WHY DOES MATTER HAVE MASS? • HOW DID DINOSAURS GROW SO BIG?

SCIENTIFIC AMERICAN

SPECIAL REPORT
With *Financial Times*

THE FUTURE OF STEM CELLS

JULY 2005
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Carbon Trap

What Burying CO_2 Can Do to Reduce Global Warming

The Many Faces of **Mars**

Virtual Archaeology **Out West**

New Clues Help Fight **Parkinson's**

july 2005

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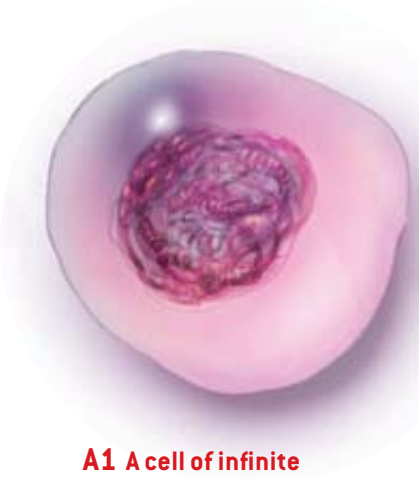

A1 A cell of infinite possibilities

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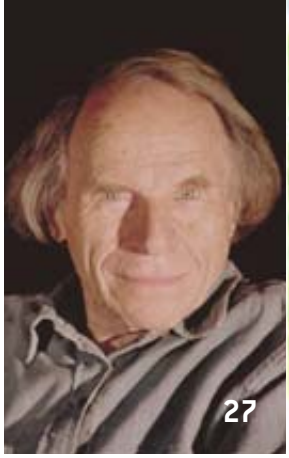

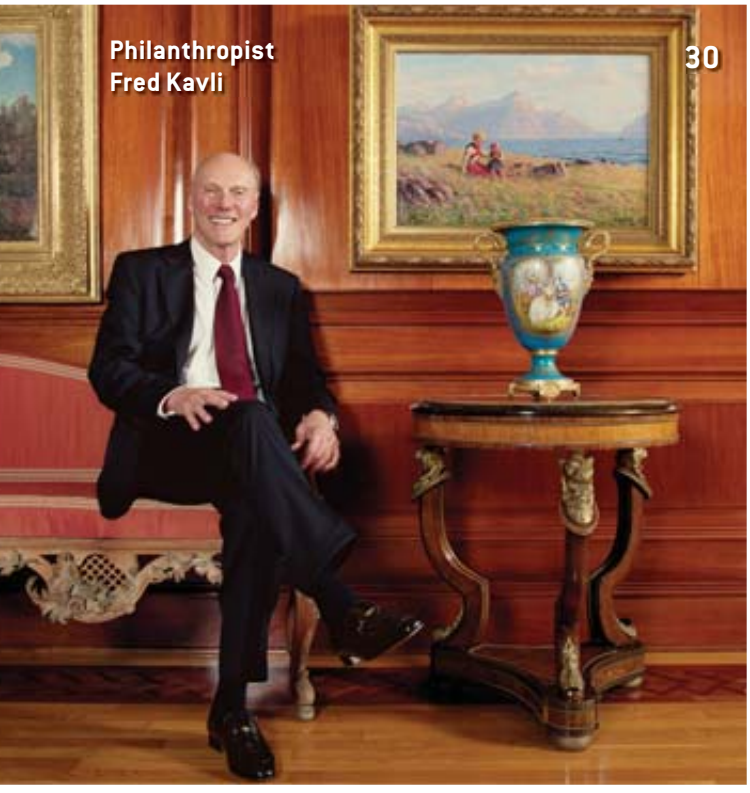

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Lost in Space

Although NASA's budget has risen about 7 percent over the past two years, its responsibilities have grown much faster. First, NASA must safely resume the flights of its space shuttles, which have been grounded since the loss of *Columbia* in 2003. Second, the agency plans to continue assembling the International Space Station, the half-built orbital outpost currently occupied by a two-person crew and supplied by Russian spacecraft. And third, President George W. Bush ordered NASA last year to develop the Crew Exploration Vehicle (CEV), a new craft designed to take astronauts back to the moon and ultimately to Mars.

Unsurprisingly, the agency's renewed commitment to human exploration is now impinging on its program of unmanned missions. Since the unveiling of NASA's budget request for the 2006 fiscal year, the impending cuts to Earth-observing satellites and interplanetary probes have led scientists to raise their voices in protest [see "Feeling the Pinch," by Mark Alpert, News Scan, on page 16]. Of course, researchers have a tendency to defend their projects to the death, no matter what their value, and NASA must sometimes make sacrifices to ensure that its limited funds go to the missions that return the best science. But the fact that the agency is even considering canceling the Voyager probes, which are now breaking through the boundaries of the solar system, is a sign that NASA's priorities are seriously out of whack.

The shuttle and space station programs would be better targets for cost-cutting. NASA originally planned about 25 shuttle flights over the next five years to deliver the trusses, solar arrays, docking nodes and laboratory modules needed to complete the station. The shuttle and station consume 40 percent of NASA's budget and will burn through at least $40 billion between now and their scheduled phase-out dates (the shuttle in 2010, the station in 2017). In contrast, the Voyager mission costs only $4.2 million a year.

When the assembly of the station began in 1998, NASA justified the expense by noting the potential benefits of conducting materials science and protein crystal experiments in orbit. Today agency officials say medical studies of station astronauts will help NASA prepare for manned missions to Mars. Yet neither argument stands up to scrutiny. Most scientists say the results from station experiments are not worth the cost of putting the laboratories in orbit. And the primary obstacle to human travel to other planets is the threat of ion bombardment in deep space, a danger that cannot be fully investigated at the station, which lies within Earth's protective magnetosphere.

Cutting the shuttle and station budgets could pose diplomatic problems: the European and Japanese space agencies have already built expensive laboratory modules and made barter agreements with NASA to ensure their delivery to the station. Those agreements can be renegotiated, however. If NASA limits the number of shuttle flights to the station to six or seven—enough to finish the core assembly—the freed-up funds could bolster both human and robotic exploration. NASA could accelerate the development of the CEV and new heavy-lift rockets intended to launch components for interplanetary missions as well as modules for the space station. A 2004 study commissioned by the Planetary Society advocated exactly this strategy; one of the leaders of the study team, Mike Griffin, became NASA's administrator in April. We urge Griffin to put this plan into effect.

DISCOVERY on the launchpad.

NASA

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SPECIAL REPORT FROM

FT FINANCIAL TIMES SCIENTIFIC AMERICAN

The Future of Stem Cells

Stem cell research has explosively grown into one of the most promising but controversial technologies in history. In this special report, the editors of the *Financial Times* and *Scientific American* explore the scientific, economic, ethical and political prospects for this astonishing field.

Earth Holding On to Sun's Heat, Study Suggests

Earth is retaining more of the sun's energy than it is sending back into space. That is the conclusion from a new simulation that takes into account such climate forcing variables as greenhouse gas and aerosol concentrations, land use and surface reflectivity and that calculates global temperatures and other climate values for the atmosphere and the oceans. And a decade of measurements of the heat content of the oceans confirms the model's predictions.

A New Dinosaur Documents Shift from Meat to Veggie Diet

A treasure trove of fossils uncovered in Utah is helping paleontologists understand why some meat-eating dinosaurs evolved into vegetarians. The bones represent a new species belonging to a group known as the therizinosaurs, plant-eating cousins of *Jurassic Park*'s vicious *Velociraptor*.

Ask the Experts

Why do most species have five digits on their hands and feet?

Michael Coates, associate professor in the department of organismal biology and anatomy at the University of Chicago, explains.

MIKE SKREPNICK

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Letters

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RESPONSES TO MARCH'S cover story, "How Did Humans First Alter Global Climate?" by William F. Ruddiman, were outnumbered only by a multitude of reader questions, observations and alternative theories addressed to "Misconceptions about the Big Bang," by Charles H. Lineweaver and Tamara M. Davis. Although many felt this article went where none had gone before in clearing up several cosmological misconceptions, the answers left one reader a tad disappointed in the possibilities an expanding universe might have afforded her interior space. Marianne Vespry of Hamilton, Ontario, writes: "As I read this article, I began to hope that my condominium closets might be getting bigger with the expansion of the universe, so that by summer there would be room for the new outfits I will undoubtedly buy. But no, I learned that the universe grows larger without expanding either Planet Earth or my closets." We trust the following will expand your knowledge—the constraints of cosmology and earthly real estate notwithstanding.

8,000 YEARS OF HUMAN WARMTH

In "How Did Humans First Alter Global Climate?" William F. Ruddiman suggests that carbon dioxide (CO_2) released as our ancestors cleared forests to plant crops over the past 8,000 years prevented the onset of the next ice age.

This claim is just plain wrong. First, the oceans have such an immense capacity to absorb CO_2 that the amount of CO_2 released by deforestation would have had to be outrageously large to drive atmospheric levels as high as Ruddiman suggests. Second, the new ice core drilled as part of the European Project for Ice Coring in Antarctica yields a rising CO_2 record similar to that of the present interglacial interval for an older interglaciation (called stage 11) that began about 420,000 years ago. This falsifies Ruddiman's tacit assumption that an early fall of CO_2 concentrations is an intrinsic behavior of the carbon cycle during the warm periods between recent ice ages. Third, the claimed deforestation would reduce the ratio of carbon 13 to carbon 12 in the atmosphere so much that existing measurements from ice cores would have identified it.

Instead we argue that CO_2 changes during the different interglacial periods are caused by the eccentricity of the earth's orbit, which was much smaller during both the present-day and stage 11 interglaciations. Other recent interglacial periods therefore cannot be used as analogues for the climate evolution of the past 8,000 years.

Wallace S. Broecker
Lamont-Doherty Earth Observatory
Thomas F. Stocker
Physics Institute, University of Bern

RUDDIMAN REPLIES: *A long interval of warmth did occur during the stage 11 interglaciation, but that warmth ended by 400,000 years ago, when solar radiation changes became similar to those in preindustrial times (the last several thousand years). At that point, CO_2 and methane levels both dropped substantially, just as they did during all three other previous interglaciations. Because the upward CO_2 trend during the past 8,000 years is unique, its most likely origin is anthropogenic.*

I agree that carbon models require larger inputs of preindustrial carbon than human emissions alone can explain, but another important factor must also be considered. I estimate that only one third of the preindustrial CO_2 anomaly resulted from carbon emissions (deforestation and coal and peat burning). The remainder occurred because agricultural emissions of methane and CO_2 canceled a natural climatic cooling that by now would have caused a large natural CO_2 drop, like those that occurred during all previous interglaciations. Because this part of the CO_2 anomaly is not tied to carbon emissions, the carbon isotope ratio would not have been re-

duced as much as Broecker and Stocker indicate. Finally, attempts to attribute the preindustrial CO_2 rise to natural causes face one insurmountable problem—CO_2 went down, not up, during all four interglacial intervals most similar to the present one.

BIG BANG BARED

As I read "Misconceptions about the Big Bang," by Charles H. Lineweaver and Tamara M. Davis, a question popped into mind: Photons lose energy as space expands, but where does that lost photonic energy go? I refer to the conservation of energy. Does the energy lost by photons contribute somehow to the expansion of space? Is space stealing energy from the universe?

Alfred A. Aburto, Jr.
via e-mail

I am an amateur astronomer. This was the first good explanation about the big bang I have seen! Numerous questions arose, including: If the farthest objects we can see are 46 billion light-years away but only 14 billion years old, did the light from them take 14 billion years to traverse 46 billion light-years?

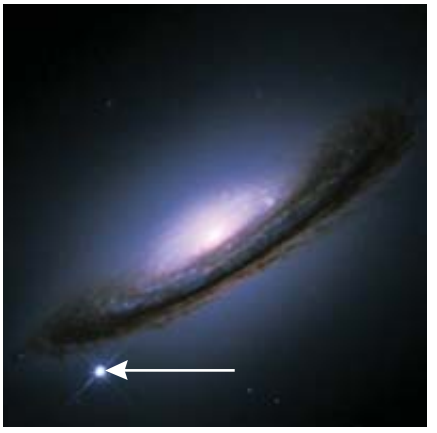
Richard Allen
Phoenix, Ariz.

For the most part, your article was great, but I'm not in total agreement. The problem: the concept of expansion of space as opposed to expansion through space is a "gauge choice"—it depends on the coordinates chosen.

James Bjorken
Menlo Park, Calif.

LINEWEAVER AND DAVIS REPLY: *The response to Aburto's question is that in a normal Doppler shift, receding observers see redshifted photons. The energy hasn't gone anywhere. It is simply that the energy is a frame-dependent quantity: just as the velocity and hence kinetic energy of a train depend on your frame of reference, photons appear to have different energies from different frames. Much the same is true of the cosmological redshift. In the reference frame we used to describe the universe's expansion, one could say that the energy goes into the gravitational potential energy of the photon or into the work done by photon pressure as the universe expands. We would get this energy back if the universe were to recollapse. These are not completely satisfactory explanations, because classical analogies do not translate perfectly into the relativistic picture.*

To answer Allen's query: The light has indeed taken 14 billion years to reach us, but it has not had to travel 46 billion light-years. The light was emitted very close to us—within the "grapefruit-size" region that has become our observable universe. The "object" that emitted the light has since receded (faster than light) to 46 billion light-years away. Because the light was emitted very close by, we can say it has taken 14 billion years to traverse the radius of a grapefruit! The reason it has taken so long to reach us is that the early universe was expanding very quickly and the light was emitted in a region that was receding superluminally. It thus spent the first few billion years receding but eventually ended up in a region that was receding subluminally and was able to approach us.



GROWTH SPACE: Supernovae (*arrow*) observations nix theories of a nonexpanding universe.

P. CHALLIS *Center for Astrophysics/STScI/NASA*

Bjorken is correct. How we describe any movement is fundamentally based on our choice of coordinate systems. We say a train arrives at a station if we consider the station to be motionless. Alternatively, we say the station arrives at the train if we choose a coordinate system in which the train is stationary. The situation hasn't changed, just the descriptive terms. In cosmology, Friedmann-Robertson-Walker coordinates (which describe expanding space) are scientists' most common choice, so we based our description on them. We could use systems that abandon expanding space in favor of expansion through space, but they also abandon well-established principles, such as the homogeneity of the universe and Hubble's law.

CHECKING MICHAEL MANN

In "Behind the Hockey Stick," by David Appell [Insights], nary a mention was made of Michael Mann's publication of a minor correction to his graph.

A detailed article in the February 14 *Wall Street Journal* pointed out how nonscientist Stephen McIntyre uncovered some flaws in Mann's math. Although Mann is adamant that his theory is correct, McIntyre forces us to take a closer look. When Mann's calculations are corrected, the global warming of medieval times and the subsequent Little Ice Age return. Bye-bye, hockey stick.

Clare Goldsberry
Phoenix, Ariz.

APPELL REPLIES: *Michael Mann has not published any corrections to his graph. As stated in the story, his corrigendum, published in the July 1, 2004,* Nature, *relates only to the existence and location of data on his Web site. He states that "none of these errors affect our previously published results." Moreover, several groups using different methods have replicated the results of Mann and his colleagues. This claim cannot be made for the work of Stephen McIntyre and Ross McKitrick, the two nonclimatologists cited in the* Wall Street Journal *article, which appeared after the March issue went to press.*

CLARIFICATION Results of the MIDAS Network simulations of pandemic influenza in "If Smallpox Strikes Portland . . . ," by Chris L. Barrett, Stephen G. Eubank and James P. Smith, expected in February were delayed, but preliminary findings appeared in "Cooping Up Avian Flu," by Christine Soares [News Scan, May].

150, 100 & 50 Years Ago

FROM *SCIENTIFIC AMERICAN*

Abusing Coal ▪ Creating Diamond ▪ Calculating Wood

JULY 1955

NEW ELEMENT—"For a few days early this year there was something new under the sun, but not much of it. Chemists at the University of California had made 17 atoms of element 101. The substance, named mendelevium (abbreviated Mv) [*now Md*] after the father of the periodic table, was produced by bombarding element 99 with energetic alpha particles from a cyclotron. The isotope thereby obtained, the atomic weight of which is 256, decays by spontaneous fission with a half-life somewhere between half an hour and several hours."

COAL—"The analysis of coal into its elemental constituents tells us almost nothing about it as a chemical substance. For this we must know the chemical structure of coal, the way in which its atoms are linked to form molecules. The effort is worthwhile because the more that is known about how coal is put together, the more precisely can it be taken apart to yield desirable chemical substances. Already one improved process has made from coal over 200 basic chemicals, some entirely new or in quantities never before achieved. It is this fact that leads chemists and conservationists to conclude that the most wasteful thing to do with coal is merely to burn it."

JULY 1905

PANAMA CANAL—"President Roosevelt has likened the stragglers that have drifted home from Panama, with their mouths full of censure and complaint, to the few faint-hearted and garrulous soldiers that fall back to the rear when the battle is on in good earnest. Nobody supposes that the Isthmus of Panama is just now either a health or a pleasure resort; at the same time, it does begin to look as though we had entered upon active construction without making that special preparation for the reception, housing, and subsistence of the working force, which the very trying tropical conditions at the Isthmus render necessary. By all means, let the army have charge of this work. It would be courting disaster to farm out the task of care and feeding to professional boarding-house keepers."

SKELETONS of man and horse compared, 1905

MAKING DIAMONDS—"Once in possession of the electric furnace, the eminent French chemist Prof. Henri Moissan tried to reproduce the process which nature was supposed to have used to form the diamond. The essential part was to dissolve the carbon in iron which has been kept in fusion at 5,000 degrees F. The next step is to cool the mass suddenly so as to form a solid crust. Then when the inside begins to cool it tries to expand, but is imprisoned in the outer layer. An immense pressure is the result, and the carbon is precipitated out of the iron as fine grains of black and transparent diamonds."

MAN AND HORSE—"Our photograph represents a beautifully mounted group consisting of the skeleton of a horse rearing and of a man, recently placed on exhibition in the American Museum of Natural History. The picture shows that the bones of a man and horse are strictly comparable, but man has retained more of the primitive features common to all mammals, the horse being far more specialized in the structure of its limbs and of its grinding teeth."

JULY 1855

SAND ANCHORS—"There has been received in the Patent Office, from Holland, the seeds of the sea reed (*arundo arenaria*), and the upright sea lyme grass (*elymus arenarius*), which have long been used in that country for reclaiming the sand drifts on the sea coast. These seeds have been imported for experiment all along the Atlantic coast, from Maine to Florida. The nutritive matter of these grasses is not sufficient to make them worthy of cultivation, but the two combined are of great utility, as they bind the loose sands of the sea shore, and thereby raise a durable natural barrier against the encroachments of the ocean upon the land. Indeed, Holland owes her very existence, in a considerable degree, to their preserving influences."

NAVY LUMBER—"How many trees make a ship? It requires 2,200 full grown trees, or the matured crop of forty-four acres of woodland to furnish timber for a single 74 gun ship."

SPACE SCIENCE

Feeling the Pinch

FLYING THE SHUTTLE MEANS CUTTING SOME SCIENCE **BY MARK ALPERT**

At more than 14 billion kilometers from the sun, Voyager 1 is farther from Earth than any other man-made object, yet the spacecraft is still within range of NASA's budget ax. The agency's new focus on human exploration—including the resumption of space shuttle flights scheduled for this month—is pulling funds from the unmanned spacecraft that study Earth, the sun and the outer reaches of the solar system.

In addition to devoting 40 percent of its $16.5-billion budget to the shuttle and the International Space Station, NASA has earmarked $753 million for the design of the Crew Exploration Vehicle, which will carry astronauts into orbit after the shuttle is retired in 2010. To help pay for this effort, the agency has proposed deep cuts to its Earth-Sun System Division, which operates Voyagers 1 and 2 and a dozen other probes that have completed their primary missions but are still yielding valuable data. Ordered to lop $20 million from the $75-million budget for the missions, the division will hold a review this fall to determine which spacecraft must be sacrificed. Potential victims include solar observatories (such as Ulysses and TRACE) as well as probes that investigate space weather around Earth (such as Polar, FAST, Geotail and Wind). To keep the craft running until the review, NASA has delayed funding research proposals to analyze the data from the missions.

VOYAGER 1, now speeding out of the solar system after 28 years in space, is one of the NASA missions facing budget cuts, even though the craft is reporting remarkable discoveries.

NASA/JPL

The uproar over the Voyagers has been the loudest. Launched in 1977, the twin probes explored Jupiter, Saturn, Uranus and Neptune and can continue operating until they use up their plutonium fuel about 15 years from now. In 2002 Voyager 1 reported a surge in particle counts; the craft may have temporarily crossed the termination shock, the turbulent boundary where the solar wind begins to merge with the interstellar medium. The probe recently detected new signs of

COLLATERAL DAMAGE

NASA's cutbacks may hurt hurricane forecasting, which has grown increasingly dependent on the agency's research satellites. Data from QuikSCAT, a satellite that uses microwave radar to measure ocean-surface winds, helped meteorologists determine the tracks and intensities of the four hurricanes that slammed into Florida last year. NASA, however, has canceled the Ocean Vector Winds Mission, which was intended to replace QuikSCAT in 2008. Instead the National Oceanic and Atmospheric Administration plans to put a passive microwave sensor on one of its weather satellites. Initial tests of the sensor in orbit have shown that it is less accurate than QuikSCAT.

turbulence, and project scientists insist that canceling the $4.2-million-a-year program would be folly. Says Stamatios Krimigis, lead investigator for Voyager's low-energy particle detector: "It's like Columbus sighting land and then saying, 'Okay, let's go back.'"

Meteorologists and geologists are up in arms, too. In April a National Research Council (NRC) report declared that NASA's system of Earth-observing satellites "is at risk of collapse." Half a dozen missions have been canceled, downsized or delayed. In some cases, the cutbacks threaten to create gaps in environmental records that NASA has been compiling for decades. For example, the agency had originally intended to launch the Landsat Data Continuity Mission to succeed the aging Landsat 7 satellite, which tracks everything from deforestation in the tropics to collapsing ice sheets in Antarctica. But now NASA plans to build only the Landsat imagers and place them on weather satellites operated by the National Oceanic and Atmospheric Administration. The delay will almost certainly cause a data gap—Landsat 7, which was launched in 1999, is already faltering, and the first of the NOAA satellites will probably not go up until at least 2009. What is more, researchers warn that the NOAA satellites will be large and hence prone to vibrations, which may ruin the quality of the Landsat images.

The budget pressures are also slowing the effort to understand climate change. The future of the Glory mission, which would make the first global measurements of soot and dust to determine their impact on climate, is now uncertain; its instruments may be reassigned to one of the NOAA satellites. "Pushing all these things back is not okay," says Richard A. Anthes, a hurricane expert who co-chaired the NRC panel. "We can't afford not to observe Earth."

The scientific community is clearly hoping that NASA's new administrator, Mike Griffin, will reverse some of the cuts to research missions. Before taking the top job at NASA, Griffin headed the space department at Johns Hopkins University's Applied Physics Laboratory. Krimigis, who held the same position before Griffin, has faith in his colleague. "I know Griffin—I interviewed him for this job," Krimigis says. "I'm quite confident he'll do the right thing."

COSMOLOGY

Flaw of Averages

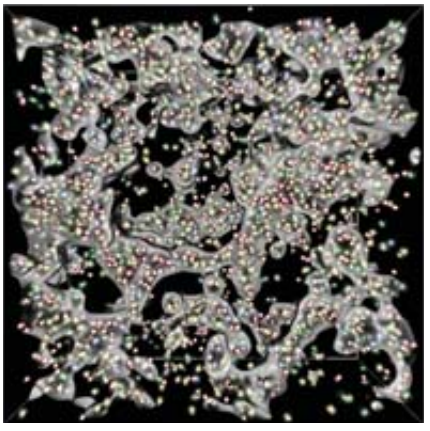
IS ORDINARY MATTER CAUSING THE COSMOS TO ACCELERATE? BY GEORGE MUSSER

One of the most profound features of the universe is that it is stratified. Our everyday world depends hardly at all on the details either of atoms or of galaxies, and the feeling is mutual. Were it otherwise, science would not be possible: we could not know anything without knowing everything. Sometimes, though, the levels of reality do get jumbled, with odd effects.

This past March a group of cosmologists—Edward Kolb of Fermi National Accelerator Laboratory and Sabino Matarrese, Alessio Notari and Antonio Riotto of the Italian National Institute of Nuclear Physics—argued that the acceleration of cosmic expansion, among the biggest mysteries of modern science, is one such effect. It could be the most elegant explanation for acceleration yet proposed, requiring neither exotic forms of energy nor new laws of physics, merely a careful accounting of how gravity interconnects structures of vastly different size. Or it could be a case of cosmological cold fusion.

Cosmologists routinely assume that the detailed arrangement of matter plays no role in the grand scheme of things. Their standard model treats the universe as though its density did not vary from place to place but had a uniform, average value of one atom per cubic meter. They solve for the expansion rate of this averaged universe and equate it with the average expansion rate of the actual universe. Individual patches of space may expand faster or slower, but researchers reckon that the discrepancies are localized.

THINK GLOBALLY, ACT LOCALLY: Small structures such as galaxies (*colored dots, arranged in a spongelike pattern*) might collectively produce cosmic acceleration. This diagram is from the 2dF Galaxy Redshift Survey.



2DF GALAXY REDSHIFT SURVEY TEAM AND PAUL BOURKE *Swinburne Center for Astrophysics and Supercomputing*

The trouble is, averages can be deceiving. A golf ball on average is a perfect sphere, but it does not fly like one. The dimples on its surface can double or triple the distance the ball travels. Gravity, like the behavior of air flowing over the dimples, is nonlinear, which led cosmologist George Ellis of the University of Cape Town in South Africa to suggest in the 1980s that the fine-scale texture of the universe might affect its large-scale behavior. This phenomenon is known as backreaction. Analogies occur in fields besides cosmology. Sound, for example, is usually stratified: it can be thought of as the sum of waves of various wavelengths, each of which ripples through a room as though the others were not even there. Yet when nonlinear processes operate, different wavelengths can cross-talk and even shift the average air density.

What cosmologists should do is track the gravitational effects of matter in all its irregularity—to take the average after they solve the equations rather than before—but that is a tall order. So although they widely agree that backreaction occurs, they argue over how big it is.

Kolb and his colleagues claimed a huge effect, but it relied on a linkage not only from small to large but also from large to even larger—basically, attributing the acceleration of the observable universe to matter beyond the observable universe. That sounds impossible by definition. Distant matter may have been in contact with our universe long ago before falling out of touch, but critics such as Christopher Hirata of Princeton University and Uroš Seljak of the International Center for Theoretical Physics in Trieste, Italy, pointed out that it cannot have an ongoing influence on us without violating relativity theory.

Kolb's team acknowledged making errors and is coming out with a new paper going back to a purely small to large backreaction. This approach might explain the so-called cosmic coincidence: why acceleration kicked in around the same time the growth of galaxies became strongly nonlinear. The sharp increase in galaxies' density could have cascaded up the line and produced a decrease in the average cosmic density, which would have accelerated expansion.

But earlier calculations by Seljak and others indicated that such an effect would not have been strong enough, and even cosmologists who are sympathetic think there is a long way to go. "At this point, this is an idea of how things could work out," says Sysky Räsänen of the University of Oxford. "It's something to motivate calculations, not something backed up by calculations."

PSYCHOLOGY

Reaching in the Dark

HOW BABIES LEARN THAT UNSEEN TOYS DON'T JUST VANISH BY MARINA KRAKOVSKY

A curious phenomenon has long puzzled developmental psychologists: Why do babies seem incredibly smart in some experiments yet utterly clueless when tested with other tasks designed to measure the same knowledge? Hide a toy under a blanket, and babies under about seven months do not reach for it, suggesting that they have not yet grasped object permanence, the idea that objects continue to exist when out of sight. Experiments involving merely looking at objects, however, show that babies as young as two and a half months are aware of the concept.

The standard explanation for such discrepancies is that babies have the concept early on, possibly from birth, but that for many months their underdeveloped motor skills keep them from lifting the blanket. Still, this account may be insufficient, because even babies taught to pull a blanket will not necessarily do it to uncover a hidden object.

So psychologist Yuko Munakata of the University of Colorado at Boulder has proposed a new key to the puzzle: that knowledge develops over time. "It's not like babies have this aha! insight one day—it's a gradual understanding," she explains. In a paper to be published in *Psychological Science*, Munakata and Jeanne L. Shinskey of the University of South Carolina offer some evidence that infants "gradually develop stronger representations of objects through experience" and that some tasks require stronger mental representations than others do.

In testing 24 babies, the researchers first made each seven-month-old thoroughly familiar with a simple clay toy. They then measured how often the baby reached for this toy compared with a new toy. As predicted by many previous studies, babies overwhelmingly preferred the novel to the familiar, 88 versus 39 percent of the time. But that was true only when the toys were in plain view. When the researchers turned off the light (and watched through an infrared camera), they found a complete reversal of infants' usual novelty preference. In the dark, the babies reached for the area where they last saw the new toy only 20 percent of the time, compared with 32 percent for the familiar one.

The researchers conclude that becoming familiar with a toy strengthened the babies' mental representations of it enough to search for it. Conversely, the babies did not reach for the cool new toy because they had not been around it long enough to recall it while in darkness.

That is just one interpretation of the data, according to Rutgers University psychologist Carolyn Rovee-Collier. It is possible that babies reach for familiar objects in the dark because that is a different game. She also wonders whether the pattern of reaching for familiar objects in the dark would hold for different degrees of familiarity, because novelty may be a special case rather than simply a lower level of familiarity.

Rachel Keen, a psychologist at the University of Massachusetts Amherst, proposes another possibility: babies are not afraid of the dark and in fact may find darkness pleasantly intriguing. She posits that "a familiar object in the novel environment of darkness is somewhat novel," noting that an intermediate level of novelty has proved more appealing than either total novelty or complete familiarity. Munakata says she is conducting another experiment that will test that explanation. But even that may not settle the question. As Keen puts it, "It's difficult to make inferences about what goes on in babies' minds, even though we do it all the time."

Marina Krakovsky, based in northern California, often writes about psychology.

FAMILIARITY may help teach infants a concept known as object permanence.

DARAMA/CORBIS

AND BABY MAKES MEMORY

In 1965 Carolyn Rovee-Collier was a new mother still finishing her doctorate. Her colicky two-month-old could only be soothed by a mobile over his crib. Tired of operating the mobile, Rovee-Collier tied a ribbon to the baby's foot and attached the other end to the mobile. Before long, the baby was purposely kicking his foot to move the mobile. "Several weeks later I realized he had learned to move the mobile," recalls the Rutgers University psychologist. This insight led to a series of pioneering experiments that debunked the entrenched notion that young babies cannot form memories.

ECOLOGY

Breeding Snail Fever

THREE GORGES DAM BOOSTS PARASITIC INFECTIONS **BY ADAM MINTER**

High in the mountains of China's Sichuan Province, George Davis of George Washington University is collecting tiny, seemingly harmless snails from a muddy ditch that runs through terraced fields. As the evolutionary biologist wields his tweezers, he contemplates how massive disruptions of the environment produce widespread problems, including emerging epidemics. "Diseases like SARS can pop up because of the interference of man in the ecosystem," he explains. "And now we have one of the most dynamic ecosystem changes in history in the Three Gorges Dam."

His concern: infections by parasitic worms, producing the fast-spreading and potentially deadly schistosomiasis that infects his collected snails—and humans. Davis and his colleagues from China's Institute for Parasitic Diseases (IPD) in Shanghai are finding that the Three Gorges Dam—the world's largest—is driving an increase in schistosomiasis infection densities around China's greatest lake.

The control of schistosomiasis—also known as snail fever—has long been a priority for China. In 1949 some 12 million people were infected, but one of history's most successful public health initiatives reined in the epidemic. Nevertheless, schistosomiasis management requires vigilance and money, and so over the past 50 years Chinese infection rates have waxed and waned with political and financial circumstances. Currently infections are on an upswing, climbing from 700,000 cases in 2000 to at least 850,000 today. "Right now schistosomiasis is the most serious parasitic disease situation in China," remarks Weiping Wu, an epidemiologist at the IPD and a Davis collaborator.

ADAM MINTER

SNAIL SWEEP: In April, trained locals in China's Sichuan Province collect snails that may harbor the schistosome worm.

PARASITIC TIME BOMB

Quietly, an even deadlier parasitic disease has reached dangerous proportions in China: hydatidosis. Caused by a parasitic worm, the disease is spreading across the Tibetan Plateau and western Sichuan Province. According to Weiping Wu of China's Institute of Parasitic Diseases, at least 600,000 Chinese are currently infected by the deadly disease, and an additional 60 million are at risk. "It is an epidemic," he says.

Humans usually contract hydatidosis via contact with the eggs of the parasite expelled in canine feces. Among other symptoms, the parasite creates liver cysts that, if not treated, result in likely death. Because drug therapy is long-term and effective in only about 30 percent of China's cases, prevention is the best medicine. The most effective measure—culling infected dog populations— is not feasible in Tibet, where the large Buddhist population strongly resists the practice.

The disease is caused by a *Schistosoma* worm that infects freshwater snails. The resulting larvae infect vertebrates (most commonly, humans and bovines) primarily via skin contact with water. The larvae then sexually reproduce within the host, which expels the eggs in feces. Effects on humans include fatigue, fever, internal lesions, distended organs and, if not treated, death.

Davis, who has spent 40 years investigating the evolution and taxonomy of Asian snail hosts for schistosomiasis, has established that in China the disease consists of at least two specific syndromes endemic to opposite sides of the natural barrier that was the Three Gorges (and now, its dam). For example, below the dam is Poyang Lake, China's biggest; the area is a highly engineered agricultural environment where water buffalo are the dominant means by which the worms complete their life cycle. Conversely, water buffalo are scarce in the mountains of Sichuan Province, above the dam. "Here it's driven by humans and the use of human waste as fertilizer," he says as he supervises his collection team in the village of Shian. "It's a different mode entirely, including genetically." And that has led to varying human infection rates: at Poyang Lake, they average 10 to 12 percent; in the mountains of Sichuan the rates can reach as high as 60 percent.

Ecogenetics is the only way to explain such divergences, Davis states. Part of his research includes data taken at Poyang Lake when the environment was influenced by the Yangtze River's annual flood cycle. When the dam's floodgates closed in June 2003, the flooding stabilized, and Poyang Lake suddenly had a new snail habitat. Within 18 months, infection of the snails by the parasites had spiked around the lake. The results, to be published in the fall, were not unexpected. "We *made* the prediction of what was going to happen in Poyang Lake in the grant application," Davis emphasizes. (His work gets backing from the National Institutes of Health, which offers grants to explore emerging parasitic diseases.)

SCHISTOSOME PARASITES infect snails and then humans, in whom they mate—here the female parasite is in the ventral groove of the male.

NIBSC *Photo Researchers, Inc.*

Davis is also watching the intermingling of the two snail subspecies that had been separated by the Three Gorges before they were dammed. Since the reservoir began to fill, those two populations have been free to mix, which may lead to higher infection rates because the parasite has more genetic diversity from which to choose. "That's very dangerous," he says.

For now, recent ecological changes probably bear little responsibility for China's resurgent schistosomiasis, which the Ministry of Health has vowed to control by 2009 or so. Davis, meanwhile, continues collecting and charting the earliest disease effects of history's most extreme engineering project.

Adam Minter is based in Shanghai.

BEHAVIOR

Training the Brain

COGNITIVE THERAPY AS AN ALTERNATIVE TO ADHD DRUGS

BY GUNJAN SINHA

To medicate or not? Millions of parents must decide when their child is diagnosed with attention-deficit hyperactivity disorder (ADHD)—a decision made tougher by controversy. Studies increasingly show that while medication may calm a child's behavior, it does not improve grades, peer relationships or defiant behavior over the long term.

Consequently, researchers have focused attention on the disorder's neurobiology. Recent studies support the notion that many children with ADHD have cognitive deficits, specifically in working memory—the

ability to hold in mind information that guides behavior. The cognitive problem manifests behaviorally as inattention and contributes to poor academic performance. Such research not only questions the value of medicating ADHD children, it also is redefining the disorder and leading to more meaningful treatment that includes cognitive training.

"This is really a shift in our understanding of this disorder from behavioral to biological," states Rosemary Tannock, professor of psychiatry at the University of Toronto. Tannock has shown that although stimulant medication improves working memory, the effect is small, she says, "suggesting that medication isn't going to be sufficient." So she and others, such as Susan Gathercole of the University of Durham in England, now work with schools to introduce teaching methods that train working memory. In fact, working-memory deficits may underlie several disabilities, not just ADHD, highlighting the heterogeneity of the disorder.

"Working memory is a bottleneck for everyday functioning independent of what category you fit into," comments Torkel Klingberg, a neuroscientist at the Karolinska Institute in Stockholm. Based on Klingberg's research, Karolinska founded Cogmed—a biotech company that has developed a software program to train working memory. In a recent paper in the *Journal of the American Academy of Child and Adolescent Psychiatry*, Klingberg reported that 60 percent of 20 unmedicated ADHD children no longer met the clinical criteria for ADHD after five weeks of training. The company has already rolled out its training service in Sweden and Germany, and Karolinska is collaborating with New York University to launch a clinical trial with ADHD kids later this year.

"It's intriguing data," Tannock remarks. "The emphasis is on visual-spatial memory, which is where we find the strongest link to inattention and ADHD. But they have to go further. You want to show that training improves ability on a range of tasks, not just holding information."

That ADHD children would respond to cognitive training does not surprise experts such as Lawrence H. Diller, a child psychiatrist and author of *Running on Ritalin*. "Hyperactivity and inattention are bell-shaped spectrum disorders," he says. "The majority of kids who are getting medication are borderline normal versus abnormal." In Diller's experience, the former benefit the most from nonpharmaceutical training approaches. Medication has been overemphasized by a pharmaceutical and medical industry "that has changed people's view of themselves," he continues. "Personal responsibility has taken a backseat to lifelong disorders."

Moreover, because there is no industry to back it, behavioral therapy has been grossly underrated, Diller and others opine. Unpublished data from the Multimodal Treatment Study—the largest U.S. long-term study of ADHD treatment in children—show that after two years, kids treated with behavioral therapy only (parent training, school intervention and a special summer camp program) functioned just as well as kids on high-dose medication, says lead researcher William Pelham of the University at Buffalo. Also, only an additional 8 percent of the children in the behavioral arm were medicated at the end of the second year, indicating that most parents in this group were satisfied with behavioral therapy.

This two-year outcome contrasts with the study's end results after 14 months, which suggested that behavioral therapy was somewhat less beneficial compared with high-dose medication. Although most experts advocate combining behavioral therapy with medication when necessary, medication is often the only option offered. "Parents need to know that there are alternative treatments," Pelham states.

The ability to tame symptoms via behavioral therapy and training suggests that many ADHD children may not need drugs. But both behavioral therapy and working memory training require diligence and patience from parents, teachers and therapists. That's not easy for a time-crunched society and far more laborious than popping a pill.

Gunjan Sinha is based in Frankfurt.

COGMED

MEMORY BOOST: RoboMemo is software made by Swedish biotech firm Cogmed that improves working memory, which helps to alleviate ADHD symptoms. Children select a highlighted number and also numbers previously highlighted. The better their recall of sequential numbers, the more game points they earn.

SCHOOL DAZE

Long-term studies increasingly link attention-deficit hyperactivity disorder with poor educational outcomes, even when children are medicated. ADHD kids drop out of high school more frequently, and their academic achievement scores average 8 to 10 percent lower than their non-ADHD peers, despite equivalent IQs. Additional support for these findings will be published by William Pelham of the University at Buffalo and Brooke Molina of the University of Pittsburgh, whose research also hints that stimulant medication may increase the risk of substance abuse later in life.

TELECOM

Copper for Fiber

FIBER OPTICS INTO THE HOME, WITH HELP FROM DSL **BY LAMONT WOOD**

FIBER-OPTIC LINES have been laid across the country, but only recently have companies started pushing them into homes.

In the 1990s telecommunications firms began laying down a glut of fiber-optic cables in preparation for hyperfast Internet connections and other data-hungry applications. Unfortunately, going the "last mile"—connecting the main optical lines to homes—proved financially burdensome, and companies largely shelved such plans after the technology stock bubble burst in 2000.

In the past year, however, serious efforts have begun to bridge the final gap, but not all of them involve using pure fiber all the way. For carriers insisting on clinging to copper, a compromise solution is taking shape in which the latest DSL (digital subscriber line) technology serves as the last link. Such systems, called active networks because they contain powered electronics, have drawbacks, but they allow carriers who are loathe to abandon their copper network to offer short-term economical answers to fiber.

The turnaround began with two little-noted events in 2003. First, the Federal Communications Commission decided that local phone companies installing modern fiber-optic lines would not have to share them at regulated rates with competitors, a possibility raised by the Telecommunications Act of 1996. The second event was economic—the average cost of installing fiber to the home in new "greenfield" developments fell to nearly the cost of a copper phone line installation (between $1,500 and $2,000 per home), notes Stuart Benington, of Tellabs in Naperville, Ill., a communications tech supplier. Consequently, in 2004, various phone companies, hoping to break out of the slumping voice market, began announcing plans for high-speed fiber-based services.

The standard-bearer for all-fiber connections, or passive networks (because they need no electronics boost to transfer a signal), appears to be Verizon Communications. It plans to offer fiber to at least three million homes by the end of 2005. Initially its data service involves splitting a signal (with a prism) from a standard 620-megabit-per-second fiber line to 32 subscriber lines, each carrying about 19.38 megabits. Subscribers who want faster connections can get a one-sixth share, or about 100 megabits.

In contrast, SBC Communications and BellSouth have adopted a less expensive solution by leaving the copper line in place as a last-mile DSL connection. The success of active networks depends on getting the fiber close enough for DSL, the speed of which is sensitive to distance. The latest DSL technology can achieve 25 megabits for homes less than 5,000 feet from the network node, making it comparable to Verizon's all-fiber offering. Improvements could boost the rate to 100 megabits for those no more than 500 feet from the node, notes Jay Fausch, a marketing director at Alcatel, the Paris-based telecom giant.

In any case, with proper data compression, a 25-megabit channel should be able to deliver one high-definition television channel along with several standard-definition channels, plus data and phone service, Benington says. (All-fiber systems require no such compression, because TV can simply be added to the same fiber but on another frequency.) SBC envisions offering DSL-based active network service to 17 million subscribers by the end of 2007.

But in the end, the hybrid DSL/fiber approach may just whet consumers' appetites for pure fiber, especially as its upgrade potential is realized—the 100-megabit maximum offered by Verizon is only one millionth the theoretical capacity of fiber. SBC in fact plans to offer full fiber as well but only to subscribers in greenfield areas, which may total one million. Qwest Communications is also considering passive networks for greenfield developments.

Meanwhile about 200 U.S. towns have given up on the private sector and have installed their own fiber networks. Ultimately, fiber appears certain to prevail. Phone companies refurbish their lines at an average annual rate of about 3 percent, observes analyst Michael Howard of Infonetics Research in San Jose, Calif. So fiber should begin replacing copper at that rate at least.

Lamont Wood writes about technology from San Antonio, Tex.

FAST FIBER

The lure of optical fiber is simple: capacity and speed. In the lab, a single strand can transfer 10 trillion bits, or terabits, per second. Theoretically, it can convey a staggering 100 terabits per second, according to Lucent Technologies' Bell Laboratories. (By comparison, cable modems rarely exceed five million bits.) Even with a sliver of that bandwidth reaching the home, various data-intensive applications could become commonplace—videoconferencing, immersive online gaming, distance learning, telemedicine, home security surveillance and video on demand. Experts predict that yet to be invented services will spring up: Jay Fausch, a marketing director at Alcatel, suggests three-dimensional holographic projections of sporting events.

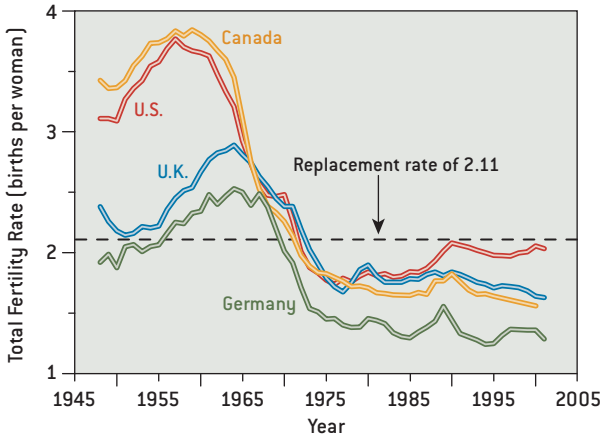
MARK E. GIBSON *Corbis*

Baby Boom Origins

CONFLUENCE OF FORCES MAY HAVE LED TO POSTWAR BIRTHS **BY RODGER DOYLE**

Fertility rates in Western countries had been trending down for more than a century, and so following World War II, demographers expected only a modest increase. What happened instead was the baby boom. Since then, social scientists have been arguing about the causes.

The best-known explanation comes from economist Richard A. Easterlin of the University of Southern California. He argues that the baby boom resulted from the unprecedented concurrence of three developments: an expansion of the economy, restricted immigration since the mid-1920s, and a relatively small cohort of new job seekers because of low fertility in the late 1920s and 1930s. This combination created unusually good job prospects for young people after World War II, and so feeling more prosperous than their parents, they married earlier and had more children.



SOURCES: United Nations Demographic Yearbook; U.S. National Center for Health Statistics. Data for Germany from 1948–1989 are for West Germany and thereafter for unified Germany. Data for the U.K. for 1948–1981 are for England and Wales only.

The Easterlin plausibly explains the U.S. baby boom but only about one third of the contemporaneous explosions in western European countries that were studied. Moreover, it seems to apply with particular force to countries without strong social protection programs, which tend to mitigate the effect of poor economic conditions on fertility. This may explain why, among Western nations, the U.S. and Canada had more vigorous baby booms than most European countries.

The late economist Alan R. Sweezy of the California Institute of Technology acknowledged Easterlin's account but believed that an even more important factor was a shift in attitudes toward family size. Noting that only 26 percent of women born in 1909 had three or more children, compared with 65 percent of those born in 1933, he argues, on the basis on an analysis of economic and demographic data, that this more or less reflects the reproductive intentions of each group.

Sociologist Norman B. Ryder of Princeton University believes that Americans, at least since the 1920s, have wanted two-child families but that poor contraceptives have undermined this desire. In the 1950s among married women with two children, the five-year failure rates of condoms, diaphragms and the rhythm method were 42 percent or more. (The comparable rate for birth-control pills, available in the 1960s, was only 6 percent.) The same contraceptive methods were used in the 1930s when fertility was low, but Ryder proposes that couples were more diligent in their use because poor economic conditions then made unwanted pregnancy a more serious matter. In addition, because people in the prosperous postwar times married sooner, women were at risk of unintended pregnancy over a longer period.

The combination of circumstances preceding the events of 1945 to 1965 is unlikely to recur soon. Indeed, the chart shows that the fertility rate has hovered around two or below for the past 30 years. (The rate is expressed as the number of births that a woman would have in her lifetime if at each year of age, she experienced the average birth rate occurring in the specified year.) Low fertility among Western nations will undoubtedly continue into the foreseeable future.

Rodger Doyle can be reached at rdoyle2@adelphia.net

FURTHER READING

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RODGER DOYLE

DATA POINTS: DON'T DRINK THE WATER

According to conventional wisdom, athletes should down fluids even before they feel thirsty. But excessive hydration can be deadly, says a study of Boston marathoners. It may lead to hyponatremia, the potentially fatal depletion of sodium, an electrolyte essential for cellular function.

Normal number of millimoles of sodium per liter of blood: 135 to 145

Number of marathoners studied: 488

Number with hyponatremia at the finish: 65

Percent who drank every mile:

Among runners with normal levels: 54

Among those with hyponatremia: 75

Percent who drank more than three liters during race:

Among normals: 26

Among those with hyponatremia: 42

Percent who weighed more at the finish (from fluid intake):

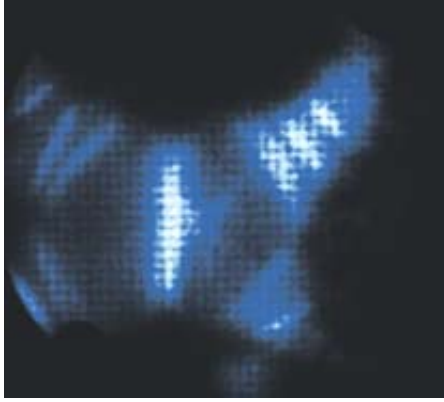
Among normals: 29

Among those with hyponatremia: 71

SOURCE: New England Journal of Medicine, *April 14*

NUCLEAR SCIENCE

Really Cold Fusion



FUSION LIGHT: A 2.5-centimeter-wide plastic target loaded with deuterium glows when hit by incoming deuterium ions.

Fusion ordinarily requires multimillion-degree heat, but a bucket-sized device fuses nuclei below freezing. The core of the machine is a lithium tantalate crystal, which generates an electric field when heated. A tungsten needle connected to the liquid-nitrogen-cooled pyroelectric substance focuses this field, such that when the crystal is warmed to roughly –3 degrees Celsius, deuterium ions surrounding the needle get kicked at speeds high enough to fuse with a deuterium-loaded target. Pyroelectric fusion power generators are unrealistic—a single run of the machine produces roughly 10 nanojoules, barely enough to heat a thimbleful of water a few millionths of a degree. Still, the process could lead to palm-sized neutron generators far simpler than conventional devices for use as thrusters in miniature spacecraft or in advanced medical therapies. Physicists at the University of California at Los Angeles report their findings in the April 28 *Nature*.

—Charles Q. Choi

CARDIOLOGY

Pressure Sensitive

Regular exercise may not help patients with severe high blood pressure as much as it does those with moderate hypertension. Yvonne Plantinga and her colleagues at the University of Pisa in Italy examined artery elasticity in 400 middle-aged volunteers. Stiffer arteries increase pressure on the heart. Regular exercise reduced stiffness in patients with normal or mildly high blood pressure but not in those with untreated, more severe conditions. "Medication and exercise would do better than just medication for those patients," Plantinga suggested at the American Society of Hypertension conference in May.

At the meeting, experts also moved to extend the definition of hypertension, suggesting it is a syndrome whose early stages can include normal blood pressure (a reading below 120/80). Exaggerated blood pressure response to exercise or mental stress, small amounts of protein in the urine, and an impaired ability to process blood sugar are among several symptoms that can be signs. Redefining hypertension may help physicians identify the disease earlier.

—Charles Q. Choi

PHYSICS

Grain Freeze

STIRRED AND SHAKEN: Plastic marble-sized beads get taken for a ride.

Heat up most forms of matter, and they flow more easily. But grainy masses seem to be an exception. Bob Behringer and Karen Daniels of Duke University filled a cylindrical hopper with marble-sized plastic beads. At rest the beads resemble a crystalline solid, like ice. When the investigators sheared the beads by turning the top of the container, the added energy "melted" the crystal into a more jumbled, flowing state, as expected. But when they injected more energy by vibrating the hopper, the beads oddly "refroze." Hard thumping causes the beads to momentarily achieve weightlessness, which may allow them to snuggle up closer together, the pair hypothesizes in the April 29 *Physical Review Letters*. The results contradict the intended goal of vibratory feeders for processing powders and grains, which "work under the presumption that shaking makes grains flow more readily," notes grain expert Troy Shinbrot of Rutgers University.

—JR Minkel

BRIAN NARANJO *UCLA (top)*; COURTESY OF BOB BEHRINGER *Duke University (bottom)*; ILLUSTRATION BY MATT COLLINS

OLFACTION

What's Smell Got to Do with It?

Chemicals that seem to act as sex-specific signals tickle the brains of gay men and straight women in a similar way. Using brain scans, Swedish researchers had found that women getting a whiff of the steroid derivative androstadienone, found in sweat, experience increased blood flow in a part of their hypothalamus known to release sexual hormones. Male sniffers responded instead to an estrogen derivative. Now the group has observed that in gay men the same brain location, called the peroptic area, responds to androstadienone rather than the estrogenlike steroid. Further experiments are needed to conclude that these activation patterns reflect sexual attraction, as opposed to discriminating between genders, or that the responses are innate or learned, cautions Ivanka Savic of the Karolinska Institute in Stockholm, co-author of the report in the May 17 *Proceedings of the National Academy of Sciences USA*.

SEX DIFFERENCES underlie odor production and preference.

LARRY WILLIAMS *Corbis*

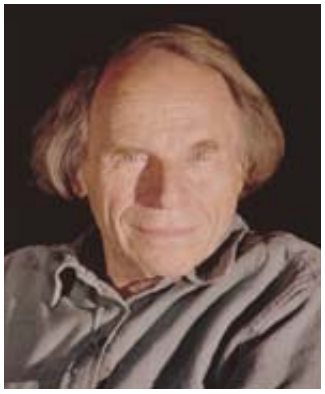
Indeed, olfactory response may be more sensitive to sexual orientation than brain scanning can resolve. In the September *Psychological Science*, researchers from the Monell Chemical Senses Center in Philadelphia will report how they collected armpit sweat from straight and gay men and women. The outcomes were not as simple as "prefers men" or "prefers women." All groups except gay men preferred the scent of lesbians to that of gay men, for example. Still, the work adds evidence for sex-based differences in odor production and preference. —*JR Minkel*

IN MEMORIAM

Philip Morrison, 1915–2005

As book reviewer and later columnist for *Scientific American*, Philip Morrison traveled often from Boston to New York to attend the monthly meeting of the editors. He was always the star turn. Speaking at machine-gun speed, yet in complete sentences and even (to my ear) complete paragraphs, he held forth illuminatingly on a great variety of subjects. His incisive quips on topics that came up at the meetings drew many a laugh. He was also a font of ideas for new articles.

Polio in childhood limited Morrison's mobility but not his vast range of interests. An assembler of the first atomic bomb, he later spoke out forcefully for international arms control. He was a pioneer in launching the search for extraterrestrial intelligence. And he was a skilled popularizer of science through his book reviews, his courses on physics for poets, many of his books, and his appearances on television and radio.



Morrison made important contributions in quantum electrodynamics, nuclear theory and radiology. Later, shifting his interest to astrophysics, he worked on cosmology, the origin and propagation of cosmic rays and gamma-ray astronomy. He taught at Cornell University from 1946 to 1964 and thereafter at the Massachusetts Institute of Technology, where in 1973 he became institute professor, the university's highest academic rank. Morrison died at his home in Cambridge, Mass., on April 22. He was 89. Additional memorial information can be found at www.memoriesofmorrison.org —*James T. Rogers (Board of Editors, 1963–1987)*

BRIEF POINTS

- **Costly recall: when starved, fruit flies that form long-term memories die 19 percent sooner than those that do not, evidently because of the protein synthesis required in creating those memories.**

  Science, May 20

- **Airlines low on air: 54 percent of passengers experience a 6 percent oxygen drop in their bodies, a point at which some physicians prescribe extra oxygen. The decline, coupled with immobility and other cabin factors, could contribute to illness.**

  Anaesthesia, May

- **Radical scrubbing: the atmosphere may naturally contain 20 percent more hydroxyl radicals than previously thought. These molecules chemically break down hydrocarbon pollutants.**

  Proceedings of the National Academy of Sciences USA, May 24

- **Lenses reveal details limited by the wavelength of light shining on an object. A superlens, made from a thin layer of silver, picked up details one-sixth the wavelength, thanks to the material's negative index of refraction.**

  Science, April 22

Hope Springs Eternal

Can nutritional supplements, biotechnology and nanotechnology help us live forever? By MICHAEL SHERMER

As a skeptic, I am often asked my position on immortality. "I'm for it, of course," is my wiseacre reply.

Unfortunately, every one of the 100 billion humans who have ever lived has died, so the outlook does not bode well. Unless you follow the trend line generated by Ray Kurzweil and Terry Grossman in *Fantastic Voyage: Live Long Enough to Live Forever* (Rodale, 2004): "The rate of technical progress is doubling every decade, and the capability (price performance, capacity, and speed) of specific information technologies is doubling every year. Because of this exponential growth, the 21st century will equal 20,000 years of progress at today's rate of progress." Within a quarter of a century, the authors say, "nonbiological intelligence will match the range and subtlety of human intelligence," then "soar past it because of the continuing acceleration of information-based technologies, as well as the ability of machines to instantly share their knowledge." Biotechnologies, such as designer drugs and genetic engineering, will halt the aging process; nanotechnologies, such as nanorobots, will repair and replace cells, tissues and organs (including brains), reversing the aging process and allowing us to live forever.

"The 21st century will equal 20,000 years of progress."

To make it to this secular Second Coming (2030 by their calculation), you need "Ray and Terry's Longevity Program," which includes 250 supplements a day and weekly rounds of intravenous "nutritionals." To boost antioxidant levels, for example, Kurzweil suggests a concoction of "alpha lipoic acid, coenzyme Q_{10}, grape-seed extract, resveratrol, bilberry extract, lycopene, silymarin, conjugated linoleic acid, lecithin, evening primrose oil (omega-6 essential fatty acids), *n*-acetylcysteine, ginger, garlic, 1-carnitine, pyridoxal-5-phosphate, and echinacea." Bon appétit.

Kurzweil is a brilliant and creative mind—the inventor of the first optical character-recognition program and CCD flatbed scanner, creator of the first reading machine for the blind with a text-to-speech synthesizer, recipient of the 1999 National Medal of Technology, and inductee into the National Inventors Hall of Fame. His books *The Age of Intelligent Machines* and *The Age of Spiritual Machines* significantly influenced the field of artificial intelligence. Thus, when Ray Kurzweil speaks, people listen. But my baloney-detection alarm went off in three areas of his work.

One, I am skeptical of the effectiveness of nutritional supplements. When I was bike racing in the 1980s, I went through a period of megadosing vitamins and minerals that produced brightly colored urine but no noticeable performance difference. The testimonials behind such nutritional claims are powerful, but the science is weak. The fact that the field is fraught with fads and ever changing claims for "X" as the elixir of health and longevity does not bode well. Nutritional science says that we get virtually all the vitamins and minerals we need through a balanced diet and that more is not better (see www.nutriwatch.org). These diets help us live longer lives, but no one can exceed the maximum human life span of 120 years. The 56-year-old Kurzweil declares that his program has reduced his biological age to about 40. I'm no aging expert or carny barker, but if I had to guess his age from his author photo I'd say, uh, 56.

Two, I question the idea of extrapolating trend lines very far into the future. Human history is highly nonlinear and unpredictable. Plus, in my opinion, the problems of creating artificial intelligence and halting aging are orders of magnitude harder than anyone has anticipated. Machine intelligence of a human nature could be a century away, and immortality is at least a millennium away, if not unattainable altogether.

Three, I am doubtful whenever people argue that the Big Thing is going to happen in *their* lifetime. Evangelicals never claim that the Second Coming is going to happen in the *next* generation (or that they will be "left behind" while others are saved). Likewise, secular doomsayers typically predict the demise of civilization within their allotted time (but that they will be part of the small surviving enclave). Prognosticators of both religious and secular utopias always include themselves as members of the chosen few. Hope springs eternal. SA

Michael Shermer is the publisher of Skeptic *(www.skeptic.com). His latest book is* Science Friction.

BRAD HINES

He'll Pay for That

The modern world exists because of science, so Fred Kavli hopes his funding of astrophysics, brain research and nanoscience will pave the way to the future By SALLY LEHRMAN

Fred Kavli collects Norwegian oil paintings and ornate Asian vases, installing them lovingly around his sprawling, 12,000-square-foot mansion overlooking the Pacific Ocean in Santa Barbara, Calif. But his most heartfelt passion has nothing to do with art or antiques. As he gazes toward an orange sunset, Kavli begins to speak of life's fundamental questions. He wonders about exploring the processes of the universe, generating nonpolluting forms of power and developing lightweight but strong nanoscale materials. Instead of spending his fortune on treasures of the past, he has dedicated it to these, the possibilities of the future.

BRAD SWONETZ

FRED KAVLI: WRITING THE CHECKS

- Made his fortune developing sensors for various military and commercial industries, including those for automobiles and airplanes.
- Has funded nine institutes at U.S. universities, another in Europe, and an operating foundation that conducts its own research and engages in public education. Current Kavli Foundation assets: $99.5 million.
- On federal funding cutbacks this past fiscal year: "We just have to be inventive and use money more efficiently; we have to do more with less."

Over the past five years, the 77-year-old Norwegian-born businessman has funded 10 basic science research institutes, created an operating foundation to explore pet research questions and laid out a plan to offer three $1-million awards biannually that would compete with the Nobel Prizes. "Because I believe in it," this unusual philanthropist explains simply, as if the reasons were obvious. "Life as we know it today would not be possible without science."

The Kavli Foundation began relatively quietly by contributing $7.5 million to a center for theoretical physics at the University of Santa Barbara in 2001 and then to an institute for particle astrophysics and cosmology at Stanford University. A year ago the foundation joined the ranks of notable small grantors by making endowments to eight more institutes at major universities. But instead of following the funding trend toward seeking nearer-term, measurable returns, the foundation pays for nondirected research in its three areas of interest: astrophysics, nanoscience and neuroscience. After Kavli finds the right people and institutions, it's hands-off. He just asks for an annual report and the occasional invitation to a lecture or event.

Kavli, who studied engineering physics at the Norwegian University of Science and Technology, says he picked these fields because he personally finds them fascinating—and because he thinks they will remain that way to scientists for many years. Even though he is committed to open-ended inquiry, Kavli takes a practical view of the potential rewards. "As we gain more knowledge about materials and processes in the universe, that could open up benefits that we can't even imagine," he says. "But you have to be willing to fund science without knowledge of the benefits."

Although the number of philanthropic organizations has doubled since 1990, the share for science

slipped to 2.4 percent in 2003 from 4 percent a decade earlier, according to the Foundation Center, a New York City–based nonprofit that tracks funding trends. The Kavli Foundation stands out even from the handful of those that do finance basic research, insists James Langer, vice president of the National Academy of Sciences. Kavli's own passion about the fields he sponsors, combined with his willingness to let researchers run with their ideas, sets him apart.

Kavli's approach also diverges from the increasingly utilitarian focus of both academic and government-funded research, points out David Auston, who serves as president of the foundation and its sister organization, the Kavli Operating Institute in Santa Barbara. Both the Department of Energy and the National Science Foundation—long known for their commitment to basic science—have nanotechnology initiatives, for instance. But Auston believes the agencies unrealistically expect these programs to deliver useful tools and applications rapidly. To win funds from any source, scientists must usually frame their ideas in the context of studies already completed and short-term impact. "It's a major impediment to significant discovery," remarks Auston, a former Bell Laboratories physicist. "The really neat things don't come easily—they come with risk."

Kavli's strategy seems a natural extension of his entrepreneurial style, which was both visionary and practical. He and his firm, Kavlico Corporation, willingly took on outlandish projects: their first contract, in 1958, involved building a linear position feedback sensor for the atomic-powered airplane being developed by the military. (That atomic project ended in 1961, after a decade of work.) By the late 1970s Kavli had constructed a solid business filling both military and commercial orders for expensive, meticulously constructed sensors for aircraft engines. Then, when Ford Motor Company wanted durable precision sensors mass-produced cheaply, the physics engineer took a gamble and promised he could make the switch. His bid won out over 41 others. "Everybody I talked to said, 'You're crazy,'" Kavli recounts.

The technological leap of faith into cars paid off, helping to transform Kavlico into a $225-million, 1,400-employee manufacturer. Its instruments can be found throughout an automobile's power train and chassis, even measuring the weight of a passenger so that air bags inflate properly. Five years ago a Canadian electronics firm paid $331 million for the business. Kavli dedicated much of the proceeds, along with his trust in the power of creative thinking, to science.

Kavli uses no application or peer-review process but consults a web of contacts in the same way a headhunter searches for executives. The foundation has chosen disciplines that are already acknowledged "growth" areas in science and has funded senior leaders within them. Eric Kandel, for instance, who directs the Kavli Institute for Brain Science at Columbia University, shared the 2000 Nobel Prize for his insights on signal transduction in the nervous system. Pasko Rakic, who heads up the Kavli Institute for Neuroscience at Yale University, is also a textbook name; his research has shaped scientific understanding of human brain development.

How these well-established investigators go forward will be critical, suggests Susan M. Fitzpatrick, a neurobiologist who is vice president of the St. Louis–based James S. McDonnell Foundation. "Will they pursue the kind of research that would not be going on otherwise?" Fitzpatrick asks. Small foundations (assets less than about $100 million) can do more than just "add on" to federal grants—Kavli institutes in Chicago and Santa Barbara, for instance, already get National Science Foundation money. Rather they best serve science by responding flexibly to emerging needs, Fitzpatrick believes.

QUANTUM SENSOR of thermoelectricity is one of many nanoscience feats accomplished by researchers using Kavli funds.

To let scientists loose on their dream ideas, Kavli says he negotiates their institutions' support and then creates or builds on research centers already in place: "What we do is very highly leveraged; that's the secret." He and Auston hope Kavli institute researchers will probe new depths as they bump into one another at interdisciplinary seminars. One field can lend strategies to another—for instance, cosmology's computational expertise might help in neuroscience and nanoscience. At the Kavli Operating Institute, such collaborations have led to studies such as one of coastal erosion.

Kavli is also exploring opportunities in the Pacific Rim and would like to fund at least one more institute in Europe, aside from the one at the Delft University of Technology in the Netherlands. And he will begin handing out his three $1-million prizes—in astrophysics, neuroscience and nanoscience—in 2008 in Norway. These awards will help build public awareness and appreciation for science, Kavli hopes.

For now, he is focusing on his commercial real-estate investments, which he knows will be necessary to keep the funds flowing. Instead of scientific journals, various travel, art-collecting and business magazines dot his sleeping quarters. "No, I don't get to dabble in science," he laughs. "I'm trying to make money so I can spend money." On science, of course. SA

Sally Lehrman is based in the San Francisco Bay Area.

M. L. ROUKES *Kavli Nanoscience Institute, California Institute of Technology*

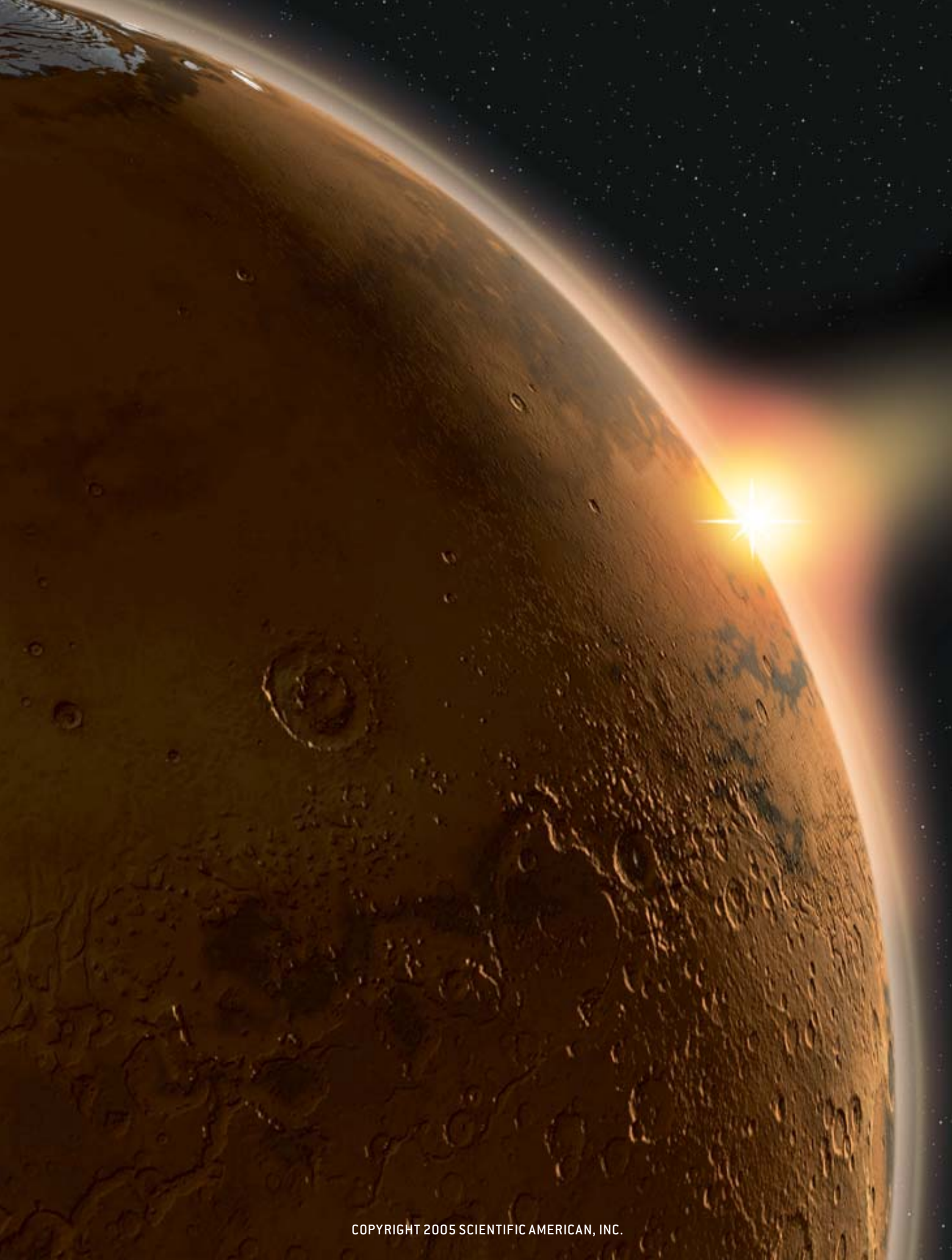
The Many Faces of Mars

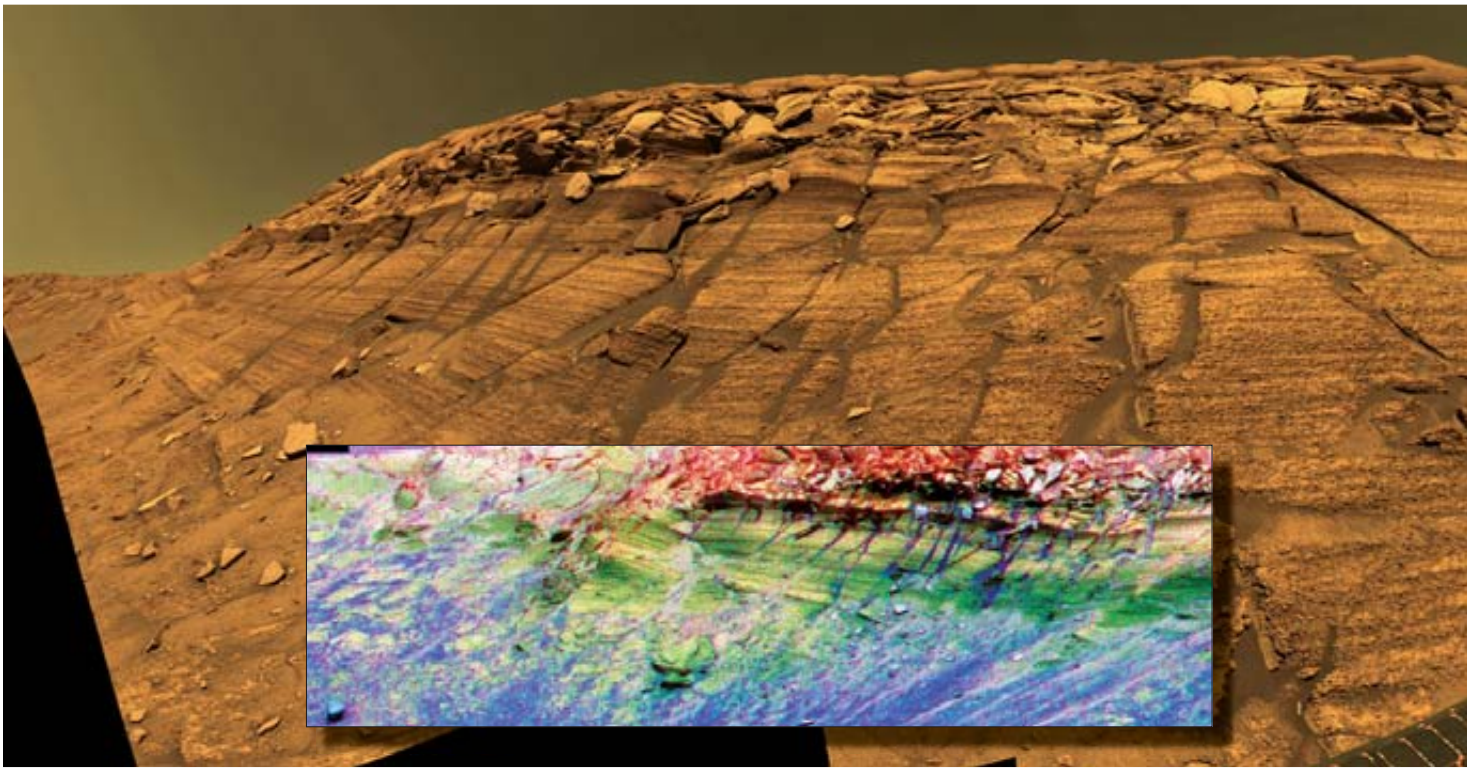
By Philip R. Christensen

One rover found an ancient desert; the other, a once watery world. The Red Planet's diversity rivals Earth's

Many people venture into the desert for its starkness and simplicity, but I go there for its complexity. The rocks of western Arizona, where I work, reveal one of the most tangled histories on Earth. Layers of carbonate limestones, silty mudstones, quartz sand and solidified lava show that within the past 600 million years, this area was a warm, shallow sea, then a muddy swamp, then a vast desert of shimmering hot dunes, then a glacial ice sheet, then a shallow sea once again. Erupting volcanoes formed islands like Japan, which in turn got shoved 100 miles onto the continent along massive faults, tilting the rock layers on edge and cooking them to create marble and quartzite. Uplift and erosion at last produced the desert landscape we see today.

SUNRISE OVER ARABIA TERRA, looking east toward Utopia Planitia: This artist's reconstruction of orbital images shows the margins of Vastitas Borealis, a vast, low plain where floodwaters from ancient channels may have ponded. Toward the center, the sun is casting its first rays on the western rim of the crater Lyot.





This kind of detailed historical reconstruction has long been impossible for Mars. Within my lifetime, the Red Planet has been transformed from a point in the night sky into a land of towering volcanoes, dried-up riverbeds, ancient lakes and windswept lava plains. Clearly, Mars has one of the most glorious histories in the solar system. Yet scientists have been able to piece together only the sketchiest outlines of that history. For years, we have debated such sweeping questions as whether Mars was once "warm and wet" and Earth-like or "cold and dry" and barren like the moon, as though the story of an entire world could be reduced to a sound bite.

Overview/*Martian Oddities*

- The Spirit and Opportunity rovers have been rambling around Mars for one and a half years, while three orbiters have mapped the planet's topography and mineral composition with a precision once available only for Earth.
- Until these missions, the primary evidence for past water on Mars was morphological: landform shapes, which are suggestive but ambiguous. Now the main evidence is mineralogical (the presence of iron oxides and sulfate salts) and textural (spherules and ripples in bedrock), leaving no doubt that the Opportunity landing site, at least, is an ancient lake bed.
- Yet the geologic history of the planet varies tremendously, and bizarrely, with location and time. Much of the planet has seen scarcely a drop of water; even the Opportunity site went through long dry spells. Other geologic features, such as volcanoes, are also unexpectedly diverse.

Over the past decade, though, we have entered the third great era of Mars exploration, the first two being the telescopic observations of the 19th century and the initial spacecraft reconnaissance of the 1960s and 1970s. Recent orbiter and rover missions have mapped the planet's topography, determined its mineralogy, imaged its surface in sufficient detail to interpret geologic processes, and merged orbital data with ground truth. Mars has finally become a place that I can study as a geologist does, using its rocks, minerals and landforms to weave a narrative.

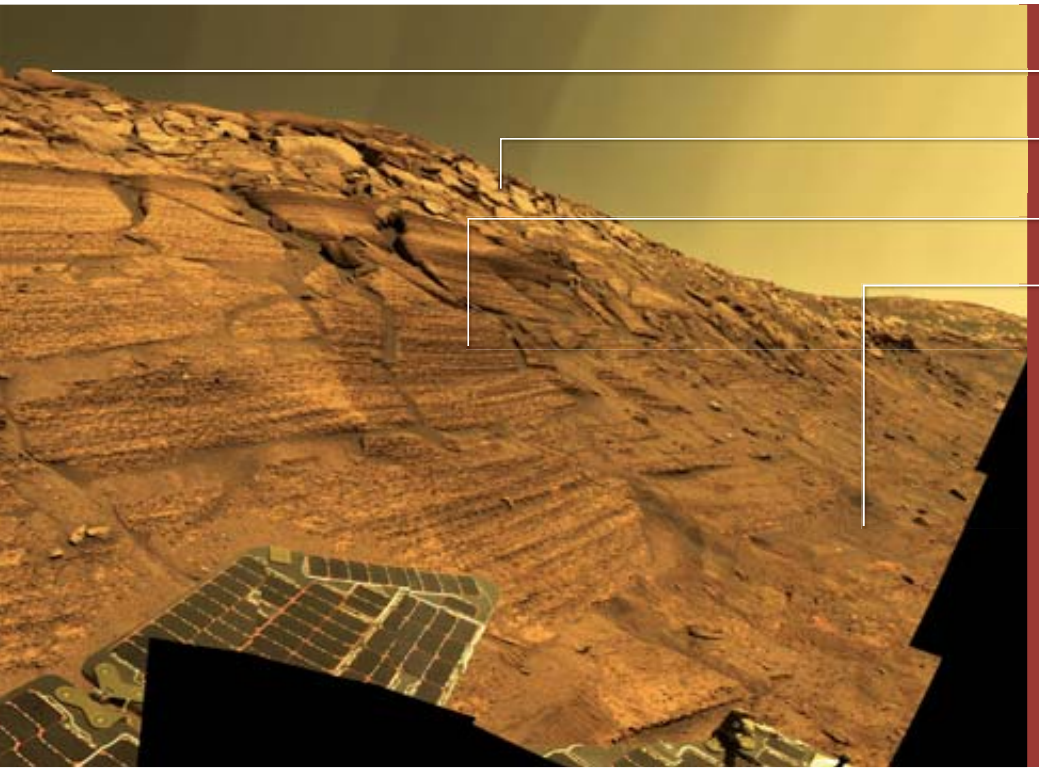
What we have discovered is that Mars has experienced a striking diversity of processes and conditions throughout its history. The Mars we are coming to know has embraced environments ranging from bone-dry to soaking wet to blanketed with snow and ice. Simple labels no longer fit. Rather than "warm" or "cold," we ask: How warm? How wet? For how long? Where? The emerging answers bear on what compels so many of us to study the Red Planet: its potential for harboring life, either now or in the past.

Two Places, Two Views

IN JANUARY 2004 NASA landed two of the most complex machines ever built at two very different sites on Mars. Packed with cameras and spectrometers to determine soil and rock composition, the Spirit and Opportunity rovers set out to answer the central question of Martian geology: What has been the role of water? Spirit bounced down in Gusev Crater, which had been chosen for the shape of its landforms: images taken from orbit have long shown that a valley, Ma'adim, opens into the crater, as if Gusev was once a lake.

Initially the site proved to be somewhat of a letdown. Spir-

RON MILLER (*preceding pages*)



BURNS CLIFF is a spectacular rock outcrop explored intensively by the Opportunity rover. The cliff, three stories tall, forms part of the rim of Endurance Crater, about 700 meters from the rover's landing site. Its uppermost rocks, like those at the landing site, are rich in sulfate salts (*red, yellow in false-color inset*) and were probably deposited as the area repeatedly flooded and dried out. Underneath are fine and coarse layers—a mixture (*green*) of the water-related mineral hematite and water-phobic basaltic minerals. These appear to be ancient sand dunes that were generally dry but located near a large basin of water. The floor of the crater is covered with basaltic sand (*blue*).

NASA/JPL/CORNELL

it found no signs of past water. What it saw were volcanic rocks, which spectrometers indicated were composed of olivine and pyroxene, minerals broken down by even the barest amount of liquid water. The rocks could not have been exposed to any significant amount of water in the three billion years or so since erupting. As Spirit climbed into the Columbia Hills, which overlook the landing site, the situation got more interesting. There the rover discovered high abundances of sulfur salts. Evidently, volcanic rocks had been ground into small grains and then cemented together by salt, a process that may have involved liquid water percolating through the rocks or sulfuric acid reacting with minerals that were already in the rock. Despite this hint of water, however, these rocks still contained significant amounts of olivine and pyroxene. Thus, even on what may once have been a lake bed, water appears to have played a minor role over the past few billion years.

The Opportunity rover headed to the plains of Meridiani. The selection of this site marked a new phase in humanity's exploration of the solar system: never before had planetary scientists sent a probe to a location for its mineralogy. Early spacecraft missions to Mars ascertained the composition of the surface in terms of chemical elements, but identifying the minerals—the compounds and crystal structures that these elements formed—required the Thermal Emission Spectrometer (TES), an instrument I developed for NASA's Mars Global Surveyor orbiter, which reached the planet in 1997. In the mineral maps we prepared, Meridiani stood out for its high abundance of crystalline hematite.

This iron oxide, common on Earth, forms by several processes, most of which involve water. One is the precipitation from fluids circulating through sediments; another, the deposition and dehydration of water-bearing iron minerals such as goethite, a reddish-brown mineral found in many desert soils. The Meridiani hematite-rich rocks appeared to be finely layered and easily eroded; they sat on top of the older, heavily cratered surface, suggesting a sedimentary deposit; and they filled in preexisting channels and other low areas of topography, suggesting that these rocks were deposited in water rather than draped across the landscape as volcanic ash or windblown dust.

Within days of landing, Opportunity confirmed that Meridiani had once been underwater. It immediately spotted outcrops of layered sedimentary rocks, the first ever seen on Mars. The rocks were so full of sulfate—30 to 40 percent by weight—that only the evaporation of sulfur-rich water could account for them. The sulfates at Gusev were not nearly so extensive. The hematite took the form of spheres (dubbed "blueberries") one to five millimeters across that were embedded in the rock layers and scattered all over the ground.

THE AUTHOR

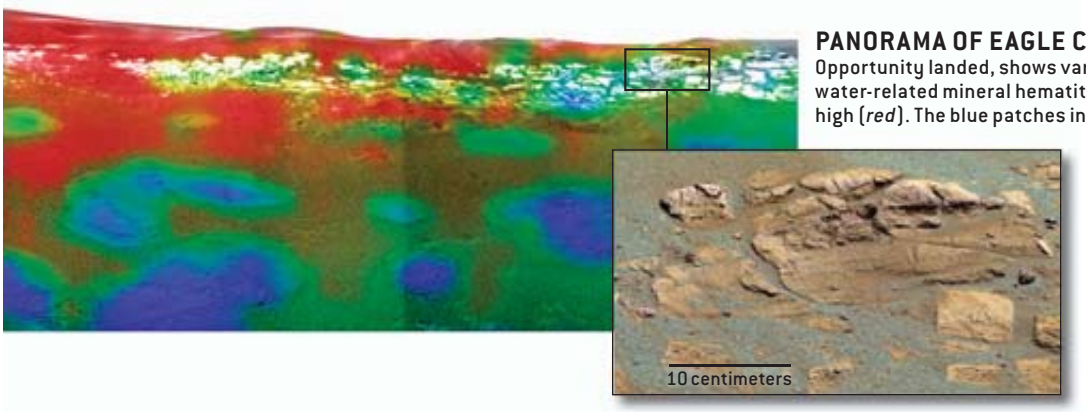
PHILIP R. CHRISTENSEN got interested in geology as a kid traveling throughout the American West. He first looked at Mars through a telescope his parents gave him when he was 12. Now a professor at Arizona State University at Tempe, he is the world's leading expert on the composition of the Martian surface. His research team developed the infrared instruments for the Mars Global Surveyor, Mars Odyssey and Mars Exploration Rover missions. In 2003 NASA awarded him its Exceptional Scientific Achievement Medal for his pioneering scientific observations of Mars in the infrared. Since the mid-1990s he has also used spacecraft observations to study environmental and urban development problems on Earth.

The largest outcrop that Opportunity explored, named Burns Cliff, appeared to be a series of preserved sand dunes that were wetted by surface and ground waters. Many of the grains in them were sulfates formed from the evaporation of standing water, perhaps in the level areas (known as playas) between the dunes. Judging from analogous features on Earth, the rocks of Burns Cliff took thousands to hundreds of thousands of years to form. The spherical hematite grains may have been created later from iron-rich fluids circulating through sediments. For the first time ever on Mars, scientists investigated an outcrop in the multifaceted way geologists on Earth do.

Even the morphology of the Meridiani plains, one of the flattest landscapes observed on any planet, looks like a lake bed. The extent of hematite mapped from orbit suggests it was an isolated large lake or small sea rather than part of a global ocean. Several craters to the south and west of the main hematite deposit also have hematite-rich layered rocks; perhaps they were separate lakes.

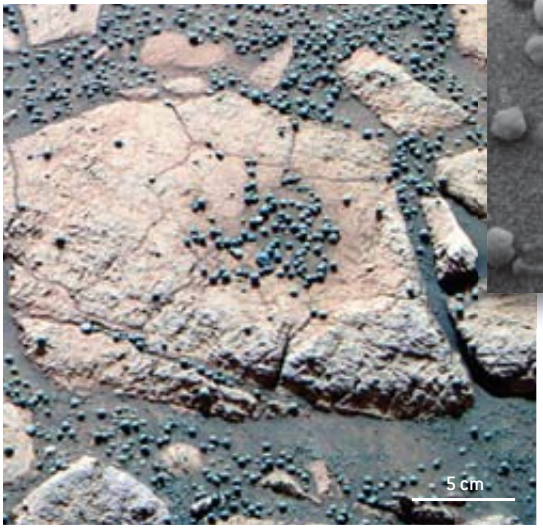
In short, it was as if the two rovers had landed on two completely different planets: one drier than any desert on

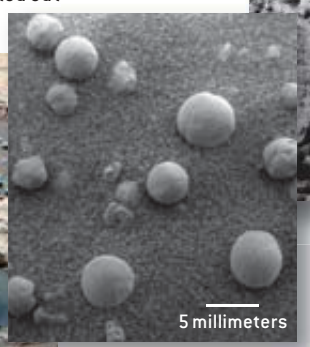
WHERE MARS WAS WET



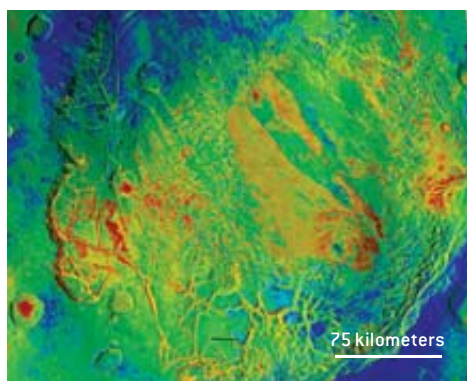
PANORAMA OF EAGLE CRATER, where Opportunity landed, shows varying amounts of the water-related mineral hematite, from low (*blue*) to high (*red*). The blue patches in the foreground are meter-size bounce marks created by the rover during landing. The white areas to the rear are rock outcrops such as El Capitan (*inset*); on detailed examination, they were found to consist of water-lain deposits of sulfate and hematite.

"BLUEBERRIES" are BB-sized spherules scattered all over the landing site. The high concentration of them on this rock, the so-called Berry Bowl (*shown here in false color*), allowed the rover to get a good reading of their composition: it is hematite, which probably precipitated out of water in the pore spaces of lake-bed sediments.



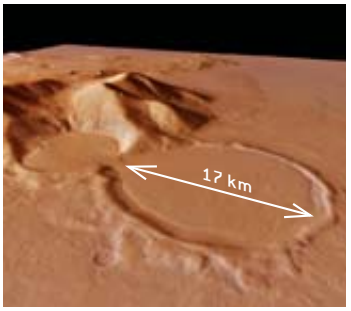


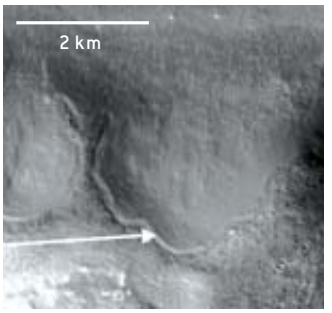
MICROSCOPE IMAGES show berries in the soil (*left*) and embedded in a rock named Upper Dells (*above*). The rock is laced with millimeter-thick layers whose shape is a telltale sign of deposition in flowing water.

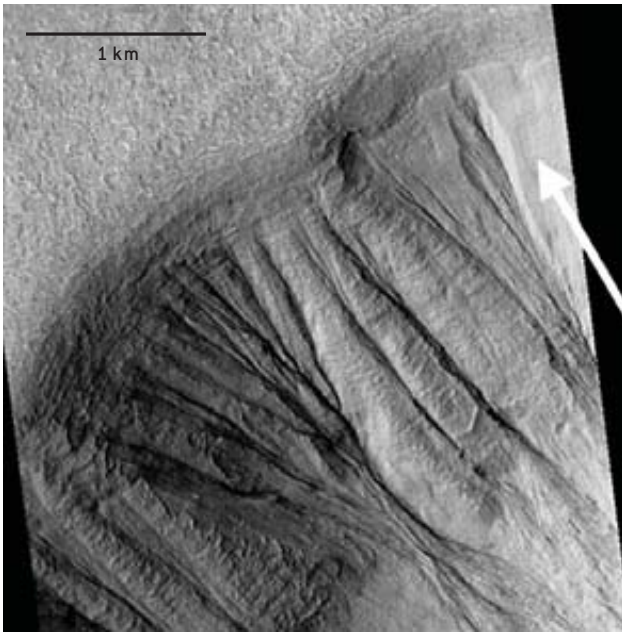


ARAM CHAOS is an impact crater that, like the Opportunity site, is flush with hematite. Nighttime temperatures, measured by the Mars Odyssey orbiter, indicate the consistency of material: warm (*red*) means rock, cold (*blue*) means dust and sand. The flat rocks in the center of the crater (*orange*) appear to be lake-bed sediments. The fractured terrain to the south indicates that the ground suddenly collapsed, perhaps when subsurface water rushed out.

NASA/JPL/CORNELL/ARIZONA STATE UNIVERSITY (*Eagle Crater panorama*); NASA/JPL/CORNELL (*El Capitan* and *Berry Bowl*); NASA/JPL/CORNELL/USGS (*microscope image of berries and embedded berries*); NASA/ARIZONA STATE UNIVERSITY/TIM GLOTCH (*Aram Chaos*)







LET IT SNOW: Mars may not be quite as dynamic as it used to be, but there is life in the planet yet. The Mars Express orbiter saw what appeared to be geologically recent glaciers flowing through mountain ranges and craters (*left*). The Mars Odyssey orbiter detected snow deposits (*arrows, center* and *right*) on pole-facing slopes. Snow may be the source of the water that produced fresh gullies (*right*). If microbes survive anywhere on present-day Mars, these snowpacks would be one obvious place.

Earth, the other a land of a thousand lakes. Are these the only possibilities, or is Martian geology even more varied? Do these two sites, thousands of kilometers apart, represent the total range of rock compositions and aqueous activity on Mars? To answer these broad questions, scientists have looked anew at data taken from orbit.

Lava Land

OVER THE PAST eight years, the TES instrument has discovered that Martian rocks and sands are composed almost entirely of the volcanic minerals feldspar, pyroxene and olivine—the components of basalt. In the spring of 2004 the European Space Agency's Mars Express orbiter, carrying the OMEGA near-infrared spectrometer, joined the effort and verified the extensive presence of these minerals. Olivine is exposed more than 4.5 kilometers below the surface in the walls of the Valles Marineris canyon system; it appears all over the equatorial plains, including the floors of channels. The discovery of basalt did not come as a great surprise. Basalt also covers much of Earth and the moon; the lava that oozes across Hawaii is basalt. It is a pristine type of lava—formed from the first stage of melting of the planet's mantle—and on Earth it continuously erupts from mid-ocean ridges to create the seafloor.

Another discovery, though, was unexpected. Whereas the rocks in the ancient heavily cratered terrains were basaltic, the younger rocks of the northern lowlands resembled a more highly evolved type of lava called andesite: they contained more glass, more silica-rich minerals and fewer iron-bearing minerals. On Earth, andesites typically form when descending tectonic plates mix water into subterranean molten rock. The possible existence of andesites on Mars is intriguing. It may indicate that the Martian mantle is wetter than Earth's or that younger lavas melted at different temperatures or pressures than the older basalts. To be sure, some scientists propose that the supposed andesites are basalts masquerading as such; a fog of water or acid could react with the minerals to create an andesitelike veneer. Researchers may have to wait for detailed surface studies of these rocks to resolve this question.

The TES instrument has fairly low spatial resolution: a pixel is several kilometers across. So the true variety of Martian mineralogy started to become apparent only in 2001, when THEMIS, an infrared camera that my group developed for another NASA orbiter, Mars Odyssey, began mapping the planet with 100-meter resolution. It and OMEGA have revealed a diversity of igneous rock compositions that rivals Earth's.

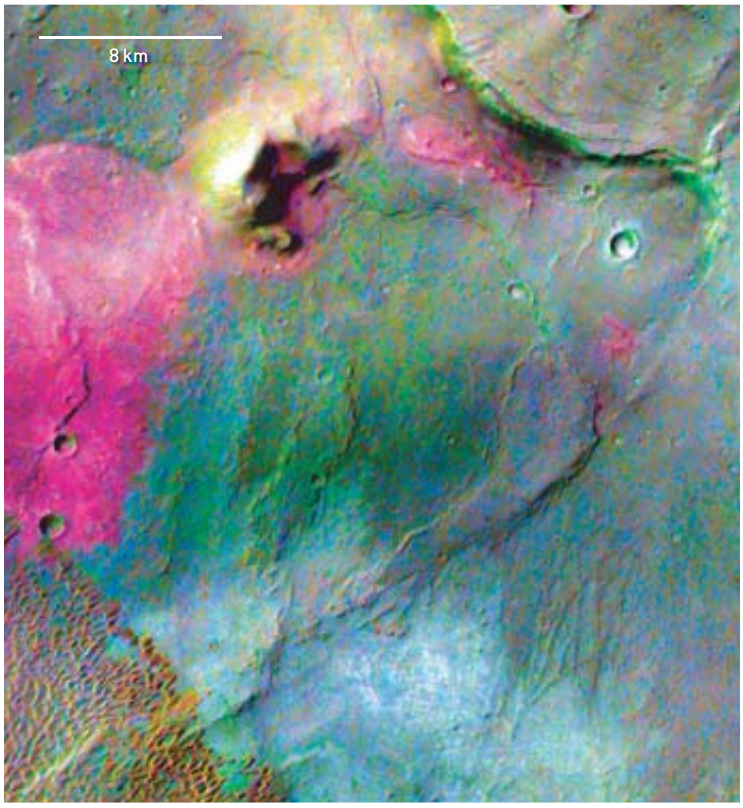
Near the Martian equator sits a volcano 1,100 kilometers in diameter named Syrtis Major. A series of collapse craters, or calderas, lie at its summit. The bulk of the volcano is basaltic, but the slopes are dotted with cones and lava flows consisting of glassy, silica-rich lavas called dacites. This rock type originates in the magma chambers that underlie volcanoes. As magma cools, the first minerals to crystallize are olivine and pyroxene, which are rich in iron and magnesium. They settle to the bottom of the chamber, leaving the remaining magma enriched in silica and aluminum—from which dacites emerge. The central peaks of several craters on the flanks of Syrtis Major are made up of an even more silica-rich rock, granite, that may have formed by extreme crystal separation or by large-scale remelting of earlier basalts.

Researchers conclude that this volcano went through many stages of development. Basaltic lava first erupted from the center and built up the volcano. As the magma evolved chemically, it withdrew from the chamber underneath the summit, causing the ground there to collapse and feeding eruptions on the flanks. Not only are Martian volcanoes huge, they are surprisingly complex.

And There Will Come Soft Rains

JUST AS IMPORTANT as what Mars has is what it lacks. Quartz is common on Earth but exceedingly rare on Mars, indicating that granite, from which it forms, is scarce. Nor is

ESA/DLR/FU BERLIN (G. NEUKUM) (*left*); NASA/JPL/MALIN SPACE SCIENCE SYSTEMS (*center*); NASA/JPL/MALIN SPACE SCIENCE SYSTEMS/PHILIP CHRISTENSEN (*right*)



NILI PATERA, a region at the summit of the giant volcano Syrtis Major, contains both older basaltic lavas (*blue*) and younger dacite cones and flows (*red*). The sand dunes (*orange*) are a mixture of the two types. Martian volcanism is more chemically complex than scientists expected.

there evidence for metamorphic minerals such as slate or marble, produced when volcanic or sedimentary rocks are subjected to high pressure or temperature. The main implication is that Mars does not have tectonics capable of driving rocks to great depths (where they are heated and squeezed) and then bringing them back to the surface.

Earth has vast deposits of carbonate rocks such as limestone, which precipitated from warm, carbon dioxide–rich oceans. Planetary scientists, reasoning that Mars used to be warmer and wetter, thought it, too, would have thick layers of carbonates. But none have been found. That means any oceans were cold or short-lived or ice-covered or otherwise hostile to carbonates. The ubiquitous dust does contain small amounts of carbonate, but it probably formed by direct interaction with water vapor in the atmosphere rather than liquid water on the surface. Another class of water-related minerals, clays, is also rare on Mars—again suggesting that the planet has been mostly dry. That accords with the widespread presence of the water-shy minerals olivine and pyroxene.

In this sense, what Spirit saw at Gusev is more representative of Mars than what Opportunity found at Meridiani. And yet Meridiani is not the only place where lakes appear in the orbital images. Aram Chaos, a 280-kilometer-diameter crater, has an outflow channel and is filled with layered rocks that contain hematite. Gigantic blocks of rock litter the crater floor. It looks as though a torrent of subsurface water was catastrophically released, causing the overlying terrain to collapse. Some of the water ponded in the crater, forming the layers of hematite-bearing sediments.

Similarly, troughs in Valles Marineris contain hematite-bearing rocks in fine, easily eroded layers, matching what one expects from deposition in standing water. These rocks, and others throughout the equatorial region, are rich in sulfates, a telltale sign of water-lain sediments. The lakes may have undergone numerous episodes of inundation, evaporation (and possibly freezing), and desiccation. In addition to the ancient lake beds are regions carved with dense networks of channels, seemingly created by rainfall and surface runoff. Some researchers have argued that Mars had extensive oceans: images and topographic data hint at shorelines and smooth ocean floors.

Together these discoveries provide strong evidence that water was stable in isolated regions for brief periods. What factors caused water to accumulate and remain stable at these sites? A leading guess is a combination of geothermal heat, large doses of salt (which lowered the freezing temperature) and a protective covering of ice. Large meteor impacts may have occasionally thickened and warmed the atmosphere.

But the idea of a once Earth-like planet seems to be passé. The overwhelming impression from the global mineral mapping is of an ancient surface whose original volcanic minerals are still preserved, little altered by water. Even at Meridiani, basaltic sands lie atop the lake sediments, indicating that the site has been parched for two billion to three billion years. Lakes and riverlike networks do exist, but water may have flowed through them only briefly. It is possible that water remained frozen for most of the time, was occasionally released and quickly refroze. Still, planetary scientists puzzle over how a world that was so arid in general could have been so watery at certain places and times.

Planet of the Long Seasons

MARS'S EPIC PAST tends to get the most attention, but two developments have reinvigorated study of its present-day activity. First is the growing consensus that Mars has been geologically active in the recent past. Most large volcanoes and lava plains are old, dating to the first half of the planet's history, but the lack of meteor impact craters on lava flows in regions such as Athabasca suggests they are young (by a geologist's standards), the result of eruptions within the past few million years. Researchers have looked for active volcanic or geothermal hot spots in nighttime infrared images but so far have seen none. Mars appears to have cooled to the point where volcanism is very rare, although lava does occasionally erupt onto the surface.

The second is the discovery that Mars has colossal reservoirs of frozen water that migrate around the planet as its climate changes. To begin with, both poles have deposits of ice or ice-rich sediments that are up to several kilometers thick over a combined area nearly twice the size of Arizona. Infrared

NASA/ASU/NOEL GORELICK

APOLLINARIS PATERA, a broad but low volcano, spewed lavas of varying composition. It may be the source of the ash found by the Spirit rover 350 kilometers to the south. The volcano's deposits have been deeply carved by water. Spacecraft have noticed active landslides in the area.

temperature readings in the 1970s demonstrated that the north polar cap is water ice but did not settle the composition of the south polar cap. Its surface temperature matches that of carbon dioxide ice, but might water ice lie underneath? Recent temperature readings by THEMIS have detected water ice poking through in certain places, so the answer seems to be yes.

Adding to the known inventory of water is the underground ice detected by the Gamma Ray Spectrometer and the High Energy Neutron Detector instruments on Mars Odyssey. These instruments measure gamma rays and neutrons, which are produced when cosmic rays collide with atoms in the soil. The energy distribution of gamma photons and neutrons reveals the elemental composition of the soil to a depth of several meters. For instance, hydrogen strongly absorbs neutrons, so a dearth of neutrons implies subsurface hydrogen—most probably the H_2 of H_2O. In the regions between 60 degrees latitude and each pole, water appears to make up more than 50 percent of the soil. Ice abundances this high could not have formed by the simple diffusion of water vapor from the atmosphere into the pores of the soil. Instead the ice must have been deposited as snow or frost.

Unusual landforms seen throughout the midlatitudes also hint at ice. A basketball-textured terrain occurs between 30 and 50 degrees latitude in both hemispheres; it may form as soil warms up and ice evaporates, causing the soil to crumble apart. A second type of deposit, found in hollows on cold, pole-facing slopes, is a layer of material up to 10 meters thick—a possible remnant of nearly pure water snow. One of the most remarkable discoveries has been the small, fresh gullies at midlatitudes, perhaps the result of spring water, melting of near-surface ice, or melting of snowpacks from the bottom up.

All these water-related features suggest that Mars, like Earth, goes through a cycle of ice ages. The tilt of the planet's spin axis oscillates by as much as 20 degrees over a period of 125,000 years. When the tilt is modest, the poles are the coldest places on the planet. More snow falls there than evaporates, leading to a net accumulation of ice. As the tilt increases, the poles receive more sunlight and warm up, at the expense of the midlatitudes. Water tends to move from the poles toward the equator. As snow builds up on the surface, running water can trickle out. Today the midlatitudes are warming up, and the snow cover has mostly disappeared. If the ice-age model is correct, they will return over the next 25,000 to 50,000 years.

The story of Mars science is like the tale of the blind men describing an elephant: the geology seems to change depending on where you look. The planet is a richly textured place with an amazingly dynamic present and an intricate, even paradoxical, past. Its volcanic rocks are as diverse as Earth's, and the manifestations of water vary tremendously. The planet experienced heavy flooding and perhaps even rainfall earlier in its history, yet its ancient rocks still contain minerals that quickly break down in a wet environment. The climate is dry and cold, yet the Opportunity rover found itself on the floor of an ancient sea, indicating that the climate used to be very different. Liquid water is unstable under present conditions, yet gullies formed recently and may continue to do so.

The diversity of surface environments from place to place and time to time is one of the most hopeful indicators for Martian biology: it provides a rich suite of environments where life may have taken hold. Water was abundant in lakes for long, if intermittent, periods. It may have been around long enough for inanimate matter to come alive. Organisms may still cling to life, hibernating during the cold spells and thawing out when climate conditions improve. The remnant snow patches, gullies and similar regions would be an excellent place to search for life on future robotic missions. SA

MORE TO EXPLORE

Global Mapping of Martian Hematite Mineral Deposits: Remnants of Water-Driven Processes on Early Mars. P. R. Christensen, R. V. Morris, M. D. Lane, J. L. Bandfield and M. C. Malin in *Journal of Geophysical Research,* Vol. 106, Part 10, pages 23,873–23,885; 2001.

Morphology and Composition of the Surface of Mars: Mars Odyssey THEMIS Results. Philip R. Christensen et al. in *Science,* Vol. 300, No. 5628, pages 2056–2061; June 27, 2003.

Spirit at Gusev Crater. Special issue of *Science,* Vol. 305, No. 5685, pages 793–845; August 6, 2004.

Opportunity at Meridiani Planum. Special issue of *Science,* Vol. 306, No. 5702, pages 1697–1756; December 3, 2004.

Roving Mars: Spirit, Opportunity, and the Exploration of the Red Planet. Steve Squyres. Hyperion, 2005.

NASA/ASU/NOEL GORELICK

MALE AFRICAN ELEPHANT (about 6,000 kilograms) and the smallest species of ant (0.01 milligram) differ in mass by more than 11 orders of magnitude—roughly the same span as the top quark and the neutrino. Why the particle masses should differ by such a large amount remains a mystery.

The Mysteries of MASS

Physicists are hunting for an elusive particle that would reveal the presence of a new kind of field that permeates all of reality. Finding that Higgs field will give us a more complete understanding about how the universe works

By Gordon Kane

BRYAN CHRISTIE DESIGN

Most people think they know what mass is, but they understand only part of the story. For instance, an elephant is clearly bulkier and weighs more than an ant. Even in the absence of gravity, the elephant would have greater mass—it would be harder to push and set in motion. Obviously the elephant is more massive because it is made of many more atoms than the ant is, but what determines the masses of the individual atoms? What about the elementary particles that make up the atoms—what determines their masses? Indeed, why do they even have mass?

We see that the problem of mass has two independent aspects. First, we need to learn how mass arises at all. It turns out mass results from at least three different mechanisms, which I will describe below. A key player in physicists' tentative theories about mass is a new kind of field that permeates all of reality, called the Higgs field. Elementary particle masses are thought to come about from the interaction with the Higgs field. If the Higgs field exists, theory demands that it have an associated particle, the Higgs boson. Using particle accelerators, scientists are now hunting for the Higgs.

The second aspect is that scientists want to know why different species of elementary particles have their specific quantities of mass. Their intrinsic masses span at least 11 orders of magnitude, but we do not yet know why that should be so [*see illustration on page 44*]. For comparison, an elephant and the smallest of ants differ by about 11 orders of magnitude of mass.

What *Is* Mass?

ISAAC NEWTON presented the earliest scientific definition of mass in 1687 in his landmark *Principia:* "The quantity of matter is the measure of the same, arising from its density and bulk conjointly." That very basic definition was good enough for Newton and other scientists for more than 200 years. They understood that science should proceed first by describing how things work and later by understanding why. In recent years, however, the *why* of mass has become a research topic in physics. Understanding the meaning and origins of mass will complete and extend the Standard Model of particle physics, the well-established theory that describes the known elementary particles and their interactions. It will also resolve mysteries such as dark matter, which makes up about 25 percent of the universe.

The foundation of our modern understanding of mass is far more intricate than Newton's definition and is based on the Standard Model. At the heart of the Standard

Model is a mathematical function called a Lagrangian, which represents how the various particles interact. From that function, by following rules known as relativistic quantum theory, physicists can calculate the behavior of the elementary particles, including how they come together to form compound particles, such as protons. For both the elementary particles and the compound ones, we can then calculate how they will respond to forces, and for a force F, we can write Newton's equation $F = ma$, which relates the force, the mass and the resulting acceleration. The Lagrangian tells us what to use for m here, and that is what is meant by the mass of the particle.

But mass, as we ordinarily understand it, shows up in more than just $F = ma$. For example, Einstein's special relativity theory predicts that massless particles in a vacuum travel at the speed of light and that particles with mass travel more slowly, in a way that can be calculated if we know their mass. The laws of gravity predict that gravity acts on mass and energy as well, in a precise manner. The quantity m deduced from the Lagrangian for each particle behaves correctly in all those ways, just as we expect for a given mass.

Fundamental particles have an intrinsic mass known as their rest mass (those with zero rest mass are called massless). For a compound particle, the constituents' rest mass and also their kinetic energy of motion and potential energy of interactions contribute to the particle's total mass. Energy and mass are related, as described by Einstein's famous equation, $E = mc^2$ (energy equals mass times the speed of light squared).

An example of energy contributing to mass occurs in the most familiar kind of matter in the universe—the protons and neutrons that make up atomic nuclei in stars, planets, people and all that we see. These particles amount to 4 to 5 percent of the mass-energy of the universe [*see box on page 45*]. The Standard Model tells us that protons and neutrons are composed of elementary particles called quarks that are bound together by massless particles called gluons. Although the constituents are whirling around inside each proton, from outside we see a proton as a coherent object with an intrinsic mass, which is given by adding up the masses and energies of its constituents.

The Standard Model lets us calculate that nearly all the mass of protons and neutrons is from the kinetic energy of their constituent quarks and gluons (the remainder is from the quarks' rest mass). Thus, about 4 to 5 percent of the entire universe—almost all the familiar matter around us—comes from the energy of motion of quarks and gluons in protons and neutrons.

Why is the Higgs field present throughout the universe? What *is* the Higgs field?

Overview/*Higgs Physics*

- Mass is a seemingly everyday property of matter, but it is actually mysterious to scientists in many ways. How do elementary particles acquire mass in the first place, and why do they have the specific masses that they do?
- The answers to those questions will help theorists complete and extend the Standard Model of particle physics, which describes the physics that governs the universe. The extended Standard Model may also help solve the puzzle of the invisible dark matter that accounts for about 25 percent of the cosmos.
- Theories say that elementary particles acquire mass by interacting with a quantum field that permeates all of reality. Experiments at particle accelerators may soon detect direct evidence of this so-called Higgs field.

The Higgs Mechanism

UNLIKE PROTONS and neutrons, truly elementary particles—such as quarks and electrons—are not made up of smaller pieces. The explanation of how they acquire their rest masses gets to the very heart of the problem of the origin of mass. As I noted above, the account proposed by contemporary theoretical physics is that fundamental particle masses arise from interactions with the Higgs field. But why is the Higgs field present throughout the universe? Why isn't its strength essentially zero on cosmic scales, like the electromagnetic field? What *is* the Higgs field?

The Higgs field is a quantum field. That may sound mysterious, but the fact is that all elementary particles arise as quanta of a corresponding quantum field. The electromagnetic field is also a quantum field (its corresponding elementary particle is the photon). So in this respect, the Higgs field is no more enigmatic than electrons and light. The Higgs field does, however, differ from all other quantum fields in three crucial ways.

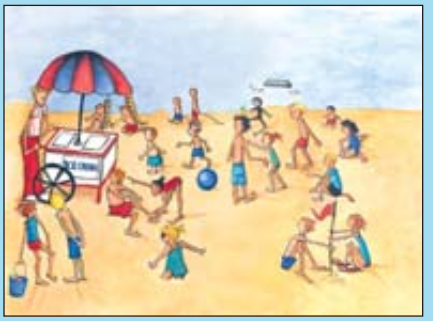
The first difference is somewhat technical. All fields have a property called spin, an intrinsic quantity of angular momentum that is carried by each of their particles. Particles such as electrons have spin ½ and most particles associated with a force, such as the photon, have spin 1. The Higgs boson (the particle of the Higgs field) has spin 0. Having 0 spin enables the Higgs field to appear in the Lagrangian in different ways than the other particles do, which in turn allows—and leads to—its other two distinguishing features.

The second unique property of the Higgs field explains how and why it has nonzero strength throughout the universe. Any system, including a universe, will tumble into its lowest energy state, like a ball bouncing down to the bottom of a valley. For the familiar fields, such as the electromagnetic fields that give us

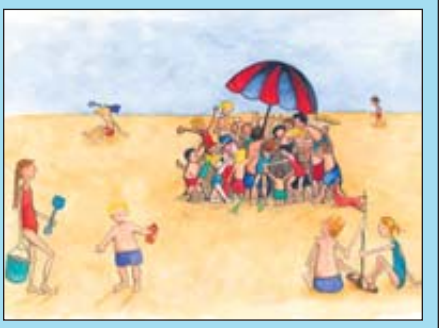
PROPERTIES OF THE ELUSIVE HIGGS

HOW THE HIGGS FIELD GENERATES MASS

"Empty" space, which is filled with the Higgs field, is like a beach full of children.



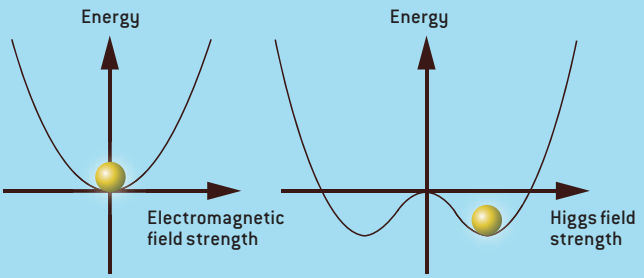
A particle crossing that region of space is like an ice cream vendor arriving . . .



. . . and interacting with kids who slow him down—as if he acquires "mass."

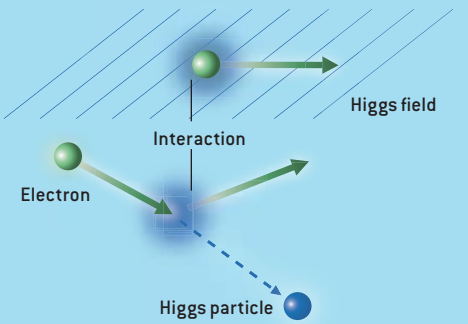
PERMEATING REALITY

A typical field, such as the electromagnetic field, has its lowest energy at zero field strength (*left*). The universe is akin to a ball that rolled around and came to rest at the bottom of the valley—that is, it has settled at a field strength of zero. The Higgs, in contrast, has its minimum energy at a nonzero field strength, and the "ball" comes to rest at a nonzero value (*right*). Thus, the universe, in its natural lowest energy state, is permeated by that nonzero value of the Higgs field.



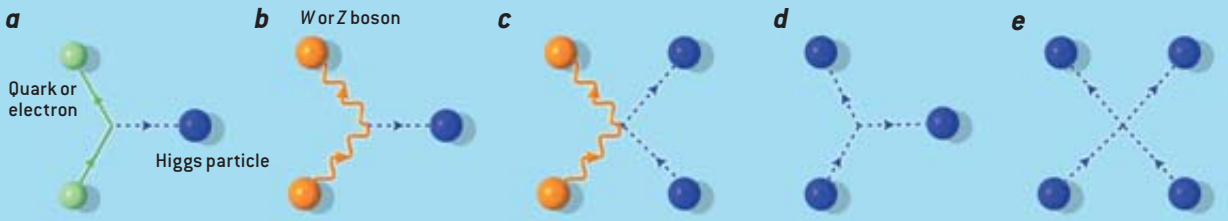
CAUSING TWO PHENOMENA

Two completely different phenomena—the acquisition of mass by a particle (*top*) and the production of a Higgs boson (*bottom*)—are caused by exactly the same interaction. This fact will be of great use in testing the Higgs theory by experiments.

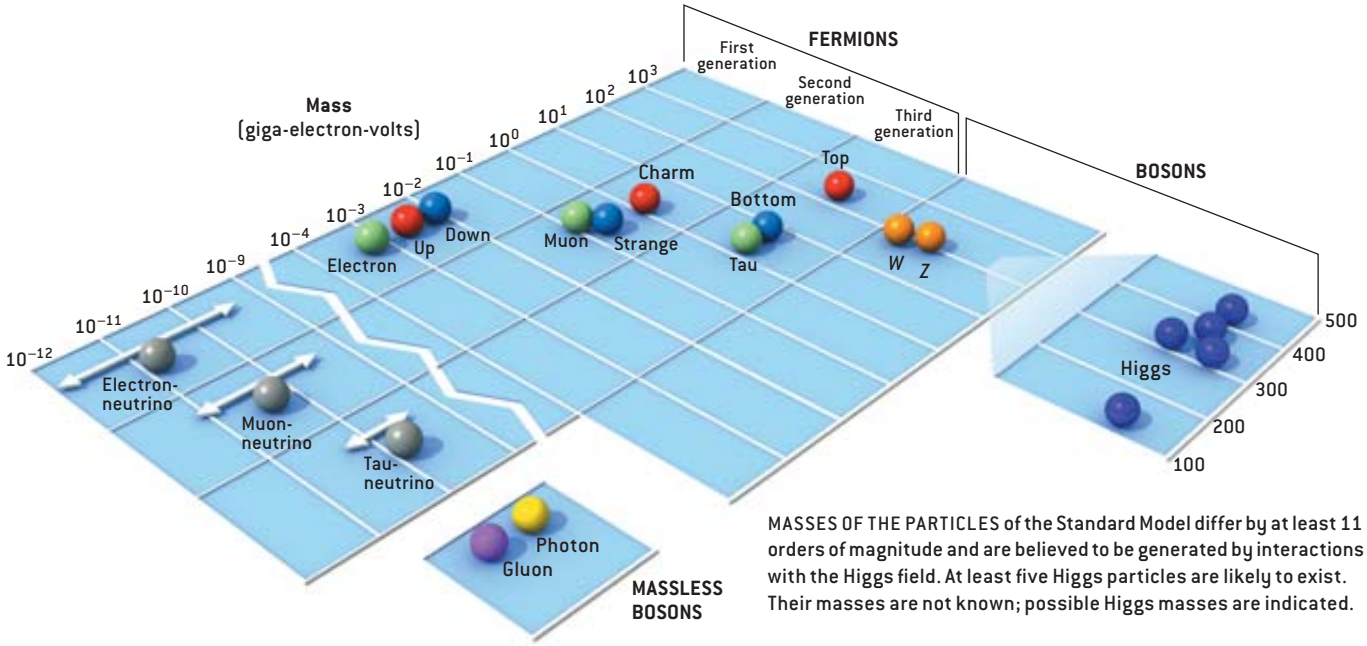


INTERACTING WITH OTHER PARTICLES

Force diagrams called Feynman diagrams represent how the Higgs particle interacts with other particles. Diagram (*a*) represents a particle such as a quark or an electron emitting (*shown*) or absorbing a Higgs particle. Diagram (*b*) shows the corresponding process for a *W* or *Z* boson. The *W* and *Z* can also interact simultaneously with two Higgs, as shown in (*c*), which also represents a *W* or *Z* scattering (roughly speaking, colliding with) a Higgs particle. The interactions represented by diagrams (*a*) through (*c*) are also responsible for generating particles' masses. The Higgs also interacts with itself, as represented by diagrams (*d*) and (*e*). More complicated processes can be built up by joining together copies of these elementary diagrams. Interactions depicted in (*d*) and (*e*) are responsible for the shape of the energy graph (*above left*).



BRYAN CHRISTIE DESIGN; CARTOONS BY EMILY HARRISON, BASED ON CONCEPT BY DAVID MILLER *University College London*



MASSES OF THE PARTICLES of the Standard Model differ by at least 11 orders of magnitude and are believed to be generated by interactions with the Higgs field. At least five Higgs particles are likely to exist. Their masses are not known; possible Higgs masses are indicated.

radio broadcasts, the lowest energy state is the one in which the fields have zero value (that is, the fields vanish)—if any nonzero field is introduced, the energy stored in the fields increases the net energy of the system. But for the Higgs field, the energy of the universe is lower if the field is not zero but instead has a constant nonzero value. In terms of the valley metaphor, for ordinary fields the valley floor is at the location of zero field; for the Higgs, the valley has a hillock at its center (at zero field) and the lowest point of the valley forms a circle around the hillock [*see box on preceding page*]. The universe, like a ball, comes to rest somewhere on this circular trench, which corresponds to a nonzero value of the field. That is, in its natural, lowest energy state, the universe is permeated throughout by a *nonzero* Higgs field.

The final distinguishing characteristic of the Higgs field is the form of its interactions with the other particles. Particles that interact with the Higgs field behave as if they have mass, proportional to the strength of the field times the strength of the interaction. The masses arise from the terms in the Lagrangian that have the particles interacting with the Higgs field.

Our understanding of all this is not yet complete, however, and we are not sure how many kinds of Higgs fields there are. Although the Standard Model requires only one Higgs field to generate all the elementary particle masses, physicists know that the Standard Model must be superseded by a more complete theory. Leading contenders are extensions of the Standard Model known as Supersymmetric Standard Models (SSMs). In these models, each Standard Model particle has a so-called superpartner (as yet undetected) with closely related properties [see "The Dawn of Physics beyond the Standard Model," by Gordon Kane; SCIENTIFIC AMERICAN, June 2003]. With the Supersymmetric Standard Model, at least two different kinds of Higgs fields are needed. Interactions with those two fields give mass to the Standard Model particles. They also give some (but not all) mass to the superpartners. The two Higgs fields give rise to five species of Higgs boson: three that are electrically neutral and two that are charged. The masses of particles called neutrinos, which are tiny compared with other particle masses, could arise rather indirectly from these interactions or from yet a third kind of Higgs field.

Theorists have several reasons for expecting the SSM picture of the Higgs interaction to be correct. First, without the Higgs mechanism, the *W* and *Z* bosons that mediate the weak force would be massless, just like the photon (which they are related to), and the weak interaction would be as strong as the electromagnetic one. Theory holds that the Higgs mechanism confers mass to the *W* and *Z* in a very special manner. Predictions of that approach (such as the ratio of the *W* and *Z* masses) have been confirmed experimentally.

Second, essentially all other aspects of the Standard Model have been well tested, and with such a detailed, interlocking theory it is difficult to change one part (such as the Higgs) without affecting the rest. For example, the analysis of precision measurements of *W* and *Z* boson properties led to the accurate prediction of the top quark mass before the top quark had been directly produced. Changing the Higgs mechanism would spoil that and other successful predictions.

Third, the Standard Model Higgs mechanism works very well for giving mass to *all* the Standard Model particles, *W* and *Z* bosons, as well as quarks and leptons; the alternative proposals usually do not. Next, unlike the other theories, the SSM provides a framework to unify our understanding of the forces of nature. Finally, the SSM can explain why the energy "valley" for the universe has the shape needed by the Higgs mechanism. In the basic Standard Model the shape of the valley has to be put in as a postulate, but in the SSM that shape can be derived mathematically.

Testing the Theory

NATURALLY, PHYSICISTS want to carry out direct tests of the idea that mass arises from the interactions with the different Higgs fields. We can test three key features. First, we can look for the signature particles called Higgs bosons. These quanta must exist, or else the explanation is not right. Physicists are currently looking for Higgs bosons at the Tevatron Collider at Fermi National Accelerator Laboratory in Batavia, Ill.

BRYAN CHRISTIE DESIGN

Second, once they are detected we can observe how Higgs bosons interact with other particles. The very same terms in the Lagrangian that determine the masses of the particles also fix the properties of such interactions. So we can conduct experiments to test quantitatively the presence of interaction terms of that type. The strength of the interaction and the amount of particle mass are uniquely connected.

Third, different sets of Higgs fields, as occur in the Standard Model or in the various SSMs, imply different sets of Higgs bosons with various properties, so tests can distinguish these alternatives, too. All that we need to carry out the tests are appropriate particle colliders—ones that have sufficient energy to produce the different Higgs bosons, sufficient intensity to make enough of them and very good detectors to analyze what is produced.

A practical problem with performing such tests is that we do not yet understand the theories well enough to calculate what masses the Higgs bosons themselves should have, which makes searching for them more difficult because one must examine a range of masses. A combination of theoretical reasoning and data from experiments guides us about roughly what masses to expect.

The Large Electron-Positron Collider (LEP) at CERN, the European laboratory for particle physics near Geneva, operated over a mass range that had a significant chance of including a Higgs boson. It did not find one—although there was tantalizing evidence for one just at the limits of the collider's energy and intensity—before it was shut down in 2000 to make room for constructing a newer facility, CERN's Large Hadron Collider (LHC). The Higgs must therefore be heavier than about 120 proton masses. Nevertheless, LEP did produce indirect evidence that a Higgs boson exists: experimenters at LEP made a number of precise measurements, which can be combined with similar measurements from the Tevatron and the collider at the Stanford Linear Accelerator Center. The entire set of data agrees well with theory only

BRYAN CHRISTIE DESIGN

A Cosmic Stocktaking

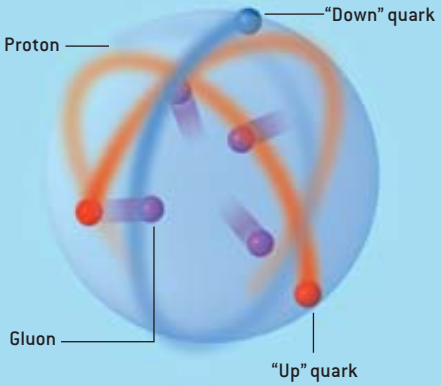
The theory of the Higgs field explains how elementary particles, the smallest building blocks of the universe, acquire their mass. But the Higgs mechanism is not the only source of mass-energy in the universe ("mass-energy" refers to both mass and energy, which are related by Einstein's $\mathcal{E} = mc^2$).

About 70 percent of the mass-energy of the universe is in the form of so-called dark energy, which is not directly associated with particles. The chief sign of the existence of dark energy is that the universe's expansion is accelerating. The precise nature of dark energy is one of the most profound open questions in physics [see "A Cosmic Conundrum," by Lawrence M. Krauss and Michael S. Turner; SCIENTIFIC AMERICAN, September 2004].

The remaining 30 percent of the universe's mass-energy comes from matter, particles with mass. The most familiar kinds of matter are protons, neutrons and electrons, which make up stars, planets, people and all that we see. These particles provide about one sixth of the matter of the universe, or 4 to 5 percent of the entire universe. As is explained in the main text, most of this mass arises from the energy of motion of quarks and gluons whirling around inside protons and neutrons.

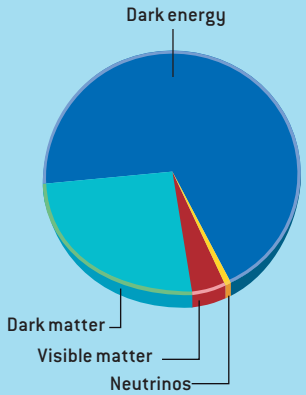
A smaller contribution to the universe's matter comes from particles called neutrinos, which come in three varieties. Neutrinos have mass but surprisingly little. The absolute masses of neutrinos are not yet measured, but the existing data put an upper limit on them—less than half a percent of the universe.

Almost all the rest of the matter—around 25 percent of the universe's total mass-energy—is matter we do not see, called dark matter. We deduce its existence from its gravitational effects on what we do see. We do not yet know what this dark matter actually is, but there are good candidates, and experiments are under way to test different ideas [see "The Search for Dark Matter," by David B. Cline; SCIENTIFIC AMERICAN, March 2003]. The dark matter should be composed of massive particles because it forms galaxy-sized clumps under the effects of the gravitational force. A variety of arguments have let us conclude that the dark matter cannot be composed of any of the normal Standard Model particles.



MOST VISIBLE MASS is locked up in protons and neutrons. Each of these consists of quarks and gluons flying around. Almost all of the proton's or neutron's mass is from the energy of motion of the quarks and gluons.

THE UNIVERSE



THE MASS-ENERGY of the universe mainly comes in four broad types: mysterious dark energy that causes the universe's expansion to accelerate; invisible dark matter that we can detect by its gravitational effects; visible matter; and neutrinos.

The leading candidate particle for dark matter is the lightest superpartner (LSP), which is discussed in greater detail in the main text. The lightest superpartner occurs in extensions of the Standard Model called Supersymmetric Standard Models. The mass of the LSP is thought to be about 100 proton masses. That the LSP was a good candidate for the dark matter was recognized by theorists before cosmologists knew that a new form of fundamental matter was needed to explain dark matter. —*G.K.*

if certain interactions of particles with the lightest Higgs boson are included and only if the lightest Higgs boson is not heavier than about 200 proton masses. That provides researchers with an upper limit for the mass of the Higgs boson, which helps focus the search.

For the next few years, the only collider that could produce direct evidence for Higgs bosons will be the Tevatron. Its energy is sufficient to discover a Higgs boson in the range of masses implied by the indirect LEP evidence, *if* it can consistently achieve the beam intensity it was expected to have, which so far has not been possible. In 2007 the LHC, which is seven times more energetic and is designed to have far more intensity

The LEP collider saw tantalizing evidence for the Higgs particle.

than the Tevatron, is scheduled to begin taking data. It will be a factory for Higgs bosons (meaning it will produce many of the particles a day). Assuming the LHC functions as planned, gathering the relevant data and learning how to interpret it should take one to two years. Carrying out the complete tests that show in detail that the interactions with Higgs fields are providing the mass will require a new electron-positron collider in addition to the LHC (which collides protons) and the Tevatron (which collides protons and antiprotons).

Dark Matter

WHAT IS DISCOVERED about Higgs bosons will not only test whether the Higgs mechanism is indeed providing mass, it will also point the way to how the Standard Model can be extended to solve problems such as the origin of dark matter.

With regard to dark matter, a key particle of the SSM is the lightest superpartner (LSP). Among the superpartners of the known Standard Model particles predicted by the SSM, the LSP is the one with the lowest mass. Most superpartners decay promptly to lower-mass superpartners, a chain of decays that ends with the LSP, which is stable because it has no lighter particle that it can decay into. (When a superpartner decays, at least one of the decay products should be another superpartner; it should not decay entirely into Standard Model particles.) Superpartner particles would have been created early in the big bang but then promptly decayed into LSPs. The LSP is the leading candidate particle for dark matter.

The Higgs bosons may also directly affect the amount of dark matter in the universe. We know that the amount of LSPs today should be less than the amount shortly after the big bang, because some would have collided and annihilated into quarks and leptons and photons, and the annihilation rate may be dominated by LSPs interacting with Higgs bosons.

As mentioned earlier, the two basic SSM Higgs fields give mass to the Standard Model particles and *some* mass to the superpartners, such as the LSP. The superpartners acquire more mass via additional interactions, which may be with still further Higgs fields or with fields similar to the Higgs. We have theoretical models of how these processes can happen, but until we have data on the superpartners themselves we will not know how they work in detail. Such data are expected from the LHC or perhaps even from the Tevatron.

Neutrino masses may also arise from interactions with additional Higgs or Higgs-like fields, in a very interesting way. Neutrinos were originally assumed to be massless, but since 1979 theorists have predicted that they have small masses, and over the past decade several impressive experiments have confirmed the predictions [see "Solving the Solar Neutrino Problem," by Arthur B. McDonald, Joshua R. Klein and David L. Wark; SCIENTIFIC AMERICAN, April 2003]. The neutrino masses are less than a millionth the size of the next smallest mass, the electron mass. Because neutrinos are electrically neutral, the theoretical description of their masses is more subtle than for charged particles. Several processes contribute to the mass of each neutrino species, and for technical reasons the actual mass value emerges from solving an equation rather than just adding the terms.

Thus, we have understood the three ways that mass arises: The main form of mass we are familiar with—that of protons and neutrons and therefore of atoms—comes from the motion of quarks bound into protons and neutrons. The proton mass would be about what it is even without the Higgs field. The masses of the quarks themselves, however, and also the mass of the electron, are entirely caused by the Higgs field. Those masses would vanish without the Higgs. Last, but certainly not least, most of the amount of superpartner masses, and therefore the mass of the dark matter particle (if it is indeed the lightest superpartner), comes from additional interactions beyond the basic Higgs one.

Finally, we consider an issue known as the family problem. Over the past half a century physicists have shown that the world we see, from people to flowers to stars, is constructed from just six particles: three matter particles (up quarks, down quarks and electrons), two force quanta (photons and gluons), and Higgs

THE AUTHOR

GORDON KANE, a particle theorist, is Victor Weisskopf Collegiate Professor of Physics at the University of Michigan at Ann Arbor. His work explores ways to test and extend the Standard Model of particle physics. In particular, he studies Higgs physics and the Standard Model's supersymmetric extension and cosmology, with a focus on relating theory and experiment. Recently he has emphasized integrating these topics with string theory and studying the implications for collider experiments.

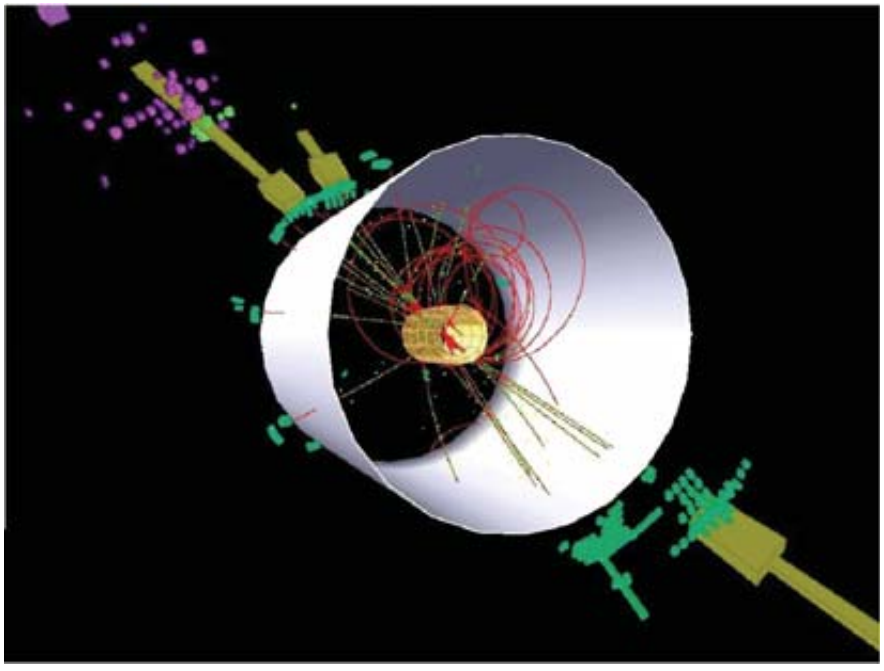
bosons—a remarkable and surprisingly simple description. Yet there are four more quarks, two more particles similar to the electron, and three neutrinos. All are very short-lived or barely interact with the other six particles. They can be classified into three families: up, down, electron neutrino, electron; charm, strange, muon neutrino, muon; and top, bottom, tau neutrino, tau. The particles in each family have interactions identical to those of the particles in other families. They differ only in that those in the second family are heavier than those in the first, and those in the third family are heavier still. Because these masses arise from interactions with the Higgs field, the particles must have different interactions with the Higgs field.

Hence, the family problem has two parts: Why are there three families when it seems only one is needed to describe the world we see? Why do the families differ in mass and have the masses they do? Perhaps it is not obvious why physicists are astonished that nature contains three almost identical families even if one would do. It is because we want to fully understand the laws of nature and the basic particles and forces. We expect that every aspect of the basic laws is a necessary one. The goal is to have a theory in which all the particles and their mass ratios emerge inevitably, without making ad hoc assumptions about the values of the masses and without adjusting parameters. If having three families is essential, then it is a clue whose significance is currently not understood.

Tying It All Together

THE STANDARD MODEL and the SSM can accommodate the observed family structure, but they cannot explain it. This is a strong statement. It is not that the SSM has not *yet* explained the family structure but that it *cannot*. For me, the most exciting aspect of string theory is not only that it may provide us with a quantum theory of all the forces but also that it may tell us what the elementary particles are and why there are three families. String theory seems able to address the question of why the interactions with the Higgs field differ among the families. In string theory, repeated families can occur, and they are not identical. Their differences are described by properties that do not affect the strong, weak, electromagnetic or gravitational forces but that do affect the interactions with Higgs fields, which fits with our having three families with different masses. Although string theorists have not yet fully solved the problem of having three families, the theory seems to have the right structure to provide a solution. String theory allows many different family structures, and so far no one knows why nature picks the one we observe rather than some other [see "The String Theory Landscape," by Raphael Bousso and Joseph Polchinski; SCIENTIFIC AMERICAN, September 2004]. Data on the quark and lepton masses and on their superpartner masses may provide major clues to teach us about string theory.

One can now understand why it took so long historically to begin to understand mass. Without the Standard Model of particle physics and the development of quantum field theory to describe particles and their interactions, physicists could not even formulate the right questions. Whereas the origins and values of mass are not yet fully understood, it is likely that the framework needed to understand them is in place. Mass could not have been comprehended before theories such as the Standard Model and its supersymmetric extension and string theory existed. Whether they indeed provide the complete answer is not yet clear, but mass is now a routine research topic in particle physics. SA



A HIGGS PARTICLE might have been created when a high-energy positron and electron collided in the L3 detector of the Large Electron-Positron Collider at CERN. The lines represent particle tracks. The green and purple blobs and gold histograms depict amounts of energy deposited in layers of the detector by particles flying away from the reaction. Only by combining many such events can physicists conclude whether Higgs particles were present in some of the reactions or if all the data were produced by other reactions that happened to mimic the Higgs signal.

CHRIS TULLY *Princeton University*

MORE TO EXPLORE

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An excellent collection of particle physics Web sites is listed at **particleadventure.org/particleadventure/other/othersites.html**

FINANCIAL TIMES & SCIENTIFIC AMERICAN

SPECIAL REPORT

The Future of STEM CELLS

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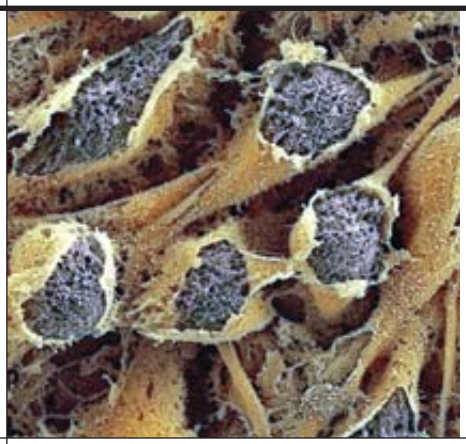

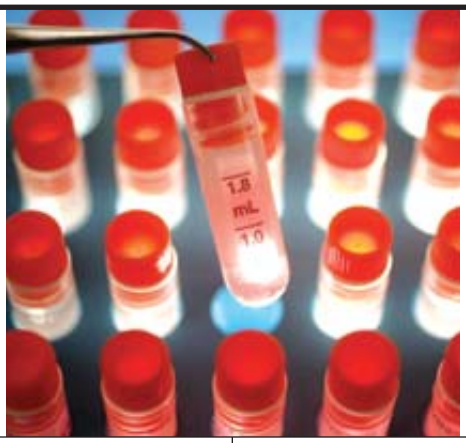

Cover montage: Tom Draper Design. Cover images: Corbis (*currency*); Laguna Design/Science Photo Library (*stem cells*); Peter Macdiarmid/Reuters/Corbis (*test tube*); Tom Draper Design (*globe* and *graph*); Q.-L. Ying and A. Smith, Wellcome Photo Library (*neurone network*). Images above: Simon Fraser/Photo Researchers, Inc. (*SEM of stem cells*); Peter Macdiarmid/Reuters/Corbis (*test tubes* and *stem cell bank*)

From the Editors

Stem cells have moved from biological obscurity to the forefront of political and technological debate in the US and around the world. Investigators are confident that someday stem cells will be the foundation for fantastic cures and therapies. Yet critics argue that stem cell research raises ethical questions no less profound than the pursuit of the nuclear bomb more than 60 years ago.

The complexity of the science and the rapid proliferation of business, ethical and political issues pose a challenge for anyone wishing to stay well informed on this vital subject. This is why we believe that stem cells represent an ideal opportunity for an editorial collaboration between the *Financial Times* and *Scientific American*.

This special report draws on the *FT*'s strength in international business and political reporting, which in turn complements *Scientific American*'s long experience in rendering scientific discussions clearly and authoritatively.

It is easy to forget that stem cell research is relatively new. Only in 1998 did scientists first identify and isolate stem cells from human embryos. Today stem cell research has opened a window of opportunity for countries looking to close the customary US lead in biotech. It has reheated discussions of whether and when human rights should inhere in embryos. It has inspired entrepreneurs and spawned new consumer services: prospective parents now routinely receive appeals to freeze the stem cells in their newborns' umbilical cord blood as a hedge against future medical needs.

Such practices have revealed to the public how unsupervised and ethically unguided some practices in fertilisation clinics have been for years. They have provoked a fiscal mutiny of sorts among American states against limitations on federal research funding. They have suggested new forms of fraud: patients in Russia have been victimised by beauty parlours promising that their "stem cell injections" could treat a variety of ills. And, of course, they have raised much technical speculation about the degree of versatility in various types of stem cells and what that may tell us about the latent capabilities of all our tissues.

Virtually no matter touched by stem cells is yet settled. Rather than spelling out final answers, this report should serve as a concise reference on the most important questions to be addressed in the years to come. Both the *Financial Times* and *Scientific American* will continue to provide first-rate coverage of the ongoing evolution of these matters—including, one hopes, the eventual news that stem cells have turned into a stable, reliable source of both practical therapies and financial opportunities.

Lionel Barber
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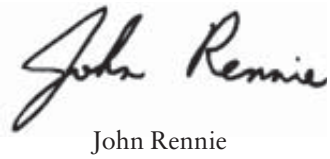

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ANDREW SWIFT

Mother of All Cells

Scientists expect enormous benefits for humankind from the surge of research on embryonic stem cells. But it could take a generation or two before the full impact is felt. Clive Cookson discusses the issues

The late 1990s was the most productive period in the history of biological research. The birth of Dolly, the first cloned mammal, was quickly followed by the first successful derivation of human embryonic stem cells and then, as the new millennium dawned, the completion of the Human Genome Project.

Since then the media have amplified these achievements, with the enthusiastic encouragement of many of the researchers involved, to create intense public excitement about a new era of regenerative medicine. Some people imagine that within a few years it will be possible, through some still obscure combination of stem cells, cloning and genetic engineering, to create new cells and eventually whole organs to replace those that fail through disease, accident or old age.

That promise is counterbalanced by ethical and religious objections to stem cell research—particularly to the idea that embryos could be created especially for research and then destroyed—and fears that therapeutic cloning could open the door to reproductive cloning.

For many people the very phrase "stem cells" sums up all the excitement and fears. But there is widespread ignorance about stem cells and wishful thinking about how quickly their potential will be achieved. This report is intended to shed scientific light on the future of stem cell research—and the associated policy issues that are driving national and state governments to commit billions of dollars of public funds to the field.

First, then, some basic definitions. Stem cells serve as a biological repair system, with the potential to develop into many types of specialised cells in the body. They can theoretically divide without limit to replenish other cells. When a stem cell divides, each daughter can remain a stem cell or adopt a more specialised role such as a muscle, blood or brain cell, depending on the presence or absence of biochemical signals. Controlling this differentiation process is one of the biggest challenges in stem cell research.

Producing embryonic stem cell lines is tricky. Fewer than 150 lines have resulted from seven years of hard work.

There is nothing new about stem cells per se. Stem cell therapies have been used for decades. The best known example is bone marrow transplantation to treat leukaemia and other blood disorders; this works because marrow is full of blood stem cells. But all therapies so far have used what are often called adult stem cells—a term that is fine when the source is actually an adult but misleading when, as often happens, the cells come from an infant or foetus. Somatic stem cells may be a better name for these cells.

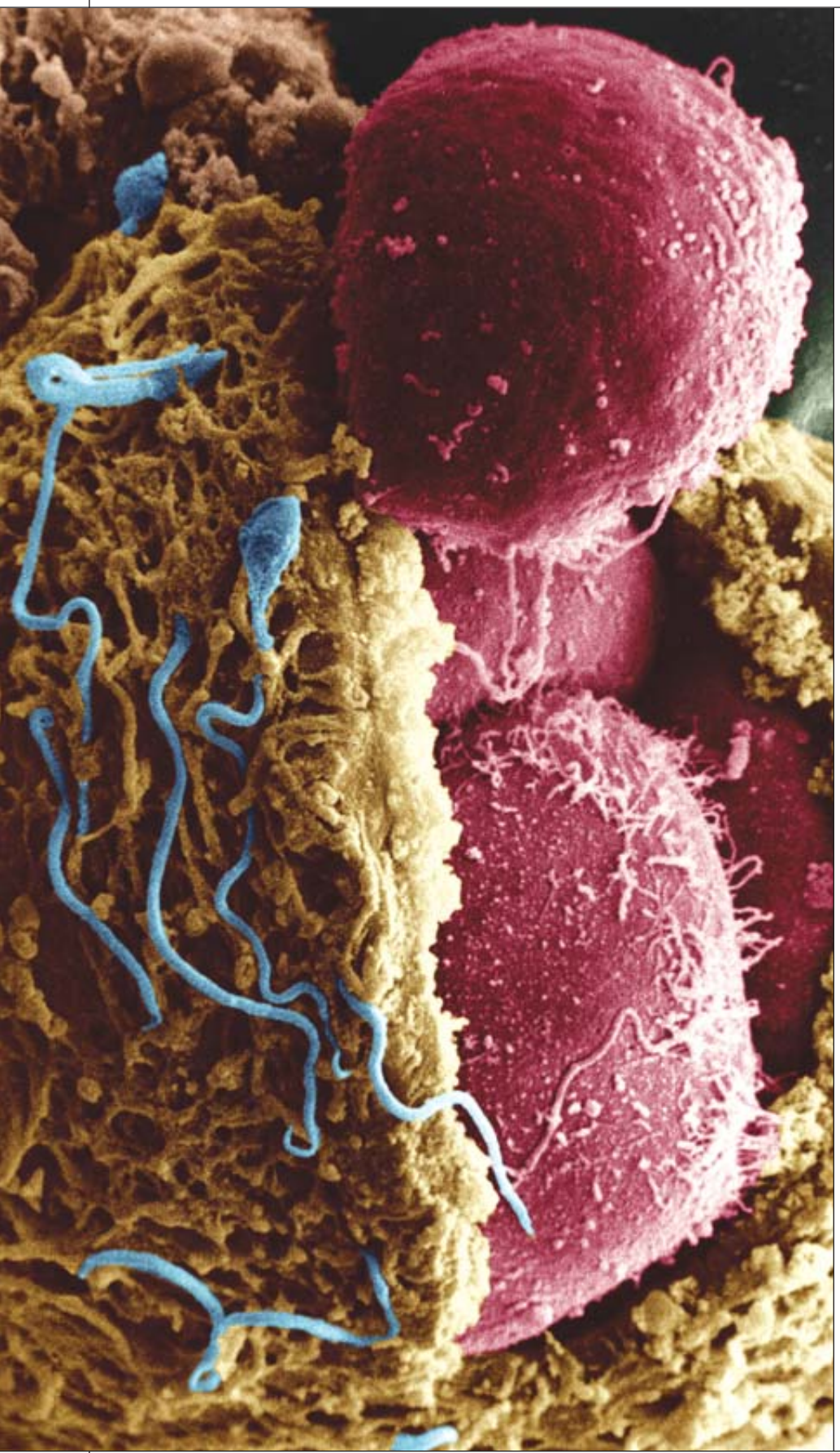
The range of specialised cells that can be obtained from somatic stem cells is limited—how limited is currently the subject of intense scientific debate that will be considered in a later article [see "Repair Workers Within," on page A12]. Early embryos are potentially a better source because all their cells are still unspecialised. Embryonic stem cells (commonly abbreviated to ES cells) are pluripotent: they can differentiate into almost any type of cell.

The first line (stable replicating population) of human ES cells was created in 1998 by James Thomson of the University of Wisconsin. The procedure involves taking cells from inside a week-old embryo (or blastocyst)—a microscopic ball of 50 to 100 cells—and culturing them in a laboratory dish with nutrients and growth factors. Embryos are normally donated by couples undergoing IVF treatment and would otherwise be discarded.

Even now, after seven years of intensive work worldwide, the world has fewer than 150 well-characterised ES cell lines, because the process of establishing them is extremely tricky. Only 22 lines are available for federally funded research in the US, where the Bush administration has decreed that the National Institutes of Health should not support work on lines created after August 2001. Once established, a stem cell line is essentially immortal. It can be frozen for storage in a cell bank, such as the one established last year in the UK, and for distribution to other researchers.

In an attempt to get round ethical objections to the destruction of human embryos for research, some scientists have been exploring alternative sources of ES cells. One approach would be to identify the least differentiated adult stem cells and wind back their developmental clock, so that they behaved as pluripotent ES cells. Another is through parthenogenesis—activating an unfertilised human egg so that

YORGOS NIKAS *Wellcome Photo Library*



PRECURSORS OF EMBRYONIC STEM CELLS (*red*) emerge from inside a four-day-old human embryo whose surrounding protein coat has been slit open. The cells can be harvested and cultured to give rise to embryonic stem cells.

it starts to divide like an early embryo. But it is not clear whether either approach will work in practice.

Until very recently, researchers have grown human ES cells on layers of mouse skin cells, known as feeder cells, which inhibit their differentiation into more specialised cells. They have also been nourished with blood serum derived from calf foetuses. Unfortunately, these nonhuman components carry a risk of contamination with animal proteins or pathogens, as in xenotransplantation, which could prevent the stem cells being used safely in the clinic.

This year several research groups have announced successful substitution of human for animal components, but some scientists maintain that contamination of the specialised media used for ES cell growth and differentiation is so pervasive that it will be hard to eliminate completely [*see box on page A11*].

ES cells, unlike adult stem cells, cannot be used directly in therapy because they cause cancer. Indeed, one laboratory test for ES cells is to inject them into mice and analyse the teratoma (a tumour formed of foetal tissue) that arises. So any therapeutic application will require scientists to drive the ES cells' differentiation into particular specialised cells for transplantation into patients—for instance, beta cells to produce insulin for diabetics or dopamine-producing neurones to treat Parkinson's disease. And rigorous screening will be required to make sure that no ES cells are still present.

If establishing ES cell lines is tricky, guiding their differentiation is a scientific nightmare. Researchers are only just beginning to understand the environmental conditions and the combinations of growth factors and other proteins required to guide human ES

Human-Animal Chimeras

Some experiments can disquietingly blur the line between species

Stem cell science has become notorious for obliging society to consider again where it draws the line between human embryonic cells and human beings. Less well known is that it also pushes us to another border that can be surprisingly vague: the one that separates people from animals. Stem cells facilitate the production of advanced interspecies chimeras—organisms that are a living quilt of human and animal cells. The ethical issues raised by the very existence of such creatures could become deeply troubling.

In Greek mythology, the chimera was a monster that combined the parts of a goat, a lion and a serpent. With such a namesake, laboratory-bred chimeras may sound like a bad idea born of pure scientific hubris. Yet they may be unavoidable if stem cells are ever to be realised as therapies. Researchers will need to study how stem cells behave and react to chemical cues inside the body. Unless they are to do those risky first experiments in humans, they will need the freedom to test in animals and thereby make chimeras.

Irving Weissman of Stanford University and his colleagues pioneered these chimera experiments in 1988 when they created mice with fully human immune systems for the study of AIDS. Later, the Stanford group and StemCells, Inc., which Weissman co-founded, also transplanted human stem cells into the brains of newborn mice as preliminary models for neural research. And working with foetal sheep, Esmail Zanjani of the University of Nevada at Reno has created adult animals with human cells integrated throughout their body.

The original chimera

MUSEO ARCHEOLOGICO, FLORENCE, ITALY/BRIDGEMAN ART LIBRARY

No one knows what the consequences will be as the proportion of human cells in an animal increases. Weissman and others, for example, have envisioned one day making a mouse with fully "humanised" brain tissue. The lawyer developmental programme and tiny size of this chimerical mouse fairly guarantee that its mental capacities would not differ greatly from those of normal mice. But what if human cells were instead put in the foetus of a chimpanzee? The birth of something less beastly could not be ruled out.

The intermingling of tissues could also make it easier for infectious animal diseases to move into humans. Diseases that hop species barriers can be particularly devastating because the immune systems of their new hosts are so unprepared for them (the flu pandemic of 1918 is widely believed to have sprung from an avian influenza virus).

There are currently no international standard governing chimera experiments. Canada's Assisted Human Reproduction Act of 2004 banned human-animal chimeras. The US has no formal restrictions, but Senator Sam Brownback of Kansas proposed legislation in March that would outlaw several kinds of chimeras, including ones with substantial human brain tissue. Some institutions that supply human stem cells set their own additional limits about what experiments are permissible.

Within the US, at least, greater uniformity may emerge from general guidelines on stem cell use recommended in late April by the National Academy of Sciences. The NAS recommended that chimeras involving most animal species generally be permitted. It urged a ban on any use of human cells in other primates, however, as well as the introduction of animal cells into human blastocysts. It also warned against allowing human-animal chimeras to breed: some human cells might have managed to infiltrate the animals' testes and ovaries. Breeding those animals could theoretically lead to the horrible (and in most cases, assuredly fatal) result of a human embryo growing inside an animal mother. *—John Rennie*

cells so that they become stable nerve or muscle or whatever other specialist cells are required for treatment.

Yet experience with mouse ES cells suggests that it will be possible to develop safe and effective therapies from their human counterparts. Researchers around the world are making a great effort to do so, because cell-based therapies are so immensely promising. Biologists believe most degenerative diseases are too complex to treat effectively just by giving patients drugs or even gene therapy. Living cells, which produce a far larger number of biologically active molecules, stand a better chance of success.

Although no clinical trials of ES cells have taken place yet, other types of cell therapy have shown that this kind of transplantation can work in people. Examples, besides the ubiquitous bone marrow transplant, include the use of neural stem cells from foetuses to treat brain disease and insulin-producing beta cells from cadavers to treat diabetes. Successes with somatic cells lie behind the hope that ES cells will eventually work even better, but a lot more research will be needed to prove the point.

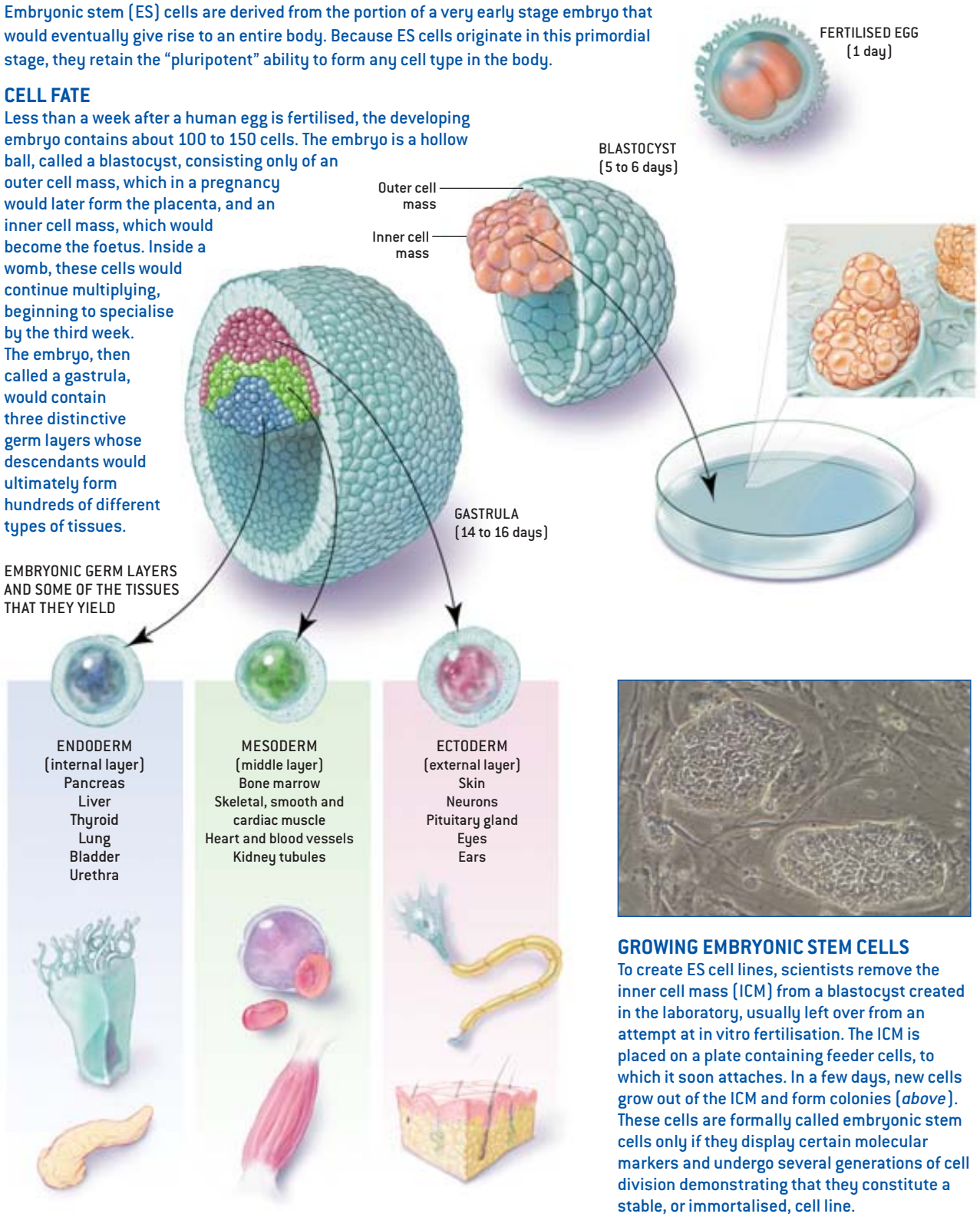
The obstacles that ES cell researchers need to overcome include better ways of obtaining ES cells efficiently; better methods to identify ES cells and their true developmental potential; ways to control their differentiation and growth inside the body; understanding whether the immune system attacks ES

The Origins and Fates of Embryonic Stem Cells

Embryonic stem (ES) cells are derived from the portion of a very early stage embryo that would eventually give rise to an entire body. Because ES cells originate in this primordial stage, they retain the "pluripotent" ability to form any cell type in the body.

CELL FATE

Less than a week after a human egg is fertilised, the developing embryo contains about 100 to 150 cells. The embryo is a hollow ball, called a blastocyst, consisting only of an outer cell mass, which in a pregnancy would later form the placenta, and an inner cell mass, which would become the foetus. Inside a womb, these cells would continue multiplying, beginning to specialise by the third week. The embryo, then called a gastrula, would contain three distinctive germ layers whose descendants would ultimately form hundreds of different types of tissues.



GROWING EMBRYONIC STEM CELLS

To create ES cell lines, scientists remove the inner cell mass (ICM) from a blastocyst created in the laboratory, usually left over from an attempt at in vitro fertilisation. The ICM is placed on a plate containing feeder cells, to which it soon attaches. In a few days, new cells grow out of the ICM and form colonies (*above*). These cells are formally called embryonic stem cells only if they display certain molecular markers and undergo several generations of cell division demonstrating that they constitute a stable, or immortalised, cell line.

ANDREW SWIFT; ROBERT P. LANZA *ACT* (*micrograph*)

Dirty and Dying, but US-Approved?

Problems with contamination and genetic abnormalities may not stop work on embryonic stem cell therapies

In August 2001 when President Bush forbade the creation of new embryonic stem cell lines with federal money, he softened the blow to biomedical research by promising that more than 60 ES cell preparations could still be used to develop prospective treatments for the sick. Yet a growing list of problems with those cells forces the Food and Drug Administration to consider whether material from them is even safe to try in people.

Only 22 of the sanctioned ES cell lines created before August 2001 have survived and remain available to researchers, although questions have arisen about their quality in light of their advancing age. The lines are supposed to be "immortal," but being kept in culture for extended periods has been known to induce deformities in other cells, so scientists were not entirely surprised when reports emerged of major genetic abnormalities in some of the National Institutes of Health registry lines. Other registry cell lines simply seemed to lose their ability to produce differentiated cell types or would only do so sluggishly.

HUMAN EMBRYONIC CELLS grown in the laboratory have been contaminated with material from supportive mouse cells in the cultures, which makes their usefulness in future therapies questionable.

Methods for handling stem cells have improved considerably since the US policy went into effect, and researchers believe that fresher cell lines can be kept much healthier. In particular, two new types of culture medium unveiled this year eliminate the need to grow ES cells on beds of mouse "feeder" cells, a practice used on all the government-approved lines in the past. Fears that the registry cells might have been contaminated with mouse molecules were recently confirmed by a study showing that human ES cells grown in this way absorb a mouse protein and carry it on their surface. When ES cells displaying the protein were exposed to human blood serum, antibodies against the animal protein attacked and killed the ES cells.

Nonetheless, California-based Geron, which owns rights to nine of the government-approved lines, says it will apply to the FDA early in 2006 for permission to go ahead with human trials of the cells for spinal repair. Thomas Okarma, Geron president, is confident the company's cells are clean after subjecting them to what he calls an "exhaustive list" of "gold standard" tests. No other US company has announced a formal application to try embryonic stem cell derivatives in people, but a director of the University of Minnesota's Stem Cell Institute, John Wagner, reportedly told state legislators last year his group had already sought FDA approval for such a trial. Wagner declined to reveal any more details.

Nor will the FDA comment on how many applications it has received for trials of ES cell derivatives or when it will rule. The possibility of animal contamination does not automatically preclude use of registry cells in humans—xenotransplantation of pig heart valves and even a baboon-to-human bone marrow transplant have gained FDA approval in the past. The only remark a spokesperson would offer was that the agency's decision will be based on the scientific soundness of the proposed trial, not politics.

—Christine Soares

cells or ones differentiated from them; and learning more about the comparative advantages of ES cells and somatic cells for various applications.

While direct use of stem cells in patients is what most excites politicians and the public, many scientists say their main medical benefits may be delivered indirectly, through their use in research to advance other therapies. If researchers can work out the complex chemical and genetic signals that control the growth and differentiation of stem cells, the results would be enormously useful in medicine. ES cells should make it possible to develop models of tissue development and function that will enable chemists to test potential drugs more effectively.

For example, if ES cells derived from embryos known by genetic screening to carry cystic fibrosis genes can be guided to become CF lung cells, these would open a new window for studying the disease and testing treatments for it. For pharmaceutical chemists, unlike biologists, the vision of regenerative medicine involves finding drugs—ideally small molecules that patients can take by mouth to stimulate their own tissues to regenerate—rather than messing around with cell therapy.

The science is still far too uncertain for us to tell how stem cell research and regenerative medicine will develop. It may take another generation or two before we derive much clinical benefit from the great biological advances of the late 1990s. But the medical payoff could eventually be spectacular.

GETTY IMAGES

The Cloning Connection

Cloned tissues from stem cells might beat immune rejection

Stem cell scientists are often irritated by the way people confuse their work with cloning, even though cloning plays no part in most ES cell research today. One reason for confusion is simply that both fields involve creating embryos.

Another may be an accident of timing: human ES cells were first cultured soon after the birth of Dolly, and commentators immediately pointed out the potential for combining the two discoveries. The term "therapeutic cloning" was coined to describe the creation of a cloned embryo as a source of ES cells; the embryo is destroyed in the process. In contrast, reproductive cloning would produce a baby from the cloned embryo.

Yet there is no denying that cloning is an important item on the stem cell research agenda, because it seems the best way to overcome a serious clinical problem with cell and organ transplantation: immune rejection. The immune system attacks any graft that is not genetically identical to the patient. Even a well-matched transplant requires lifelong treatment with immunosuppressive drugs, which have serious side effects, including increased susceptibility to infection and cancer.

Therapeutic cloning uses somatic cell nuclear transfer (SCNT), the technique that gave rise to Dolly: the nucleus of one of the patient's cells is transferred into a donated egg whose own nucleus has been removed. The egg is then stimulated to behave as if it has been fertilised, developing into an embryo that could be a source of ES cells with the same DNA as the patient. (Opponents of cloning point out that the same embryo could be implanted into a womb and grow into a baby.)

Unfortunately, SCNT is an inefficient process, in animals and people. The first scientifically credible account of human cloning came last year from Woo Suk Hwang and his colleagues at Seoul National University; they used 242 eggs to obtain 30 early embryos, from which they derived just one viable line of ES cells. South Korea has a culture of egg donation for research, which enabled the scientists to obtain good-quality eggs.

Indeed, even if therapeutic cloning can be made efficient, it is hard to see how enough human eggs could be made available to use the procedure in the clinic on a large scale (unless there is an unforeseen technical breakthrough).

In the more immediate future, however, scientists hope to use therapeutic cloning as a research tool that could give new insights into disease. While genetic disorders such as cystic fibrosis can be studied by deriving ES cells from embryos known to carry the single defective gene in question (*see main article*), this is not possible for diseases that result from multiple or unknown factors.

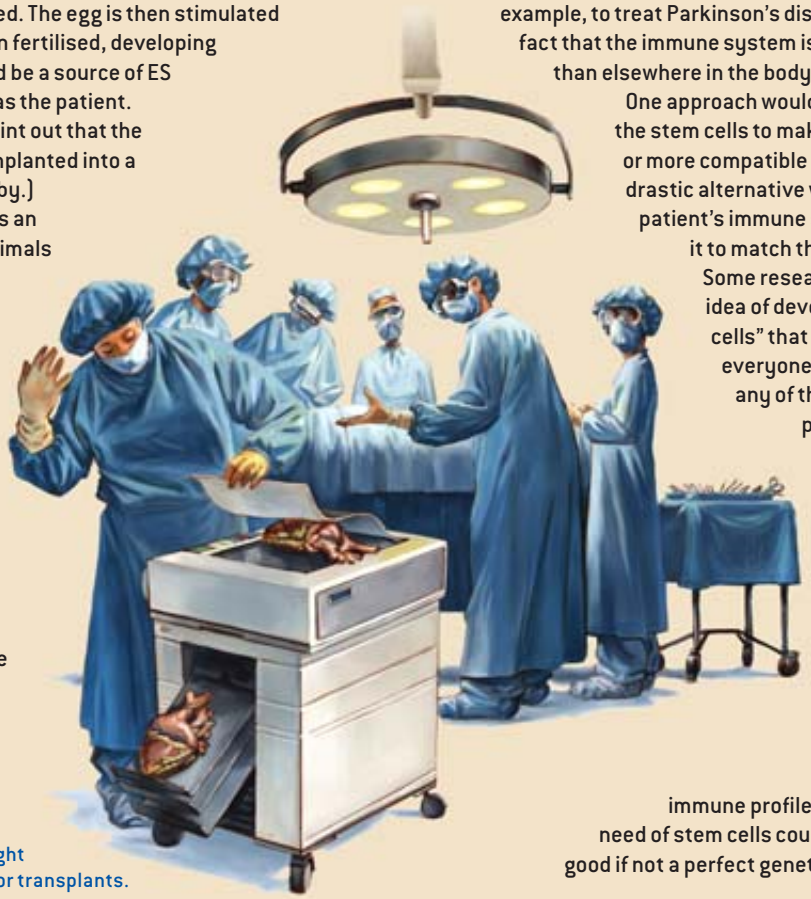
Last Month Hwang's group in Korea announced the derivation of ES cell lines cloned from a range of patients suffering from inherited diseases or spinal cord injury. The efficiency of the process has improved, too: 185 donated human eggs yielded 31 cloned embryos and 11 ES cell lines. Lab tests confirmed that each cell line was immunologically compatible with the patient from whom it was derived.

Meanwhile other researchers are looking for alternative approaches to reducing immune rejection of stem cells. Some say even that the whole issue may have been exaggerated, because embryonic and foetal cells are intrinsically less immunogenic than adult cells—and they point out that neural transplants, for example, to treat Parkinson's disease, will benefit from the fact that the immune system is less active in the brain than elsewhere in the body.

One approach would be somehow to engineer the stem cells to make them less immunogenic or more compatible with the patient. A more drastic alternative would be to wipe out the patient's immune system and reconstruct it to match the transplanted cells.

Some researchers have floated the idea of developing "universal donor cells" that would be compatible with everyone. But it is not clear whether any of these methods would work in practice.

Perhaps more achievable, though still an ambitious long-term project, is the idea of minimising rejection, rather than avoiding it altogether, by building up stem cell banks with many hundreds or thousands of cell lines representing as complete a spectrum of immune profiles as possible. Any patient in need of stem cells could then expect to receive a good if not a perfect genetic match. *—C.C.*



THERAPEUTIC CLONING might duplicate organs needed for transplants.

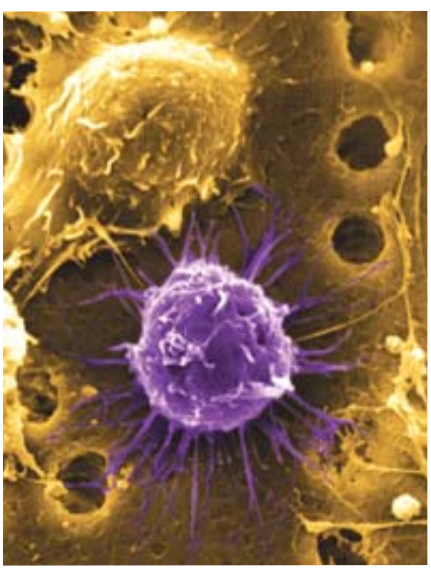
MATT COLLINS

Repair Workers Within

Adult stem cells may escape the ethical controversies of their embryonic counterparts, but as Christine Soares notes, their practical clinical value is far more murky

Using stem cells for clinical therapies is an idea still bathed in a futuristic glow, but one such treatment already has a history of success going back almost 40 years. Tens of thousands of patients treated with bone marrow transplants have shown that an infusion of healthy stem cells can regenerate a failing body part. In most of these cases, the patients suffered from congenital blood or immune disorders, or their bone marrow had been damaged by cancer treatment. As a result, the haematopoietic stem cells in their marrow, which normally produce billions of blood and immune cells daily, needed replacing.

Since 1968, these transplants have triumphantly repaired patients' capacity to manufacture healthy blood and immune cells. Over the past decade, as scientists discovered additional stem cell types throughout the human body, enthusiasm has grown for the possibility that other failing body parts might also be regenerated with a transplant of stem cells.



HAEMATOPOIETIC STEM CELL (*purple*) is derived from bone marrow. This was the first type of adult stem cell used therapeutically to regenerate blood and immune cells via bone marrow transplants.

Yet the more researchers learn about the characteristics and behaviour of adult stem cells, the less they seem to agree on answers to some fairly fundamental questions, such as what these cells really are, where they originate, what they are capable of doing, and how they do it. Consequently, although adult stem cells may not provoke much political rancour today, they have become more scientifically controversial than their embryonic counterparts.

Fortunately, the majority of scientists can at least agree on a basic definition: a stem cell (whether adult or embryonic) must renew itself indefinitely through cell division, while remaining in its generic state and retaining its potential to give rise to daughter cells of more specialised types. These progeny often start out only partially differentiated themselves, with some flexibility to serve as progenitors of several cell varieties within a particular organ or system [*see box on opposite page*]. For example, descendants of mesenchymal stem cells found in bone marrow can become bone, as well as cartilage, fat cells, various kinds of muscle and the cells that line blood vessels.

Although the tissues that sprout from these bone marrow stem cells are seemingly diverse, they have one thing in common: when the human body is first forming, they all originate in the middle layer, or mesoderm, of the developing embryo. This fact is at the heart of one of the most important questions debated by stem cell scientists: whether adult stem cells can transdifferentiate, that is, produce functional new tissues outside the lineage of their embryonic layer. The answer could be crucial to some of the more ambitious regenerative therapies based on adult stem cells.

Traditionally, adult stem cells have been considered limited in their potential, able only to manufacture cell varieties within their own lineage. Hence, they are usually described as multipotent, rather than pluripotent like embryonic stem cells. In recent years, however, many research groups have claimed to have made adult stem cells cross lineage lines—for example, by turning haematopoietic stem cells into liver, neural stem cells into blood vessels and mesenchymal stem cells into neurones.

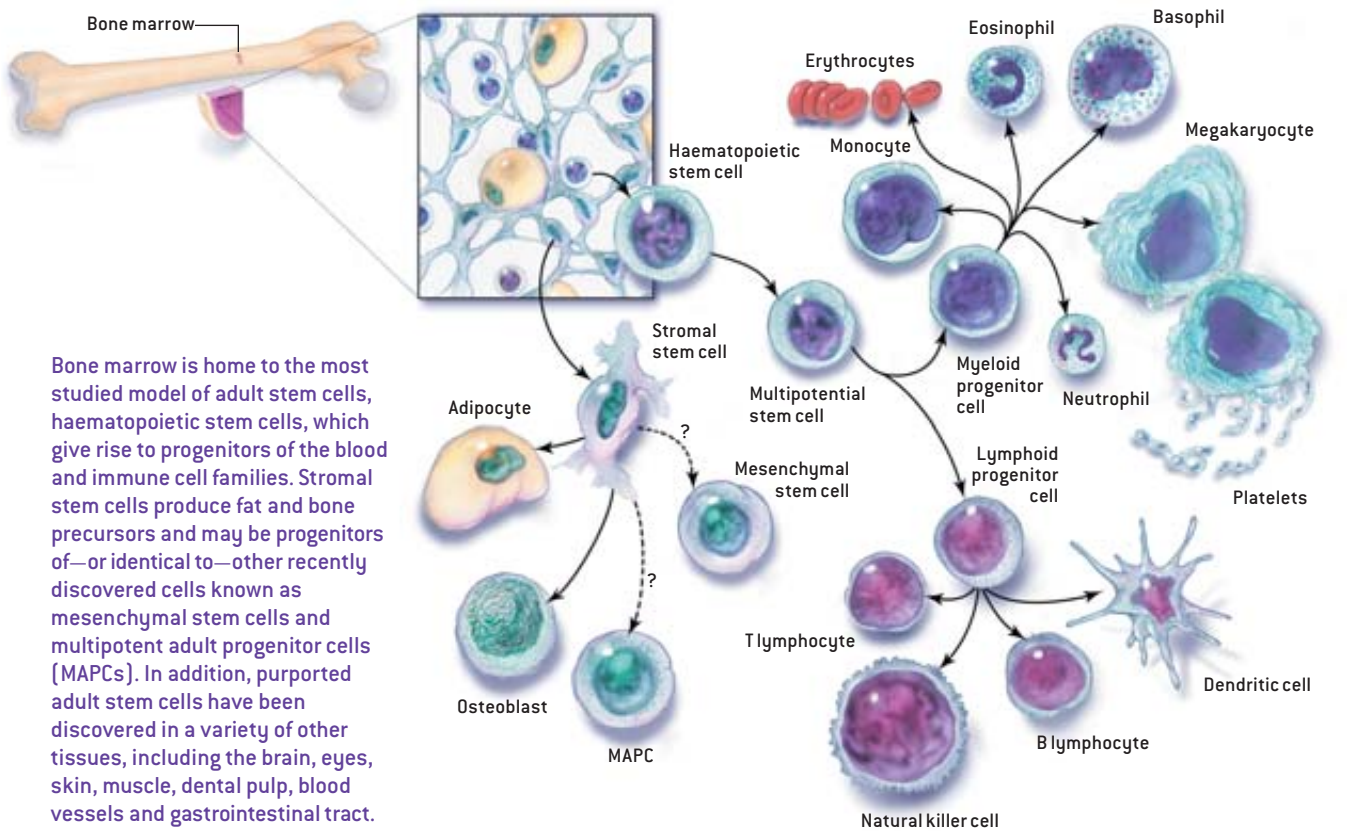
In 2002 Catherine Verfaillie of the University of Minnesota first described a new adult stem cell from bone marrow that could produce cell types of all three embryonic lineages. Dubbing it a multipotent adult progenitor cell (MAPC), Verfaillie speculated that its flexibility might equal that of embryonic stem cells. Indeed, she thought MAPCs might be left over from embryonic development to serve as a universal repair mechanism for the adult body.

Such a one-size-fits-all adult stem cell would certainly solve the problem of regenerating tissues where no local progenitors have been discovered, such as in the adult heart, or where local stem cells are extremely rare and difficult to obtain, as in the brain. Unfortunately, other investigators have had difficulty reproducing some of the original MAPC results, so the jury is still out on their real potential. Further scrutiny has also thrown cold water on many of the transdifferentiation claims for other types of adult stem cells.

Even in tissues that share a lineage, transplanted stem cells do not always work enthusiastically. In particular, at-

ANDREW LEONARD *Photo Researchers, Inc.*

Stem Cell Storehouse



Bone marrow is home to the most studied model of adult stem cells, haematopoietic stem cells, which give rise to progenitors of the blood and immune cell families. Stromal stem cells produce fat and bone precursors and may be progenitors of—or identical to—other recently discovered cells known as mesenchymal stem cells and multipotent adult progenitor cells (MAPCs). In addition, purported adult stem cells have been discovered in a variety of other tissues, including the brain, eyes, skin, muscle, dental pulp, blood vessels and gastrointestinal tract.

tempts to make stem cells taken from blood or bone marrow generate new tissue in the heart have produced conflicting results.

In clinical trials involving patients whose hearts were scarred by heart attacks, modest tissue regeneration has sometimes been observed. This improvement can occur even when the studies find no evidence that the stem cells contributed new heart cells to the healing organ. The key to this seeming paradox may be that stem cells can secrete helpful growth-signalling chemicals and contribute to the formation of new blood vessels. In other words, the transplanted bone marrow stem cells may not be producing new heart cells themselves, but they could be laying essential groundwork for the heart's own as yet undiscovered progenitor cells to do so.

Opponents of further human testing have argued that performing these transplants before the regenerative mechanisms at work are fully understood puts patients unnecessarily at risk for tumourlike growths or abnormal heartbeats. Given the lack of effective alternatives for people with failing hearts, however, the trials are very likely to continue, making heart repair potentially the first widespread therapeutic application of adult stem cell therapy beyond traditional bone marrow transplants.

Treatments for less life-threatening conditions may not be far behind. An ongoing clinical trial is already testing the safety of breast reconstruction material created from the stem cells found in fat. In the past two years, both skin and hair stem cells have also been discovered, each of which might be marshalled for cosmetic work. Dental researchers hope to make stem cells discovered in and around teeth regenerate enamel or crowns, although growing an entirely new tooth from scratch might be more than adult stem cells could muster anytime soon.

So far the cells seem to do best when applied within their own lineage to produce small amounts of new tissue or to boost natural regeneration. Last December, for example, German doctors reported having repaired a large gap in a young girl's skull using a combination of bone graft and stem cells derived from her own fatty tissue.

Injections of fat-derived stem cells are already gaining popularity as a means to speed healing of bone and cartilage injuries in horses. For certain uses in humans, too, these cells could be easier to harvest than mesenchymal stem cells from bone marrow. Researchers are finding, however, that like all other adult stem cells studied to date, this type shows a definite decline in vi-

ANDREW SWIFT

Patient, Heal Thyself

Revving up the body's own stem cells could be the simplest route to new therapies

The body's innate capacity for regeneration is what all stem cell therapies strive to emulate and improve upon. For that reason, the simplest route to many treatments may involve recruiting and activating the stem cells already hiding within our tissues. A major medical research effort now focuses on learning the subtle chemical language that directs stem cell behaviour during natural wound healing. Mastering this idiom could in some cases help to eliminate the need for therapeutic infusions of lab-grown cells. The right chemical cues might even restore the vigour to cells in older patients. The potential benefits are many—but there are also dangers.

To see the benefits, consider the aftermath of an overzealous workout that leaves muscles screaming in pain. Individual muscle cells release chemical signals as their own cry for help. Homing to the sites of microscopic tears in the muscle fibres, the stem cells then immediately get to work making repairs.

Early this year a newly discovered protein dubbed Delta was credited with rejuvenating the muscle-building stem cells of mice. A group led by Stanford University's Thomas Rando paired old and young mice, connecting their circulatory systems so that the old mice had the youngsters' blood running through their veins. Rando found that something in the young blood, purportedly the Delta protein, restored youthful activity levels to stem cells belonging to the old mice.

Researchers have in the past successfully regenerated muscle mass in animals through experimental gene therapies that deliver a different protein, called insulinlike growth factor-1 (IGF-1). (Indeed, the experiments worked so well they have triggered fears that future athletes will engage in "gene doping".) IGF-1 both triggers stem cell activity and, when its call is amplified, can summon stem cells from afar to the site of an injury. Rather than requiring transplanted stem cells to regenerate tissue damaged by a heart attack, therefore, some researchers believe a dose of IGF-1 could kick-start repairs by stem cells already circulating in the bloodstream or hiding within the heart itself. A similar approach might work in any number of organs or tissues, provided scientists can learn which signals call the correct stem cells to duty.

But even more important may be knowing how to shut the stem cells off when the repairs are done. One of the darker revelations to have come from stem cell research in recent years is the connection to some varieties of cancer. At least one leukaemia is known to be caused by bone marrow stem cells gone awry. Certain brain, stomach and breast cancers are also now suspected to be triggered by stem cells turned malignant.

One theory holds that this may happen when stem cells, which are usually dormant, get stuck in wound-repair mode. Remaining activated too long makes the stem cells vulnerable to genetic mutations, and then they can become a biological nightmare: a rogue cancer cell with a stem cell's proliferation power.

Yet researchers are already finding ways to turn the stem/cancer cell connection back to patients' advantage. The homing instinct of stem cells has been exploited in animal experiments to deliver a "suicide gene" to tumour cells, leaving normal tissues unharmed. The physical similarities of cancer and stem cells also recently led to a mechanical test that makes it easier to find both types of cell in a person's blood. And, of course, widespread attempts to parse the signalling language of stem cells in order to turn a patient's own healing powers on may also reveal commands that turn tumour cells off. *—C.S.*

MATT COLLINS

gour as their owners age. Late in life when repairs are most likely to be needed, one's own stem cells might therefore not be the best bet. Where, then, might patients turn?

One potential source of fresh therapeutic stem cells is the donated tissue of miscarried and aborted foetuses. These stem cells are classified as "adult" because they are found in differentiated tissues. Their extreme youth, however, gives scientists hope that when transplanted they will adapt easily to new surroundings and energetically produce new cells.

A major test for both foetal stem cells and the prospects of cell-based brain therapies in general could come in the next year if California-based StemCells, Inc., receives US government approval for its proposed clinical trial. The company, co-founded by the Salk Institute's Fred Gage, who first discovered neural stem cells, plans to transplant foetal neural stem cells into the brains of children with Batten disease. That lethal illness arises from the failure of brain cells to produce an enzyme that clears away cellular wastes. If the stem cells manufacture healthy new brain cells that produce the missing enzyme, the treatment could alleviate the disease, with exciting implica-

tions for other related brain disorders.

The Batten trial would be Western scientists' first transplant of neural stem cells into the human brain, an environment that some fear could be difficult for stem cell therapy. Unlike skin, liver and other tissues that naturally repair themselves after an injury, the brain, spinal cord and other nervous tissues do not, and no one is quite sure why. The very existence of adult neural stem cells suggests that they should be able to replace damaged neural tissue. Their failure to do so has prompted speculation that something inhibits them.

Researchers at the Schepens Eye Research Institute in Boston, Mass., reported a breakthrough on this problem earlier this year. Just by manipulating genes responsible for sending "blocking" signals to stem cells, they were able to regrow damaged optic nerves in mice. The experiment highlights a new and promising approach to stem cell therapy. The idea is to learn the language of signals that normally direct stem cells' behaviour well enough to be able to recruit a patient's own stem cells to make repairs on demand [*see box on opposite page*].

Studying the cues that stem cells send and receive in their natural environment is also improving scientists' basic understanding of what gives a stem cell its potential. If the secret to "stemness" were as simple as having particular genes active at specific times, then any cell of the body might conceivably be turned into a stem cell as needed [*see box at right*].

Ongoing investigations of both adult and embryonic stem cells will likely reveal whether such a feat is feasible. The adult versions so far appear to lack the versatility of the embryonic kind, and even within their own tissue families they show diminishing vigour. Still, certain types of adult stem cells have already proved themselves extremely useful for modest regeneration and repairs. The diverse research currently focused on these cells worldwide promises to unlock further the power of the body's own repair system.

ANDREW SWIFT

Making Stem Cells on Demand

Changing muscle into bone and regrowing organs could be the fruits of work on "dedifferentiation"

What can a simple newt do that humans are trying to learn? The tiny amphibian can regenerate an entire lopped-off limb, or a whole organ, by taking normal, differentiated body cells—bone, skin, muscle and so on—and winding back their clocks to an undifferentiated state of stemness. Newts create these instant stem cells at the site of an injury, then immediately begin rebuilding the missing body part.

In contrast, once a mammal's cells have gone down the path of becoming bone or skin or brain cells, there is normally no turning back. They are said to be terminally differentiated. If humans could undo differentiation, though, doctors might not have to hunt for rare and elusive stem cells within the body or try to force stem cells from one tissue to regenerate tissue of another type. Instead an ordinary pancreas cell might be turned into a progenitor of the insulin-producing cells lost in Type 1 diabetes. Normal nerve cells could become a neurone factory for brain or spinal cord repair.

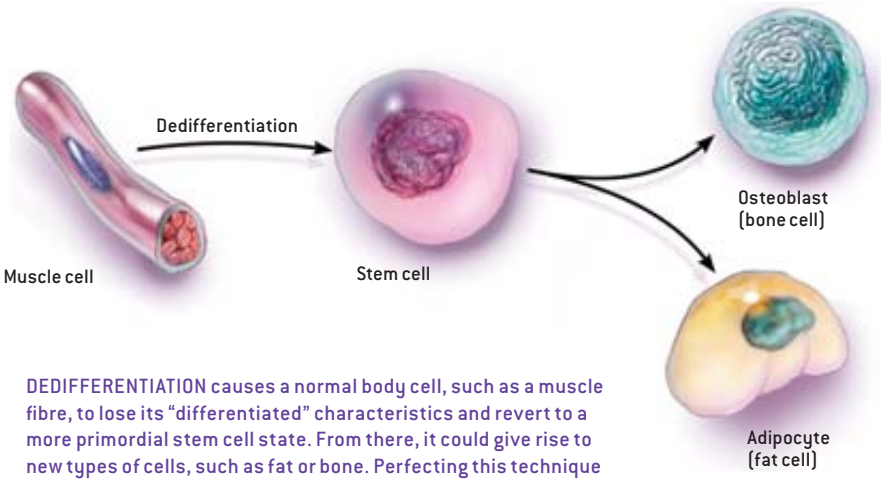
Investigations of this approach are just beginning, but early results are both encouraging and intriguing. Harvard Medical School's Mark Keating and his colleagues first showed in 2001 that dedifferentiation in mammals might be possible by regressing mouse muscle cells with an extract from regenerating newt limbs. They attributed the reversion to proteins in the extract having switched on one or more genes in the cells.

Last year a group from the Scripps Research Institute also reported dedifferentiating mouse muscle and then turning the cells into bone or fat. They used a small-molecule chemical that they found by trial and error and have named reversine, but as yet they are not sure how it worked.

Others are studying the natural environments, or niches, that stem cells usually inhabit within the body to figure out which environmental cues may tell stem cells what to do and when to do it. Allan Spradling and Toshie Kai of the Carnegie Institution of Washington have used this kind of information to control fruit-fly stem cells that normally produce the female's eggs. By manipulating niche signals, they could make the stem cells differentiate, then dedifferentiate again.

These kinds of results fuel speculation that such environmental signals may be crucial to creating and maintaining the stemness of stem cells. As Dov Zipori of the Weizmann Institute of Science in Rehovot, Israel, put it in a recent review article, a stem cell may turn out to be not an entity so much as a state—one that any cell could enter under the right conditions.

—C.S.



DEDIFFERENTIATION causes a normal body cell, such as a muscle fibre, to lose its "differentiated" characteristics and revert to a more primordial stem cell state. From there, it could give rise to new types of cells, such as fat or bone. Perfecting this technique would mean that regular body cells might be turned into an unlimited supply of stem cells for tissue regeneration.

A Patchwork of Laws

Richard Gardner and Tim Watson find much disagreement around the world about what should be allowed with stem cells—in spite of attempts at finding consensus

Whether scientists can capitalise on the huge potential that stem cell research and therapeutic cloning promise depends on where in the world they work. There is a disparate and confusing patchwork of legislation, with little agreement between countries on exactly what should be permitted and what should be banned. Attempts to reach consensus have failed in Europe and at the United Nations, and in some countries the debate remains unresolved at the national level.

The science is complex, and the ethical dimensions equally so. But the problem lies in the major differences of opinion over which parts of the science are considered acceptable.

There are three main scientific issues at the heart of the debate—human embryonic stem cells, reproductive cloning and therapeutic cloning. To some, all three are equally unacceptable, but to others they are different enough to merit separate consideration.

The source of human embryonic stem cells is a major point of contention, as they are taken from embryos that are just a few days old. They are primarily taken from embryos that have been left over from fertility treatments, but this limits the types of research that can be carried out. A possible alternative, and one that raises further moral quandaries, is to produce cloned embryos.

Since the cloning of Dolly the sheep in 1997, the world has had to grapple with the serious prospect that cloning a human might indeed be possible. The single point which all countries seem agreed upon is that, for now, attempting to create a human clone, also known as reproductive cloning, is scientifically unsafe, ethically unsound and unacceptable socially.

But there is a related procedure known as therapeutic cloning whereby the early embryo never develops beyond a microscopic ball of cells in the laboratory. During this time, research is carried out on it, most often to extract stem cells, but it can also be to understand better the early development of genetically based diseases.

Some countries have put in place total bans on all forms of human cloning, others have banned reproductive cloning but still allow therapeutic cloning and some have so far failed to introduce any regulations, often as the result of a failure to reach agreement. Many countries also have regulations on the derivation and use in research of human embryonic stem cells.

To illustrate the range of regulation, we can look at the huge differences between the US and the UK.

The UK is one of a handful of countries to have introduced legislation with the express purpose of allowing the use of human embryos for stem cell research and therapeutic cloning. In 2001 the UK introduced primary legislation against reproductive cloning; however, this action was taken after it had extended the terms of the Human Fertility and Em-

BRAZIL'S SCIENCE AND TECHNOLOGY MINISTER Eduardo Campos (*at far left in back row*) celebrates with handicapped people the passage of a stem cells law on March 2, 2005. Their T-shirts trumpet, in Portuguese, the *esperança*, or hope, that people from all over the world hold for therapies that may come from *células-tronco*, or stem cells.

ROSE BRASIL *AP Photo*

The Next Frontier: The Courtroom

As arguments mount over who will own the future technologies born of stem cell research, corporate lawyers prepare for battle

Who owns stem cells? And more to the point, who should own the life-altering medical treatments that may one day emerge from this futuristic and highly contentious field of research?

It may seem premature to worry about ownership rights for technologies that do not yet exist—and may never prove commercially viable. But with more money pouring into embryonic stem cell research—especially after the success of a ballot initiative in California last year, mandating $3bn in state funding for embryonic stem cells—disputes over ownership rights cannot be far behind, legal experts say.

There has been very little US litigation over stem cells. The truce may not last.

Stem cell research has been a focus for intense political and ethical battles for years. Now the next frontier is in the courts: battles over who owns what in a field where intellectual-property rights are far from clear.

"Typically litigation only arises when there are commercially available products and a very real market for the technology", notes Bill Warren, an expert on biotechnology patents at the law firm Sutherland Asbill & Brennan in Atlanta. But now that California and other states are getting into the game of financing stem cell research, that will hasten the development of the technology, says Warren, and "litigation will definitely be coming", possibly in the next five years.

Up to now, legal experts point out, there has been very little US litigation involving stem cells, even though one organisation claims to own the patent rights to all embryonic stem cells. That group, the Wisconsin Alumni Research Foundation (WARF), says its patents cover "a method of culturing human embryonic stem cells and composition of matter which covers any cells with the characteristics of stem cells"—in other words, pretty much anything to do with embryonic stem cell research.

Critics, in the academic and commercial research communities, complain that this patent is too broad. But WARF and the US Patent and Trademark Office defend it, on the grounds that if others believe they have rival rights, they can fight it out in court.

And despite the breadth of its patents, WARF is so far not impeding anyone else's research activities, says Arti Rai, an expert on scientific patents at Duke University Law School, pointing out that WARF freely licenses its patent for research purposes. But the current truce may not last long, she states, once WARF's rivals in the field are ready to commercialise their own technology. At that point, the breadth and validity of WARF's patents will be challenged in court.

Critics who see stem cell patents as an impediment to the development of lifesaving technologies are just plain wrong, says Michael Werner, chief of policy at BIO, the Biotechnology Industry Organisation. "Intellectual property is critical to scientific advancement", he observes. "There would be no private investment without patent rights". The only thing that will stifle stem cell research, he adds, is threatening the IP rights of those who carry it out for profit.

He places the debate over stem cell patents squarely at the centre of a larger social debate—in the US and elsewhere—over how to balance the intellectual-property protection needed to convince companies to invest in innovation with the need to maintain the kind of vibrant public domain that also is capable of fostering progress.

Everybody knows somebody who could one day be helped by a medical treatment based on stem cell technology. But the legal questions surrounding this promising technology are almost all as yet unresolved. And the issue of who owns the results of stem cell research can only get more complicated, as more and more American states start their own programmes to fund stem cell experimentation, creating a tangled web of private and public financing that can only, in the end, be resolved by the courts.

—Patti Waldmeir

bryology Act governing licensed research on early human embryos.

These measures were taken following wide public debate and were passed by majorities of more than two to one in both Houses of Parliament. The Royal Society, as the UK's national academy of science, played a significant role in informing the debate during this process. The result has been a carefully regulated process, which has so far resulted in two licences being granted to carry out research into diabetes and into motor neurone disease.

By stark contrast, in the US, despite an influential religious lobby consistently condemning any research involving embryos, there is no primary federal legislation to regulate any form of human cloning. This reflects a split between those who strongly believe all cloning should be banned and those who wish to see only reproductive cloning banned and an inability to come up with suitable legislation, despite numerous and ongoing efforts.

The latest development was the resubmission of the Human Cloning Prohibition Act of 2005 to Congress by Senator Sam Brownback of Kansas on March 17. This proposed a federal ban, which makes no distinction between reproductive and therapeutic cloning and has strong support but has already failed to make it into law twice since 2001. Brownback has also declared his equally strong opposition to any effort in the House of Representatives to reconsider an existing ban on

Engineering Aside the Morality

Researchers ponder how to procure ES cells without destroying embryos

What if science, with a shake of a test tube, could circumvent the ethical objections to embryonic stem cell research? Several proposals would in principle let scientists obtain precious embryonic stem cells without harming embryos (equally precious to some) in the process. For eager biotechnologists, that arrangement would sound almost too good to be true—and indeed, it most likely is.

William B. Hurlbut of Stanford University, a member of the US President's Council on Bioethics who is a firm believer in the "implicit moral dignity" of the embryo, has attracted attention by suggesting a combination of genetic engineering and cloning called altered nuclear transfer. In one scheme, the nucleus of a mature cell would be extracted and altered to turn off one or more genes that are vital during an embryo's development. The nucleus would be injected into a prepared egg cell that is then zapped with electricity to activate it, as in cloning. If all goes as it should, this biological entity, which Hurlbut says "never rises to the level of what can properly be called a living being", would become at most an unorganised clump of embryonic cells suitable for scientific research and possibly clinical treatments.

> Production of what amounts to sacrificial monsters is unlikely to satisfy those who believe that any tinkering with the primordial stuff of life is wrong.

Not all bioethicists share Hurlbut's enthusiasm for this plan. That cellular clump would bear a great likeness to a teratoma—a grotesque tumour mixing together different cell types, from hair to muscle to teeth. Although it may not be classifiable as an embryo, in the eyes of many, it certainly triggers what Leon Kass, the chairman of the council, has called the "yuck factor" for viscerally identifying unethical practices. Critics have also questioned whether intentionally creating a doomed abomination is morally superior to destroying embryos that already have no future. And yuckiness aside, to make successfully even one line of stem cells in this way, hundreds of human eggs might be needed, which itself entails ethical and technical problems.

Two Columbia University researchers have circulated a perhaps more pragmatic idea: pluck living ES cells from the many embryos produced in vitro that have died spontaneously. Donald W. Landry and Howard A. Zucker have begun work on tests for assessing markers such as the final arrest of cell division, which the scientists equate with "brain death" for embryos.

Ironically, the Landry/Zucker scheme would rescue nominally healthy cells from dead embryos, while healthy but unused IVF embryos would continue to be discarded. It also forgoes the dream of someday cloning ES cells from a patient's own body for use in treatments. Such bespoke stem cells would be safe from immune rejection; ones derived from dead embryos would not be. Hundreds of thousands of cell lines might therefore need to be cultured and stored to provide all patients with immunologically compatible cells.

Other would-be solutions include techniques for extracting individual stem cells without harming embryos and for using unfertilised human eggs coaxed into a short-lived process resembling embryo formation. Another straightforward strategy would avoid ever going near an embryo. Instead an adult stem cell would be forced to "dedifferentiate", or revert to its more embryonic pluripotent state. At the moment, however, such a concept borders more on alchemy than biochemistry. A US National Academy of Sciences report issued in April summarised these approaches as seeming to have numerous technical hurdles for now.

A critique in the *New England Journal of Medicine* specifically aimed at Hurlbut's proposal may further dampen all these ideas. Douglas Melton, George Daley and Charles Jennings of Harvard University argued that the switching off of a gene does not represent "a transition point at which a human embryo acquires moral status". No similar developmental or biochemical benchmark may ever lend ethical certitude to this field. Industrial-scale production of sacrificial monsters is unlikely to satisfy those who believe that any tinkering with the primordial stuff of life is wrong.

—Gary Stix

federal funding of some embryonic stem cell research.

Worryingly, no federal legislation exists to stop a privately funded laboratory attempting to create a human clone. But any outcome of research would then be subject to Food and Drug Administration approval, which it would be extremely unlikely to pass.

Scientists can receive federal funds to use human embryonic stem cells in their research, but only the cell lines created prior to 2001, of which only 22 are available. Also, some states have now enacted their own legislation, in some cases to ban all cloning and embryonic stem cell research and in others to allow therapeutic cloning and even pledge millions of dollars of funding, most notably in California.

Countries where therapeutic cloning and stem cell research are permitted often regard it as great news that the US is lagging behind. Levels of investment in this kind of research in the UK are testament to this. But in the long term, losing out on the expertise and resources of the world's leading scientific nation means patients around the world will lose out, too, because a global effort is needed to make the most rapid progress.

Elsewhere, the opinions and legislation are equally varied. Europe is

divided on the issues. Most countries, including Germany, Austria, France and the Netherlands, have brought in legislation to ban reproductive and therapeutic cloning. Yet they are in the curious position of not going as far as countries such as Italy, Ireland, Norway and Denmark, which have also restricted research using human embryonic stem cells. This raises an interesting moral question of whether these nations will allow their patients to receive the treatments developed in the future using technologies that they consider unacceptable.

Belgium, Sweden and Spain allow therapeutic cloning and human embryonic stem cell use in similar frameworks to the UK, and there is now public pressure in Germany and Italy to revisit their legislation, while Ireland is already doing so.

In Asia, the picture is very different. Japan, China, Singapore and South Korea all follow the UK's approach. India is embracing human embryonic stem cell research, as realised recently at an Indo-UK meeting organised by the Royal Society and aimed at spawning international collaborations in the field. But so far it still has a ban on therapeutic and reproductive cloning.

South America is as divided as Europe. Ecuador bans embryonic stem cell research and both types of cloning; Brazil bans cloning, but a new law allows and funds embryonic stem cell research; Argentina, Chile, Peru and Uruguay ban both types of cloning, and legislation either allows or does not cover embryonic stem cells, and only Colombia permits therapeutic cloning as well as human embryonic stem cell research.

A global scientific effort is needed to make the most rapid possible progress. Yet opinions and legislation around the world are deeply divergent.

In the Middle East, only Israel and Turkey have any relevant legislation. Israel permits therapeutic cloning and embryonic stem cell research while banning reproductive cloning. Turkey has effectively the same—although stem cell research is not explicitly permitted, it is just not mentioned.

On the continent of Africa, only South Africa (embryonic stem cell research—yes; both types of cloning—no) and Tunisia (embryonic not specifically prohibited; both types of cloning—banned) have enacted laws.

For the countries that do not have national legislation we can gain an idea of their attitudes from the ill-fated attempts to gain consensus at the European and international levels.

The Council of Europe has introduced the ambiguous European Convention on Human Rights and Biomedicine. It is not clear whether it bans therapeutic cloning. Thirty-one of the 45 member states have signed, of which 15 have also ratified. In response to the

GAUTAM SINGH *AP Photo*

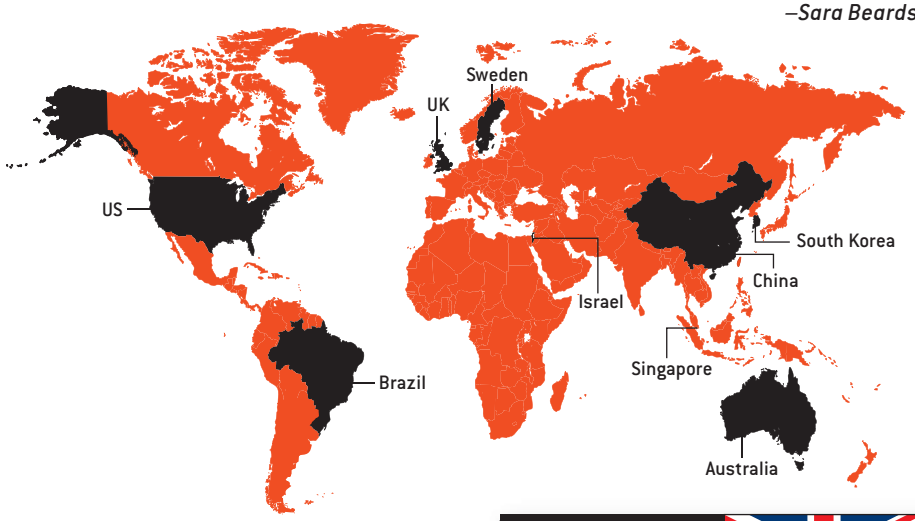
SIR MICHAEL ARTHUR (*right*), British High Commissioner to India, confers with K. VijayRaghavan, director of India's National Centre for Biological Sciences, at a stem cell workshop in April. The UK intends to take some of its stem cell research to India.

A World of Approaches to Stem Cells

Around the globe, stem cell research has met with reactions varying from enthusiasm (as in the UK) to suspicion and distaste. Despite increasingly permissive international laws, no consensus on supporting the research has emerged, even among the selection of "stem cell progressive" countries considered here. The US government, for example, provides an enormous sum ($550m) for stem cell investigations by global standards, but the portion for human embryonic stem cell (hESC) studies ($24m) is only slightly above the spending by countries with much smaller budgets where investments go farther.

Nations also differ on how much regulatory control they choose to exercise. Some have laws that specifically permit or prohibit certain practices associated with hESC work, such as therapeutic cloning, but others keep such experiments in a legal limbo. Critics have raised concerns about the inconsistency of the resulting systems: one scientist notes that EU funding has created a "bizarre situation" in Germany, where scientists can apply for projects that are officially deemed illegal. (Funding figures represent estimates of the current annual spending in US dollars on all types of human stem cell research, except where noted.)

–Sara Beardsley



EU

Production of new hESC lines: Permitted from unused IVF embryos where legal in member nations

Therapeutic cloning: Prohibited

Funding: $170m on stem cells over the past three years (only $650,000 for hESC research)

Status in some member nations:
- **France:** Creation of hESC lines from IVF embryos legal as of October 2004; public funding is $4m
- **Germany:** Only work on hESC lines predating 2002 is legal; public funding is $4m
- **Finland:** Permits research with IVF embryos; public funding is $5m
- **Italy:** June 12 referendum will consider permitting IVF embryo research; public funding is $6m

EU will not increase funding for hESC projects despite a doubling of the total research budget.

US

Number of published hESC lines: 46

Production of new lines: Legal, but prohibited with federal funds

Therapeutic cloning: Legality varies from state to state

Federal government funding: About $550m for all stem cell research ($24m for hESC)

Private funding: About $200m

Public funding at state level:
- **California:** $3bn over 10 years
- **New Jersey:** $11.5m (another $380m proposed)
- **Wisconsin:** $375m proposed
- **Illinois:** $1bn proposed
- **Connecticut:** $20m proposed

Federal government allows its funds to be used only on the 22 available hESC lines created before August 2001.

Pending legislation would relax some of these federal restrictions.

UK

Number of published hESC lines: 3

Production of new lines: Legal

Therapeutic cloning: Legal

Government funding: About $80m

Private funding: $15m–$20m

The Wellcome Trust alone has spent $12m annually since 2002.

First licence for human ES cell research was granted in 1996.

The Human Fertilisation and Embryology Act of 1990 allows the UK to fund hESC research flexibly.

UK's first licence for human cloning research granted in 2004. Its recipients in May announced the country's first cloned human embryo.

SWEDEN

Number of published hESC lines: 8

Production of new lines: Legal

Therapeutic cloning: Legal as of April

Number of researchers: 400

Government funding: $10m–$15m

Private funding: Cellartis and NeuroNova, the two largest stem cell research companies in Sweden, contribute the bulk of the $35m spent annually there

Cellartis, the single largest source of defined hESC lines in the world, maintains more than 30—two of which are approved by the US National Institutes of Health.

JEN CHRISTIANSEN; REPORTING BY SARA BEARDSLEY

BRAZIL

Production of new hESC lines: As of March, legal from IVF embryos at least 3 years old

Therapeutic cloning: Banned

Government funding: $4.5m annually planned, allocated by the Health Ministry and the Science and Technology Ministry

SOUTH KOREA

Number of published hESC lines: 29

Production of new lines: Permitted with case approval from Ministry of Health

Therapeutic cloning: Permitted with case approval from Ministry of Health

Number of researchers: 300-400

Government funding: About $10m

Private funding: About $50m

First to create a hESC line from a cloned embryo. In May the same researchers announced that they had created 11 new hESC lines cloned from patients with spinal cord injuries, juvenile diabetes and a blood disorder.

SINGAPORE

Number of published hESC lines: 1

Production of new lines: Legal, if embryos are destroyed within 14 days

Therapeutic cloning: Legal, as above

Number of researchers: About 150, in industrial and academic settings

Academic spending: About $10m, from public and private sources

Industrial spending: About $10 million

A pending government proposal would spend $60m over the next four years.

ISRAEL

Number of published hESC lines: 1

Production of new lines: Legal

Therapeutic cloning: Legal

Government spending: About $5m

Private spending: $15m–$30m

Israeli scientists led one of the research teams that first isolated hES cells. They were also the first to show that hES cells could be changed into heart cells, and to show that hES cells can integrate with tissues.

CHINA

Production of new hESC lines: Legal

Therapeutic cloning: Legal

Number of researchers: 300–400

Public and private funding: About $40m

The journal *Nature* reports that "China has probably the most liberal environment for embryo research in the world", with little public opposition to such studies. No laws govern stem cell research, but the recommendations of the Ministry of Health endorse it.

AUSTRALIA

Number of published hESC lines: 1

Production of new lines: Conditionally legal

Therapeutic cloning: Banned

Number of researchers: 200–250

Government funding: The Australian Stem Cell Centre has $90m to spend through 2011.

debate in the UK, which preceded the introduction of its legislation on cloning, an additional Protocol on the Prohibition of Cloning Human Beings was drafted to try to influence the outcome. Unsurprisingly, the UK has not signed either, but as neither the convention nor the protocol gives any sanctions for violation it is unlikely to have any major effect. Portugal, though, has signed and ratified the convention, despite no national legislation, which is a likely indication of its views.

At the United Nations we see a similarly confused picture. A committee was formed in 2001 to consider "the elaboration of an international convention against the reproductive cloning of human beings". Four years of stop-start debate and negotiations saw member states unable to get anywhere near a consensus on whether therapeutic cloning should be included in the ban.

One of the most influential groups during the tail end of the debate was the Organisation of Islamic Countries (OIC). It is suspected that part of the reason that those seeking a ban on all forms of cloning, such as the US and Costa Rica, did not push for a convention was because of a last-minute indication that the OIC would support an alternative proposal. Initiated by Belgium and supported by the UK, the proposal asked that individual countries be allowed to make their own decision on therapeutic cloning.

Instead the result was a poorly worded and ambiguous political declaration that appears to ban all forms of cloning. But because it is nonbinding, it will have absolutely no effect on countries that wish to forge ahead with therapeutic cloning.

Unfortunately, this outcome also means that no clear message has been sent to maverick scientists that the entire world believes that reproductive cloning is unacceptable.

Richard Gardner is chair of the Royal Society's working group on stem cell research and cloning. Tim Watson (tim.watson@royalsoc.ac.uk) is a press officer at the Royal Society.

Stem Cells: East ...

Country Report: CHINA

Generous staffing and permissive laws aid Asia's largest stem cell effort

China has Asia's most extensive stem cell research effort, with a particular emphasis on driving innovative adult stem cell therapies toward clinical trials. Although it is hard to find statistics that pull together China's fast-growing patchwork of stem cell initiatives, the country must have at least 300 researchers in the field, working in 30 separate institutions.

A delegation sent late last year by the UK Department of Trade and Industry to look at stem cell research in Asia visited a dozen Chinese labs and concluded: "The facilities were, in every case we saw, equipped, funded and staffed to levels at least as good—in most cases better—than equivalent centres in the UK". Chinese stem cell labs have plenty of well-motivated junior staff, many of whom have returned from postgraduate training in Europe and North America. The senior researchers, who have also worked abroad, are providing strong leadership, but there seems to be a temporary gap in the middle, among the cadre of postdoctoral scientists who form the background of the scientific effort in the West. China has a few rudimentary stem cell companies, but commercialisation is still at an early stage.

Like their counterparts elsewhere in Asia, Chinese stem cell researchers benefit from an ethical and regulatory environment that is generally more favourable to stem cell research than in even the most permissive Western countries. "The status accorded to the embryo is similar to that in the UK, but regulations are operated in China with a fairly light touch", says Genevra Richardson, professor of public law at Queen Mary, University of London. "Most ES research teams in China use fresh embryos".

LINDA WELLS (*center*) of Albuquerque, NM, watches as a technician inspects a stem cell sample at a laboratory in Tianjin, China. Wells went to China after doctors discovered stem cell samples from a Chinese child that would provide a match for her daughter, Kailee, who suffers from aplastic anemia.

GREG BAKER *AP Photo*

China is well represented in embryonic stem cell work, with at least 10 ES cell lines established in the country—and is working on therapeutic cloning. "China has better access to human oocytes than we have in the West—and fantastic nuclear transfer skills", says Peter Mountford, chief executive of Stem Cell Sciences, based in Edinburgh. "There are many extremely dextrous hands available to manipulate those tiny dots [human eggs]".

But the Chinese scene is still dominated by adult stem cell work. "There is a very significant focus on clinical translation, which is much more palatable in China than in the US or Europe", says Stephen Minger of King's College London. "Treatments will be pushed ahead more quickly than in the West".

A colourful example is Jianhong Zhu of Huashan Hospital, part of Shanghai's Fudan University. He is working with adult neural stem cells, extracted from brain tissues exposed in patients who suffer open head wounds. (A classic local example is the "chopstick injury", in which a barbed bamboo chopstick is pushed—usually through an eye socket—into the head during an argument over a meal; when the stick is removed, enough brain tissue sticks to it to be a source of neural stem cells.) Zhu has obtained encouraging results from a clinical trial in which eight such patients had their own neural stem cells cultured and transplanted back into the site of their injury; they fared significantly better than eight matched controls who had open brain surgery but no cell grafting.

—*Clive Cookson*

... and West

Country Report: UNITED KINGDOM

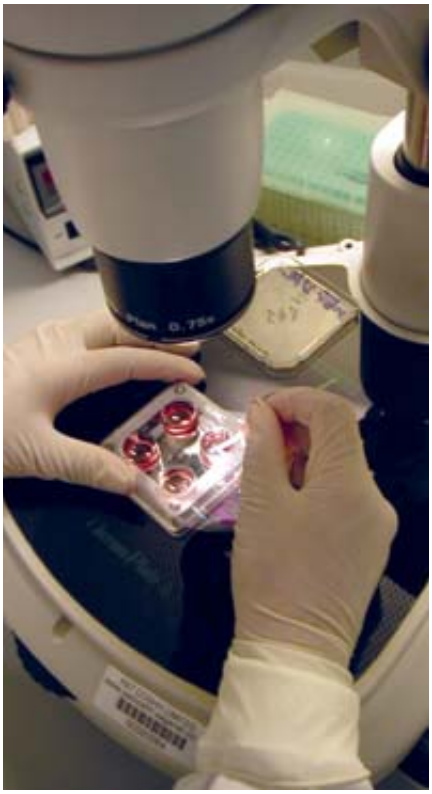
Positive public attitudes lift British scientists above the destructive fray

When the international stem cell research race got started at the end of the 1990s, two factors put Britain in a strong position. One was the historical strength of embryology and related sciences in the UK, the other its well-established regulatory framework.

Any researcher working with early human embryos owes an immense scientific debt to Patrick Steptoe and Robert Edwards, the British pair who developed the IVF techniques that led to the birth in 1978 of Louise Brown, the world's first test-tube baby. That led to an intense debate about the ethics of using "spare" embryos for research, culminating in 1984 with Mary Warnock's landmark official report that recommended allowing controlled research on human embryos up to 14 days after fertilisation—a limit that remains a de facto world standard.

Warnock's conclusions were enshrined in law six years later, with the establishment of the Human Fertilisation and Embryology Authority to regulate the field. So, when human ES cells and cloning came along, it was relatively straightforward for the UK to amend its legislation to allow research for therapeutic purposes on cells derived from human embryos (including cloned embryos) while banning reproductive cloning. Two therapeutic cloning projects are already under way, at Newcastle University and the Roslin Institute.

Although Britain has a vocal anti-abortion lobby opposed to embryo research, it is very much in the minority. In the UK, unlike many other countries, stem cells and cloning are not party political issues. Stem cell researchers who have come to Britain from other countries, such as Roger Pedersen to Cambridge and Stephen Minger to King's College London from the US and Miodrag Stojkovic to Newcastle from Germany, emphasise the importance of the supportive public and political attitude to their work.



INVESTIGATOR at Stem Cell Biology Laboratory at King's College London works with human embryonic stem cells.

KING'S COLLEGE LONDON

The positive attitude of the UK government—and even more enthusiasm from Scotland, which has set out with some success to become a regional hotbed of stem cell science—has already given Britain a good research infrastructure in this field. It has the world's first stem cell bank, which is leading an international initiative to characterise all the ES cell lines now available around the world, identify their salient features and assess the degree of diversity that different lines may exhibit.

Still, the public funding position for stem cell research in the UK is not so rosy by international standards. In 2002 the government announced a £40m ($70m) investment in stem cell science by the country's research councils—and, although this has been supplemented with some further funds, Britain's financial commitment falls short of some of its competitors in the Asia Pacific region as well as individual American states.

Although Britain is home to a few small stem cell companies, such as ReNeuron and Stem Cell Sciences, there is little investment from traditional private sector sources such as venture capitalists and fund managers who see the field as too long-term and risky [see "Tough Cell to Investors," on page A32]. In an attempt to fill the funding gap, a powerful group of scientists and business people has set up the UK Stem Cell Foundation, a nonprofit organisation that aims to raise £100m to support the development of stem cell therapies, in collaboration with existing government and charitable programmes.

—Clive Cookson

The California Gambit

Biologists applauded the Golden State's $3bn wager on stem cell science. But as W. Wayt Gibbs reports, the stakes may be higher than they realise

Last November, Californians elected an action hero to fix their broken budget and simultaneously agreed to borrow billions for a massive taxpayer bet on long-shot research into embryonic stem cell therapies. This is clearly not a state for the risk averse. But by rushing in where Congress feared to tread, Californians initiated a policy experiment—or a political end run—with national repercussions. Even as many stem cell biologists revel at their good fortune, some worry that this seismic shift in policy could fragment the field, delay scientific progress and raise unrealistic expectations among the public. The scale of these risks is not yet clear.

What is clear, at least to most scientists in the field, is that the previous system was not working. Under rules laid out by President Bush, researchers cannot use funding from the National Institutes of Health or other federal agencies to experiment on any of the 200-odd lines of human embryonic stem (ES) cells derived since August 2001, when the rules went into effect. Unfortunately, all of the 22 ES cell lines created before that date have been contaminated by nonhuman molecules that invite immunological attack, which greatly limits their medical use.

"There is no question that the NIH attitude and political climate had cast a real chill on this area", says Arnold Kriegstein of the University of California at San Francisco. To work around the federal restrictions, UCSF created a stem cell research programme in 2002 with $5m (£2.7m) donated by former Intel chairman Andy Grove and hired Kriegstein to run it. Stanford University set up a similar programme with a $12m anonymous donation, and last year Harvard University joined the fray with its own private stem cell institute.

Despite these efforts, Kriegstein says: "It is difficult to get involved in a field where research you may want to do may be criminalised at some time in the future". (Indeed, in some states, such as Arizona and Pennsylvania, deriving a new stem cell line from human embryos is already a felony.)

"For a young investigator starting a new lab, focusing on embryonic stem cells involves enormous risk", says Melissa Carpenter, who directs stem cell biology at CyThera in San Diego. "If the NIH decides to cut you off, then where will you be? It's an extreme shame. I know a number of good scientists who avoid the area altogether because it is so ethically charged".

As a result of the federal freeze, says Mahendra Rao of the National Institute on Aging, "the US has ceded leadership in this new field to other countries. When we talk about new markers and antibodies to identify stem cells, we point to work done in England. For progress in bioprocessing and scale-up, we look to Israel or Singapore. I now go out of my way to attend scientific meet-

STEFANI OKASAKI AND TIM HARRISON (*UCSF*); LEE SNIDER/PHOTO IMAGES/CORBIS (*Harvard University*); DAVID MCNEW/GETTY IMAGES (*Arnold Schwarzenegger*)

2002 // 2004

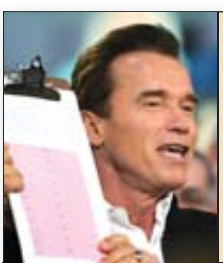
AUG 2002
University of California, San Francisco, launches a $5m stem cell biology program

DEC 2002
Stanford University creates a stem cell research centre with a $12m anonymous donation

MAR 2004
Douglas Melton of Harvard University creates 17 new ES cell lines with private funds

APR 2004
Harvard launches its stem cell institute

JUN 2004
Stem Cell Research Enhancement Act is introduced into the US House but never makes it to a vote



NOV 2004
Proposition 71 passes in Calif., clearing the creation of a 10-year, $3bn Institute for Regenerative Medicine (CIRM)

Wis. governor Jim Doyle proposes devoting $375m over 10 years to a new research institute for stem cell biology and other medical research. Doyle also proposes giving $75m over five years to state medical schools for research, including on stem cells

ings in China in order to hear new and unpublished work". Many biologists are frustrated, Rao says, "because the US still could easily be the leader in this kind of science. These cells were discovered here, and we have the best infrastructure for analysing them. We just haven't figured out how to put together the policy to do it".

That is precisely the problem that California aims to solve. California's answer to the president's restrictions is its new Institute for Regenerative Medicine, CIRM. Created by the 59 per cent of voters who favoured Proposition 71 on last November's state ballot, the institute is to be governed by a small staff of about 40 scientists (only three of whom had been hired by the end of April), a handful of administrators, and an oversight committee of 29 academics, businesspeople and medical activists. Its purpose is to spend $300m a year on stem cell research for a decade, an unprecedented growth spurt for a field so nascent and so controversial.

The move set alarms ringing in dean's offices and state legislatures around the country. The governors of Wisconsin and New Jersey quickly launched campaigns to boost stem cell research funding for their state universities. Lawmakers introduced bills legalising human ES cell experiments in biotech-heavy states such as Maryland and Massachusetts [*see timeline below*].

"When Prop 71 was passed, we became anxious that it would be difficult to attract talented leaders to Connecticut for our own stem cell research programme", says Robert Alpern, dean of the Yale University School of Medicine. He and others have persuaded the governor to support a bill that would condone work with certain human ES cells and would provide $10m a year for stem cell science. So far, Alpern reports, the bill faces no organised opposition but has yet to reach a vote.

"Human ES cells are so new, and few people are trained to use them properly to do good, innovative experiments on how they grow and differentiate. In the US there are just a few dozen people at most", observes Gordon Keller, a stem cell biologist at Mount Sinai School of Medicine in New York City.

The competition for these people is rising fast, Kriegstein says. In addition to international demand, "lots of institutions in California are trying to build or strengthen programmes right now, and they are all looking at the same candidates. That may increase the cost of attracting the best people", he states.

Keller worries that "if you funnel too much money into a field that doesn't yet have enough talent to absorb it, it is going to be wasted". CIRM's interim president, Zach Hall, plans to address that problem by using the institute's initial rounds of grants to train more scientists and build more labs. (NIH restrictions prohibit work on unapproved human cell lines in any lab that runs on federal funds.)

FRAZER HARRISON/GETTY IMAGES

ELECTORAL CAMPAIGN for Proposition 71 succeeded, but the research campaign for stem cell therapies is just beginning.

In the first round, "the intent is to encourage institutions to put together coherent training programmes for stem cell science", Hall says. Organisations will compete for 18 awards to be announced in late 2005 that will provide up to $1.25m a year, depending on the size of the training initiative. Although some of the $15m a year will go toward student stipends, Hall notes, the grants cannot pay for

2005

JAN 2005

Scientists report that all NIH-approved human ES cell lines have been contaminated by foreign antigens

NJ governor Richard Codey proposes raising $380m for a state stem cell institute

NY state senator David Paterson proposes the creation of a stem cell research programme funded with $1bn over 10 years

FEB 2005

Mass. governor Mitt Romney urges state legislators to criminalise the creation of new human stem cell lines for research

Stem Cell Research Enhancement Act reintroduced to Congress, with 186 sponsors in the House and strong support in the Senate

MAR 2005

UCLA launches an institute for stem cell biology

Calif. Supreme Court dismisses two lawsuits challenging the constitutionality of CIRM

Ill. comptroller proposes to issue $1bn in bonds and to tax cosmetic surgeries to fund a state stem cell institute

APR 2005

Md. state senate kills a bill, which had passed the House, to create a stem cell research programme with $23m a year in state funding

MAY 2005

Mass. legislature passes a bill permitting ES cell research with enough votes to override an expected veto by the governor

AUG 2005

Construction to begin on $150m stem cell research centre in New Jersey

AUTUMN 2005

CIRM plans to award its first grants

Scientists Follow the Money

A brain drain out of the US turns into a gusher for California

Shortly after President Bush announced in August 2001 that federally funded stem cell biologists in the US would have to work under tight restrictions, Roger Pedersen packed his bags for the UK. Pedersen, whose research at the University of California at San Francisco had earned him a place near the top of his field, moved his lab to the more liberal environment of University of Cambridge.

Leaving the US proved to be a good career move for Pedersen: last year Cambridge made him co-director of a new $30m stem cell institute. And Pederson was hardly alone in his emigration, observes Mahendra Rao, who directs stem cell research at the US National Institute on Aging. Rao points to several scientists who left lucrative biotech posts in the US to set up lab-keeping overseas.

But if there was a brain drain of stem cell investigators from the US, the attraction of a $3bn honeypot in California seems to be reversing the flow. "A number of leading scientists in our field have been interviewing in California for lead positions", says Melissa Carpenter, an American pioneer in the field who jumped two years ago to the Robarts Research Institute in Ontario, Canada. "UC Irvine is recruiting aggressively", Carpenter reports, "and so is Stanford". Carpenter herself just decided to return to the US to head up stem cell research at CyThera, a startup in San Diego. The passage of Proposition 71 was not the only reason for her return, she says, but it was an important factor.

Indeed, the Golden State is beckoning to many in the field, including those elsewhere in the US. At the National Institutes of Health, Rao says "it has been getting harder to recruit, and we are losing people [to California]". Arlene Chiu, who directed a stem cell research programme at the NIH, quit in April to take a job with the new California Institute of Regenerative Medicine (CIRM). James Battey, the current director of the National Institute on Deafness and Other Communication Disorders, says he has applied to CIRM for the job of president.

"We cannot compete by giving them more money", Rao explains. "And many people have a real worry about federal funding being available in the future. I myself have been tempted" to join the California bandwagon, he admits.

Although the westward pull is strongest for senior researchers, it seems to be influencing young scientists as well. "We have recruited a group of students for next year", says Arnold Kriegstein, who leads a stem cell training program at UCSF. "I think Prop 71 made some of them choose UCSF over institutions back east".

"The US is competing with Singapore, Australia, the UK—there are considerable resources there, too, and the restrictions are considerably fewer", Carpenter says. "Before joining CyThera, I looked at those as options for myself", she adds. "It's definitely a competition, and it will be interesting to see how it all falls out". —*W.W.G.*

MATT COLLINS

PhD programmes, and no school will receive more than one grant.

So when will the California money start flowing to do actual science? Hall cannot answer that question yet, as the agency must first clear several significant obstacles. Six months after its birth, CIRM was still without permanent offices, a permanent president, a slate of experts to review research proposals, or authorisation to issue the bonds from which it will draw its budget.

The bonds were hung up by a pair of lawsuits that challenged the legitimacy of CIRM. In March the California Supreme Court declined to hear the suits but left plaintiffs with the option of bringing them to lower courts. One of the suits, by two pressure groups called People's Advocate and the Life Legal Defense Foundation, landed before a superior court in April. It asserts that the new institute violates a provision in the state constitution. A CIRM official says that the state finance committee might approve bonds to raise money for the institute before the legal dispute is settled.

Even before the money valve opens, scientists could start sending in their requests for research grants. But the institute must seat a panel of 15 stem cell experts from outside California to conduct peer review of the proposals. This is no small feat. Many researchers in the field are being recruited to California [*see box above*] and thus have a conflict of interest. Among those who are qualified, few may be willing.

"I've been asked by CIRM to sit on various panels", Keller says. So far he has declined. "We already do a lot of

reviewing for NIH, from which we also draw funds. When they ask us to do the same for California but don't allow us to apply for their money … well, there are only so many hours in the day".

Ironically, in setting themselves up for financial success, the state's researchers have also set themselves up for possible political failure. By emphasising medical breakthroughs (as Richard Nixon did in the "war on cancer") rather than technical milestones (as Francis Collins did in the Human Genome Project), the campaign for Proposition 71 placed a sizeable bet on an uncertain outcome.

"Science is being put under its own microscope", reflects Fred Gage, a neuroscientist at the Salk Institute. "We are going to be accountable for coming up with major discoveries. There clearly is an expectation that before the end of the decade there will be financial as well as therapeutic benefits to the state".

At stake, too, are precedents of national importance. California's action appears to have spurred support for the Stem Cell Research Enhancement Act, a bill that died in the US Congress last year but was resurrected in February. Republican leaders have promised to put the bill to a vote this summer. Were it to pass and survive an expected presidential veto, it would remove the August 2001 restrictions on federally funded stem cell research, freeing the NIH to compete with private and state initiatives on a level pitch. The law could also be a boon to CIRM, however, because it would allow the agency to spend less on scientific construction and equipment and more on the science itself.

Ultimately, if the California gambit succeeds—whether politically, economically or scientifically—it could become a new model for funding those kinds of research that offend the majority in some parts of America but enthrall most people in other regions. That may not be the most efficient way to do science, but it might yet prove to be the most expedient.

STANFORD UNIVERSITY/GETTY IMAGES

The Ghost of Lysenko

Biologist **Irving Weissman** warns of the cost of irrational restrictions

By many measures, the US leads the world in biomedical discoveries, technologies and therapies. Recombinant DNA technologies for genetic manipulation were born in America and have produced a multitude of drugs and diagnostic devices by means of a new commercial entity, the biotech startup.

At a critical stage in US history, federal and local governments nearly banned recombinant DNA technology. But instead new regulations required academic and commercial research entities to submit their plans for approval to national and local advisory committees—and research prospered. This kind of regulation, which preserves the essence of unfettered research with the least intrusive bureaucracy and meaningfully protects scientists and society, could be called the American way. Pioneering research moves forward while society continually monitors and receives the benefits by translating discoveries into patient care.

History shows the folly of more oppressive interventions. Trofim Lysenko was a maverick biologist who convinced Josef Stalin in the 1920s that the Darwinian view of natural selection was wrong. Darwinian genetics consequently had no home in Russia for decades, while American agriculture and medicine prospered, very significantly aided by migrant Russian geneticists. The Russian way, then, held that ideology trumps science, leading to the loss of good science for generations.

The spectre of Lysenkoism haunts the US debate over stem cells. Because the isolation of stem cells from an embryo ends the possibility that it could be implanted in a uterus, people who feel any biological entity beyond fertilisation is human think this research is immoral. That view underlies the bills by Senator Sam Brownback of Kansas and Representative Dave Weldon of Florida that criminalise this practice.

As part of the administration's current policy that restricts federally funded use of stem cell lines to those made before August 2001, President Bush included a funding ban on production of pluripotent stem cells derived by nuclear transfer, which some call therapeutic cloning. The Weldon/Brownback bills would criminalise that practice, effectively limiting such research to non-US science. Thus, ideology has severely curtailed a foundation technology critical for rapid advances in human developmental biology, an understanding of the causes of human disease and development of potential human therapies. (The Weldon/Brownback bills are not law because a bipartisan coalition in the Senate has blocked their passage.)

Who loses from this federal ban? Not just life science research; not just the young scientists who wish to spend their lives pushing scientific frontiers for knowledge and for therapies. Most of all, it is the tens of thousands of patients who might have been helped. Which is the higher moral ground: saving the world from "therapeutic cloning" or saving the lives of the sick?

Fortunately, consistent with its constitutional right, in 2002 California passed bills to encourage and regulate embryonic stem cell and therapeutic cloning research. In November 2004 the state passed, by a 59 to 41 margin, a $3bn initiative to fund this research over 10 or more years. California has taken on the task of funding mainly basic research in these areas. The timelines to therapies are essentially what should be expected if the National Institutes of Health had funded this research.

While many people think it is a serious problem to substitute state for federal funding of science, I am not among them. I hope that this current intrusion of religion and ideology into federal research is only a transient aberration, but the lessons from the Lysenko experience tell us this situation could last a long time.

—Irving Weissman is professor of pathology and developmental biology at Stanford University, director of the university's Institute for Cancer/Stem Cell Biology and Medicine, and a co-founder of StemCells, Inc., and Cellerant, Inc, both in Palo Alto, Calif.

Growing Pains for the

ES Cell International

In Singapore, a company with ambitious goals leads a "privileged existence"

Singapore-based ES Cell International (ESI) has emerged as one of world's first commercial ventures to focus on developing stem cells for therapeutic purposes.

Established in 2000, ESI sought to draw on the pioneering research of Ariff Bongso and other researchers at the National University of Singapore in growing stem cell lines from human embryos. As part of Singapore's quest to become a global centre of medical research, the government's Economic Development Board agreed to finance ESI in co-operation with several wealthy Australian investors.

The company received a boost in 2001 when ESI was among 10 groups selected by the US National Institutes of Health to have stem cells eligible for federal funding under the Bush administration's stem cell plan. But ESI's original business plan to produce and sell human embryonic stem cell lines promised to produce only "minimal" profits of around $300,000 (£160,000) a year, according to Alan Colman, ESI's new chief executive.

Colman, who gained fame as head of the research team that cloned Dolly the sheep in Scotland, joined ESI in 2002 as its chief scientist with the aim of turning stem cells into treatments for a range of illnesses. One project is to try to induce stem cells to turn into insulin-producing "islet" cells that could be implanted into diabetics.

ESI works closely with researchers from Australia's Monash University, Israel's Hadassah University, the National University of Singapore and the Netherlands' Utrecht University, with the first three holding an 18 per cent stake in the company. ESI would serve as the exclusive worldwide licensee of any resulting patents from their research. ESI has an ambitious goal to gain approval from the US Food and Drug Administration by 2010 for products derived from stem cells that would combat diabetes and heart diseases.

"We have a privileged existence", declares Colman, referring to the financial support given by the Singapore government, which holds a 44 per cent stake in ESI.

Nonetheless, he is worried about whether that support will last long enough for ESI to reap commercial benefits from its research work. "Singapore appears to be shifting its biomedical financing from applied research with start-ups to basic research", he says.

Although ESI has raised a total of $24m in the form of equity investments and loans since 2000, its annual cash "burn" amounts to $3.6m. For ESI, it is a race against time. —*John Burton*

Geron

The former patent powerhouse works on new therapies

California-based Geron was once feared for its patent might. Because the company held exclusive rights to many embryonic stem cells developed at the University of Wisconsin, biotechnology rivals believed the company would establish a stem cell monopoly. In 1999 Geron purchased rights to the cloning technology used to make Dolly the sheep in Scotland, a technique given patent protection by the British government a year later.

The controversy over Geron's extensive patent holdings only subsided in 2002 when the company and the University of Wisconsin reached an agreement that limited Geron's patent rights and promised to allow other scientists access to the stem cell lines.

Today the company is still operating at a loss—$9.7m (£5.2m) in the first three months of 2005—and fears of its domination of the stem cell market have evaporated. Yet Geron is still an important force in this area of research and is expected to be one of the main beneficiaries of a new California fund for stem cell research.

Geron, founded in 1992, was one of the first public companies to study embryonic stem cells. In the late 1990s its attention turned to telomerase, a compound the group identified through its study of stem cells as key to the aging process. Cell levels of telomerase decline as humans age. Geron scientists hope that by boosting amounts of the compound in the body, they can battle diseases such as AIDS and cancer. In March the company founded TA Therapeutics, a joint venture with a Hong Kong University research institute, to explore telomerase applications.

But Geron's interest in embryonic stem cells as a therapy in their own right has been renewed. The company is pursuing research in a wide number of disease areas, including Parkinson's, heart disease, diabetes, arthritis, blood disease, osteoporosis and organ transplantation. While none of the therapies has been tested in humans yet, Geron says it may soon initiate clinical trials in spinal cord injury.

In March the company published research explaining how human embryonic stem cells could be grown without the help of "feeder cells". Feeders such as mouse cells were used to propagate early stem cell populations. Geron had posted research on how to grow the cleaner embryonic stem cells on its Web site in September of 2002, but until this year's publication in the journal Stem Cells, many had doubted the technology really worked.

—*Victoria Griffith*

LUCY READING-IKKANDA

New Industry

STEM CELL CORPORATE LEADERS

ES International www.escellinternational.com	ALAN COLMAN, ESI's chief executive, wants to try to induce stem cells to turn into insulin-producing "islet" cells. Colman had an accomplished career as an academic, which included research and teaching appointments at the University of Oxford and the University of Warwick and the appointment of professor of biochemistry at the University of Birmingham.	
Geron www.geron.com	THOMAS OKARMA, Geron's chief executive, plans to lead his company soon into clinical trials of stem cells for spinal cord injury. Okarma holds an AB from Dartmouth College and an MD and PhD from Stanford University.	
ACT Holdings www.advancedcell.com	MICHAEL WEST, ACT Holding's chairman and president, shifted the corporate focus to embryonic stem cell research. West received an MS in biology from Andrews University in 1982 and a PhD from Baylor College of Medicine in 1989. West recently relinquished the chief executive's position to William M. Caldwell IV (*not shown*).	
Stem Cell Sciences www.stemcellsciencesltd.com	PETER MOUNTFORD shepherds a business plan to commercialise ES cells, first as a research tool and later as cell-based therapies. He received a doctorate from Melbourne University and was a Royal Society (London) Endeavor Fellow at the University of Edinburgh. He is the inventor of technologies that have been widely adopted in stem cell research.	

POLAK MATTHEW/CORBIS SYGMA (*Colman*); GERON CORPORATION (*Okarma*); ACT (*West*); STEM CELL SCIENCES (*Mountford*)

Stem Cell Sciences

Once a "virtual company", it has grown over a decade into the most international force in stem cells

Stem Cell Sciences must be the most global of any stem cell company. SCS has corporate research and development centres in the UK, Japan and Australia and plans to set up a US operation this year. Its bold business plan is based on commercialising human embryonic stem cells, first to sell as a research tool to the pharmaceutical industry and later to develop cell-based therapies.

Peter Mountford, the chief executive, set up SCS in his native Australia as a "virtual company" in 1994, shortly after returning home from a productive period working in Scotland with Austin Smith, the Edinburgh stem cell pioneer. In 2000 it became a real company with employees and staff in Melbourne, and the following year Mountford set up a Japanese operation, SCS KK, in Kobe, where it collaborates with stem cell researchers at the RIKEN Centre for Developmental Biology.

In 2003 Mountford moved back to Scotland and set up SCS's corporate headquarters in Edinburgh. Mike Dexter, a stem cell biologist who had just completed a five-year term as director of the Wellcome Trust, became company chairman. Mountford was attracted by Scotland's emergence as a centre of excellence in stem cell research and above all by the prospect of working again with Smith, who now runs the Institute for Stem Cell Research at Edinburgh University.

SCS directly employs about 40 people—half in Japan and the others divided between Scotland and Australia. Over its lifetime, the company has raised about £5m ($9.25m) from investors and another £5m through collaborative research and licensing deals with pharmaceutical companies, including Pfizer, GlaxoSmithKline and Aventis. Stem cell therapies lie further in the future, with Parkinson's disease one possible target.

While Mountford has nothing but praise for Scotland's scientific credentials and the encouragement his company has received from government bodies such as Scottish Enterprise and the UK Department of Trade and Industry, he is critical of Britain's venture-capital community for failing to see the long-term value in SCS.

The next funding round will focus on American investors, with a possible listing on London's Alternative Investments Market, to raise money to start a US operation. The location for the US development centre has yet to be decided. Mountford says the long-term aim is a Nasdaq listing in New York City, although he wants to keep the corporate headquarters in Scotland. *—Clive Cookson*

ACT Holdings

The tiny company that ignited a political battle over human therapeutic cloning continues to punch above its weight

ACT Holdings has long received attention out of proportion to its size. The tiny biotechnology company employs just a couple dozen people in cramped offices in Worcester, Mass.

The group has attained notoriety for its work in human therapeutic cloning. In 2001 Advanced Cell Technology (ACT), as it was then known, announced it had cloned a short-lived human embryo, igniting a political battle in the US Congress over the practice. In March the British science journal *Lancet* reported that the company had created human embryonic stem cells without using cell "feeders", about the same time rival Geron published similar research. The breakthrough is important because exposing stem cells to mouse or human cell feeders contaminates them, rendering them potentially unusable for medical therapies.

Despite the controversy and excitement surrounding its science, ACT has always operated on a shoestring. Its executives have publicly lamented their tight budgets, saying they have often had trouble paying their small staff.

With a new name and management structure and fresh plans to expand to California, the group is hoping for renewed corporate life. In February the company went public in a "reverse merger" into the shell of a publicly traded group, Two Moons Kachinas. The Utah firm was founded in 2000 to sell Native American ceremonial dolls originally used to promote fertility. The collectible dolls have been forgotten, but the deal allowed ACT to avoid the high cost of an initial public offering.

The group has a new CEO: William Caldwell IV. Former CEO Michael West—who in 1998 left Geron, which he founded, to head ACT—has become chairman and president. At the time of the merger, the company received a much needed infusion of cash, $8m from venture capitalists and private investors. The company hopes its new standing will help it raise even more money. ACT Holdings trades over-the-counter.

While ACT says it will stay in Massachusetts, the company plans to set up a satellite research facility in California to take advantage of the just approved $3bn programme to finance stem cell research.

ACT was founded in 1994 for the purpose of cloning livestock and transgenic animals used to make human medicines in their milk. Although the company still works with animal cloning, the focus shifted under West's leadership to human embryonic stem cell research. The company says it will not pursue cloning for the purpose of reproduction and is only interested in using the technique for regenerative medicine. *—Victoria Griffith*

LUCY READING-IKKANDA

Tough Cell to Investors

Venture capitalists fully understand the rich potential of stem cells. Yet a host of reasons also makes them hesitate to invest, as Nuala Moran explains

Not only is stem cell research the most politicised field in the history of science, it is also one of the most dauntingly complex. So while stem cells have the potential to provide therapies for a vast range of ills, it is proving hard to attract the investment needed to develop them.

Many venture capitalists make the comparison with monoclonal antibodies, which took more than 20 years to translate from basic research to marketed products. As Lutz Giebel, venture partner at SV Life Sciences in San Francisco, remarks: "The promise of monoclonal antibodies was obvious, but VCs [venture capitalists] that invested at an early stage pretty much lost their shirts".

Not that stem cell companies are entirely unattractive. In the first biotech initial public offering of 2005, ViaCell, Inc., a specialist in umbilical cord stem cells, raised $52.5m (£28.4m).

At the point that ViaCell went public, it had annual revenues of $36.8m from umbilical cord blood banking, combined with a cord stem cell product in the clinic, and the potential for forming corporate partnerships. But there are few similar opportunities where the risks inherent in the science are mitigated by a healthy revenue stream.

"ViaCell exemplifies how a lot of VCs feel about the risks of investing in stem cells", says Denise Pollard-Knight, head of Nomura Phase4 Ventures, the VC investment arm of the investment bank Nomura International plc, which was one of ViaCell's major venture-capital backers. "You just have to look at the numbers. VCs have invested $300m to date into stem cell companies as a whole, versus $20bn into other technology platforms".

In many respects this is due to the preliminary nature of the science. G. Steven Burrill, CEO of Burrill & Company in San Francisco, a life sciences merchant bank, says that a VC funding a stem cell company now would be paying for basic research that would ordinarily be carried out in academic laboratories. "We are beginning to see some business plans for stem cell companies, but we are still in the science end of it", he states.

This lack of basic research creates a major risk because it is not clear where the intellectual property might go, says Paul McCubbin, head of Ventures at BTG plc in London. "In the current model if you screen against a receptor and get a hit, you have novel IP; when you stimulate differentiation of stem cells, you have no idea whose IP you might cross", he explains.

Brian Kerr, director at Scottish Equity Partners (SEP) in Glasgow and sees almost every life sciences opportunity in Scotland, examines hundreds of business plans each year. Despite Scotland's scientific standing in the field, SEP has yet to fund a stem cell company. Kerr objects that not only is the science too preliminary, but the business plans per se are too risky.

"Businesses need to be more sophisticated about how they control risk", he says. Stem cells have not been developed as a platform, and too many com-

CORBIS

panies are focusing on a single treatment for a specific disease. "You wouldn't back a conventional science company that had only one product", observes Kerr.

On top of this he believes a further obstacle has developed in Europe, where the funding engine has broken. After the genomics boom and bust, the public markets have continued to shun biotechs, forcing VCs to fund companies for longer. "It's almost impossible to make money in Europe with a first-round investment in any sort of biotech", states Kerr.

The situation in Europe contrasts with Australia where a number of stem cell companies have listed on the Australian Stock Exchange. But Alison Coutts, director of the investment bank eG Capital in Sydney, says these tend to be early stage: "I think Australia is unique in this respect. While there has been a lot of criticism of the Australian Stock Exchange that it lets companies list 'too early'—quite often when there have been no clinical trials on any product—it has been the primary mechanism for funding a lot of great science that we produce here, and it has even started to attract international companies".

Stem cell startups may also get a sympathetic hearing from Bio*One Capital, the investment arm of Singapore's Economic Development Board. "The potential of stem cell research is too enormous for us to ignore", says Swee Yeok Chu, CEO. "We recognised that we need to take a long-term approach in this field". Bio*One Capital mitigates risk by investing in companies at different stages of development, with different research projects and business models.

That public expectations of the ability of stem cells to provide cures for degenerative disease and severe trauma have gotten so far ahead of what the science can to deliver is largely because of the publicity given to small-scale trials with adult stem cells.

But while there is evidence of efficacy, adult stem cells are not attractive to VCs, says Giebel of SV Life Sciences:

BURRILL & COMPANY

"We are beginning to see some business plans for stem cell companies, but we are still in the science end of it".
—G. STEVEN BURRILL

"You just have to look at the numbers. VCs have invested $300m to date into stem cell companies as a whole, versus $20bn into other technology platforms".
—DENISE POLLARD-KNIGHT

"Most people are talking about autologous transplants using cells harvested from patients. But from an investment point of view that's not scalable. It's also difficult for the FDA to get an arm around it. Every single time it is different cells".

While much legwork remains, embryonic stem cells conversely do have the potential to be produced to Good Manufacturing Practice standards.

One VC who has intimate experience of the difficulties of producing potentially commercial stem cell lines is Sir Christopher Evans, founder and chairman of Merlin Biosciences in London. Merlin put £250,000 ($460,000) seed capital into ReNeuron Ltd when it was formed in 1997, followed by £5m a year later. The company went public in November 2000, raising £19.5m and becoming the only quoted stem cell company in Europe.

But ReNeuron was beset by genetic instability problems in its foetal neural stem lines, and in 2003 the Merlin Consortium put fellow investors out of their misery, paying £3.6m to make ReNeuron private again.

The company has since overcome problems with the cell lines and is aiming to get regulatory approval before the end of 2005 (in either the US or the UK) to carry out a clinical trial.

"We have had to pay for work that would normally be done in an academic laboratory, but if ReNeuron came to us today we'd back it again. But as for backing any other stem cell companies—there aren't any", remarks Evans.

This prompted him to form the Stem Cell Foundation, a charity designed to plug the gap between academic research and mid-stage clinical trials. "In three years we should have 10 to 15 projects approaching or in the clinic. With the usual attrition rate this will translate into two or three successes, and we will then get [private investment] money flowing in", says Evans. "The foundation is the catalyst—we will create a phenomenon in stem cells".

Evans is keen to get the foundation up and running before the money starts flowing from California's Proposition 71 and other US state funding schemes for stem cells and thus prompts a brain drain of researchers from the UK to the US.

But the fact that California and other states are raising their own budgets for stem cell research highlights yet another hurdle in the way of its commercialisation. Uniquely, for a medical product, it is unclear whether it will be possible to get a single regulatory approval to sell a stem cell therapy across the US or whether the states with bans on embryonic stem cell research will ban products based on them also.

The situation is no better in Europe, where there is a patchwork of different regulation, most of it militating against embryonic stem cell research.

Cathy Prescott, science director at Avlar BioVentures in Cambridge, UK, says: "The major issue is on the regulatory side of things at the moment. National rules are applying in Europe, and in the US different states have taken a different stance, and therefore there is a fragmented marketplace".

Most biotechnology companies rely on doing deals with big pharmaceutical companies to get their products through the later stages of clinical trials and on to the market.

"The market fragmentation is making stem cells a very, very difficult business model for big pharma", says Prescott. "If biotechs haven't got partners, how can they take it forward"?

No doubt VCs are daunted by the ethical and regulatory baggage surrounding stem cells. Several prominent firms in North America and Europe did not wish to be interviewed for this article. Others were prepared to discuss the scientific challenges but not the baggage.

Proposition 71 will change attitudes, believes Burrill of Burrill & Company: "At present, stem cell science is tainted. Proposition 71 will legitimise a lot of research in the US, which under federal guidelines is perceived to be not investible".

Nuala Moran is UK correspondent for BioWorld.

"Businesses need to be more sophisticated about how they control risk. You wouldn't back a conventional science company that had only one product".
—BRIAN KERR

NOMURA PHASE4 VENTURES (*top*); SCOTTISH EQUITY PARTNERS (*bottom*)

The Search for Cells That Heal

Ian Wilmut, creator of Dolly the cloned sheep, urges looking past the controversies to the ultimate payoff

Extraordinary opportunities to study and to treat human diseases are provided by the recently acquired ability to derive stem cells from human embryos. Because these cells form all of the tissues that make up an adult, they afford a chance to study normal human development in the laboratory, to define the abnormalities associated with inherited disease and, in time, perhaps to treat diseases, many of which have no effective treatment at present.

Consider just three situations among many. Cells derived from embryo cells could be used to repair spinal cord injury. It is far from clear exactly what type of cell should be used, how many cells are needed or where they should be placed. Nevertheless, speedy treatment might provide real benefit.

Cells from cloned embryos will reveal the molecular mechanisms that cause inherited diseases such as amyotrophic lateral sclerosis (known as motor neurone disease in some countries). This will allow us to study the disease process in minute detail for the first time and, more important, to screen thousands of compounds that might potentially arrest or even reverse the degeneration.

Finally, genetic diseases may eventually be corrected in children. Imagine a child who has no immune response to infection because of an error in a specific gene. The error could be corrected in cells derived from a cloned embryo, which might then be converted to bone marrow cells that provide the absent immune response. The corrective marrow cells could then be returned to the child.

COLIN McPHERSON *Corbis*

Clearly, success with embryonic stem cells will depend upon detailed research, and it will take several years, perhaps decades, to bring these ideas to the clinic. Over time, embryo-derived stem cells will revolutionise many aspects of medicine. And yet society hesitates.

In discussing stem cell research, investigators face several critical issues. To some people the idea of producing and using a human embryo is deeply offensive, and these sincerely held views must be recognised. Yet many others do not share these qualms. The early embryo from which stem cells are derived is a ball of cells smaller than a grain of sand. While it has the potential to become a person, it lacks the fundamental human characteristics of being conscious and aware.

An urgent need exists for an informed debate about what we consider to be critical human characteristics, just as there was an equivalent debate about the end of life when decisions were first made to remove organs from accident victims who were brain-dead but had healthy organs.

The potential benefits of stem cells should inspire optimism, but this must also be tempered with the frank admission that we still have far, far more to learn about embryonic stem cells. Unfortunately, the time required for the development of clinical treatments will be beyond that usually accepted by venture-capital investors, and it seems likely that a partnership will be needed between government sources of funds and private capital.

Anyone who knows or has cared for a person with an inherited or degenerative disease knows only too well the great need for new treatments. We should be excited by the opportunity rather than afraid.

Ian Wilmut is Chair in Reproductive Science at the University of Edinburgh in Scotland and a visiting scientist at the Roslin Institute.

Can We Bury GLOBAL WARMING?

Pumping carbon dioxide underground to avoid warming the atmosphere is feasible, but only if several key challenges can be met

By Robert H. Socolow

When William Shakespeare took a breath, 280 molecules out of every million entering his lungs were carbon dioxide. Each time you draw breath today, 380 molecules per million are carbon dioxide. That portion climbs about two molecules every year.

No one knows the exact consequences of this upsurge in the atmosphere's carbon dioxide (CO_2) concentration nor the effects that lie ahead as more and more of the gas enters the air in the coming decades—humankind is running an uncontrolled experiment on the world. Scientists know that carbon dioxide is warming the atmosphere, which in turn is causing sea level to rise, and that the CO_2 absorbed by the oceans is acidifying the water. But they are unsure of exactly how climate could alter across the globe, how fast sea level might rise, what a more acidic ocean could mean, which ecological systems on land and in the sea would be most vulnerable to climate change and how these developments might affect human health and well-being. Our current course is bringing climate change upon ourselves faster than we can learn how severe the changes will be.

If slowing the rate of carbon dioxide buildup were easy, the world would be getting on with the job. If it were impossible, humanity would be working to

STRIPPER TOWERS at an Algerian gas-extraction facility deep in the Sahara Desert chemically separate carbon dioxide from natural gas bound for European markets. The CO_2 is then pumped two kilometers below ground.

adapt to the consequences. But reality lies in between. The task can be done with tools already at hand, albeit not necessarily easily, inexpensively or without controversy.

Were society to make reducing carbon dioxide emissions a priority—as I think it should to reduce the risks of environmental havoc in the future—we would need to pursue several strategies at once. We would concentrate on using energy more efficiently and on substituting noncarbon renewable or nuclear energy sources for fossil fuel (coal, oil and natural gas–the primary sources of manmade atmospheric carbon dioxide). And we would employ a method that is receiving increasing attention: capturing carbon dioxide and storing, or sequestering, it underground rather than releasing it into the atmosphere. Nothing says that CO_2 must be emitted into the air. The atmosphere has been our prime waste repository, because discharging exhaust up through smokestacks, tailpipes and chimneys is the simplest and least (immediately) costly thing to do. The good news is that the technology for capture and storage already exists and that the obstacles hindering implementation seem to be surmountable.

Carbon Dioxide Capture

THE COMBUSTION of fossil fuels produces huge quantities of carbon dioxide. In principle, equipment could be installed to capture this gas wherever these hydrocarbons are burned, but some locations are better suited than others.

If you drive a car that gets 30 miles to the gallon and go 10,000 miles next year, you will need to buy 330 gallons—about a ton—of gasoline. Burning that much gasoline sends around three tons of carbon dioxide out the tailpipe. Although CO_2 could conceivably be caught before leaving the car and returned to the refueling station, no practical method seems likely to accomplish this task. On the other hand, it is easier to envision trapping the CO_2 output of a stationary coal-burning power plant.

It is little wonder, then, that today's capture-and-storage efforts focus on those power plants, the source of one quarter of the world's carbon dioxide emissions. A new, large (1,000-megawatt-generating) coal-fired power plant produces six million tons of the gas annually (equivalent to the emissions of two million cars). The world's total output (roughly equivalent to the production of 1,000 large plants) could double during the next few decades as the U.S., China, India and many other countries construct new power-generating stations and replace old ones [*see illustration on page 52*]. As new coal facilities come online in the coming quarter of a century, they could be engineered to filter out the carbon dioxide that would otherwise fly up the smokestacks.

Today a power company planning to invest in a new coal plant can choose from two types of power systems, and a third is under development but not yet available. All three can be modified for carbon capture. Traditional coal-fired steam power plants burn coal fully in one step in air: the heat that is released converts water into high-pressure steam, which turns a steam turbine that generates electricity. In an unmodified version of this system—the workhorse of the coal power industry for the past century—a mixture of exhaust (or flue) gases exits a tall stack at atmospheric pressure after having its sulfur removed. Only about 15 percent of the flue gas is carbon dioxide; most of the remainder is nitrogen and water vapor. To adapt this technology for CO_2 capture, engineers could replace the smokestack with an absorption tower, in which the flue gases would come in contact with droplets of chemicals called amines that selectively absorb CO_2. In a second reaction column, known as a stripper tower, the amine liquid would be heated to release concentrated CO_2 and to regenerate the chemical absorber.

The other available coal power system, known as a coal gasification combined-cycle unit, first burns coal partially in the presence of oxygen in a gasification chamber to produce a "synthetic" gas, or syngas—primarily pressurized hydrogen and carbon monoxide. After removing sulfur compounds and other impurities, the plant combusts the syngas in air in a gas turbine—a modified jet engine—to make electricity. The heat in the exhaust gases leaving the gas turbine turns water into steam, which is piped into a steam turbine to generate additional power, and then the gas turbine exhaust flows out the stack. To capture carbon from such a facility, technicians add steam to the syngas to convert (or "shift") most of the carbon monoxide into carbon dioxide and hydrogen. The combined cycle system next filters out the CO_2 before burning the remaining gas, now mostly hydrogen, to generate electricity in a gas turbine and a steam turbine.

The third coal power approach, called oxyfuel combustion, would perform all the burning in oxygen instead of air. One version would modify single-step combustion by burning coal in oxygen, yielding a fuel gas with no nitrogen, only CO_2

Overview/*Entombing CO_2*

- A strategy that combines the capture of carbon dioxide emissions from coal power plants and their subsequent injection into geologic formations for long-term storage could contribute significantly to slowing the rise of the atmospheric CO_2 concentration.
- Low-cost technologies for securing carbon dioxide at power plants and greater experience with CO_2 injection to avoid leakage to the surface are key to the success of large-scale CO_2 capture and storage projects.
- Fortunately, opportunities for affordable storage and capture efforts are plentiful. Carbon dioxide has economic value when it is used to boost crude oil recovery at mature fields. Natural gas purification and industrial hydrogen production yield CO_2 at low cost. Early projects that link these industries will enhance the practitioners' technical capabilities and will stimulate the development of regulations to govern CO_2 storage procedures.

COURTESY OF BP plc (*preceding page*)

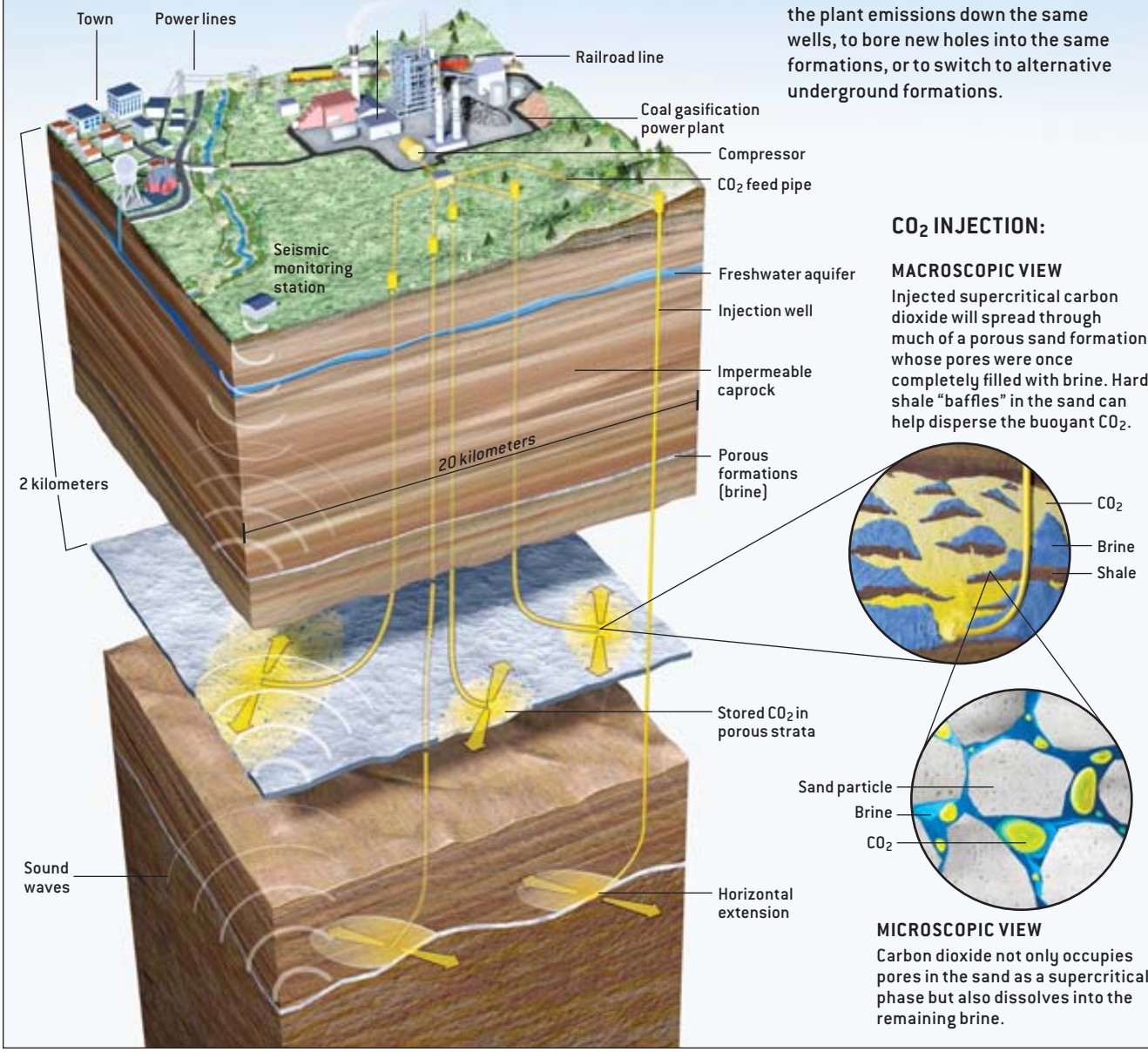
FUTURE FOSSIL-FUEL POWER PLANT

Consider a hypothetical town near a future 1,000-megawatt coal gasification power plant that has been sequestering carbon dioxide for 10 years. The town receives water from a shallow aquifer, unaffected by the CO_2 injection. The rail line transports coal to the plant, and the power lines carry away the electricity it generates.

Some 60 million tons of CO_2 have been captured during the plant's first 10 years of operation, and by now very large pancake-shaped deposits of CO_2 sit in the porous subterranean strata. The carbon dioxide was injected through horizontal wells into two deep brine (saltwater) formations, each located under impermeable caprock more than two kilometers below the surface. At seven tenths the density of water, the high-pressure "supercritical" CO_2 occupies almost 90 million cubic meters. In both formations, 10 percent of the volume is pore space, and a third of the pores are filled with CO_2 [*see insets for detailed views of the porous strata*]. Two thirds of the injected gas has been pumped into the 40-meter-thick upper formation, and one third has been sent into the 20-meter-thick lower formation. As a result, the total (horizontal) area of porous rock soaked with supercritical carbon dioxide in each formation is about 40 square kilometers.

Note that the horizontal and vertical scales depicted here differ. The depth of each injection well and the length of their horizontal extensions are really about equal in length, around two kilometers. Nor are the building structures to scale.

Technicians at a seismic monitoring station keep track of the CO_2 locations by beaming sound waves into the ground. During the power station's initial decade of operation, utility managers learned many details about the local geology by observing how the CO_2 spread through the area. This information will help them decide whether to continue injecting the plant emissions down the same wells, to bore new holes into the same formations, or to switch to alternative underground formations.



CO_2 INJECTION:

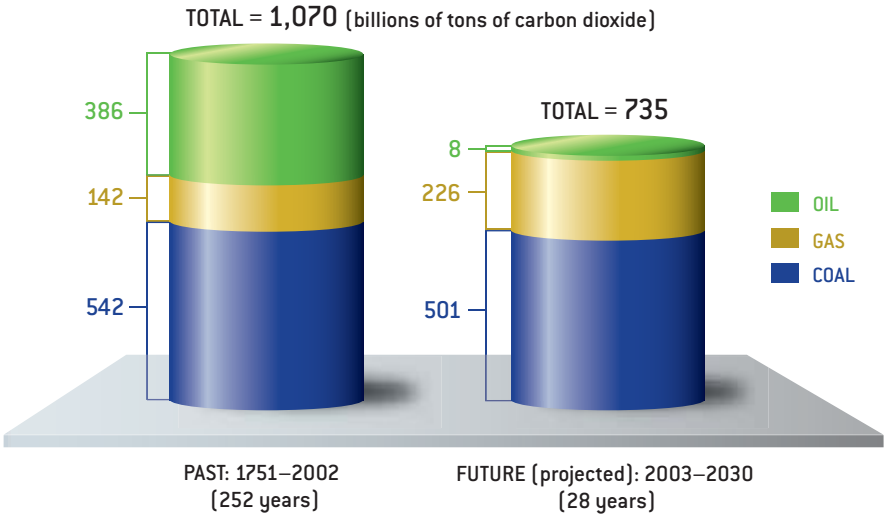
MACROSCOPIC VIEW

Injected supercritical carbon dioxide will spread through much of a porous sand formation whose pores were once completely filled with brine. Hard shale "baffles" in the sand can help disperse the buoyant CO_2.

MICROSCOPIC VIEW

Carbon dioxide not only occupies pores in the sand as a supercritical phase but also dissolves into the remaining brine.

ILLUSTRATION BY DAVID FIERSTEIN; CONCEPT BY JULIO FRIEDMANN *Lawrence Livermore National Laboratories*



LIFETIME FOSSIL-FUEL EMISSIONS from power plants projected to be built during the next quarter of a century will be comparable to all the emissions during the past 250 years. The left column shows the cumulative carbon dioxide emissions produced by burning coal, oil and natural gas for all uses (including transportation and building heating) from 1751 to 2002, whereas that on the right depicts the lifetime CO_2 emissions from fossil-fuel power generation plants projected by the International Energy Agency to come online between 2003 and 2030. Coal-fired power plants are assumed to operate for 60 years and gas-fired power stations for 40 years.

and water vapor, which are easy to separate. A second version would modify the coal gasification combined-cycle system by using oxygen, rather than air, at the gas turbine to burn the carbon monoxide and hydrogen mixture that has exited the gasifier. This arrangement skips the shift reaction and would again produce only CO_2 and water vapor. Structural materials do not yet exist, though, that can withstand the higher temperatures that are created by combustion in oxygen rather than in air. Engineers are exploring whether reducing the process temperature by recirculating the combustion exhaust will provide a way around these materials constraints.

Tough Decisions

MODIFICATION FOR carbon dioxide capture not only adds complexity and expense directly but also cuts the efficiency of extracting energy from the fuel. In other words, safely securing the carbon by-products means mining and burning more coal. These costs may be partially offset if the plant can filter out gaseous sulfur simultaneously and store it with the CO_2, thus avoiding some of the considerable expense of sulfur treatment.

Utility executives want to maximize profits over the entire life of the plant, probably 60 years or more, so they must estimate the expense of complying not only with today's environmental rules but also with future regulations. The managers know that the extra costs for CO_2 capture are likely to be substantially lower for coal gasification combined-cycle plants than for traditional plants. Removing carbon dioxide at high pressures, as occurs in a syngas operation, costs less because smaller equipment can be employed. But they also know that only a few demonstration gasification plants are running today, so that opting for gasification will require spending extra on backup equipment to ensure reliability. Hence, if the management bets on not having to pay for CO_2 emissions until late in the life of its new plant, it will probably choose a traditional coal plant, although perhaps one with the potential to be modified later for carbon capture. If, however, it believes that government directives to capture CO_2 are on their way within a decade or so, it may select a coal gasification plant.

To get a feel for the economic pressures the extra cost of carbon sequestration would place on the coal producer, the power plant operator and the home owner who consumes the electricity, it helps to choose a reasonable cost estimate and then gauge the effects. Experts calculate that the total additional expense of capturing and storing a ton of carbon dioxide at a coal gasification combined-cycle plant will be about $25. (In fact, it may be twice that much for a traditional steam plant using today's technology. In both cases, it will cost less when new technology is available.)

The coal producer, the power plant operator and the home owner will perceive that $25 cost increase quite differently. A coal producer would see a charge of about $60 per ton of coal for capturing and storing the coal's carbon, roughly tripling the cost of coal delivered to an electric utility customer. The owner of a new coal power plant would face a 50 percent rise in the cost of power the coal plant puts on the grid, about two cents per kilowatt-hour (kWh) on top of a base cost of around four cents per kWh. The home owner buying only coal-based electricity, who now pays an average of about 10 cents per kWh, would experience one-fifth higher electricity costs (provided that the extra two cents per kWh cost for capture and storage is passed on without increases in the charges for transmission and distribution).

First and Future Steps

RATHER THAN WAITING for the construction of new coal-fired power plants to begin carbon dioxide capture and storage, business leaders are starting the process at existing facilities that produce hydrogen for industry or purify natural gas (methane) for heating and power generation. These operations currently generate concentrated streams of CO_2. Industrial hydrogen production processes, located at oil refineries and ammonia plants, remove carbon dioxide from a

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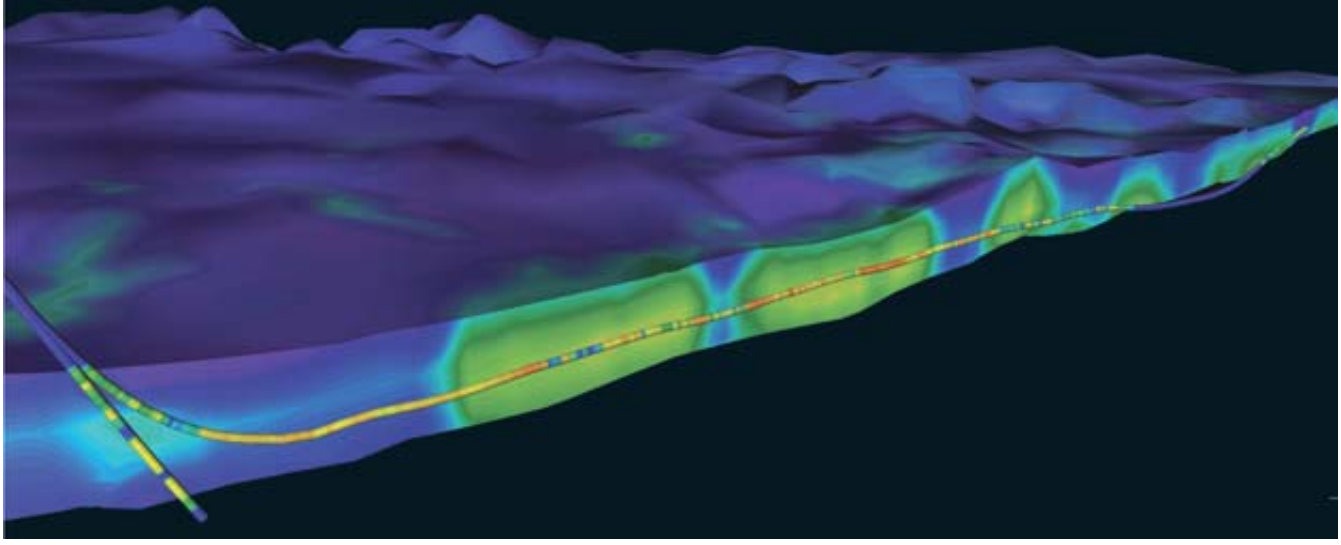
ILLUSTRATION BY ALISON KENDALL; CONCEPT BY DAVID HAWKINS *Natural Resources Defense Council*; PAST DATA FROM GREGG MARLAND *Oak Ridge National Laboratory*



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POROSITY OF A GEOLOGIC FORMATION near a carbon dioxide injection well (*thin tubing*) at the Krechba field in the Algerian desert was revealed by two sets of measurements. (Red and yellow represent high porosity regions of the 20-meter-thick reservoir; blue indicates low porosity areas.) BP engineers used the coarse mapping of the geologic layers, which was derived from seismic echolocation soundings, to determine where best to place the well. A down-hole electric sensor probe, which gave a finer depiction of porosity (looking like colored beads), revealed porosity within a few centimeters of the well. Engineers employed these more accurate readings to hunt for and steer the drilling apparatus toward regions of high porosity.

high-pressure mix of CO_2 and hydrogen, leaving behind carbon dioxide that is released skyward. Natural gas purification plants must remove CO_2 because the methane is heading for a liquefied natural gas tanker and must be kept free of cold, solid carbon dioxide (dry ice) that could clog the system or because the CO_2 concentration is too high (above 3 percent) to be allowed on the natural gas distribution grid.

Many carbon dioxide capture projects using these sources are now under consideration throughout the oil and gas industry. Hydrogen production and natural gas purification are the initial stepping-stones to full-scale carbon capture at power plants; worldwide about 5 percent as much carbon dioxide is produced in these two industries as in electric power generation.

In response to the growing demand for imported oil to fuel vehicles, some nations, such as China, are turning to coal to serve as a feedstock for synthetic fuels that substitute for gasoline and diesel fuel. From a climate change perspective, this is a step backward. Burning a coal-based synthetic fuel rather than gasoline to drive a set distance releases approximately double the carbon dioxide, when one takes into account both tailpipe and synfuels plant emissions. In synthetic fuels production from coal, only about half the carbon in the coal ends up in the fuel, and the other half is emitted at the plant. Engineers could modify the design of a coal synfuels plant to capture the plant's CO_2 emissions. At some point in the future, cars could run on electricity or carbon-free hydrogen extracted from coal at facilities where CO_2 is captured.

Electricity can also be made from biomass fuels, a term for commercial fuels derived from plant-based materials: agricultural crops and residues, timber and paper industry waste, and landfill gas. If the fossil fuels used in harvesting and processing are ignored, the exchanges between the atmosphere and the land balance because the quantity of carbon dioxide released by a traditional biomass power plant nearly equals that removed from the atmosphere by photosynthesis when the plants grew. But biomass power can do better: if carbon capture equipment were added to these facilities and the harvested biomass vegetation were replanted, the net result would be to scrub the air of CO_2. Unfortunately, the low efficiency of photosynthesis limits the opportunity for atmospheric scrubbing because of the need for large land areas to grow the trees or crops. Future technologies may change that, however. More efficient carbon dioxide removal by green plants and direct capture of CO_2 from the air (accomplished, for example, by flowing air over a chemical absorber) may become feasible at some point.

Carbon Dioxide Storage

CARBON CAPTURE is just half the job, of course. When an electric utility builds a 1,000-megawatt coal plant designed to trap CO_2, it needs to have somewhere to stash securely the six million tons of the gas the facility will generate every year for its entire life. Researchers believe that the best destinations in most cases will be underground formations of sedimentary rock loaded with pores now filled with brine (salty water). To be suitable, the sites typically would lie far below any source of drinking water, at least 800 meters under the surface. At 800 meters, the ambient pressure is 80 times that of the atmosphere, high enough that the pressurized injected CO_2 is in a "supercritical" phase—one that is nearly as dense as the brine it replaces in geologic formations. Sometimes crude oil or natural gas will also be found in the brine formations, having invaded the brine millions of years ago.

The quantities of carbon dioxide sent belowground can be expressed in "barrels," the standard 42-gallon unit of volume employed by the petroleum industry. Each year at a 1,000-megawatt coal plant modified for carbon capture, about 50 million barrels of supercritical carbon dioxide would be secured—about 100,000 barrels a day. After 60 years of operation, about three billion barrels (half a cubic kilometer) would be sequestered below the surface. An oil field with a capacity to produce three billion barrels is six times the size of the smallest of what the industry calls "giant" fields, of which some 500 exist. This means that each large modified coal plant would need to be associated with a "giant" CO_2 storage reservoir.

Alternative CO_2 Storage Schemes

Captured carbon dioxide might be stored not only in depleted oil and gas reservoirs and subterranean brine formations but also in minerals that form carbonate compounds, in coal seams and in the deep ocean.

Minerals that can become carbonates could potentially sequester even more carbon dioxide on the earth's surface than brine formations could store underground. The magnesium oxide in two abundant iron-magnesium minerals, serpentine and olivine, combines with CO_2 to produce highly stable magnesium carbonate. The big challenge is to get CO_2 to react quickly with bulk quantities of these rocks, perhaps by grinding them into fine powders to increase the surface area at which the chemical reactions occur.

The pore surfaces within coal formations adsorb methane. During mining, some of this methane can be released, too often causing underground explosions and, consequently, the deaths of miners. Pressurized carbon dioxide could be introduced into unexploited coal seams where it would replace the adsorbed methane, which could then be recovered and sold as fuel.

Ocean injection of carbon dioxide is controversial. Advocates of storage in the deep ocean point out that atmospheric CO_2 passes continuously into the ocean surface, as the air and ocean system seeks chemical equilibrium. Slowing the increase of CO_2 levels in the air will reduce the amount dissolving into the surface water. Thus, deep-ocean injection would shift some CO_2 from the surface waters to the lowest layers, reducing environmental impacts near the surface, where most marine life is found. Opponents of ocean storage cite international law that protects the oceans from certain kinds of industrial uses and the difficulties of monitoring carbon dioxide transport after injection. In many parts of the world, opponents tap into a strong cultural preference for leaving the oceans alone. —*R.H.S.*

About two thirds of the 1,000 billion barrels of oil the world has produced to date has come from these giant oil fields, so the industry already has a good deal of experience with the scale of the operations needed for carbon storage.

Many of the first sequestration sites will be those that are established because they can turn a profit. Among these are old oil fields into which carbon dioxide can be injected to boost the production of crude. This so-called enhanced oil recovery process takes advantage of the fact that pressurized CO_2 is chemically and physically suited to displacing hard-to-get oil left behind in the pores of the geologic strata after the first stages of production. In this process, compressors drive CO_2 into the oil remaining in the deposits, where chemical reactions result in modified crude oil that moves more easily through the porous rock toward production wells. In particular, CO_2 lowers crude oil's interfacial tension—a form of surface tension that determines the amount of friction between the oil and rock. Thus, carbon dioxide injects new life into old fields.

In response to British government encouragement of carbon dioxide capture and storage efforts, oil companies are proposing novel capture projects at natural gas power plants that are coupled with enhanced oil recovery ventures at fields underneath the North Sea. In the U.S., operators of these kinds of fields can make money today while paying about $10 to $20 per ton for carbon dioxide delivered to the well. If oil prices continue to rise, however, the value of injected CO_2 will probably go up because its use enables the production of a more valuable commodity. This market development could lead to a dramatic expansion of carbon dioxide capture projects.

Carbon sequestration in oil and gas fields will most likely proceed side by side with storage in ordinary brine formations, because the latter structures are far more common. Geologists expect to find enough natural storage capacity to accommodate much of the carbon dioxide that could be captured from fossil fuels burned in the 21st century.

Storage Risks

TWO CLASSES of risk must be addressed for every candidate storage reservoir: gradual and sudden leakage. Gradual release of carbon dioxide merely returns some of the greenhouse gas to the air. Rapid escape of large amounts, in contrast, could have worse consequences than not storing it at all. For a storage operation to earn a license, regulators will have to be satisfied that gradual leakage can occur only at a very slow rate and that sudden leakage is extremely unlikely.

Although carbon dioxide is usually harmless, a large, rapid release of the gas is worrisome because high concentrations can kill. Planners are well aware of the terrible natural disaster that occurred in 1986 at Lake Nyos in Cameroon: carbon dioxide of volcanic origin slowly seeped into the bottom of the lake, which sits in a crater. One night an abrupt overturning of the lake bed let loose between 100,000 and 300,000 tons of CO_2 in a few hours. The gas, which is heavier than air, flowed down through two valleys, asphyxiating 1,700 nearby villagers and thousands of cattle. Scientists are studying this tragedy to ensure that no similar man-made event will ever take place. Regulators of storage permits will want assurance that leaks cannot migrate to belowground confined spaces that are vulnerable to sudden release.

Gradual leaks may pose little danger to life, but they could still defeat the climate goals of sequestration. Therefore, researchers are examining the conditions likely to result in slow seepage. Carbon dioxide, which is buoyant in brine, will rise until it hits an impermeable geologic layer (caprock) and can ascend no farther.

Carbon dioxide in a porous formation is like hundreds of helium balloons, and the solid caprock above is like a circus tent. A balloon may escape if the tent has a tear in it or if its surface is tilted to allow a path for the balloon to move sideways and up. Geologists will have to search for faults in the caprock that could allow escape as well as determine the amount of injection pressure that

UNDERGROUND STORAGE of carbon dioxide is being performed today at the In Salah gas project in the Algerian desert. The raw natural gas produced at this site by BP, Statoil and Sonatrach contains too much CO_2 for commercial use, so the excess is removed by chemical absorbers (*two pairs of stripper towers at center of plant*), compressed and then injected under pressure into a brine formation two kilometers below the surface. Subterranean injection proceeds at a rate that is only about six times less than what would be required at a 1,000-megawatt coal gasification plant fitted for CO_2 capture and storage.

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could fracture it. They will also evaluate the very slow horizontal flow of the carbon dioxide outward from the injection locations. Often the sedimentary formations are huge, thin pancakes. If carbon dioxide is injected near the middle of a pancake with a slight tilt, it may not reach the edge for tens of thousands of years. By then, researchers believe, most of the gas will have dissolved in the brine or have been trapped in the pores.

Even if the geology is favorable, using storage formations where there are old wells may be problematic. More than a million wells have been drilled in Texas, for example, and many of them were filled with cement and abandoned. Engineers are worried that CO_2-laden brine, which is acidic, could find its way from an injection well to an abandoned well and thereupon corrode the cement plug and leak to the surface. To find out, some researchers are now exposing cement to brine in the laboratory and sampling old cements from wells. This kind of failure is less likely in carbonate formations than in sandstone ones; the former reduce the destructive potency of the brine.

The world's governments must soon decide how long storage should be maintained. Environmental ethics and traditional economics give different answers. Following a strict environmental ethic that seeks to minimize the impact of today's activities on future generations, authorities might, for instance, refuse to certify a storage project estimated to retain carbon dioxide for only 200 years. Guided instead by traditional economics, they might approve the same project on the grounds that two centuries from now a smarter world will have invented superior carbon disposal technology.

The next few years will be critical for the development of carbon dioxide capture-and-storage methods, as policies evolve that help to make CO_2-emission reduction profitable and as licensing of storage sites gets under way. In conjunction with significant investments in improved energy efficiency, renewable energy sources and, possibly, nuclear energy, commitments to capture and storage can reduce the risks of global warming. SA

MORE TO EXPLORE

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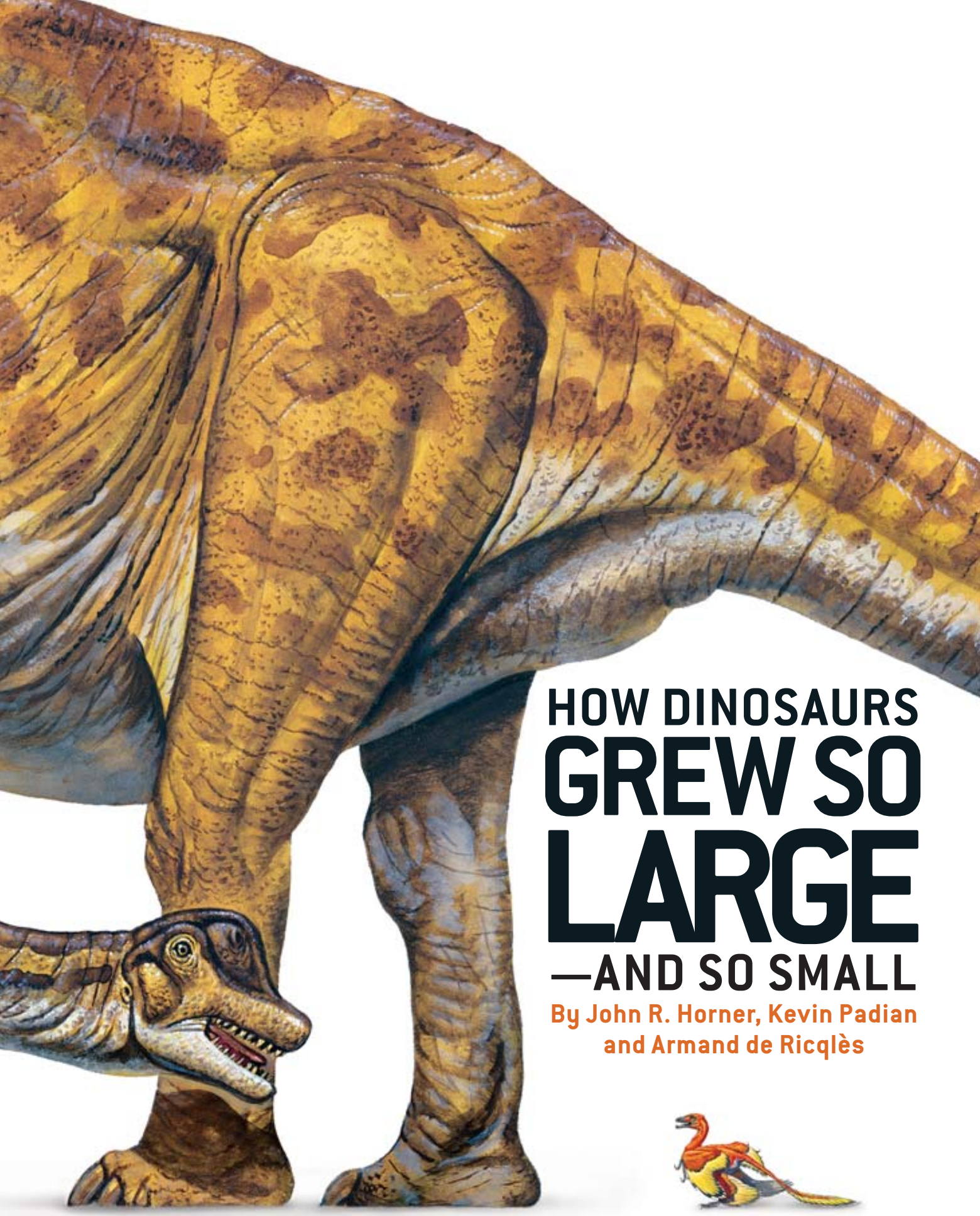
Intergovernmental Panel on Climate Change (IPCC): **www.ipcc.ch/index.html** (Look for the "Special Report on Carbon Dioxide Capture and Storage" expected in late 2005.)

International Energy Agency (IEA) Greenhouse Gas R&D Program: **www.ieagreen.org.uk/index.html**

Office of Fossil Energy, U.S. Department of Energy: **www.fe.doe.gov/programs/sequestration/**

CO_2 Capture Project: **www.co2captureproject.org**

ONE OF THE LARGEST dinosaurs, *Brachiosaurus* reached adulthood in less than 20 years and the chicken-sized *Microraptor* in far less time. Scientists can measure the age of extinct animals by examining annual growth lines in the ancient bones and calculating rates of bone tissue growth in living animals.



HOW DINOSAURS GREW SO LARGE —AND SO SMALL

By John R. Horner, Kevin Padian and Armand de Ricqlès

Most people can stand comfortably under the jawline of a mounted *Tyrannosaurus rex* or walk under the rib cage of a *Brachiosaurus* without bumping their heads. *T. rex* is as big as the largest known African elephant, and *Brachiosaurus,* like other great sauropods, was much larger than any land animal alive today. We are so used to the enormous size of dinosaurs that we almost forget to think about how they grew to be so large. How long did it take them, and how long did they live? And does the way they grew tell us about the way their bodies worked?

Until recently, we had no way to measure age in a dinosaur. Paleontologists had generally assumed that because dinosaurs were reptiles, they probably grew much as reptiles do today—that is, rather slowly. Thus, the thinking went, large dinosaurs must have reached very old ages indeed, but no one knew how old, because no living reptiles attain anything near the size of a dinosaur.

This attitude can be traced back to English paleontologist Sir Richard Owen. When he named the Dinosauria in 1842, he was putting a label on a very small, poorly known group of very large, unusual reptiles. Not only were they big, he said, but they were terrestrial, unlike the seagoing ichthyosaurs and plesiosaurs that had been known since the early 1800s. They had five vertebrae (backbones) connected to the hips, not two like living reptiles. And they held their limbs underneath their bodies, not sprawled out to the sides. Despite these differences, he continued, the anatomical features of their bones—the shapes, joints and muscle attachments—showed them to be reptiles. So they must have had a reptilian physiology—that is, a typically "cold-blooded," slow metabolism. The image stuck, and well into the 1960s dinosaurs were portrayed as sluggish, lumbering beasts that must have grown slowly to great size in a sort of benign hothouse where huge beasts reigned and raged.

Yet evidence for the ages of dinosaurs, and so for how they must have grown, was there all the time—locked inside the bones themselves. Although paleontologists had known for many years that the bones of dinosaurs contain growth lines, something like the circumferential growth rings we see in trees, it was only in the second half of the 20th century that they began to use these growth lines and other structures inside the bones to figure out how these extinct animals actually grew.

The Bones Tell the Story

LIKE THE RINGS in trees, the lines in the bones of dinosaurs were annual. But they aren't quite as simple to interpret. A tree carries nearly the entire record of its growth inside its trunk. Cut it down, and you can count the rings one by one from the center to the bark. Only the outer layer is making new wood; the inside is really deadwood. The center of a bone, in contrast, is a busy place. Cells called osteoclasts hollow out the center of a long bone, such as the femur (thigh) or tibia (shin), by breaking down existing bone and allowing its nutrients to be recycled. This center, or marrow cavity, is also the factory that produces red blood cells [*see box on opposite page*].

To accomplish these tasks, the whole bone constantly grows and changes throughout life. As a bone grows, new tissue is deposited on the outside, and in the long bones growth also occurs at the ends of the shafts. Meanwhile, in the marrow cavity, osteoclasts are eroding the bone that was deposited early in life, and other cells are making secondary bone tissue along the perimeter of the cavity or invading the cortex (outer layer) of the remaining bone to remodel it.

This activity at the center of the bone often erodes the record of growth during the youngest stages of an individual's life. Consequently, it is difficult to cut open the bone of a dinosaur and find a complete record of growth just by counting the rings. So we reconstruct the early history of the bone in several ways. One is to use the bones of younger individuals to fill in the missing record. These younger bones contain the tissues that have been eroded in older bones. By examining these tissues and counting the growth lines, we can approximate the number of years that are missing from the older bones. When we have no juveniles available, we can "retrocalculate" the number of growth lines by examining distances between growth lines that are preserved.

We recently tried retrocalculation on the most famous dinosaur of all: *T. rex*. The Museum of the Rockies at Montana State University has a dozen specimens of this giant carnivore, and seven of them have reasonably well preserved hind-limb bones that allowed us to make thin sections—slices of the bone that are so thin they can be examined under a microscope.

The microscopic slides of *T. rex* limbs revealed only four to eight preserved growth lines. Others, near the

Overview/*Growing Fast to Great Size*

- Until recently, we had no way to measure the age of dinosaurs and thus to figure out how they grew.
- It turns out that this information has been locked in the animals' bones all along—many of the bones contain growth lines, something like the rings in trees.
- Using these lines and other structures within the bone, scientists have now shown that dinosaurs grew to full size quickly—much in the way that birds and mammals do today and not at all like the more slowly growing living reptiles.
- This fast growth implies that these ancient creatures had a high metabolic rate closer to that of warm-blooded animals than to cold-blooded reptiles.

MARK HALLETT (*preceding pages*)

center, had been obscured by the growth of secondary bone tissue. Even more striking, the marrow cavity is so large in these dinosaurs that two thirds of the original bone cortex is eroded away. We also noticed that in some individuals the space between the growth lines suddenly became very small toward the outermost surface of the bone. We had seen this before in other dinosaurs, such as the plant-eating duckbill *Maiasaura*. It signifies the end of active growth, essentially the point at which the animal reached full size.

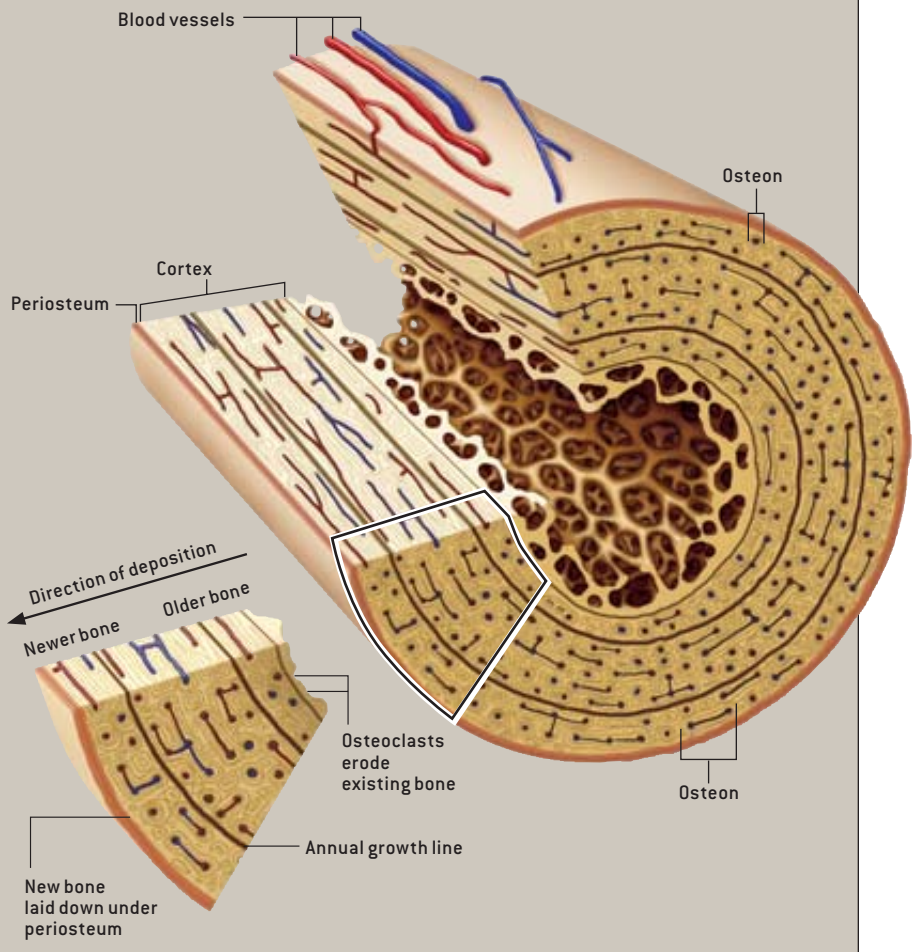
Our retrocalculations estimated that *T. rex* took 15 to 18 years to attain full size, which is to say a hip height of three meters (10 feet), a length of 11 meters (34 feet), and a weight of 5,000 to 8,000 kilograms (five to eight tons). (We were pleased to see that our estimates matched those of Gregory M. Erickson of Florida State University and his colleagues, which were completed at about the same time.) If that seems like rapid growth, it is. At least, for a reptile. It turns out that dinosaurs grew much faster than other living or extinct reptiles do.

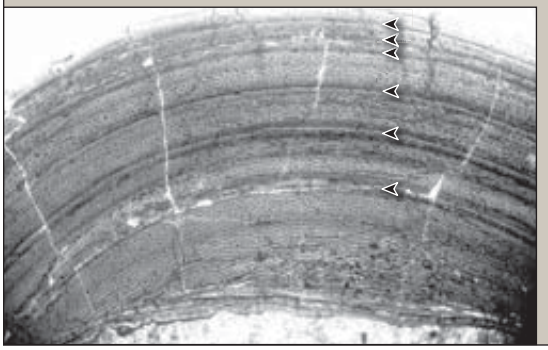
For example, Erickson and Christopher A. Brochu of the University of Iowa charted the growth of the giant crocodile *Deinosuchus,* which lived during the Cretaceous period, some 75 million to 80 million years ago [*see illustration on next page*]. These huge reptiles reached estimated lengths of 10 to 11 meters. Examining the growth lines in the skin armor of the neck, Erickson and Brochu determined that such an animal required nearly 50 years to reach this length—three times as long as it took *T. rex* to reach the same size. A closer comparison for *T. rex* proves to be the African elephant, which reaches about the same mass (5,000 to 6,500 kilograms) in 25 to 35 years. So *T. rex* grew to its adult size even faster than an elephant does.

Further research showed that *T. rex* is not unusual for dinosaurs—except that it actually grew a little bit more slowly for its size than other large dinosaurs did. Anusuya Chinsamy-Turan, now at the University of Cape Town in South Africa, found that the plant-eat-

READING A DINOSAUR BONE

The bones of dinosaurs contain growth lines, somewhat similar to the annual rings in trees, although they are more complicated to interpret. The cortex of bone is built by minerals such as calcium phosphate and proteins such as collagen, which are carried by blood vessels. When the vascular canals, which contain the blood vessels, begin to deposit bone along their insides in concentric layers, they are called osteons. In the femur, or thighbone, and other long bones, growth is concentrated just underneath an outer membrane, the periosteum. Meanwhile the inner margin of the bone is being eaten away by osteoclast cells. A secondary series of osteons may invade preexisting bone, eroding it and depositing new bone. Because of all this activity, researchers cannot simply slice open a dinosaur bone and determine the age of the animal, but they can gain such information by performing various analyses of the rings and other features.

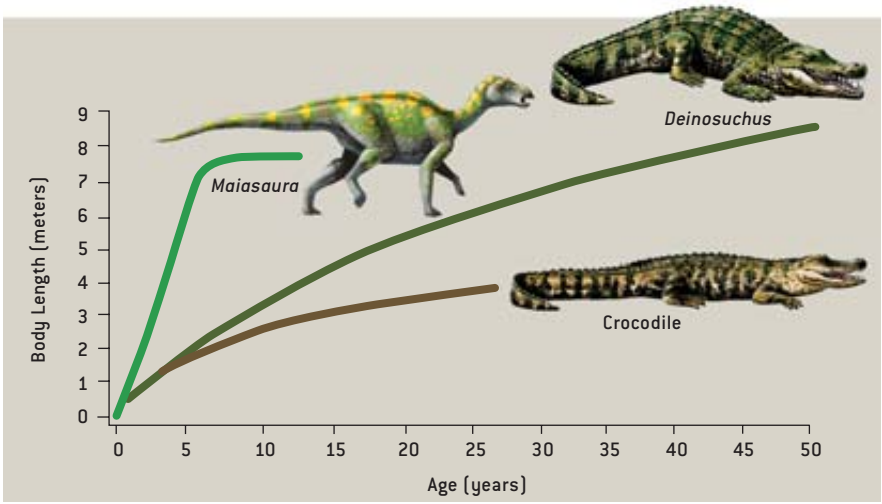




GROWTH LINES

The annual growth lines in the diagram above left can be seen in the photograph of the inside of the femur of *Troodon,* a small carnivorous dinosaur. These lines (*arrows*) become more closely spaced toward the outside of the bone, which was deposited in the later period of growth when the animal was slowing its growth, as we all do with age.

SHAWN GOULD (*illustrations*); JOHN R. HORNER, KEVIN PADIAN AND ARMAND DE RICQLÈS (*photograph*)



GROWTH CURVES show that even the largest dinosaurs were actually teenagers when they reached their huge sizes. They grew to adult size far faster than conventional reptiles do.

ing *Massospondylus* took about 15 years to reach a length of two to three meters. Erickson and Tatanya A. Tumanova of the Paleontological Institute in Moscow found that the small ceratopsian (horned) *Psittacosaurus* was mature at 13 to 15 years. And we calculated that the duckbill *Maiasaura* reached adulthood at between seven and eight years, by which time it was seven meters long. The giant sauropods ("brontosaur" types) outdo all the others, though: Martin Sander of the University of Bonn in Germany discovered that *Janenschia* reached maturity at about 11 years, although it continued to grow substantially after that. Frédérique Rimblot-Baly and her colleagues at the University of Paris VII determined that *Lapparentosaurus* attained full size before it was 20 years old. Kristina Curry Rogers of the Science Museum of Minnesota found that *Apatosaurus* (more familiarly known as *Brontosaurus*) matured in eight to 10 years—an annual weight gain of nearly 5,500 kilograms.

Inside a Dinosaur Bone

WHY SHOULD dinosaurs grow more like elephants than like giant crocodiles? And what does this mean for other aspects of their biology? To answer these questions, we have to look inside a dinosaur bone at the kind of tissues it laid down.

The tissue in a typical long bone of a dinosaur is primarily a type called fibrolamellar: it is highly fibrous or "woven" in texture, and it forms around a matrix of poorly organized collagenous fibers that is well supplied with blood vessels. In contrast to what we would expect in conventional reptiles, this is the same kind of tissue that predominates in the bones of large birds and large mammals,

EARLY BIRDS

Do new insights about the rapid pace at which extinct dinosaurs grew give us any new information about the evolution of birds, the living dinosaurs? Why, for example, are birds so much smaller than extinct dinosaurs? Did they change their growth rates somehow? We began looking into these questions by examining the bone tissues of *Confuciusornis*, an ancient bird from the Early Cretaceous (125 million years ago) of China that appears on the avian family tree shortly after *Archaeopteryx*, the first known bird. The inner part of the bone tissues of the crow-sized *Confuciusornis* is of a fast-growing, fibro-lamellar type (like those of other dinosaurs), but toward the outside it becomes a slower-growing type—a sign that the growth rate waned after a short, youthful spurt. We compared these tissues with those of *Troodon*, a small raptorlike dinosaur about 1.5 meters long, which David J. Varricchio of Montana State University had studied. *Troodon* tissues indicate faster growth overall.

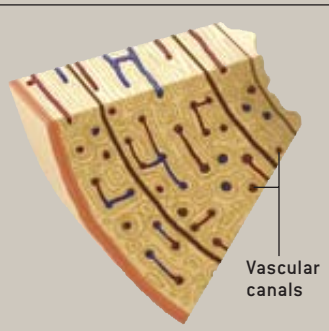
As *Confuciusornis* shows, to become small these ancient bird species truncated the juvenile burst of growth that was most rapid in other dinosaurs, which caused the birds in effect to become miniaturized. Miniaturization had an important influence on locomotion, because the feathers that were present on the forelimbs of the closest dinosaurian relatives of birds would have been more likely to help these smaller animals become airborne. Small animals can flap their wings faster than large ones, and in a smaller animal the wing loading (the ratio of weight to wing area, or how much a given unit of area has to carry) will be proportionally smaller and so aerodynamically more advantageous.

But birds today reach full size quickly, usually in weeks to months. What changed? It appears that after slowing early in their evolution, birds over time sped up their growth rate again—to rates that are often even faster than those in extinct dinosaurs. Some years ago Anusuya Chinsamy-Turan, now at the University of Cape Town, and her colleagues studied the bone tissue of early birds a bit farther along the evolutionary tree than *Archaeopteryx* and *Confuciusornis*. These Late Cretaceous birds included a primitive enantiornithine, the flightless *Patagopteryx,* the diving *Hesperornis,* and the ternlike *Ichthyornis* [*see box on pages 62 and 63*]. They, too, grew more slowly than dinosaurs, but the forms closer to living birds had tissues that indicated somewhat more rapid growth than in the very early birds.

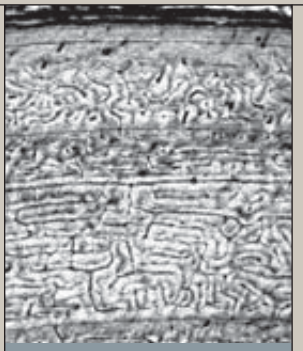
Close to the Cretaceous-Tertiary boundary, about 65 million years ago, growth rates increased substantially, so much so that all living birds—even the ostrich—attain full size within less than a year (seven days in the case of the sparrow). Only examination of birds from the Early Tertiary will tell us whether the living groups of birds acquired their habit of rapid growth to adult size gradually or relatively suddenly. *—J.R.H., K.P. and A.d.R.*

SHAWN GOULD (*illustrations*); JEN CHRISTIANSEN (*graph*)

DINOSAURS DIDN'T GROW LIKE REPTILES



FIBRO-LAMELLAR BONE TISSUE



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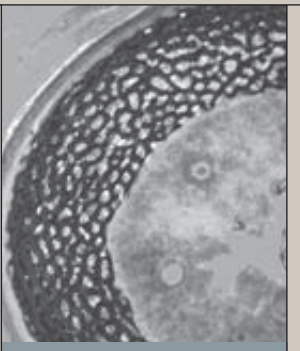

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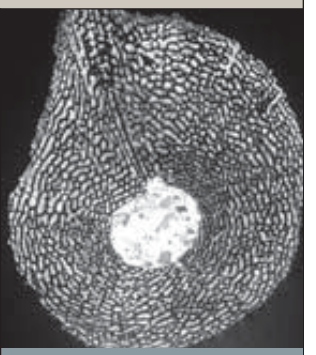

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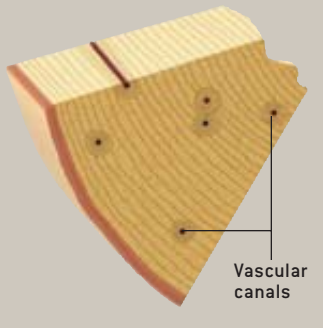
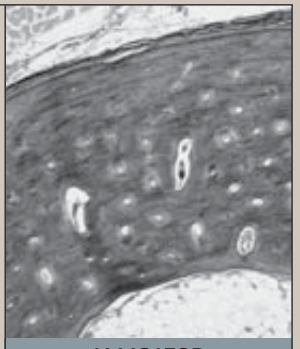


LAMELLAR-ZONAL BONE TISSUE



ALLIGATOR

Dinosaur bones, on the inside, look much like the bones of large birds and mammals (*above*). These animals, unlike reptiles (*left*), lay down a type of bone tissue called fibro-lamellar, which grows on a scaffold of minerals and collagen fibers that are produced in discrete layers. Their bone tissue is usually very well vascularized. Lots of blood vessels imply rapid deposition of tissue, and so rapid growth. The elk and alligator bones shown here are of nearly mature individuals. Toward the outside of the bone are far fewer vascular canals, reflecting a slowing of growth. The *Maiasaura* and ostrich bones are from near-hatchling individuals. The vascular spaces in their bones are copious, indicating very rapid growth that has not yet settled into the fibro-lamellar pattern.

which grow to full size faster than typical reptiles do. A crocodile bone, on the other hand, is formed mostly of lamellar-zonal tissue—compact, highly mineralized bone that contains more regularly organized fibers and much sparser, smaller vascular canals. Furthermore, the growth lines in crocodile bones are more tightly spaced than those in dinosaur bones, another indication that crocodile bones grow more slowly [*see box above*].

Rodolfo Amprino of the University of Turin in Italy recognized in the 1940s that the type of tissue laid down in a bone at any given place or time during growth was mainly a function of how fast the tissue was growing at that point. Fibro-lamellar tissue, no matter where or when it is deposited, reflects locally rapid growth, whereas lamellar-zonal tissue signals slower growth. An animal can lay down either of these tissues at different times—as the growth strategy warrants. The type of tissue that predominates through the animal's life provides the best guide to its growth rate.

One difference between dinosaurs, on the one hand, and crocodiles and other reptiles, on the other, is that dinosaurs deposit fibro-lamellar tissue all through growth to adult size, whereas other reptiles switch very soon to lamellar-zonal bone. We inferred from this that dinosaurs sustained more rapid growth until the adult stage, because there would be no other good explanation for the persistence and predominance of fibro-lamellar tissue.

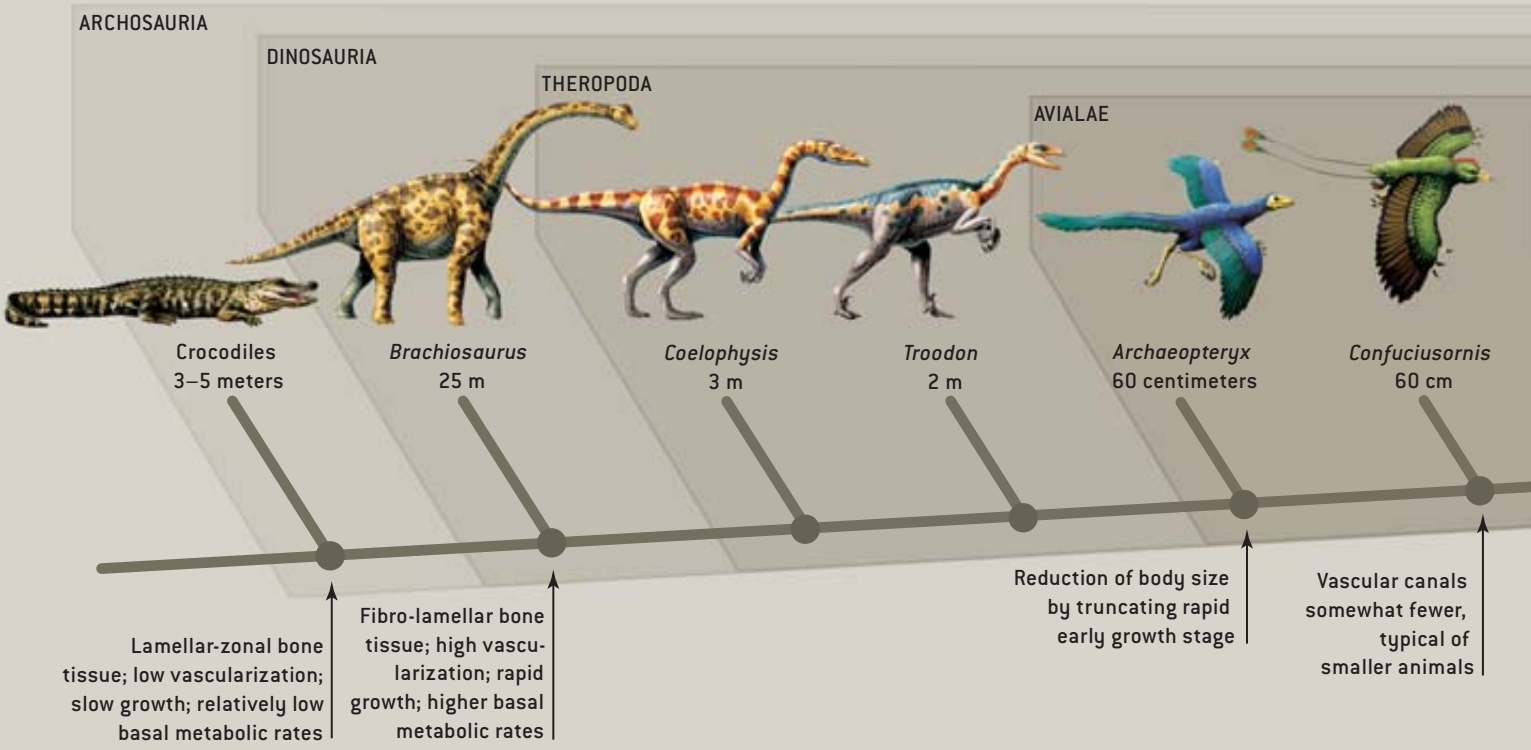
The pace at which dinosaurs grew was assessed in a different way by Erickson, Rogers and Scott A. Yerby of Stanford University. Using estimates of the body mass of dinosaurs, they plotted the animals' mass against time to derive growth curves for a variety of species and compared the curves with those for other groups of vertebrates. They found that all dinosaurs grew faster than all living reptiles, that many dinosaurs grew at rates comparable to those of living marsupials, and that the largest dinosaurs grew at rates comparable to those of rapidly maturing birds and large mammals. We confirmed their results for body mass with our own studies using length.

THE AUTHORS

JOHN R. HORNER, KEVIN PADIAN and *ARMAND DE RICQLÈS* have worked together on investigations of dinosaur bones for more than 12 years. Horner is curator of paleontology at the Museum of the Rockies and Regents Professor of Paleontology at Montana State University. Padian is professor of integrative biology and curator of the Museum of Paleontology at the University of California, Berkeley. De Ricqlès is professor at the Collège de France in Paris, where he occupies the chair in historical and evolutionary biology; his CNRS research team at the University of Paris VII works on the formation of bone and other skeletal tissues.

SHAWN GOULD (*illustrations*); JOHN R. HORNER, KEVIN PADIAN AND ARMAND DE RICQLÈS (*photographs*)

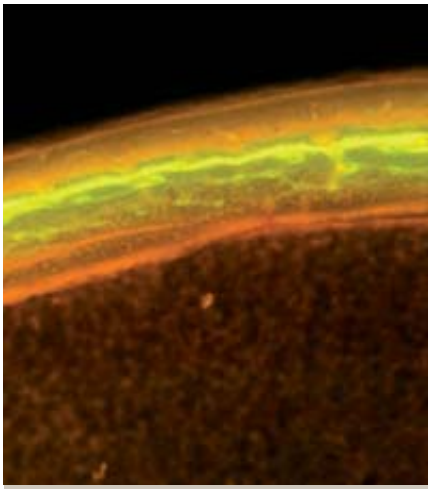
BONE GROWTH AND EVOLUTION IN BIRDS



In one sense, such findings were not unexpected. Many years ago Ted J. Case of the University of California at Los Angeles showed that within any group of vertebrates (fishes, amphibians and so on), larger species grow at absolutely higher rates than smaller species do; so, although larger species reach adult size in a longer time, they grow more quickly to do so. What was surprising is that dinosaurs grew as fast as they did.

We were curious about when in the course of their evolution dinosaurs acquired this habit of rapid growth, so we plotted our estimated growth rates on a cladogram, or diagram of relationships, that was built on hundreds of independent characteristics from all parts of the skeleton. We added the estimated growth rates for pterosaurs (flying reptiles closely related to dinosaurs, which grew much like them), crocodiles and their extinct relatives, and lizards. We put birds among the dinosaurs, because birds evolved from dinosaurs and so are technically included with them [see "The Origin of Birds and Their Flight," by Kevin Padian and Luis M. Chiappe; SCIENTIFIC AMERICAN, February 1998].

For added help in estimating the growth rates of dinosaurs, we looked at



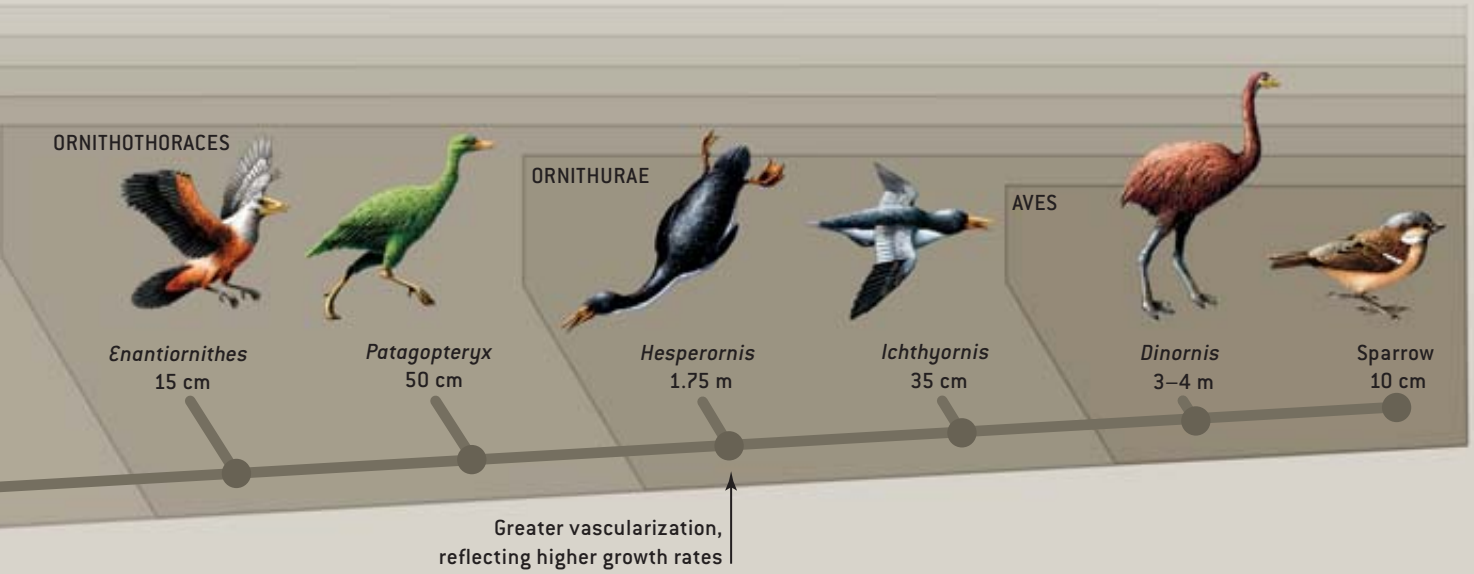
DISCRETELY DEPOSITED BONE layers are revealed by green, yellow and orange fluorescent dyes, injected weekly into a mallard duck. These dyes show exactly how much growth occurred each week.

living birds, which show the same range of tissues expressed in dinosaur bones. Jacques Castanet and his colleagues at the University of Paris VII injected mallard ducks with solutions that would stain the growing bones. By using different colors at different times, they were able to measure rates of weekly growth in the sacrificed birds [*see illustration at left*]. Using these calibrations, we determined that, without exception, dinosaurs and pterosaurs grew at much higher rates than other reptiles. We did find considerable variation among the dinosaurs and pterosaurs, a variation mirrored by Castanet's findings in birds: the animals that grew relatively more slowly than others were the smaller ones—just as Ted Case's patterns would predict.

Unconventional Reptiles

THE STUDY OF dinosaur bones has told us a great deal about the evolution of some of the major features of these animals. About 230 million years ago,

SHAWN GOULD (*illustrations*); JEN CHRISTIANSEN (*cladogram*); JACQUES CASTANET (*photograph*)



Dinosaurs, from their beginning, had bone tissues that differed greatly from those of other reptiles. Their bones grew more rapidly, as in birds and mammals of today. When the first birds (Avialae) evolved, their substantial reduction in size was a result of slower growth of their bone. But their growth was still more rapid than in other reptiles. Then, as the living bird groups (Aves) began to emerge, growth accelerated again, so that pigeon-sized birds matured in weeks instead of months. All birds today, even the ostrich, reach adult size within a year, and most do so much more quickly—the sparrow in seven days. When birds evolved, they slowed down their growth rates at exactly the time when growth is highest in their dinosaur ancestors, their juvenile period, effectively miniaturizing them as adults.

in the early part of the Triassic period, the lineage that would produce dinosaurs, pterosaurs and their relatives split from the lineage that would produce crocodiles and their relatives. The dinosaurian lineage soon acquired sustained elevated growth rates that set them apart from other reptiles. This speedy growth may have played a role in the success that dinosaurs and pterosaurs enjoyed toward the end of the Triassic, when so many crocodile relatives and other archaic groups with more typical reptilian bone structure became extinct.

The high growth rates of dinosaurs also give us a firmer idea about their metabolic features. The higher the metabolic rate—that is, the more energy devoted to building up and breaking down bone and other tissues—the faster the tissues will grow. So evidence of sustained rapid growth, even into late juvenile and subadult stages, implies that the animals in question had relatively high basal metabolic rates. Because dinosaurs were not like living reptiles in the way they grew, but much like birds and mammals, their basal metabolic rates were probably more like those of birds and mammals than like those of today's reptiles. This suggests that they were much more likely to have been warm-blooded, in a general sense, than cold-blooded, but it is difficult to know the details, such as body temperature and how much it varied, or how much body heat dinosaurs could acquire from (or needed to shed to) the air around them. Clearly, many questions remain. Dinosaurs were perhaps even more unusual creatures than we had previously thought—not exactly like any animals of today and certainly not conventional reptiles. If anyone ever discovers a five-ton living bird, a lot of these questions will be settled. SA

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Dinosaur bone histology: **http://ltc.smm.org/histology/**

Shrinking Circuits with Water

Semiconductor manufacturers are giving their products a dousing in the name of faster, smaller, cheaper

By Gary Stix

Physicist Giovanni Battista Amici

placed a drop of liquid on a specimen in his Florence laboratory, improving the quality of the image seen through his microscope's eyepiece. Now, 165 years later, the global semiconductor industry is just getting around to adopting Amici's innovative technique.

The decision to baptize chips under a thin liquid stratum will allow the making of circuits with features that measure the breadth of a virus. Such a retro solution—the 19th century meets the 21st—also serves as a fitting commemoration of the 40th anniversary of the semiconductor industry's most influential technical paper, a treatise by Intel co-founder Gordon E. Moore entitled "Cramming More Components onto Integrated Circuits." Moore's prediction that the number of transistors on a chip would double every 12 months (later revised to every 24 months) transmuted from mere forecast into ironclad edict, the equivalent of a law of nature that ordains that the industry will suffer some unspecified but assuredly grievous injury if chip power does not continue to grow in exponential leaps every two years.

If it were not for the power of water, Moore's Commandment might have been broken when plans for a new generation of chipmaking technology hit what seemed to be an unbreachable obstacle. In 2002 both chipmakers and their suppliers had failed to achieve critical milestones in the development of the world's most sophisticated cameras—the lithography machines that project a circuit image onto a photochemical "resist" covering the silicon wafer, the disk that is later cut up into individual chips. A developing chemical removes, say, the exposed area, and then an etching chemical transfers the pattern into the wafer.

The most common method of making circuits smaller is to reduce the wavelength of light with a machine that traces progressively tinier circuit features on a wafer. Lithography toolmakers had bumped up against numerous obstacles in making a machine that radiates wavelengths of 157 nanometers. Going from one lithography generation to another requires adoption of new lasers, masks (the stencillike pattern of circuits through which laser light is projected), lenses that reduce the image size and exposure, and photoresists. For 157 nanometers, equipment companies could not figure out how to fashion lenses from calcium fluoride with few enough defects and optical aberrations to

INDELIBLE IMAGE of a microscopic bubble gets imprinted on a wafer during immersion lithography, compromising the integrity of electrical circuits.

IMAGE CREATED BY ASML TWINSCAN ™ XT:1150I, COURTESY OF ASML

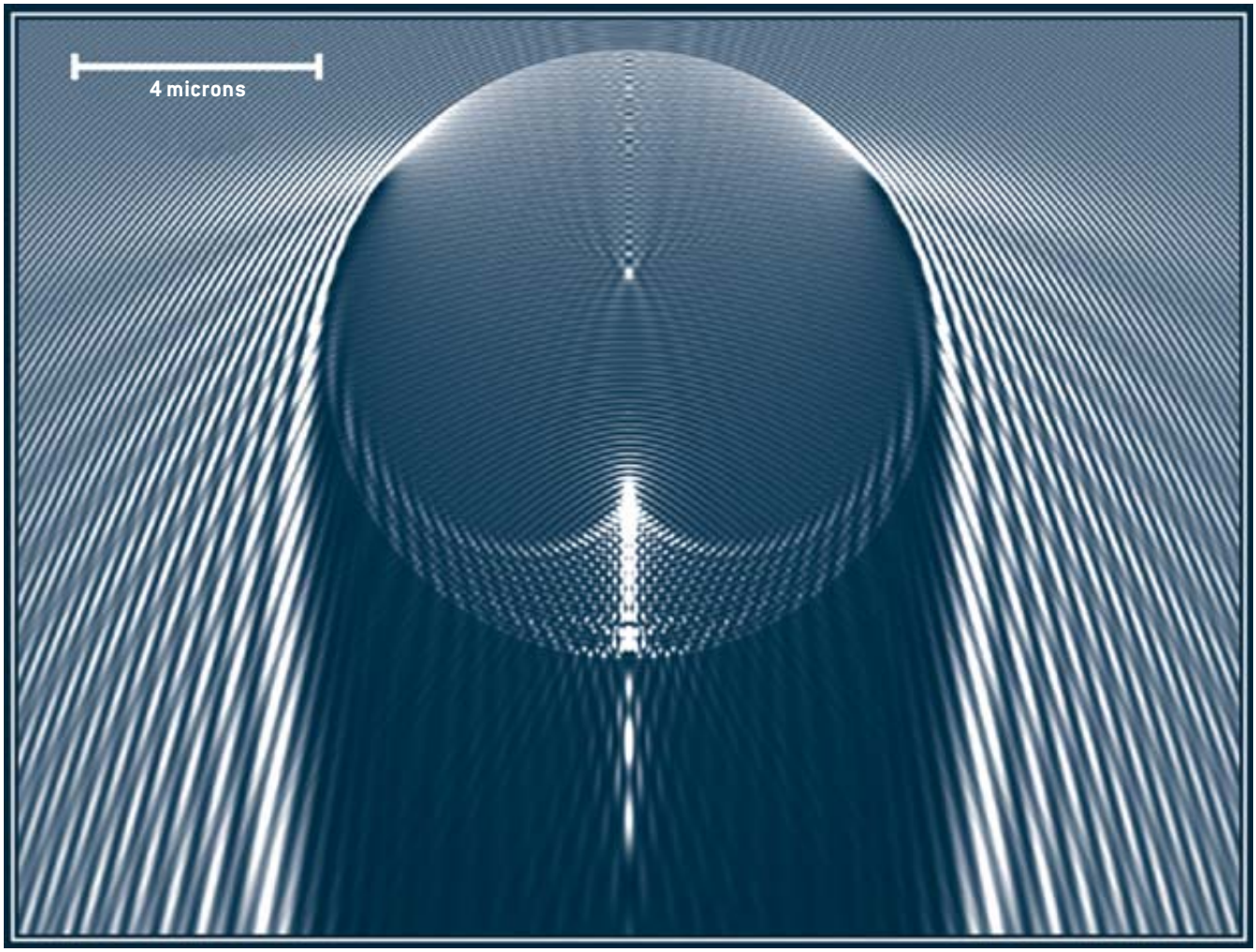
form a clear image on the wafer. "There was a very large problem with the quality of materials and the manufacturing yields," notes George A. Gomba, senior manager of advanced lithography development at IBM Microelectronics.

A way forward arrived during the summer of 2002 at a workshop on 157-nanometer lithography sponsored by Sematech, the semiconductor research consortium. At the meeting, Burn Lin, an executive from Taiwan Semiconductor Manufacturing Company, the world's largest contract chip manufacturer, was scheduled to give a speech on immersion lithography, a hand-me-down from Amici's ideas. Lin, who had researched immersion while at IBM during the 1980s, was supposed to describe how immersion might be used for 157 nanometers by exploiting a viscous machine oil. Instead he spent his lecture describing why lithography at that scale would not work—and why the industry should set its sights on applying immersion to a previous generation of already fielded lithographic equipment that employed a wavelength of 193 nanometers.

By concentrating on immersion at 193 nanometers, chipmakers could enhance resolution of tried-and-true lithography equipment until it actually bested what 157-nanometer equipment was supposed to achieve. "That sort of caught the attention of all in attendance," Lin says. "And of course they forgave me for saying 157 nanometers was no good." Water, which is transparent to 193-nanometer radiation but not to 157, can enhance resolution because it enables a lithography machine to be built with a higher numerical aperture, a key factor in its ability to resolve fine detail. Water also improves the depth of focus—the distances from the camera at which the image projected onto the photoresist stays acceptably sharp. Depth of focus remains a particular concern in advanced chipmaking because the slightest unevenness on the wafer surface can spoil the image.

Lin's presentation lay down a challenge. Immersion lithography at 193 nanometers would be an extension of an existing technology. So it might not take the decade of development or more typically required when moving from one wavelength of imaging to another. Still, despite sporadic immersion research dating back to the 1980s, no one knew whether the technology would work. Water sloshing around

TOXIC MICROBUBBLE, shown here in a computer simulation, can distort light focused on the surface of a semiconductor wafer and thereby affect the fidelity of an image projected onto a photosensitive film. Researchers addressed this problem, in part, by removing the gas from the water.



MICHAEL YEUNG *Boston University*

on the wafer might wreak havoc. Microscopic bubbles that formed while the wafer moved under the machine at half a meter each second could create defects in the image.

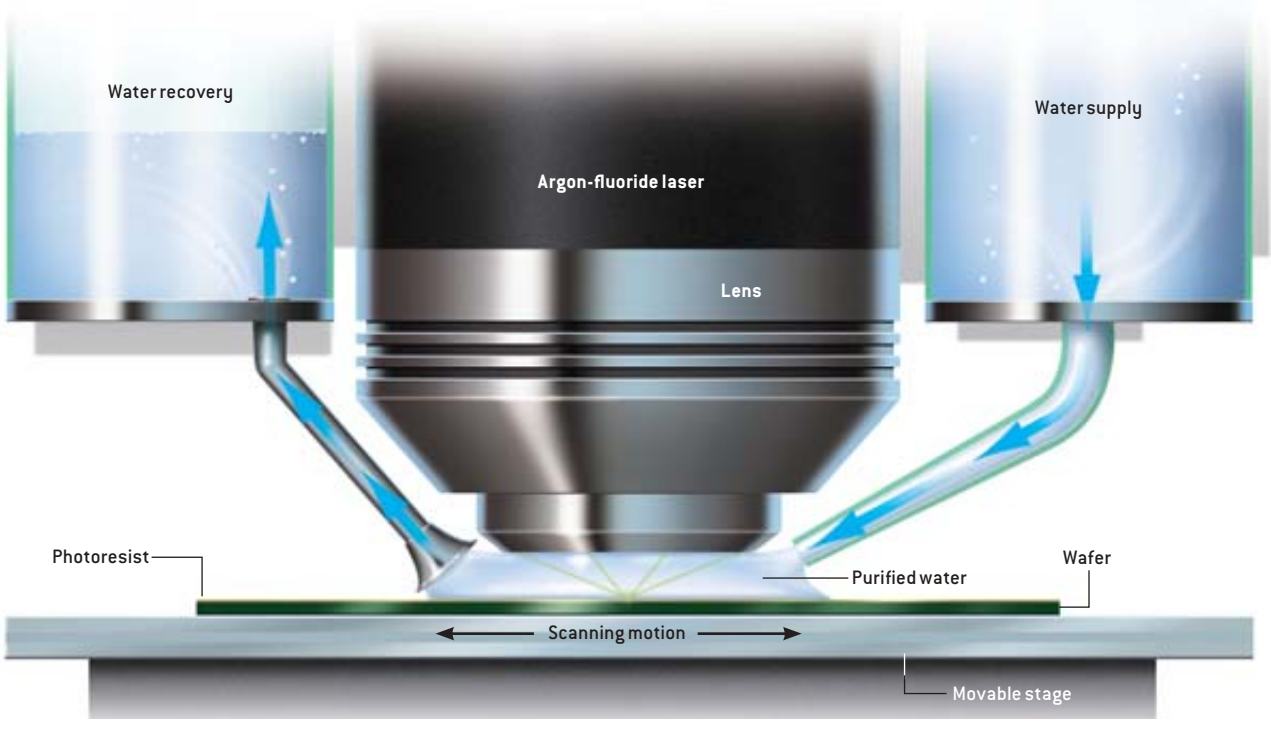
In December 2002 Sematech set up a colloquy at which 100 tool and chip manufacturers and scientific researchers gathered to compile a long worry list about immersion lithography. The group identified 10 essential hurdles that needed to be surmounted to make the technology a reality. They ranged from modeling the potentially damaging effects of water on the lens and photoresist to understanding what really are the basic physical characteristics of water. The refractive index of water—the ratio of the speed of light in a vacuum to that of its speed in a medium such as water (essentially a measure of water or another medium's ability to bend light and a critical parameter for figuring numerical apertures)—was known to only two decimal places at 193 nanometers. "Everyone agreed that we had to know it to five decimal places and possibly six," says Walter J. Trybula, a Sematech senior fellow who led the early meetings.

The behavior of bubbles was another unknown. A task force was dispatched to work on this problem. The Massachusetts Institute of Technology's Lincoln Laboratory—a major research center for advanced lithography—went so far as to freeze-dry nano-size bubbles to study them. Larger microscopic bubbles could also cause harm. "We were studying how to get water to flow without bubbles when the wafer is moving around fast under the imaging machine," says Michael Switkes, a Lincoln Lab researcher. It turned out that pure, degassed water helped to meet the relevant technical specifications for bubble prevention.

In July 2003 another Sematech workshop on immersion lithography drew a huge crowd to the IBM Almaden Research Center. Six months of simulations and experiments provided potential solutions to all 10 technical difficulties. "All the things that we thought would be a tremendous issue turned out to be manageable," remarks Andrew Grenville, Sematech's program manager for immersion lithography strategy. The pace of development quickened further. By December 2003 ASML, a lithography toolmaker, had introduced a prototype immersion machine, and by the end of 2004 IBM had made a pilot batch of microprocessors, the smallest features of which measured 90 nanometers. The introduction of immersion, along with a series of what lithographers call "tricks" (a change in the phase of the light, for instance), allows for the printing of features at a small fraction of the laser's actual 193-nanometer wavelength. "We basically said, 'We can work with this,'" comments IBM's Gomba. Other tool manufacturers, chipmakers and academic institutions have followed suit with new products and lithographic printing demonstrations. Immersion lithography will probably achieve commercial production in 2009, at which point the separation from one transistor to another will hover around an astonishing 45 nanometers, less than the width of a hepatitis C virus.

Adding water has enabled one of the fastest introductions ever for a new lithography technology, and it may have saved the industry from getting derailed from its addiction to Moore's law. A new chip generation might have been delayed by two years, perhaps waylaying the long-awaited arrival of the high-definition video recorder flip phone. Immersion has also

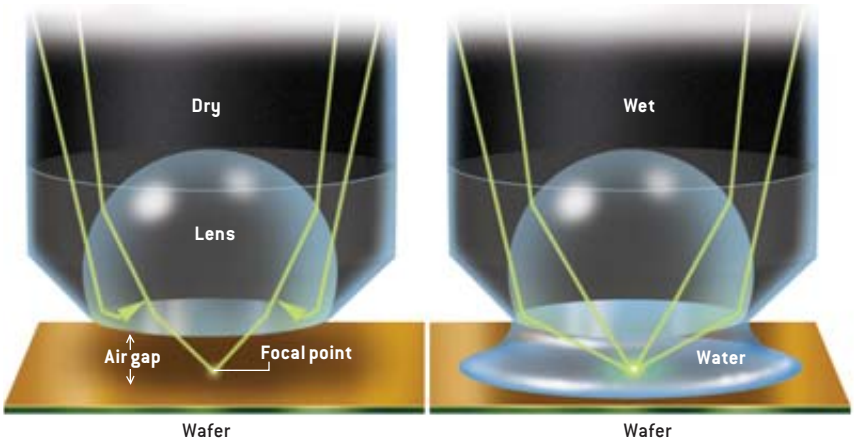
IMMERSION LITHOGRAPHY works by channeling water through the gap between the imaging machine and the photoresist that coats a semiconductor wafer, improving resolution of chip features and depth of focus. As a staging table moves the wafer underneath the lens, the water is sucked away from the area that has already been imaged.



KENT SNODGRASS *Precision Graphics*

marked a watery doom for 157-nanometer lithography, after the industry spent an estimated $2 billion–plus on the now scrapped technology. "It's dead as a rock," says Phillip M. Ware, a senior fellow at Canon, one of the Big Three lithography manufacturers, along with Nikon and ASML.

Investigators are also eyeing immersion for the 2011 chip generation that will achieve transistor spacings of 32 nanometers. To achieve that goal will require new lenses and chemical additives for water—what some wags call "Kool-Aid"—that will increase its refractive index and therefore allow for higher numerical apertures. At an optical engineering meeting this past March, Bruce W. Smith and his colleagues at the Rochester Institute of Technology reported on "solid-immersion" lithography that could deploy a sapphire lens that comes into direct contact with the photoresist, perhaps enabling 25-nanometer transistor spacings for the 2015 generation.



RESOLUTION of lithography for chipmaking improves if a tool has water placed in the gap between the lens and the wafer. Light that travels through the lens at a very sharp angle—the rays that image the smallest circuit features—reflects back once it encounters an air gap (*left*). Meanwhile a light wave that hits water at the same angle is bent so that it reaches the focal point (*right*). Immersion lithography also improves depth of focus—the distance from the lens that an image remains sharp.

If that happens, lithographers' ingenuity could seal the fate of the technology championed by the world's leading manufacturer, Intel, intended to bring conventional chipmaking to the end of its days, perhaps even marking the end of Moore's law. Extreme ultraviolet lithography (EUV), as it is known, trains 13-nanometer radiation onto a series of multilayer mirrors that reduce the size of the image projected onto the wafer. Lenses do not work, because materials become opaque at these wavelengths. Some of the EUV technology got its start in the "Star Wars" program.

EUV was supposed to start making chips with features of about 100 nanometers, but immersion and other advances have pushed its commercial arrival further and further back. At the optical engineering conference in March, two keynote speakers—R. Fabian Pease, a professor of electrical engineering at Stanford University, and C. Grant Willson, a professor of chemical engineering and chemistry at the University of Texas at Austin and a founder of a company that is pushing an EUV alternative—both projected that the Intel-backed technology would never reach commercial production because of costs and challenges with the lasers and materials. "EUV, in my personal opinion, is not likely to make a part for profit," Willson said during an interview.

If EUV falls by the wayside, after billions in spending by the industry, it would share the fate of x-ray lithography, a technology championed by IBM that required synchrotron-generated radiation and consumed more than $1 billion in expenditures by IBM and the Defense Advanced Research Projects Agency. EUV wavelengths, in fact, are not far from x-rays on the electromagnetic spectrum. Employing slightly longer wavelengths, EUV was known as soft x-ray projection lithography until the name "x-ray" began to take on the connotation of a developmental sinkhole.

For its part, Intel remains confident that EUV will be needed once the spacing between transistors reaches less than 50 nanometers. "EUV will be able to go for many generations," says Peter J. Silverman, Intel's director of equipment technology strategy. But analysts have predicted the demise of traditional forms of optical lithography from the time chip features were nearing half a micron—and immersion is likely to buy still more time for established technology, perhaps to the detriment of EUV.

A theme appears to underlie the advances that have pushed Moore's law forward as chip features draw close to absolute physical limits: circuit elements approaching the size of individual atoms and chip designers' gradual loss of control over electrons as they course through a transistor. As often as not, solutions to immense engineering problems seem to be the simplest ones. Merely adding water allows argon-fluoride lasers to print features at a quarter or less of their 193-nanometer wavelength. And a new form of nonimmersion lithography, called nanoimprint, bears a strong likeness to shaping Jell-O in a mold, a possible solution to lithography at 25 nanometers and below.

"We end up going back in terms of complexity," observes John H. Burnett, a scientist at the National Institute of Standards and Technology who has investigated the optical properties of fluids and lenses used in immersion lithography. So Occam and his shaving implement may end up facilitating Moore and his law in packing in the maximum number of components that can be accommodated on a nanochip. SA

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KENT SNODGRASS *Precision Graphics*

New Movement in PARKINSON'S

Recent genetic and cellular discoveries are among the advances pointing to improved treatments for this increasingly common disorder

By Andres M. Lozano and Suneil K. Kalia

Parkinson's disease, first described in the early 1800s by British physician James Parkinson as "shaking palsy," is among the most prevalent neurological disorders. According to the United Nations, at least four million people worldwide have it; in North America, estimates run from 500,000 to one million, with about 50,000 diagnosed every year. These figures are expected to double by 2040 as the world's elderly population grows; indeed, Parkinson's and other neurodegenerative illnesses common in the elderly (such as Alzheimer's and amyotrophic lateral sclerosis) are on their way to overtaking cancer as a leading cause of death. But the disease is not entirely one of the aged: 50 percent of patients acquire it after age 60; the other half are affected before then. Furthermore, better diagnosis has made experts increasingly aware that the disorder can attack those younger than 40.

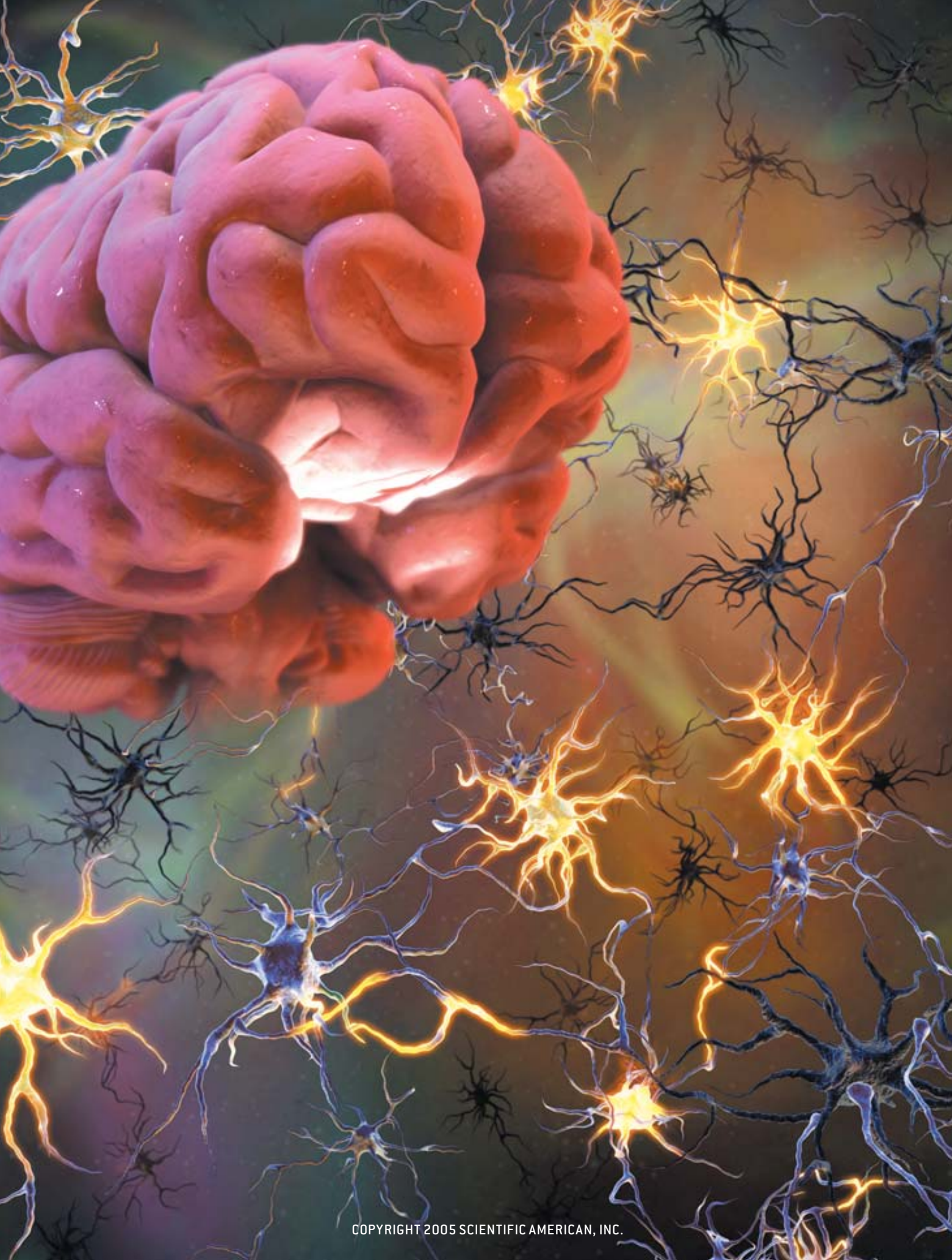
So far researchers and clinicians have found no way to slow, stop or prevent Parkinson's. Although treatments do exist—including drugs and deep-brain stimulation—these therapies alleviate symptoms, not causes. In recent years, however, several promising developments have occurred. In particular, investigators who study the role proteins play have linked miscreant proteins to genetic underpinnings of the disease. Such findings are feeding optimism that fresh angles of attack can be identified.

As its 19th-century name suggests—and as many people know from the educational efforts of prominent Parkinson's sufferers such as Janet Reno, Muhammad Ali and Michael J. Fox—the disease is characterized by movement disorders. Tremor in the hands, arms and elsewhere, limb rigidity, slowness of movement, and impaired balance and coordination are among the disease's hallmarks. In addition, some patients have trouble walking, talking, sleeping, urinating and performing sexually.

These impairments result from neurons dying. Although the victim cells are many and found throughout the brain, those producing the neurotransmitter dopamine in a region called the substantia nigra are particularly hard-hit. These dopaminergic nerve cells are key components of the basal ganglia, a complex circuit deep within the brain that fine-tunes and coordinates movement [*see box on page 70*]. Initially the brain can function normally as it loses dopaminergic neurons in the substantia nigra, even though it cannot replace the dead cells. But when half or more of these specialized cells disappear, the brain can no longer cover for them. The deficit then produces the same effect that losing air traffic control does at a major airport. Delays, false starts, cancellations and, ultimately, chaos pervade as parts of the brain involved in motor control—the thalamus, basal ganglia and cerebral cortex—no longer function as an integrated and orchestrated unit.

Proteins Behaving Badly

In many Parkinson's cases, the damage can be seen in autopsies as clumps of proteins within the substantia nigra's dopaminergic neurons. Such protein masses also feature in Alzheimer's and Huntington's—but in



Parkinson's they are called Lewy bodies, after the German pathologist who first observed them in 1912. Like researchers studying those other neurodegenerative diseases, Parkinson's investigators heatedly debate whether the protein clusters themselves cause destruction or are protective and endeavoring to remove toxic molecules from the neurons. Regardless of their position, however, most agree that understanding these accumulations is key to understanding Parkinson's.

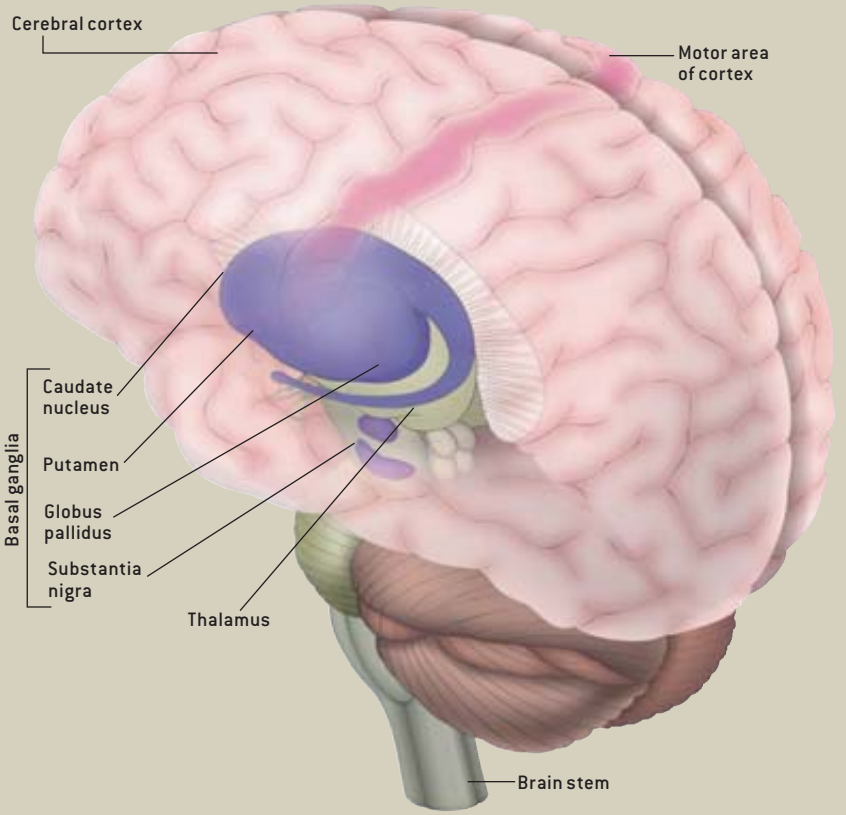
Two cellular processes occupy a central place in this emerging story: protein folding and protein elimination. Cells synthesize proteins, which are chains of amino acids, based on instructions written in the DNA of genes. As the proteins are produced, molecules called chaperones fold them into the three-dimensional form they are supposed to take. These chaperones also refold proteins that have become unfolded.

If the chaperone system fails for some reason, proteins not properly folded in the first place or those that did not correctly refold become targeted for disposal by what is called the ubiquitin-proteasome system. First, ubiquitin, a small protein, is attached to a misshapen protein in a process called ubiquitinylation. Such tagging is repeated until ubiquitin chains of varying lengths end up draped over the ill-fated protein. These chains become the kiss of death. They alert the nerve cell's proteasome, a garbage disposal system, to the existence of the bedecked protein. The proteasome then digests it into its constituent amino acids. Aaron Ciechanover and Avram Hershko of Technion-Israel Institute of Technology and Irwin Rose of the University of California at Irvine were awarded the 2004 Nobel Prize in Chemistry for their work describing this system.

In the past few years, many scientists have come to believe that Parkinson's emerges when the chaperone and ubiquitin-proteasome systems malfunction. They reason that the disease process might go something like this: some form of injury to neurons of the substantia nigra triggers a cascade of cellular stresses [see "Understanding Parkinson's Disease," by Moussa B. H. Youdim and Peter Riederer; SCIENTIFIC AMERICAN, January 1997]. These stresses result in a wealth of misfolded proteins that congregate. This buildup might initially be protective because all the renegade proteins are herded together and thus prevented from causing trouble elsewhere in a cell. Chaperones then set to work refolding, and the disposal system starts eliminating those proteins that cannot be reformed. When the production of poorly folded proteins overwhelms the cell's

BRAIN REGIONS AFFECTED BY PARKINSON'S

Most cell death occurs in the substantia nigra, which controls voluntary movement and helps to regulate mood. Although the rest of the brain can initially compensate, it can no longer do so when 50 to 80 percent of the cells in the substantia nigra have been lost. At that point, other parts of the brain engaged in motor control, including the rest of the basal ganglia (of which the substantia nigra is part), the thalamus and the cerebral cortex, can no longer work together, and movement becomes disjointed and uncontrollable.



JEFF JOHNSON *Hybrid Medical Animation (preceding pages)*; SARA CHEN (*this page*)

Overview/*Proteins and Parkinson's*

- One of the most pervasive neurological diseases, Parkinson's disease cannot be slowed, stopped or prevented. The two standard forms of treatment, medications and surgery, can only reduce symptoms.
- Recent discoveries about how proteins malfunction and the genetic underpinnings of Parkinson's have opened new avenues for research, and investigators are feeling some optimism about finding new treatments.
- Protein folding and disposal systems gone awry now appear to be central to the disorder, and the genetic causes for those failures have come to light.

ability to process them, however, trouble arises: The ubiquitin-proteasome system becomes inhibited, chaperones get depleted, and toxic proteins accumulate. Neuronal cell death follows.

Researchers espousing this hypothesis think it could explain Parkinson's two forms. An estimated 95 percent of patients suffer from sporadic disease—the results of a complex interplay between genes and the environment. When someone with a susceptible genetic background encounters certain environmental factors, such as pesticides or other chemicals [*see box on this page*], the cells in that individual's substantia nigra suffer more stress and accumulate more misfolded proteins than do the same cells in other people. In the remaining 5 percent of patients, Parkinson's appears to be controlled almost entirely by genetics. Discoveries in the past eight years have revealed a connection between mutations and either the buildup of misshapen proteins or the failure of the cell's protective machinery. These genetic insights have been the most exciting developments in the field in years.

The Genetic Frontier

AT THE NATIONAL Institutes of Health in 1997, Mihael H. Polymeropoulos and his colleagues identified a mutation in a gene for a protein called alpha-synuclein in Italian and Greek families with an inherited form of Parkinson's. It is an autosomal dominant mutation, meaning just one copy (from the mother or the father) can trigger the disease. Mutations in the *alpha-synuclein* gene are extremely rare and insignificant in the worldwide burden of Parkinson's (they account for far less than 1 percent of patients), but identification of the link between the encoded protein and Parkinson's set off an explosion of activity—in part because alpha-synuclein, normal or otherwise, was soon found to be one of the proteins that accumulates in the protein clumps. Investigators reasoned that a better understanding of how the mutation leads to Parkinson's could suggest clues to the mechanism underlying Lewy body formation in dopamine-producing cells of the substantia nigra in patients with sporadic disease.

The *alpha-synuclein* gene codes for a very small protein, only 144 amino acids long, which is thought to play a role in signaling between neurons. Mutations result in tiny changes in the amino acid sequence of the protein—in fact, several such mutations are now known, and two of them result in the change of a single amino acid in the sequence. Studies of fruit flies, nematodes (roundworms) and mice have shown that if mutated alpha-synuclein is produced in high amounts, it causes the degeneration of dopaminergic neurons and motor deficits. Other studies have revealed that mutated alpha-synuclein does not fold correctly and accumulates within Lewy bodies. Altered alpha-synuclein also inhibits the ubiquitin-proteasome system and resists proteasome degradation. In addition, it has recently become clear that having extra copies of the normal *alpha-synuclein* gene can cause Parkinson's.

In 1998, one year after the discovery of the *alpha-synuclein* mutation, Yoshikuni Mizuno of Juntendo University and Nobuyoshi Shimizu of Keio University, both in Japan, identified a second gene, *parkin*, that is mutated in another familial form of Parkinson's. This mutation appears most often in individuals diagnosed before age 40; the younger the age of onset, the more likely the disease is caused by a *parkin* mutation. Although people who inherit a defective copy from both parents (that is, when the mutation is autosomal recessive) inevitably develop the disease, those who carry a single copy of the mutated gene are also at

ENVIRONMENTAL CULPRITS

The idea that Parkinson's disease may be caused by something in the environment has been around for decades. But proof came only in the early 1980s, when J. William Langston of the Parkinson's Institute in Sunnyvale, Calif., studied a group of drug abusers in the San Francisco Bay Area. These young addicts had developed parkinsonian symptoms within days of taking China white, a synthetic heroin. It turned out that the batch contained an impurity called MPTP, a compound that can kill neurons in the brain's substantia nigra region. Through treatment, some of the "frozen addicts," as they came to be called, recovered some movement control; in most, however, the effects were irreversible.

In subsequent years, investigators searched for other compounds with similar effects, and in 2003 their work was bolstered when the National Institute for Environmental Health Sciences put $20 million behind efforts to identify and study environmental causes of Parkinson's. To date, epidemiological and animal studies have linked some cases to high exposure to various pesticides, herbicides and fungicides, including paraquat and maneb. J. Timothy Greenamyre of Emory University has also discovered in animal studies that exposure to rotenone, a pesticide often used in organic farming because it is made from natural products, is capable of inducing protein aggregation, killing dopamine-producing neurons, inhibiting the cells' energy-producing organelles and giving rise to motor deficits.

SOME PESTICIDES, including one routinely used in organic farming, can induce parkinsonian conditions in animals.

Just as some agents may trigger Parkinson's, others might confer protection. Experts now accept that smoking and coffee drinking can be somewhat protective—although clearly the risks of smoking far outweigh this particular benefit.

—A.M.L. and S.K.K.

ANNIE GRIFFITHS BELT *Corbis*

CURRENT THERAPIES

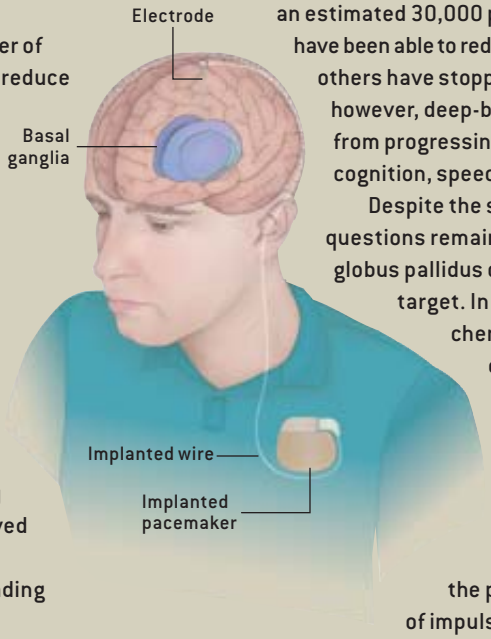
Physicians take two basic approaches to treating Parkinson's disease. Both can produce striking benefits, but they also have disadvantages, which is why patients and researchers are so eager for new strategies.

MEDICATIONS

The principal treatments encompass medications that mimic dopamine, compounds used to create dopamine in the brain (such as levodopa), and drugs that inhibit the breakdown of dopamine. Several others act on some of the nondopamine systems affected in Parkinson's, including those mediated by the neurotransmitters acetylcholine and glutamate. Many of these drugs help during the initial phases of the disease, but their ongoing use can become problematic. Chief among the long-term adverse effects are unpredictable oscillations between periods of good motor function and periods of freezing, tremor and rigidity. In addition, some of the medications can cause involuntary twisting, writhing movements called dyskinesias, which are particularly prominent in young patients and are extremely disabling.

DEEP-BRAIN STIMULATION

At the turn of the century, investigators discovered that destroying a small number of cells in the brain's motor pathways could reduce parkinsonian tremors. Although the procedure often caused muscle weakness, patients preferred that to the shaking. Then, in 1938, surgeons injured the basal ganglia and found even more marked improvement in Parkinson's patients. It appeared that eliminating the cells that were misbehaving—that is, those misfiring or firing too much—apparently allowed the rest of the brain to function normally. Unfortunately, creating lesions was not a perfect solution. If they were not precisely placed or if they involved both sides of the brain, they could cause severe damage, impairing speech and leading to cognitive problems.



In the 1970s investigators discovered that high-frequency electrical stimulation of parts of the brain could mimic lesions, without reproducing the side effects. Various forms of deep-brain stimulation are used for many neurological disorders today [see "Stimulating the Brain," by Mark S. George; SCIENTIFIC AMERICAN, September 2003]. In Parkinson's patients, an electrode is placed in one of two basal ganglia targets—the globus pallidus or subthalamic nucleus—and attached to a pulse-generating device implanted in the chest (*below*). The pacemaker typically delivers 90-microsecond, three-volt pulses of electricity up to 185 times per second and needs to be replaced every five years.

The pioneers of the technique, Alim Louis Benabid and Pierre Pollak of the University of Grenoble in France, report that such stimulation dramatically reduces tremor and rigidity. Indeed, in the past decade or so it has become a mainstay of treatment, and an estimated 30,000 patients have undergone the surgery. Some have been able to reduce the doses of medicines they take, whereas others have stopped taking them altogether. At the same time, however, deep-brain stimulation cannot prevent the disease from progressing, and it cannot alleviate the problems with cognition, speech and balance that may arise.

Despite the success of deep-brain stimulation, many questions remain. For one thing, it is not clear whether the globus pallidus or the subthalamic nucleus is a better target. In addition, the precise electrical and chemical mechanisms by which electrical energy improves Parkinson's disease remain to be determined, and much of the data are conflicting. For example, researchers used to think deep-brain stimulation worked the same way lesioning did, by inactivating cells. Recently, however, they have learned that the procedure seems to cause faster firing of impulses.

—A.M.L. and S.K.K.

greater risk. *Parkin* mutations appear to be more common than *alpha-synuclein* gene mutations, but no good figure on incidence is currently available.

The parkin protein contains a number of amino acid sequences, or domains, common to many proteins. Of particular interest are two so-called RING domains; proteins with these RING domains are involved in the protein degradation pathway. Findings now suggest that neuronal death in this form of Parkinson's stems in part from the failure of the ubiquitinylation component of the protein disposal system: parkin attaches ubiquitin to misfolded proteins—without it, there is no tagging and no disposal. Our own work has recently shown that a protein called BAG5, which is found in Lewy bodies, can bind to parkin to inhibit its function and cause the death of dopamine-producing neurons.

Interestingly, some patients with *parkin* mutations lack Lewy bodies in their nigral neurons. This observation suggests that proteins may not form aggregates unless the ubiquitinylation process is functioning. It also suggests that when harmful proteins are not huddled together within Lewy bodies they create cellular havoc. Because patients with *parkin* mutations develop the disease early in life, it seems likely that they miss some initial protection conferred by having toxic proteins quarantined in clumps.

Several other recent discoveries highlight further genetically induced muck-ups in the cellular machinery. In 2002 Vincenzo Bonifati and his colleagues at Erasmus Medical Center in Rotterdam identified a mutation in a gene called *DJ-1*. Like that in *parkin*,

SARA CHEN

this mutation is responsible for an autosomal recessive form of Parkinson's and has been found in Dutch and Italian families. Investigators have seen mutations in another gene, *UCHL1,* in patients with familial Parkinson's. A paper in *Science* just described a mutation in *PINK1* that may lead to metabolic failure and cell death in the substantia nigra. And other work has identified a gene called *LRRK2,* which encodes the protein dardarin (meaning "tremor" in the Basque region, where the affected patients came from). It, too, is involved with metabolism and appears in familial Parkinson's. But researchers are not far along in understanding exactly what all these mutations set wrong.

New Avenues for Treatment

BECAUSE THE INSIGHTS just described involve molecules whose activity could potentially be altered or mimicked by drugs in ways that would limit cell death, the discoveries could lead to therapies that would do more than ease symptoms—they would actually limit the neuronal degeneration responsible for disease progression.

This strategy has yielded two intriguing results. Increasing the levels of chaperones in cells of the substantia nigra has been found to protect against the neurodegeneration set in motion by mutated alpha-synuclein in animals. Recent studies using fruit-fly models of Parkinson's have shown that drugs that induce chaperone activity can offer protection against neurotoxicity. Perhaps one day chaperone-type drugs can be developed to limit degeneration in people, or gene therapy could be devised to trigger the production of needed chaperones. In addition, investigators have found that increasing the amount of normal parkin protein in cells protects against the neurodegeneration resulting from noxious, misfolded proteins. Much more study will be needed, however, to determine whether such interventions could be made to work in humans.

In addition to pursuing the preliminary leads that have arisen out of the new protein-related and genetic findings, investigators have begun introducing neurotrophic factors—compounds promoting neuronal growth and differentiation—into the brain. These agents not only alleviate symptoms but also promise to protect neurons from damage or even to restore those already harmed.

One line of research in animals, for instance, suggests that a family of proteins called glial cell line-derived neurotrophic factor (GDNF) can enhance the survival of injured dopamine neurons and dramatically reduce parkinsonian symptoms. Steve Gill and his colleagues at Frenchay Hospital in Bristol, England, have embarked on a pilot study to give Parkinson's patients GDNF. Surgeons insert a catheter into the left and right striatum, the main recipients in the basal ganglia of the dopamine secreted by neurons of the substantia nigra. Minute volumes of GDNF are then continuously infused to the brain from a pump set into the abdomen. The pump holds enough GDNF to last one month and is replenished during an office visit; a syringe pierces the skin and refills the pump reservoir.

Initial results in a handful of patients suggested that symptoms had improved, and PET scans indicated some restoration in dopamine uptake in the striatum and substantia nigra. But the results of a larger, more recent trial have been unconvincing: patients who received saline solution fared no better than those who received GDNF. Nevertheless, many of us who work in this area feel that this approach is still worth pursuing. It is not unusual in medicine for the first forays into a treatment to be negative. Levodopa, for instance, initially showed no benefit and only unwanted side effects; now it is one of the principal treatments for Parkinson's.

Other researchers are using gene therapy instead of surgery to administer GDNF, hoping the delivered gene will provide a long-term supply of this neurotrophic agent. Jeffrey H. Kordower of Rush Presbyterian-St. Luke's Medical Center in Chicago and Patrick Aebischer of the Neurosciences Institute at the Swiss Federal Institute of Technology and their colleagues engineered a lentivirus to carry the gene for GDNF and deliver it to dopamine-producing striatal cells in four parkinsonian monkeys. The results were impressive: the monkeys' motor problems significantly diminished, and they were unaffected by a subsequent injection of MPTP, a chemical toxic to dopamine neurons of the substantia nigra. The introduced gene induced cells to make the protein for up to six months, after which the experiments were stopped. Based on these studies, scientists at Ceregene in San Diego are using a similar technique to deliver the protein neurturin, a member of the GDNF family. Although the studies are in the preclinical phase, researchers plan to test a gene similar to the gene for neurturin in human patients.

Still other forms of therapy are being investigated. Working with Avigen near San Francisco, Krys Bankiewicz has shown in animals that placing the

Perhaps one day CHAPERONE-TYPE DRUGS can be developed to limit degeneration in people.

THE AUTHORS

ANDRES M. LOZANO and *SUNEIL K. KALIA* have worked together for several years, studying various aspects of Parkinson's disease. Lozano, who was born in Spain and obtained his M.D. from the University of Ottawa, is professor and R. R. Tasker Chair in Stereotactic and Functional Neurosurgery at the Toronto Western Hospital and the University of Toronto. He has devoted his career to understanding the causes of Parkinson's and developing novel surgical treatments. Kalia recently completed his doctoral degree working with Lozano. His research focused on the role of chaperone molecules in Parkinson's.

gene for an enzyme called aromatic amino acid decarboxylase in the striatum can enhance dopamine production in this area of the brain. In rats and monkeys this approach has also ameliorated parkinsonian symptoms. Trials in patients have been approved and will be launched soon.

Michael Kaplitt of Cornell University and his team are taking a different tack, using gene therapy to shut down some of the brain regions that become overactive when dopamine released from the substantia nigra falls too low—including the subthalamic nucleus of the basal ganglia. (The loss of dopamine causes neurons making glutamate, an excitatory neurotransmitter, to act unopposed and thus overstimulate their targets, causing movement disorders.) Kaplitt will begin human trials using a virus to introduce the gene for glutamic acid decarboxylase—which is crucial to the production of the inhibitory neurotransmitter gamma amino butyric acid (GABA)—to these sites. He and his co-workers hope that the GABA will quell the overexcited cells and thus calm parkinsonian movement disorders. In the experiments, they thread a tube about the width of a hair through a hole the size of a quarter on top of a patient's skull. The tube delivers a dose of virus, which ferries copies of the gene into neurons of the subthalamic nucleus. The chemical released from the altered cells should not only quiet the overactive neurons residing in that region but may be dispatched to other overactive brain areas.

Perhaps the most hotly debated potential treatment entails transplanting cells to replace those that have died. The idea has been to implant embryonic stem cells or adult stem cells and to coax these undifferentiated cells into becoming dopamine-producing neurons. Because embryonic stem cells are derived from days-old embryos created during in vitro fertilization, their use is highly controversial. Fewer ethical questions surround the use of adult stem cells, which are harvested from adult tissue, but some scientists believe these cells are more difficult to work with.

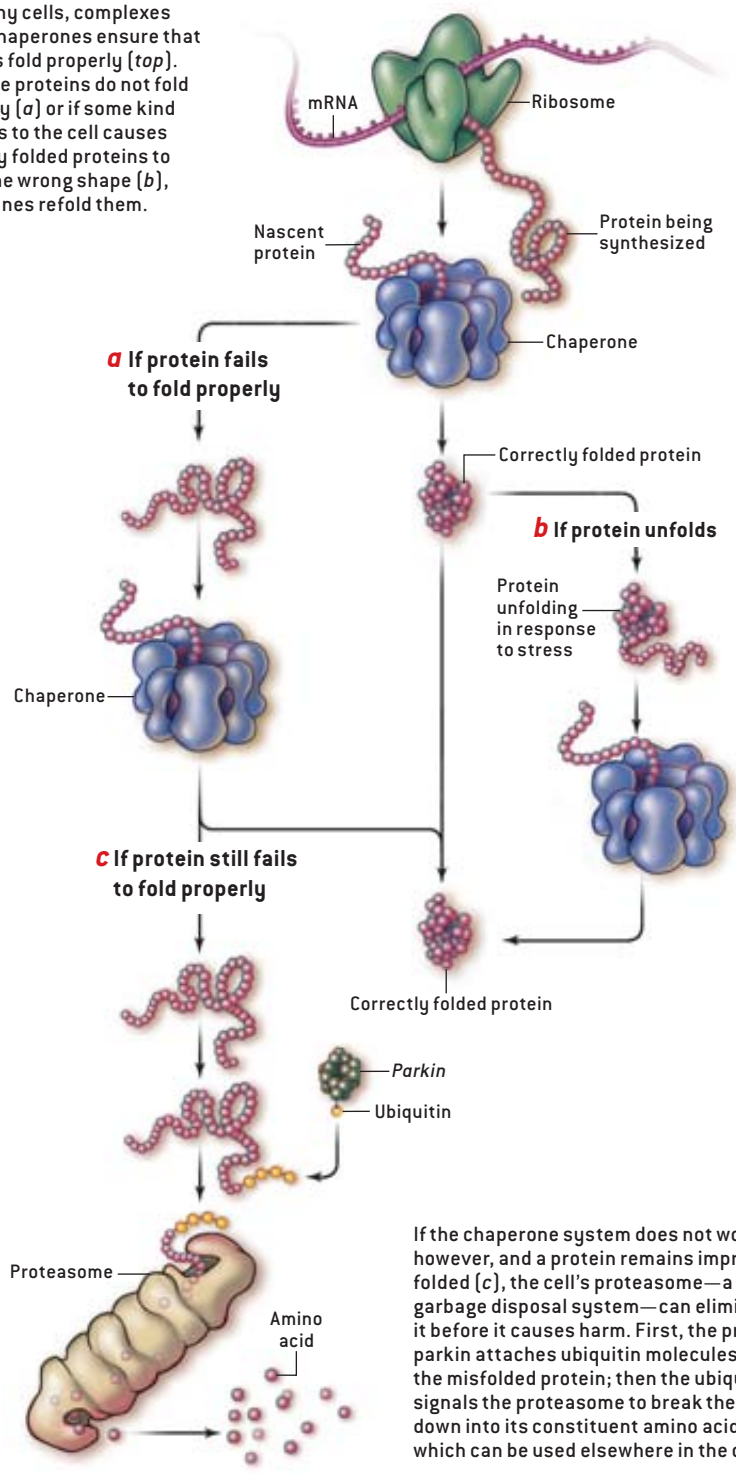
Despite important progress in iden-

PROTEINS AND PARKINSON'S

Accumulations of misfolded proteins called Lewy bodies have been recognized for decades as a hallmark of Parkinson's. Scientists do not yet know whether these protein clusters are protective

PROTEIN FOLDING IN NORMAL CELLS

In healthy cells, complexes called chaperones ensure that proteins fold properly (*top*). When the proteins do not fold correctly (*a*) or if some kind of stress to the cell causes normally folded proteins to adopt the wrong shape (*b*), chaperones refold them.



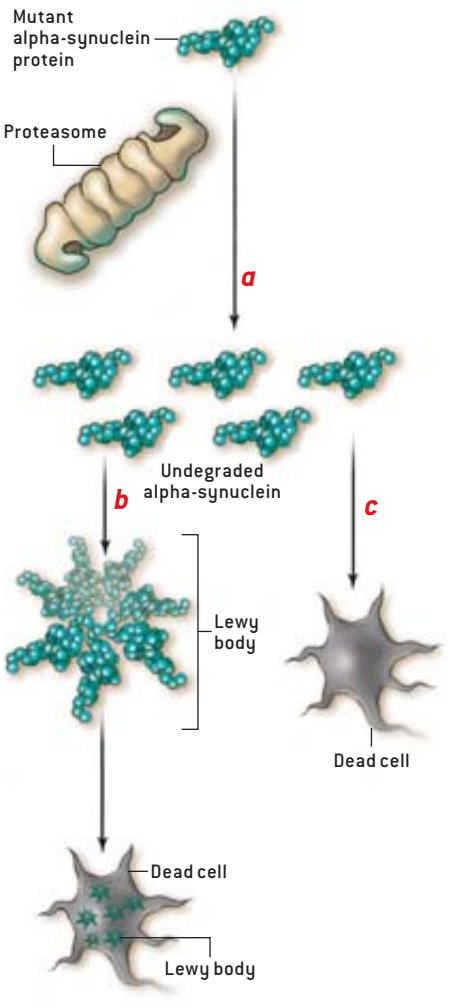
If the chaperone system does not work, however, and a protein remains improperly folded (*c*), the cell's proteasome—a garbage disposal system—can eliminate it before it causes harm. First, the protein parkin attaches ubiquitin molecules to the misfolded protein; then the ubiquitin signals the proteasome to break the protein down into its constituent amino acids, which can be used elsewhere in the cell.

TAMI TOLPA

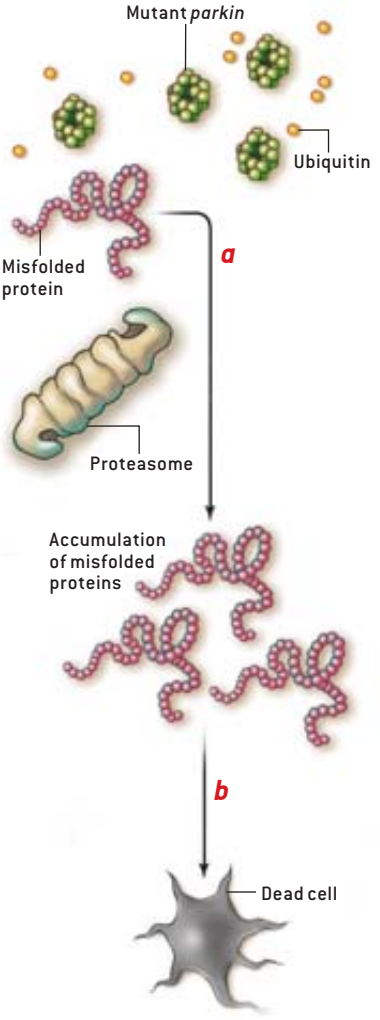
(because they keep the toxic proteins out of mischief) or whether they ultimately trigger the death of nerve cells. Nevertheless, it is clear that proteins gone awry underlie this devastating disease.

WHAT GOES WRONG IN PARKINSON'S

For reasons not fully understood, the chaperone and proteasome system fail in people who become ill with Parkinson's. Misfolded proteins accumulate in cells because the chaperones cannot keep up or the proteasome system cannot break down the miscreant proteins fast enough; this buildup can damage and kill affected neurons. Recent genetic studies have suggested that mutant forms of two proteins—alpha-synuclein (*left*) and parkin (*right*)—can help undermine the chaperone and protein disposal system.



A very rare mutation in the *alpha-synuclein* gene can cause Parkinson's by giving rise to a form of the protein that resists breakdown by proteasomes (*a, above*). In a sign that Lewy bodies might sometimes be protective, groups of mutant alpha-synuclein that end up in a Lewy body (*b*) appear to be less damaging initially than copies of the protein that roam the nerve cell, causing its quick demise (*c*).



In the case of parkin, the mutated versions fail to add ubiquitin to misfolded proteins. As a result, the proteasome cannot break down the proteins (*a, above*), which ultimately cause cell death (*b*). Mutated parkin does not give rise to Lewy bodies.

tifying the molecular cues and recipes for pushing undifferentiated cells to produce dopamine, no one yet knows whether transplantation of any kind will be as fruitful a strategy as has been hoped. The clinical trials using the most meaningful protocols have so far been conducted with fetal material. These have shown hundreds of thousands of surviving transplanted dopamine-producing cells in patients, yet the functional benefits have been at best modest and inconsistent, and the treatment has been associated with serious adverse effects, including dyskinesias (uncontrollable writhing and twisting movements). Scientists are trying to determine why transplantation has not been more helpful and why side effects have arisen, but for now they are not conducting human trials of the procedure in the U.S.

Finally, researchers continue to investigate and refine the approach behind deep-brain stimulation: applying electric pulses. Several months ago Stéphane Palfi and his colleagues at the CEA Frédéric Joliot Hospital Service in Orsay, France, reported that gently stimulating the brain surface could improve symptoms in baboons with a version of Parkinson's. Clinical trials are under way in France and elsewhere to determine whether this surgical intervention is similarly effective in humans.

Although much remains unknown about Parkinson's, the genetic and cellular insights that have come to light in just the past few years are highly encouraging. They give new hope for treatments that will combine with existing ones to slow disease progression and improve control of this distressing disorder. SA

MORE TO EXPLORE

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SIMULATING ANCIENT SOCIETIES

Computer modeling is helping unravel the archaeological mysteries of the American Southwest

By Timothy A. Kohler, George J. Gumerman and Robert G. Reynolds

Only a small fraction of human history is known through texts. For the rest, archaeology is the main source. By examining ruins, artifacts and remains, archaeologists have painstakingly constructed a series of pictures showing human societies as they existed thousands and even millions of years ago. It is much more difficult, however, to determine the processes that produced and changed these societies. Researchers are still struggling to understand the long chain of cause-and-effect (and chance events) stretching from our hominid ancestors of four million years ago—small bands of upright-walking primates with no stone tools and scarcely any conversation—to the communities and cultures we see around the world today.

With the advent of computers, archaeologists began to experiment with simulation as an aid to exploring human prehistory. The logic is simple: you program the computer to mimic processes such as population growth and resource usage, then see how well the software's predictions coincide with the archaeological record. An early example is the well-known attempt in the late 1970s to examine the collapse of the Classic Maya civilization, which dominated a vast swath of Mexico and Central America from A.D. 300 to 900. Led by researchers at the Massachusetts

BILL PROUD (*photograph*); DIGITAL MANIPULATION BY SLIM FILMS

PAINTED HAND, a 760-year-old ruin in the Mesa Verde region of southwestern Colorado, lies within a study area where researchers are using computer models to simulate the settlement and land-use patterns of the ancient Puebloan peoples.

Institute of Technology, this effort looked at the relations between variables such as total population and the rate of construction of Mayan monuments. Because the study considered the variables in aggregate form, however, it could not provide information on spatial relations—for instance, which areas of the Mayan territory had the highest agricultural production.

In recent years, though, a new style of computer language has encouraged the development of more detailed simulations of ancient societies. Object-oriented programming languages such as Java allow researchers to create models containing many interacting agents, which can represent individual households distributed across a landscape. The interactions between the agents can simulate the formation of alliances or the exchange of resources or information. Programmers give the agents built-in rules to specify their actions, but the agents can learn to acquire new behaviors as well.

Our own simulations have focused on the prehistory of the North American Southwest, particularly the Four Corners area where the states of Arizona, New Mexico, Colorado and Utah meet [*see box on page 82*]. This region, home to the ancient Puebloan peoples (also called the Anasazi), has one of the best-known archaeological records in the world, especially for the 1,000 years before the Spaniards arrived in the 16th century. Puebloan culture in this area reached its apex between A.D. 1000 and 1300 with the construction of elaborate towns and cliff dwellings, but by the end of this period the Puebloans had abruptly abandoned their settlements and migrated south to central and eastern Arizona, western New Mexico and the northern Rio Grande Valley.

By comparing the cut timber at Puebloan sites with the tree-ring records for the area, archaeologists can often date the occupation of the settlements quite precisely. Also, paleoclimatologists can use data from tree rings, pollen analysis and the local geology to determine the temperatures and precipitation at the time. Currently we have two agent-based modeling projects that employ this information to reconstruct Puebloan settlement and land-use patterns in the Long House Valley in Arizona and the Central Mesa Verde region in Colorado. This research promises to enhance our understanding of the ancient Puebloans and perhaps shed some light on the mysterious calamities that engulfed their society about 700 years ago.

This research promises to shed some light on the calamities that engulfed Puebloan society.

A Virtual Prehistory

LONG HOUSE VALLEY is a 180-square-kilometer landform in northeastern Arizona that was inhabited by Puebloans from about 1800 B.C. to about A.D. 1300. The valley has been the subject of intensive archaeological investigation for a century, and over the past 25 years multidisciplinary teams led by Jeffrey S. Dean of the University of Arizona's Laboratory of Tree-Ring Research have reconstructed its past environment in great detail. Basing their analysis on precipitation patterns, water-table fluctuations, and cycles of erosion and deposition, Dean and one of us (Gumerman) estimated the maize-growing potential for each hectare in the valley for every year from A.D. 400 to 1450.

Our simulations for the Long House Valley derived from an agent-based computer program developed by Joshua M. Epstein and Robert L. Axtell of the Brookings Institution and the Santa Fe Institute. We began by entering the environmental data on a digitized map of the valley, then placed the agents—simulated households—randomly on the map. The characteristics of the modeled households, such as their nutritional requirements, were based on archaeological data as well as ethnographic studies of contemporary Pueblo groups and other subsistence farmers. In our original model we assumed that each household consisted of five individuals, each individual consumed 160 kilograms of maize per year, only 64 percent of the potential maize yield could be eaten (to account for losses from rodents, insects and so on), and up to 1,600 kilograms of corn could be stored.

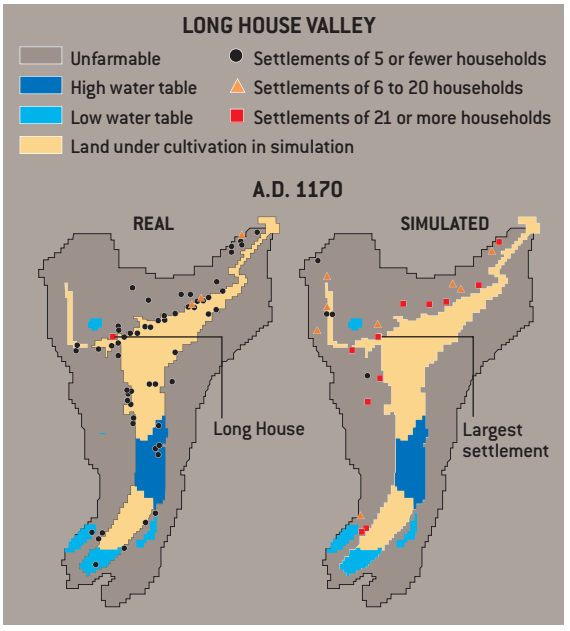
The program implemented simple rules to model settlement patterns. A household would move to a different location in the valley if the expected yield from its farm plot, combined with the amount of grain in storage, fell below what was necessary to sustain the family. Also, a new household would be created whenever a daughter reached the age of 15 (when she would presumably marry and move out). A household's residence had to be located within one kilometer of its farm plot and as close as possible to water sources. The program allowed

Overview/*Virtual Archaeology*

- With the help of new agent-based software, archaeologists have created computer models showing how environmental conditions could have shaped the history of the Puebloan peoples of the U.S. Southwest.
- The simulations suggest that the mysterious disappearance of the Puebloans from Mesa Verde and adjacent areas cannot be entirely explained by the severe drought that occurred in the late 1200s.
- To examine other factors that may have influenced the Puebloans, researchers are building new models that simulate the effects of hunting, fuelwood collection, and cultural processes such as trade and gift giving.

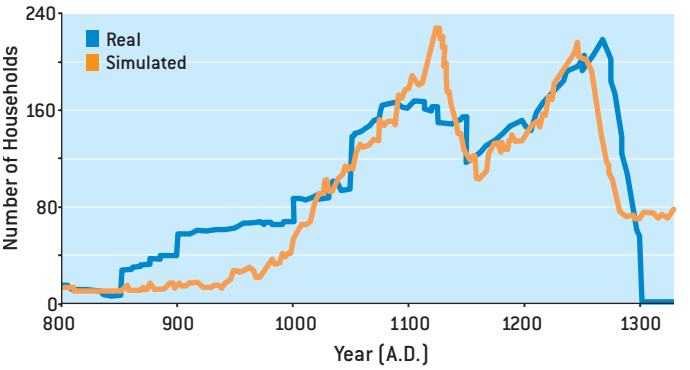
A PREHISTORIC RISE AND FALL

Computer modelers have focused on the Long House Valley in northeastern Arizona, which was inhabited by Puebloan peoples from about 1800 B.C. to about A.D. 1300. By simulating maize-farming and settlement patterns, scientists have tried to explain why the Puebloans suddenly abandoned the valley some 700 years ago.



Researchers constructed the model by entering environmental data—precipitation, water-table fluctuations and so forth—on a digitized map of the valley. The program places simulated households randomly on the map and traces their movements as they seek the best plots for growing maize. By A.D. 1170 the simulation shows the population clustering along the valley's northwestern margin, which matches the actual pattern found by archaeologists (*top left*). Although the simulated settlements are more aggregated than the real ones, the location of the largest settlement in the simulation is within 100 meters of the valley's biggest ruin, the Long House. By 1270 erosion of farmland forces the simulated households to abandon the southern part of the valley, which again mirrors the archaeological record (*middle left*). Ruin Eight, a cliff dwelling, dates from this period (*above*).

In the following years, however, a discrepancy arises. In the simulation, a depleted population survives a long drought; in reality, the valley was completely depopulated by 1305 (*bottom left*). A revision of the model reduced the number of simulated households so that it closely tracked the actual number, but the divergence after 1300 remained (*below*). The results suggest that sociopolitical or ideological factors may have led the surviving Puebloans to leave the valley.

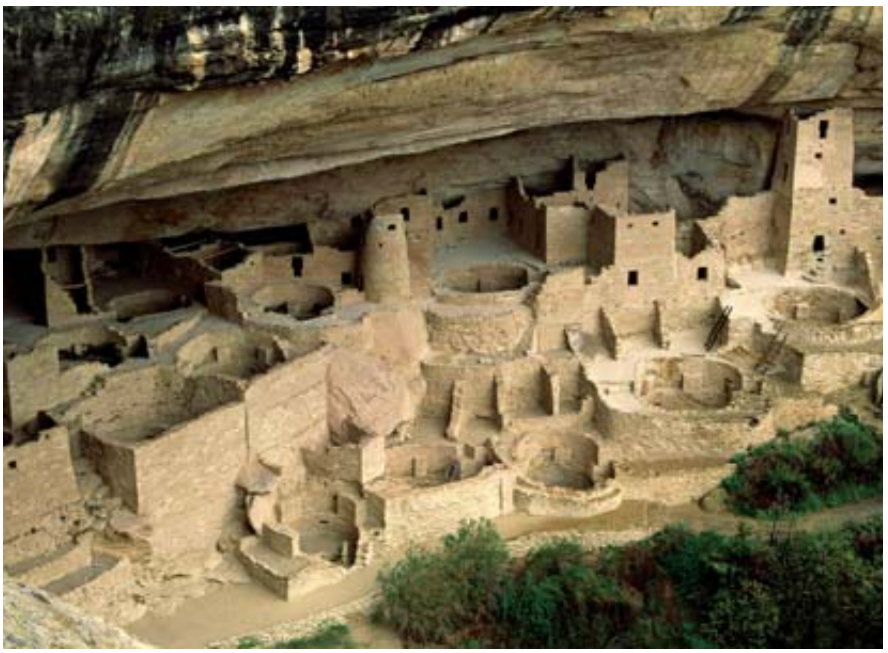


LUCY READING-IKKANDA; SOURCE: JEFFREY S. DEAN *University of Arizona*, GEORGE J. GUMERMAN *School of American Research* AND JOSHUA M. EPSTEIN AND ROBERT L. AXTELL *Brookings Institution* (*maps and graphs*); MUENCH PHOTOGRAPHY, INC. (*photograph*)

researchers to adjust certain variables, such as fertility and life expectancy.

The simulations indicated that environmental conditions largely determined the placement and size of the residences as well as the ebb and flow of population density over time [*see box on preceding page*]. The locations of the virtual residences turned out to be quite near the actual house sites discovered and dated by archaeologists working in the Long House Valley. The original model had one significant discrepancy from reality: the program predicted a population about six times as large as that estimated from archaeological evidence. But when we readjusted the farm production levels to those expected for prehistoric varieties of maize and varied the fertility and longevity of the households, the predicted populations tracked the actual numbers much more closely.

The studies also showed the dramatic effects of the deteriorating environment during the late 1200s, when a long drought coincided with falling groundwater levels. The number of virtual households dropped from more than 200 in 1250 to about 80 half a century later. According to the archaeological evidence, however, Long House Valley was completely empty by the 1300s. Although the environmental conditions could have supported a small population, all the Puebloans in the valley either died or moved away. We can only conclude that sociopolitical, ideological or environmental factors *not* included in our model must have contributed to the total depopulation of the valley. Perhaps the dearth of food made the Puebloans more susceptible to epidemic diseases. Or perhaps the devastated population could no longer maintain their cultural or religious institutions, leading to a collective decision to leave the valley.



CLIFF DWELLINGS grew rapidly at Mesa Verde in the mid-1200s as the Puebloans shifted to more defensible locations. The settlements were abandoned, however, by 1300.

Pit Houses to Great Houses

AN ALLIED SERIES of experiments begun at the Santa Fe Institute uses agent-based modeling to study the prehistory of southwestern Colorado. This area, most of which was originally covered with sagebrush parklands or sparse forests of piñon and juniper, was colonized by farmers around A.D. 600 during the period archaeologists call Basketmaker III. Households lived in pit houses, semisubterranean dwellings where the earthen sides of a shallow pit formed the lower parts of the walls. Pit houses were grouped in hamlets, which were in turn organized in small neighborhoods or communities. Hunting was almost as important as agriculture in their diet. The pioneers were very successful, and aided by additional immigration, their numbers increased markedly. Villages of hundreds of people—a dramatic change in settlement form—appeared in the area in the late 700s, and some became considerably larger by the late 800s. Two of us (Kohler and Reynolds) are investigating why these villages formed where and when they did: Was it perhaps a response to the economic advantages of those locations? Or was it for protection?

These villages were abandoned around 900 when most of the Puebloan peoples left the area. The reasons for this depopulation are under debate. Two possible causes may be deforestation near the villages and a series of cool, dry summers. (The normal climatic variation in this area is from warm, dry weather to cool, wet conditions; cool, dry weather presents special problems for local farmers who depend on rainfall rather than irrigation.) During the 900s and 1000s the conditions for farming improved, both here and throughout the

THE AUTHORS

TIMOTHY A. KOHLER, GEORGE J. GUMERMAN and *ROBERT G. REYNOLDS* have applied their various talents and expertise to the problem of simulating ancient societies. Kohler is a professor in the department of anthropology at Washington State University and a research associate at the Crow Canyon Archaeological Center in Cortez, Colo. He has worked in the U.S. Southwest for more than 20 years, primarily in southwestern Colorado and the northern Rio Grande Valley in New Mexico. Gumerman, the interim president of the School of American Research in Santa Fe, has done archaeology in the Southwest for more than 30 years and published more than 20 volumes on the topic. (Both Kohler and Gumerman are also external faculty members at the Santa Fe Institute.) Reynolds is a professor of computer science at Wayne State University and an associate research scientist in the Museum of Anthropology at the University of Michigan at Ann Arbor. He has written two books and numerous articles on cultural algorithms. The authors would like to acknowledge the support of the National Science Foundation.

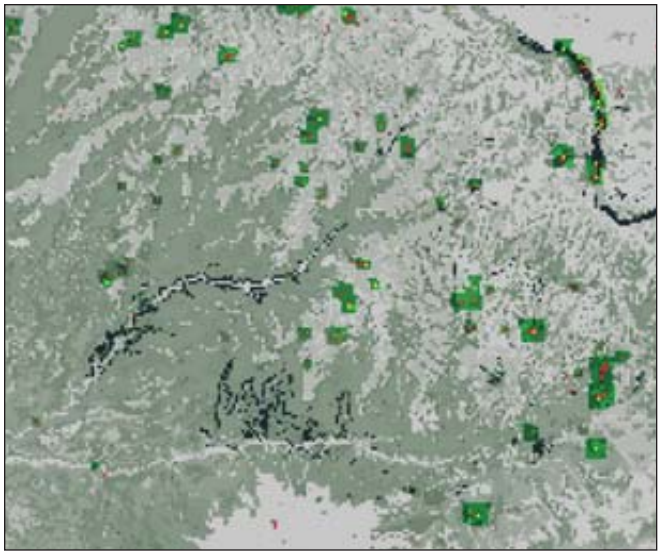
northern Southwest, and local populations slowly rebounded. The raising of domesticated turkey became increasingly important in this period. Once again, most people lived in small hamlets grouped in loose communities. By the late 1000s the villages that acted as centers for these dispersed communities became larger and more numerous. Many appear to have been influenced by the complex Puebloan settlements in Chaco Canyon to the south, in what is now northwestern New Mexico. Some of the Colorado villages have "great houses"—multistory buildings containing many rooms—that resemble structures at Chaco more than they do local architectural styles. The presence of some stockaded sites in our study area in the mid-1000s may represent resistance, ultimately futile, to a Chacoan expansion.

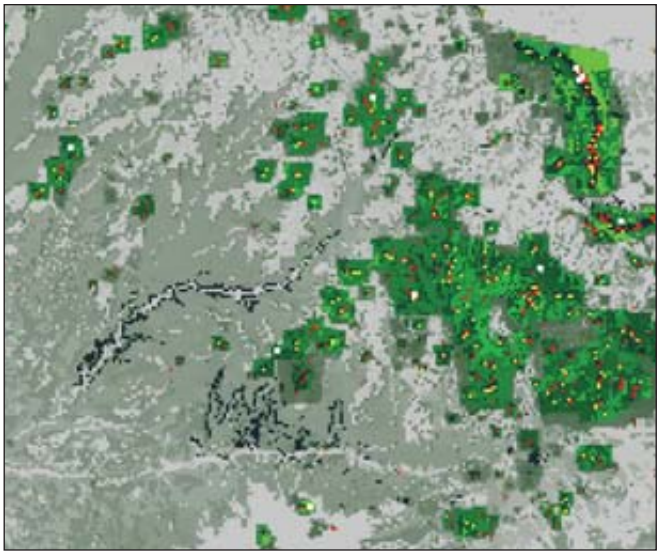
Chaco-style great houses ceased to be built around 1135 at the beginning of a severe 45-year-long drought, a transition marked by episodes of extreme violence, including possible cannibalism. Population growth slowed in the Central Mesa Verde region, but the pattern of larger community centers and smaller surrounding hamlets persisted. By the mid-1200s most community centers shifted to more defensible canyon-head locations or alcoves such as the famous cliff dwellings in Mesa Verde National Park. As elsewhere in the northern Southwest, the occupation of this area terminated in the late 1200s as the remaining population fled to the south and east from the large canyon-head villages amid unfavorable climatic conditions and violence. Explaining this dramatic depopulation remains one of the classic problems of archaeology.

Our simulations cover an 1,800-square-kilometer area northwest of Mesa Verde National Park. We divided the virtual landscape into 45,400 square cells, each 200 meters on a side, with the potential maize productivity for each cell based on its soil type and elevation as well as the yearly precipitation. (Carla R. Van West, now at Statistical Research in Tucson, Ariz., constructed our original annual productivity landscapes as part of her Ph.D. project at Washington State University.) Our early research examined only the period from 900 to 1300. As with the Long House Valley simulation, we generated a random distribution of households and endowed them with rules specifying that they should locate on or near the highest-productivity farming areas not already in use.

The settlement patterns produced by these agents roughly matched the real patterns known from archaeological research in the region. When we also required that the agents take into account the distribution of water in their decisions about where to live—a reasonable assumption given the semiarid landscape—the results were better approximations of the real patterns. Finally, when we adjusted the program to account for the slow degradation of soil under subsistence farming, which would cause households to periodically seek out new plots, the settlement patterns fit the known record better still.

Once again, however, none of our simulations terminated with a population decline as dramatic as what actually happened in the Mesa Verde region in the late 1200s. What other factors could have contributed to the catastrophe? One factor that we *didn't* model is the distribution of surface water in the area, which probably changed as the climate shifted. During the late 1200s, the Puebloan villages clustered around springs, and any cessation of their flow could have been disastrous. Furthermore, the depopulation of our study area (and the rest of the northern Southwest) took place near the onset of the Little Ice Age, a generally cold period from about 1300 to 1850





TIMOTHY A. KOHLER, C. DAVID JOHNSON AND JASON A. COWAN *Washington State University*

ANCIENT EXPLOITATION of the forests of Mesa Verde is illustrated in a computer model simulating the Puebloans' use of fuelwood. The model assumes that the Puebloan settlements—represented on the maps by red (one to two households), yellow (three to nine) and white (10 or more) dots—burned 1.1 metric tons of wood per person each year.

At A.D. 650 (*left*), when the simulated population is relatively low, most of the region contains plentiful amounts of deadwood (*gray areas*). But after 250 years of population growth and continuous foraging (*right*), the areas surrounding the settlements have been stripped of deadwood, leaving only the live vegetation (*green*).

whose effects in the Southwest remain controversial. Because our area is both high in elevation and near the local northern limit for maize farming at this time in prehistory, even a slight decline in growing-season temperatures or in the length of the growing season could have had perilous consequences.

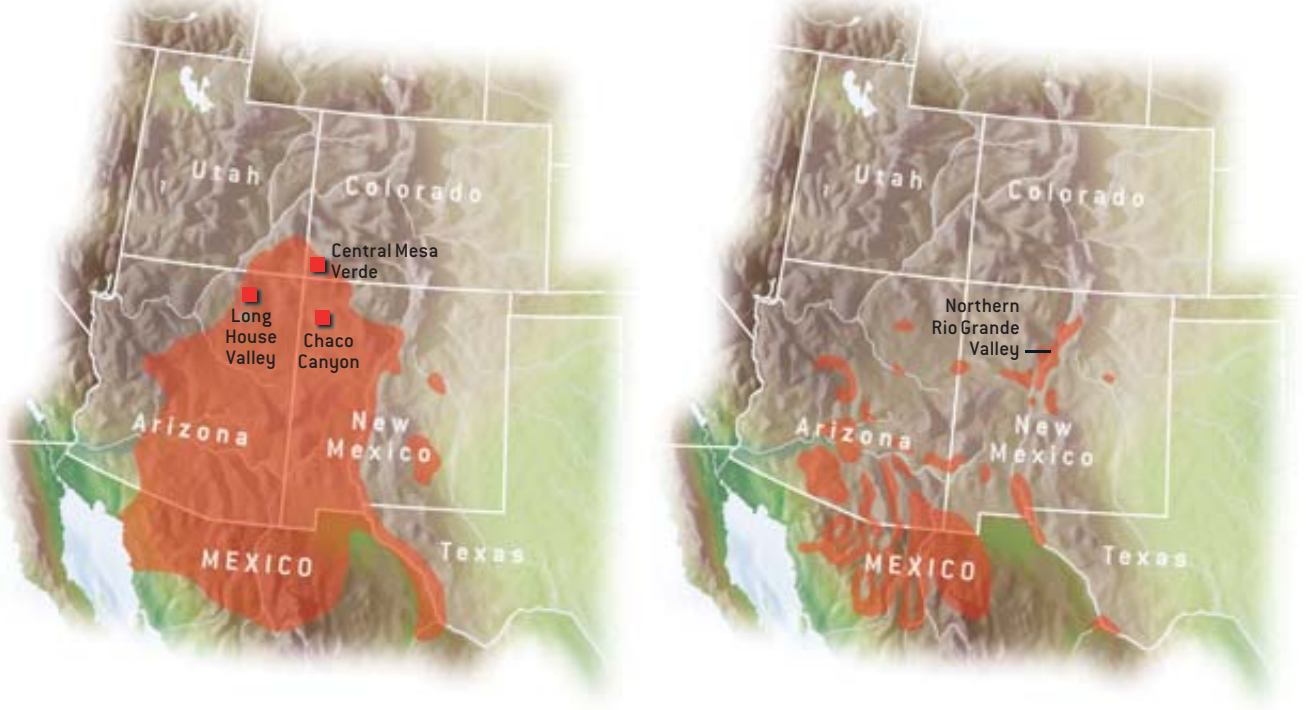
One thing that is becoming apparent from work now being conducted by Washington State University graduate students C. David Johnson and Jason A. Cowan is that the Puebloan peoples depleted the fuelwood in the Mesa Verde region. Johnson and Cowan assumed that Puebloan households burned 1.1 metric tons of wood per person every year, similar to the rates observed for societies in Pakistan at roughly similar elevations and latitudes. Simulations showed that 700 years of fuel use would have denuded large tracts around the settlements [*see box on preceding page*]. We are now creating similar programs to model the long-term effects of hunting on the major game in the region (deer, rabbits and jackrabbits). Our initial studies strongly suggest that hunting would have wiped out most of the deer in the area, which may explain why domesticated turkey became so important to the Puebloan diet after 900.

One of the great benefits of computer simulation is that it allows researchers to conduct experiments, a luxury that is otherwise impossible in an historical science such as archaeology. Scientists can incrementally add detail to their models, testing new environmental and social factors to see if they bring the virtual prehistory closer to the archaeological record. As we extend our research back to 600, we are now using simulations to study the dramatic growth and decline of the early Pueblo villages. The Crow Canyon Archaeological Center in Cortez, Colo., has recently completed new field surveys and an extensive program to redate the more than 3,300 residential sites found in our study area. This work has significantly increased our knowledge of the distribution of Puebloan households over time, providing more precise maps to compare with the simulated household behavior.

Meanwhile Kenneth E. Kolm, a hydrologist at Washington State University and BBL, Inc., and Schaun Smith, a graduate student at the Colorado School of Mines, are developing a model that estimates how much the swings in temperature and precipitation in the study area affected the local springs and streams. When this model is coupled with our settlement simulation, we will be able to see whether changing distributions of water resources could have influenced the decisions of the Puebloan peoples about where to live and farm. We are also incorporating the effects of temperature on farm productivity. Finally, and perhaps most intriguingly, we are making attempts to simulate some of the social and cultural factors that shaped Puebloan societies.

A MYSTERIOUS RETREAT

In the late 1200s the range of the farming peoples of the Southwest stretched north into what is now Utah and Colorado and encompassed mesas as well as river valleys (*left*). By the early 1400s, though, the Puebloan peoples had retreated from the northern areas and settled largely in valleys where irrigated farming was possible (*right*). Computer simulations can help archaeologists study the causes behind this change, which may not be fully explained by environmental factors.



LUCY READING-IKKANDA

Modeling Culture

ONE OF THE PIONEERS of modeling in archaeology, Jim Doran of the University of Essex in England, once stated that "comprehensive models are built, if at all, by many hands over many decades." The models discussed here are no exception. Cultural algorithms—the framework for simulating social and cultural changes—arose from efforts by Kent V. Flannery of the University of Michigan at Ann Arbor to produce a model for the emergence of agriculture in Central American prehistory. Flannery suggested that the transition from hunting and gathering to incipient farming in Mexico's Oaxaca Valley began when people learned to schedule cultivation and harvesting activities. One of us (Reynolds) implemented Flannery's model using data on ancient plant remains from a cave in Oaxaca known as Guilá Naquitz. In these simulations, agents generated plans for procuring resources; the plans that proved most productive were selectively transmitted to a "belief space" in which individual experiences were generalized to produce rules that in turn guided the behavior of other agents in the simulated world. Over time, the model resulted in a cumulative rescheduling of activities that strongly resembled the patterns observed in the archaeological record during the transition to agriculture.

Reynolds, along with Ziad Kobti of the University of Windsor in Ontario, used cultural algorithms in the Mesa Verde simulation to see what happens when households in a kinship network exchange maize with one another. This project models what University of Chicago anthropologist Marshall Sahlins called generalized reciprocity: the exchange, among close kin, of gifts that do not have to be repaid in full measure. (For example, we do not ordinarily expect our children to repay us for their braces, clothes and college.) In the simulations, households employ cultural algorithms to decide which kin they wish to interact with, determining from past experience the kinds of exchanges that are most likely to lead to mutual benefits. If generalizations can be made about the best kinds of exchanges, this knowledge enters the belief space, where it becomes available to other households.

We have found that the addition of these kinship networks to the simulations tends to increase the overall population. As one might expect, households are better able to weather downturns in farm production when they can exchange maize with one another. In some experiments, we restrict the households from moving very far from their present locations when they try to find better places to live; this restriction represents the dangers facing isolated households in a hostile social environment. In such situations, the volume of exchange increases dramatically within each community, but the exchange linkages between the communities disappear, making the population as a whole more vulnerable to climatic fluctuations. The clustering of households also makes it more difficult to collect fuelwood and to hunt, because the land surrounding the communities becomes thoroughly stripped.

Our simulations are not mature enough to specify the exact combination of causes that led to the periodic aggregations of population in the Mesa Verde region or the exodus that began by 1260 and ended shortly after 1280. The computer models make it quite clear, however, that the people living in this area (and presumably elsewhere in the northern Southwest) faced troubles on many fronts in the 13th century. The negative trends probably multiplied as time went on; for example, increased deforestation most likely limited the availability of game and some important nondomesticated plant foods, such as piñon seeds. These declines in turn fostered increased dependence on maize and its exchange and on domesticated turkey, which could be fed maize. If the exchange of maize, perhaps in the context of feasting, was also a chief lubricant for social relationships, then both subsistence and society were precariously poised on the uncertain fortunes of farming.

> These simulations may point to methods for sustaining natural resources in the future.

Although the artificial worlds we create in these experiments are vastly more simple than reality, they still yield some fabulously complex patterns. We have found that virtual households often affect their environment in ways that limit the options of their offspring and even threaten their long-term survival. In addition to illuminating the distant past, these simulations may point to methods for sustaining natural resources in the future. For instance, models showing the effects of deforestation in the Mesa Verde region can help policy makers draw up conservation plans for forests in developing nations. Thanks to computer simulations, the lessons gleaned from ancient societies may soon be applied to the modern world. SA

MORE TO EXPLORE

Guilá Naquitz: Archaic Foraging and Early Agriculture in Oaxaca, Mexico. Edited by Kent V. Flannery. Academic Press, 1986.

Growing Artificial Societies: Social Science from the Bottom Up. Joshua M. Epstein and Robert L. Axtell. Brookings Institution Press and MIT Press, 1996.

Dynamics in Human and Primate Societies: Agent-Based Modeling of Social and Spatial Processes. Edited by Timothy A. Kohler and George J. Gumerman. Oxford University Press, 2000.

Seeking the Center Place: Archaeology and Ancient Communities in the Mesa Verde Region. Edited by Mark D. Varien and Richard H. Wilshusen. University of Utah Press, 2002.

More information on the Central Mesa Verde simulations can be found online at **www.wsu.edu/~village/**

RAPID PROTOTYPING

Make It Quick

Before manufacturing a new product, companies craft models or prototypes to check designs, assess appearance, test fit and function with other parts, or fine-tune molds and dies for the production line. For decades, prototypes have typically been made by hand from drawings, a slow and expensive exercise. But in recent years, various rapid-prototyping techniques that automatically produce three-dimensional parts from computer-aided-design data have reduced the time from weeks to days or hours.

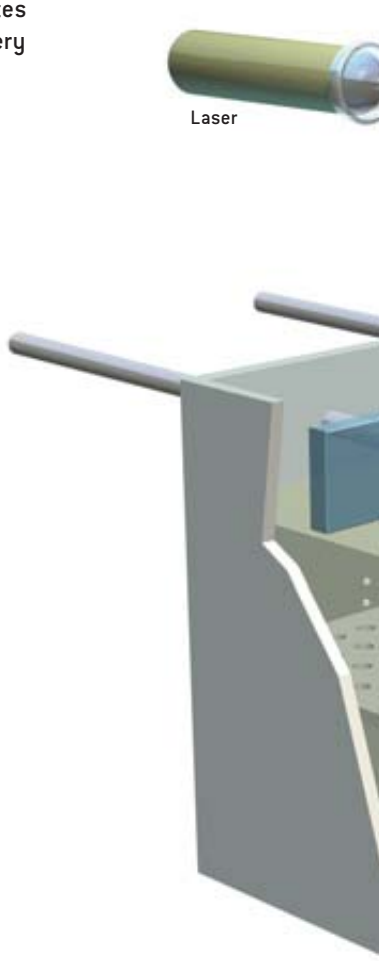
Automotive, consumer-products and medical-device engineers are among the most avid users, along with service providers that make models for clients. Objects are built additively as a series of very thin layers of resin, extruded plastic or powder that are hardened [*see illustrations*].

Stereolithography was the first process and is now the most widely employed. "Maybe 30 other processes have been attempted, but only five or six" have prevailed, says Ron Barranco, owner of Stereolithography.com, a service in Palo Alto, Calif. Among the alternatives are fused deposition modeling and so-called 3-D printers, which can crank out pieces quickly and inexpensively, although they may be a bit less accurate and long-lasting. Stereolithography machines may range from $180,000 to more than $500,000, whereas 3-D printers can cost $25,000 to $60,000.

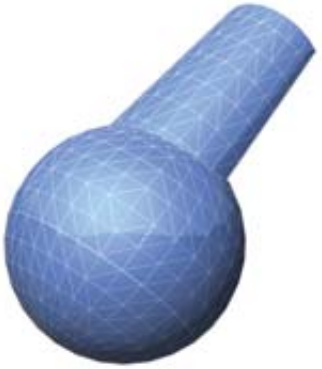
Object size is typically less than 24 inches along the *X*, *Y* and *Z* axes, but larger machines are emerging. Some can build commercial goods directly, eliminating the need for molds, dies and machining, but most products still struggle to match the mechanical, thermal, durability or low-cost properties achieved by traditional manufacturing. Nevertheless, "if production cost is high, volume is low and the object's shape is complex," then rapid prototyping can excel, says Terry Wohlers, president of Wohlers Associates, prototyping consultants in Fort Collins, Colo. For example, most in-ear hearing aids are made this way, because each piece must be custom-fit to each patient's ear canal.

The rapid-prototyping market is growing fast. Proponents say rapid manufacturing is the next step, as tougher materials and still greater precision are demonstrated.

—Mark Fischetti



STEREOLITHOGRAPHY: Software translates design data for an object into a series of very thin cross sections. A perforated platform in a vat of liquid photosensitive polymer rises to the surface. The fluid bubbles up through the platform, and a blade sweeps across, leaving a film. An ultraviolet laser beam, directed by a mirror, traces out the first cross section, converting precise portions of the coating into a solid. The platform drops slightly,and the blade smoothes the liquid just over the solidified area. The laser hardens the second layer on top of the first, and so on, building up the structure. Support columns are added as needed and are later removed.



COMPUTER-AIDED-DESIGN software may define an object as a series of triangles, in part to encode a designer's raw solid-modeling data. A stereolithography machine would then redefine the model as layers for fabrication.

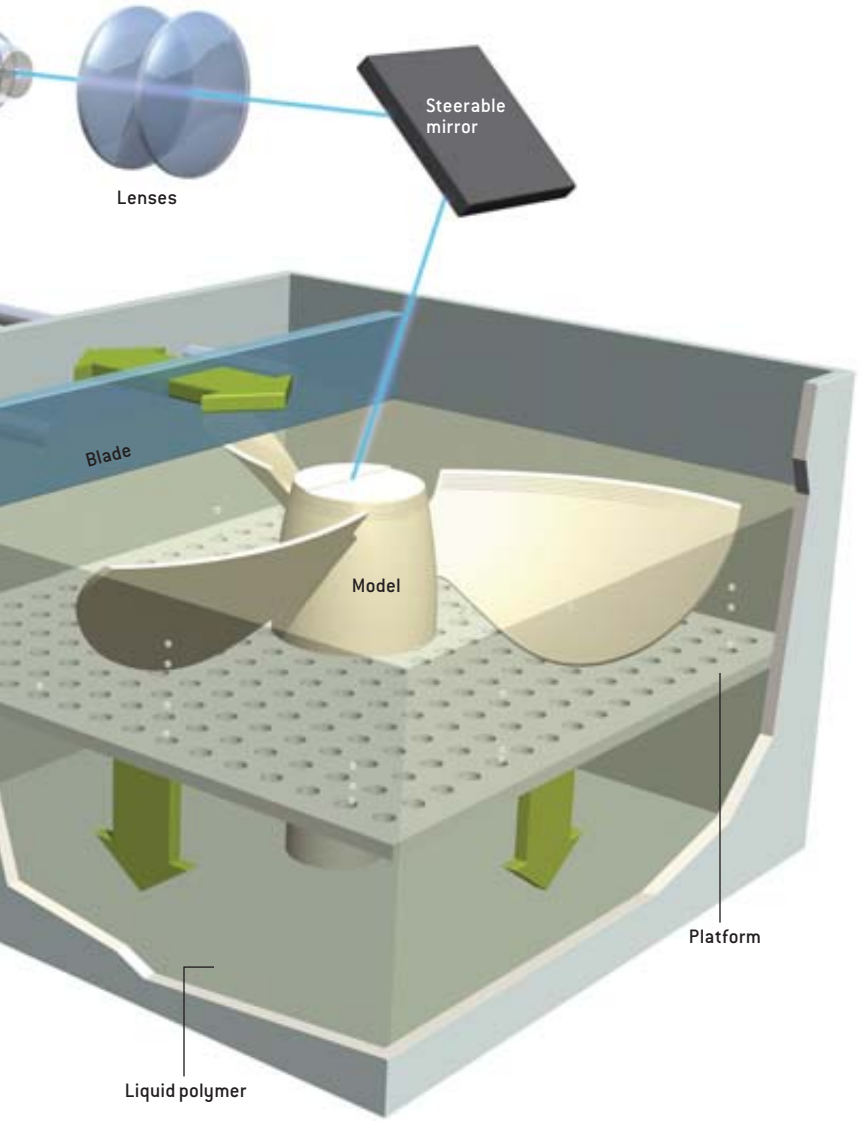
GEORGE RETSECK

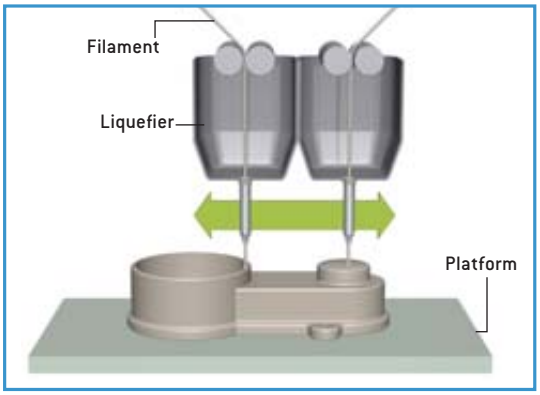
DID YOU KNOW...

JUST ADD HEAT: So-called selective laser sintering is growing in use. A laser forms layers by fusing heat-sensitive nylon or metal powder that is spread on a platform like that employed in 3-D printing. The process creates end products, typically those that must be custom-made for each buyer, such as hearing aids. Other goods include air ducts for Boeing's F-18 fighter jet and parts for the U.S. space shuttle and the International Space Station.

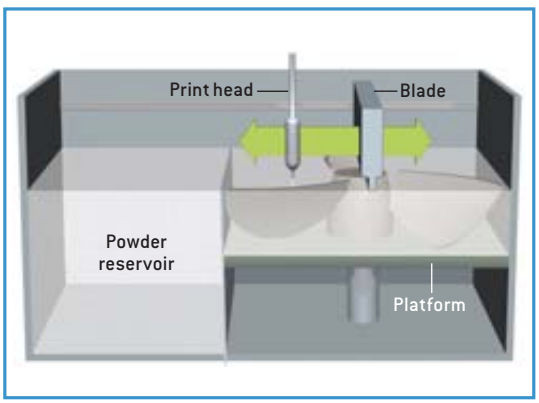
3-D AT HOME: Enthusiasts say homeowners could someday construct their own kitchenware or parts for the car with a rapid-prototyping machine in their basement, from design data sent online by a service provider. But Terry Wohlers of Wohlers Associates thinks that scenario is unlikely "when they could go to Wal-Mart" and buy the item inexpensively. Engineers might do such work from home, but the real market, Wohlers says, will be kids: "The computer design game SimCity, for example, uses 3-D data; a 3-D printer could make all the items. In 10 years, if printer prices drop to $300, just imagine the school projects kids could do."

SOLID, NOT GAS: Despite the many materials employed in stereolithography, Ron Barranco of Stereolithography.com says the key factor in improving quality and reducing cost has been the switch from gas lasers to solid-state lasers. "The gas lasers were less accurate and wore out," he explains.





FUSED DEPOSITION MODELING: Filaments of thermoplastic are warmed and liquefied. An extrusion head deposits a thin bead of material onto a platform, tracing out the object's first layer, like a baker decorating a cake. The platform is kept cool so the plastic sets quickly. After the platform lowers, a second layer is extruded, and so on.

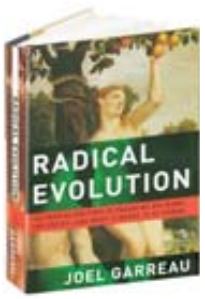


3-D PRINTING: A blade brushes a thin layer of composite, ceramic or casting powder across a platform, and a print head, like that in an inkjet printer, sprays a fine pattern of binder fluid that hardens the powder where needed to form the object's initial layer. The platform lowers, more powder is spread, binder makes the second tier firm, and so on. Excess powder is later blown away. Wax or resin can be impregnated into final parts to enhance durability.

Topic suggested by readers Carl Groat and Yang Zhou. Send ideas to workingknowledge@sciam.com

The Future of Humankind

SCENARIOS FROM HEAVEN TO HELL, WITH STOPS ALONG THE WAY **BY NICK BOSTROM**



RADICAL EVOLUTION: THE PROMISE AND PERIL OF ENHANCING OUR MINDS, OUR BODIES—AND WHAT IT MEANS TO BE HUMAN
by Joel Garreau
Doubleday, 2005 ($26)

What's in store for humanity? It is becoming clear that we will use our growing technological powers to transform not only the world around us but ourselves, too. Many forms of human enhancement are already routine—sports medicine, psychotropic mood drugs, wakefulness and alertness enhancers, cosmetic surgery, drugs for sexual performance. Much more will become possible in coming decades.

Joel Garreau's *Radical Evolution* joins several recent titles that attempt to make sense of the radical future possibilities for our species. The potential prospects include superintelligent machines, nonaging bodies, direct connections between human brains or between brain and computer, fully realistic virtual reality, and the reanimation of patients in cryonic suspension. As enablers of such miracles, Garreau mentions especially "GRIN technologies"—genetics, robotics, information technology and nanotechnology.

The focus of Garreau's book, however, is not on the nuts and bolts of the technology itself but rather on what it will all mean for us humans. His reporting skills well honed by his work as a journalist and editor at the *Washington Post*, Garreau is constantly on the lookout for the human story behind the ideas. Biographical sketches of the people he has interviewed for the book get approximately equal airtime with their opinions about human extinction and transcendence. The bulk of one interviewee's beard, the size of another's collection of musical instruments, the length of a third's pants: as Garreau knows all too well, these are the indispensable rivets to hold the attention of the current version of *Homo sapiens* while we try to ponder whether we will have indefinite life spans or whether the world will end before our children have a chance to grow up.

Garreau organizes his material around several scenarios. Unfortunately, these are not very carefully delineated. It is not clear whether all of them are meant to represent separate possibilities.

In the Curve Scenario, information technology continues to improve exponentially, and this progress bleeds over into adjacent fields such as genetics, robotics and nanotechnology. In the Singularity Scenario, "the Curve of exponentially increasing technological change is unstoppable" and leads, "before 2030, to the creation of greater-than-human intelligence," which proceeds to improve itself "at such a rate as to exceed comprehension." There is a Heaven Scenario, which serves as a rubric for a future in which "almost unimaginably good things … including the conquering of disease and poverty, but also an increase in beauty, wisdom, love, truth and peace" are happening pretty much on their own accord, without deliberate steering. Garreau associates this view with the distinguished inventor Ray Kurzweil. We are told that one of the early "warning signs" that we are entering the Heaven Scenario is that the phrase "The Singularity" enters common usage.

There is also a Hell Scenario. The chief talking head assigned to this scenario is Bill Joy, who was a co-founder of Sun Microsystems. In April 2000 Joy published a bombshell article in *Wired* entitled "Why the Future Doesn't Need Us," which described how the author had come to the realization that advances in genetics, nanotechnology and robotics will eventually pose grave threats to human survival. The article argued for the relinquishment of some lines of research in these fields. Since then, we

"I was wondering when you'd notice there's lots more steps."

learn, Joy has got divorced, quit Sun, and put the book he was preparing on hold. "Overall his affect was markedly flat," Garreau writes.

One of the early warning signs that we are entering Hell is that "almost unimaginably bad things are happening, destroying large chunks of the human race or the biosphere, at an accelerating pace." Aside from Bill Joy, the chapter on the Hell Scenario features appearances by Francis Fukuyama, Martin Rees, Bill McKibben, Leon Kass and Frankenstein. The common denominator of these fellows is that they have confronted the potential for catastrophic technological downsides. But their worries are not all of the same kind. For example, while Joy focuses on direct threats to human survival (such as bioterrorism), Kass, who is chairman of President Bush's Council on Bioethics, is more concerned about subtle ways in which our quest for technological mastery could undermine the foundations of human dignity. These very different sorts of concerns could have been kept more clearly distinct.

Garreau's last scenario, Prevail, extols the human knack for muddling through—"the ability of ordinary people facing overwhelming odds to rise to the occasion because it is the right thing." The defining characteristic of the Prevail Scenario is that human beings are picking and choosing their futures in an effective manner. The main representative selected for this scenario is Jaron Lanier (the guy with the large collection of musical instruments). Lanier dreams of creating more ways for people to share their thoughts and experiences, and he is fond of pointing out that faster computer hardware does not necessarily lead to equivalent improvements in the usefulness of the software that runs on the computers.

In the final chapter, Garreau asks: "Will we forever keep mum about our obviously intense desire to break the bonds of mortality? Or should we lift the taboo and start dealing with it?" His implied answer is yes. He then asks, "Shall we be bashful about these lines we are crossing because we do not have a way to make them meaningful?" At this point, Garreau has a constructive proposal: let's create some new rituals. Perhaps, he suggests, we should have "a liturgy of life everlasting as a person receives her first cellular age-reversal workup." Why not indeed?

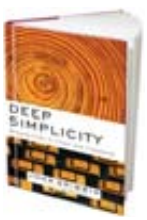
In the meantime, there is still some work left to do in the laboratories. If we develop the cure for aging in a timely fashion, while steering clear of the disasters that Joy and others have foretold, we may one day get to enjoy indefinite life spans with much improved physical and mental capacities—and some cracking new ceremonies, too. SA

Nick Bostrom is in the faculty of philosophy at the University of Oxford. Many of his papers are available at www.nickbostrom.com

THE EDITORS **RECOMMEND**

DEEP SIMPLICITY: BRINGING ORDER TO CHAOS AND COMPLEXITY

by John Gribbin. Random House, 2004 ($24.95)



"The surprise that we unfold in this book is that chaos begets complexity, and complexity begets life," Gribbin writes. "The great insight is that chaos and complexity obey simple laws." Chaos in everyday life is random and unpredictable. "But the kind of chaos we are discussing here is completely orderly and deterministic, with one step following from another in an unbroken chain of cause and effect which is completely predictable at every stage—in principle."

Yet sometimes, in chaos theory, the complex outcome is not predictable. Gribbin, a science writer trained in astrophysics and currently a visiting fellow in astronomy at the University of Sussex in England, smoothly traces the steps from chaos to complexity in such things as weather, earthquakes, the properties of the solar system, and the rise of the most complex system now known—life on Earth. And then he explores "the biggest question," which is whether there is "life beyond Earth."

THE GRAIL BIRD: HOT ON THE TRAIL OF THE IVORY-BILLED WOODPECKER

by Tim Gallagher. Houghton Mifflin, 2005 ($25)

This book is an outstanding example of the behind-the-recent-headlines genre. It tells the story of the obsessive quest to find the ivory-billed woodpecker, which was feared to be extinct (no confirmed sightings since 1944). Big, mysterious, iconic, the bird is "a symbol of everything that has gone wrong with our relationship to the environment." In the 19th century, it was plundered by collectors, and in the 20th, extensive habitat destruction seemingly drove it to extinction.

Gallagher, editor of the Cornell Laboratory of Ornithology's publication *Living Bird,* has searched for the bird off and on for three decades. One day in February 2004 he read a posting on a canoe club Web site about a strange woodpecker that a kayaker named Gene Sparling had seen on a float trip down a remote bayou in eastern Arkansas. Less than two weeks later Gallagher and his fellow seeker, Bobby Ray Harrison, were in the swamp with Sparling, looking for the elusive bird. As readers of headlines know, they found it. The discovery gives us, Gallagher writes, "one final chance to get it right, to save this bird and the bottomland swamp forests it needs to survive."

The Big Dig

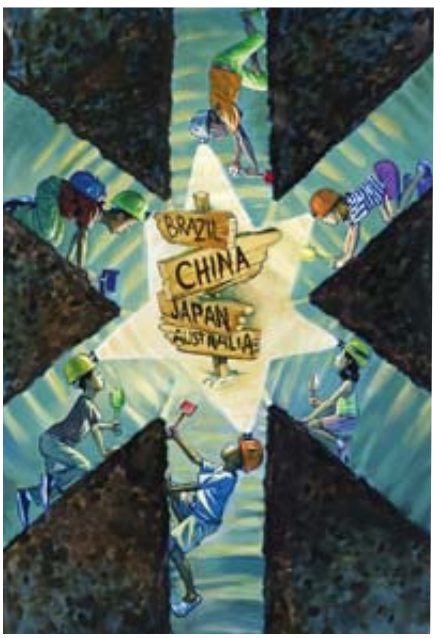
A CROSS-CULTURAL LOOK AT CULTURAL CROSSINGS **BY STEVE MIRSKY**

Generations of American kids have been told that if they dig down far enough they'll get to China. Of course, this assertion is not true. For one thing, most kids dig with spoons or those cheap, red plastic shovels, which could never make it through the planet. Another reason is that kids are notoriously bad at shoring up the sides of deep holes, resulting in inevitable cave-ins once they reach a depth of six inches.

The subject of kids digging to China recently came up in casual conversation among some friends who apparently had even more free time than kids attempting to dig to China. I first asked *Scientific American* editor in chief John Rennie where he thought an American kid would actually wind up. "If we had a globe in the office, I could check," he responded. "But of course there's not a globe to be found. Nor an astrolabe. And all our mortars and pestles are broken."

The question then arose as to where wee ones worldwide wonder they'll wind up. I e-mailed acquaintances around the world. While awaiting responses, I located a globe—start from most of the contiguous U.S., and you'll end up drowning in the Indian Ocean. (Although if you start in Albany, N.Y., you'll come out suspiciously close to Albany, Australia. And *Scientific American* copy editor Michael Battaglia says, "In Buffalo, with all the snow, we would dig to the driveway surface.")

Although globe-trotting *Scientific American* editor George Musser hadn't heard any international versions of it, he likes the dig-to-China idea despite its inaccuracy. "Sure, the antipodal geography is incorrect, but it helps turn the idea of a spherical planet from an abstraction into something concrete," Musser says. "I considered it a success when I asked a roomful of middle school boys what they'd see if they looked straight down and they answered, 'Up girls' skirts.'



When you're teaching, you take what you can get."

Then the variations rolled in. Claudio Angelo writes, "In the Brazilian case, Japan. And it's not a myth! I have friends of friends who indeed dug long enough and wound up (or down) in Japan." Taro Mitamura sends word that Japanese kids reciprocate by heading for Brazil.

South African Rehana Dada says, "We got Australia, but that's because we're Anglocentric." Many Europeans likewise start for Australia or New Zealand, with some exceptions. "We are less ambitious than Americans," says France's Odile Eisenstein. "We dig till the center of the earth." *Scientific American* art director Mark Clemens grew up in England. "At the age of six, I chose the lowest point in the local park," Clemens says, "and with four other friends we started digging, determined to reach my friend's cousin in Australia." Even with the advantage of starting at the local minimum altitude, they didn't get too far. "Seven feet. About to India, I believe," he recalls.

Aussie Natasha Mitchell and New Zealander Graham Collins, a *Scientific American* editor, say they also dug for China. (Even though the Antipodes Islands, near New Zealand, got their name for being straight across from Greenwich, England.) "Digging to Britain just doesn't have the same ring as digging to China," Collins says. He also recommends a 1988 New Zealand movie called *The Navigator,* which "features medieval miners in England who dig through the earth to modern-day New Zealand seeking a cure for the Black Death," ironically while inventing black lung.

The last word goes to Chinese journalist Li Hujun: "I don't think there is a similar expression in China. The ancient Chinese believed that the sky was round and the earth was flat—the tortoise was the symbol of heaven and earth, its shell compared to the vaulted heaven and the underside to the flat disk of the earth." And who can't dig that? SA

ILLUSTRATION BY MATT COLLINS; PHOTOGRAPH BY FRANK VERONSKY

ASK THE EXPERTS

Q Why do flowers have scents?

—H. James, Woodbridge, Va.

Natalia Dudareva, associate professor in the department of horticulture and landscape architecture at Purdue University, offers an answer:

Scent is a chemical signal that attracts pollinators to a particular flower in search of nectar or pollen, or both. The volatile organic compounds emitted play a prominent role in the localization and selection of blossoms by insects, especially moth-pollinated flowers, which are detected and visited at night. Species pollinated by bees and butterflies have sweet perfumes, whereas those pollinated by beetles have strong musty, spicy or fruity smells.

To date, little is known about how insects respond to the individual chemical components, but it is clear that they are capable of distinguishing among complex aroma mixtures. In addition to attracting insects and guiding them to food resources within the bloom, floral volatiles are essential for insects to discriminate among plant types and even among individual flowers of a single species. For example, closely related plant species that rely on different types of insects for pollination produce different odors, reflecting the olfactory sensitivities or preferences of the pollinators. By providing species-specific signals, the fragrances facilitate an insect's ability to learn particular food sources, thereby increasing its foraging efficiency. At the same time, successful pollen transfer (and thus sexual reproduction) is ensured, benefiting the plants.

Scent outputs tend to be at the highest levels only when the flowers are ready for pollination and when potential pollinators are active. Bees and butterflies tend to plants that maximize their output during the day, whereas flowers that release their fragrance mostly at night are visited by moths and bats. During development, recently opened and young buds, which are not ready to function as pollen donors, produce fewer odors and are less appealing to pollinators than older flowers are. Once a flower has been sufficiently fertilized, its bouquets are again reduced, encouraging insects to select other blossoms instead.

Q How are tattoos removed?

—T. Durkee, Berkeley, Calif.

Dermatologist Joshua L. Fox, director of Advanced Dermatology's Center for Laser and Cosmetic Surgery in New York City, explains:

Industry experts say that 50 percent of people with tattoos will someday consider getting rid of their body art. Doctors remove the markings using three types of lasers: alexandrite, YAG and ruby. Each works on different pigment colors and compounds, so the dermatologist will use one or a combination of lasers depending on the nature of a given tattoo. (It follows that you would want to select a dermatologist who has the specific laser necessary for removing your tattoo.) Tattoo pigment is inserted into the dermal layer of the skin through ruptures in the top layer, or epidermis. To remove that pigment, the laser emits very short pulses, which are selectively absorbed by the color of the tattoo ink. This high energy fragments the pigment into smaller particles that are then removed by the body's immune system. In most cases, a series of laser treatments can remove 90 to 95 percent of the original design.

Patients who want a tattoo removed should seek a dermatologist with experience and equipment specific for the procedure. Good questions to ask include how many such procedures the practitioner has done and whether he or she owns the lasers or leases them. Doctors who own their lasers typically do more tattoo removals and as such have more practical experience. SA

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

MATT COLLINS