EVOLUTION
Human Hybrids

PLANETARY SCIENCE
Mars in Motion

NEUROSCIENCE
Seeds of Dementia

SCIENTIFIC AMERICAN

ScientificAmerican.com
MAY 2013

SPECIAL REPORT

How to Make the Next Big Thing

The Future of Manufacturing

Robot Bosses

Next-Gen Materials

3-D Printing

Nanotech Machines

Code Factories

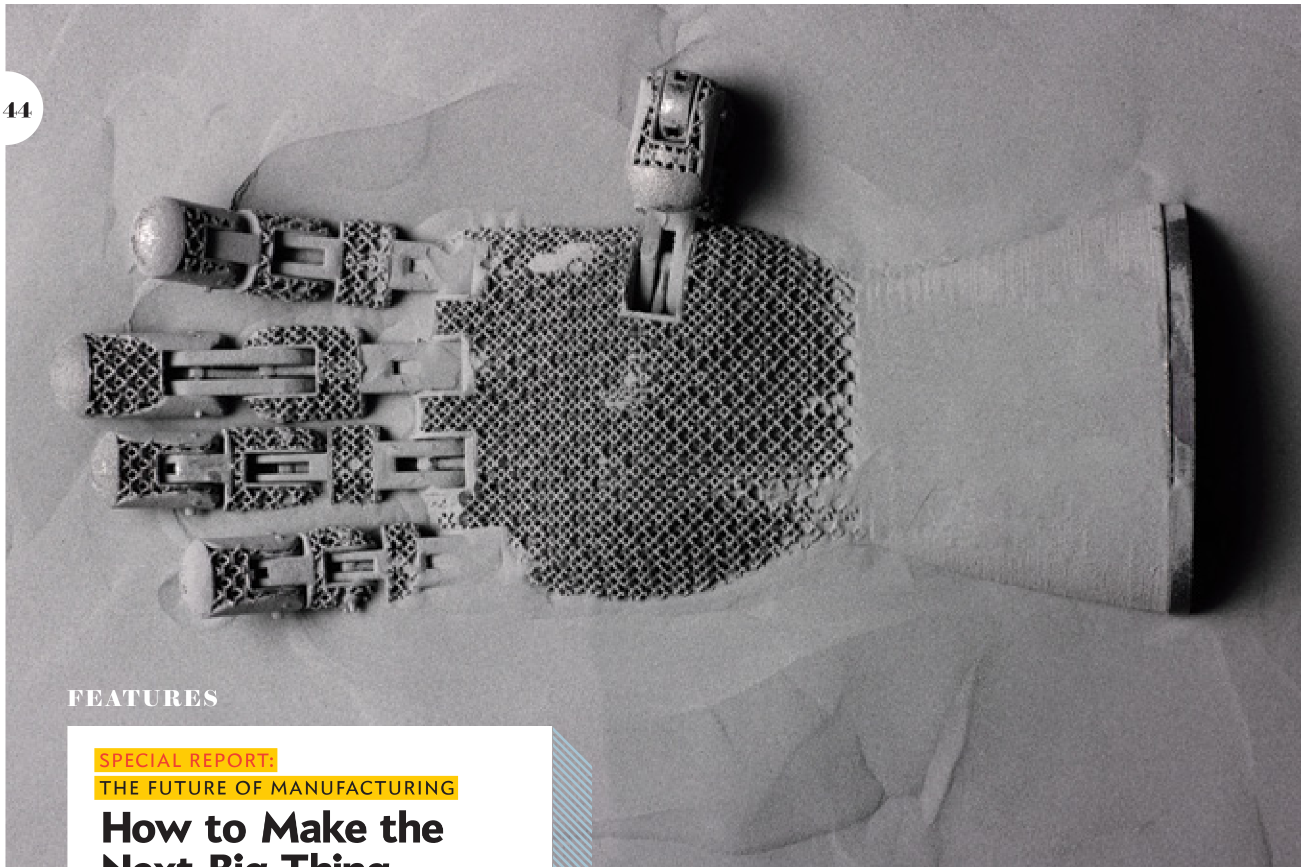
My Beloved Brontosaurus
ON THE ROAD WITH
OLD BONES, NEW SCIENCE,
AND OUR FAVORITE DINOSAURS
Brian Switek

SCIENTIFIC AMERICAN

May 2013 Volume 308, Number 5

ON THE COVER

When we are unable to find what we need in nature, we make it. Our manufacturing special report, "How to Make the Next Big Thing," examines new materials, methods and technologies shaping the future of fabrication. Humans and robots will increasingly work together as peers—giving or taking orders based on ability—in a bid to improve efficiency. Illustration by Justin Metz.

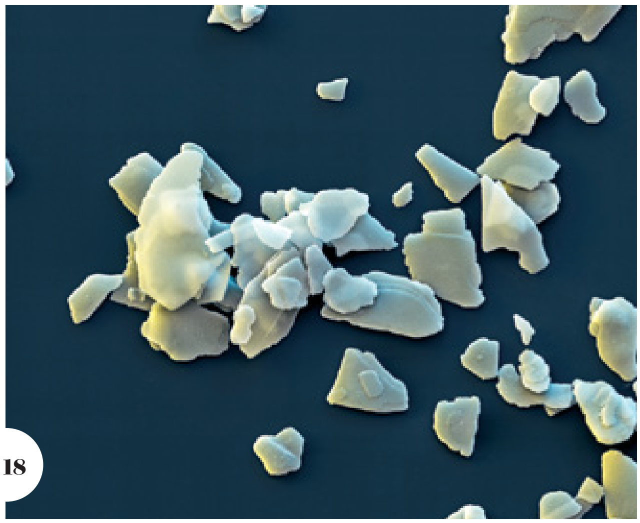


FEATURES

SPECIAL REPORT:
THE FUTURE OF MANUFACTURING

How to Make the Next Big Thing

Photograph by Travis Rathbone



SCIENTIFIC AMERICAN

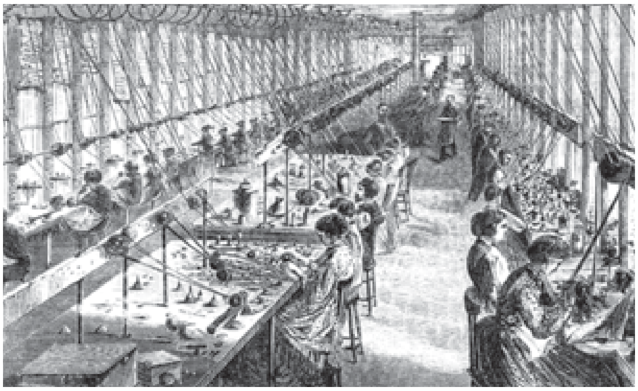
DEPARTMENTS

ON THE WEB

Obama's Second-Term Appointments
As President Barack Obama fills posts for the Department of Energy, the Environmental Protection Agency and other key agencies, we examine what the next four years hold for U.S. science policy.
Go to www.ScientificAmerican.com/may2013/cabinet

Scientific American (ISSN 0036-8733), Volume 308, Number 5, May 2013, published monthly by Scientific American, a division of Nature America, Inc., 75 Varick Street, 9th Floor, New York, N.Y. 10013-1917. Periodicals postage paid at New York, N.Y., and at additional mailing offices. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 40012504. Canadian BN No. 127387652RT; TVQ1218059275 TQ0001. Publication Mail Agreement #40012504. Return undeliverable mail to Scientific American, P.O. Box 819, Stn Main, Markham, ON L3P 8A2. **Individual Subscription rates:** 1 year $39.97 (USD), Canada $49.97 (USD), International $61 (USD). **Institutional Subscription rates:** Schools and Public Libraries: 1 year $72 (USD), Canada $77 (USD), International $84 (USD). Businesses and Colleges/Universities: 1 year $330 (USD), Canada $335 (USD), International $342 (USD). Postmaster: Send address changes to Scientific American, Box 3187, Harlan, Iowa 51537. **Reprints available:** write Reprint Department, Scientific American, 75 Varick Street, 9th Floor, New York, N.Y. 10013-1917; fax: 646-563-7138; reprints@SciAm.com. **Subscription inquiries: U.S. and Canada (800) 333-1199; other (515) 248-7684. Send e-mail to sacust@sciam.com.** Printed in U.S.A.


WE NEED
TO START
BUILDING
AGAIN.
WE AGREE.
John P. Surma
Chairman and CEO
United States Steel Corporation
Gary Luquette
President, Exploration & Production
Chevron North America
Chevron
Human Energy®
Manufacturing is key to a strong economy.
At Chevron, we're putting over $8 billion
back into our economy this year.
In pipes. Steel. Cement. And jobs.
Producing the things that help us produce
reliable, affordable energy.
We're making an investment in America.
Building the groundwork for growth.
And making a real difference.
Learn more at chevron.com/weagree
CHEVRON, the CHEVRON Hallmark and HUMAN ENERGY are registered trademarks
of Chevron Intellectual Property LLC. © 2012 Chevron U.S.A. Inc. All rights reserved.



Mariette DiChristina is editor in chief of *Scientific American.* Follow her on Twitter @mdichristina

Making the Future

In its first issue, dated Thursday, August 28, 1845, under the elaborate woodcut illustrating its logo, *Scientific American* summed up its mission: "The Advocate of Industry and Enterprise, and Journal of Mechanical and Other Improvements."

Founder and editor Rufus Porter, himself an inventor and painter, noted that the new publication "is especially entitled to the patronage of Mechanics and Manufacturers, being the only paper in America, devoted to the interests of those classes." With the industrial revolution in full swing in the still young U.S., the issue listed dozens of recent patents and innovations. Most focused on mechanizing processes that previously required backbreaking toil or the fine work of human hands.

Highlights for me include mentions of the new experiments Michael Faraday was conducting with zinc wires, speculation about the coming of the "electro-magnetic light as a substitute for oil or gas," and the beginning of the information age: Samuel Morse's telegraph was then in operation only between Washington and Baltimore, but the editors predicted "this wonder of the age" would come into "general use through the length and breadth of our land." (For a gallery from our archives, such as the watch factory from 1870 at the left, visit www.ScientificAmerican.com.)

A different kind of industrial revolution is under way today—one that combines the transformative power of information with our human need to remake pieces of the world to improve our lives. Put another way, "Manufacturing is order, intelligently applied," writes Ricardo Hausmann of Harvard University in the introduction to our special report and cover story. Turn to page 36 for our package on "How to Make the Next Big Thing." The feature articles cover such topics as human-robot collaboration, next-generation materials, 3-D printing, atomic-scale machines and digital simulations. In providing this essential guide to understanding the forces shaping the world today, *Scientific American* continues to fulfill a role it has held for 167 years. SA

SCIENCE IN ACTION

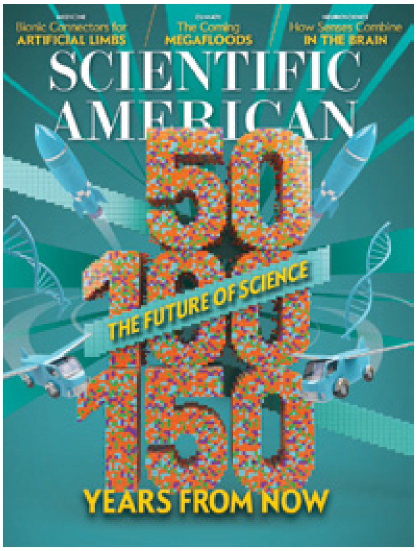
Last Call for Entries

Open to students ages 13 to 18, the Google Science Fair closes entries on April 30—also the deadline for being considered for the $50,000 Science in Action Award sponsored by *Scientific American*. I'm judging again and eager to see the ideas. *—M.D.*

SCIENTIFIC AMERICAN, VOL. XXIII, NO. 11; SEPTEMBER 10, 1870

Illustration by Nick Higgins

editors@sciam.com



January 2013

WHAT THE FUTURE HOLDS

All the predictions for scientific and technological advancement over the next century or so in "The Future in 50, 100 and 150 Years" are predicated on the existence of humans for that duration, with only some addressing attempts to ensure it.

Of the many tempting fields of discovery and development, it is incumbent on us to focus our scientific resources on the collection of global conditions that most immediately threaten our very existence: pollution, overpopulation and the squandering of natural resources. Any other research will be a case of putting the scientific cart before the soon to be extinct horse.

Dennis B. Appleton
Madison, Wis.

While I wouldn't mind having, say, a personal automated plane, as described by Mary Cummings in "A Drone in Every Driveway," in my view, none of the possible positive achievements detailed could compensate for our causing the extinction of so many of our fellow species as described by Thomas Lovejoy in "A Tsunami of Extinction." If that happens at the levels Lovejoy predicts, our own species will have been a failure of the most dismal sort.

Phil Freeman
Washburn, Wis.

"A Bold and Foolish Effort to Predict the Future of Computing," by Ed Regis, focused too much on technology in surveying experts to answer where computing is going—and missed the main area that will demand innovation in the field.

That area will be how to simplify and enhance life with computing. The future can be grasped by looking at what you do now and thinking about how that could be optimized and simplified. As an example, a pair of sunglasses could evolve into a head-up display for your cell phone while you are navigating a city. To accomplish these types of innovations, computing will continue following established trends: improving size, weight and power and increasing network connectivity.

Anthony Gabrielson
Lawrence, Mass.

"Whether cognition looks like a Swiss Army knife or a giant amoeba may depend on what aspect we are analyzing."

E. N. Anderson
University of California, Riverside

POLITICS IN SPACE

In "Starship Humanity," Cameron M. Smith discusses people traveling to other planets and into interstellar space and potential results, such as genetic and cultural changes from environmental factors.

There is another very important factor to consider: politics. Smith talks about having 2,000 people on a spacecraft and compares that with twice that number being typical for an aircraft carrier. Politically, there is a very big difference. People are on the carrier for short periods rather than their entire lifetimes. Also, there is a well-defined government on a carrier, which sailors are trained to accept, so there is little chance of a mutiny. A ship or colony will have to select new leaders and representatives as time goes on, and there are bound to be at least two groups wanting different things. Because the population will be fairly small, more laws will affect people directly than they do on Earth.

In addition, the original travelers will be replaced by future offspring. It's unlikely that the next generations will feel the same way about the "adventure" as their forebears.

Political aspects of an interstellar trip could be more important to its success than anything else. Before we launch any ships, we should try to develop guidelines that the travelers and following generations can use as a starting point.

Ted Grinthal
Berkeley Heights, N.J.

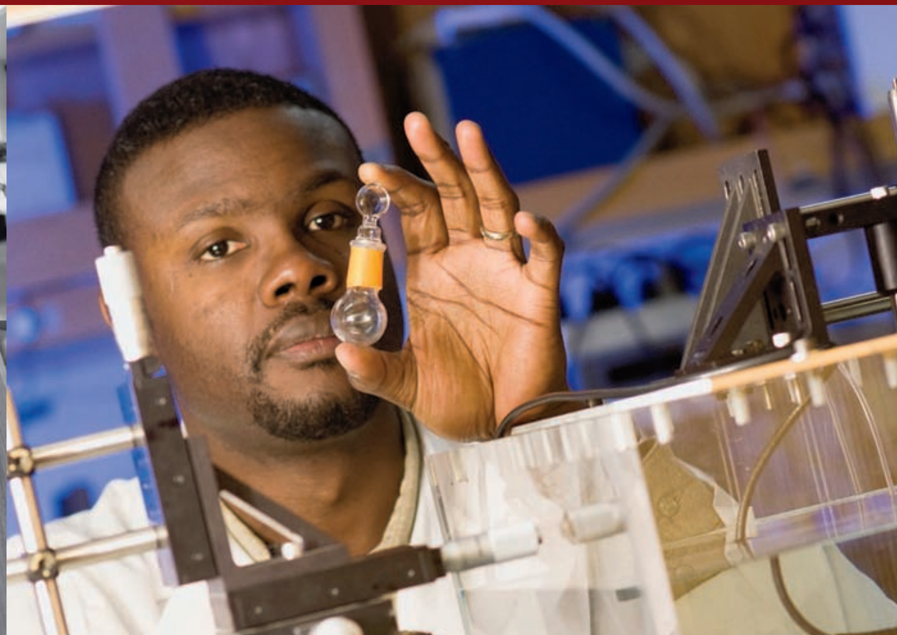
ARE MINDS MODULAR?

In "A Confederacy of Senses," Lawrence D. Rosenblum writes, "Neuroscientists and psychologists have largely abandoned early ideas of the brain as a Swiss Army knife, in which many distinct regions are dedicated to different senses." In contrast, in "Logic-Tight Compartments" [Skeptic], Michael Shermer writes, "the brain evolved as a modular, multitasking problem-solving organ—a Swiss Army knife of practical tools." Nothing like some healthy disagreement! It's great to get both sides and no overediting to make everything come out neat.

The truth is that one can model some aspects of the brain as modular, compartmentalized or functionally specific, but even they are linked to the total thinking brain by many strands. Language is a unified, specific system that can be (and very often is) seen as a "module," but it is made up of many mental activities, from sound perception to hierarchical recursive planning, and of course, it is used to talk about anything and everything, including cognition and thought. So cognition is complicated, and whether it looks like a Swiss Army knife or a giant amoeba may depend a great deal on what aspect of it we are analyzing at the time.

E. N. Anderson
Professor of Anthropology, Emeritus
University of California, Riverside

SHERMER REPLIES: Anderson's point is important because it highlights the contextual nature of the metaphor and where it does or does not apply. As University of Pennsylvania evolutionary psychologist Robert Kurzban told me, "Many, if not most, psychologists in my experience agree that the mind/brain contains specializations, and there seems to be broad agreement that, for instance, the sensory sys-



ANNOUNCING INCREDIBLY SMALL NEWS IN THE FIGHT AGAINST CANCER.

One of the biggest developments in cancer treatment could soon come from an extremely small source. Using nano-engineered carriers, we may be able to release chemotherapy drugs inside tumors — with no damage to the rest of the body's cells. And tumors simply will never see what hit them. Continuously exploring ways to combine disciplines like engineering and medicine is another reason why Boston University has become one of today's great research institutions. And why thinking differently about our world begins with BU. Find out more at **bu.edu/discover/cancer**

The world needs to know.

BOSTON UNIVERSITY

tems are specialized. There is disagreement about other areas, and as one gets 'higher,' to use a fraught metaphor, there is probably more disagreement." Harvard University psychologist Steven Pinker, meanwhile, made a distinction between mind and brain when it comes to the proper (or improper) use of the metaphor: "Functionally distinct systems at the level of information processing could be distributed and intertwined at the level of brain tissue, just as a program in your computer can be distributed in pieces all over your hard drive until you defragment it."

As with all metaphors in science, we would be wise to employ them judiciously and remind ourselves that the actual physical system is likely more complicated.

KATRINA'S LESSONS

We agree with Klaus Jacob's conclusion, referred to in an interview with Mark Fischetti in "How to Survive the Next Big Storm" [Advances], that cities need to alter their building and transportation infrastructure to avoid catastrophic flooding. Yet Jacob makes a statement that might be misleading: "Hurricane Katrina in New Orleans overcame man-made barriers because the city kept [sinking] and the sea had risen after the [levees] and walls went up."

We know of no reliable evidence that sinking within the city limits was a major factor in the disaster. The flooding of metro New Orleans was primarily a result of the failure of levees and floodwalls that should have performed their function and of the human-caused destruction of protective wetlands in southern Louisiana that had historically acted as storm surge buffers.

Often it is the details outside an article's main point that people are likely to notice and repeat.

Sandy Rosenthal
Founder, Levees.org

CLARIFICATION

"Safe from Scorpions," by Erik Vance [Advances], should have noted that the Instituto Bioclon in Mexico was involved in developing the new generation of antivenoms described in the piece and holds patents to the new black widow antivenom and the scorpion antivenom cited.

LETTERS TO THE EDITOR

Scientific American
75 Varick Street, 9th Floor
New York, NY 10013-1917
or editors@sciam.com

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/may2013

HOW TO CONTACT US

Subscriptions
For new subscriptions, renewals, gifts, payments, and changes of address: U.S. and Canada, 800-333-1199; outside North America, 515-248-7684 or www.ScientificAmerican.com

Submissions
To submit article proposals, follow the guidelines at www.ScientificAmerican.com. Click on "Contact Us." We cannot return and are not responsible for materials delivered to our office.

Reprints
To order bulk reprints of articles (minimum of 1,000 copies): Reprint Department, Scientific American, 75 Varick Street, 9th Floor, New York, NY 10013-1917; 212-451-8877; reprints@SciAm.com. For single copies of back issues: 800-333-1199.

Permissions
For permission to copy or reuse material: Permissions Department, Scientific American, 75 Varick Street, 9th Floor, New York, NY 10013-1917; randp@SciAm.com; www.ScientificAmerican.com/permissions. Please allow three to six weeks for processing.

Advertising
www.ScientificAmerican.com has electronic contact information for sales representatives of Scientific American in all regions of the U.S. and in other countries.


TEACH.
INSPIRE.
HIRE.

The Spies Who Sabotaged Global Health

The U.S. was wrong to use health workers to target Osama bin Laden

Not long after midnight on May 2, 2011, U.S. Navy SEALs attacked a three-story compound in Abbottabad, Pakistan, raced to the main building's top floor and killed Osama bin Laden. Few mourn the man responsible for the slaughter of many thousands of innocent people worldwide over the years. But the operation that led to his death may yet kill hundreds of thousands more. In its zeal to identify bin Laden or his family, the CIA used a sham hepatitis B vaccination project to collect DNA in the neighborhood where he was hiding. The effort apparently failed, but the violation of trust threatens to set back global public health efforts by decades.

It is hard enough to distribute, for example, polio vaccines to children in desperately poor, politically unstable regions that are rife with 10-year-old rumors that the medicine is a Western plot to sterilize girls—false assertions that have long since been repudiated by the Nigerian religious leaders who first promoted them. Now along come numerous credible reports of a vaccination campaign that *is* part of a CIA plot—one the U.S. has not denied.

The deadly consequences have already begun. Villagers along the Pakistan-Afghanistan border chased off legitimate vaccine workers, accusing them of being spies. Taliban commanders banned polio vaccinations in parts of Pakistan, specifically citing the bin Laden ruse as justification. Then, last December, nine vaccine workers were murdered in Pakistan, eventually prompting the United Nations to withdraw its vaccination teams. Two months later gunmen killed 10 polio workers in Nigeria—a sign that the violence against vaccinators may be spreading.

Such attacks could not come at a worse time. The global polio campaign has entered what should be its final stages. The number of cases has dropped from 350,000 in 1988 to 650 in 2011. The disease spreads naturally in only three countries—Afghanistan, Pakistan and Nigeria—down from more than 125 countries a quarter of a century ago. Disrupting or postponing vaccination efforts could fan a resurgence of polio around the world.

The distrust sowed by the sham campaign in Pakistan could conceivably postpone polio eradication for 20 years, leading to 100,000 more cases that might otherwise not have occurred, says Leslie F. Roberts of Columbia University's Mailman School of Public Health. "Forevermore, people would say this disease, this crippled child is because the U.S. was so crazy to get Osama bin Laden," he argues.

The vaccination ruse also poses a moral problem. Physicians take a Hippocratic oath to do no harm. Humanitarian workers adhere to an international code of conduct that requires that their services be provided independently of national agendas, on the basis of need alone. The misguided vaccine program in Pakistan was started in a poor neighborhood of Abbottabad, no doubt to give it an air of legitimacy. Yet after the first in a standard series of three hepatitis B shots was given, the effort was abandoned so that the team could move to bin Laden's wealthier community. This lapse in protocol proves that the best interests of the recipients were not the guiding principle of the effort—while not coincidently betraying the program for the sham it was.

There must be a red line drawn between humanitarian efforts and the machinations of warfare, no matter how unconventional. The costs to future humanitarian endeavors, global stability and U.S. national security of doing otherwise are too high—even when weighed against the liquidation of one of the U.S.'s most fearsome enemies and even if no other option is available. As outlined in a letter signed by the deans of a dozen prominent schools of public health that was sent to the White House, President Barack Obama should direct all U.S. military and intelligence agencies to refrain from using a medical or humanitarian cover to achieve their objectives. Such efforts are bad medicine and bad spy craft. A wise leader would disavow them. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/may2013

Illustration by Sam Washburn

We see progress in extending the lives of cancer patients, and even cures. But the result is not victory but a long war of attrition. Find out why.

Targeting the Cancer Genome

Knowing the cancer genome in detail leads to precise targeting of potential cancer triggers in the cell. Two spectacular recent successes in targeting certain types of leukemia and breast cancer led to a proliferation of very expensive drugs similarly targeted to specific cancers. Are these drugs worth it? Explore the scientific accomplishments and ethical issues involved in medical progress.

Natural Medicine and the War on Cancer

Faced with a dreadful diagnosis, many cancer patients supplement or substitute their doctor's recommendations by "going alternative." Turns out that some common cancer-fighting drugs originated in traditional medicines. Learn about the process of transforming a traditional treatment to a mainstream therapy. How are alternative medicines evaluated? Are they effective? Join Dr. Sadava and make some surprising discoveries.

Archaeology

Speaker: Lynne Lancaster, Ph.D.

Introduction to Culture and Technology in Gaul

Gaul was influenced by the Iberians, Celts, Greeks, and Romans. Each culture brought skills and technologies such as town planning, architecture and construction, mining of salt and metals, and the adoption of coinage. Get an overview of the technology, culture, and politics of the Greek and Roman colonization of France.

Fire-Based Technologies in Gaul: Terracotta Production and Metal-Working

Terra cotta and metal artisans had to master techniques of balancing chemical interaction to achieve the desired results. Find out how the Romans adopted Greek methods to mass produce pottery. In contrast to this imported knowledge, learn about Celtic metal-working skills, which the Romans assimilated and put to military use.

Building an Amphitheater

Along with bath buildings, the construction of an amphitheater was one of the greatest investments a community could take on. Dig into the engineering and construction process: site preparation for enormous loads, quarrying and transporting great numbers of stone blocks, erecting the structure and distributing loads. Enrich your appreciation of ancient architecture in the Roman world and beyond.

Aqueducts, Baths and Water Mills

The Romans exploited water technology much earlier and on a greater scale than has been realized. This was all possible due to the mastery of aqueducts. We will explore the principles behind the laying out and functioning of Roman aqueducts, including the use of inverted siphons, tunnel cutting, and arch construction.

Cosmology

Speaker: Mark Whittle, Ph.D.

The Birth of Our Universe: Evidence for the Big Bang

Is the current evidence for the Big Bang strong enough to consider it a fact? Survey the contents of the Universe and scrutinize the six key pieces of evidence for its birth in a "Hot Big Bang."

Billion Years of History: the Birth and Maturation of Galaxies

Study the natural history and structure of galaxies directly, from infancy to maturity. Orient yourself to our own Milky Way, and the types of galaxies that form a web of galaxies filling the Universe. Contemplate dark matter and black holes, and get the latest thought in cosmology.

The Universe's First Million Years: Primordial Light and Sound

Take a trip back in time to explore the incandescent fireball of the infant Universe, just ½ million years after the Big Bang. Learn the astounding qualities of its light and how cosmologists use the primordial sound of this period to measure a number of the Universe's properties. Listen, think, and wonder at the cosmological Dark Age before the first stars.

Cosmic Inflation: Making Universe(s) from Nothing!

How was our expanding Universe created? We'll look to cosmic inflation theory for answers and food for thought. Using the astonishing fact that the total mass/energy of the Universe is zero, and its implications, we can begin to understand how cosmic inflation both creates and launches our expanding Universe — out of nothing! Examine cosmic puzzles, possibilities, and intriguing speculation.

Oenology

Speaker: James Kennedy, Ph.D.

Climate Change and Impact on the Wine World

Wine's chemical composition varies widely across different areas of the world. Much of a wine's uniqueness stems from the impact of place on wine composition. Discover how the climates in the wine regions of the world are changing, and what this means for wine as we know it. In a lab session, we'll taste wine from warm regions.

The Rhone and Its Wines

The Rhone River region produces some of the finest wines in the world. As the Rhone River flows south to the Mediterranean, the grapes and the wines produced from them change considerably. Combining a lecture with a wine tasting, Dr. Kennedy will discuss this amazing wine-growing region and the wines it produces.

Wine and Health

From the French Paradox to resveratrol and beyond, Dr. Kennedy investigates the composition of wine and the role that wine plays in human health. Is wine the wonder beverage as often portrayed in popular media, or is the fascination just a means to feel good about alcohol consumption?

Advances in Grape and Wine Production

Wine labels often evoke the tradition, romance, and history of winemaking. The flowery language and imagery obscures the technological progress made over the past century in viticultural and winemaking practices. Discover how some of the finest wines in the world are produced using sophisticated, state-of-the-art technology and science.

SCIENTIFIC AMERICAN Travel HIGHLIGHTS

RHONE RIVER NOV. 29 – DEC. 6, 2013

INSIDER'S TOUR OF CERN

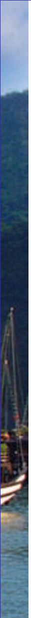
Pre-cruise: November 28, 2013—From the tiniest constituents of matter to the immensity of the cosmos, discover the wonders of science and technology at CERN. Join Bright Horizons for a private pre-cruise, custom, full-day tour of this iconic facility. (If the LHC is still undergoing its scheduled maintenance it is anticipated we will go into the LHC Cavern.)

Whether you lean toward concept or application there's much to pique your curiosity. Discover the excitement of fundamental research and get a behind-the-scenes, insider's look at the world's largest particle physics laboratory.

We'll have an orientation, visit an experiment, get a sense of the mechanics of the Large Hadron Collider (LHC). If at all possible, we'll go down inside the LCH tunnel (picture left), then make a refueling stop for lunch, and have time to peruse the grounds and exhibits on the history of CERN and the nature of its work. And if you're so inclined, you can visit the CERN gift shop.

The price is $899 per person (based on double occupancy). This trip is limited to 50 people. NOTE: CERN charges no entrance fee to visitors.

For more info please call 650-787-5665 or log on to ScientificAmerican.com/Travel



The Neurobiology of Mindfulness

As psychotherapists adapt ancient contemplative practices to the challenges of treating modern psychopathology, researchers are using FMRI, EEG, and other brain imaging techniques to investigate the neurobiological mechanisms by which mindfulness practices work. This presentation will explore the implications of these investigations for learning how to change our brains.

ARCHAEOLOGY

Speaker: John R. Hale, Ph.D.

A Land of Natural Wonders

Learn about the spectacular natural wonders of Southeast Asia, from ancient rainforests to stunning coral reefs. We'll cover the wealth of unique plant and animal species native to this region, as well as the history of the first domestication of rice, chicken, and pigs here. It's a trove of geology, biology, and natural history.

Cradle of Human Evolution

Find out why Southeast Asia is at the forefront of evolutionary research, and why 19th century scientists believed the human species originated here. We'll cover some of the most game-changing fossils found in the region, from "Java Man" to "Peking Man" to Gigantopithecus and "Flores Man."

Land of Lost Kingdoms

Fascinating kingdoms, from the Khmer rulers who built Angkor Wat to the Siamese kings who defied European colonialists, once reigned in Southeast Asia. Though always living under the threat of Chinese takeover, these powers nonetheless created unique cultures and artistic traditions. We'll discuss this rich history and the monuments they left behind.

Faiths in Collision

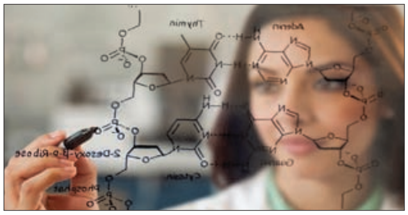
Learn how three of the world's major religions — Hinduism, Buddhism, and Islam — gained firm footholds in Southeast Asia, eventually overcoming the region's native animistic religious cults. We'll discuss the remarkable architecture — temples, monasteries, mosques — of these religions, as well as the ways their beliefs continue to permeate everyday life.

The Story of the Spice Trade

The spices of Southeast Asia — pepper, cinnamon, cloves, nutmeg, cardamom, and others — led Europeans to forge sea-routes seeking out these treasures, and even motivated Columbus' search for a shortcut to Asia (which led him to stumble on America). Learn how the global trade that we take for granted today had its origins in the spice trade.

Shipwrecks of Southeast Asia

Beneath the seas of Southeast Asia lies a museum of Arab dhows, Chinese junks, European trading ships, and World War II warships that were lured by commerce or war. Learn how ancient coins, woodcarvings, bronzes, and the wooden hulls of ships themselves helped archaeologists reconstruct the trade routes that linked East and West.



GENETICS & EVOLUTION

Speaker: John Mattick, Ph.D.

The Story of the Molecular Biology Revolution

Learn about the heady days when enzyme chemists joined physicists to decipher the genetic code, and later joined the bacterial geneticists to develop the tools that launched the gene cloning and genomic revolutions that are laying bare the programming of life. It's a story of great characters, rivalries and debates, pioneering vision and crippling hubris.

The Origin of Life

The story of life is a dramatic, mysterious tale, originating in a primordial soup of organic molecules, and ultimately resulting in species that can remember, learn, sing, think, and write. Learn how evolution navigated cellular biology, and probe the complex innovations that must have occurred along the way.

Junk DNA: Challenging the Dogma

Non-coding sequences of DNA were dismissed as junk when discovered, but scientists now are realizing that these segments are copied into RNA in precise patterns that orchestrate gene expression during development. Learn how what once was thought to be junk actually holds the secret to understanding human evolution, development, diversity, and cognition.

Evolving Evolution

We'll contrast two early views of evolution by Charles Darwin and Jean-Baptiste Lamarck, and discuss how scientists' understanding of evolution has itself evolved over time. The traditional picture, that mutation is random and selection acts only on the progeny, may be incorrect. Evolution, it seems, has learned how to learn, and we're the result.

Your Genome and You

Gene sequencing, once a costly and difficult process, is set to become routine in the near future. Medicine is evolving from the art of crisis management to the science of good health, increasingly tailored to individuals' genetic and environmental circumstances. Learn what we stand to gain, and what surprises may be in store.

HISTORY OF SCIENCE

Speaker: Steven Goldman, Ph.D.

The Global Roots of Modern Science

Learn how modern science emerged in Western Europe in the 17th century, and grew to maturity in the 19th century. We'll also discuss how the development of modern science is deeply indebted to important contributions from China, the Arabic-speaking lands, and India, as well as from ancient Greece and Rome.

Order Out of Chaos

We'll discuss the profound change the natural sciences underwent in the late 1900s, when scientists in multiple disciplines simultaneously discovered the power of top-down systems thinking, as opposed to bottom-up world building. In this session, become familiar with systems thinking and investigate the possibilities it offers.

The Mind, the Brain, and You

Learn how theories of the mind have evolved throughout time, from the 19th century, when philosophical speculation gave way to the sciences of psychology and physiology, to the late 20th century, when psychology and physiology converged with cognitive neuroscience and computer-based artificial intelligence technologies.

Innovation, Globalization and the Future of America

The steam power-based Industrial Revolution of the mid-19th century quickly gave way to economies that critically depend on continuous technological innovation and access to global markets for growth and sustained prosperity. We'll discuss what America's people, institutions, and policy need to compete in global markets.

SCIENTIFIC AMERICAN Travel HIGHLIGHTS

SOUTHEAST ASIA FEB. 3 – 17, 2014

CHINA TOUR

PRE-CRUISE — Sunday, January 26 to February 3, 2014: A fabulous, definitive, high-end eight-day excursion through China taking in Tian'anmen Square, the Summer Palace, and the Forbidden City in Beijing; the Great Wall; Xi'an and its Terracotta warriors; Guilin and a look at rural village life.

This tour was designed specifically for the Bright Horizons guests and is provided by our colleagues at Imperial Tours.

For more info please call 650-787-5665 or visit scientificamerican.com/travel

Geoffrey West is a distinguished professor at the Santa Fe Institute and is chair of the World Economic Forum's Global Agenda Council on Complex Systems.

Wisdom in Numbers

Just as the industrial age produced the laws of thermodynamics, we need universal laws of complexity to solve our seemingly intractable problems

As the world becomes increasingly complex and interconnected, some of our biggest challenges have begun to seem intractable. What should we do about uncertainty in the financial markets? How can we predict energy supply and demand? How will climate change play out? How do we cope with rapid urbanization? Our traditional approaches to these problems are often qualitative and disjointed and lead to unintended consequences. To bring scientific rigor to the challenges of our time, we need to develop a deeper understanding of complexity itself.

What does this mean? Complexity comes into play when there are many parts that can interact in many different ways so that the whole takes on a life of its own: it adapts and evolves in response to changing conditions. It can be prone to sudden and seemingly unpredictable changes—a market crash is the classic example. One or more trends can reinforce other trends in a "positive feedback loop" until things swiftly spiral out of control and cross a tipping point, beyond which behavior changes radically.

What makes a "complex system" so vexing is that its collective characteristics cannot easily be predicted from underlying components: the whole is greater than, and often significantly different from, the sum of its parts. A city is much more than its buildings and people. Our bodies are more than the totality of our cells. This quality, called emergent behavior, is characteristic of economies, financial markets, urban communities, companies, organisms, the Internet, galaxies and the health care system.

The digital revolution is driving much of the increasing complexity and pace of life we are now seeing, but this technology also presents an opportunity. The ubiquity of cell phones and electronic transactions, the increasing use of personal medical probes, and the concept of the electronically wired "smart city" are already providing us with enormous amounts of data. With new computational tools and techniques to digest vast, interrelated databases, researchers and practitioners in science, technology, business and government have begun to bring large-scale simulations and models to bear on questions formerly out of reach of quantitative analysis, such as how cooperation emerges in society, what conditions promote innovation, and how conflicts spread and grow.

The trouble is, we don't have a unified, conceptual framework for addressing questions of complexity. We don't know what kind of data we need, nor how much, or what critical questions we should be asking. "Big data" without a "big theory" to go with it loses much of its potency and usefulness, potentially generating new unintended consequences.

When the industrial age focused society's attention on energy in its many manifestations—steam, chemical, mechanical, and so on—the universal laws of thermodynamics came as a response. We now need to ask if our age can produce universal laws of complexity that integrate energy with information. What are the underlying principles that transcend the extraordinary diversity and historical contingency and interconnectivity of financial markets, populations, ecosystems, war and conflict, pandemics and cancer? An overarching predictive, mathematical framework for complex systems would, in principle, incorporate the dynamics and organization of *any* complex system in a quantitative, computable framework.

We will probably never make detailed predictions of complex systems, but coarse-grained descriptions that lead to quantitative predictions for essential features are within our grasp. We won't predict when the next financial crash will occur, but we ought to be able to assign a probability of one occurring in the next few years. The field is in the midst of a broad synthesis of scientific disciplines, helping reverse the trend toward fragmentation and specialization, and is groping toward a more unified, holistic framework for tackling society's big questions. The future of the human enterprise may well depend on it. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/may2013

Illustration by Eva Vazquez

YOU DON'T LOOK FOR EXCUSES. YOU LOOK FOR ANSWERS.

More than half of men over 40 have some degree of erectile dysfunction (ED).* If you think you're one of them, talk to your doctor about VIAGRA (*sildenafil citrate*) and see if America's most prescribed ED treatment is right for you. 20 million men already have.

For more information go to viagra.com or call 1-888-484-2472 (1-888-4VIAGRA).

THIS IS THE AGE OF TAKING ACTION. VIAGRA.

VIAGRA is prescription medication to treat erectile dysfunction (ED).

IMPORTANT SAFETY INFORMATION BELOW.

Do not take VIAGRA if you take nitrates, often prescribed for chest pain, as this may cause a sudden, unsafe drop in blood pressure.

Discuss your general health status with your doctor to ensure that you are healthy enough to engage in sexual activity. If you experience chest pain, nausea, or any other discomforts during sex, seek immediate medical help.

In the rare event of an erection lasting more than 4 hours, seek immediate medical help to avoid long-term injury.

If you are older than age 65, or have serious liver or kidney problems, your doctor may start you at the lowest dose (25 mg) of VIAGRA. If you are taking protease inhibitors, such as for the treatment of HIV, your doctor may recommend a 25-mg dose and may limit you to a maximum single dose of 25 mg of VIAGRA in a 48-hour period. If you have prostate problems or high blood pressure for which you take medicines called alpha blockers, your doctor may start you on a lower dose of VIAGRA.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including VIAGRA) reported a sudden decrease or loss of vision or hearing. It is not possible to determine whether these events are related directly to these medicines or to other factors. If you experience sudden decrease or loss of vision or hearing, stop taking PDE5 inhibitors, including VIAGRA, and call a doctor right away.

VIAGRA should not be used with other ED treatments. VIAGRA should not be used with REVATIO or other products containing sildenafil.

VIAGRA does not protect against sexually transmitted diseases, including HIV.

The most common side effects of VIAGRA are headache, facial flushing, and upset stomach. Less commonly, bluish vision, blurred vision, or sensitivity to light may briefly occur.

Please see Important Facts for VIAGRA on the following page or visit viagra.com for full prescribing information.

*Data taken from the *Massachusetts Male Aging Study*. Of 1,290 respondents, 52% stated that they had some degree of ED.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

The blue diamond tablet shape is a registered trademark of Pfizer Inc.

VIAGRA®
(sildenafil citrate) tablets

Pfizer

IMPORTANT FACTS

VIAGRA®
(sildenafil citrate) tablets

(vi-AG-rah)

IMPORTANT SAFETY INFORMATION ABOUT VIAGRA

Never take VIAGRA if you take any medicines with nitrates. This includes nitroglycerin. Your blood pressure could drop quickly. It could fall to an unsafe or life-threatening level.

ABOUT ERECTILE DYSFUNCTION (ED)

Erectile dysfunction means a man cannot get or keep an erection. Health problems, injury, or side effects of drugs may cause ED. The cause may not be known.

ABOUT VIAGRA

VIAGRA is used to treat ED in men. When you want to have sex, VIAGRA can help you get and keep an erection when you are sexually excited. You cannot get an erection just by taking the pill. Only your doctor can prescribe VIAGRA.

VIAGRA does not cure ED.

VIAGRA does not protect you or your partner from STDs (sexually transmitted diseases) or HIV. You will need to use a condom.

VIAGRA is not a hormone or an aphrodisiac.

WHO IS VIAGRA FOR?

Who should take VIAGRA?

Men who have ED and whose heart is healthy enough for sex.

Who should NOT take VIAGRA?

- If you ever take medicines with nitrates:
  - Medicines that treat chest pain (angina), such as nitroglycerin or isosorbide mononitrate or dinitrate
- If you use some street drugs, such as "poppers" (amyl nitrate or nitrite)
- If you are allergic to anything in the VIAGRA tablet

BEFORE YOU START VIAGRA

Tell your doctor if you have or ever had:

- Heart attack, abnormal heartbeats, or stroke
- Heart problems, such as heart failure, chest pain, angina, or aortic valve narrowing
- Low or high blood pressure
- Severe vision loss
- An eye condition called retinitis pigmentosa
- Kidney or liver problems
- Blood problems, such as sickle cell anemia or leukemia
- A deformed penis, Peyronie's disease, or an erection that lasted more than 4 hours
- Stomach ulcers or any kind of bleeding problems

Tell your doctor about all your medicines. Include over-the-counter medicines, vitamins, and herbal products. Tell your doctor if you take or use:

- Medicines called alpha-blockers to treat high blood pressure or prostate problems. Your blood pressure could suddenly get too low. You could get dizzy or faint. Your doctor may start you on a lower dose of VIAGRA.
- Medicines called protease inhibitors for HIV. Your doctor may prescribe a 25 mg dose. Your doctor may limit VIAGRA to 25 mg in a 48-hour period.
- Other methods to cause erections. These include pills, injections, implants, or pumps.
- A medicine called REVATIO. VIAGRA should not be used with REVATIO as REVATIO contains sildenafil, the same medicine found in VIAGRA.

POSSIBLE SIDE EFFECTS OF VIAGRA

Side effects are mostly mild to moderate. They usually go away after a few hours. Some of these are more likely to happen with higher doses.

The most common side effects are:

- Headache
- Feeling flushed
- Upset stomach

Less common side effects are:

- Trouble telling blue and green apart or seeing a blue tinge on things
- Eyes being more sensitive to light
- Blurred vision

Rarely, a small number of men taking VIAGRA have reported these serious events:

- Having an erection that lasts more than 4 hours. If the erection is not treated right away, long-term loss of potency could occur.
- Sudden decrease or loss of sight in one or both eyes. We do not know if these events are caused by VIAGRA and medicines like it or caused by other factors. They may be caused by conditions like high blood pressure or diabetes. If you have sudden vision changes, stop using VIAGRA and all medicines like it. Call your doctor right away.
- Sudden decrease or loss of hearing. We do not know if these events are caused by VIAGRA and medicines like it or caused by other factors. If you have sudden hearing changes, stop using VIAGRA and all medicines like it. Call your doctor right away.
- Heart attack, stroke, irregular heartbeats, and death. We do not know whether these events are caused by VIAGRA or caused by other factors. Most of these happened in men who already had heart problems.

If you have any of these problems, stop VIAGRA. Call your doctor right away.

HOW TO TAKE VIAGRA

Do:

- Take VIAGRA only the way your doctor tells you. VIAGRA comes in 25 mg, 50 mg, and 100 mg tablets. Your doctor will tell you how much to take.
- If you are over 65 or have serious liver or kidney problems, your doctor may start you at the lowest dose (25 mg).
- Take VIAGRA about 1 hour before you want to have sex. VIAGRA starts to work in about 30 minutes when you are sexually excited. VIAGRA lasts up to 4 hours.

Don't:

- Do not take VIAGRA more than once a day.
- Do not take more VIAGRA than your doctor tells you. If you think you need more VIAGRA, talk with your doctor.
- Do not start or stop any other medicines before checking with your doctor.

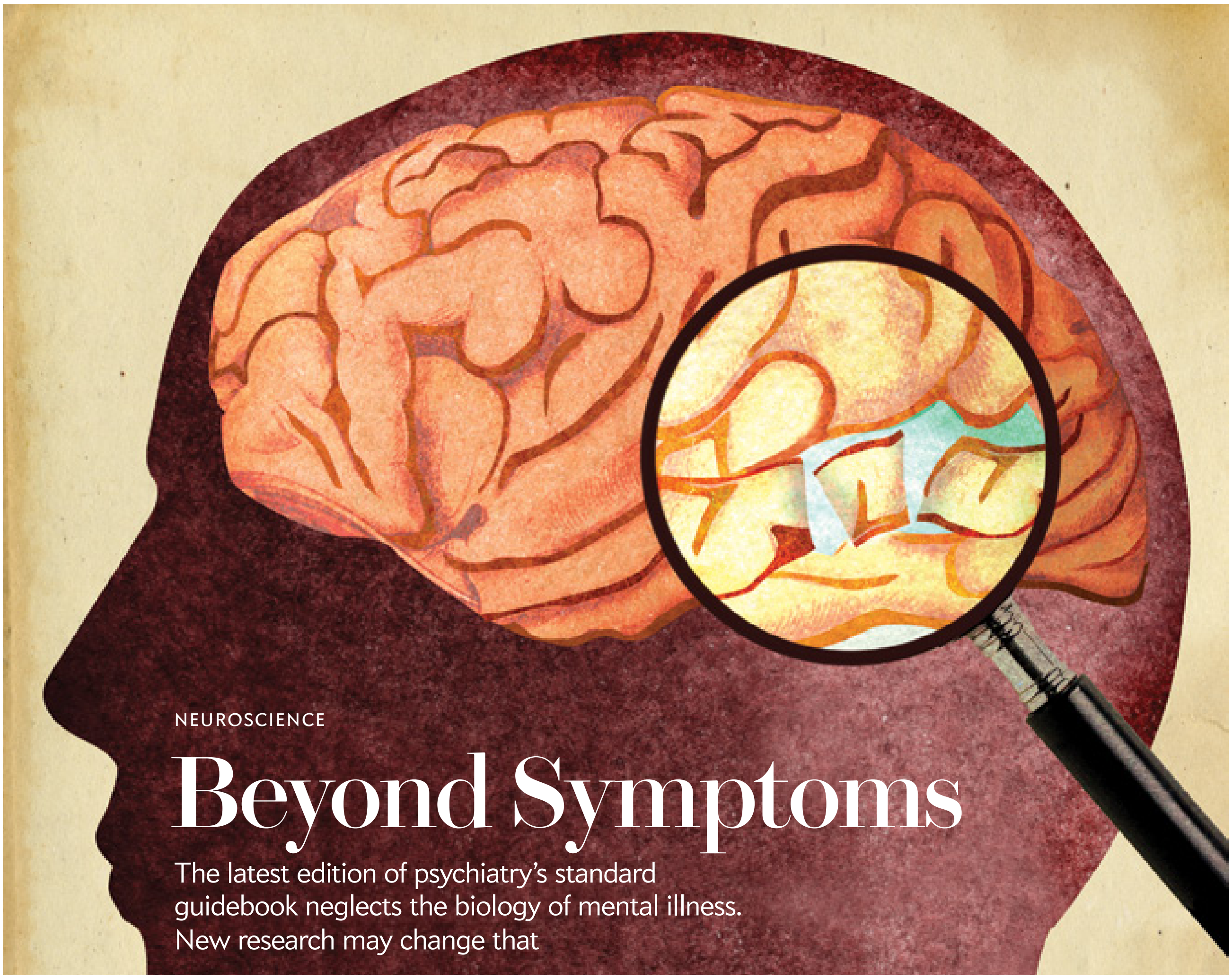
NEED MORE INFORMATION?

- This is only a summary of important information. Ask your doctor or pharmacist for complete product information OR
- Go to **www.viagra.com or call (888) 4-VIAGRA (484-2472).**

Pfizer Helpful Answers®
Filling a need for prescription assistance

Need help paying for your Pfizer medicines? Pfizer Helpful Answers® may be able to help, regardless of your insurance situation. Learn how at www.PHAHelps.com

Distributed by:
Pfizer Labs
Division of Pfizer Inc., NY, NY 10017
Rx Only
Printed in the USA.
VGIF Rev 6 01/13



NEUROSCIENCE

Beyond Symptoms

The latest edition of psychiatry's standard guidebook neglects the biology of mental illness. New research may change that

This month the American Psychiatric Association (APA) will publish the fifth edition of its guidebook for clinicians, the *Diagnostic and Statistical Manual of Mental Disorders,* or *DSM-5.* Researchers around the world have eagerly anticipated the new manual, which, in typical fashion, took around 14 years to revise. The *DSM* describes the symptoms of more than 300 officially recognized mental illnesses—depression, bipolar disorder, schizophrenia and others—helping counselors, psychiatrists and general care practitioners diagnose their patients. Yet it has a fundamental flaw: it says nothing about the biological underpinnings of mental disorders. In the past, that shortcoming reflected the science. For most of the *DSM*'s history, investigators have not had a detailed understanding of what causes mental illness.

That excuse is no longer valid. Neuroscientists now understand some of the ways that brain circuits for memory, emotion and attention malfunction in various mental disorders. Since 2009 clinical psychologist Bruce Cuthbert and his team at the National Institute of Mental Health have been constructing a classification system based on recent research, which is revealing how the structure and activity of a mentally ill brain differs from that of a healthy one. The new framework will not replace the *DSM,* which is too important to discard, Cuthbert says. Rather he and his colleagues hope that future versions of the guide will incorporate information about the biology of mental illness to better distinguish one disorder from another.

Cuthbert, whose project may receive additional funding from the Obama administration's planned Brain Activity Map initiative, is encouraging researchers to study basic cognitive and biological processes implicated in many types of mental illness. Some scientists might explore how and why the neural circuits that detect threats and store fearful memories sometimes behave in unusual ways after traumatic events—the kinds of changes that are partially responsible for post-traumatic stress disorder. Others may investigate the neurobiology of hallucinations, disruptions in circadian rhythms, or precisely how drug addiction rewires the brain.

The ultimate goal is to provide new biological targets for medication. "We understand so much more about the brain than we used to," Cuthbert says. "We are really in the middle of a big shift."

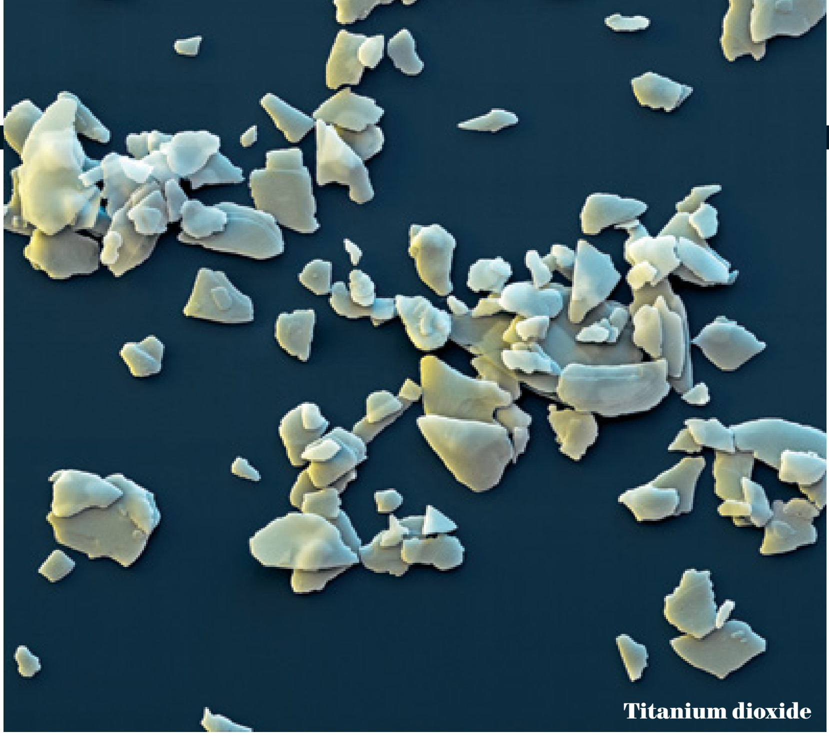
—Ferris Jabr

Illustration by Ellen Weinstein

TECHNOLOGY

The Tiniest Bites

Doughnuts dusted with nanopowder? Blech! But is it harmful?



Titanium dioxide

There are nanosize particles in your food. Does this make you nervous?

Food companies have been interested in using nanotechnology to intensify flavors and make products creamier without added fat. But that has nothing to do with the titanium dioxide nanoparticles, less than 10 nanometers across, that were found recently in the powdered-sugar coating on doughnuts from Dunkin' Donuts and the now defunct Hostess. The microscopic flakes may have ended up there by happenstance—a result of the milling process used on the powdered-sugar mixture. We may have been ingesting them for years.

The environmental health group As You Sow found the nanoparticles in samples it sent to an independent laboratory. The tiny particles are worrisome, health advocates argue, because they are so small they can enter cells throughout the human body more readily than larger particles. If the particles are toxic in cells, they could cause trouble. So far no one knows whether these titanium dioxide particles or other nanomaterials in food or food packaging pose a health risk. The European Union requires foods that contain nanomaterials to be labeled, and the U.S. Food and Drug Administration has said it did not have enough information to determine if such products are safe.

Many companies appear not to know if their food contains nanoparticles or may be reluctant to submit to scrutiny. As You Sow attempted to survey 2,500 food companies for its report. Only 26 responded, and only two had specific policies regarding nanoparticles. Ten of the companies did not know whether they used nanoparticles, and two admitted to intentionally incorporating them in packaging. "We plan to work with scientists to understand if they will leach into food," says As You Sow chief executive Andrew Behar.

As You Sow is now trying to crowdfund further testing of M&Ms, Pop-Tarts, Trident gum and other comestibles—all likely to employ the same titanium dioxide found in the doughnuts and equally likely to be unintentional. "What are the health implications of nanomaterials that we know are in our food supply?" Behar asks. "How do we set up a system to make sure that they are safe?" As You Sow argues that nanoparticles of any kind have no business in food until safety testing is done. *—David Biello*

MEDICINE

A Cure Is Born

A fetus's unique immune system may help it cope with HIV

Earlier this year doctors reported that they had cured, for the first time, a child born to an HIV-infected mother after a swiftly administered course of drugs. If the advance holds up to further scrutiny (some wonder if the child was perhaps never infected or is not actually cured), it may be at least partly because the immaturity of a newborn's immune system enables it to cope better with HIV, says Joseph M. McCune, a professor of experimental medicine at the University of California, San Francisco, who was not involved in the research.

Previous work shows that the inflammatory response mounted by an immune system under threat can make the HIV virus multiply more readily. The inflammation brings more immune cells to the site of injury or infection, increases cell division and boosts the production of proteins called cytokines that cells use to communicate. The HIV virus has evolved to take advantage of each of these processes—because the virus spreads from cell to cell, rapid division nearby helps HIV replicate quickly, McCune says.

Inside the womb, a fetus's immune system is set to "calm" because it "doesn't want to make an inflammatory response against the mother," McCune explains. That "do not respond" signal may hold over to the first few days of the newborn's life, robbing the new HIV infection of additional fuel. The delay, combined with a short course of aggressive treatment, may give the body enough of a head start to eradicate the virus on its own.

The case, reported in March at the Conference on Retroviruses and Opportunistic Infections in Atlanta, raises multiple questions, and the National Institute of Child Health and Human Development has put out a call for research proposals related to the new findings. "Now people are aware of this and can bring other children to our attention," says Lynne Mofenson, chief of the institute's Maternal and Pediatric Infectious Disease Branch. "Within a year or two we hope to have better answers." *—Marissa Fessenden*

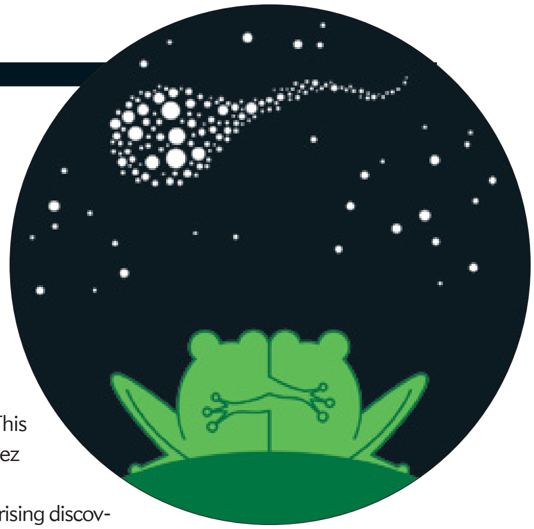
SCIENCE SOURCE

FURTHER READINGS AND CITATIONS ScientificAmerican.com/may2013/advances

ASTRONOMY

Tadpoles in Space

Exotic galaxies provide snapshots of the Milky Way's youth



Giant spiral galaxies such as Andromeda and the Milky Way outshine and outweigh most of their galactic peers. They grew so large both by swallowing lesser galaxies and by grabbing gas from the space around them. New observations of exotic "tadpole" galaxies are shedding light on how the Milky Way assembled its most luminous component: the starry disk that is home to the sun and Earth.

First spotted in the 1990s, tadpole galaxies sport bright heads, which spawn brilliant new stars, and long, faint tails. Most tadpoles are billions of light-years distant, meaning they were more common when the universe was young. From such great distances, though, studying the odd galaxies is difficult.

Thus, Jorge Sánchez Almeida of the Astrophysics Institute of the Canary Islands and his colleagues scrutinized seven rare tadpoles that happen to lie much closer, within 600 million light-years of Earth. Analyzing light from telescopes on the island of La Palma, the astronomers determined the speeds of different parts of each galaxy, demonstrating that most of the tadpoles rotate, just as the disks of spiral galaxies do.

The astronomers also got a shock, however. In the Milky Way, oxygen abounds most in the bright star-rich central regions where massive stars forge oxygen and expel it when they explode. Yet the tadpoles exhibited the opposite oxygen pattern: their brilliant heads had less oxygen than their faint tails. "This is very strange," Sánchez Almeida says.

To explain the surprising discovery, published April 10 in the *Astrophysical Journal,* the astronomers invoke pristine intergalactic gas, little altered since the big bang, the primordial inferno that produced only elements much lighter than oxygen. In this scenario, a stream of oxygen-poor gas slams into one section of a nascent galactic disk and triggers the birth of bright new stars, which light a tadpole's head but harbor little oxygen.

If this idea is right, celestial tadpoles resemble their terrestrial namesakes: they are primitive creatures that are growing larger. "The Milky Way could have done this," says team member Bruce Elmegreen of IBM Research, who thinks tadpoles show how, billions of years ago, giant spiral galaxies gathered gas from their surroundings and built their spinning disks of stars, which ultimately grew into galactic superpowers like the Milky Way. *—Ken Croswell*

Illustrations by Thomas Fuchs

ENTOMOLOGY

Ant Invasion!

In a fierce battle for dominance, Asian needle ants are displacing other species and threatening U.S. ecosystems

The Argentine ant has spread to every continent except Antarctica, overwhelming native ants with its sheer numbers and fierce battle tactics. But this invader may have met its match in a recent U.S. arrival: the Asian needle ant. The cross-species face-off, a surprise to entomologists, could harm ecosystems where the battle lines are drawn.

Although invading ants make up just a handful of the more than 12,400 described ant species in the world, they have an outsized impact on ecosystems, economies and human health. Invasive ants often kill, eat or outcompete native ant species that play key roles in their environment. Whereas many native ants are gardeners, tilling the soil and planting seeds, alien ants do not usually pick up the jobs of those they push out. The Asian-Argentine rivalry is a rare opportunity for researchers to observe an invasion in progress.

Scientists at North Carolina State University stumbled on the unfolding ant war several years ago. Eleanor Spicer Rice, an entomology graduate student at the time, was tracking a network of Argentine ant nests in an office park in Morrisville, N.C., and found a few nests of Asian needle ants. She remembers thinking that it was "really weird that another ant could be nesting within the Argentine territory." (Argentine ants do not tolerate competition.) Weirder still, the Asian ants were driving the others back.

The researchers wondered how the outnumbered Asian ants were gaining a leg (or six) up. Cold-tolerance tests in the laboratory hinted that they were better adapted to the temperate North Carolina climate than the tropical Argentine ants; whereas the Asian needle ants shook off their winter sluggishness as early as March, the Argentine ants did not resume activities until late April or early May, the entomologists reported on February 8 in *PLOS ONE*. If so, Asian needle ants may be winning the war in North Carolina simply because the state is at the northern limit of the Argentine ant's range.

An Asian needle ant takeover would be bad news for Argentine and native ants and for humans. The Asian ant's burning sting can induce a life-threatening allergic reaction in sensitive individuals. "More people are allergic to Asian ant stings than to honeybee stings," Spicer Rice says.

To figure out how far the Asian ants are spreading, North Carolina State researchers have turned to citizen scientists. Their project, School of Ants, asks volunteers to find insects in cities and suburbs and send in specimens. To date, they have found Asian ants from New York City to Washington State.

As climate change, travel and disrupted habitats offer more opportunities for invading ants, the species wars will continue. *—Marissa Fessenden*


ALEX WILD

Asian needle ants (*brown*) attacking a termite

COMMENT AT ScientificAmerican.com/may2013

ENERGY

Heated to the Core

A trove of decades-old documents could speed discovery of geothermal wells

Geothermal energy is cheap, clean and constant. Over the next 50 years the U.S. Geological Survey estimates that a new technology known as an enhanced geothermal system (EGS) could supply about 10 percent of the country's current electrical capacity. Unlike conventional power plants that rely on near-surface hydrothermal systems such as springs and geysers, EGS can draw energy from depths of up to three to five kilometers.

Yet drilling for the wells is a financially risky endeavor. Two to five out of every 10 geothermal wells prospected end up dry. Companies need good data on the distribution and quantity of geothermal energy in the upper part of the earth's crust. But apart from using volcanoes as reference points, the data have been hard to come by.

Perhaps not for long, however. The Arizona Geological Survey is leading a coalition of universities and national agencies on a project to find and digitize data from extensive surveys of geothermal resources that were funded in the 1970s, 1980s and 1990s but that have been sitting unused in state and federal filing cabinets for decades. The coalition expects to have as many as three million wells in the system by the end of 2013, and Microsoft Research is using the data to build 3-D interactive maps.

—*William Ferguson*

SMALL TALK

Exploiting Physics for Serious Laughs

The co-executive producer of CBS's hit comedy and author of the forthcoming book *Does Santa Exist? A Cheerful Philosophical Investigation* talks about how his show helps to humanize scientists

PROFILE

Eric Kaplan

TITLE
Co-executive producer, *The Big Bang Theory*

LOCATION
Los Angeles

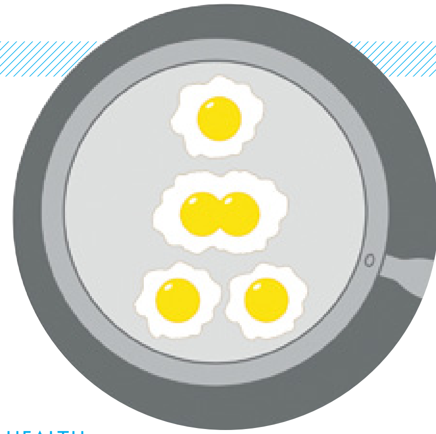
Is science education an important part of* The Big Bang Theory, *which revolves around two physicist roommates and their friends?
It bears a family resemblance to science education. What we try to do is to make people feel that scientists are real people and that science is something that real people, like themselves, could do.

How do you balance scientific discourse with character development?
We try not to make too strong a dualism between the two because our characters are people who care passionately about science. For example, we had a fight between Sheldon [a main character], who is a physicist, and his girlfriend, Amy, who is a neuroscientist. And the content of the fight got pretty philosophical because he said, "My research is intrinsically more important than yours because reality is physical, and the physical will ultimately explain biology and therefore explain the human brain." And she said, "My research is more fundamental than yours because when you're doing physics, something is going on in your brain, which my biology will be able to understand." And then they broke up. All you really need to know is that she was saying she's smarter than he is, and he was saying that he's smarter than she is—the emotional reality of what was going on.

For the most part, the show's writers don't have science backgrounds. What do you do to prepare?
We read science journalism, and we familiarize ourselves as much as we can with things that our characters would be concerned with. For example, I was listening to an NPR story about the neuroscience behind habit formation and habit extirpation. That would be an interesting thing to deal with. And we have a consultant who is an actual physics professor at U.C.L.A.—David Saltzberg—so we run stuff by him.

Is there any rhyme or reason to the animations of atoms that break up the scenes? I think I noticed lithium once.
I think I asked the same question when I showed up. I was like, "Hey, is that lithium?" And the answer I was given was, "Yes, it is lithium." But it's not [there] because lithium is an antidepressant or anything like that.

—Erik Vance



HEALTH

It's Your Food Talking

Meals alter how cells communicate

It's not very appetizing to think of food as a cocktail of hormones, but it may help explain how diet affects health. "It's really clear," says Donald Jump, a biochemist at Oregon State University, "that food is just a pile of biochemicals."

The biochemicals in a cookie or a piece of broccoli can elicit reactions from human cells that are similar to that of hormones, write Randy J. Seeley and Karen K. Ryan of the University of Cincinnati in the February 22 *Science*. Hormones are chemicals that travel from one part of the body to another and instruct targeted cells to produce a chemical or action.

For instance, in 2010 a team of researchers in California and Japan showed that omega-3 fatty acids from food bind to a specialized protein called GPR120 that studs the surfaces of fat and muscle cells. When an omega-3 fatty acid attaches to the protein like a key in a lock, GPR120 sets off a chain reaction that ultimately protects the body against weight gain and inflammation.

Both weight gain and inflammation have been implicated in type 2 diabetes, and Seeley speculates that food choices aimed at enhancing the cellular process triggered by GPR120 and the like might help protect against the disorder.

Fatty acids are not the only hormonelike food elements. Amino acids can activate a chain reaction of events in cells that control cell division and influence the activity of insulin. Vitamin D and other vitamins are involved with the body's immune response. The receptor activated by omega-3 fatty acids is part of a family of proteins called G-protein coupled receptors that convey signals from outside the cell to the interior. Scientists know the specific functions of many members of that family, but they still do not know which molecules turn on some of the receptors, Seeley says.

The missing keys to those locks could be found in food. Translating research findings into clear dietary recommendations, Jump says, will be "a challenge." *—Marissa Fessenden*

COURTESY OF ERIC KAPLAN

COMMENT AT ScientificAmerican.com/may2013

Best of the Blogs

EVOLUTION

Yes, We're Related

Meet the first placental mammal

They may run, swim or fly. They may weigh less than a penny or more than a dozen school buses. From humans to whales to bats, the placental mammals—so named for the placenta that nourishes the fetus during development—are mind-bogglingly diverse. (The placental mammals are one of three major groups of mammals; the other two are the egg-laying monotremes and the pouched marsupials.) For years researchers have been attempting to piece together when the placentals originated and when the group's modern orders, such as the primates and the bats, first emerged. Now an analysis of thousands of anatomical features of modern and extinct mammals, as well as molecular sequences from living species, is helping them to do just that. The study also hints at what the ancestral placental mammal—the one that ultimately gave rise to creatures as disparate as tree sloths and sea lions—looked like.

Previous attempts to reconstruct the evolutionary history of mammals yielded conflicting scenarios. Fossil evidence suggested that the placentals burst onto the scene shortly after a dinosaur-snuffing asteroid slammed into the earth around 65 million years ago. Studies that instead rely on molecular data indicate that the group appeared as early as 100 million years ago, when dinosaurs were still thriving.

The new study controverts the early origin model, concluding that the placentals originated after the mass extinction event, with the first modern groups evolving two million to three million years later—after the breakup of the supercontinent Gondwana. Maureen A. O'Leary of Stony Brook University and her collaborators described their findings in the February 8 *Science.*

Perhaps the coolest part of the paper is the bit where the authors reconstruct the characteristics of the hypothetical placental ancestor (*above*)—a tree-climbing, insect-eating beastie that weighed between six and 245 grams and gave birth to one hairless baby at a time, among other fascinating details. I'd love to see what other hypothetical ancestors look like—last common ancestor of chimps and humans, anyone? *—Kate Wong*

Adapted from Observations at blogs.ScientificAmerican.com/observations

ASTROPHYSICS

Space Race

A comparison of the speediest spacecraft

Of all the spacecraft humans have launched, there have been some impressively fast movers. But which holds the record? Apart from the wow factor, it's an interesting yardstick for gauging our capacity to explore the cosmos, from familiar planets to the icy depths of space. But it's not always an easy quantity to evaluate. For one thing, launch velocities differ from eventual cruise velocities. They also depend on what you measure velocity *relative* to. Far away from Earth, it makes more sense to work with heliocentric (sun-relative) measurements.

The record holder for launch velocity is the New Horizons probe to Pluto and the Kuiper belt. Launched by NASA in 2006, it shot directly to a solar system escape velocity, which consisted of an Earth-relative launch of 36,000 miles per hour, plus a velocity component from Earth's orbital motion. Altogether these factors set New Horizons barreling off into the solar system with an impressive heliocentric speed of about 100,000 mph.

In terms of pure heliocentric velocity, the current champions are two probes called Helios I and II that were launched in 1974 and 1976. They entered orbits that took them closer to the sun than the planet Mercury. The nearer you orbit to a huge mass like the sun, the faster you have to move, and both Helios crafts hit orbital velocities in excess of 150,000 mph.

They are not going to hold on to pole position for much longer, however. First, NASA's Juno probe to Jupiter will be arriving in the Jovian system in 2016 and will enter a polar orbit around the gas giant. But Jupiter weighs in at 317 times the mass of Earth. Falling deep into its gravity well will accelerate Juno to a velocity of about 160,000 mph relative to the planet before it can swing by, drop speed and get into its mission orbit.

In 2018 a new NASA mission—Solar Probe Plus—will be launched. Designed to come within 3.7 million miles of the sun, it will hit orbital velocities as high as 450,000 mph. To put that incredible figure into perspective, going this fast would get you from Earth to the moon in about half an hour. It is also about 0.067 percent the speed of light. *—Caleb A. Scharf*

Adapted from Life Unbounded at blogs.ScientificAmerican.com/life-unbounded

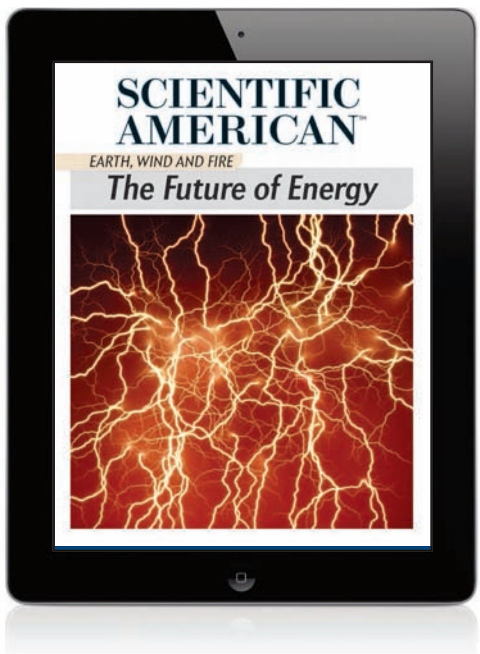
COURTESY OF CARL BUELL

COMMENT AT ScientificAmerican.com/may2013

EBooks that raise your tablet IQ

Science to enrich your life in a format to fit your lifestyle
From the Editors of Scientific American

Recent years have seen a lot of hype about Higgs. Does it exist? Have scientists really found it? Do we need to worry about it creating a black hole? This eBook chronicles the continuing search for the elusive Higgs boson: the theories, the search and the ongoing questions. In essence, what you need to know to separate Higgs from hype.



For our continued survival, humanity has no choice but to change the way we power our lives. But how? Renewable energy comes in many forms, each with its own merits and drawbacks. This eBook examines sustainable energy technology from wind turbines to geothermal plants to hydroelectric power to alternative sources of fuel.

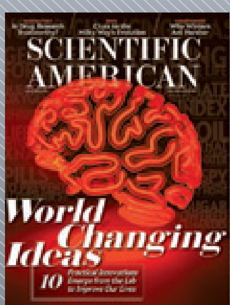
What is time? Time is precious. Time is money. Time is relative. Perhaps one of the reasons we have so many idioms for time is because it is so difficult to define. This eBook summarizes what science has discovered about how time pervades both our physical and our inner mental worlds.

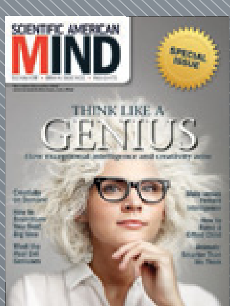
LOOK FOR THESE OTHER TITLES

Storm Warnings: Climate Change and Extreme Weather
Beyond Human: A.I. and Genius Machines
Understanding Autism: The Search for Answers
Cyber Hacking: Wars in Virtual Space
Lights Out: How It All Ends

Download Scientific American eBooks now, available wherever eBooks are sold.
| books.scientificamerican.com/sa-ebooks |

SCIENTIFIC AMERICAN™





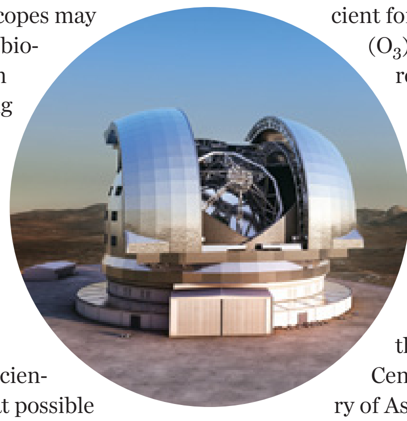
SPACE

Anybody Home?

Next-generation telescopes could pick up hints of extraterrestrial life

Even as astronomers work toward the hotly anticipated milestone discovery of an Earth-like twin orbiting another star, researchers are already asking what it will take to detect the existence of extraterrestrial life on such a planet. The good news is that observatories now being planned could have a shot. Yet it is hardly a lock.

The next generation of giant, ground-based telescopes may be able to tease out biomarker signals from the starlight filtering through exoplanetary atmospheres, according to research recently published in the *Astrophysical Journal* and in *Astronomy & Astrophysics*. The two groups of scientists calculated what possible biomarkers might be detectable with the planned European Extremely Large Telescope (E-ELT) (*above*), which would dwarf the twin Keck telescopes on Mauna Kea in Hawaii that are now on the cutting edge of astronomy.



COURTESY OF L. CALÇADA ESO

Living organisms on Earth leave numerous chemical imprints on the environment via, for instance, the production of oxygen by plants and bacteria, the release of methane during digestion, and the generation and consumption of carbon dioxide in the global carbon cycle. Measurements of those chemical species in an exoplanet's atmosphere could provide strong indications of the presence of life there.

Astronomers using the world's best telescopes have already identified specific atoms and molecules in the atmospheres of massive, highly irradiated exoplanets. To do the same for smaller planets in cooler orbits—objects from which photons are relatively scarce—will require much bigger telescopes and many years of observations.

With a high-resolution spectrograph to break down the collected light from an exoplanet into its component wavelengths, the E-ELT would, in principle, be able to spot oxygen gas in the atmosphere of a temperate, Earth-like world. The giant observatory may also be able to identify water, which is thought to be important but not sufficient for life as well as ozone (O_3), a molecule closely related to oxygen gas. "When we are sure there is ozone, we could be pretty sure that there is oxygen in the atmosphere," explains astrophysicist Pascal Hedelt of the German Aerospace Center and the Laboratory of Astrophysics of Bordeaux in France, who is the lead author of the *Astronomy & Astrophysics* study. Methane might also be detectable in some of the scenarios explored by Hedelt's group.

The connection between chemistry and life is not always straightforward, however, and the detection of oxygen, methane or some other biologically relevant molecule will require careful interpretation. Venus has an ozone layer, and Mars, according to research that is somewhat controversial in the planetary science community, releases occasional plumes of methane. Yet no solid evidence indicates that either planet hosts any microbes. "Only finding oxygen in principle is not enough," says Ignas Snellen of Leiden University in the Netherlands, who led the *Astrophysical Journal* study. Regarding future exoplanet studies, Snellen cautions, "You really need to characterize the atmosphere as a whole."

—John Matson

COMMENT AT ScientificAmerican.com/may2013

RICHARD HERRMANN *Getty Images*

CONSERVATION

Tailing Tuna

Cesium from Fukushima may help scientists track wildlife

Traces of radiation from Japan's earthquake-damaged Fukushima Daiichi nuclear power plant are showing up in the muscles of bluefin tuna off California. Although this sounds like bad news, the levels are too low to harm humans or fish but just high enough to help conservation scientists track and protect the overfished species.

Last spring Dan Madigan, a doctoral student at Stanford University, and his colleagues found traces of cesium 137 and cesium 134 in the flesh of bluefin tuna caught off the San Diego coast, which the fish probably picked up by feeding on contaminated plankton and small fish near Japan. They then devised a way of using the half-life of radioactive isotopes to study the fish. Cesium 134 has a half-life of 2.1 years; cesium 137 has a half-life of 30.1 years. The scientists calculated the ratio of the two isotopes in each fish to see if it would reflect how recently the migrants had arrived. (A higher ratio of 134 to 137 would indicate a more recent immigrant.)

The results jibed with what scientists knew about the fish: Pacific bluefin spawn in waters surrounding Japan and spend the first year of their lives foraging there before either staying put or migrating to the California coast to fatten up for mating. Madigan's team found that all fish aged 1.6 years or younger were migrants and that the trip from Japan had taken around two months, which validated their approach. They reported their results in *Environmental Science & Technology* in March.

The new technique shows promise for tracking the movement of other Pacific migratory species, including whales, turtles and sharks. Although cesium 134 levels will soon be too low to be useful, Madigan's team has correlated cesium levels with those of longer-lived stable isotopes such as carbon and nitrogen so that researchers will be able to use them as proxies. "One method is finite, and one is infinite," Madigan says. "Once you've hammered down the relationship, you can just use the infinite one in the future." *—Marissa Fessenden*

PATENT WATCH

Human emotion metrics for navigation plans and maps: Imagine choosing not just the quickest path to your destination but the one that is most likely to lift your mood. Patent no. 8,364,395 fuses advances in mapping and traffic data with those in mood detection to form an emotionally intelligent navigation system.

Route-planning devices and maps already allow users to choose a path that avoids tolls or traffic jams. And some technologies can gauge mood: microphones detect vocal stress in drivers asking for directions or screaming expletives; sensors detect a driver's pulse and sweaty palms on the steering wheel; and software mines social-media streams for users' emotions and locations.

A new device, designed by IBM researchers, could help tourists navigate unfamiliar cities, avoiding protests and road-rage incidents but taking in buzz-generating restaurants or tranquil scenery. Emoticons displayed along the routes would serve as guides.

The device factors in recent history. "You can choose a destination where people are happiest now or where people over the last week" have been happy, says co-inventor Paul B. French, a systems architect at IBM. If an area cheered visitors up, the system would classify the route as mood-enhancing. "The change of mood," he says, "is key." *—Marissa Fessenden*

ASTRONOMY

Preventing the Next Chelyabinsk

More asteroid-detecting telescopes are coming soon

In the next few years NASA will amass reams of new data about near-Earth objects (NEOs), including asteroids and comets. Unfortunately, nothing is likely to protect us from a meteor the size of the one that barreled into the sky over the Russian city of Chelyabinsk (*below*) in February, injuring more than 1,000 people. That 17-meter object was too small to be systematically tracked—asteroid spotters naturally focus on the largest objects that could cause the most mayhem. Fortunately, impacts on the scale of Chelyabinsk occur only once a century, so perhaps humankind will have figured out even better techniques by then.

Here is a rundown of some of the best tools that researchers currently have for asteroid detection and defense:

Since the mid-2000s the Catalina Sky Survey has been the leading project for near-Earth object detection and now discovers about 600 NEOs every year from telescope sites in Arizona and Australia. It has helped NASA reach its goal of cataloguing 90 percent of all NEOs more than one kilometer in diameter.

The first of four planned Panoramic Survey Telescope and Rapid Response System (Pan-STARRS) telescopes in Hawaii recently came online and is now the second-leading NEO search in existence, in terms of objects detected per year. It should help discover many asteroids with diameters in the hundreds of meters, but the bulk of smaller objects will remain out of reach.

The Large Synoptic Survey Telescope (LSST), planned for the end of the decade in Chile, will be a survey instrument of astonishing capability. The 8.4-meter telescope, equipped with a three-gigapixel digital camera, will eventually catalogue the vast majority of much larger objects—those 140 meters and up in diameter—thereby meeting NASA's next asteroid-detection goal.

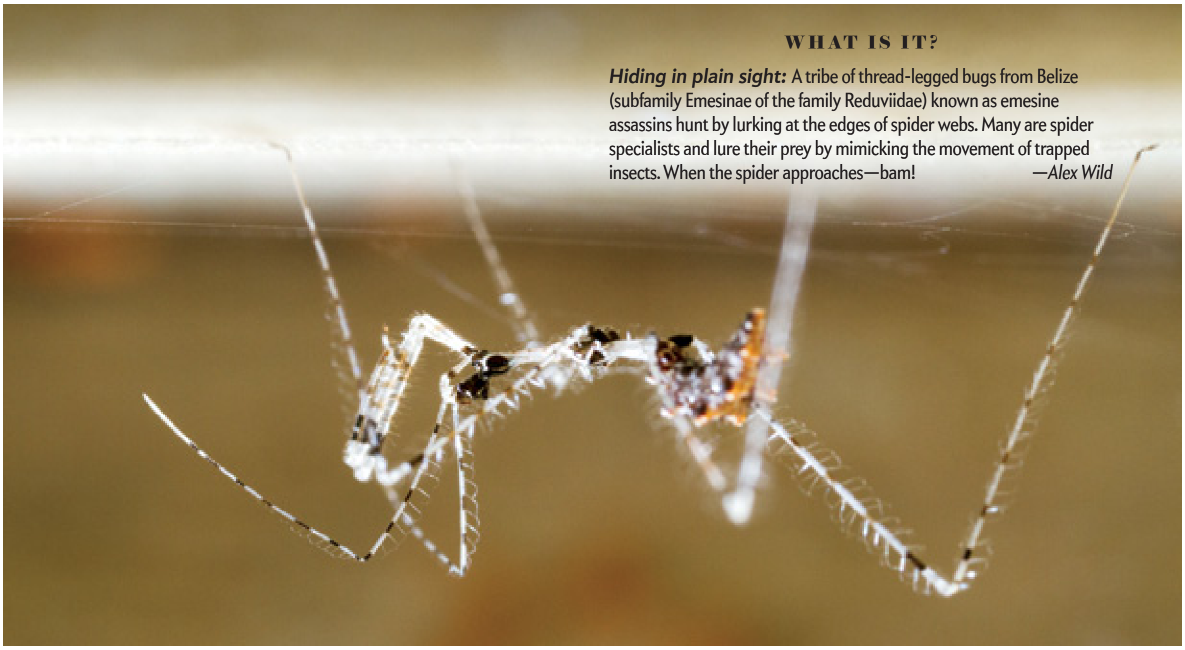
The Asteroid Terrestrial-Impact Last Alert System (ATLAS), due in 2015, has the goal of detecting asteroids in time for threatened areas to be evacuated. Planners estimate that the series of small Hawaii-based telescopes could identify a 50-meter "city killer" one week ahead of possible collision.

The nonprofit B612 Foundation recently unveiled plans to build the Sentinel space telescope, which would scan the inner solar system from an orbit similar to the planet Venus. It would be launched in 2018 and would make quick work of the truly dangerous asteroids out there, with the goal of cataloguing 90 percent of NEOs bigger than 140 meters over its 5.5-year mission. —*John Matson*

Meteor damage

GETTY IMAGES

COMMENT AT ScientificAmerican.com/may2013

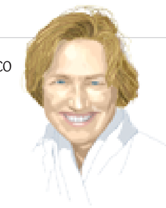


WHAT IS IT?

Hiding in plain sight: A tribe of thread-legged bugs from Belize (subfamily Emesinae of the family Reduviidae) known as emesine assassins hunt by lurking at the edges of spider webs. Many are spider specialists and lure their prey by mimicking the movement of trapped insects. When the spider approaches—bam! *—Alex Wild*

ALEX WILD

Deborah Franklin is based in San Francisco and has reported on science and medicine for NPR, the *New York Times, Fortune* and *Health Magazine.*



Good Bacteria for Bad Breath

Curing halitosis requires the right balance of oral microbes

Most adults have bad breath occasionally, particularly when their mouth dries out after, say, a full night's sleep or a long, dehydrating plane flight. About 25 percent of people worldwide, however, have chronic foul breath. Researchers around the world figured out years ago that gas-emitting bacteria on the tongue and below the gum line are largely responsible for rotten breath. But determining how best to eradicate these microbes' tenacious odors has been difficult.

Solutions to date offer only temporary relief. Even scrupulously skipping onions and garlic, swishing mouthwash after every meal, and brushing and flossing one's teeth until they gleam like pearls will probably not sweeten a case of stubbornly stinky breath. Lightly scraping away any coating on the tongue can greatly improve the fragrance of one's breath for at least a few hours. Certain bacteria-slaying mouthwashes provide short-term freshness, too, although many produce unpleasant side effects, such as a tingling sensation in the mouth.
Lately some scientists have developed innovative mouth rinses that neutralize the rancid compounds produced by bacteria.

Recent evidence from international research suggests, however, that the most effective strategy for beating back bad breath may be more about nurturing helpful bacteria in the mouth than about destroying the offending germs and their by-products. Instead of singling out ostensible culprits, microbiologists are now shifting their focus to entire communities of microbes on the tongue, gum and teeth to figure out why some people have a sweeter-smelling oral village than others.

BREATH'S CHEMICAL CODE

BAD BREATH has, of course, plagued humans for ages. Young girls, Hippocrates advised, should regularly rinse their mouths with wine, anise and dill seed. By the early 1970s Joseph Tonzetich of the University of British Columbia had begun to tackle the problem with technology. He used his lab's gas chromatograph, a machine that separates a complex gaseous bouquet into its constituent compounds, to tease out reeking breath's signature chemicals.

Sulfur compounds that easily vaporize were among the stinkiest chemicals Tonzetich identified in bad breath, especially hydrogen sulfide, which smells like rotten eggs, and methyl mercaptan, which smells like rotten cabbage. Since then, scientists have detected around 150 molecular components of human exhalations, many of them putrid. Dimethyl sulfide (think rotten

GREG CEO *Getty Images (mouth)*; LEFT, TOP TO BOTTOM: SCIENCE SOURCE; HAZEL APPLETON *Health Protection Agency Center for Infections/Science Source*; LINDA M. STANNARD *University of Cape Town/Science Source*; RIGHT, TOP TO BOTTOM: KARI LOUNATMAA *Science Source*; A. BARRY DOWSETT *CAMR/Science Source*

seaweed) and the tellingly named cadaverine, putrescine and skatole are just a few such pungent molecules. Still, hydrogen sulfide and methyl mercaptan stand out: in study after study, the higher the levels of these two molecules in breath, the more that breath offends the human nose.

These smelly compounds are waste products released by the millions of bacteria feasting on particles of food and tissue in our mouth. Above the gum line, gram-positive species, which have relatively simple cell walls, dominate dental plaque—the living film of bacteria coating teeth. *Streptococcus mutans* and other sugar-loving gram-positives spew acid and dissolve enamel but are not heavy producers of foul-smelling compounds. In contrast, gram-negative bacteria—which have an extra cell wall layer—live mostly below the gum line and are much gassier. Some of these resilient bacteria, including *Porphyromonas gingivalis, Treponema denticola* and *Prevotella intermedia,* thrive in gaps between the gum and tooth and in the mosh pit crevices of the tongue.

Common Scents

Researchers have identified around 150 different molecules in human breath, many of which offend the human nose. Here are what some of the more malodorous compounds smell like.

Rotten eggs
Hydrogen sulfide (H_2S)

Rotten cabbage
Methyl mercaptan (CH_3SH)

Garlic
Allyl mercaptan (C_3H_6S)
Allyl methyl sulfide (C_4H_8S)

Fish
Dimethylamine (C_2H_7N)
Trimethylamine (C_3H_9N)

BACTERIAL COLLEAGUES

GRAM-NEGATIVE BACTERIA on the tongue may produce most of the foul odors in breath, but recent research emphasizes that no single type of oral bacterium creates bad breath on its own. Mel Rosenberg, an emeritus professor of microbiology at Tel Aviv University, and his colleague Nir Sterer recently found, for example, that some strains of gram-positive bacteria secrete an enzyme that clips sugar molecules off the proteins found in food, which in turn makes those proteins more digestible for nearby gram-negative organisms. The more proteins the gram-negatives digest, the more odors they emit.

Such interactions illustrate why researchers are increasingly interested in oral ecology, viewing the mouth as a kind of densely populated tide pool. Fresh breath reflects a healthy mouth, which is not necessarily one that lacks “bad” bacteria, scientists are realizing, but rather one in which overlapping bacterial colonies hold one another in check.

Bacterial geneticists contributing to the Human Microbiome Project, funded by the National Institutes of Health, have so far identified about 1,000 species of bacteria that commonly inhabit human mouths. Yet one person’s particular mix of “bacterial colleagues,” as Rosenberg calls them, is probably quite different from another’s. “Each person has maybe 100 to 200 of those bacterial species colonizing their mouth at any given time,” says Wenyuan Shi, a microbiologist at the University of California, Los Angeles.

During birth our previously sterile mouth picks up some of our mother’s bacteria, and in childhood we quickly acquire new microbial colonizers. Studies suggest that a preschooler’s population of mouth microbes most closely mimics his or her primary caregiver’s. As the years go on, diet, stress, illness, antibiotics and other forces can shift the demographics of an individual’s microbial community—and change its collective aroma. When bacteria that release smelly compounds dominate, chronic bad breath may be one of the consequences.

Many current treatments do not improve oral ecology—in fact, they might make matters worse. Although some mouthwashes merely mask unpleasant odors, alcohol-based rinses sold in drugstores and prescription rinses containing chlorhexidine or other antiseptics target all oral bacteria, stinky and otherwise. Shi says that approach has several drawbacks. A chlorhexidine rinse, for example, may improve breath for as long as 24 hours but can temporarily change the taste of food. In one study, 25 percent of subjects experienced a tingling or burning sensation on the tongue after a week of use. Heavy use of rinses with alcohol can dry out the mouth, sometimes exacerbating bad breath. Further, wiping out too many of the mouth’s native bacteria could disrupt the usual checks and balances, making way for opportunistic species responsible for gum disease and other infections to move in and take over.

A number of researchers are now working on promising alternatives to basically carpet bombing all oral bacteria. Some new mouthwashes go after the stink rather than the stinkers with ions of zinc or other metals that bind and neutralize sulfur compounds. Rosenberg, who started his career as a petroleum microbiologist, has developed a two-phase oil-and-water rinse that temporarily reduces bad breath by sopping up some of the oral debris and microbes that toothbrushing, flossing and tongue scraping miss.

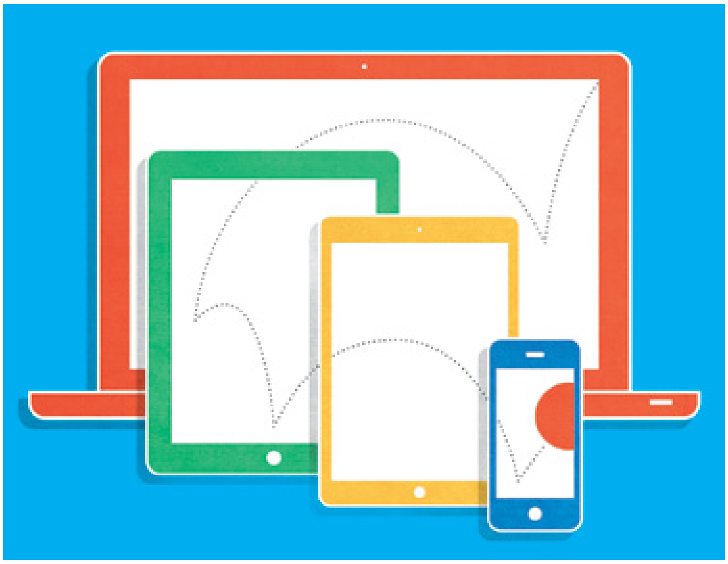
Other teams are investigating whether probiotics rife with a gram-positive bacterial strain known as *Streptococcus salivarius* K12 can fight halitosis. A common resident of the mouth and respiratory tract, *S. salivarius* K12 is benign and known to produce substances that deter harmful bacteria. In a recent study by researchers in New Zealand and Australia, volunteers gargled with a chlorhexidine mouthwash to clear their palate of many native bacteria and subsequently sucked on lozenges laced with K12. Seven and 14 days later they had much sweeter breath. Presumably K12 outcompeted its foul-smelling kin, opening up niches for less offensive species.

At U.C.L.A., Shi and his team are working on a mouthwash that contains a peptide—a chain of amino acids smaller than a protein—tailored to selectively kill *S. mutans,* the ringleader behind tooth decay. Researchers could develop an analogous peptide to weed out the bacteria behind bad breath, Shi says. A rinse containing such peptides might free up real estate on the tongue for less malodorous microbes, if used in moderation. Rinsing every day risks a sudden and drastic shift in oral ecology that could have unexpected repercussions.

Shi himself brushes and flosses daily but does not use a mouthwash or even a tongue scraper because his family assures him that his breath smells fresh. “I’m one of the lucky ones,” he says. “My goal is to help other people be lucky, too.” SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/may2013

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



The Strange Magic of Micro Movies

Why animated GIFs and other crude videos are taking over the Web

Since the invention of motion pictures, video science has proceeded steadily in a single direction: upward. Better resolution. Higher frame rates. Richer audio.

Yet online, something weird has been going on. The hot thing in video these days isn't big, sharp and smooth. It's tiny, jerky and often low-res and mostly silent.

EXHIBIT A: The animated GIF. This format—which creates small, looping, silent videos with limited colors—was invented by CompuServe in 1987. Before Flash, QuickTime, AVI or other modern video formats, the animated GIF was an early way to put moving images online. It popularized the dancing baby, the waving American flag, funny cats—and much of Myspace.

Weirdly, 26 years later, this ancient, limited format is still around. In fact, these jerky snippets are more popular than ever. They're the dominant currency on popular "What's cool online" sites such as Tumblr and Reddit. They're still passed around in e-mail signatures. It's baffling, really—as though the Betamax were suddenly making a comeback.

EXHIBIT B: The Nikon 1 cameras, that company's flagship midsize camera line. Their mode dials, which on most cameras have various scene presets, offer only four choices—and one of them is Motion Snapshot, which captures a one-second video clip without recording the sound. Somehow these cameras have become best sellers. Nikon must have known what it was doing.

EXHIBIT C: Vine, an iPhone app that lets you capture six-second videos and then post them via the app's own social network or on Twitter or Facebook.

Who would go for such a limited tool? Everybody. Vine became an instant sensation. Hundreds of thousands of its short videos flooded the Web, companies used it for ads and contests, and *The Daily Show with John Stewart* made fun of it.

What is going on? What happened to the quest for better, bigger, brighter videos?

THEORY 1: Technical limitations. Big, beautiful video takes up a lot of bandwidth, which costs money on your cell-phone plan and takes time to load on other devices. Small, jerky, short video gets the message across but loads almost instantly and doesn't run up your bill or waste your time.

Animated GIFs have another advantage: you can post them almost anywhere, even on comment boards and profile pictures. And after all these decades, they play in every browser and on just about every gadget on earth—which you can't say for more modern formats like Flash.

THEORY 2: Limitations foster creativity. Twitter is the standard for this concept: hard-coded limits force you to be more concise, more creative. Most people don't complain about Twitter's 140-character limit; they embrace it. That brevity is what helps make Twitter a force of nature.

Surely compression is a key to Vine's success. A six-second video may seem very easy to shoot, but it takes thought and ingenuity to tell a story in that time, and some of what people come up with are masterpieces. You can also compose a Vine video of many shorter shots, so some of the stop-motion Vine videos are especially impressive.

THEORY 3: Video is the wrong comparison. In the end, maybe the growing popularity of the short, crude video snippet is no mystery at all. True, these clips look limited when compared with the video images we see in theaters, on TV or even on YouTube—but maybe these aren't so much stripped-down movies as they are live-action photographs.

A photograph is intended to capture a single moment, to present it for thoughtful examination. In the end, that's what a one- or six-second looping video does so well—it's just that it expands the scope of the still image, explodes it to an almost infinite variety of new possibilities, moments and stories. Maybe the micro video is best considered an improvement on a still picture, not a downgrade from video.

Or maybe the online micro video is neither photo nor video but something in between, with artistic merits all its own. Maybe it's simply a new form of expression.

It just took us 26 years to recognize it. SA

SCIENTIFIC AMERICAN ONLINE
Watch 12 micro video apps that aren't Vine: ScientificAmerican.com/may2013/pogue

Illustration by Oliver Munday and James Bamford

Haven't seen our tablet edition? How strange...

Get closer to the leading edge of science and technology: experience the SCIENTIFIC AMERICAN Tablet Edition - available for iPad®.

Available on the App Store

TO RENEW
SCIENTIFICAMERICAN.COM/UPGRADE

TO SUBSCRIBE
SCIENTIFICAMERICAN.COM/TABLET


How to
Make
the Next
Big Thing
A Special Report on
THE FUTURE OF
MANUFACTURING

Manufacturing is order, intelligently applied.

Because nature does not present the world in the form we would like, we must reorder it. To create this new order, we need information about what that order is supposed to look like, knowledge about how to build it and energy to get it into shape. Many technological revolutions of the past have focused on the energy part of this equation—waterpower, the steam engine, the electric motor and the internal-combustion engine, to name a few.

The technological revolution under way now is not driven by energy, however. It is driven by information. A Boeing 747 or an iPhone is made mostly out of fairly common materials that are worth, at most, just a few dollars a pound. Yet the finished product sells for thousands of dollars per pound. Most of the value is in the information content. That is where the jobs and the livelihoods are going.

In his 2013 State of the Union Address, President Barack Obama spoke of "bringing jobs back" to the U.S., a phrase that suggests a return to a better past. The truth is that new jobs are not "coming back"—they are moving forward. Most manufacturing growth now takes place in China, India and other "developing" economies—helping to make these relatively poor regions of the world a little bit richer—but their machinery, materials and know-how must come from somewhere. The opportunity for advanced countries lies in building the high-tech tools needed to make more tools and in supplying the programming, finance, logistics and marketing required to intelligently manipulate matter. In this way, manufacturing will continue to pack more information and knowledge into less matter while using less energy, making the world to order.

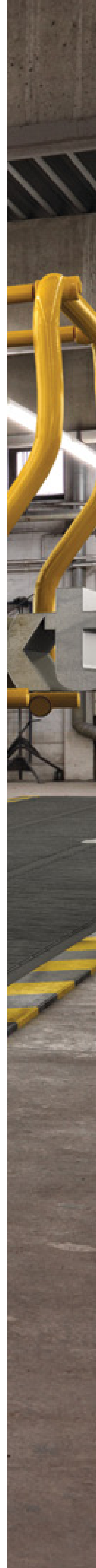
—Ricardo Hausmann

What's Inside:

***Ricardo Hausmann** is director of the Center for International Development and professor of the practice of economic development at Harvard University.*

For an extended version of this essay, go to ScientificAmerican.com/may2013/manufacturing

Illustration by Justin Metz




baxter
rethink robotics

My Boss the Robot

Humans and robots will work elbow to elbow on the shop floor, but you'll be surprised by who's giving the orders

By David Bourne

THE MINUTE MICHAEL DAWSON-HAGGERTY burst into my office, clad in a blackened lime-green welding jacket and wearing a big smile, I knew he and his partner had won. Their test: weld a metal space frame for a Humvee—a military vehicle ubiquitous in Iraq and Afghanistan—faster than a team of experts with decades of experience.

This was Dawson-Haggerty's first professional job—he had just completed his master's degree and joined the engineering staff at Carnegie Mellon University's Robotics Institute—and it is fair to say that he had been a little nervous as he got started. Truth be told, I was more worried about his partner, who was reliable enough but generally lacked people skills.

The cohort on this project was a robot, similar to those huge industrial machines we typically associate with assembly-line

TO SERVE HUMANS: Baxter has two arms and an array of sensors that make it easier to program and safer to work with than previous industrial robots.

work at Ford or General Motors. Yet whereas those mechanical monsters operate inside cages to keep humans safely apart from unforgiving automated thrusts, we modified Spitfire—our 13-foot-tall, one-armed welding robot equipped with a laser for an eye—to work right alongside a person. And instead of Spitfire taking orders from Dawson-Haggerty, the team tended to work the other way around: the robot dictated the next steps, with the hard work of positioning and welding divided between Dawson-Haggerty and Spitfire according to who could most efficiently complete the task. The robot, not the human, often called the shots.

DYNAMIC DUO: Smart division of labor improves efficiency. Here the dexterous human, Carnegie Mellon engineer Michael Dawson-Haggerty, sets a piece of steel into place (*left*) before the robot makes precise welds (*right*).

With the work so split, Dawson-Haggerty and his robot partner built the frame in 10 hours for $1,150, including raw materials and labor. The experts we had hired to serve as our control group performed the same task in 89 hours and billed us $7,075.

The economic consequences of a human's ability to work with a robot, and vice versa, are potentially enormous. Factories could could do away with painstakingly configured assembly lines, saving billions in equipment setup costs. Need to modify a popular product? Human-robot teams can create custom versions of anything from electronics to airplanes without the need for expensive retooling. The technology will allow companies to quickly respond to consumer demand, updating products in cycles measured in weeks, not years. And workers should find rewarding the ever changing challenges of the factory floor. For these reasons and more, we need to realize that robots may ultimately be more effective as supervisors, not slaves.

KEEPING YOUR HEAD

THERE IS ALWAYS a lot of discussion surrounding what, exactly, a "robot" is. The robotics research community defines them as machines that can sense, think and act autonomously. This is not quite right—your house's thermostat can do all these things, yet you would not classify your house as a robot. The difference is that your thermostat is just a small part of what your house does. Only when "robotic" functions are used in service of an object's core responsibility can the object itself be considered a robot. For example, when a self-driving car uses sensors and artificial intelligence to enable transportation—a car's essential function—it becomes a robot.

Manufacturers have deployed robots for more than half a century to improve efficiency through automation. Yet robots have been special-purpose machines—excellent at, say, welding a certain set of joints on every car coming down an assembly line. Humans have done the organization, setting up the assembly line to capitalize on their robots' strength and precision.

The process works well for products such as cars that come down assembly lines by the tens of thousands. Yet with the rise of custom manufacturing, where suppliers create small batches of products on demand, the time it takes to set up a process such as welding or machining becomes a major bottleneck. It takes far too long to prep the robot for its job—sometimes months. People must plan the welding sequence, fasten the parts, program the robot, prepare stock material and optimize welding parameters.

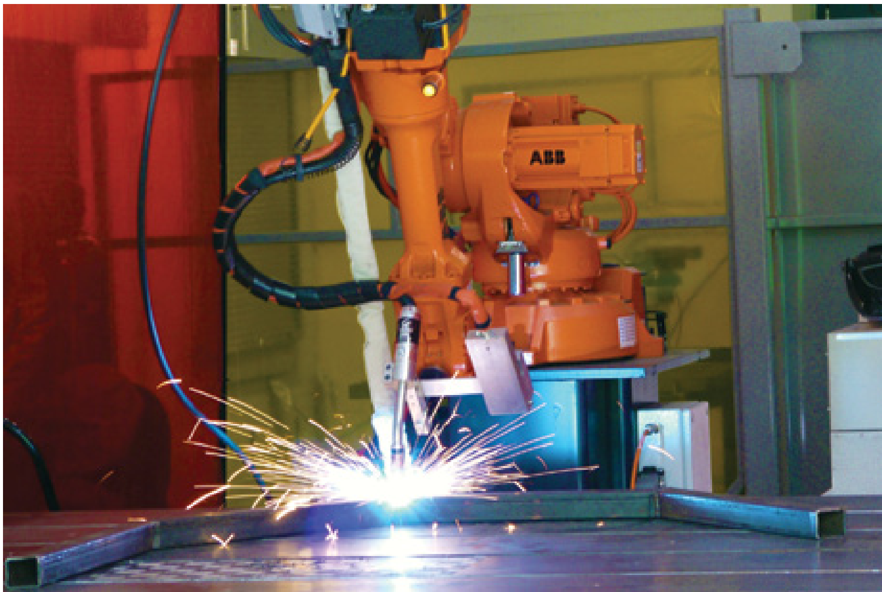
Partnering someone like Dawson-Haggerty with a manufacturing robot could cut setup time down dramatically. In the past, programmers used special code to tell robots how to move. Now a product's computer-aided design (CAD) file is all that's needed to set up a smart assembly line. Algorithms will translate these designs into the robot's to-do list.

Designing an assembly line is not the only challenge, however. Robots and people have had a hard time working together. Industrial robots move from position to position and essentially insist on reaching their final destination—whether or not a person is in the way. Manufacturers program their robots to do the same task over and over again until the parts run out. If a rigid object makes a move impossible, industrial robots go into an error state and basically power down. This condition is better than the alternative of going through someone's head, but neither is it helpful. Consider how much would get done if co-workers just froze when they got too close to one another.

Next-generation industrial robots will be intrinsically safe around humans. If a robot accidently hits a human, the blow should not be fatal or even dangerous. Machines will have awareness of where the people are in their work space, and they should be able to communicate with their human counterparts using voices, gestures, "facial" expressions, text and graphics.

Robot makers are already building machines to meet modern manufacturing's workforce needs. Spitfire is based on a robot made by Zurich-based ABB, augmented with special features designed and built at Carnegie Mellon. ABB also offers Frida, a two-armed robot designed to operate safely around people. Meanwhile Boston-based Rethink Robotics, established by iRobot co-founder Rodney Brooks, has developed Baxter, which has two arms as well as an array of sensors to make programming easier than it was for previous generations of robots.

PRECEDING PAGES: DORON GILD



ABOVE: COURTESY OF THE ROBOTICS INSTITUTE, CARNEGIE MELLON UNIVERSITY

The economic consequences of a human's ability to work with a robot, and vice versa, are potentially enormous.

An operator programs Baxter by manually guiding the machine through a series of motions, which the robot later repeats. This feat is accomplished with simple learning algorithms and image processing. For example, if a person shows Baxter how to pick parts off a moving conveyor belt, Baxter will adapt and learn how to do it—even if the parts come down the belt at irregular places and times.

Willow Garage in Menlo Park, Calif., has created a mobile demonstration robot called the PR2 with two arms, a head and an array of sensors. Like Frida and Baxter, the PR2 is designed to work safely side by side with humans. Here at Carnegie Mellon we use the PR2 to serve drinks and snacks to visitors in relatively chaotic environments.

DEFERENTIAL TREATMENT

SPITFIRE does not just learn from humans. It is also smart enough to instruct them. Spitfire breaks up big projects into little steps and divides those tasks according to who can do them faster—robot or human—with no preference given to either.

Dawson-Haggerty and Spitfire began their frame-welding job by extracting a "bill of materials" from the space frame's CAD description. Based on this shopping list, the robot's computer automatically planned which parts to order from suppliers and how to cut standard-size steel tubing to precise lengths. The computer then planned the best sequence to perform the welding operations and specified the optimal way to hold parts so they were secure during the welding.

We also gave Spitfire a miniature classroom projector so it could display images and text directly on the space frame. The images became a type of augmented reality. The robot used its projector to tell Dawson-Haggerty, step by step, how to set up the complex construction process—where the parts and the fixtures went in the work space and the order of welding operations. Dawson-Haggerty moved everything into place. Here the human was the better option for what we would consider "grunt work" because the parts were relatively lightweight and came in a variety of shapes that could be easily grasped by a human hand.

Spitfire also used its laser-displacement sensor to accurately perceive its three-dimensional work space and check to make sure that all parts were properly aligned. Using the projector and the sensor, it could highlight precise locations on the space frame and lead the human through the building process.

Once the team arranged the parts to be welded, Spitfire could take over and make quick work of that job. Not only is Spitfire a fast welder—taking just five seconds to make a two-inch weld—its welds are superb. Typically before each job, a welding expert will tune about 20 critical welding parameters such as voltage, welding speed and weld-wire feed rate. In our experiment, we instructed Spitfire to set up trials that it could run on its own to optimize all these variables. As these experiments proceeded, Spitfire measured the results of trial runs and adjusted its settings to improve its performance. The robot taught itself to be an expert welder.

Considering there were 400 required welds for the space frame, Spitfire's speed and prowess is a huge advantage. But Spitfire is not perfect. In some cases, the robot could not reach particular welds, so it instructed Dawson-Haggerty to step in to perform the tricky operations.

LIGHTS ON

WHILE IT IS DIFFICULT to predict exactly how soon human-robot teams will first dance on the factory floor—manufacturers are often slow to adopt new technologies—the clear advantages of intelligent automation should push companies toward collaborative systems within the next five years. Our vision of advanced manufacturing has come a long way from "lights out" production, made famous in Kurt Vonnegut's 1952 novel *Player Piano,* wherein automated factories do all the work. As the story goes, automation makes labor obsolete, but it also makes people embittered by their meaningless lives—an unacceptable (and unnecessary) path.

A better way forward is robots and humans cooperating as teams in which tasks are dynamically assigned according to capability. The hope is that people can take pleasure from the satisfaction of being deeply involved in the process of making things—even if they are sometimes taking orders from a machine.

__David Bourne__ is senior systems scientist at the Robotics Institute of Carnegie Mellon University.

Future Stuff

Seven next-generation materials promise to change the way the world is made

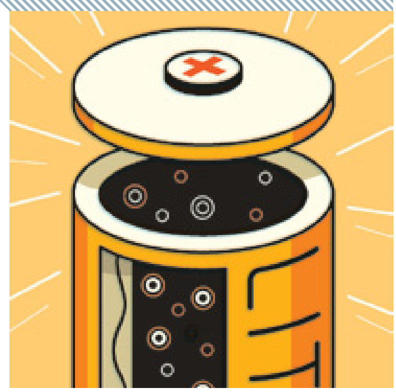
By Steven Ashley

Space Suit Stuffing

Superinsulating aerogels are more than 85 percent air by volume, earning them the nickname "solid smoke." Yet existing silica aerogels are brittle, like cheap Styrofoam. A much tougher alternative comes from the NASA Glenn Research Center and the Ohio Aerospace Institute, both in Cleveland, where scientists have invented new polymer-based versions some 500 times stronger. These aerogels, composed of heat-resistant polyimide plastics, are flexible enough to be folded in half. NASA engineers hope to use them as space suit insulation or as part of parachute-like decelerators to help safely deliver large payloads to the surface of Mars.

The Forever Battery

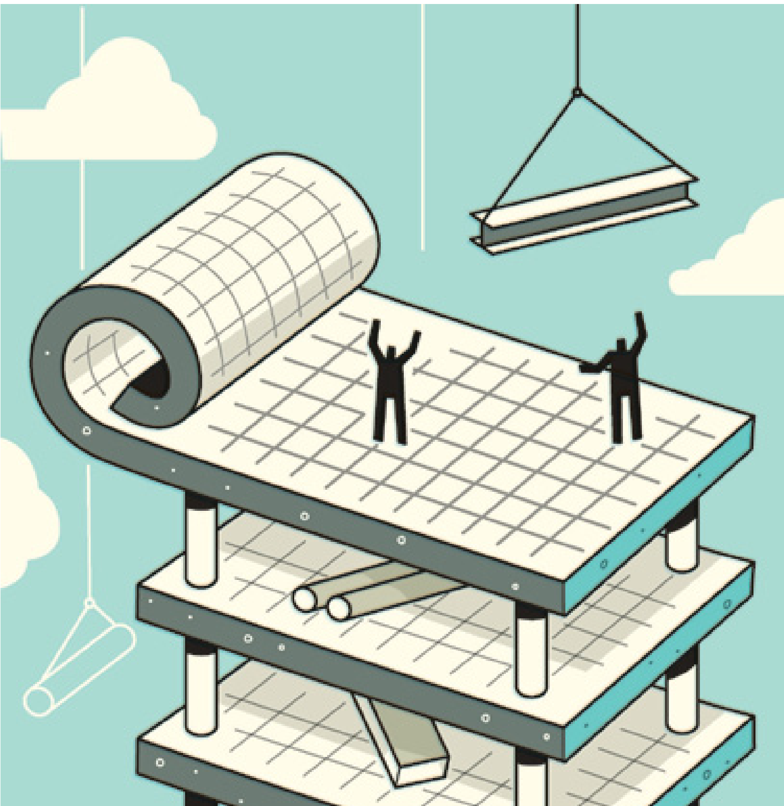
Nanotube-based batteries now under development could make rechargeable batteries last 20 times longer. Lithium-ion batteries often break down because the anodes, or positive electrodes, degrade from repeated expansion and contraction as charge-carrying lithium ions move around. A team of researchers at Stanford University has created anodes made of silicon nanotubes surrounded by permeable silicon oxide shells. The strong outer shells keep the inner nanotubes from expanding too much and failing as lithium ions pass in and out. Whereas today's lithium-ion batteries typically withstand between 300 and 500 charge-and-discharge cycles, the nanotube versions can cycle more than 6,000 times while retaining more than 85 percent of their initial capacity.



Slippery Sandpaper

A new type of surface coating is so slick that it can make molasses slide like olive oil. These SLIPS—for slippery liquid-infused porous surfaces—can cut friction in crude-oil pipes, halt ice formation on airplane wings or shed spray-painted graffiti from walls. The chemically inert substance, developed by researchers at Harvard University's Wyss Institute for Biologically Inspired Engineering, seeps into porous or textured solids (such as a concrete wall) to form a smooth lubricating film.

Illustrations by Harry Campbell



Plant Plastic

A complex natural polymer found in plant matter might replace bisphenol A (BPA), a chemical that has been used to make the clear, polycarbonate plastic of shatter-resistant headlights, eyeglass lenses, DVDs and baby bottles—and one that poses a potential health risk. Researchers at the Industrial Technology Research Institute in Zhudong, Taiwan, are using lignin as the basic building blocks for new nontoxic plastics, including a protective varnish for the inside surfaces of food cans and a substitute for polyurethane foams and polyester.

Flexible Concrete

Concrete Cloth lets engineers move flexible concrete sheets where they want them, freeing builders from the millennia-old constraints of having to pour concrete in place. The material starts off as a big, flexible sheet wound on a cylinder. After workers roll it out and spray it with water, it dries into a tough block that can be used to line a ditch, stop slope erosion or reinforce a wall. The sheets are made of concrete powder sandwiched between two fabric surfaces that are linked by connecting fibers. The fibers and dry concrete draw water into the cloth, and the cross-linked fibers help to create a tough matrix once the material dries.

Fireproof Fatigues

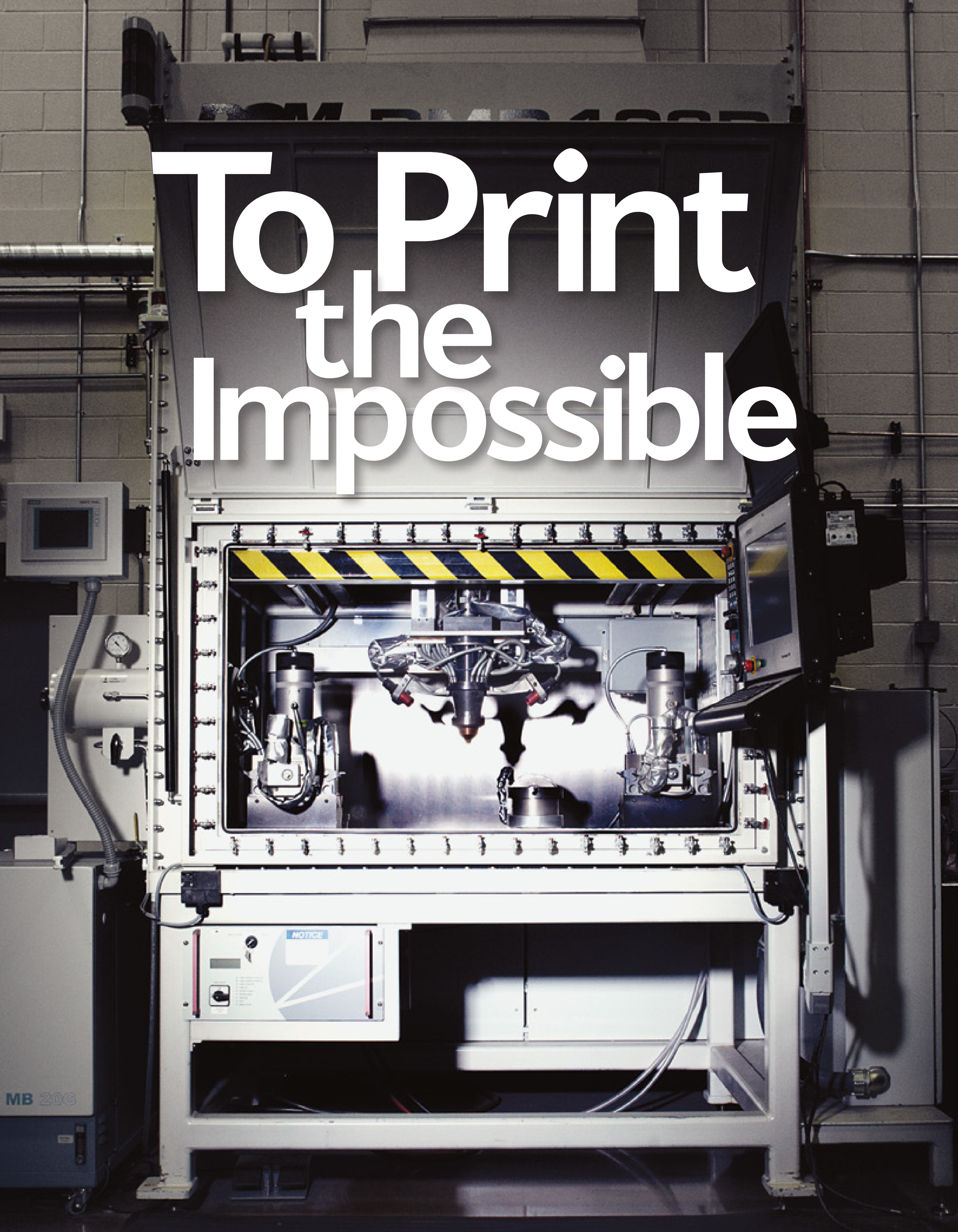
A soldier's fatigues should defend against fire and heat, but current protective fabrics use heavy coatings or fail to insulate against heat. Milliken & Company in Spartanburg, S.C., turned to an unlikely fabric: cotton. Chemists treated the fabric with a phosphorus-based additive that promotes charring; the residue serves to insulate the cloth and prevent it from burning further.

Cyber Steel

One of the most difficult challenges in the metals business is developing alloys for military aircraft landing gear, which must be superstrong and ultratough while being as lightweight as possible. Gregory B. Olson, a Northwestern University materials scientist and chief science officer at QuesTek Innovation in Evanston, Ill., leads a team that has invented two stainless alloys that do not need toxic cadmium plating for corrosion protection, unlike current high-priced titanium alloys and steels that make up modern landing gear. The new alloys are some of the first that have been developed using potentially revolutionary computer models that simulate chemical thermodynamics.

Steven Ashley is a New York City–based writer and editor.

To Print the Impossible



Will 3-D printing transform conventional manufacturing?

By Larry Greenemeier

TOUGH GRIP: This prosthetic hand was assembled from 46 individually printed titanium parts. Oak Ridge National Laboratory plans to build it as a single printed object.

Photographs by Travis Rathbone

OAK RIDGE NATIONAL LABORATORY'S ROBOTIC PROSTHESIS LOOKS LIKE something out of medieval times—a hand clad in chain mail more appropriate for wielding a broadsword than a mug of coffee. Both the underlying skeleton and thin, meshlike skin are made of titanium to make the hand durable and dexterous while also keeping it lightweight. The powerful miniature hydraulics that move the fingers rely on a network of ducts integrated into the prosthesis's structure—no drilled holes, hoses or couplings required.

Yet what makes this robot hand special is not what it can make or do but rather how it was made and what it represents. Conceived on a computer and assembled from a few dozen printed parts by so-called additive manufacturing, more popularly known as 3-D printing, Oak Ridge's invention offers a glimpse into the future of manufacturing—a future where previously impossible designs can be printed to order in a matter of hours.

"You're looking at a very, very complex design that has internal hydraulic tubing that can be run in excess of 3,000 pounds per square inch," says Craig Blue, director of Oak Ridge's energy materials program. "You have meshing to make it a lightweight structure, putting material only where you need it. There's no technology today, other than additive manufacturing, that can make that [robotic hand]."

As 3-D printing matures to the point where it can make complex machinery that can't be made any other way, big-volume manufacturers such as Boeing and GE are starting to apply the technology to their advanced product lines. Instead of the old approach of carving a usable part out of a large block of material, additive manufacturing builds an object up layer by layer. This shift in thinking has the potential to affect every facet of manufacturing—from prototype design to mass-produced product.

Yet technical challenges continue to bedevil 3-D printing. Compared with ordinary subtractive manufacturing, additive manufacturing can be slow, the fit and finish of its materials inconsistent. Further, 3-D printers have trouble building objects out of multiple kinds of materials, and they cannot yet integrate electronics without frying the circuits.

Researchers are working hard to overcome these limitations—and few doubt that for customizable, small-volume applications, additive manufacturing has tremendous power. As the technology expands into the mass marketplace, 3-D printing could begin to power a widespread manufacturing revolution.

ADDITIVE ADVANCES

THE ORIGINS OF 3-D PRINTING stretch back to the late 1980s, when start-up companies and academics—most notably at the University of Texas at Austin—invented machines that could build three-dimensional models of digital designs in minutes. For decades those systems and similar types, which first cost around $175,000, gained notoriety for their ability to help inventors and engineers rapidly and relatively inexpensively produce their prototypes.

Since then, 3-D printing has taken two paths. At one extreme, hobbyists and would-be entrepreneurs can whip up plastic models using machines that cost $2,000 and less. These kitchen-counter devices allow users to invent new objects—a technology that has invited comparisons between 3-D printing and personal computers. "In the same way the Internet, the cloud and open-source software have allowed small teams to live on ramen noodles for six months and build an app, post it and see if anyone is interested, we're beginning to see that same phenomenon spread to manufactured goods," says Tom Kalil, deputy director of technology and innovation at the White House's Office of Science and Technology Policy.

At the other extreme, large manufacturers are cultivating advanced, industrial-strength approaches to produce aircraft parts and biomedical devices such as replacement hips. The machines required to do this cost upward of $30,000, with laser-based appliances that make high-quality metal products selling for as much as $1 million. These printers can use polymers, metals or other materials in liquid or powder form. Objects begin as digital files, enabling designers to tweak their work before the building begins, with little impact on cost.

Printing in 3-D could replace certain conventional mass-production processes such as casting, molding and machining by 2030, especially in the case of short production runs or manufacturers aiming for more customized products, according to the "Global Trends 2030: Alternative Worlds" report issued last November by the National Intelligence Council, a team of analysts supporting the Office of the Director of National Intelligence. Aerospace companies are at the forefront of this trend. GE Aviation, which has been making aircraft engines for nearly a century, recently bought two suppliers that specialize in making aircraft parts via additive manufacturing processes. Boeing already uses 3-D printing to make more than 22,000 parts used on its civilian and military aircraft.

Such companies are discovering that 3-D printing can also be more efficient than conventional production, both in terms of energy and materials. "If you're machining a part, it's not unusual that 80 to 90 percent of the block [of material] you start with can end up as chips or scraps on the floor," says Terry Wohlers, principal consultant and president of Wohlers Associates, an additive manufacturing consulting firm in Fort Collins, Colo.

BREAKING THE MOLD

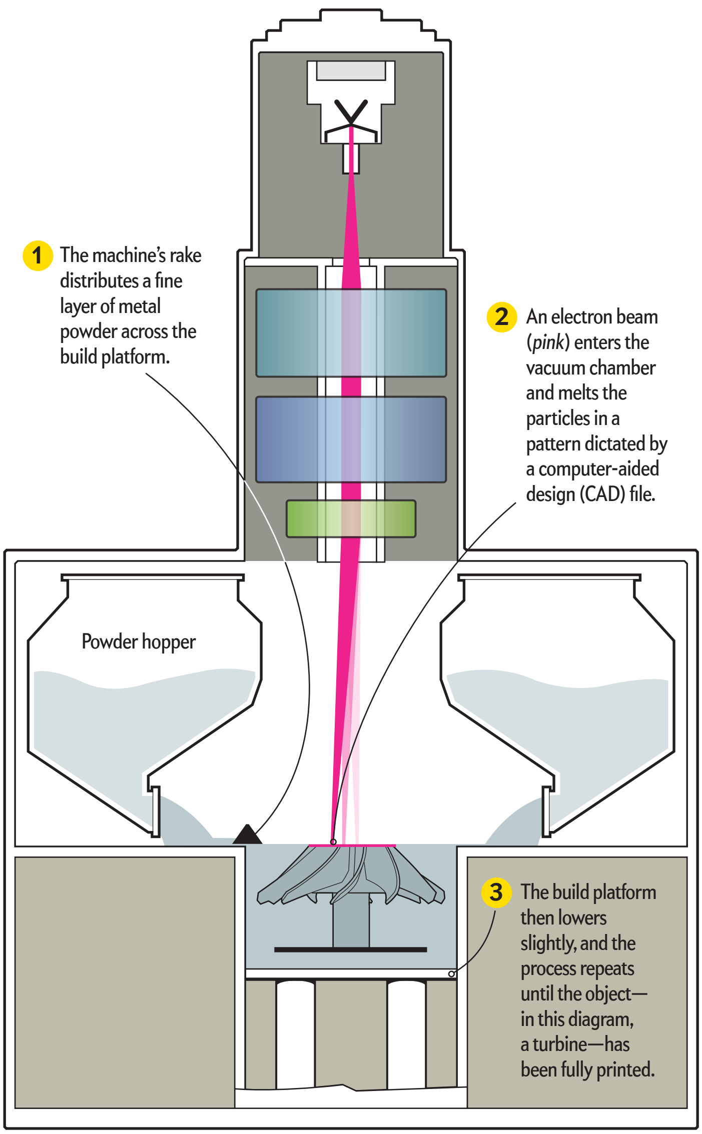
DESPITE THESE ADVANTAGES, manufacturers still largely think of 3-D printing as a way of making prototypes rather than industrial-grade products. The reasons are threefold: slow speeds, inconsistent quality and the difficulty of building complex objects.

Foremost, additive processes are relatively slow, depending on the level of detail required. Oak Ridge engineers, led by principal designer Lonnie Love, spent 24 hours making the parts for their 1.3-pound robotic hand and another 16 hours assembling it. (They are developing hardware that will print the entire prosthesis in a single piece.) "If you were building something the size of a softball and you wanted fine features and definition, you could envision that taking six to eight hours to build," says Richard Martukanitz, co-director of the Center for Innovative Materials Processing through Direct Digital Deposition at Pennsylvania State University. At those speeds, building thousands of units using 3-D printers would take years.

HOW IT WORKS

The Building Beam

Oak Ridge researchers used an electron beam melting (EBM) machine to build their robotic prosthetic hand. The intensely hot process melts powdered alloys such as titanium or cobalt chrome into durable metal parts ready for use without additional heat treatment to stabilize those materials.



SOURCE: ARCAM.COM

Some additive manufacturing systems work faster. Those developed for the U.S. Navy can deposit 20 to 40 pounds of material per hour. In this case, however, speed comes at the expense of feature definition, which is poor; finished parts also require postprocess machining, Martukanitz says. To speed things up, researchers are working on systems that print at variable speeds—quickly laying bulk material but slowing down when a part requires more detail. "This is getting a lot of attention now because people are seeing the limitations of the additive process from a productivity standpoint," he notes.

Another option to boost speed is to distribute workloads across several manufacturing facilities. Yet this approach requires a higher level of standardization than what currently exists. A critical component of a GE jet engine should look, feel and perform reliably, regardless of how or where GE (or one of its suppliers) makes it. ASTM International, formerly known as the American Society for Testing and Materials, is one organization active in developing standards for 3-D printing, although its work is in the early stages.

Scientists are also trying to make self-monitoring 3-D printers that could quickly churn out consistent designs. The system would analyze high-speed video of the object as it is built or use infrared thermography to detect flaws, then immediately correct those imperfections without stopping the building process, Blue says. "You download the plans for the part to the printer and get the perfect part every time," he adds.

The growing complexity of products—which increasingly incorporate many different materials, along with embedded electronics—poses a further challenge to 3-D printing. One approach is to develop 3-D printers with multiple extrusion heads, each depositing a different type of material. One of those heads could be used to embed wires directly into a device as it is being built.

Researchers at Oak Ridge, the University of Texas at El Paso's W. M. Keck Center for 3D Innovation, and elsewhere are designing 3-D printers that can also print circuitry. The challenge has been to avoid overheating and damaging electrical components while adding on the surrounding layers of plastic or metal. Investigators are testing ways to print insulating material around electrical components to protect them. "Within the next decade you'll see coupling of printed electronics with other materials," Blue says.

Taken together, such advances hold good promise for Oak Ridge's robotic hand, not to mention anyone using it. The scientists envision a time when doctors will be able to scan a person's healthy hand, make a mirror image of it electronically and then print the new, preassembled prosthesis ready to use.

Larry Greenemeier is an associate editor at Scientific American.

Illustration by George Retseck

Rise of the Nano Machines

Scientists are building the next generation of atomic-scale devices

By Mihail C. Roco

FOR DECADES INDUSTRIAL MANUFACTURING HAS MEANT long assembly lines. This is how scores of workers—human or robot—have built really big things, such as automobiles and aircraft, or have brought to life smaller, more complex items, such as pharmaceuticals, computers and smartphones.

Now envision a future in which the assembly of digital processors and memory, energy generators, artificial tissue and medical devices takes place on a scale too small to be seen by the naked eye and under a new set of rules. The next few years begin an important era that will take us from manufactured products that simply contain nanotechnology—sunscreen with UV-blocking bits of titanium dioxide, as well as particles for enhancing medical imaging, to name two—to products that *are* nanotechnology.

Successful manufacture of these crucial nanotechnologies will require a better understanding of how matter behaves at the atomic scale, along with new tools and processes for assembly.

One approach is bottom-up directed self-assembly, which joins small or subordinate units such as atoms and nanoscale modules (nanotubes and the like) into larger, more substantial components. Scientists can also use DNA strings or other natural or engineered molecules as programmable building materials for precise, molecular-scale devices and motors. Another high-efficiency method is roll-to-roll assembly, in which miniature devices are printed on continuous rolls of polymer-based sheets.

Nanomanufacturing also requires ultraprecise tools. Some tools will be chemical catalysts; others will be biological, optical, mechanical or electromagnetic. Further in the future, the nanomanufacturing toolbox will very likely include novel molecules and so-called metamaterials engineered to have properties that seem to defy nature—for example, a material that refracts light in an unexpected way.

Here is a look at some of the most exciting nanoscale technologies on the horizon and how we will make them.

Mihail C. Roco is the senior adviser for nanotechnology at the National Science Foundation.

Illustration by Harry Campbell

Cyborg Tissue Scaffolding

Artificial tissue laced at the cellular level with nanoscale electronics could someday take on a "cyborg-ish" role within the human body. Instead of implanting electronic devices into existing organs, synthetic tissues could be grown from scaffolds that contain multiple nanoscale electronic sensors. Such nanoelectronic scaffolds could become the foundation for engineered tissues that are used to detect and report on a variety of health problems. They could connect part of the nervous system with a computer, machine or other living body. Scientists at Harvard University and the Massachusetts Institute of Technology built a scaffold from very fine and elastic nanowires that can interface with individual cells. The researchers say their goal is to merge tissue with electronics in such a way that it becomes difficult to determine where the tissue ends and the electronics begin.

Minuscule Memory

Nanomanufacturing has great potential to deliver smaller, more powerful electronics with denser, more efficient and less expensive memory. That is good because at some point scientists and engineers will no longer be able to shrink computer chips and cool circuits via the complementary metal-oxide semiconductor (CMOS) technology they have used for decades to make integrated circuits. One work-around is to use electron spin as the information carrier in both memory and logic devices. IBM, Intel and other companies are developing so-called spintronic memory and logic devices that promise to be reliable, fast and low in power consumption. Many other approaches involve writing and storing data with help from nanoscale magnets. A Cornell University research team has demonstrated an energy-efficient way to switch the magnetic polarization of a nanomagnet, a step toward creating a tiny form of magneto-resistive random-access memory, or MRAM, which devices can use to store data even when they are powered down. The team applied current to a lithographically patterned layer of tantalum. This current led to a deflection of electron spins large enough to flip the magnetization of a neighboring magnet. To flip the spin back, the researchers simply reversed the current. When no current flowed, the magnet stayed in place and retained data even if the device was dormant. This research could yield devices such as an instant on/off smartphone or notebook computer with no standby battery drain.

Laser-Fast Communication

Photonic integrated circuits that use light to carry information should speed up our shrinking electronic devices. Yet photonic devices still face a fundamental challenge: there is a limit to how small you can make them. The diffraction limit of light prevents confining light into spaces smaller than half of its wavelength, yet light wavelengths would be at least 10 or 100 times larger than any nanoscale electronic devices themselves.

Researchers are working to defy these limitations using a solid-state "plasmon" laser to ferry data. The plasmon laser consists of a grid of nanoscale semiconductor wires and similarly sized metal wires. The grid intersections form square cavities that are used to confine light. These cavities can be as small as 1 percent of the diffraction limit—coincidentally, about the size of a transistor on a computer chip. If the scientists can successfully coax the cavities formed between the wires to produce tiny bursts of laser light, the advance could serve as the basis for optical systems small enough to nestle among these microscopic transistors. The work is being led by Xiang Zhang and his colleagues at the University of California, Berkeley.

Plastic Muscles

Artificial muscles help human eyes blink, robotic fish swim and floating buoys extract energy from the ocean. Soon chemists will use threadlike "dendronized" nanoscale polymers, which expand or contract when heated or cooled, to act as cell membranes, drug delivery agents and artificial heart fibers. University of Pennsylvania researchers led by Virgil Percec have already shown that these thin polymers can be made strong enough to lift a dime about 250 times heavier than the polymer itself. The key challenge to manufacturing this technology is finding the building-block polymers that can predictably self-assemble into structures—heart tissue, for example—that behave like mini artificial muscles.

Power Plants Made of Viruses

Viruses can be used to build energy-generating nanoscale devices. The genetically engineered M13 bacteriophage virus is especially good at this. The rod-shaped virus, roughly seven nanometers in diameter and 900 nanometers long, converts mechanical energy to electric energy (and vice versa). Experiments led by U.C. Berkeley bioengineer Seung-Wuk Lee have used the virus to build a piezoelectric biomaterial that can pull enough juice to power a 10-square-centimeter LCD screen. The nanomanufacturing approach here is based on nature's unique ability to synthesize biomaterials in viruses, which can self-replicate, evolve and self-assemble with atomic precision. Virus-based piezoelectric materials could power future nanoscale sensors and other medical devices (either outside or within the human body) by harvesting vibrational energy from, for example, a heartbeat.

Assembled in Code

Digital simulations have become so powerful that companies send their products through the wringer—sometimes literally—before ever building a prototype

By James D. Myers

DIGITAL WASH: P&G used intensive simulations to ensure that Tide Pods would behave properly inside the chaotic environment of a washing machine.

WHEN THOMAS EDISON invented a practical electric lightbulb more than 130 years ago, he performed thousands of experiments on prototypes, and we still marvel at his methodical patience today. A modern inventor proposing a similar approach, however, would more likely elicit laughter than praise. Product research and development more and more lives in the realm of bits and bytes, with engineers designing, testing, tweaking and even demonstrating new ideas via computer before any physical version exists.

Powerful computer servers performing highly calculation-intensive tasks, aka high-performance computing (HPC), now make all the difference between new technologies that launch and those that languish. This "digital manufacturing" takes place across thousands to millions of processors before a company produces any physical parts. Consumer goods manufacturers are using digital modeling techniques that far exceed those that big firms in industries such as aerospace introduced years ago. The strategy lowers design and production costs and helps to move goods from concept to store shelves faster than ever before. Computer-drawn models and complex digital simulations increasingly dictate what those items look like, how they are made, what they are made of and how they will perform together. Driven by Moore's law, which holds that computer processing power doubles roughly every 18 months, HPC capabilities should advance another 1,000-fold in the coming years. It is no surprise, then, that in the words of the nonprofit Council on Competitiveness, we are entering an age in which "to outcompete is to outcompute."

The following examples provide a glimpse of state-of-the-art digital manufacturing as well as some hints about where technology will take the process in the near future.

***James D. Myers** is associate director of research and development at the Computational Center for Nanotechnology Innovations at Rensselaer Polytechnic Institute.*

Photograph by Travis Rathbone

Turning Tide

Procter & Gamble (P&G) engineers realize that most consumers do not devote much thought to how a lot of everyday products are made, dismissing as "easy" the manufacture of essentials such as food, cleaning products and even toilet paper. (The machine P&G uses to manufacture its toilet tissue, by the way, costs nearly $250 million and has more moving parts and lines of code than many military aircraft.) Several years ago, when the company still owned the Pringles brand of potato chips (now in the hands of Kellogg), P&G digitally modeled the airflow over the snacks as they moved—very, very rapidly—down the production line. This research led to adjustments that kept the chips from taking off like little aircraft and crashing in a pile.

Tide Pods were at an entirely different level of complexity. The laundry packets consist of three chambers filled with liquid detergent, stain remover and brightener and are enveloped in a dissolvable film. P&G relied on several million hours of computer processing time to ensure that its Tide Pods properly reacted with washing machine water to release their liquids and effectively clean dirty laundry.

Much of that time went to figuring out how to manufacture the pods. P&G performed structural analysis to calculate and minimize how much the dissolvable film would wrinkle when cut. Fluid dynamics calculations determined how to quickly fill the pods with detergent without splashing any over the edge, which would make the pods hard to seal.

Surfactant-based liquids have interesting behaviors, which meant P&G researchers also needed to perform molecular modeling to understand how the formation of nanoscale structures—micelles and vesicles—might inhibit the product's stability and performance. Digital models depicting how the soft, squishy pods would settle over time when not in use also helped P&G design the container in which they are sold. The work enabled the company to meet its goals for production: each packet is assembled in about a second at a defect rate of less than a one in a billion.

Power Pump

Despite P&G's successes, switching from traditional methods to HPC-based digital manufacturing is a significant challenge. It requires three simultaneous shifts: from physical testing facilities to computing facilities, from approximate methods to more complex but more accurate techniques, and from a culture of troubleshooting to predictive up-front design.

In New York State's Finger Lakes region, ITT Goulds Pumps has made pumps for chemical, mining, power and several other industries since the 1840s. Goulds did not have in-house resources like P&G did to build its own digital manufacturing capability. Instead the company approached the Computational Center for Nanotechnology Innovations, a partnership among Rensselaer Polytechnic Institute, IBM and New York State. Rensselaer helped Goulds transform its computer-aided design (CAD) drawings into "meshed" 3-D models—broken into millions of small areas across which engineers could calculate fluid flow. It also created a process that set up, ran and analyzed pump design options. Goulds went on to develop an award-winning new pump design. Going forward, massively parallel computing will help the company's engineers avoid cavitation—bubble formation—which can rob performance and cause wear.

In Indiana, Jeco Plastic Products tells a similar story. In response to a major auto manufacturer's search for shipping pallets, Jeco proposed plastic transport structures that could outperform metal ones from foreign competitors. Yet the cost of retooling its facility to make and test different prototype plastic pallets—without any guarantee of a buyer—was daunting. Nor could Jeco accurately model new designs on its computers in-house. So the company partnered with Purdue University and the Ohio Supercomputer Center to digitally develop and test Jeco's design. The consortium—a Council on Competitiveness public-private partnership—develops software, purchases supercomputer time and trains smaller manufacturers in this technology. The result: a new order and entry into a market Jeco estimates could bring $23 million in revenue and create 15 jobs.

Born Digital

When there are millions of combinations of materials, manufacturing processes and designs to choose from—rather than the thousands Edison faced—the ability to model and explore many options at once is perhaps the only way to bring new products to market. Pliant Energy Systems knows this well. The Brooklyn-based start-up has a revolutionary concept for generating power from moving water using so-called smart materials that generate power as they flex and bend. Pliant's hydrokinetic devices could literally be dropped into a stream and start generating electricity or be configured as self-powered irrigation pumps. The breadth of design options—and the challenges of building physical prototypes and understanding their behavior—made predictive computational analysis crucial.

Digitally modeling water flow in an open stream requires massively parallel computation that divides the work among many processors to increase speed. Predicting how long, flexible fronds or tubes of electroactive polymers will bend in flowing water—not to mention optimizing the power output of a device using these materials—requires the coupling of device and water-flow models, a feat at the cutting edge of what high-performance computers can do today. Working with Rensselaer, Pliant won a U.S. Small Business Administration grant of nearly $300,000, in part because it demonstrated the digital tools and expertise needed for cost-effective development of its technology. Now the company can create even more sophisticated physics-modeling capabilities and digitally design more advanced prototypes.

Pliant's digital manufacturing success is part of a larger trend. Chris Bystroff, an associate professor in Rensselaer's biology and computer science departments, has developed techniques to design and manufacture custom proteins. Such proteins could act as molecular biosensors that glow in the presence of, for example, dengue fever or H5N1 viruses. Bystroff and the University at Buffalo, S.U.N.Y., are packaging his digital design process behind a Web interface that does in hours what used to take days using antibodies.

Digital manufacturing may seem like a familiar concept, but faster, more affordable computers and increasingly complex software mean that new products, whether they fight grass stains on jeans or viruses invading the human body, will now do so first in the land of 0's and 1's.

For more on the future of manufacturing, go to ScientificAmerican.com/may2013/manufacturing

NEUROSCIENCE

SEEDS OF DEMENTIA

A chain reaction of toxic proteins may help explain Azheimer's, Parkinson's and other killers—an insight that could lead to desperately needed new treatment options

By Lary C. Walker and Mathias Jucker

UNDER A MICROSCOPE, A PATHOLOGIST SEARCHING through the damaged nerve cells in a brain tissue sample from a patient who has died of Alzheimer's disease can make out strange clumps of material. They consist of proteins that clearly do not belong there. Where did they come from, and why are there so many of them? And most important, what do they have to do with this devastating and incurable disorder? The search for answers has turned up a startling discovery: the clumped proteins in Alzheimer's and other major neurodegenerative diseases behave very much like prions, the toxic proteins that destroy the brain in mad cow disease.

Prions are misshapen yet durable versions of proteins normally present in nerve cells that cause like proteins to misfold and clump together, starting a chain reaction that eventually consumes entire brain regions. In the past 10 years scientists have learned that such a process may be at work not only in mad cow and other exotic diseases but also in major neurodegenerative disorders, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (also known as ALS or Lou Gehrig's disease) and the concussion-related dementia of football players and boxers.

IN BRIEF

A Nobel Prize–winning discovery found that mad cow and related infectious diseases occur when aberrant proteins—prions—wreak havoc by causing normal versions of those proteins to become malformed.

Prionlike disease processes also appear to be at work in major neurodegenerative disorders, including Alzheimer's, Parkinson's and Lou Gehrig's, although they are not transmitted from person to person.

How proteins contort into a form that causes others to undergo a similar transformation may lead to new approaches to preventing and treating some of the world's leading neurological illnesses.

Illustration by Ronald Kurniawan

Alzheimer's and Parkinson's, all evidence suggests, are not contagious like mad cow or, for that matter, the flu. Rather the significance of these recent findings is that they provide scientists with a prime suspect for a slew of devastating brain disorders—a signpost that points toward a pathway for eventual treatments. Drugs developed for Alzheimer's might be used directly—or else inspire new pharmacology—for Parkinson's, traumatic brain injury or other terrifying conditions that rob an individual of a basic sense of self—good news for tens of millions worldwide who suffer from neurodegenerative disorders.

The new thinking owes a debt to research that first led to the discovery of prions. It began in the early 18th century, with reports of a curious, fatal disease of sheep called scrapie, so named because affected animals compulsively rubbed the wool from their skin. Later, as scientists began to investigate the disease, they noticed under the microscope that the nervous system was shot through with holes. In the 1930s French and British researchers determined that scrapie could be transmitted from one sheep to another, but the infectious agent was elusive and behaved strangely: the incubation time between exposure and symptoms was much longer than for conventional disease-causing agents such as bacteria or viruses, and the immune response that usually kicks in to eliminate such invaders seemed to be absent.

Those oddities were a hint that the usual suspects were not the cause, but for about 20 years after these reports scrapie remained just an obscure veterinary malady. In the 1950s, though, William Hadlow, then at the British Agricultural Research Council Field Station at Compton, noted conspicuous similarities in brain pathology between scrapie and a mystifying human disease called kuru. Kuru is a progressive neurodegenerative disease, mainly confined to the Fore people of Papua New Guinea, in which a steady decline in coordination and mental function invariably ends in death. The disease among the Fore was ultimately found to result from the ritual cannibalism of tribe members who had died of the disease, which implied that some infectious agent was at fault and somehow reached the brain from elsewhere in the body.

In the 1960s D. Carleton Gajdusek of the U.S. National Institutes of Health and his colleagues confirmed that the disease was transmissible, showing that kuru could be conveyed by the direct injection of brain material from victims of the disease into the brains of nonhuman primates. Gajdusek's team also recognized key parallels in brain pathology between kuru and another neurodegenerative brain disorder: Creutzfeldt-Jakob disease (CJD), a rapidly progressive type of dementia that occurs in roughly one in a million people worldwide. Gajdusek went on to demonstrate that CJD is transmissible to primates in the same way as kuru, although CJD most often arises in people spontaneously.

In the 1980s Stanley B. Prusiner of the University of California, San Francisco, identified the agent responsible for scrapie and related disorders, which are known collectively as spongiform encephalopathies for the way they cause the brain to take on the appearance of Swiss cheese [see "The Prion Diseases," by Stanley B. Prusiner; Scientific American, January 1995]. In a beautiful series of experiments, he and his co-workers amassed persuasive evidence that the infectious agent consists solely of a misfolded version of an otherwise innocuous protein called PrP. Prusiner also coined the term "prion" (pronounced "pree-on") at that time, for "proteinaceous infectious particle," to distinguish protein agents that spread disease on their own from viruses, bacteria, fungi and other known pathogens. (Today the term is expanding to include other proteins that impose their shape on like proteins and does not necessarily imply infectiousness.) Prusiner's ideas sparked a huge controversy when he proposed that a protein could transmit disease, but in 1997 his efforts were rewarded when he won the Nobel Prize for this work.

Lary C. Walker is a research professor at the Yerkes National Primate Research Center and associate professor of neurology at Emory University.

Mathias Jucker is a research professor at the Hertie Institute for Clinical Brain Research at the University of Tübingen in Germany and at the German Center for Neurodegenerative Diseases, also in Tübingen. The authors have collaborated extensively over the past two decades on research into brain aging and Alzheimer's disease.

Recently in-depth research into Alzheimer's and other neurodegenerative conditions indicates that these disorders, though lacking the infectiousness of classic prion diseases, may arise and amplify in the brain in a similar way; that is, by a process we call pathogenic protein seeding. Like the prions responsible for scrapie and its kin, the proteinaceous seeds can be released, taken up and transported by cells, which may explain how disease spreads from one place to another. These commonalities suggest that the prion paradigm could soon unify our thinking about how seemingly diverse diseases arise and wreak havoc.

IS MISFOLDING BEHIND ALZHEIMER'S?

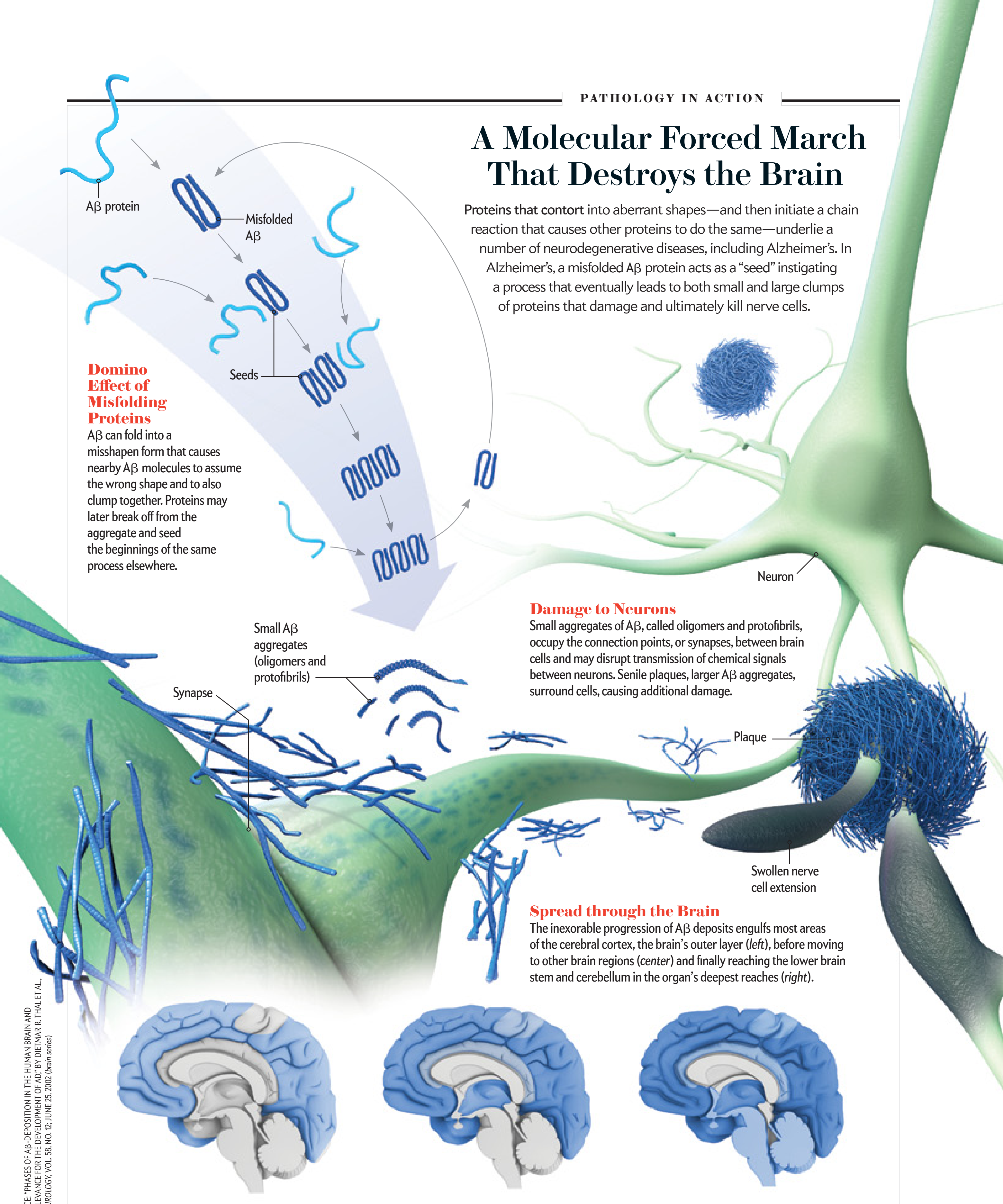
The first hint of this connection came as far back as the 1960s, when researchers struggling to grasp the mysteries of prion diseases began to notice some suggestive similarities to the brain changes that occur in other neurodegenerative disorders, especially Alzheimer's. The most common cause of dementia in aging humans, Alzheimer's appears stealthily and progresses relentlessly over the course of many years, robbing the victim of memory, personality and, ultimately, life itself. The incidence of Alzheimer's doubles every five years after the age of 65 until, by 85 years, nearly one in three adults is afflicted.

Researchers of the time also understood that protein clumping was involved. In 1906 Alois Alzheimer, after whom the disease is named, associated dementia with two peculiar microscopic abnormalities in the brain: senile plaques (now known to be clumps of a misfolded protein fragment named amyloid-beta, or Aβ), located outside of cells, and neurofibrillary tangles (filaments composed of aggregations of a protein called tau), located inside the cell. When these clumps are highly magnified with an electron microscope, the proteins can be seen to form long fibers made up of Aβ or tau. In addition, the proteins form smaller assemblies known as oligomers and protofibrils that can also interfere with the normal function of neurons.

In the late 1960s Gajdusek's team set out to test the hypothesis that Alzheimer's, like scrapie, kuru and Creutzfeldt-Jakob, might be transmissible—so they injected processed brain matter from Alzheimer's patients into the brains of nonhuman primates. Independently, a team led by Rosalind Ridley and Harry Baker, then at the Clinical Research Center in Harrow, England, later under-

A Molecular Forced March That Destroys the Brain

Proteins that contort into aberrant shapes—and then initiate a chain reaction that causes other proteins to do the same—underlie a number of neurodegenerative diseases, including Alzheimer's. In Alzheimer's, a misfolded Aβ protein acts as a "seed" instigating a process that eventually leads to both small and large clumps of proteins that damage and ultimately kill nerve cells.



Domino Effect of Misfolding Proteins

Aβ can fold into a misshapen form that causes nearby Aβ molecules to assume the wrong shape and to also clump together. Proteins may later break off from the aggregate and seed the beginnings of the same process elsewhere.

Damage to Neurons

Small aggregates of Aβ, called oligomers and protofibrils, occupy the connection points, or synapses, between brain cells and may disrupt transmission of chemical signals between neurons. Senile plaques, larger Aβ aggregates, surround cells, causing additional damage.

Spread through the Brain

The inexorable progression of Aβ deposits engulfs most areas of the cerebral cortex, the brain's outer layer (*left*), before moving to other brain regions (*center*) and finally reaching the lower brain stem and cerebellum in the organ's deepest reaches (*right*).

SOURCE: "PHASES OF Aβ-DEPOSITION IN THE HUMAN BRAIN AND ITS RELEVANCE FOR THE DEVELOPMENT OF AD," BY DIETMAR R. THAL ET AL., IN *NEUROLOGY*, VOL. 58, NO. 12; JUNE 25, 2002 (*brain series*)

Illustration by AXS Biomedical Animation Studio took similar experiments. The results of the Gajdusek studies were indeterminate, and neither group reported that it had triggered fully developed Alzheimer's. The British researchers, however, found a hint of an effect: after an incubation period of at least five years, Aβ plaques were more abundant in marmosets that had received the processed Alzheimer's brain matter than in a comparison group of control marmosets.

At this point, our research groups considered initiating studies to see if misfolded Aβ—in the form of small aggregates—acted as a seed that set off a chain reaction of protein misfolding and clumping that eventually led to the type of protein deposits that overwhelm the brain in Alzheimer's. But we were discouraged by the five years or so it took to incubate seeded plaque formation in monkeys.

Our outlook changed considerably in the mid-1990s with the advent of "transgenic" mice that were genetically engineered to produce the precursor protein from which the human Aβ fragment is generated—APP (for amyloid precursor protein). Together with a talented group of colleagues and students, we began a series of experiments exploring the Aβ-seed hypothesis in these mice. The transgenic animals do not embody all features of Alzheimer's (which appears to be unique to humans), but they offer considerable advantages for our experiments: they are small, easy to maintain and short-lived, and each transgenic mouse spontaneously develops Aβ brain deposits at a relatively consistent age.

Our research team set out to see if misfolded proteins act as seeds that set off a chain reaction that eventually produces toxic deposits that overwhelm the brain.

In our studies, we concentrated on Aβ rather than tau because even though plaques and tangles both contribute to the neurodegeneration that causes dementia in Alzheimer's, much of the evidence implies that misfolded Aβ is a key catalyst for the disease's development. Indeed, many of the risk factors for Alzheimer's influence cellular processes involved with the production, folding, aggregation or removal of Aβ. Genetic mutations that cause disease onset at a very early age alter APP or the enzymes that splice Aβ from that precursor [see "Shutting Down Alzheimer's," by Michael S. Wolfe; Scientific American, May 2006]. Scientists also now know that the brain begins to show signs of Alzheimer's a decade or more before the symptoms appear—and that the abnormal clumping of proteins occurs very early in the disease process [see "Alzheimer's: Forestalling the Darkness," by Gary Stix; Scientific American, June 2010]. Aware that the accumulation of misfolded Aβ is pivotal to the development of Alzheimer's, we wanted to know what first spurs protein aggregation in the brain.

During our first experiments, we set out to determine whether extracts of brain tissue from patients who had died of Alzheimer's would initiate Aβ aggregation in the brains of APP-transgenic mice. In other words, could we induce and propagate Aβ aggregation in the same way that prions trigger PrP aggregation in the spongiform encephalopathies? Using methods developed for the study of those prions, we first took small brain samples from Alzheimer's patients or from control patients who had died of causes other than Alzheimer's. We ground up the tissue and spun the samples briefly in a centrifuge to remove the larger debris. Then we injected a tiny amount of the extract into the brains of young transgenic mice.

The results were positive. Three to five months later, before the mice would normally start generating their own Aβ plaques, substantial aggregated Aβ appeared in the brains of mice that received the Alzheimer's brain extracts. The degree of Aβ plaque formation was proportional to the amount of Aβ in the donor brain extract and to how long it had to incubate—patterns you would expect to see if the extracts caused the plaques. Most crucially, donor brains lacking aggregated Aβ did not seed plaque formation in the transgenic mice.

DEFINING THE Aβ SEED

Although these experiments showed that Aβ deposition could be initiated by Alzheimer's brain extracts, they did not definitively indicate that Aβ in the extracts accounted for the plaques. That uncertainty compelled us to address several additional questions. First, we asked whether the Aβ deposits that we saw in the mice were merely the material that was injected. Here the answer was no: one week later no evidence could be found of aggregated Aβ in the brain. Rather plaques became apparent only after a lag of a month or more.

Second, we considered the possibility that plaque formation was stimulated by some component of the human brain extract besides the Aβ, perhaps a human virus. We ruled out this prospect by confirming that brain extracts from aged but pathogen-free APP-transgenic mice can seed as effectively as human brain extracts, as long as the samples contain ample aggregated Aβ. In addition, because extracts from non-Alzheimer's brains did not cause Aβ clumping, we could eliminate the possibility that the plaques were just a response to brain injury incurred during the process of delivering the extract.

Although the evidence now strongly pointed to Aβ as the culprit, we wanted more direct proof. Our third step was to selectively remove Aβ from the brain extracts using antibodies that specifically mop up Aβ. This simple procedure abolished the ability of the Alzheimer's brain samples to induce plaque formation. Finally, when we used a strong acid to make the misfolded proteins unfold, the brain extracts failed to induce plaque formation. We thus confirmed that the shape of the protein governs its ability to induce the misfolding and aggregation of other Aβ molecules.

We were now reasonably certain that misfolded Aβ was the active seeding agent in the brain samples, but a key piece of the puzzle remained elusive. If aggregated Aβ alone is the seed, it should be possible to induce plaques using Aβ that is synthesized and made to clump in a test tube in the absence of the many other substances in the brain. We knew that seeding with synthetic proteins might be challenging because studies with prions had shown that laboratory material can differ in subtle but apparently important ways from that taken directly from the brain.

With this caveat in mind, we injected various forms of synthetic, aggregated Aβ into APP-transgenic mice, then waited out the usual incubation period of three to five months. The results were disappointing; no obvious initiation of plaque formation was apparent in this time frame. Recently, however, Prusiner, Jan Stöhr, Kurt Giles and their collaborators at U.C.S.F. injected synthetic Aβ fibers into the brains of APP-transgenic mice. After a prolonged incubation period of more than six months, the mice showed clear evidence of seeded Aβ deposition in the brain. Although the synthetic seeds proved less potent than naturally generated Aβ seeds, the findings provide a persuasive demonstration that pure, aggregated Aβ alone, in the absence of other factors, is able to stimulate the formation of Aβ deposits in the brain.

In more recent experiments, we have begun to investigate the features of Aβ seeds that enable them to promote protein clumping in the brain. Because most of the Aβ protein in the seeding extracts is contained in the long, insoluble fibers, we expected that these fibers would be the most effective seeds. The results surprised us. By spinning the brain extracts at high speed in a centrifuge, we divided the Aβ-rich brain extracts into two components: an insoluble pellet containing mostly Aβ fibers at the bottom of the centrifuge tube and a clear liquid above the pellet containing very small, soluble forms of the Aβ protein. As anticipated, the vast majority of the Aβ settled into the pellet, which, when broken up and injected into the brains of transgenic mice, induced Aβ aggregation as effectively as did the whole-brain extract. Unexpectedly, though, the soluble portion also strongly induced Aβ aggregation and plaque formation, despite containing less than one one-thousandth as much Aβ as the pellet fraction. What is more, the soluble seeds were readily destroyed by an enzyme, proteinase K, whereas the insoluble seeds were not.

There is good news and bad news in the variable size and fragility of Aβ seeds. The bad news is that small, soluble assemblies, which can move through the brain with greater ease than the larger fibers, are particularly potent seeds. On the other hand, their sensitivity to proteinase K hints that soluble seeds might be especially amenable to treatments designed to eliminate them from the brain. Also, being soluble, the small seeds might be readily detectable in bodily fluids and so might serve as molecular sentinels for the early diagnosis of Alzheimer's, possibly well before the onset of dementia. Because protein seeding appears to begin at the very earliest stages of the disease, having a way to detect and neutralize those seeds could go a long way toward preventing brain damage and dementia.

BEYOND ALZHEIMER'S

NATURE SELDOM MISSES an opportunity to exploit a mechanism for multiple purposes, and seeded protein aggregation is no exception. It turns up not only in disease but also in beneficial processes. In the 1990s, for instance, Reed Wickner of the NIH proposed that some fungal proteins use this strategy to aid in cell survival, a postulate that now has been confirmed in numerous labs. Moreover, Susan Lindquist of the Massachusetts Institute of Technology and Eric R. Kandel of Columbia University have championed the intriguing hypothesis that the prionlike propagation of specific proteins helps to stabilize brain circuits, thereby acting to preserve long-term memories.

So far, however, the lion's share of the research points to a role for seeded protein aggregation in disease. Proteins whose seeded aggregation has been implicated in brain disorders include α-synuclein (in Parkinson's), superoxide dismutase-1 (in ALS), TDP-43 (in ALS and frontotemporal dementia), huntingtin (in Huntington's disease) and tau (in a number of neurodegenerative diseases). Many other neurodegenerative diseases involve protein aggregation, and it will be important to see whether the seeding principle applies to these as well.

In a new development, investigators have discovered that some proteins involved in the regulation of gene function include a prionlike domain—that is, a stretch of amino acids that enables a protein to induce its same structure in like molecules. By their nature, these proteins tend to aggregate, a proclivity that can be augmented by certain mutations. A research team led by J. Paul Taylor of St. Jude Children's Research Hospital in Memphis and James Shorter of the University of Pennsylvania has reported that mutations in the prionlike domains of nucleic acid–binding proteins called hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy, a complex malady affecting the nervous system, muscle and bone. Moreover, seeded aggregation has been demonstrated experimentally for other proteins that cause conditions outside the nervous system, such as certain amyloidoses—and the spectrum of disorders involving prionlike propagation of proteins may continue to grow.

If therapies are to emerge from our growing understanding of the seeding concept, we must establish how misfolded proteins injure cells and tissues; such information could help block damage even if halting unwanted protein aggregation itself proves difficult. Research shows that aggregated proteins can disable cells in many ways, ranging from toxic interactions of the aggregates with a cell's components to preventing normal proteins from reaching the sites where they usually function. At the same time, we must understand more fully how pathogenic proteins arise and break down and the conditions under which they misfold and form seeds. Further insights into the progression of disease will also certainly come from clarifying how cells take up, transport and release protein seeds. Finally, a critical open question is why growing old so strongly increases risk for neurodegenerative diseases. Answers to these questions could suggest new ways to defang pathogenic proteins.

The weight of evidence increasingly favors the once unorthodox notion that a simple change in shape can transform a protein from friend to foe. In his Nobel Prize lecture describing the discovery of prions, Prusiner predicted that the basic process by which prions involved in mad cow and related illnesses impose their toxic features on normal proteins would be found to operate in other degenerative diseases. The past decade has witnessed the experimental confirmation of this prediction. Indeed, prionlike seeded protein aggregation may explain the origin of some of the most feared diseases of old age—and provide a compelling conceptual framework that may one day translate into treatments that alter the relentless progression of neurodegenerative illnesses. SA

MORE TO EXPLORE

Pathogenic Protein Seeding in Alzheimer Disease and Other Neurodegenerative Disorders. Mathias Jucker and Lary C. Walker in *Annals of Neurology,* Vol. 70, No. 4, pages 532–540; October, 2011.

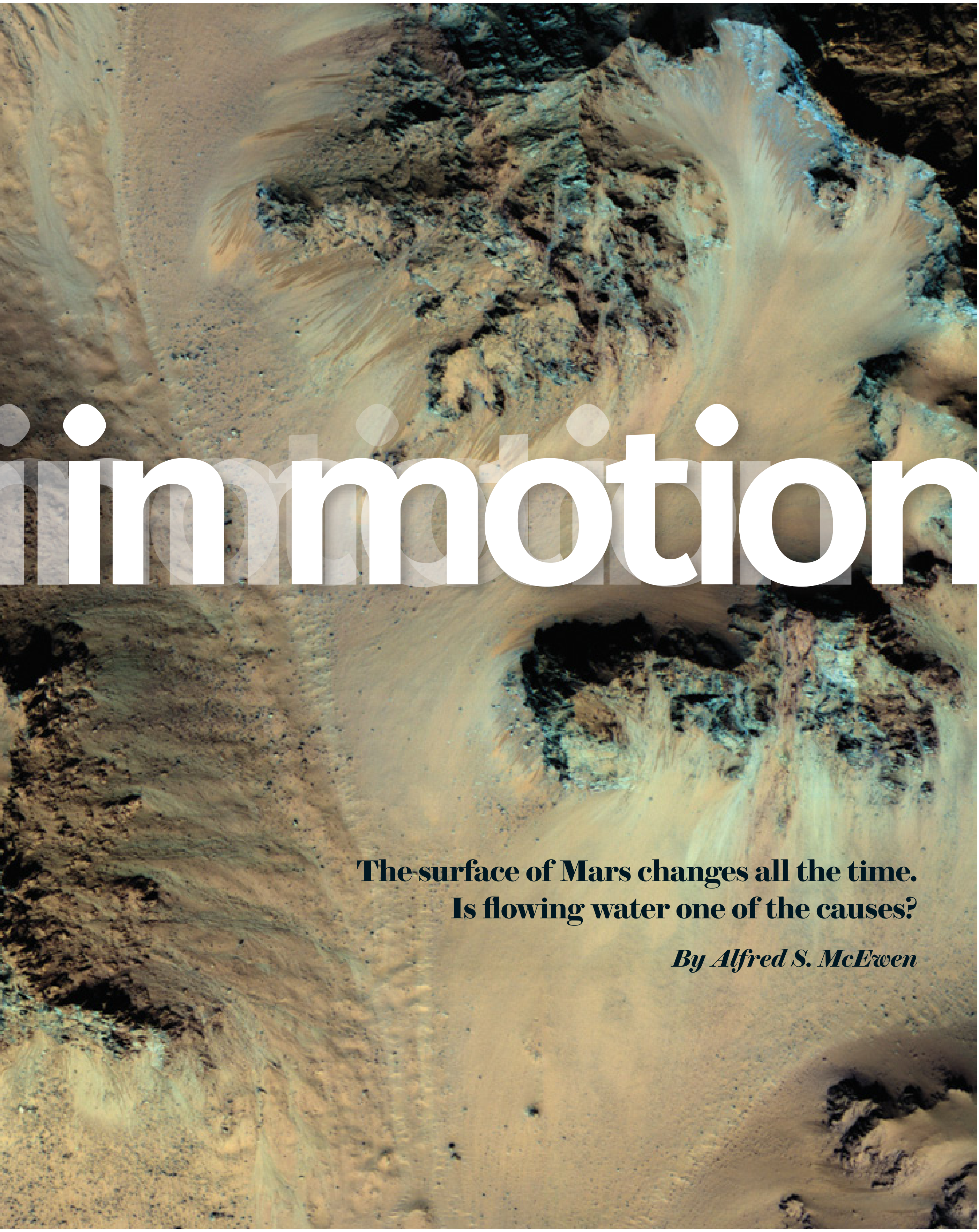
Prion-Like Spread of Protein Aggregates in Neurodegeneration. Magdalini Polymenidou and Don W. Cleveland in *Journal of Experimental Medicine,* Vol. 209, No. 5, pages 889–893; May 7, 2012.

SCIENTIFIC AMERICAN ONLINE
To watch a slide show of a cascading chain of toxic proteins, go to **ScientificAmerican.com/may2013/prions**

PLANETARY SCIENCE

mars

HALE CRATER on Mars may contain liquid water, as evidenced by streaks such as these lining steep hillsides inside the crater.



in motion

The surface of Mars changes all the time. Is flowing water one of the causes?

By Alfred S. McEwen

Alfred S. McEwen is a professor of planetary science at the University of Arizona. He is currently the principal investigator for HiRISE and is also working on missions to Saturn and Earth's moon.

Discoveries of water on Mars are now so common that the subject has become the butt of jokes among planetary scientists:

"Congratulations—you've discovered water on Mars for the 1,000th time!"

Most of these findings have involved either visual evidence for ancient, long-gone water or evidence for present-day ice, vapor or hydrated minerals. The discovery of actual liquid water on the surface, in the present day, could change the course of Mars exploration. Where there is water on Earth, there is almost always life. Confirming the existence of water on Mars would therefore greatly improve the prospect of finding extraterrestrial life. This is the story of continuing efforts to uncover what role, if any, liquid water plays on Mars today.

The first credible evidence of modern-day water arrived in 2000, when NASA unveiled news that the Mars Global Surveyor (MGS) spacecraft had identified plentiful surface features that closely resembled gullies on Earth carved by flowing water. The Martian gullies suggested that "there may be current sources of liquid water at or near the surface of the red planet," a NASA press release asserted at the time. The gullies drew the attention of many planetary scientists because they were widely believed to form by running water or flows of wet debris.

Yet troubling questions soon arose. Tens of thousands of these gullies, some of them several kilometers long, dot slopes in the Martian middle latitudes, implying quantities of liquid that are very difficult to explain. The planet's atmospheric pressure is so low, less than 1 percent of that on Earth, that pure water on the surface will rapidly freeze, evaporate or boil away.

Some researchers argued that the gullies must be relics of the past, when the planet experienced greater seasonal temperature swings. Then, in 2006, new data from MGS showed that light-colored material had spilled out of gullies just within the preceding few years. The gullies were not fossils after all.

Fortunately, as the gully intrigue began to swell, a capable new spacecraft had just arrived at Mars. The Mars Reconnaissance Orbiter (MRO) carries the High-Resolution Imaging Science Experiment (HiRISE), for which I am the principal investigator. The most powerful camera ever flown on an interplanetary mission, HiRISE would soon provide critical evidence about the gullies. But it would also give us something more.

While MRO's detailed new imagery unraveled the mysteries

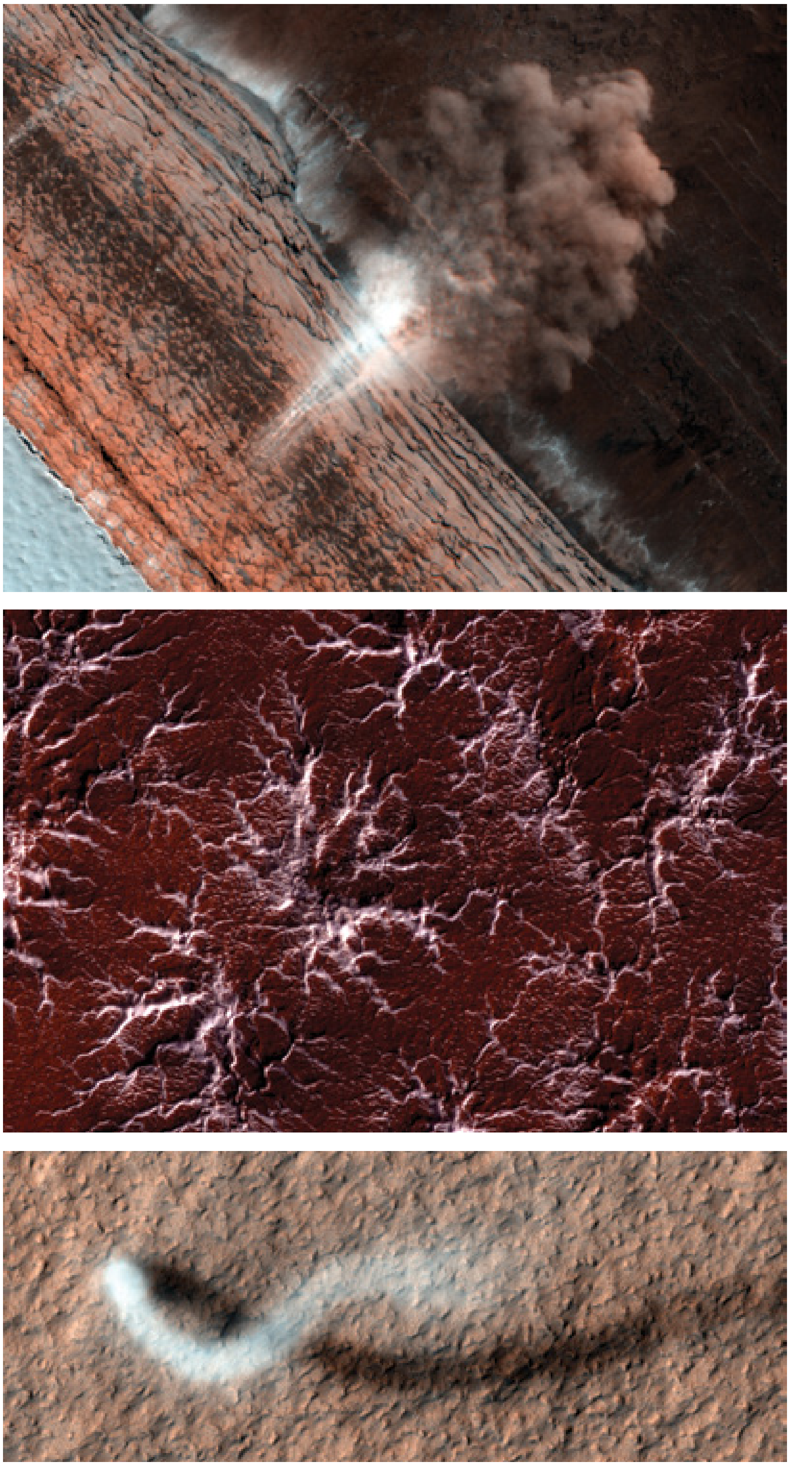
IN BRIEF

High-resolution orbital imaging over multiple Martian years is revealing all manner of surface changes, some of which may involve liquid water.

Surface features known as gullies were once thought to require the presence of water, but recent evidence suggests otherwise.

A newly discovered class of features on warm slopes may mark the flow of salty water. These sites could be the best places to look for microbial life on Mars.

ALL PHOTOGRAPHS COURTESY OF NASA/JPL/UNIVERSITY OF ARIZONA



SURFACE ACTIVITY documented from orbit includes avalanches, "spiders" carved by carbon dioxide and a dust devil 800 meters tall (*top to bottom*).

of the gullies, a student in my laboratory discovered a perplexing feature of Mars's surface that had never been seen before—streaks across the surface, flowing downhill, that grow slowly and change with the seasons in ways that suggest they are flows of liquid water. These streaks have turned out to be the strongest evidence for the presence of flowing water on Mars. They have provided us with new ideas about how liquid water could exist in such a forbidding environment—and the best indication yet that Mars might still contain a niche near the surface in which life can survive.

FOREIGN BUT FAMILIAR

FROM ITS INCEPTION, we designed HiRISE with gullies and other small-scale structures in mind, and the camera has allowed us to examine these features in greater detail than ever before. HiRISE can photograph any part of the Martian surface, in color, at submeter resolution (0.25 to 0.32 meter per pixel). MRO can also precisely point the camera at a feature of interest on multiple orbits to look for changes in the landscape. In addition, the spacecraft can map the topography in stereo to create a three-dimensional view.

HiRISE's combination of high-resolution stereo and color, along with repeated imaging over several Martian years, has dramatically improved our knowledge of the changing surface of the planet. We have documented windblown dust and sand, avalanches of rocks, frost and ice, and new impact sites dotting the surface [*see photographs at left*].

One of our very first HiRISE images from its mapping campaign showed a slope in the southern midlatitudes with the mysterious gullies that MGS had discovered. Much of the south-facing slope was still in the shadow of the crater rim at the time, during the southern winter season. Frost, primarily frozen carbon dioxide, largely covered the slope—except in some of the gully channels. This missing frost suggested that something was happening within the gully itself.

It took about two Martian years (nearly four Earth years) to catch numerous gullies in the act of changing, but the data eventually revealed a startling trend. The gullies became active—developing new alcoves, channels and fans—when carbon dioxide frost covered the ground. We had seen frozen carbon dioxide, or dry ice, in action before. In the polar regions of Mars, carbon dioxide's seasonal sublimation (its change from a solid to a gas) produces bizarre cold jets, similar to geysers. On the layered deposits of ice and dust near Mars's south pole, the sublimation of carbon dioxide creates "spiders," radial networks of channels from the flow and erosion of gas trapped underneath dry ice. These are very unusual landforms, not seen on Earth, so it makes sense that they developed by an alien process.

In contrast, the gullies on Mars look so much like ravines or very large gullies on Earth that many researchers assumed they were shaped by Earth-like processes. Instead we would discover that they also can arise by a process that does not happen at all on the familiar terrain of Earth.

The carbon dioxide, my colleagues and I ultimately concluded, must trigger the formation of gullies by waterless processes, such as the sublimation of dry ice. These processes might cause rock and soil to flow downhill like a liquid.

Invoking dry ice frost as the cause of the gullies explained a number of mysteries. First, we had wondered why gullies formed predominantly on pole-facing slopes lying between 30 and 40 degrees south latitude and on all steep slopes poleward of 40 degrees south latitude. That pattern, it turns out, matches the seasonal distribution of carbon dioxide frost. Second, we could not explain why the gullies were far more active in the southern hemisphere than in the north. During Mars's current position in the cycle of orbital precession, southern winters are longer than northern winters, so more frost accumulates. When dry ice coats the ground, the surface and atmospheric temperatures stabilize at the carbon dioxide frost point, about –125 degrees Celsius. Pure water freezes at zero degrees C, so the season of dry ice frost is the least likely time of the year for liquid water to be present.

SOMETHING NEW UNDER THE SUN

I WAS BEGINNING to conclude that most of the surface erosion on Mars today was driven by carbon dioxide frost—that the idea of modern-day water on Mars might be "all wet." At all latitudes on Mars, the surface shifts in response to dry environmental processes, such as the wind, but the most extensive changes take place in the region of seasonal carbon dioxide cover.

Then, in mid-2010, an undergraduate HiRISE researcher discovered something very different. Lujendra ("Luju") Ojha was working to produce digital terrain models from stereo pairs of HiRISE images. I suggested that he use change-detection techniques on a stereo pair in an area where we had seen channel incision in a gully. The first image of the stereo pair was acquired two months before the second, and we wanted to find out if anything had changed in that brief interval. Ojha created the digital terrain model, then used those data to synthesize an overhead view, as if the orbiter had been looking straight down at its target. Finally, he compared the images to seek out subtle changes.

What Ojha found was puzzling. In the later image, many narrow, dark lines extended downhill from steep, rocky areas. Those streaks were absent from the first image.

I did not know what to make of the anomalous lines on the surface, so we gathered more information. First, we examined all stereo pairs acquired over steep slopes. We had already acquired hundreds of such pairs to study gullies, well-preserved impact craters and bedrock exposures. Among those images, we found other examples of the curious surface features. Each time we saw the same thing: dark lines, with no discernible topography, on steep slopes near bedrock. All the images capturing these features were acquired in the southern midlatitudes on equator-facing slopes during the summer—the opposite season of when carbon dioxide drives surface activity.

Dark lines running downhill naturally makes us earthlings think of water or wet soils, but my colleagues and I chose to be cautious.

CAUGHT IN THE ACT

BEFORE WE COULD DETERMINE the cause of the streaky slopes, we needed to collect more evidence about when and where they occur. We suspected several things about these summertime flows: that they grew slowly and incrementally over a period of weeks or months, then faded or disappeared in the colder seasons, and then re-formed once more the next summer.

Because we did not recognize the warm-season flows until the second southern summer of MRO's residence at Mars, we had to wait until the third southern summer, in early 2011, to test our hypotheses. We picked six sites to intensively monitor for changes, and we spot-checked other ones. These observations confirmed our suspicions, and we published our findings in *Science* in August 2011.

In our *Science* paper, we called the flow features "recurring slope lineae," or RSL, a purely descriptive name that does not assume we know their origin. If we had instead called them "water tracks," we would have wrongly conveyed that we knew with certainty how they had come about.

By that time, however, we had become more convinced that water was somehow involved with this newfound phenomenon. After all, RSL favored unusual environments: the middle latitudes, on especially warm slopes in the south, where the summers are hotter than in the north [*see box on opposite page*]. An instrument on the Mars Odyssey spacecraft has measured afternoon surface temperatures as high as 27 degrees C in such locations.

Temperatures above zero degrees C would seem perfectly adequate for liquid water, were it not for the thin Martian air, which forces pure water to rapidly evaporate or even boil away. Yet salty water is a quite different substance. The surface of Mars is very salty, as documented by every successful lander and rover, by spectrometers in orbit, and by the chemical analysis of Martian meteorites. Water flowing on the surface or in the subsurface of Mars must also contain high levels of salts.

When salty water cools, it either partially freezes into ice or precipitates some of its salts, or both. Whatever liquid is left over is now in its so-called eutectic composition, which is water with just the right salt concentration to remain liquid at the coldest possible temperatures. A salty brine of iron sulfate or calcium perchlorate (two common salts on Mars), in its eutectic composition, can remain liquid down to about –68 degrees C.

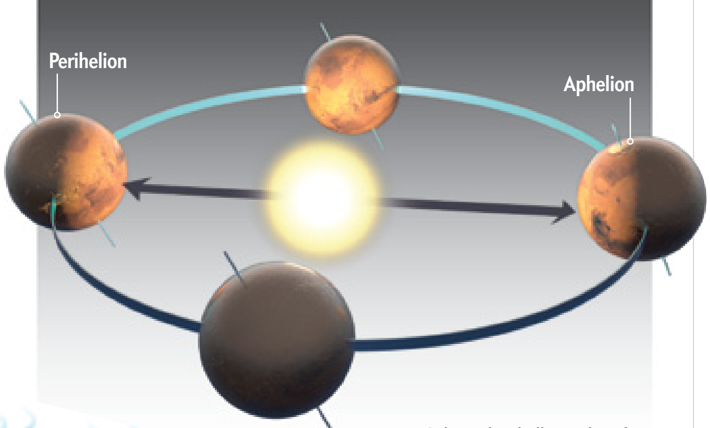
Newly discovered dark streaks on Mars have emerged as the strongest evidence for the presence of flowing water on the planet—and provide the best indication yet that Mars might still contain a niche in which microbial life can survive.

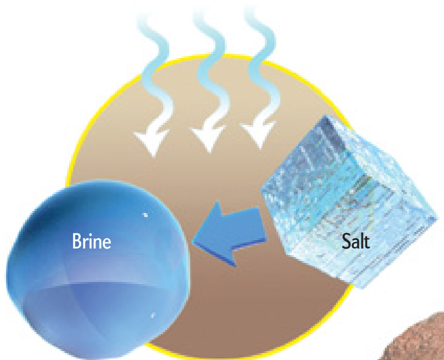
How Can Water Exist on Mars?

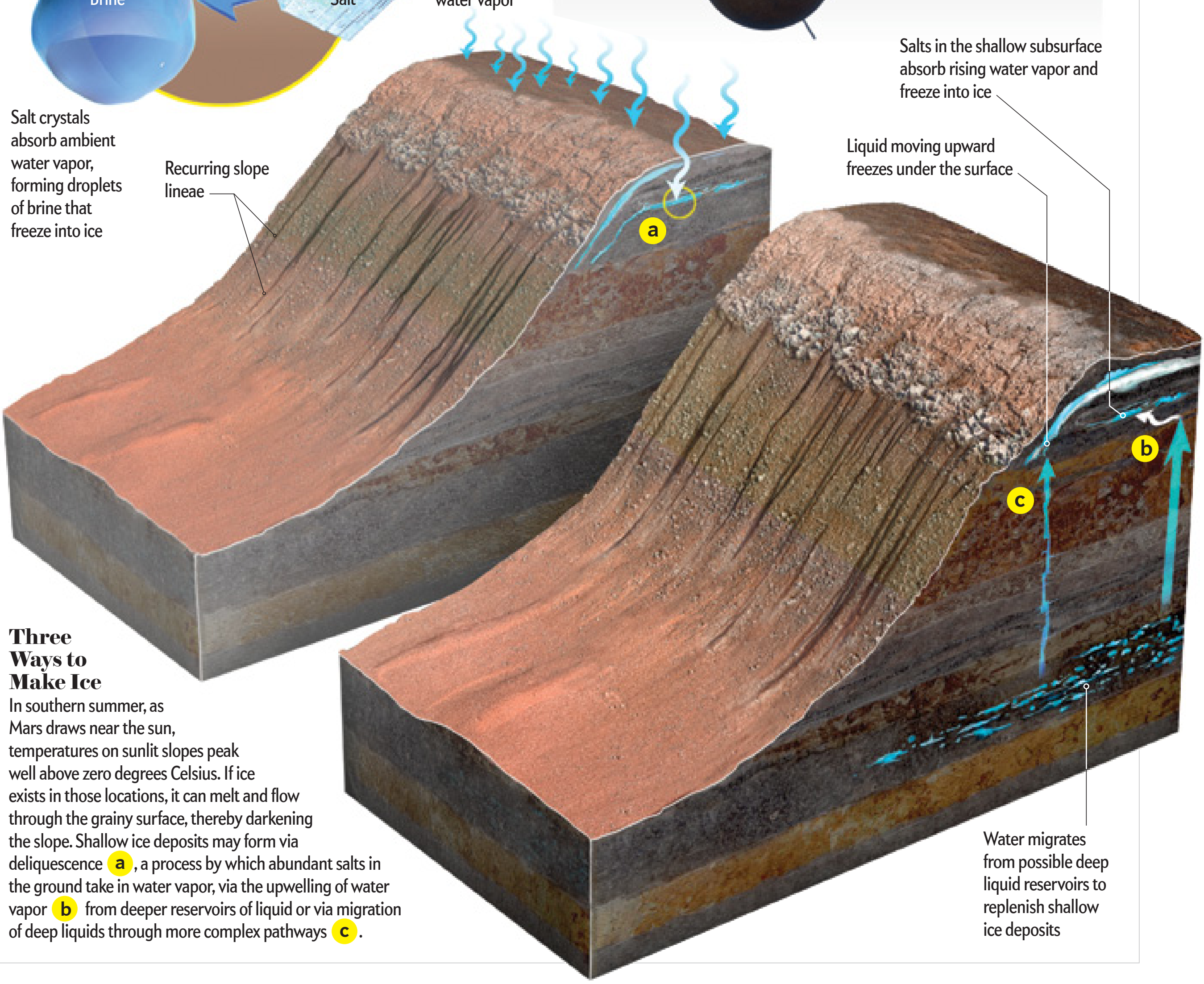
Planetary scientists are still debating what causes dark lines to appear annually on southern Martian slopes. But numerous lines of evidence, including the fact that these streaks are found on warm, sun-facing hillsides, implicate the seasonal melting of shallow deposits of salty frozen water. The slope cutaways (*below*) demonstrate possible mechanisms for delivering water ice to the shallow subsurface, where sunlight can melt it in warmer Martian months (*right*).

Southern Summer: The Great Thaw

Mars follows an elliptical orbit that carries the Red Planet significantly closer to the sun at perihelion (the closest point in its orbit) than at aphelion (the farthest point). Mars's orbital orientation shifts, or precesses, on timescales of tens of thousands of years; currently the planet reaches perihelion around southern summer, producing relatively hot summers on that hemisphere. Dark lines appearing on southern slopes during warm months could therefore represent melting ice.



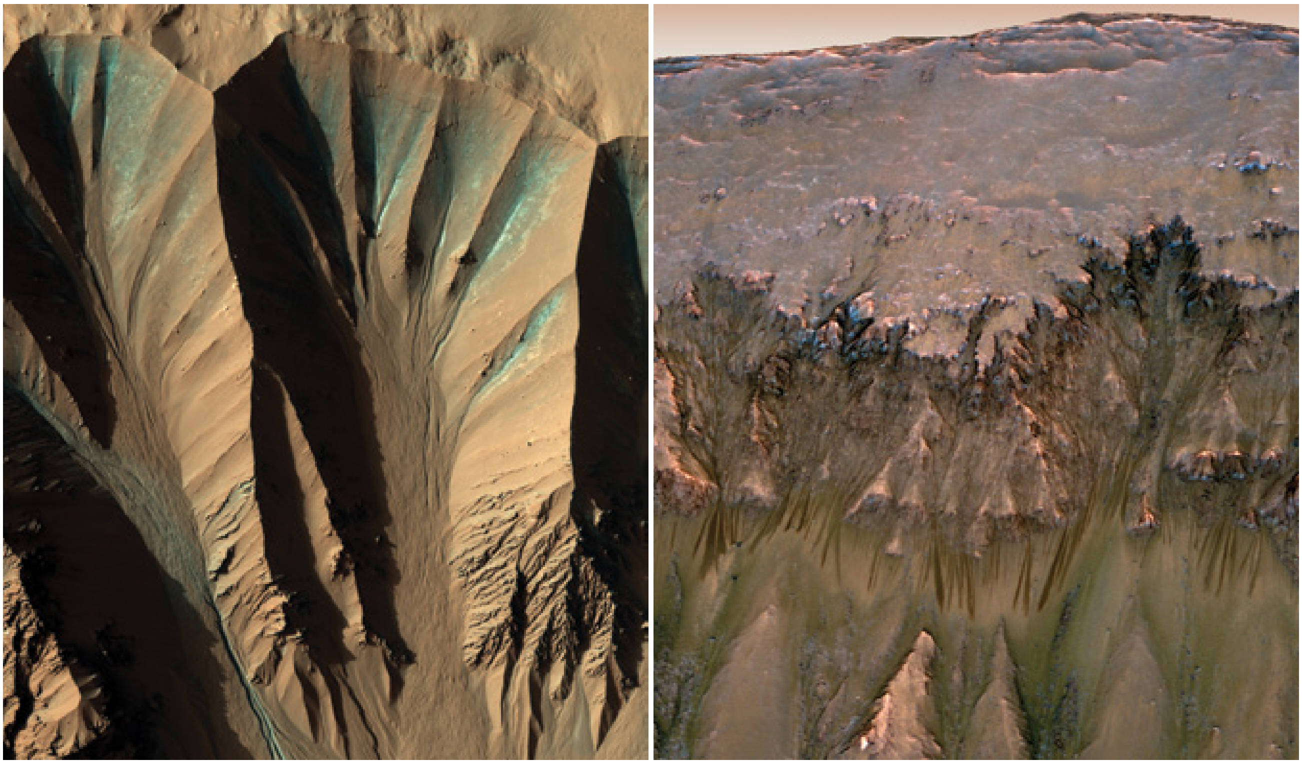




Three Ways to Make Ice

In southern summer, as Mars draws near the sun, temperatures on sunlit slopes peak well above zero degrees Celsius. If ice exists in those locations, it can melt and flow through the grainy surface, thereby darkening the slope. Shallow ice deposits may form via deliquescence (a), a process by which abundant salts in the ground take in water vapor, via the upwelling of water vapor (b) from deeper reservoirs of liquid or via migration of deep liquids through more complex pathways (c).

Illustration by Chuck Carter



RECENT EPISODES of erosion or deposition in Martian gullies (*left*), presumably driven by dry ice frost rather than water, appear blue in a false-color image. Flowing water may, however, produce the recurring slope lineae streaking crater walls (*right*).

Furthermore, such eutectic liquids can survive environmental exposure much better than water can—they evaporate at less than one tenth the rate of pure water. The unusual properties of eutectic brines would make them far more stable on Mars than pure water, so we began to believe that these strange flows on warm slopes might, in fact, be the result of salty water.

Nevertheless, we followed the standard practice of pursuing multiple working hypotheses. Could some dry—or nearly dry—phenomenon explain these observations? No purely dry process, such as rockfalls or landslides, has been described that can account for the seasonality, the incremental growth and the sensitivity to temperature, and we had never seen anything like them on Earth's desiccated moon.

Next we considered that volatile compounds such as water might be involved but only as minor players. If volatiles make soil particles stick together, the warmest temperatures could sublimate away that adhesive, thus releasing dry grains to flow downhill. (NASA's Phoenix mission had encountered such stickiness in 2008, when soil stubbornly stuck to the inside of the robot's inverted scoop instead of falling into the intake openings for the onboard instruments.) Yet that hypothesis could not explain why RSL show no topographic relief nor why they fade. Water that darkens the soil and flows only when warm, before freezing again at night, best explained the observations.

A watery origin for such surface activity would not be totally alien. In Antarctica, similar-looking water tracks do form from the shallow subsurface flow of salty brines. Tantalizingly, researchers have found microbes living in these Antarctic water tracks. So why not declare, "Eureka"? We have learned from the gullies to be circumspect—appearances can be deceiving. (Interestingly, though, we have found many RSL near small channels or gullies, suggesting that some subset of the gullies may be carved by water after all.) Additionally, the terrestrial analogues can carry us only so far: Mars gets much colder at night than Antarctica does, so the active layer of unfrozen soil is much thinner.

CLAIMS OF WATER, WATER EVERYWHERE

WE WERE NOT THE FIRST, nor even the second, batch of researchers to suggest the presence of liquid water on modern-day Mars. Photographs from the Phoenix mission showed what looked like water droplets on the legs of the robotic lander. That idea seemed pretty crazy to me until I learned about deliquescence, a process by which salts absorb water from the atmosphere when both the temperature and relative humidity of the air are sufficiently high. If Phoenix's retrorockets kicked up perchlorate salts when it landed, the conditions may have been right for the salts to absorb water and create droplets of liquid. I thought saltiness was a new paradigm for producing water on Mars until I realized that Robert B. Leighton and Bruce C. Murray of the California Institute of Technology had published this idea in 1966.

Deliquescence appears to be a tempting way to explain RSL, but the process produces very tiny amounts of water from the thin Martian air—not enough to flow down slopes unless some mechanism allows it to accumulate over time.

Perhaps melting subsurface ice is responsible for RSL. We know, based on the remote sensing of neutrons from orbit, that the middle to high latitudes harbor shallow ice deposits. Some of the fresh impact craters we have discovered with HiRISE exposed this ice down to 40 degrees north latitude, somewhat closer to the equator than expected.

What are these ice deposits like? Surprisingly, the ice excavated from below the rock-strewn surface is remarkably clean, with very little soil mixed into the frozen layer. This means that the ice is not the product of condensation from the atmosphere, which fills the spaces between fine-grained regolith particles. Nor does it seem to be a remnant of snowfall, which does not last long on the surface before it sublimates away. Instead perhaps thin films of salty water migrate from below and refreeze into a clean subsurface ice layer.

This mechanism avoids various problems with sublimation. Because nonsalty ice sublimates much faster than frozen brine, almost all of the ice that formed in a past climate in the shallow subsurface would have sublimated away by now. Only the saltiest ice would remain. Steep sun-facing slopes may then absorb the warmth needed, in the summer, to melt the briny ice in places where it persists.

We have observations that support this idea. Peak RSL activity corresponds not to the peak surface heating but to peak temperatures in the shallow subsurface, which occur months later. On the other hand, if summer temperatures are warm enough to melt the briny ice, then the ice should disappear over time. Perhaps it *is* disappearing, and RSL are only active for a few Martian years or decades at each location, or maybe the water is somehow replenished [*see box on page 63*].

In Antarctica, similar-looking water tracks form from the flow of salty brines in the shallow subsurface. Tantalizingly, researchers have found microbes living in these water tracks. But Mars gets much colder than Antarctica.

LOOKING FOR LIFE IN ALL THE RIGHT PLACES

AS OF YET, there has not been any direct identification of water at the RSL sites. The spectrometer on MRO is our best hope for accomplishing this, but it may lack the necessary spatial resolution to pinpoint such narrow stripes across the surface. To make matters worse, MRO's orbit ensures that the spacecraft observes perpetual afternoon on Mars, when water is probably not present or abundant at the surface. From lab studies, we now understand that salty water can be stable on the Martian surface during some seasons and at some locations, principally at two times of day: early morning and early evening. The relative humidity of the air decreases as it warms in the morning and increases as it cools in the evening. There may be brief periods when both the temperature and relative humidity are high enough for certain types of salts to absorb and hold on to water via deliquescence. In the evening, this process may happen after sunset, which is a difficult time to conduct targeted observations. In the morning, the deliquescence happens after sunrise, and the water persists even as the relative humidity drops substantially.

The ideal instrument for confirming or disproving that RSL are formed by liquid water would be a spectrometer with a high spatial resolution (better than five meters, the width of the largest of the RSL) that we can use to observe at multiple times of day, including in the morning. Some of my colleagues and I presented such a mission concept at a recent workshop on future Mars exploration. The mission would also acquire imaging, topographic mapping and temperature mapping, all at high resolution. Such a spacecraft would allow us to confirm the presence of water (or not) and to say something about habitability. If we did not detect water, the phenomenon behind RSL would require a different explanation—something perhaps even more surprising.

If RSL indeed reflect the presence of flowing liquid water, the natural next question is whether that water creates a habitable environment for some salt-loving microbe. We have learned much about extremophile organisms on Earth—species that can survive especially low or high temperatures, extreme aridity or salinity, high levels of radiation, and so on. We know that such organisms do not just survive but can actually reproduce at temperatures below –20 degrees C in certain liquids. Some eutectic solutions are not habitable (as far as we know), so it is not always true that where there is liquid water, there is life on Earth. Yet many of the RSL sites most likely are warmer than –20 degrees C down to a depth of a few centimeters for parts of summer days. And Red Planet extremophiles, if they exist, may be even more tolerant than terrestrial microbes to Martian extremes.

The possible implications of a water-streaked Mars are immense. For now, my colleagues and I are still working to better understand the nature of RSL. We have identified many more sites with active RSL than we reported in our initial *Science* paper in 2011. Other researchers have conducted laboratory studies and Antarctic fieldwork to try to observe or replicate on Earth what HiRISE sees from orbit around Mars. We hope that our combined efforts will shed light on this newfound phenomenon and on whether flowing water is indeed the best candidate for its origins. Perhaps, among the myriad discoveries of water on Mars, the 1,001st time will be the charm. SA

MORE TO EXPLORE

Evidence for Recent Groundwater Seepage and Surface Runoff on Mars. Michael C. Malin and Kenneth S. Edgett in *Science*, Vol. 288, pages 2330–2335; June 30, 2000.

Seasonal Flows on Warm Martian Slopes. Alfred S. McEwen et al. in *Science*, Vol. 333, pages 740–743; August 5, 2011.

Hydrological Characteristics of Recurrent Slope Lineae on Mars: Evidence for Liquid Flow through Regolith and Comparisons with Antarctic Terrestrial Analogs. Joseph Levy in *Icarus*, Vol. 219, No. 1, pages 1–4; May 2012.

SCIENTIFIC AMERICAN ONLINE
View a slide show of recurring slope lineae and other active surface features on Mars at **ScientificAmerican.com/may2013/mars**

EVOLUTION

HUMAN HYBRIDS

DNA analyses find that early *Homo sapiens* mated with other human species and hint that such interbreeding played a key role in the triumph of our kind

By Michael F. Hammer

It is hard to imagine today, but for most of humankind's evolutionary history, multiple humanlike species shared the earth. As recently as 40,000 years ago, *Homo sapiens* lived alongside several kindred forms, including the Neandertals and tiny *Homo floresiensis*. For decades scientists have debated exactly how *H. sapiens* originated and came to be the last human species standing. Thanks in large part to genetic studies in the 1980s, one theory emerged as the clear front-runner. In this view, anatomically modern humans arose in Africa and spread out across the rest of the Old World, completely replacing the existing archaic groups. Exactly how this novel form became the last human species on the earth is mysterious. Perhaps the invaders killed off the natives they encountered, or outcompeted the strangers on their own turf, or simply reproduced at a higher rate. However it happened, the newcomers seemed to have eliminated their competitors without interbreeding with them.

This recent African Replacement model, as it is known, has essentially served as the modern human origins paradigm for the past 25 years. Yet mounting evidence indicates that it is wrong. Recent advances in

IN BRIEF

A long-reigning theory of the origin of *Homo sapiens* holds that our species arose in a single locale—sub-Saharan Africa—and replaced archaic human species, such as the Neandertals, without interbreeding with them.

But recent studies of modern and ancient DNA indicate that these modern humans from Africa did mate with archaic humans and hint that this interbreeding helped *H. sapiens* thrive as it colonized new lands.

Illustration by Brian Stauffer

DNA-sequencing technology have enabled researchers to dramatically scale up data collection from living people as well as from extinct species. Analyses of these data with increasingly sophisticated computational tools indicate that the story of our family history is not as simple as most experts thought. It turns out that people today carry DNA inherited from Neandertals and other archaic humans, revealing that early *H. sapiens* mated with these other species and produced fertile offspring who were able to hand this genetic legacy down through thousands of generations. In addition to upsetting the conventional wisdom about our origins, the discoveries are driving new inquiries into how extensive the interbreeding was, which geographical areas it occurred in and whether modern humans show signs of benefiting from any of the genetic contributions from our prehistoric cousins.

MYSTERIOUS ORIGINS

To fully appreciate the effect of these recent genetic findings on scientists' understanding of human evolution, we must look back to the 1980s, when the debate over the rise of *H. sapiens* was heating up. Examining the fossil data, paleoanthropologists agreed that an earlier member of our genus, *Homo erectus,* arose in Africa some two million years ago and began spreading out of that continent and into other regions of the Old World shortly thereafter. Yet they disagreed over how the ancestors of *H. sapiens* transitioned from that archaic form to our modern one, with its rounded braincase and delicately built skeleton—features that appear in the fossil record at around 195,000 years ago.

Proponents of the so-called Multiregional Evolution model, developed by Milford H. Wolpoff of the University of Michigan and his colleagues, argued that the transformation occurred gradually among archaic populations wherever they lived throughout Africa, Eurasia and Oceania because of a combination of migration and mating that allowed beneficial modern traits to spread among all these populations. In this scenario, although all modern humans shared particular physical features by the end of this transition, some regionally distinctive features inherited from archaic ancestors persisted, perhaps because these traits helped populations to adapt to their local environments. A variant of Multiregional Evolution put forward by Fred Smith, now at Illinois State University, called the Assimilation model, acknowledges a greater contribution of modern traits by populations from Africa.

In contrast, champions of the Replacement model (also known as the Out of Africa model, among other names), including Christopher Stringer of the Natural History Museum in London, contended that anatomically modern humans arose as a distinct species in a single place—sub-Saharan Africa—and went on to completely replace all archaic humans everywhere without interbreeding with them. A looser version of this theory—the Hybridization model proposed by Günter Bräuer of the University of Hamburg in Germany—allows for the occasional production of hybrids between these modern humans and the archaic groups they met up with as they pushed into new lands.

With only the fossil evidence to go on, the debate seemed locked in a stalemate. Genetics changed that situation. With the advent of DNA technology, scientists developed methods for piecing together the past by analyzing genetic variation in contemporary human populations and using it to reconstruct evolutionary trees for individual genes. By studying a gene tree, researchers could infer when and where the last common ancestor of all the variants of a given gene existed, thus yielding insights into the population of origin for the ancestral sequence.

Michael F. Hammer is a population geneticist at the University of Arizona. He studies patterns of genetic variation in modern-day populations to gain insights into the evolutionary origins of *Homo sapiens*.

In a landmark study published in 1987, Allan C. Wilson of the University of California, Berkeley, and his colleagues reported that the evolutionary tree for the DNA found in mitochondria—the energy-producing components of cells—traced back to a female ancestor who lived in an African population around 200,000 years ago. (Mitochondrial DNA, or mtDNA, is passed down from mother to child and treated as a single gene in ancestry studies.) These findings fit the expectations of the Replacement model, as did subsequent studies of small sections of nuclear DNA, including the paternally inherited Y chromosome.

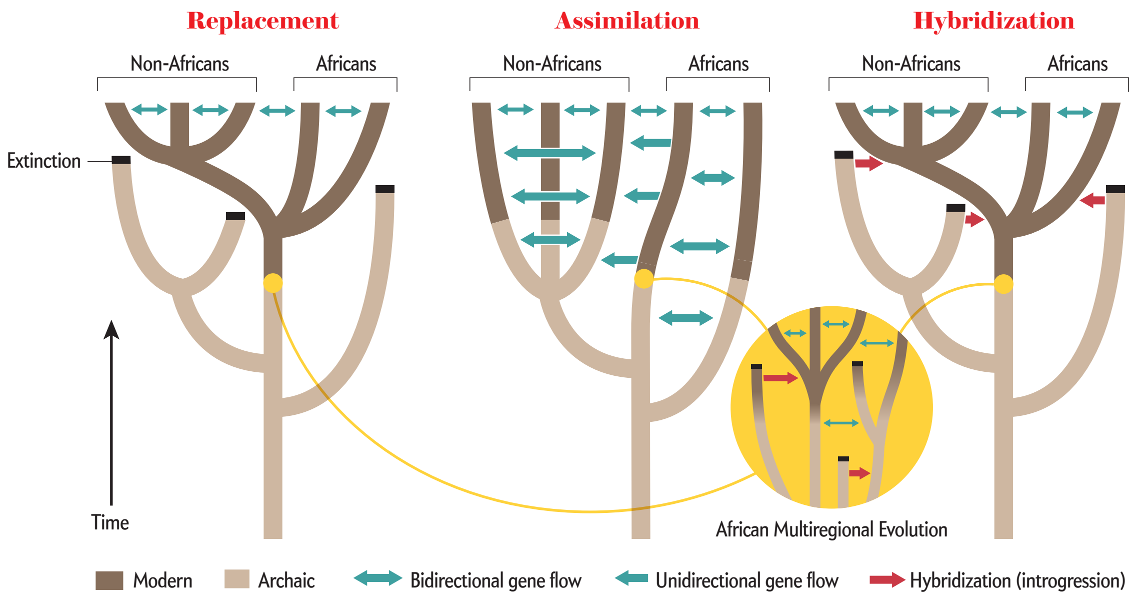
Further genetic support for the Replacement model came a decade later, when Svante Pääbo, now at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and his colleagues succeeded in extracting and analyzing a fragment of mtDNA from Neandertal bones. The study found that the Neandertal mtDNA sequences were distinct from those of contemporary humans and that there was no sign of interbreeding between them—a result that subsequent studies of mtDNA from additional Neandertal specimens confirmed.

To many researchers, these ancient mtDNA findings put the nail in the coffin of the Multiregional Evolution and Assimilation models. Others, however, maintained that their reasoning suffered from a fundamental problem. The absence of a signal for interbreeding in any single independent region of the genome, such as in mtDNA, does not necessarily mean that other regions of the genome also lack signs of interbreeding. Further, any particular region of the genome that is tested could lack signs of interbreeding even if interbreeding did occur because DNA from other species (introgressed DNA) that provided no survival advantage to *H. sapiens* would tend to disappear from the gene pool over time by chance.

The best way to approach the question of whether *H. sapiens* interbred with archaic species, such as the Neandertals, is thus to compare many regions of their genomes or, ideally, their entire genomes. Yet even before such data became available for archaic humans, some early genetic studies of modern human DNA bucked the majority trend and found data contrary to the Replacement model. One clear example came from a 2005 study led by Daniel Garrigan, then a postdoctoral researcher in my laboratory. Garrigan looked at DNA sequences from a nonfunctional region of the X chromosome known as RRM2P4. Analyses of its reconstructed tree pointed to an origin for the sequence, not in Africa but in East Asia around 1.5 million years ago, implying that the DNA came from an archaic Asian species that intermixed with the *H. sapiens* originally from Africa. Similarly, that same year our lab discovered variation in another nonfunctional region of the X chromosome, Xp21.1, with a gene tree showing two divergent branches that had probably been evolving in complete isola-

Sourcing *Homo sapiens*

Scientists have long debated how anatomically modern humans (*dark brown lines*) evolved from their archaic predecessors (*light brown lines*). In the theories depicted here, modern humans originated in Africa. According to the Replacement model, they then replaced archaic human species throughout the Old World without interbreeding with them. The Assimilation model, in contrast, holds that beneficial modern features from Africa spread among these archaic groups by means of a combination of steady migration and mating known as gene flow (*green arrows*). The Hybridization model, for its part, posits that modern humans mated only rarely, or hybridized (*red arrows*), with archaic species as they replaced them. The African Multiregional Evolution model focuses exclusively on the archaic-to-modern transition period in Africa and argues for gene flow and hybridization between distinctive archaic groups there. Such a scenario could theoretically have preceded Replacement, Assimilation or Hybridization.



tion from one another for around a million years. One of these branches was presumably introduced into anatomically modern populations by an archaic African species. The RRM2P4 and Xp21.1 evidence thus hinted that anatomically modern humans mated with archaic humans from Asia and Africa, respectively, rather than simply replacing them without interbreeding.

OUR ARCHAIC DNA

MORE RECENTLY, advances in sequencing technology have enabled scientists to quickly sequence entire nuclear genomes—including those of extinct humans, such as Neandertals. In 2010 Pääbo's group reported that it had reconstructed the better part of a Neandertal genome, based on DNA from several Neandertal fossils from Croatia. Contrary to the team's expectations, the work revealed that Neandertals made a small but significant contribution to the modern human gene pool: non-Africans today exhibit a 1 to 4 percent Neandertal contribution to their genomes on average. To explain this result, the researchers proposed that interbreeding between Neandertals and the ancestors of all non-Africans probably occurred during the limited period when these two groups overlapped in the Middle East, perhaps 80,000 to 50,000 years ago.

Hot on the heels of the Neandertal genome announcement, Pääbo's team revealed an even more startling discovery. The researchers had obtained an mtDNA sequence from a piece of an approximately 40,000-year-old finger bone found in Denisova Cave in the Altai Mountains in Siberia. Although researchers could not determine from the anatomy of the bone what species it represented, the genome sequence showed that this individual belonged to a population that was slightly more closely related to Neandertals than it or Neandertals were to our species. Further, after comparing the Denisovan sequence with its counterpart in modern populations, the team found a significant amount of DNA from a Denisovan-like population—a contribution of 1 to 6 percent—in Melanesians, Aboriginal Australians, Polynesians, and some related groups in the western Pacific but not in Africans or Eurasians.

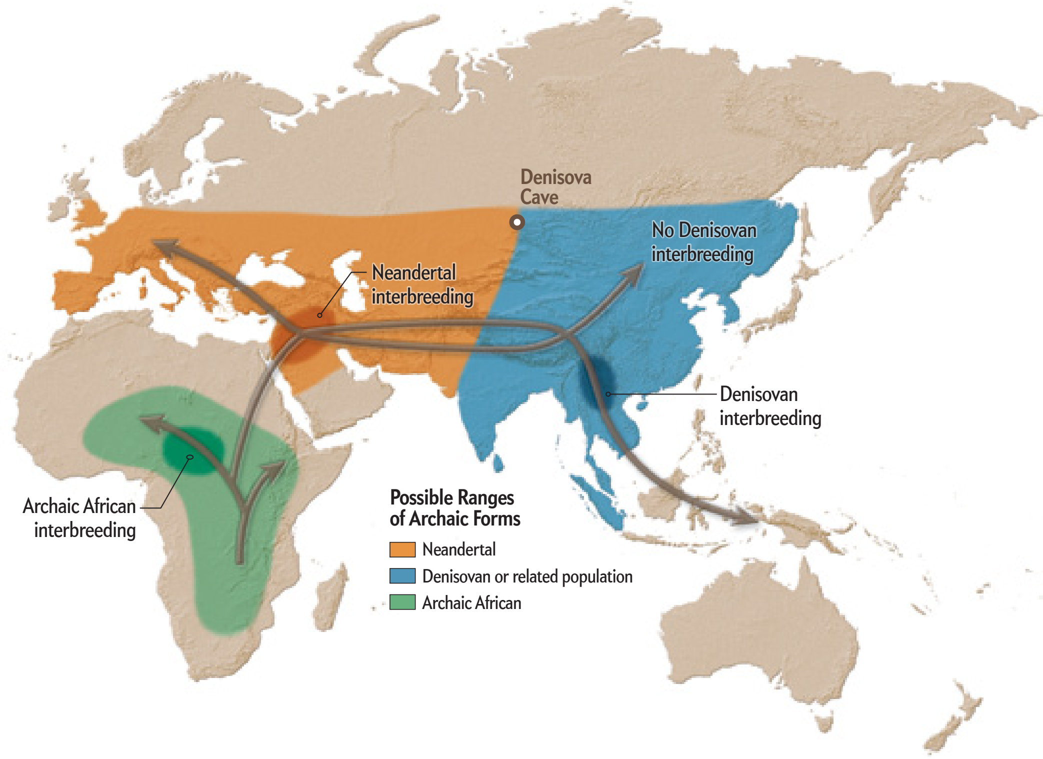
To explain this increasingly complex pattern of DNA sharing, the researchers proposed that interbreeding with various archaic forms had occurred at two different times: first, when anatomically modern humans initially migrated out of Africa and mated with Neandertals and, later, when the descendants of these initial migrants made their way to Southeast Asia and encountered Denisovan-like humans. The doubly mixed ancestors of present-day groups such as Melanesians then reached Oceania around 45,000 years ago, and a second wave of anatomically modern humans migrated to East Asia without interbreeding with Denisovan-like ancestors.

SOURCE: MICHAEL F. HAMMER

Graphic by Jen Christiansen

Evidence for Interbreeding

The fossil record indicates that *Homo sapiens* originated in Africa by around 200,000 years ago. Recent DNA studies suggest that these anatomically modern humans mated with the archaic humans they happened on as they migrated within Africa and out into the rest of the Old World (*gray arrows*). The map below shows ranges of archaic species—including a species recently identified on the basis of DNA from a fossilized finger bone from Denisova Cave in Siberia—and regions where interbreeding with moderns may have occurred (*ellipses*), based on the available DNA evidence.



Although discussion of interbreeding in human evolution typically focuses on mating between anatomically modern humans and Neandertals in Europe or other archaic forms in Asia, the greatest opportunity for interspecies coupling would have been in Africa, where anatomically modern humans and various archaic forms coexisted for much longer than they did anywhere else. Unfortunately, the tropical environments of the African rain forest do not favor the preservation of DNA in ancient remains. Without an African ancient DNA sequence to reference, geneticists are currently limited to scouring the genomes of modern-day Africans for signs of archaic admixture.

To that end, my team at the University of Arizona, in collaboration with Jeffrey D. Wall of the University of California, San Francisco, gathered sequence data from 61 regions of the genome in a sample of three sub-Saharan African populations. Using computer-based simulations to test various evolutionary scenarios, we concluded in a 2011 report that these populations received a 2 percent contribution of genetic material from an extinct human population. This group would have split off from the ancestors of anatomically modern humans some 700,000 years ago and interbred with moderns around 35,000 years ago in Central Africa.

Another genetic hint of archaic admixture in Africa has come from a study of an unusual Y chromosome sequence obtained from an African-American man living in South Carolina whose DNA was submitted to a direct-to-consumer genetic testing company for analysis. His particular variant had never been seen before. Comparing his Y sequence against those of other humans, as well as chimpanzees, my team determined that his sequence represents a previously unknown Y chromosome lineage that branched off the Y chromosome tree more than 300,000 years ago. We then searched a database of nearly 6,000 African Y chromosomes and identified 11 matches—all of which came from men who lived in a very small area of western Cameroon. The finding, published in March in the *American Journal of Human Genetics,* indicates that the last common ancestor of all modern Y chromosome variants is 70 percent older than previously thought. The presence of this very ancient lineage in contemporary people is a possible sign of interbreeding between *H. sapiens* and an unknown archaic species in western Central Africa.

Recently the fossil record, too, has yielded support for the possibility of interbreeding within Africa. Just after the publication of our results in 2011, a group of paleontologists working at the Iwo Eleru site in Nigeria reanalyzed remains that exhibit cranial features intermediate between those of archaic and modern

SOURCE: "GENOMIC DATA REVEAL A COMPLEX MAKING OF HUMANS," BY ISABEL ALVES ET AL., IN *PLOS GENETICS,* VOL. 8, NO. 7; JULY 19, 2012

Map by XNR Productions

humans and determined that they date to just 13,000 years ago—long after anatomically modern *H. sapiens* had debuted. These results, along with similar findings from the Ishango site in the Democratic Republic of the Congo, suggest that the evolution of anatomical modernity in Africa may have been more complicated than any of the leading models for modern human origins have envisioned. Either archaic humans lived alongside modern ones in the recent past, or populations with both modern and archaic features interbred over millennia.

BENEFICIAL CONTRIBUTIONS?

ALTHOUGH THE ANALYSES of Neandertal and Denisovan DNA provide increasing evidence that archaic humans contributed to our genetic heritage, many aspects of this interbreeding remain unresolved. Current estimates of the percentage of our genome that was contributed by Neandertals and Denisovan-like humans are based on a method that does not provide much information about how and when mixing occurred. To learn more, researchers need to improve their understanding of exactly which stretches of the genome came from archaic humans and which archaic species contributed what. During his dissertation work in my lab, Fernando L. Mendez took steps toward doing exactly that. He found strong evidence that some contemporary non-Africans carry a stretch of chromosome 12 containing the gene *STAT2* (which is involved in the body's first line of defense against viral pathogens) that came from Neandertals.

Detailed studies of DNA regions inherited from archaic ancestors will also help tackle the question of whether acquiring these genetic variants conferred an adaptive advantage to early *H. sapiens*. Indeed, *STAT2* provides a fascinating example of an apparently advantageous archaic variant entering the modern human gene pool. Approximately 10 percent of people from Eurasia and Oceania carry the Neandertal-like variant of *STAT2*. Interestingly, it occurs at a roughly 10-fold higher frequency in Melanesia than in East Asia. Analysis suggests that this DNA segment rose to high frequency through positive natural selection (that is, because it aided reproductive success or survival) rather than merely by chance, implying that it benefited the anatomically modern populations of Melanesia.

Similarly, a Neandertal-like section of the so-called human leukocyte antigen (HLA) region of the genome appears to have risen to relatively high frequency in Eurasian populations as a result of positive natural selection related to its role in fighting pathogens. Perhaps we should not be surprised to find archaic contributions containing genes that function to increase immunity. It is easy to imagine that the acquisition of a gene variant that is adapted to fending off pathogens in non-African environments would immediately benefit human ancestors as they expanded from Africa into new habitats.

In light of the accumulating evidence for interbreeding between anatomically modern *H. sapiens* and archaic humans both inside Africa and beyond its confines, the Replacement model is no longer tenable. Modern and archaic species of *Homo* were able to produce viable hybrid offspring. Thus, archaic forms could go extinct while still leaving behind their genetic footprints in the modern human genome. That said, the genomes of people today seem to derive mostly from African ancestors—contributions from archaic Eurasians are smaller than either the Multiregional Evolution or Assimilation models predict.

A number of researchers now favor Bräuer's Hybridization model, which holds that mating between *H. sapiens* and archaic species was limited to a few isolated instances. I agree that such interbreeding appears to have been rare after modern humans began spreading out of Africa, but I think there is more to the story than that. Given the complexity of the African fossil record, which indicates that a variety of transitional human groups, with a mosaic of archaic and modern features, lived over an extensive geographic area from Morocco to South Africa between roughly 200,000 and 35,000 years ago, I favor a model that involves interspecies mating during the archaic-to-modern transition. Sometimes called African Multiregional Evolution, this scenario allows for the possibility that some of the traits that make us anatomically modern were inherited from transitional forms before they went extinct. To my mind, African Multiregional Evolution, in combination with Bräuer's Hybridization model, best explains genetic and fossil data to date.

The roots of modern humans trace back to not just a single ancestral population in Africa but to populations throughout the Old World.

Before scientists can assess this model for modern human origins fully, we will need to better understand which genes code for anatomically modern traits and decipher their evolutionary history. Further analysis of both archaic and modern genomes should aid researchers in pinpointing when and where mixing occurred—and whether the archaic genes that entered the modern human gene pool benefited the populations that acquired them. This information will help us evaluate the hypothesis that interbreeding with archaic populations that were well adapted to their local environments lent traits to *H. sapiens* that spurred its rise to global preeminence. The sharing of genes through occasional interspecies mating is one way that evolutionary novelties arise in many species of animals and plants, so it should not be surprising if the same process occurred in our own past.

Many loose ends remain. Yet one thing is clear: the roots of modern humans trace back to not just a single ancestral population in Africa but to populations throughout the Old World. Although archaic humans have often been seen as rivals of modern humans, scientists now must seriously consider the possibility that they were the secret of *H. sapiens'* success. SA

MORE TO EXPLORE

A High-Coverage Genome Sequence from an Archaic Denisovan Individual. Matthias Meyer et al. in *Science,* Vol. 338, pages 222–226; October 12, 2012.

An African American Paternal Lineage Adds an Extremely Ancient Root to the Human Y Chromosome Phylogenetic Tree. Fernando L. Mendez et al. in *American Journal of Human Genetics,* Vol. 92, No. 3, pages 454–459; February 28, 2013.

SCIENTIFIC AMERICAN ONLINE
Learn about personal paleoancestry tests at **ScientificAmerican.com/may2013/dna**

EMERGING DISEASES

HOW KITTY IS KILLING THE DOLPHINS

The pathogens of land animals are spreading to the oceans, threatening otters, seals, whales, coral and other sea creatures

By Christopher Solomon

The detective story always do, with a ring was on the line. He A few days later he having found another. coming "again and Miller recalls. "At the were getting four a piled up, so did the

DOMESTIC CATS carry a parasite, *Toxoplasma gondii*, that has sickened dolphins found stranded in the Mediterranean Sea.

had begun, as they
ing phone. A biologist
had found a corpse.
called a second time,
Soon the calls were
again," Melissa A.
highest point, we
day." As the bodies
questions.

Christopher Solomon, a former reporter for the *Seattle Times,* writes frequently on the environment and the outdoors for the *New York Times, Outside* and other publications.

Miller is a wildlife pathologist and veterinarian. The dead were California sea otters, a threatened subspecies of sea otter that today numbers fewer than 2,800 along the state's central coast. In all, more than 40 sick and dying otters washed ashore during that terrible April 2004 episode—an astounding number in such a short time.

Miller spent many days with her hands inside the dead animals, looking for what went wrong. She was stymied. During their last breaths, many had shaken with seizures. Autopsies showed extensive neurological damage. Finally, a pattern emerged of severe brain inflammation. Hunched over microscopes, Miller and her colleagues finally fingered a surprise killer. The opossum did it.

More precisely, the culprit was *Sarcocystis neurona,* a single-celled parasite that is related to malaria, whose primary host is the Virginia opossum. Yet *S. neurona* is a terrestrial disease, and opossums are natives of the Appalachian backwoods, not the American West. How could this parasite be scything through sea otters in the Pacific?

Further gumshoe work teased out a tale too strange for fiction. People moving from east to west in the early 1900s helped the opossum travel to the San Jose area. The invasive animal thrived and eventually spread north into British Columbia. Infected opossums shed *S. neurona*'s sporocysts, hardy reproductive structures, in their feces. Miller and her associates surmised that a big, late-winter rainstorm washed a load of sporocysts downstream and into the waters just off Morro Bay, Calif., where they were taken up by filtering razor clams. Otters then gorged on the clams.

Although disease agents such as canine distemper virus had previously migrated from land to sea and killed thousands of seals, this case was the first documented mass killing of marine mammals by a land-based parasite.

We are all familiar with diseases such as rabies that can make the jump from nonhuman animals to humans. Yet what about a jump in the other direction? In the past decade ocean researchers have found a disturbing trend: we are making marine life ill with human diseases, as well as those of our pets, livestock and wildlife that have hitched a ride with us. Scientists have even coined a new term—pollutagens (polluting pathogens)—to describe the land-based bacteria, fungi and parasites flowing into the seas. Transmission is happening worldwide and is sickening and killing marine mammals such as harbor seals, sea lions and porpoises, not to mention those hapless California otters.

Frequently the examples are bizarre, even jarring. In 2010 scientists reported that a strain of *Salmonella* Newport*,* which is normally associated with birds and livestock, most likely killed a newborn killer whale that had washed ashore in Ventura County in California—and orcas swim at a distance from the coast, presumably far from pollution. In South Carolina, Atlantic bottlenose dolphins have been found carrying the "superbug" methicillin-resistant *Staphylococcus aureus* (MRSA).

Our diseases are making more than just mammals sick, evidence shows. In 2011 scientists genetically linked the pathogen *Serratia marcescens*—which causes meningitis and is responsible for the white pox epidemic that has wiped out 90 percent of the Caribbean's elkhorn coral—to human sewage. It was the first time that a human disease had been shown to infect a marine invertebrate.

This notion that land-based pathogens are moving seaward is so novel that scientists are still trying to grasp its scale and severity—and how new the issue really is. Some argue that our beleaguered oceans face more pressing problems, such as acidification. Others, however, say the breakdown of barriers be-

IN BRIEF

Pathogens from people, cats and other land animals are entering the oceans and attacking sea mammals. A parasite from opossums is killing California sea otters; a parasite from cats is killing dolphins.

Although data are still new, these "pollutagens" seem to be on the rise. Furthermore, drug-resistant bacteria from humans have been found in sharks and seals, raising the chance that the bugs could mutate and reinfect humans, who might be ill equipped to fight them.

Thoroughly cleansing wastewater and expanding wetlands that buffer land from sea could lessen the pollutagen threat.

PRECEDING PAGES: SHERI L. GIBLIN *Getty Images (cat)*; HIROYA MINAKUCHI *Getty Images (dolphin)*

tween land and sea could allow pollutagens to sicken or kill a wide array of ocean life. The trend could also give pathogens a way to mutate and reinfect people; after all, we work and play in the sea and eat many of its creatures. We need to better understand what is happening and to take actions—which sometimes can be quite simple—to help the ocean's creatures and, in turn, ourselves.

CAT POOP SICKENS DOLPHINS

ALTHOUGH THE SPECTER of pollutagens seems frightening, researchers first have to determine how recent and widespread the problem is. The most studied terrestrial pathogen currently affecting sea animals comes courtesy of America's favorite house pet, the cat. *Toxoplasma gondii,* a relative of *S. neurona,* is a protozoan parasite—a single-celled organism. *T. gondii* completes its reproductive cycle inside felines and has adapted so that it can invade and thrive inside the tissue of other creatures. Up to one quarter of the U.S. human population aged 12 years and older now carries *T. gondii,* with few to no ill effects, although pregnant women are warned against cleaning out the cat box because the parasite can cause birth defects. Today *T. gondii* has invaded sea life worldwide, from Miller's California sea otters, to dolphins that have become stranded in the Mediterranean Sea, to the critically endangered Hawaiian monk seals, of which few remain. "It truly is a cosmopolitan disease," says Stephen Raverty, a veterinary pathologist at British Columbia's Animal Health Center and a leading sleuth of pollutagens.

How can Whiskers be responsible for that ailing Guadalupe fur seal in Mexico? Credit the parasite's remarkable instincts for survival. In just 10 days a newly infected cat can shed up to 100 million *T. gondii* oocysts—tiny egglike structures—in its feces, says Michael Grigg, chief of the molecular parasitology unit at the National Institute of Allergy and Infectious Diseases. When an infected cat poops in the garden or an owner flushes used kitty litter down the toilet, the oocysts enter the environment. Persisting in soil or saltwater is no sweat for these sturdy structures. "In the lab, we store them in dilute sulfuric acid," Grigg says. "For up to 10 years they'll remain infective." In theory, just a single oocyst ingested, say, from the meat of a clam can infect a sea animal. Multiply that by some 70 million pet cats and 60 million feral felines in the U.S. alone, and the threat looms large. (Humans do not contribute to the problem directly, because they do not pass the oocysts through their feces.)

Even though *T. gondii* can kill outright, Grigg says that more often it weakens creatures with "kind of a chronic, smoldering infection." The infection can flourish when an animal is stressed by illness or an environmental problem such as sewage spills. Grigg's work in the Pacific Northwest, where much of the pollutagen research is centered, has found that more than half of dead raptors and more than one third of dead seabirds examined had the *T. gondii* parasite. "That was much higher than we had envisioned," he says.

When sea animals get more than one such disease, the "cocktail" is even more lethal than either pathogen on its own. A 2011 study of 161 Pacific Northwest marine mammals ranging from a sperm whale to harbor porpoises that had either become stranded or died found that 42 percent tested positive for both *T. gondii* and *S. neurona.*

The problem sounds alarming, but it is hard to tell definitively whether pollutagens are indeed on the rise "because we don't have any background data," Grigg acknowledges. "Is this just better detection?" Until 10 or 15 years ago, scientists never thought to examine sea mammals for land-based pathogens. Now the hunt is on, and Miller, for one, has seen too many dead California sea otters to hedge anymore. She says 70 percent of the otters have *T. gondii,* which they can get only from the rear end of a feline. "I don't think there is any question that this is

SEA OTTERS found beached and dying on California's shore had brain inflammation from *Sarcocystis neurona,* a parasite carried by the Virginia opossum.

STEVE AND DAVE MASLOWSKI *Getty Images (opossum);* MARC SHANDRO *Getty Images (otters)* increasing," she says of pollutagens. *T. gondii* was found recently in beluga whales in Arctic waters thought to be pristine, a dubious first.

ORCAS VAPORIZE GERMS

HEIGHTENED INVESTIGATION has expanded the rogue's gallery of ocean interlopers. A few years ago researchers in the Pacific Northwest wondered whether the thin, frothy film on the surface of seawater in Puget Sound, called the sea-surface microlayer, was contaminated—and whether those contaminants might be making orcas sick. When the killer whales surface to breathe, they vaporize this layer and then inhale it deeply into lungs that have few sinus protections. A significant number of orcas that have died over the past few decades have had respiratory ailments.

To investigate, scientists in boats chased the endangered whales to capture whale breath in petri dishes dangling from a stick. They also dipped dishes into the microlayer.

What grew in the petri dishes surprised them. In both kinds of samples, researchers found bacteria that did not seem to belong, including "significant human pathogens," according to the resulting 2009 study. They found strains of *Salmonella*. They found a rare bacterium, usually originating in sewage, that causes pneumonia in humans. They found *Clostridium perfringens,* a bacterium responsible for foodborne illnesses. In all, the researchers recovered more than 60 different pathogens "that are probably all terrestrial," says J. Pete Schroeder, the study's lead author and a marine mammal veterinarian now at the San Diego–based National Marine Mammal Foundation. "We've found stuff I've never even heard of, and I've been a veterinarian for more than 40 years," Schroeder says.

Schroeder's group did not directly link the contamination in orcas and in the microlayer to orca deaths. Yet orcas along the Pacific Northwest today are stressed by everything from cruise ship noise to declines in their preferred chinook salmon—which weakens their immune system. "The bacteria are out there, lying in wait for just the right set of circumstances, which is an immunocompromised animal," Schroeder says.

Scientists are increasingly worried about drugs entering the ocean, too, be it caffeine or estrogen in birth-control pills. In a study published in February, for instance, researchers at Umeå University in Sweden found that perch that swam in waters laced with the anxiety-moderating drug oxazepam left their schools to look for food on their own, a risky behavior because schooling protects them from predators.

DRUG-RESISTANT BACTERIA ALSO THRIVE

LAND-BASED POLLUTAGENS swimming in the sea are not the only concern. Some of the bugs are resistant to medications, which could be especially bad news for humans. A few years ago researchers at Woods Hole Oceanographic Institution and their colleagues concluded an unprecedented, three-year study of 370 live and dead marine animals found from the Bay of Fundy to Virginia. Surprisingly, three out of four animals had at least one antibiotic-resistant bacterium, and 27 percent had bacteria resistant to five or more antibiotics. Most of the bacteria found also live in humans. The booby prize went to a harp seal; it harbored bacteria that were resistant to 13 of the 16 drugs tested, according to research leader Andrea Bogomolni, including antibiotics used in agriculture, such as gentamicin, or for domesticated animals, such as enrofloxacin.

Resistant bacteria have been found to reside in sharks off Belize and Louisiana. Further, Raverty has recovered *Escherichia coli* and *Enterococcus* from the intestines of dead harbor seals off the Pacific coast that were resistant to all eight common livestock antibiotics that he and his colleagues screened for. "Even on land we don't see that level of resistance in the same bacteria recovered from livestock," he says.

HARBOR SEALS that died off Washington State's coast were infected with *Neospora caninum*, a parasite that causes infectious abortions in British Columbia's dairy cows.

Some naturally resistant bacteria can be found in the environment, of course. And again, the data are so recent that it is hard to know if the levels of resistance are steady or rising. As Bogomolni puts it, "What's normal?" Still, scientists suspect that something is out of whack. They think marine mammals are encountering antibiotics and antibiotic-resistant bacteria from plumes of ill-treated human sewage and from the effluent from large farms, where livestock antibiotics are often overused.

For example, people who consume the widely prescribed antibiotic tetracycline excrete a whopping 65 to 75 percent of it unchanged, Raverty says. A 2008 investigation by the Associated Press found that in the U.S. alone millions of pounds of pharmaceuticals are flushed down the drain annually by individuals, hospitals and nursing homes. Everything from anticonvulsants to sex hormones were found in the drinking water of at least 46 million Americans. If wastewater is not properly treated, such compounds can find their way to the sea.

Drug-resistant bacteria coursing through the ocean is worrisome for several reasons. A surfer or fisher with an open wound or someone who gulps water while swimming could get an infection that is hard to treat, Raverty says. And as Bogomolni points out, the harp seal he examined was mistakenly caught in a fishing net, which means that "you're getting your food from the same place that that animal is getting its food."

Another concern is that sea mammals could serve as swimming petri dishes, nurturing and transforming diseases—particularly viruses—until they reemerge among humans as something even more difficult to defeat. Viruses (which are unaffected by antibiotics) can mutate rapidly. In 2010 researchers at the Hubbs-SeaWorld Research Institute in San Diego and their colleagues discovered astroviruses in several marine mammals—

ANTHONY LEE *Getty Images*

star-shaped viruses that are a leading cause of viral diarrhea in young children and weak adults.

More sinister, perhaps, the investigators found that human and marine mammal astroviruses may have recombined (joined together) to form a new kind of virus. Although Hubbs-SeaWorld scientist Rebecca Rivera cautions that the virus is not about to sweep the land, she says the discovery highlights how sea mammals could throw an unforeseen curve back at humans. In 2011, for instance, 162 New England harbor seals died in a pneumonia outbreak. The seals, according to a study last year in the journal *mBio,* had contracted an avian flu virus that had "acquired mutations that are known to increase transmissibility and virulence in mammals"—including, possibly, humans.

Others worry about human viruses going into hiding until they can return with a vengeance. In 2000 researchers discovered that harbor seals in the Netherlands had acquired the same influenza B virus that had circulated among humans four to five years before, says Albert Osterhaus of Erasmus Medical Center Rotterdam, a top influenza scientist. Such a "reservoir" of human illness could return from animals, when our immune systems are more vulnerable to them, and infect us all over again.

PATRICK ENDRES *Getty Images*

Still, some scientists are not alarmed. Michael Moore, a well-regarded whale researcher at Woods Hole, who has participated in some of the studies, says the seas right now face other enormous challenges: ocean acidification, the "huge, huge problem" of marine mammals becoming entangled in fishing nets. "I don't see a tidal wave of new zoonotic agents coming back across the land-sea margins as being the same level of concern," he says. As for humans getting sick, "most of us have pretty darned good immune systems," says Moore, who has handled hundreds of ill and dead sea animals. If there had been any major threat from marine life, he points out, "I'd have been dead many times over."

WETLANDS TO THE RESCUE

WHETHER MARINE POLLUTAGENS are increasing or are just more prevalent than we knew, the way to reduce their presence is to figure out how they are getting into the ocean. Researchers have a pretty good idea. Humans have increasingly knocked down traditional barriers between land and sea. When people move to new habitats, they "get rid of wetlands, which are great natural kidneys for pollution," Miller says. And our increasingly dense landscape of streets, drains and pipes often whisks runoff directly into the sea. Both trends leave nature with little chance to grab sketchy water and let it soak into the seafloor along the shoreline, where it can be buffered and filtered. Ever resourceful, the bugs have taken advantage. Changing the environment "has given them opportunities to find new homes and be amplified," Grigg says. "This is evolution happening," and we are contributing to it.

Bringing our critters wherever we go has hastened the problem, whether cats, dogs, opossums—or cows. A few years ago sea otters, sea lions and harbor seals started stranding and dying along the coast of British Columbia and neighboring Washington State. Raverty and Grigg found them infected with *Neospora caninum,* a protozoan parasite that is the chief cause of infectious abortion in British Columbia's dairy cattle.

The problem, Miller says, is fixable—and not by killing all the house cats. Communities should preserve wetlands that cleanse runoff before it reaches open water. Large waste lagoons at animal farms must be prevented from leeching into streams and rivers that lead to the sea. Simple measures can often suffice. One study showed that adding a grassy strip between dairy fields and a riparian area dramatically reduced the number of pollutants entering the waterway.

As for cats, scientists are working on a vaccine against *T. gondii*. Until a practical one is created, the otter's future may be in our hands. Miller says cat owners should keep their pets indoors so they do not poop outside and should spay and neuter them to keep unwanted felines from proliferating. All of us should make smarter use of antibiotics and not toss extra medications down the drain. The best way to dispose of old drugs is through programs such as the National Take-Back Initiative or others that any local pharmacy can recommend.

Communities should also require better scrubbing of human and animal sewage. We need to filter our wastewater, Grigg says, because "chlorine is insufficient." Miller still recalls her elementary school teacher saying, "Dilution is the solution to pollution." Now our own effluents "are coming back to haunt us, as well as the animals who are downstream," she says. "Luckily, small steps can cumulatively make a big difference." If saving a sea otter is not sufficient inspiration to better clean up our own waste, then saving ourselves from a mutant pollutagen may be. SA

MORE TO EXPLORE

A Protozoal-Associated Epizootic Impacting Marine Wildlife: Mass-Mortality of Southern Sea Otters (*Enhydra lutris nereis*) due to *Sarcocystis neurona* Infection. Melissa A. Miller et al. in *Veterinary Parasitology,* Vol. 172, Nos. 3–4, pages 183–194; September 20, 2010.

Polyparasitism Is Associated with Increased Disease Severity in *Toxoplasma gondii*–Infected Marine Sentinel Species. Amanda K. Gibson et al. in *PLOS Neglected Tropical Diseases,* Vol. 5, No. 5; May 24, 2011.

Human Pathogen Shown to Cause Disease in the Threatened Elkhorn Coral *Acropora palmata.* Kathryn Patterson Sutherland et al. in *PLOS ONE,* Vol. 6, No. 8; August 17, 2011.

More information on sea otter diseases: **http://seaotterresearch.org**

SCIENTIFIC AMERICAN ONLINE
For a list of specific antibiotic-resistant bacteria found in sea mammals, see **ScientificAmerican.com/may2013/drug-resistance**

BIOCHEMISTRY

Mirror Molecules

In the chemistry of life, left-handed amino acids are the rule. Why does nature make so many exceptions?

By Sarah Everts

IRRITATE A MALE PLATYPUS DURING BREEDING season, and you may end up trapped by its stumpy hind legs, threatened by a set of sharp spurs that are armed with venom. The painful poison hobbles male competitors and is a handy defense against pesky humans and dogs. It is also a somewhat odd concoction, as might be expected from a mammal that is famous for its egg-laying, duck-billed weirdness. Platypus venom contains a class of molecules that biologists once thought did not occur naturally outside the microscopic world of bacteria.

Those molecules are mirror images of the amino acids that cells normally string together to make all of life's proteins, which are vital to proper functioning. The mirror images are composed of the same atoms that make up the 20 or so standard amino acids in biology's tool kit, and the atoms are attached to one another in the same order. Yet the orientation of the attachments diverges slightly, resulting in structures that differ from classic amino acids in much the way a right hand differs from a left hand. The two forms are not, however, interchangeable in biological reactions. Indeed, classic amino acids are now referred to as left-handed, and their mirror images are said to be right-handed.

IN BRIEF

Amino acids, the building blocks of proteins, can adopt forms that, like our right and left hands, are mirror images of each other. When life arose on the earth, it favored so-called left-handed amino acids over right-handed ones to carry out cellular activities.

For a long time the only exceptions to this pattern were found in bacteria. In recent years, though, more and more examples have been found in higher organisms, including humans.

Biomedical researchers are studying applications of the exotic amino acids to treat medical conditions, such as schizophrenia, cystic fibrosis and macular degeneration.

Photograph by Dan Saelinger

Sarah Everts, a native of Montreal, is the Berlin correspondent for the weekly magazine *Chemical & Engineering News*. She also blogs about art and science at Artful Science.

Right-handed amino acids were once assumed to play a minimal role in higher organisms because they would be mismatched to, and thus unable to work in, the molecular machinery of most plants and animals. In recent years, however, biologically active right-handers have been turning up in all kinds of unexpected places—from substances that lobsters produce to initiate sex to a hallucinogenic drug used by indigenous hunters in Peru. Most intriguingly, right-handed amino acids have been found to perform important jobs in human physiology, and they hold exciting potential for the development of new treatments, including for cystic fibrosis, schizophrenia and macular degeneration.

Solomon Snyder, a neuroscientist at Johns Hopkins University who did much of the early research into the function of right-handed amino acids in the brain, says he met considerable resistance when he tried to publish his first papers on the subject. Yet to him, the chemicals were intriguing precisely because they seemed to "break the first rule of mammalian biology," as he puts it. "Like most of science, whenever there is something really new or different, some people say, 'That's ridiculous.'"

As it happens, flipping a left-handed amino acid into its mirror image often takes just a few simple steps, biochemically speaking. Thus, it was probably inevitable that evolution would experiment with making right-handed amino acids. "Nature was clever enough to use them all these years," says Richard Losick, a cell biologist at Harvard Medical School. "We were just slow to realize it."

A USEFUL ACCIDENT

HOW IS IT that left-handed amino acids came to predominate over their right-handed siblings—so much so that the diverse biological functions of right-handed forms long escaped serious notice despite the molecules having been characterized in the late 1800s? Some scientists argue that the left-handers' edge stems from the cosmological equivalent of a coin toss. The first chemical entities able to replicate themselves successfully just happened to use left-handed amino acids, and this bias was "grandfathered in," suggests Robert Hazen, who is a geophysicist and origins-of-life researcher at George Mason University. Another popular theory holds that polarized light emanating from a rapidly rotating star in our primordial galaxy somehow selectively destroyed right-handed amino acids, improving the odds that left-handed amino acids would emerge as life's building blocks. The two forms are also known as L-amino acids and D-amino acids, respectively, after the Latin words for left (*laevus*) and right (*dexter*).

Once the choice was established, evolution had a clear incentive to perpetuate a dominant amino acid, explains Gerald Joyce, who studies the origins of life at the Scripps Research Institute in La Jolla, Calif. "By analogy, the convention in Western countries is to greet people by shaking right hands. It would work just as well if we all agreed to shake left hands, but if there was no convention, then there would be many awkward encounters." Thus, most of the machinery of living cells, from the enzymes that produce amino acids to the complex structures known as ribosomes, which string amino acids together to form proteins, is compatible only with L-amino acids and not with their D counterparts.

Indeed, the early decision by life to favor left-handed amino acids may have influenced the "handedness" of another class of organic compounds—the carbohydrates. Many research groups in the past decade have demonstrated that the predominance of certain simple left-handed amino acids in experimental solutions that mimic the primordial soup that may have existed on the earth four billion years ago tends to favor, for complex chemical reasons, the formation of right-handed carbohydrates, which is in fact the orientation seen throughout the biological realm.

The exceptions to the left-handed rule for natural amino acids gained wider attention in the 1990s, after Snyder showed that some right-handed compounds serve as neurotransmitters in the human brain. In 2002 Philip Kuchel, a chemist at the University of Sydney, determined that platypus poison contains D-amino acids. In 2009 researchers at Harvard and the Howard Hughes Medical Institute reported that several D-amino acids performed new and unexpected functions in bacterial cell walls. By 2010 investigators were finding that complex assemblies of bacteria that spread out in films over various surfaces—from hot springs to medical equipment—seemed to be using D-amino acids as a cue for when the biofilms should disperse.

In humans, the amino acid D-aspartate has been shown to be a neurotransmitter that is involved in normal brain development. Meanwhile D-serine teams up with the L-amino acid glutamate to co-activate neuronal molecules essential to what neuroscientists call synaptic plasticity—a property that is, in turn, key to learning and forming memories. D-serine also seems to be an important factor in the multifaceted disorder schizophrenia. People suffering from the disease have lower quantities of D-serine in their brain, a finding that has inspired drug companies to look for ways to top up D-serine levels as a possible treatment. Too much D-serine, however, can cause problems in other circumstances. For those suffering from a stroke, an overabundance can lead to increased brain damage. So researchers are also trying to develop drugs that decrease D-serine levels to mitigate a stroke's harmful consequences.

Our cellular factories produce only L-amino acids, so how, researchers wondered, do we end up having D-amino acids as well? Snyder found that brain cells do not build D-serine from scratch. Instead they make an enzyme that flips the handedness of the amino acid serine from its L form to its D form. That is a nifty way to capitalize on the abundant levels of L-amino acids already available in the cell.

Life employs the same strategy when a D-amino acid is part of a peptide—a small chain of amino acids—such as in platypus venom. In these cases, the trusty ribosome builds up the peptide from regular L-amino acids. Then an enzyme tweaks one of the individual amino acids in the chain to flip the L form into its D alter ego. By piggybacking on the machinery for making or connecting L-amino acids, nature does not need to evolve the entire team of right-handed biosynthetic enzymes that would normally be required to build a right-handed molecule, explains Günther Kreil, a chemist at the Austrian Academy of Sciences in Vienna, who in 2005 found an enzyme that poisonous South American tree frogs use to make the D-amino acids found in their venom.

Kreil became interested in tree frog venom when he first heard of an indigenous people in Peru, called the Matsés, who exploit peptides containing D-amino acids that are found on the skin of a tree frog called *Phyllomedusa bicolor* as potent hallucinogens in their hunting rituals. The Matsés first burn their chests and then apply the frog skin extract to their singed wounds, which induces in them immediate diarrhea and heart palpitations before briefly knocking them out. When they awake, they have heightened senses and a feeling of superhuman strength. The frog peptide is almost entirely composed of L-amino acids, but without the single D-amino acid in the peptide, the drug has no hallucinogenic effect, Kreil says.

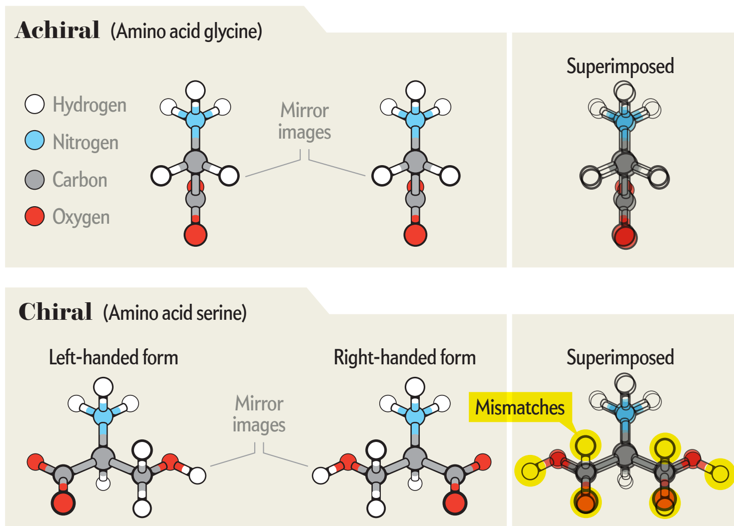
SHADOW WORLD

ALTHOUGH D-amino acids show up in the poisons of a wide range of organisms, in other creatures the molecules have more peaceful purposes. Lobsters, for example, use D-amino acids for catalyzing romance and to keep their salt levels in order.

A HANDY TEST

How to Spot a Mirror Molecule

Of the 20-some amino acids in nature's standard tool kit, only glycine (*top*) is achiral, meaning it exhibits neither right-handed nor left-handed properties; mirror images of the molecule will exactly match each other if superimposed. The amino acid serine, in contrast, is chiral; its mirror images cannot be superimposed.



Yet the biggest users of D-amino acids are still microbes—although even here researchers are discovering new functions for the right-handed molecules. Most bacteria build their cell walls out of a sticky sugar-protein matrix called peptidoglycan, which is doctored with D-alanine and other D-amino acids. In 2009 Matthew Waldor of Harvard and Howard Hughes found that bacteria also reinforce the peptidoglycan with a mortar that includes D-methionine and D-leucine. These D-amino acids can also remodel the peptidoglycan of bacterial neighbors—even across species—a discovery that suggests, Waldor says, that the microorganisms may use the molecules to coordinate activities such as turning on fluorescence or building a biofilm. Understanding how these bacteria exploit D-amino acids for communication is of tantalizing interest to those wanting to develop drugs or products that break up the biofilms on our teeth, in the lungs of cystic fibrosis patients, in fuel pipelines and in medical equipment such as catheters.

One reason that bacteria and poisonous creatures employ D-amino acids is that when they are present in a peptide or a larger protein, they are not easily broken down by the enzymes of their host or enemy. All organisms have protease enzymes, whose job is to rapidly degrade and recycle L- but not D-amino acid proteins. In fact, drug developers have tried adding D-amino acids to therapeutic peptides and proteins to sidestep these janitorial proteases and thus enable drugs to last longer in the body.

Now that researchers are actively exploring this strange new world of right-handed amino acids, they are exploring additional roles that D-amino acids might play. Losick and others speculate, for example, that at least some of the D-amino acids produced by the trillions of bacterial cells that live on our skin, in our digestive tracts and elsewhere in the body may be important for human well-being, health and maybe even behavior.

One of the big questions in D-amino acid research now is whether any other part of the human body—besides the brain—actively makes D-amino acids. Preliminary evidence is suggestive. Yoko Nagata's group at Nihon University in Tokyo has reported D-amino acids in human saliva, while researchers led by Kenji Hamase of Kyushu University in Japan have observed D-alanine packed in high concentration in rats in the insulin-secreting beta cells of their pancreas. Also, in recent preliminary experiments in his laboratory in Australia, Kuchel has discovered enzymes in mouse and human hearts to convert L-amino acids into D-amino acids similar to the one in platypus venom.

What precise role such enzymes might play in human physiology, Kuchel says, is still, however, "a total mystery." At least the idea that they might have important functions no longer seems ridiculous. SA

MORE TO EXPLORE

The New Ambidextrous Universe: Symmetry and Asymmetry from Mirror Reflections to Superstrings. Third revised edition. Martin Gardner. Dover, 2005.

High Dose D-Serine in the Treatment of Schizophrenia. Joshua Kantrowitz et al. in *Schizophrenia Research,* Vol. 121, No. 1, pages 125–130; August 2010. **www.ncbi.nlm.nih.gov/pmc/articles/PMC3111070**

D-Amino Acids in Chemistry, Life Sciences, and Biotechnology. Edited by Hans Brückner and Noriko Fujii. Wiley, 2011.

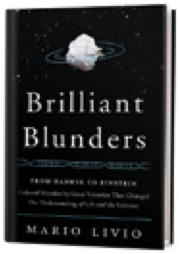
Emerging Knowledge of Regulatory Roles of D-Amino Acids in Bacteria. Felipe Cava et al. in *Cellular and Molecular Life Sciences,* Vol. 68, No. 5, pages 817–831; March 2011. **www.ncbi.nlm.nih.gov/pmc/articles/PMC3037491**

SCIENTIFIC AMERICAN ONLINE
Learn more about the chirality of life from the serious (thalidomide) to the silly (hair parts) at **ScientificAmerican.com/may2013/mirror-molecules**

GRAPHIC CONSULTANT: MARTIN MA *Johns Hopkins University School of Medicine*

Illustration by Jen Christiansen

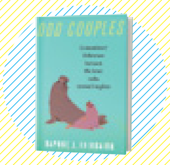
Recommended by Anna Kuchment



Brilliant Blunders: From Darwin to Einstein: Colossal Mistakes by Great Scientists That Changed Our Understanding of Life and the Universe

by Mario Livio. Simon & Schuster, 2013 ($26)

Astrophysicist Livio unmasks the flaws in the work of some of our greatest scientific minds in this meditation on the winding, unpredictable path of discovery. Chemist Linus Pauling, a favorite to win the race to determine the structure of DNA in the 1950s, astonished his colleagues by proposing an erroneous "triple helix" model. The mistake allowed James Watson, Francis Crick and Maurice Wilkins to sneak past him to the Nobel podium. Charles Darwin was slow to grasp that the concept of "blended inheritance"—the theory that parental traits are blended in offspring the way paint colors might mix on a palette—was incorrect and in conflict with natural selection. Livio shows how these mistakes and others acted as catalysts that enabled scientific breakthroughs.



Odd Couples: Extraordinary Differences between the Sexes in the Animal Kingdom

by Daphne J. Fairbairn. Princeton University Press, 2013 ($27.95)

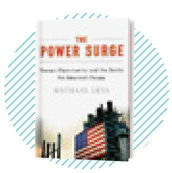
Biologists have long debated the specific traits that set humans apart from other animals: Is it self-awareness, or morality, or emotions? Recent research has cast doubt on each of these premises, but *Odd Couples* notes that we are exceptional in at least one respect: how we distinguish men from women. Throughout the animal world, it is far more common for males than for females to be petite and brightly colored. Fairbairn, a biologist at the University of California, Riverside, traces the evolutionary reasons behind these and other sexual differences, while exploring some extreme and fascinating examples. Cases include populations of elephant seals (*above*), in which large, aggressive males sexually harass harems of females, and of deep-sea anglerfishes, in which males live as tiny parasites permanently attached to the bellies of their large, predatory female partners. One constant across all species seems to be: there's no accounting for taste.

Scatter, Adapt, and Remember: How Humans Will Survive a Mass Extinction

by Annalee Newitz. Doubleday, 2013 ($26.95)

Newitz, a science journalist and founding editor of the Web site io9, set out to write about the looming disaster of the sixth mass extinction but instead found hope for humanity's endurance. Natural history is riddled with survivors' tales, she writes. For example, the *Lystrosaurus,* a reptile ancestor of mammals, probably relied on large lungs and underground tunnels to persevere in a low-oxygen world created by cataclysmic volcanic eruptions. Humankind's endurance may depend on new technologies such as space elevators to transport humans off the planet or biological cities filled with skyscraper farms and bacteria-based, self-healing concrete. Survival, Newitz argues, will involve radical transformation, but humans may just be up to the challenge.

—*Marissa Fessenden*



The Power Surge: Energy, Opportunity, and the Battle for America's Future

by Michael Levi. Oxford University Press, 2013 ($27.95)

The U.S. is in the midst of a transformation in the way the country produces and uses energy. Blasting deep shale formations with water—also known as fracking—and the ability to drill wells horizontally as well as vertically have freed a bonanza of previously untapped oil and natural gas. At the same time, government programs have mandated more efficient vehicles and helped to jump-start the development of alternative sources of energy, such as solar and wind power. President Barack Obama calls this an "all of the above" strategy, and that's a plan Levi, who is an energy expert at the Council on Foreign Relations, endorses in this engaging and illuminating book. He also argues that we'll need oversight and regulations to ensure that activities such as fracking are done right.

—*David Biello*

SCIENTIFIC AMERICAN ONLINE
For more recommendations, go to ScientificAmerican.com/may2013/recommended

YVA MOMATIUK AND JOHN EASTCOTT *Minden Pictures*

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

Gun Science

How data can help clarify the gun-control debate

According to the Centers for Disease Control and Prevention, 31,672 people died by guns in 2010 (the most recent year for which U.S. figures are available), a staggering number that is orders of magnitude higher than that of comparable Western democracies. What can we do about it? National Rifle Association executive vice president Wayne LaPierre believes he knows: "The only thing that stops a bad guy with a gun is a good guy with a gun." If LaPierre means professionally trained police and military who routinely practice shooting at ranges, this observation would at least be partially true. If he means armed private citizens with little to no training, he could not be more wrong.

Consider a 1998 study in the *Journal of Trauma and Acute Care Surgery* that found that "every time a gun in the home was used in a self-defense or legally justifiable shooting, there were four unintentional shootings, seven criminal assaults or homicides, and 11 attempted or completed suicides." Pistol owners' fantasy of blowing away home-invading bad guys or street toughs holding up liquor stores is a myth debunked by the data showing that a gun is 22 times more likely to be used in a criminal assault, an accidental death or injury, a suicide attempt or a homicide than it is for self-defense. I harbored this belief for the 20 years I owned a Ruger .357 Magnum with hollow-point bullets designed to shred the body of anyone who dared to break into my home, but when I learned about these statistics, I got rid of the gun.

More insights can be found in a 2013 book from Johns Hopkins University Press entitled *Reducing Gun Violence in America: Informing Policy with Evidence and Analysis,* edited by Daniel W. Webster and Jon S. Vernick, both professors in health policy and management at the Johns Hopkins Bloomberg School of Public Health. In addition to the 31,672 people killed by guns in 2010, another 73,505 were treated in hospital emergency rooms for nonfatal bullet wounds, and 337,960 nonfatal violent crimes were committed with guns. Of those 31,672 dead, 61 percent were suicides, and the vast majority of the rest were homicides by people who knew one another.

For example, of the 1,082 women and 267 men killed in 2010 by their intimate partners, 54 percent were shot by guns. Over the past quarter of a century, guns were involved in greater number of intimate partner homicides than all other causes combined. When a woman is murdered, it is most likely by her intimate partner with a gun. Regardless of what really caused Olympic track star Oscar Pistorius to shoot his girlfriend, Reeva Steenkamp (whether he mistook her for an intruder or he snapped in a lover's quarrel), her death is only the latest such headline. Recall, too, the fate of Nancy Lanza, killed by her own gun in her own home in Connecticut by her son, Adam Lanza, before he went to Sandy Hook Elementary School to murder some two dozen children and adults. As an alternative to arming women against violent men, legislation can help: data show that in states that prohibit gun ownership by men who have received a domestic violence restraining order, gun-caused homicides of intimate female partners have been reduced by 25 percent.

Another myth to fall to the facts is that gun-control laws disarm good people and leave the crooks with weapons. Not so, say the Johns Hopkins authors: "Strong regulation and oversight of licensed gun dealers—defined as having a state law that required state or local licensing of retail firearm sellers, mandatory record keeping by those sellers, law enforcement access to records for inspection, regular inspections of gun dealers, and mandated reporting of theft of loss of firearms—was associated with 64 percent less diversion of guns to criminals by in-state gun dealers."

Finally, before we concede civilization and arm everyone to the teeth pace the NRA, consider the primary cause of the centuries-long decline of violence as documented by Steven Pinker in his 2011 book *The Better Angels of Our Nature:* the rule of law by states that turned over settlement of disputes to judicial courts and curtailed private self-help justice through legitimate use of force by police and military trained in the proper use of weapons. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/may2013

Illustration by Doug Chayka

The ongoing search for fundamental farces

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 33 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

Bacon, Lettuce and Tasteless

Trying to return tomatoes to their salad days

The Martian Giant is not a big dude discovered by the Curiosity rover. The Mexico Midget is not the most popular wrestler south of the Rio Grande. The Three Sisters is not the title of a play by Anton Chekhov. Well, actually, it is, but that's not this Three Sisters. This Three Sisters—like the Martian Giant and the Mexico Midget—is a tomato.

All are varieties of heirloom tomatoes being crushed, pureed, ground up and analyzed in a noble and flavorful quest. As per the title of a session at the Annual Meeting of the American Association for the Advancement of Science in Boston in February, they are doing their part in "Fixing the Broken Tomato."

Indeed, the industrial, three-in-a-cellophane-wrapped-pack tomato stinks. Everybody knows it, and everybody has known it for decades. "The loss of flavor probably coincides with the period of really intensive breeding that started at the end of World War II," said session speaker Harry J. Klee, who works in the horticultural sciences department and the plant molecular and cellular biology program at the University of Florida. "I've got this great article from the *New Yorker* magazine that [asks] what's wrong with our tomatoes. It's from 1977. So in the 1970s we already knew this was a problem."

The modern supermarket tomato became damaged goods as part of the attempt to keep it from becoming damaged goods. In the pursuit of a storable, transportable tomato, appearance, firmness and shelf life all trumped taste. Another big driver was having more spheroids per stalk: "Modern tomatoes focus on yields, basically making too many fruit at same time," Klee said. "The plant can't keep up with filling those fruits with nutrients. So the effect of what the modern breeders have done is basically to take the old tomatoes and add water."

You might assume that making a tomato that ships well and lasts forever but tastes like cardboard would be a bad business model, like bus drivers sticking to timetables by not stopping to pick up passengers. But that assumption is based on the notion that the tomato eater is the customer. "The customer of the breeders is the grower, not the consumer," Klee said. "Growers want what will make them money, not what people want. And breeders typically do not interact with the people who tell them what they think of the final product," by, for example, letting half-masticated messages fall from their mouths.

Shipping often involves refrigeration, which kills whatever flavor is left by wiping out what are called volatiles—odoriferous chemical compounds that go up the nose and influence the perception of taste. "By and large," Klee said, "the postharvest system is set up to destroy flavor."

Clearly, one way to address our bad tomatoes would be to reform the entire industrial agricultural system. Rather than breeding the flying pigs that would signal that development, Klee is simply trying to reverse engineer the tomato.

He and Linda M. Bartoshuk, a taste-and-smell researcher at the University of Florida who also spoke at the session, start with dozens of varieties of heirloom tomatoes of old lineages, such as the aforementioned Martian Giant et al. A panel of taste testers rate the tomatoes. Then the research team pulverizes them (the tomatoes, not the taste judges), somehow resists the urge to ladle the resulting sauce over linguine and analyzes the produce's makeup.

Klee and Bartoshuk have found six specific volatile compounds that enhance sweetness—which turns out to be the single most important factor in people's ratings of tomatoes—and two volatiles that suppress sweetness. These volatiles can really fool the brain. A variety of tomato called the Matina is rated twice as sweet as one called Yellow Jelly Bean, despite having less sugar. "If we look at those six volatiles that enhance sweetness," Bartoshuk said, "the Matina has all of them in higher concentrations than the Yellow Jelly Bean." What's in a name? Indeed.

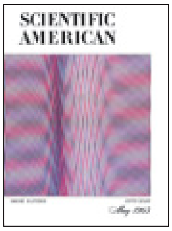
The trick now is to use these new data to breed flavorful tomatoes that still have the qualities that make them suitable for mass production. So that when you say tomato, I don't say blehhh. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/may2013

Illustration by Matt Collins

50, 100 & 150 Years Ago compiled by Daniel C. Schlenoff

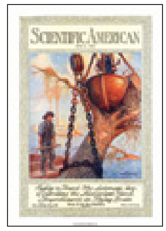
Innovation and discovery as chronicled in *Scientific American*



May 1963

Pheromone Messages

"It is conceivable that somewhere on other worlds civilizations exist that communicate entirely by the exchange of chemical substances that are smelled or tasted. Unlikely as this may seem, the theoretical possibility cannot be ruled out. It is not difficult to design, on paper at least, a chemical communication system that can transmit a large amount of information with rather good efficiency. The notion of such a communication system is of course strange because our outlook is shaped so strongly by our own peculiar auditory and visual conventions. This limitation of outlook is found even among students of animal behavior; they have favored species whose communication methods are similar to our own and therefore more accessible to analysis. It is becoming increasingly clear, however, that chemical systems provide the dominant means of communication in many animal species, perhaps even in most. —Edward O. Wilson"



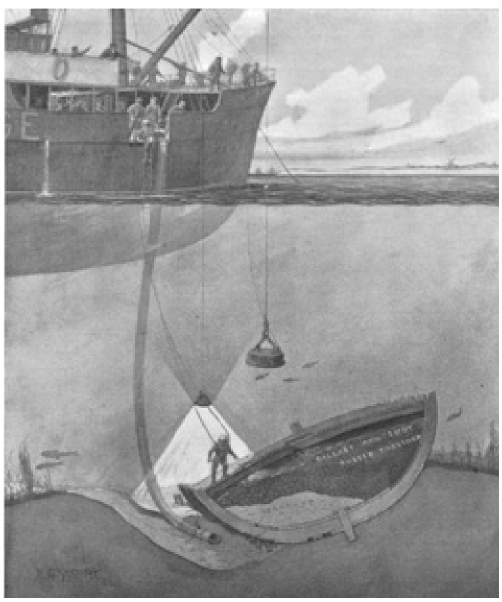
May 1913

Burning Peat in Germany

"A colossal 'smoke nuisance,' from which the greater part of Europe once suffered more or less, is now rapidly abating with the decline of the time-honored German custom of burning the moors. Moorland, a soil consisting of peat, formed by the partial decomposition of mosses and other vegetation, is in its natural state unfit either for cultivation or grazing. As compared with the modern methods of thorough draining, rolling, mixing with the subsoil, and otherwise permanently reclaiming the moors, the burning process is so wasteful of land that it has generally been given up except in districts remote from settlements."

Treasure Hunt

"The British frigate 'Lutine' sank in 1799 with ten tons of gold and silver on board. The principal difficulty to be dealt with is presented by the enormous masses of rusted shot and ballast in which the specie is embedded. When operations are renewed early in the coming spring the 'Lyons' will have on board an electric lifting magnet with a lifting capacity of three tons [*see illustration*]. The masses of metal will be broken up by means of small charges of explosive into pieces small enough for the magnet to deal with."



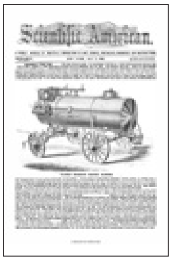
HEAVE-HO: Salvagers planned to use a powerful electromagnet to get at buried treasure, 1913

SCIENTIFIC AMERICAN, VOL. CVIII, NO. 20; MAY 17, 1913

Manufacturing Shoes

"Many manufacturers in other industries cannot afford to discard obsolete machines. They have invested too much money in them. Their manufacturing costs are often high because their equipment is out of date. However, every new invention produced by the United Shoe Machinery company means the 'scrapping' of hundreds of machines at the company's expense; in a single year no less

than 4,000 machines have been withdrawn to make room for machines embodying the latest improvements. That is why the public is able to buy shoes at a price to meet every purse.”
For a slide show on manufacturing as it used to be, see www.ScientificAmerican.com/may2013/factories



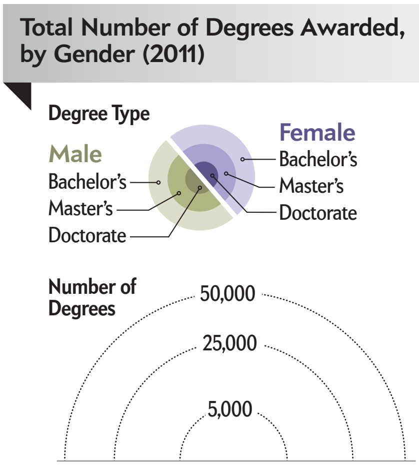
May 1863

Darwin Not an Infidel?

“Of late years men of science and others have wrangled much over Mr. Darwin’s work on ‘The Origin of Species.’ In most of the English and American reviews his treatise has been severely criticized, as having an infidel tendency; not on account of the facts therein given, but the conclusions of the author. He appears to have been very generally misunderstood, judging from the publication of six lectures delivered to workingmen, by Thomas H. Huxley, F.R.S. Broadly stated, the subject of these lectures consists of an inquiry into the origin of species and a discussion on the causes of the phenomena in organic nature. The meaning of organic nature is something that grows, has life and reproductive powers. It is exemplified in the seed of a plant in contradistinction to a grain of sand. Every organism commences existence in an egg cell or seed, and each seed is believed to have been specially created, with special functions and powers of reproduction, as stated in the Scriptures.”

Coffee Goes to War

“Coffee is the soldier’s luxury, deprived of which he imagines himself the worst used individual that he is capable of conceiving. On a march, for convenience sake, the coffee and sugar are mixed together. Every man carries his tin cup or can for making his coffee, and he would as soon think of leaving his musket as the cup wherein to make his coffee.”



Gender Gaps

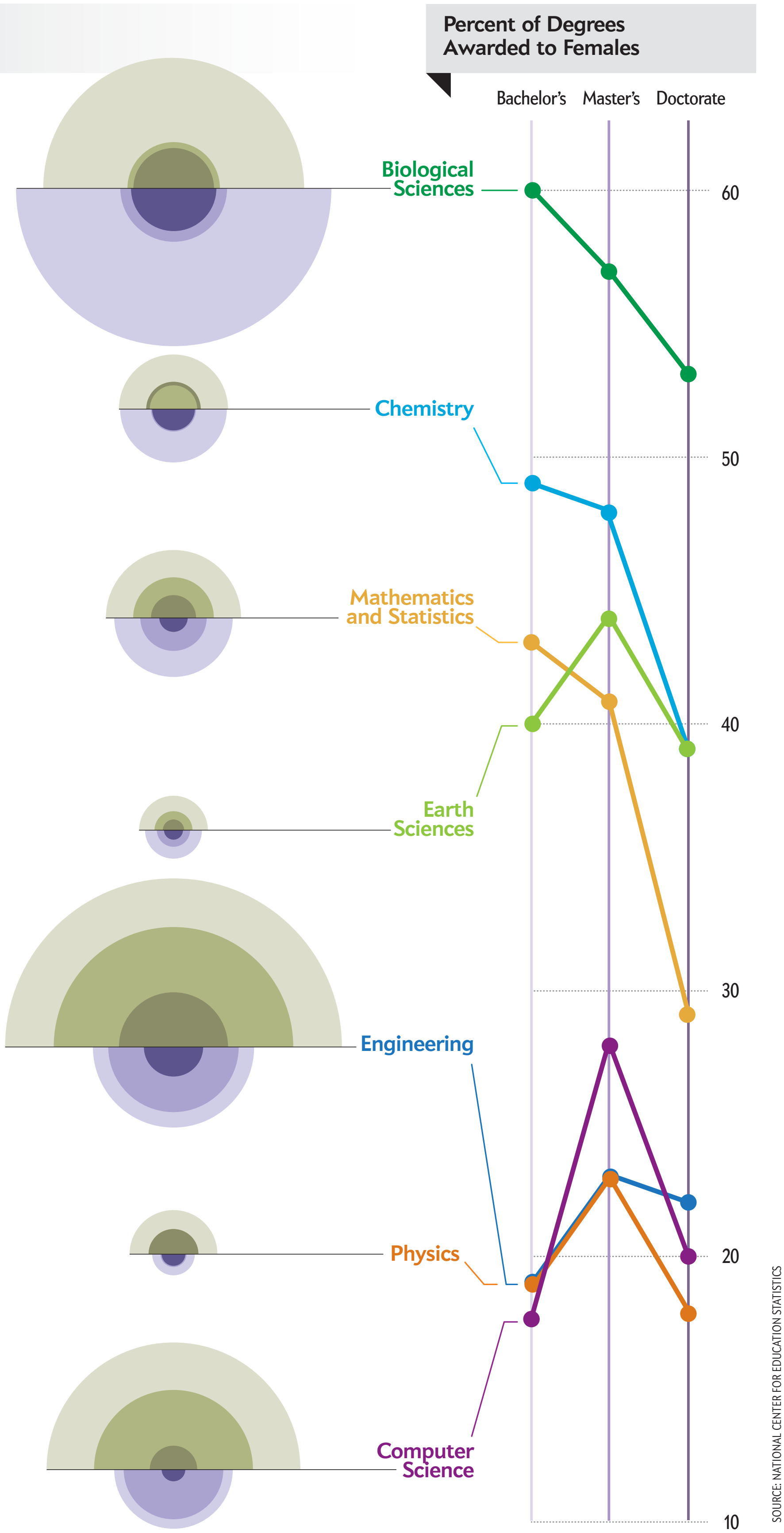
Women are more likely than men to withdraw from science

In 2008, for the first time, U.S. women earned more doctorates in biology than men did. But advanced degrees in other core disciplines of science, technology, engineering and mathematics (STEM) remain stubbornly gender-imbalanced. In chemistry, for instance, women now garner 49 percent of bachelor's degrees but only 39 percent of Ph.D.s. What dissuades so many from further study?

Possible explanations include gender bias, the prospect of short-term postdoctoral jobs that complicate child rearing, and a lack of role models. Female STEM professors are slowly increasing in number, however. "It seems like many of the indicators are pointing toward parity, but at different scales and different rates," says science education professor Adam V. Maltese of Indiana University Bloomington, adding that fields such as engineering have a long way to go. "That's not going to happen overnight, not in the next decade, and maybe not for the next 20 or 25 years."

—John Matson

SCIENTIFIC AMERICAN ONLINE
Read more about gender and science education at ScientificAmerican.com/may2013/graphic-science



Graphic by Jen Christiansen