. Is the hat a way of branding yourself and of branding Egypt?
When I wore this hat, people loved it. I don't know why. It's something that became a part of me. I'm very proud that children all over the world buy [replicas of] this hat, and the money goes to the children's museum.

What do you say to the people who claim that you're too authoritarian?
If you need to control the antiquities of Egypt, you have to be very strong on the job. If you are not strong, you will never do that. Our antiquities were robbed by everyone before [I came to office]. The antiquities directors were not that strong before. When I do this, I do it for the sake of the antiquities.

Tourism is vital to the Egyptian economy, but at the moment only the most intrepid visitors are touring the Nile. What can be done?
I'm going to use discoveries and the opening of museums to bring tourists back, and at the same time the government will do more to improve the security of the sites. Then people can come back and enjoy the magic and mystery of Egypt. SA

Jeffrey Bartholet *was formerly* Newsweek's *Washington bureau chief and foreign editor.*

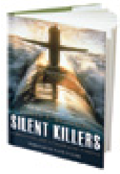
MORE TO EXPLORE

The Pharaoh. Ian Parker in *New Yorker;* November 16, 2009. www.newyorker.com/reporting/2009/11/16/091116fa_fact_parker

Chasing Mummies. A History Channel reality television series featuring Hawass: www.history.com/shows/chasing-mummies

The blog by Hawass: www.drhawass.com/blogs/zahi-hawass

SCIENTIFIC AMERICAN ONLINE
Read more of the interview with Hawass at ScientificAmerican.com/aug2011/hawass



Silent Killers: Submarines and Underwater Warfare

by James P. Delgado. Osprey, 2011 ($24.95)

Dive into the history of submarines with maritime archaeologist and writer James P. Delgado of the National Oceanic and Atmospheric Administration. He traces the evolution of these undersea vehicles from their humble wooden ancestors to modern submersibles built for deep-sea exploration.

Submarine warfare in World War I

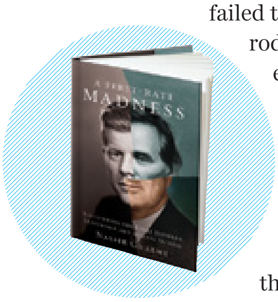
IAN PALMER *Osprey Publishing*

EXCERPT

A First-Rate Madness: Uncovering the Links between Leadership and Mental Illness

by Nassir Ghaemi. Penguin Press, 2011 ($27.95)

***Some kinds of insanity** can produce better leadership during times of crisis. So contends Nassir Ghaemi, director of the Mood Disorder Clinic at Tufts Medical Center, who surveys the careers and psyches of history's great leaders. Below he describes the demons that plagued Winston Churchill.*



"Other prominent British statesmen had failed to fill the role that Churchill rode to glory. Churchill alone emerged as the great leader, the wartime genius, the deliverer of democracy. And although some acknowledge that he had mental problems, few appreciate the relevance of those problems to his prodigious leadership abilities. I believe that Churchill's severe recurrent depressive episodes heightened his ability to realistically assess the threat that Germany posed.

"One might suppose that such a great man would have to be especially whole, healthy and fit in mind and body, full of mental and spiritual capabilities that escape average men. But Churchill belied this notion. In fact, he was quite ill, and his story, if belonging to a middle-class American living in the twenty-first century, would seem a sad but typical tale of mental illness....

"When he was not depressed, Churchill's moods shifted frequently. He was never 'himself,' because his 'self' kept changing.... Said his military chief of staff General Ismay, 'He is a mass of contradictions. He's either on the crest of the wave, or in the trough: either highly laudatory, or bitterly condemnatory: either in an angelic temper, or a hell of a rage....'

"These observations suggest that when he wasn't depressed Churchill probably had cyclothymic personality: he was high in energy, highly sociable and extraverted, rapid in his thoughts and actions, and somewhat impulsive.... He was incredibly productive, not only serving as minister or prime minister for decades, but writing forty-three books in seventy-two volumes (not to mention an immense body of correspondence).... His mind never stopped; he was always thinking, always plotting and planning, whether or not he had reason to do so.... These hyperthymic personality traits are, clinically and biologically, mild versions of mania. They would alternate with milder periods of depressive mood and energy and activity and, not infrequently, with severe depressive episodes that would last months or longer."

ALSO NOTABLE

The Inquisition of Climate Science, by James Lawrence Powell. Columbia University Press, 2011 ($27.95)

On the Origin of Tepees: The Evolution of Ideas (and Ourselves), by Jonnie Hughes. Free Press, 2011 ($28.99)

Radioactivity: A History of a Mysterious Science, by Marjorie C. Malley. Oxford University Press, 2011 ($21.95)

The Wild Life of Our Bodies: Predators, Parasites, and Partners That Shape Who We Are Today, by Rob Dunn. HarperCollins, 2011 ($26.99)

Brain Bugs: How the Brain's Flaws Shape Our Lives, by Dean Buonomano. W. W. Norton, 2011 ($25.95)

The Case for Mars: The Plan to Settle the Red Planet and Why We Must (revised from the 1996 edition), by Robert Zubrin. Free Press, 2011 ($19.99)

Demon Fish: Travels through the Hidden World of Sharks, by Juliet Eilperin. Pantheon Books, 2011 ($26.95)

The Beekeeper's Lament: How One Man and Half a Billion Honey Bees Help Feed America, by Hannah Nordhaus. Harper Perennial, 2011 ($14.99)

First Life: Discovering the Connections between Stars, Cells, and How Life Began, by David Deamer. University of California Press, 2011 ($28.95)

Weeds: In Defense of Nature's Most Unloved Plants, by Richard Mabey. Ecco, 2011 ($25.99)

COMMENT AT ScientificAmerican.com/aug2011

Viewing the world with a rational eye

Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His new book is *The Believing Brain.* Follow him on Twitter @michaelshermer

Globaloney

Why the world is not flat … yet

Fast-forward to the year 2100. Computers, writes physicist and futurist Michio Kaku in *Physics of the Future* (Doubleday, 2011), will have humanlike intelligence, the Internet will be accessible via contact lenses, nanobots will eliminate cancers, space tourism will be cheap and popular, and we'll be colonizing Mars. We will be a planetary civilization capable of consuming the 10^{17} watts of solar energy falling on Earth to meet our energy needs, with the Internet as a worldwide telephone system; English and Chinese as the contenders for a planetary language; a unified culture of common foods, fashions and films; and a truly global economy with many more international trading blocs such as we see today in the European Union and NAFTA.

Kaku's vision of how the exchange of science, technology and ideas among all peoples will create a global civilization with greatly weakened nation-states and almost no war is epic in its scope and heroic in its inspiration. Many have felt similar hope for a united, peaceful future through globalization. Indeed, I evoked a similar image in my book *The Mind of the Market* (Holt, 2009), and I was inspired in part by Thomas Friedman's wildly popular *The World Is Flat* (Farrar, Straus and Giroux, 2005), in which he argues for "a global, Web-enabled playing field that allows for multiple forms of collaboration on research and work in real time, without regard to geography, distance or, in the near future, even language."

The problem for Kaku, Friedman, me and other globalization proponents (and even opponents) is that such a future may be unattainable because of our evolved tribal natures. In fact, this is all a bunch of "globaloney," says Pankaj Ghemawat, professor of strategic management and Anselmo Rubiralta Chair of Global Strategy at IESE Business School at the University of Navarra in Barcelona, in his new book *World 3.0: Global Prosperity and How to Achieve It* (Harvard Business Review Press, 2011). According to Ghemawat, only 10 to 25 percent of economic activity is international (and most of that is regional rather than global). Consider the following percentages (of the total in each category): international mail: 1; international telephone calling minutes: less than 2; international Internet traffic: 17 to 18; foreign-owned patents: 15; exports as a percentage of GDP: 26; stock-market equity owned by foreign investors: 20; first-generation immigrants: 3. As Ghemawat starkly notes, 90 percent of the world's people will never leave their birth country. Some flattened globe.

The problem, Ghemawat says, is that globalization theories fail to account for the very real distance factors (geographic and cultural). He crunches these factors into a distance coefficient akin to Newton's law of gravitation. For example, he computes, "a 1 percent increase in the geographic distance between two locations leads to about a 1 percent decrease in trade between them," a distance sensitivity of –1. Or, he calculates, "U.S. trade with Chile is only 6 percent of what it would be if Chile were as close to the United States as Canada." Likewise, "two countries with a common language trade 42 percent more on average than a similar pair of countries that lack that link. Countries sharing membership in a trade bloc (e.g., NAFTA) trade 47 percent more than otherwise similar countries that lack such shared membership. A common currency (like the euro) increases trade by 114 percent."

That analysis actually sounds encouraging to me if we use Kaku's projected time frame of 2100. But Ghemawat reminds us of our deeply ingrained tendencies to want to interact with our kin and kind and to retain our local customs and culture, which may forever balkanize any globalized scheme. Even as the E.U. expands, for instance, an average of "Eurobarometer" surveys of residents of 16 E.U. countries between 1970 and 1995 made in 2004 by researchers at the Center for Economic and Policy Research found that 48 percent trust their fellow nationals "a lot," 22 percent trust citizens of other E.U.-16 countries a lot and only 12 percent trust people in certain other countries a lot.

Human nature's constitution dictates the constitution of human society. In this sense, the world we make very much depends on the world we inherit. SA

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Illustration by Kagan McLeod

Does anyone consult "how to" books to learn to walk, run, or ride a bicycle? Do children know they are conforming to natural laws, as they perform those feats? No, of course not! Whoever or whatever created those laws waited untold centuries for people to identify the laws of physics.

There is a natural law of behavior that was not identified until the past century by Richard W. Wetherill. It calls for people's thinking and behavior to be rational and honest, according to the dictates of a self-enforcing natural law.

Wetherill spent decades trying to explain that the social, health, and economic woes of mankind were being caused by people's contradiction of a natural law: a law he called the ***law of absolute right***.

In general, people resent being told what they can and cannot think, say, and do. Their reason seems to be that it is "their business": a mistake made by those who overlook where the gift of life originates.

Introduction to the law of absolute right and its influence on behavior is vital information urgently needed by every member of society.

Strange as it might seem, it could be said, the only choice people have is whether they will live in accord with the dictates of natural laws or be penalized for ignoring them.

Researchers diligently sought to learn of natural laws and how they functioned in order to avoid penalties for ignoring them. So people surrender to laws of physics, telling them what they can and cannot do.

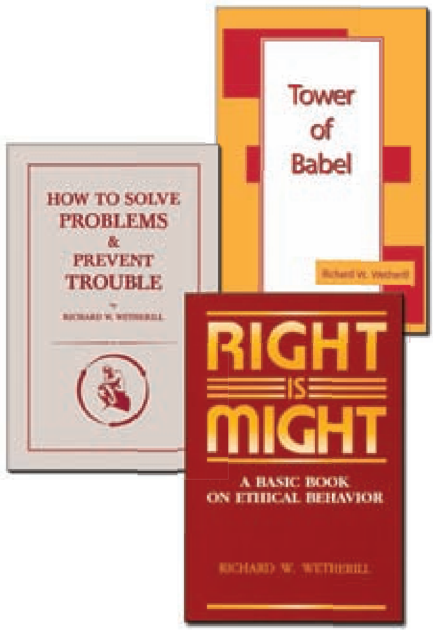
But to date, those researchers' failure to acknowledge nature's law of absolute right and its impact on human life is perpetuating countless human miseries.

We suggest that the behavioral law is nature's way to create a group of survivors that have resolved their former problems and trouble. Having adjusted their decisions to be rational and honest, a common comment heard from those persons is, "It works."

For example, one person reported that he had made friendly overtures to a long-time estranged, close relative and introduced him to the law of absolute right. Later this person reported a phone call from his formerly estranged relative who agreed with others and said, "It works."

We invite readers to face all future situations with a decision to respond rationally and honestly despite any past reactions. In that moment you will have yielded to yet another of nature's laws. And you will discover that it works.

By conforming to nature's law of absolute right, you join other people already enthusiastically benefiting from having changed their former motivation. All it takes is to be rational and honest in all your thoughts, words, and deeds.



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This public-service message is from a self-financed, nonprofit group of former students of Mr. Wetherill.

The ongoing search for fundamental farces

Steve Mirsky has been writing the Anti Gravity column since he was a man trapped in the body of a slightly younger man. He also hosts the *Scientific American* podcast Science Talk.

Out of the Brains of Babes

Small children can have big ideas

Parents often wonder what their little ones are absorbing from them. For example, my mother had a wonderful vocabulary. So it may be more than a family fable that when I was asked as a two-year-old whether I was wet, I allegedly responded, "No, I'm saturated." Then again, my father has always tended to interpret things quite literally, which may explain why, a year or two later, my supposed response to the question of how my favorite record went was "'round and around and around." (This all happened shortly after the invention of movable type, when music was literally pressed onto large vinyl disks that "turned" on what was fittingly called a turntable. For more on turntables, see this space in the June issue.)

I was reminded of preposterously precocious utterances by tiny tykes during a brief talk that string theorist Brian Greene gave at the opening of the 2011 World Science Festival in New York City on June 1. Greene said he sometimes wondered about how much information small children pick up from standard dinner-table conversation in a given home. He revealed that he got some data to mull over when he hugged his three-year-old daughter and told her he loved her more than anything in the universe, to which she replied, "The universe or the multiverse?"

Closer to home (well, my home at least), my seven-year-old grandnephew has often exhibited an interest in various science and math topics. He, like many preschoolers at the time, was deeply disappointed by the 2006 demotion of Pluto from the family of planets. So great was his grief then that when I asked him about Pluto's fall, he only said, "I don't want to talk about it." More recently, he was a passenger when his grandfather exited a highway onto a cloverleaf that took them off their northern route toward the east, then south and then west onto the next road. With that maneuver complete, the kid said, "That was a 270-degree turn." Which he either learned from his smart parents or from watching the X Games.

Of course, not all children are destined for a life in the sciences. Many, if not most, seem well suited, if you will, for the law. Take the case of another seven-year-old of my acquaintance who was given "five more minutes" by her parents to enjoy the beach. When they sounded the alarm to leave, she announced that it was simply unfeasible for that much time to have passed: "THAT WATH LIKE 10 THECONDTH," she explained. Of course, it is possible that she had been moving at relativistic speeds, in which case both she and her parents could have been correct.

After I turned this column in to *Scientific American* editor in chief Mariette DiChristina, she told a story about her then five-year-old daughter Mallory's ability to calculate rapidly. Mallory wondered aloud how old Mariette would be when Mallory reached her mom's age, 42 at the time. "Let's see...," Mariette began. Then Mallory answered her own question, laughing at her mother's silliness for even bothering to try to do the math: "Oh, Mom, you'll be dead!"

The young people discussed so far are obviously charming and insightful. And yet for truly scary little-kid brain activity, it's hard to beat the very young Carl Friedrich Gauss. As legend has it, the budding mathematician was in grade school when his instructor assigned him the mundane task of adding up all the numbers from 1 to 100. The teacher might have been hoping to catch some zzz's in the corner while Gauss would be busy adding 1 to 2 to get 3, then 3 to that sum to get 6, then 4 to that sum to get 10, ad literally nauseam. But just a moment passed—perhaps merely 10 thecondth—before Gauss announced that the answer was 5,050. Which it sure is.

If you don't know how he did it, just search the Web using the terms "Gauss" and "series." Or give the problem to a wee one. If you get a correct answer almost instantly, he or she might be one of the smartest kids in the multiverse. SA

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Illustration by Matt Collins

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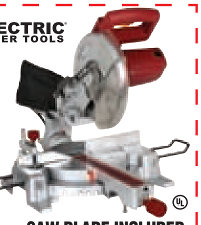

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Includes two 1.5V button cell batteries.

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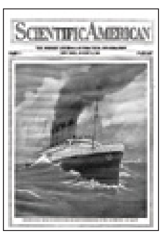
Innovation and discovery as chronicled in *Scientific American*

August 1961

Polymers and Manufacturing

"Seven years have now passed since our laboratory in the Politecnico di Milano discovered 'stereospecific' catalytic processes for creating 'stereoregular' polymers from simple asymmetric hydrocarbon molecules such as those of propylene. The new stereoregular polypropylene polymers produced by our methods, and by similar methods successfully developed by others, have been in large-scale production in the U.S. since early this year, following the completion last year of three major plants. Only last year our laboratory was successful in carrying stereospecific polymerization methods another step forward, suggesting that still-new varieties of stereoregular polymers may achieve practical importance before too many years have passed. —Giulio Natta"

Natta shared in the 1963 Nobel Prize in Chemistry. These molecules are used as catalysts in the large-scale commercial production of plastics and rubbers.



August 1911

A Million Great Ideas

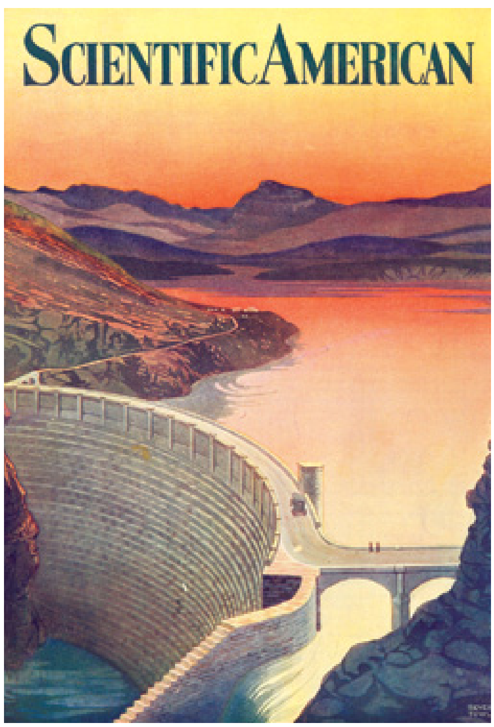
"Unmarked by any pomp or ceremony and with a lack of ostentation that seemed totally inappropriate to the importance of the occasion, the one millionth patent was issued on Tuesday, August 8th, 1911. The wheel of chance which decided the recipient of the epoch-making patent—awarded to the patent which happened to be on the top of the pile when the numbering machine passed 999,999—decided in favor of Frank H. Halton, of Cleveland, Ohio, who had applied for exclusive rights to manufacture and sell an improvement on inflated automobile tires. It was fitting that this patent, itself a monument to progress, should have been awarded to an improvement on the automobile."

Water and Power

"The Roosevelt Dam in southern Arizona, recently completed, contains over 350,000 cubic yards of masonry, and forms the largest artificial reservoir now in existence; the construction of this reservoir required the expenditure of nearly $300,000 in wagon roads alone, to make the region accessible and to replace public roads submerged by the artificial lake."

Opium Toll

"Some unexpected results are found from the movement against the production of opium in China. In the Yunnan, one of the provinces where opium was produced in large quantities, it appears that the poppy is no longer cultivated, owing to the recent measures. However, this has had a disastrous effect on the honey culture of the region. As the bees find no more flowers, the production of honey is stopped. The new crops which replace the poppy, such as wheat or peas, are not such as will give as good a honey yield. On another side of the question, it appears that the opium habits of the population are not suppressed by the present legislation, as some supposed would be the case, but are again on the rise."



The Theodore Roosevelt Dam, built to store water, control floods and provide electricity, 1911

SCIENTIFIC AMERICAN, VOL. CV, NO. 7: AUGUST 12, 1911

August 1861

Drinking Lead

"There is no subject of more importance, especially in cities possessing the inestimable blessing of waterworks, than the corrosion of lead in water pipes. All the salts of lead are extremely poisonous, and, like all the metallic poisons, they accumulate in the system. We have long regarded the fact of the salts of lead being insoluble in water as entirely inconclusive in regard to the safety of employing lead pipes for the conveyance of water. When water is driven with great velocity, under a high head [pressure] through a pipe, the feathery particles of the mineral are then washed off and mingled with the water passing as certainly into the system as if they were dissolved."

Civil War at Sea

"The schooner *S. J. Waring,* which had been captured by the privateer *Jeff. Davis,* arrived in this port on Sunday, July 21st, having been retaken by the black steward, with the assistance of one of the seamen. When the *S. J. Waring* was taken, her captain and mate were taken off, but the colored steward, two of the seamen and a passenger were left on board. The steward having discovered, by a conversation which he heard, that it was the intention of the prize master Capt. Amiel to sell him into slavery as soon as the schooner arrived in Charleston, determined to make a desperate attempt to retake the vessel. The steward's name is William Tillman."

The account we published of the event is at www.ScientificAmerican.com/aug2011/waring

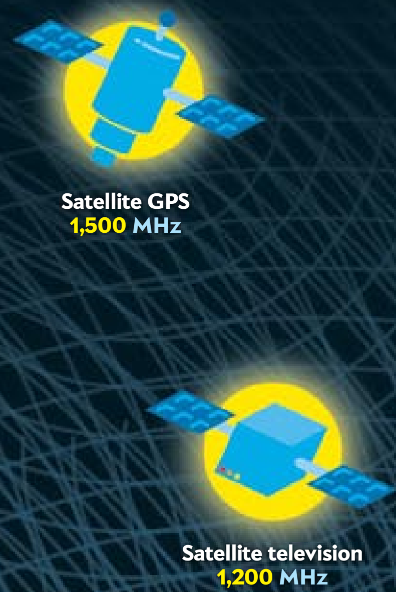

Mike Rowe and his mom, Peggy, a breast cancer survivor.
Mike & Peggy's photo by Randall Slavin ©2011 Lee Jeans, a division of VF Jeanswear Limited Partnership
WHAT'S ALWAYS THE RIGHT SIZE,
NEVER THE WRONG COLOR,
AND CAN'T GO OUT OF STYLE?
A DONATION.
One in eight women will be diagnosed with breast cancer.
Help us change that number by giving a little more.
Give what you would spend on a pair of jeans to fight breast cancer.
MAKE A DIFFERENCE AT denimday.com
Lee NATIONAL DENIM DAY® OCTOBER 7, 2011
EIF Women's Cancer Programs Entertainment Industry Foundation Initiatives
CANCER SUPPORT COMMUNITY
There are more than 2.5 million breast cancer survivors in the United States.
Talk to your doctor about getting screened.

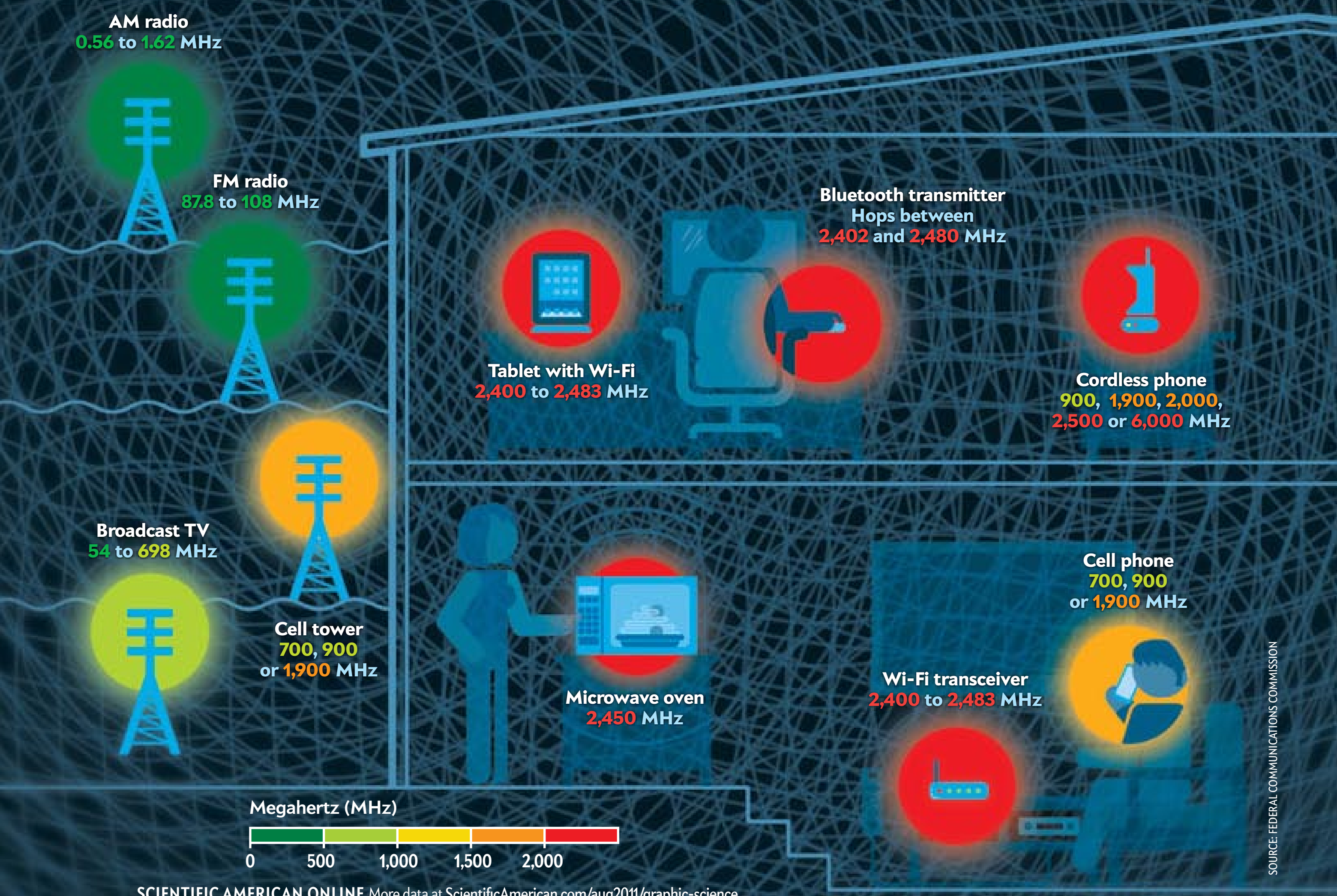
Bombarded

More and more electromagnetic radiation of our own making fills the “empty” air

You cannot see them, but radio waves pervade your peaceful living space. They emanate from an increasingly large menagerie of electronic gadgets, appliances and satellites. FM radio and broadcast television have been around for years; more recently, cell phones and Wi-Fi routers have added their high frequencies to the mix.

Should we worry? In May the International Agency for Research on Cancer declared that long-term cell-phone use could “possibly” cause cancer; it says the same for coffee drinking. The intensity of exposure is proportional to distance, and cell phones are held close to the brain, but many studies conclude that evidence of a cancer link is nonexistent. The sheer number of radio-frequency sources is not a concern either. Exposures “do not all add collectively at any one point in space,” says Jerrold T. Bushberg, head of health physics programs at the University of California, Davis. And average exposure is still far below safety standards, which have a large margin built in. —*Mark Fischetti*





SCIENTIFIC AMERICAN ONLINE More data at ScientificAmerican.com/aug2011/graphic-science

Graphic by Jude Buffum