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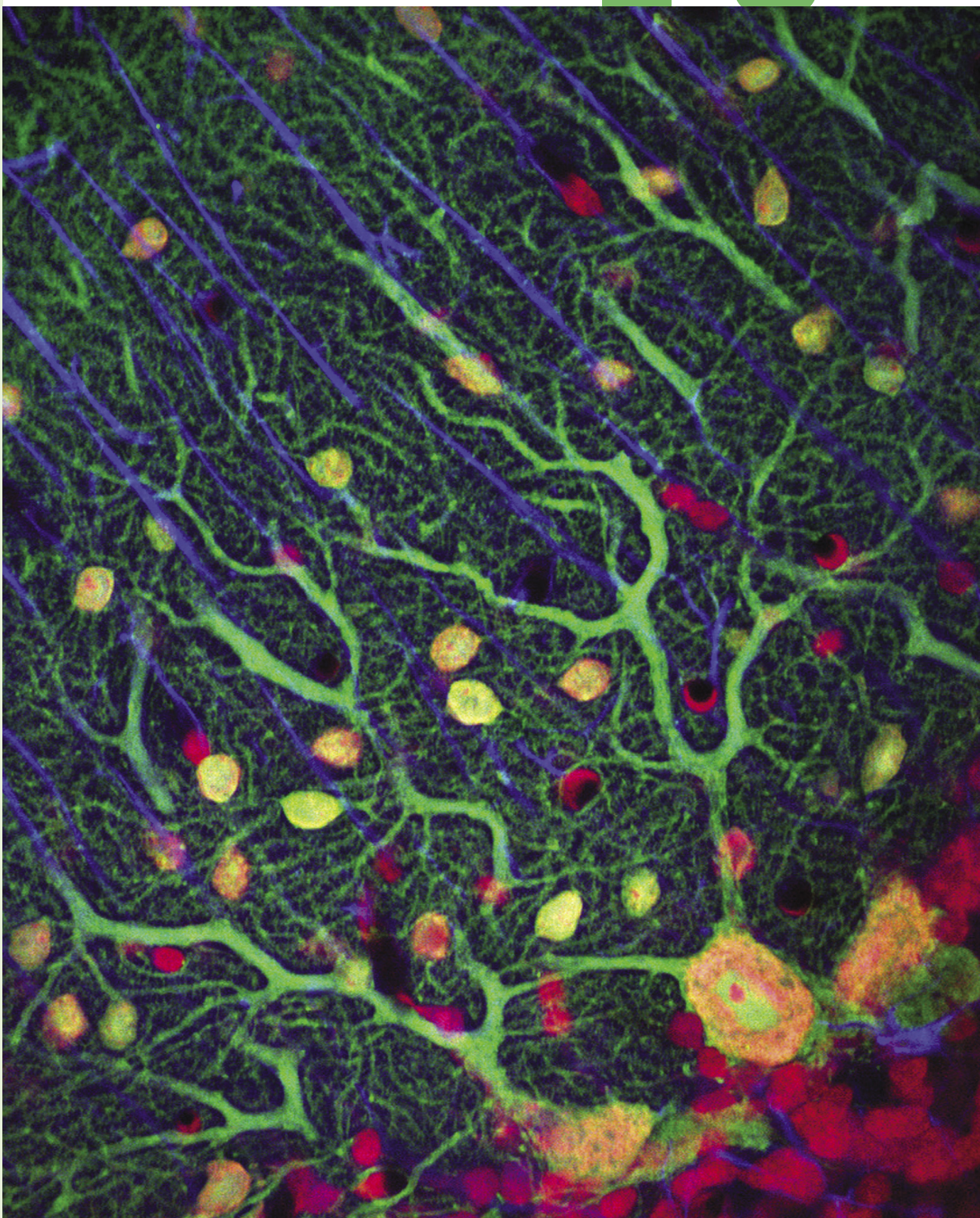

Volume LXIV, Number 2, 2001

IN THIS ISSUE

This wide-angle view of Mars's south pole was shot by JPL's Mars Global Surveyor on September 12, 2001, four years to the day after it arrived at the Red Planet. The bright, layered-looking region in the center is the permanent cap, and the bright halo surrounding it is the seasonal frost cap that was deposited during the southern winter, which ended on June 17. The frost contains both water and carbon-dioxide ices. The hazy zone on the left side of the image is afternoon clouds and fog. For scale, the permanent cap is about 420 kilometers across.

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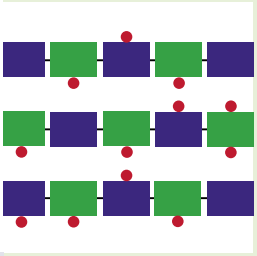

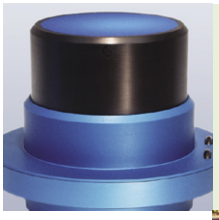

On the cover: This jungle scene, reminiscent of the paintings of Henri Rousseau, is just a tiny, tiny part of the forest of dendrites emanating from the Purkinje cells in a rat's cerebellum. Each of those green branches carries messages to other nerve cells. For more on how nerve cells talk to one another and keep all their messages straight, see the story on page 14. (Image courtesy of John Crum and Thomas Deerinck, National Center for Microscopy & Imaging Research, UC San Diego.)

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BSI Wraps It Up

Caltech has successfully completed a $111-million fundraising effort that began in 1998 to expand the biological sciences, exceeding the original $100-million goal. Funds raised during the Biological Sciences Initiative (BSI) will make possible a new building, new professorships and fellowships, new faculty appointments, and a wide range of new research programs. "Caltech's biological heritage and traditional interdisciplinary strength give us a powerful advantage when addressing fundamental biological questions," says President David Baltimore. This research will result in new drugs and therapies to address diseases such as cancer and AIDS, and will also lead to a deeper understanding of how organisms develop and why they sometimes develop anomalies, as well as an understanding of the biological basis of higher-level brain functions such as consciousness and cognition.

Cochairs for the BSI were Caltech alumnus Ben Rosen (who has since been named chairman of the board of trustees), who contributed $5 million and thereby single-handedly met the campaign's goal for endowed graduate fellowships, and senior trustee Camilla Frost, who contributed $5 million toward construction of the Broad Center for the Biological Sciences.

The Broad Center is named for Caltech trustee and Los Angeles business and civic leader Eli Broad and his wife, Edythe, who provided $23 million—the lead gift—for the building. It will house about a dozen research groups working in such areas as structural, behavioral, and computational biology, and will also contain shared facilities for electron microscopy and magnetic resonance imaging. Additional funding for the building's construction and equipment has come

Work goes on apace inside and outside the Broad Center, slated to open for business in the summer of 2002.

from the estate of William Hacker (BS '31), which provided $8 million in capital funds and $1.4 million in discretionary funds. And more than 5,500 alumni responded to a challenge from Ron and Maxine Linde, in which the Lindes agreed to match new and increased gifts toward the naming of the Ronald and Maxine Linde/Caltech Alumni Laboratories on the Broad Center's ground floor.

The BSI endowed eight new professorships. Trustee Donald Bren contributed $10 million through the Donald L. Bren Foundation to support new faculty as Bren Scholars and eventually endow five Bren Professorships. Also, Caltech received $5 million from the late William and Georgina Gimbel, to be designated for the William T. Gimbel Discovery Fund in Neuroscience. The Keck Foundation, too, provided a $5-million Discovery Fund.

Caltech has already appointed several new young faculty members whose interests embody the initiative's interdisciplinary nature. For example, David Chan, assistant professor of biology, uses cell-biological, biophysical, and genetic approaches to study how membrane-bound systems like organelles and

John Hume to Give DuBridge Lecture

Northern Irish political leader John Hume, who regularly strode through tear gas and dodged rubber bullets in his quest for peace, will be the featured guest at Caltech's Lee A. DuBridge Distinguished Lecture. "A Conversation with John Hume" will take place Tuesday, November 20, at 8:00 p.m. in Beckman Auditorium. The *Boston Globe*'s Kevin Cullen, who served as the newspaper's bureau chief in Dublin and London, will conduct the interview.

Hume was the corecipient of the 1998 Nobel Peace Prize with David Trimble, leader of Ireland's Ulster Unionist party. Until recently, Hume led that country's Social Democratic and Labour Party (SDLP). Hume is Catholic; Trimble, a Protestant. Together they helped negotiate the so-called Good Friday agreement, which remains the basis for negotiations in Northern Ireland.

The event is free and open to the public. No tickets are necessary; at least 500 seats will be available on a first-come, first-served basis. Doors open at 7:30 p.m. For more information, call 626-395-4652 or, toll free, 888-222-5832. □—*MW*

viruses fuse under certain circumstances. In particular, he is interested in understanding the fusion mechanism of mitochondria—organelles important for energy production and cell death. He also studies how the human immunodeficiency virus (HIV), the agent of the disease AIDS, enters human cells by fusing with the cell membrane. And Dianne Newman, the Clare Boothe Luce Assistant Professor of Geobiology and Environmental Engineering Science, is leading a project to investigate how microorganisms and Earth's near-surface environments have interacted over billions of years. Her work integrates molecular microbiology with geochemistry and field geology to try to identify chemical signatures of early life in the geological record.

"The biological sciences today present an intellectual challenge that is changing the environment at Caltech," said Mel Simon, the former chair of the Division of Biology, who played a pivotal role in the BSI. "So the resources are here, the vision is here, and some of the people are here. Now all we have to do is great science." □—*RT*

Undergrads Ride the "Vomit Comet"

Though the nickname "Vomit Comet" would scare most people off, four Techers couldn't wait to board NASA's modified KC-135 jet tanker last summer in the name of science. (The plane allows Earthbound scientists fleeting access to zero gravity by flying a parabolic trajectory that produces about 30 seconds of weightlessness; some people handle this worse than others.) Twice a year, university students across the country are encouraged by NASA's Johnson Space Center in Houston to submit proposals to its Reduced Gravity Student Flight Opportunities Program. The winners get to fly the Comet to conduct their experiments.

One of 2001's 35 winning teams consisted of Serena Eley, Dirk Englund, and John Ferguson, all senior physics majors, and sophomore aeronautics major Joseph Jewell. They made tiny droplets of a type of glass called ZBLAN—named for the zirconium (Zr), barium (Ba), lanthanum (La), aluminum (Al), and sodium (Na) it contains—that for some years now has been touted as the fiber-optic material of the future. The optical fibers that are the backbone of today's high-speed data lines are based on silicon dioxide, as is ordinary window glass, and transmit a fairly narrow range of wavelengths. Ultraviolet light, for example, is blocked—you can't get a suntan though a picture window. Near-infrared light is transmitted reasonably well, but the glass quickly turns opaque at longer wavelengths. And even in the visible spectrum, ordinary glass is pretty absorptive—try looking through a piece of glass end-on some time.

ZBLAN is a radically different material that contains no silicon or oxygen. It is a complex mixture of the five previously mentioned metals and fluorine—one of a family of "heavy-metal fluoride" glasses that has been known for about 20 years. ZBLAN is nearly perfectly transparent from the near-ultraviolet to the near-infrared. It's a very tricky material to make here on Earth, however, as molten ZBLAN generally begins to crystallize as it cools. Presumably, the heavier molecules—the zirconium and lanthanum fluorides—have the slightest tendency to sink, while the lighter ones rise. This inadvertent sorting leads to crystallization as like molecules congregate. Each crystal acts somewhat like a tiny mirror, and there go your optical properties—the sample turns milky. But previous experiments on the Comet and elsewhere have shown that zero-G ZBLAN retains its amorphous character as it cools, remaining crystal-clear.

Jewell (left) and Ferguson with the experimental setup, which was kept under helium to prevent oxygen or moisture contamination.

When you hit the top of the parabola, even a harness won't stop you from floating, as Englund (left) and Eley (below) discover.

So if fibers are the name of the game, why were the Techers making droplets? Because ZBLAN microspheres some 300 to 400 microns (millionths of a meter) in diameter could act as "resonators" to store photons of light for long periods of time. These resonators could be married to silicon chips to make oscillators, switches, modulators, and even tiny lasers. Such components are essential to fiber-optic networks, advanced surgical devices, CD players, supermarket scanners, and what have you. And resonators are a staple of the cavity quantum-electrodynamics (QED) experiments that might one day lead to quantum communications networks, quantum cryptography, and even quantum computers, and are of keen interest to the experiment's sponsors—Hideo Mabuchi (PhD '98), associate professor of physics; and Lute Maleki, senior research scientist, and Vladimir Iltchenko, senior member of the technical staff of the Quantum Sciences and Technology Group at JPL. "There has been a lot of excitement about the possibility of using microspheres for cavity QED, but a lot of technical groundwork has to be laid for it to be practical," says Mabuchi. For one thing, making crystal-free ZBLAN microspheres on the ground is no easier than making clear ZBLAN fibers—in fact, it has only been done once, says Maleki.

The experiment's goal is to compare the optical properties of three sets of microspheres made beforehand at Caltech and JPL with three sets made using the same procedures in zero gravity. The microspheres were made with a fiber splicer, which employs a tiny high-voltage arc to melt the ends of two optical fibers and fuse them. In this case, the students melted the tip of a single fiber, allowing surface tension to cause the molten glass to bead up into a sphere. "The result is like a lollypop, a fiber stem with a small sphere on the end," says Eley. The samples' Q factors are now being measured in the lab. "The Q factor is a quality factor," explains Maleki. "If you think of the microsphere as a cavity, the Q factor measures its resonance. The narrower the resonance, the longer the energy-storage time." "In a sense, it's like tapping a wine glass with a fork and measuring how long it takes to stop ringing," says Englund. "The longer it rings, the larger the Q factor."

Eley, Englund, Ferguson, and Jewell were at Johnson Space Center from August 22 to September 1. Several days of training led up to a "chamber flight" on August 28—a room the size of a school bus, says Ferguson, that simulates high-altitude conditions. "They make us breathe pure oxygen for half an hour to get the nitrogen out of our blood, and then they pump it down to 25,000 feet and see how we do. Some people don't feel much of an effect. But some people get really giddy, and some people can't do simple math problems, like 3 + 4, even with a pencil and paper. They do it partly to show us what it's going to be like if there's an emergency in flight and we lose cabin pressure, and partly to document our reactions."

The actual flights followed a couple of days later. Eley and Englund went first, on August 30, logging "about 26" parabolas before deteriorating weather forced them back to Earth. Ferguson and Jewell were slated to go the following day, on the last flight of the season. The weather did not let up, and the flight was very nearly scrubbed. But at the last minute, says Ferguson, "they got access to some airspace they don't normally have. And it turned out to be an

absolutely perfect flight." Ferguson and Jewell did 32 parabolas—"close to 15 minutes of total weightlessness. We were lucky enough to be on a very special flight. It was the fourth 'no kill' flight, out of hundreds of flights in the past seven years, where no one actually hurled." The first 30 parabolas were zero-G and strictly business, but the last two were reduced gravity and just for fun. "They did one to simulate lunar gravity and one for Martian gravity. So instead of floating weightless, you drifted very slowly toward the floor. Or you could do pushups, and feel like the strongest man in the world."

The program pays for the training and the cost of the Comet flight, but the team had to raise money for equipment, transportation to and from Houston, and accommodations. Says Englund, "We've been very fortunate with our funding. There are not many schools that would support a group of undergrads wanting to do some science experiment as readily, and as generously, as Caltech and JPL did. JPL put up about $6,000 for fibers and some other things such as shipping the equipment. And Thomas Tombrello, the chair of Physics, Math, and Astronomy, put up a similar amount from the physics department." Each team must also participate in a community project, so the students will be presenting their experiments at a number of Southern California elementary and high schools. □—*DS*

Making Every Vote Count

Though over 100 million Americans went to the polls on election day 2000, as many as 6 million might just as well have spent the day fishing. Researchers at Caltech and MIT call these "lost votes" and think the number of uncounted votes could easily be cut by more than half in the 2004 election with just three simple reforms. "This study shows that the voting problem is much worse than we expected," said Caltech president David Baltimore, who initiated a nonpartisan study after the November election debacle. "It is remarkable that we in America put up with a system where as many as six out of every hundred voters are unable to get their vote counted. Twenty-first-century technology should be able to do much better than this."

According to the comprehensive Caltech-MIT study, faulty and outdated voting technology together with registration problems were largely to blame for many of the 4-to-6 million votes lost during the 2000 election. With respect to the votes that simply weren't counted, the researchers found that punch-card methods and some direct recording electronic (DRE) voting machines were especially prone to error. Lever machines, optically scanned, and hand-counted paper ballots were somewhat less likely to result in spoiled or "residual" votes. Optical scanning, moreover, was better than lever machines. As for voter registration problems, lost votes resulted primarily from inadequate registration data available at the polling places, and the widespread absence of provisional ballot methods to allow people to vote when ambiguities could not be resolved at the voting precinct.

The three most immediate ways to reduce the number of residual votes would be to:

- replace punch cards, lever machines, and some underperforming electronic machines with optical scanning systems;
- make countywide or even statewide voter registration data available at polling places;
- make provisional ballots available.

The first method, it is estimated, would save up to 1.5 million votes in a presidential election, while the second and third would combine to rescue as many as 2 million votes.

"We could bring about these reforms by spending around $3 per registered voter, at a total cost of about $400 million," says Tom Palfrey, a professor of economics and political science who headed the Caltech effort. "We think the price of these reforms is a small price to pay for insurance against a reprise of November 2000." Approximately half the cost would go toward equipment upgrades, while the remainder would be used to implement improvements at the precinct level, in order to resolve registration problems on the spot. The $400 million would be a 40 percent increase over the money currently spent annually on election administration in the United States.

In addition to these quick fixes, the report identifies five long-run recommendations.

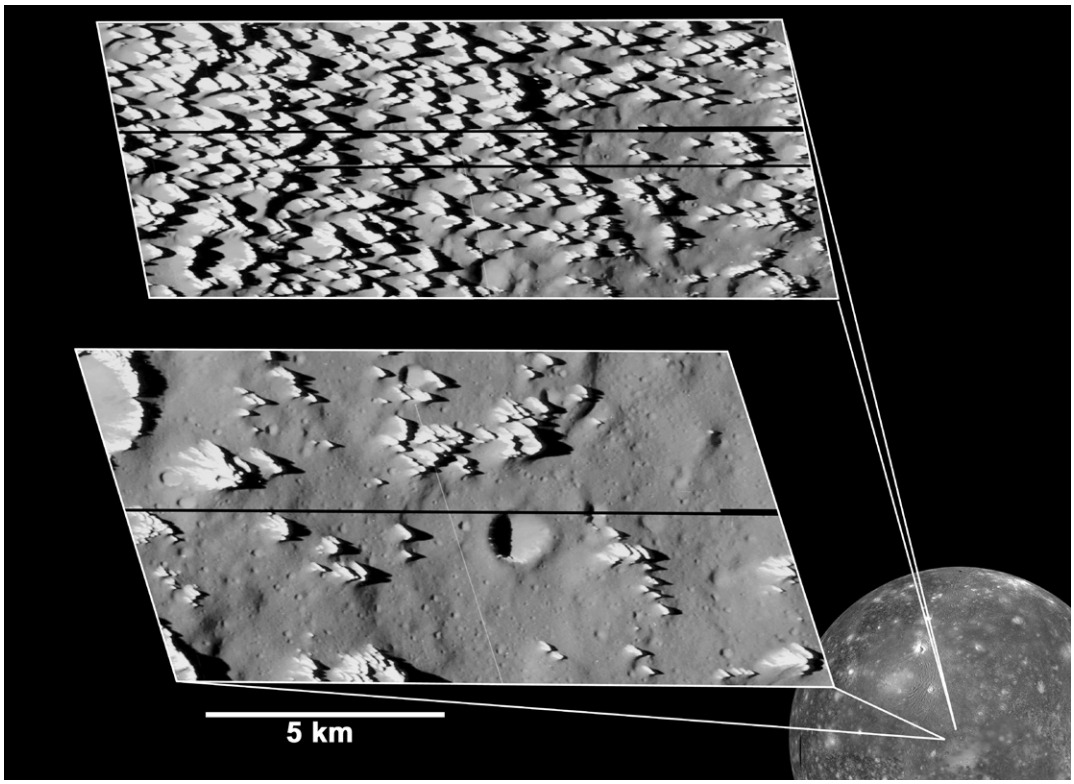
- First, institute a program of federal matching grants for equipment and registration system upgrades, and for polling-place improvement.
- Second, create an information clearinghouse and data-bank for election equipment and system performance, precinct-level election reporting, recounts, and election finance and administration.
- Third, develop a research grant program to field-test new equipment, develop better ballot designs, and analyze data on election system performance.
- Fourth, set more stringent and more uniform standards on performance and testing.
- Fifth, create an election administration agency, independent of the Federal Election Commission. The agency would be an expanded version of the current Office

of Election Administration, and would oversee the grants program, serve as an information clearinghouse and databank, set standards for certification and recertification of equipment, and administer research grants.

The report also proposes a new modular voting architecture that could serve as a model for future voting technology and offer greater opportunity for innovation in ballot design and security.

Despite the fact that there is strong pressure to develop Internet voting, the team recommends caution, due to the potential for fraud, coercion, hacking, and service disruptions. Also, many Americans are still unfamiliar with the technology.

Baltimore and MIT president Charles Vest announced the study on December 15, two days after the outcome of the presidential election was finally resolved. Funded by a $250,000 grant from the Carnegie Corporation, the study was intended to "minimize the possibility of confusion about how to vote, and offer clear verification of what vote is to be recorded," and "decrease to near zero the probability of miscounting votes." The report is publicly available on the Caltech-MIT Voting Technology Project Website, <http://vote.caltech.edu>. □—*RT*



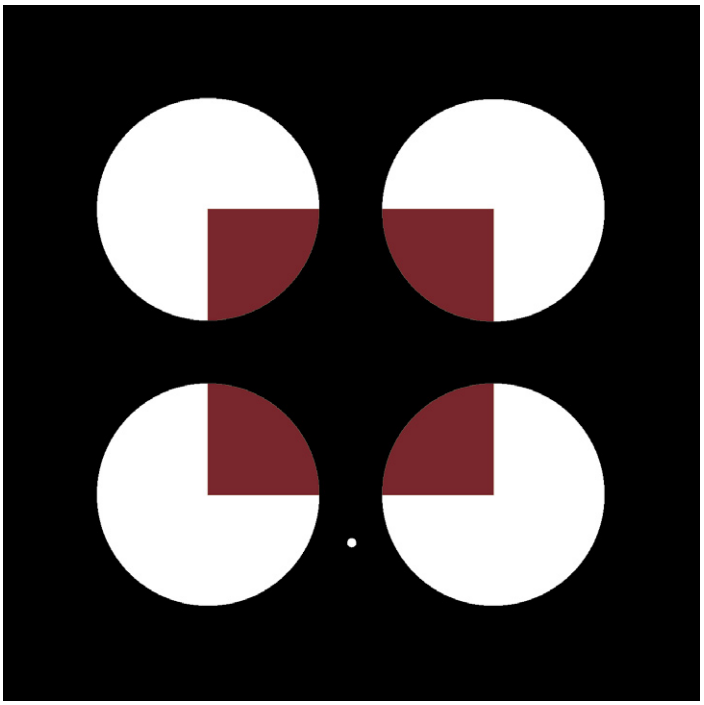
These weird spires on Jupiter's moon Callisto were revealed in the highest-resolution shot ever taken of anything in the Jovian system. Snapped by JPL's Galileo spacecraft in May 2001 as it whistled a mere 138 kilometers (83 miles) overhead, the smallest discernable features are about three meters (10 feet) across. The spires are about 80 to 100 meters (260 to 330 feet) tall, and they may consist of material ejected from the Asgard impact basin, which lies to the north of the sites. Callisto's dense cratering shows that its icy crust may be as much as four billion years old, but these spires indicate that the crust may not be completely frozen in time. As the icy spires seen in the top inset erode, the darker dust contained within them apparently slides down and collects in low-lying areas. The spires will probably disappear one by one over time, producing a scene similar to the bottom inset, where erosion on the plains has essentially ceased, as shown by the accumulation of craters.

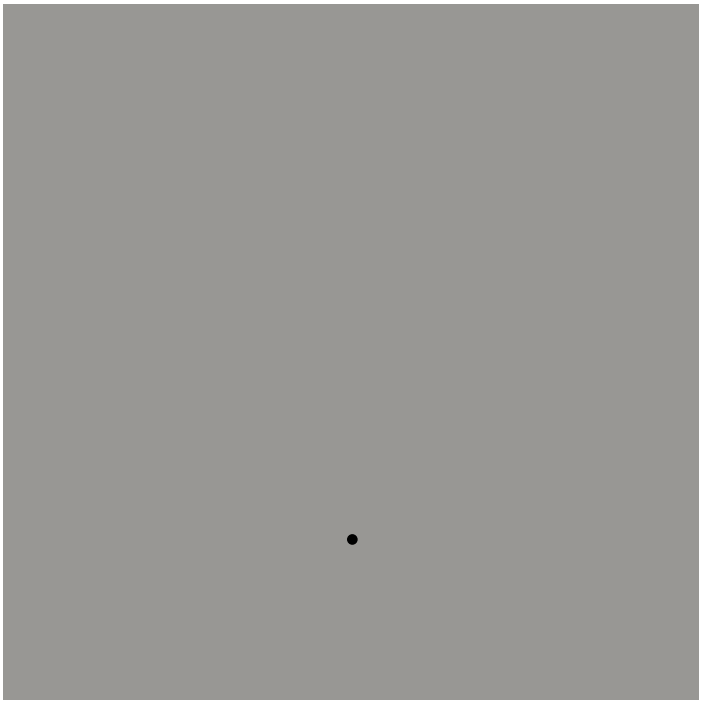
Red Square, Green Square

If you stare at a bright red disk for a time and then glance away, you'll soon see a green disk of the same size appear and then disappear. The green disk, called an afterimage, has long been thought to be an effect of the "bleaching" of photochemical pigments or adaptation of neurons in the retina—merely a part of the ocular machinery that makes vision possible. Now, Professor of Biology Shinsuke Shimojo, leading a joint team from Caltech and NTT Communication Science Laboratories, has demonstrated that higher visual centers in the brain are involved. The team showed that an optical illusion in which the brain fills in a color that is not actually present in the visual stimulus could generate a reverse-color afterimage of the filled-in surface.

The team used a graphic in which a red semi-transparent square is perceived on top of the four white disks. Only the right-angled sections of the disks are colored, and there is no local stimulus or indication of redness in the central portion of the display, yet the brain fills in the "missing" red to give an impression of a red square. An observer staring at a real red square would see a reverse-color (green) square for a few seconds after looking at a blank screen. However, subjects who stared at this image and then at a blank screen usually saw four black disks, followed by a second, global afterimage of a solid green square. Try it yourself, by staring first at the white dot in the bottom center of the pattern below left for, say, 30 seconds, and then at the black dot directly below. (This works better on a luminous computer monitor than it does on the printed page, so don't be alarmed if you can't see it; just point your Web browser to http://neuro.caltech.edu/~kamitani/fillingInAfterimage.)

The fact that no light from





the center of the original square was red demonstrates that the effect was not merely caused by a leaking-over or fuzziness of neural adaptation, because the four white disks are at first clearly distinct as black local afterimages. So the global afterimage is distinct from a conventional afterimage. Were the local afterimages of the disks and wedges—but only those—induced first, and then the filling-in occurred to give an impression of the global square, just as the red filled in initially? This is called the "element-adaptation" hypothesis. Or, since circuits using cortical neurons are known to cause the red square's center to fill in, does this same circuit undergo adaptation to directly create the green afterimage—the "surface-adaptation" hypothesis?

Three lines of evidence support the second hypothesis. First, the local and the global afterimages were visible with different timing, and tended to be exclusive of each other. This argued against the first hypothesis that the local afterimages are necessary to see the global afterimage. Second, the strength of the global afterimage was positively correlated with how strongly the initial color filled in, as predicted by the surface-adaptation hypothesis but not by the element-adaptation hypothesis. Finally, the researchers prepared a dynamic stimulus designed specifically to minimize the local afterimages, yet to maximize the impression of color filling-in during adaptation. If the element-adaptation hypothesis is correct, then test subjects would not observe the global afterimage. If, on the other hand, the surface-adaptation hypothesis is correct, the observers would see a vivid global afterimage without local afterimages. The result turned out to be the latter.

The study has no immediate applications, but furthers the understanding of perception and the human brain, says Shimojo. "This has profound implications with regard to how brain activity is responsible for our conscious perception." According to Shimojo, the brain is the ultimate organ by which humans adapt to our environment, so it would make sense if it, as well as the retina, could modify its activity—and perception as a result—due to experience and adaptation. The paper, whose other authors are Yukiyasu Kamitani, a grad student in computation and neural systems; and Shin'ya Nishida of the NTT Communication Science Laboratories in Atsugi, Kanagawa, Japan, appears in the August 31 issue of *Science*. □—*RT*

The Origin of Sex

Biologists have long known the advantages of sexual reproduction to the evolution and survival of species. With a little sex, a fledgling creature is more likely to pass on the good mutations it may have, and at the same time would be more able to deal with the sort of environmental adversity that would send its asexual neighbors floundering into the shallow end of the gene pool. The only problem is figuring out how sex got started in the first place. Not only do many single-celled organisms do just fine with asexual reproduction, but mathematical models show that a sexual mutant in an asexual population is usually unable to compete successfully and pass on its genes. But postdoc Claus Wilke and Chris Adami, a faculty associate in computation and neural systems and a research scientist at the Jet Propulsion Lab, used "digital organisms" and simulations of RNA to conclude that established asexual bacteria could be nudged to evolve into sexual reproduction by environmental stresses that raise the mutation rate, such as perhaps catastrophic meteor or comet impacts or high radiation levels.

The "organisms" in Adami's Digital Life Laboratory are self-replicating computer programs that behave much like certain common bacteria. The organisms live in a dedicated portion of the computer's memory, and they must compete with one another for the processor time that allows them to reproduce themselves. The digital organisms offer the advantage that many generations can be studied in a brief period of time. "If you took a population of *E. coli* and subjected it to high mutation rates for many years—for example by irradiation or introducing mutagenic factors—at some point you might observe that exchange of genetic material, a precursor to sexual recombination, would become favorable to the organisms and thus selected for, if at the same time the environment changes fast enough that enough mutations are beneficial," Adami says. "But that's a very difficult experiment to pull off with living organisms because of the time involved, and because it is difficult to construct constantly changing environments in a petri dish. This is easier with digital organisms."

One reason the origin of sexual reproduction has been a mystery is because of an effect known as "mutation accumulation." Organisms tend to adapt so as to decrease the effects of mutations in order to become less vulnerable. But this kind of single-mutation robustness is poisonous to a sexually reproducing species, because deleterious mutations are allowed to accumulate and lead to a gradual loss of genes. This guarantees the extinction of sexual creatures when competing against asexual ones. But it can be avoided if the effects of mutations are compounding—that is, if the effect of two or more simultaneous deleterious mutations is worse than the combined effect of each of the mutations. Now an organism may be robust to a few mutations, but incapable of surviving a large number of them. Thus the mutations cannot accumulate.

Wilke and Adami found that a conservation law

applies to the compounding of mutations and the fitness decay due to single mutations. This law says that robustness to a few mutations implies vulnerability to a large number, while robustness to many mutations must go hand in hand with vulnerability to single mutations. Thus, increasing robustness to single mutations automatically makes multiple mutations intolerable, removing organisms with multiple deleterious mutations from the population and allowing sexual recombination to reap the rewards from sharing beneficial mutations. Because stressful environments with high mutation rates push organisms to become robust to single mutations, the conservation law guarantees that this evolutionary pressure also pushes asexual organisms on to the road toward sexual recombination.

The researchers studied the evolution of digital organisms and RNA secondary structure, because accurate data on the decay of fitness and the effect of multiple mutations (either compounding or mitigating) on living organisms is quite rare. In the RNA study, the researchers used known sequences with well-understood folds and then tried various mutations to see which mutations mattered and which didn't, using a system that computationally predicts RNA secondary structure. The results supported the conservation law.

Though the study did not involve actual living organisms, Adami has collaborated in the past with experts on bacteria to demonstrate that the digital organisms are indeed realistic. In a 1999 study, for example, Adami's collaborator was a leading expert on the evolution of *E. coli*.

"The reason the origin of sexual reproduction has been such a big mystery is that we look at the world as it is now," Adami says. "But the early world was a much more stressful place, sometimes changing very rapidly. We can't say how or when sexual reproduction came to take hold in nature, but we can now say that high mutation rates can, under the right conditions, force an asexual organism to become sexual."

The paper was published in the July 22 issue of the Royal Society journal *Proceedings: Biological Sciences B*. □—*RT*

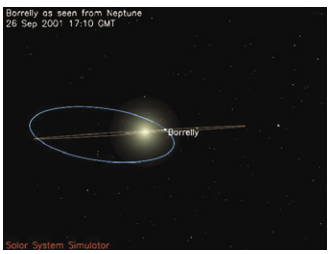
Deep Space 1 Meets Comet Borrelly

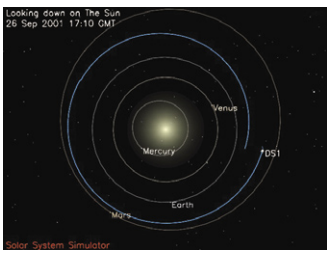
On September 22, an experimental JPL spaceraft named Deep Space 1 (DS1) took the most detailed pictures ever made of a comet's nucleus. The visuals were stunning enough, but the biggest payoff may come from the infrared imaging spectrometer, whose data are still being analyzed. Comets are frozen samples of the primordial solar system—water ice, dry ice, rock, and organic guck—and knowing what's in this one may tell us a lot about where Earth, and the life on it, came from. The flyby was not unlike going over Niagara Falls in a barrel, as Comet Borrelly had been heated to a frenzy of activity by its swoop into the inner solar system. Monstrous jets of gas and dust spew forth as the sun vaporizes the icy terrain, forming a vast cloud, or coma. The daredevil DS1, which was never designed for such a job and carries no shielding of any sort, plunged through the coma a mere 2,200 kilometers from the nucleus, and lived to tell the tale. (At the encounter speed of 16 kilometers per second, a dust grain 80 millionths of a meter in diameter packs the wallop of a bowling ball.) Meanwhile, DS1's plasma experiment, which includes ion and electron spectrometers, was busy analyzing the coma's gaseous components and gathering data on how they interact with the solar wind. (The solar wind is a stream of charged particles that pervades the solar system and pushes a comet's tail away from the sun.) This collection of data and images is but the latest bonus from a mission that has far outlived and outperformed everybody's expectations.

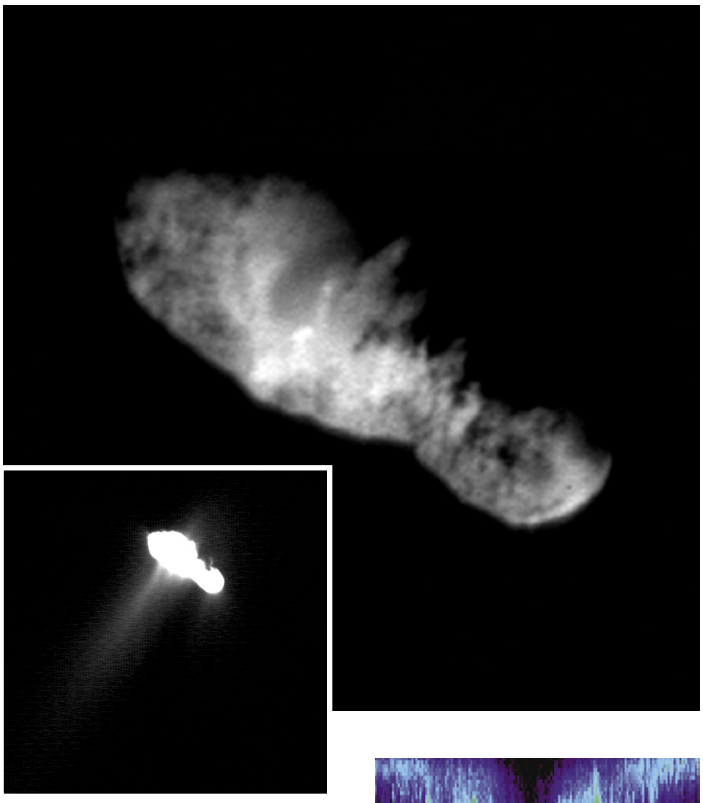
The telephone-booth-sized spacecraft—a midget compared to the school-bus-sized Cassini, or even the VW-bus-sized Galileo—was launched in October 1998. The first of the New Millennium series of high-risk, low-cost missions, its job was to flight-test a package of 12 new technologies for future use. These included an ion drive straight out of *Star Trek*, an autonomous navigation and control system that allows the spacecraft to figure out where it is and what to do next without help from Earth, and miniaturized camera, spectrometer, and electronics packages.

All of these newfangled gizmos had been thoroughly checked out to great acclaim by September 1999, when two months later the star tracker—ironically, a tried-and-true, off-the-shelf item—went belly-up. The star

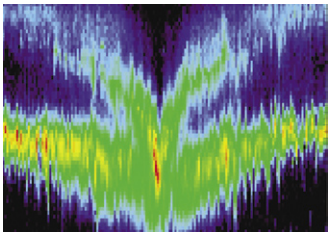
Comet Borrelly's roughly 6.9-year orbit stretches from just beyond Jupiter's to just within Mars's, and is tilted at an angle of about 30 degrees. Deep Space 1 caught Borrelly, which is "one of the most active comets that regularly visit the inner solar system," near its closest approach to the sun.







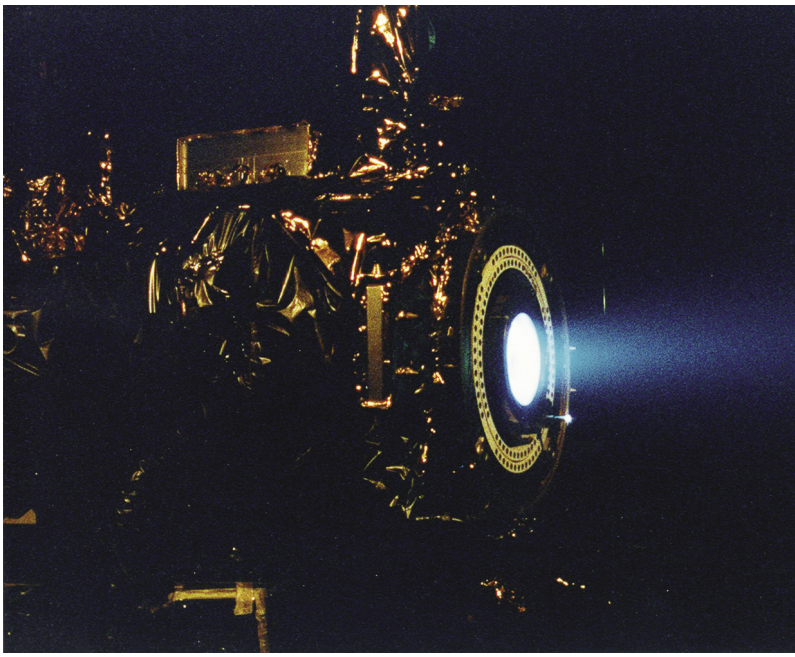
Left: Comet Borrelly's nucleus looks like an 8-kilometer-long bowling pin in this shot, taken 160 seconds before closest approach from a distance of 3,417 kilometers. The smallest visible detail is about 45 meters across. The line dividing the dark and sunlit sides is quite jagged, showing the terrain there to be ridged, even mountainous. This rugged region contains dark patches that appear to be higher than the surrounding areas. In some places, the dark material accentuates deep fractures that may be faults. The central region consists of brighter, smooth, rolling plains that seem to be the source of the dust jets seen in the faint inner coma (inset). This more distant view has been enhanced to show the dust, and reveals that the main jet has at least three smaller features spread over an active region about three kilometers long. A second jet is visible at lower right, as is a cloud of dust floating over the comet's dark side. Although the nucleus is overexposed, the dark side shows what appears to be a crater's rim catching the last rays of the setting sun. The sunlight is coming from below, so the comet's tail (not visible in these images) would be going out the top of the pictures.



Left: In this graphic, the horizontal axis represents DS1's flight path, and the energies of the ions DS1's plasma spectrometer encountered are plotted on the vertical axis. The color shows the number of ions at each energy, with blue being the fewest. The broad V is the solar wind slowing down as it slams into Borrelly's coma; the sharper V is a high-energy stream of ionized water molecules from Borrelly's surface. The comet's nucleus lies at the point of the Vs. It had been assumed that the ion flow around the nucleus would be symmetrical, but the red and yellow region on the left side indicates elevated ion concentrations that are probably related to the visible dust jets. The ions are heated to about 1 million Kelvin.

tracker, which has a field of view about the size of the Big Dipper, recognizes patterns in the background stars to tell the spacecraft which way it (and its camera, spectrometers, and antennas) are pointing. Since DS1 had already fulfilled its primary mission, the logical thing to have done would have been to give it a hearty thank-you and let it die a natural death. Instead, project manager Marc Rayman and his team worked out a way to reprogram the miniaturized experimental camera, which has a field of view about the size of the full moon, to take over the tracking job. Then they had to figure out how to coax the blindly flying spacecraft to point its high-gain antenna toward Earth so the new software could be uploaded. Fortunately, the sun sensor was still working, providing a reference point from which DS1 could sweep out a cone of space that included Earth. □—*DS*

Right: DS1's ion drive being tested in a vacuum chamber at JPL. A rocket engine burns a chemical fuel and shoots the expanding gas out a nozzle to generate thrust. This engine ionizes atoms of the inert gas xenon and accelerates them through a high-voltage grid. The thrust thus provided is very gentle—at full throttle, it's comparable to the force exerted by a single sheet of paper lying on your outstretched palm—but over the long haul it delivers 10 times the acceleration that the same weight of chemical fuel would.



"By virtue of the magnification afforded by the foreground cosmic lens, we are witnessing a source much smaller than a normal galaxy forming its first generation of stars."

Gravity's Magnifying Glass

Exploiting a phenomenon known as gravitational lensing, an international team of astrophysicists has detected a very small, faint stellar system in the process of its formation during the first half billion years or so of the universe's existence. The discovery is being reported in an upcoming issue of the *Astrophysical Journal*. According to lead author Richard Ellis, professor of astronomy and director of the Palomar Observatory at Caltech, the faint object is an excellent candidate for the long-sought-after "building blocks," thought to be abundant at early times, which later assembled to make present-day galaxies.

The discovery was made possible by systematically examining small areas in the tract of sky that we see through a massive intervening cluster of galaxies called Abell 2218, which is two billion light-years away. The cluster acts as a powerful gravitational lens, magnifying distant objects and allowing the scientists to probe how distant galaxies assembled at very early times.

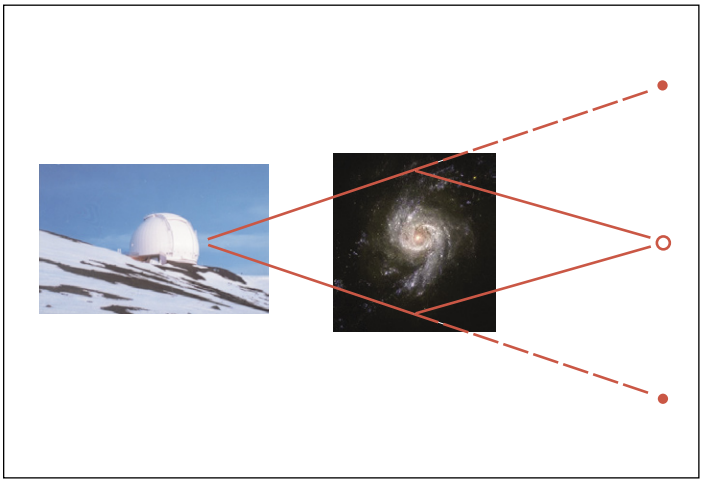
Gravitational lensing, a dramatic feature of Einstein's theory of general relativity, means that a massive object in the foreground bends the light rays radiating from one in the background because mass curves space. As a result, an object behind a massive foreground galaxy cluster like Abell 2218 can look much brighter because the foreground object has bent additional photons toward Earth, in much the same way that the glass lenses in a pair of binoculars will bend more photons toward your eyes. This effect makes the system detected by Ellis and coworkers appear at least 30 times brighter than would be the case if Abell 2218 were not in the foreground. Without this boost, neither the Keck Telescopes nor the Hubble Space Telescope would have detected the object. Ellis explains, "Without the benefit of the powerful cosmic lens, the intriguing source would not even have been detected in the Hubble Deep Fields, historic deep exposures taken in 1995 and 1998."

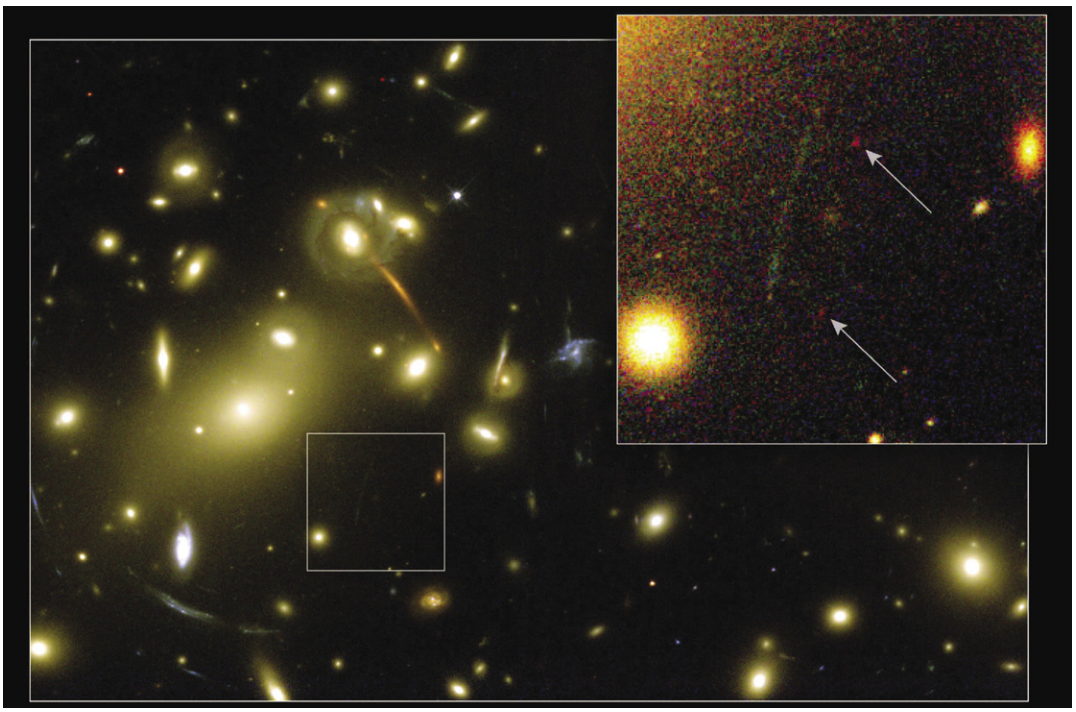
Using the 10-meter Keck Telescopes at Mauna Kea, the collaboration found a faint signal corresponding to a pair of feeble images later recognized in a deep Hubble Space Telescope picture. (Gravitational lensing can turn a single object into two or more images, as the light converging on the telescope will appear to be coming from different directions.) Spectroscopic studies made possible with the superior light-gathering power of the Keck confirmed that the images arise via the magnification of a single source diagnosed to be extremely distant and in the process of formation. And team member Jean-Paul Kneib of the Observatoire Midi-Pyrénées near Toulouse, France, an expert in the rapidly developing field of gravitational lensing, derived the magnification factor by determining the precise location of the pair of images in relation to the lensing cluster.

"The system contains about a million or so stars at a distance of 13.4 billion light-years, assuming that the universe is 14 billion years old," claims Ellis. "While more distant galaxies and quasars have been detected with the Keck Telescopes, by virtue of the magnification afforded by the foreground cosmic lens, we are witnessing a source much smaller than a normal galaxy forming its first generation of stars."

"Our work is a little like studying early American history," says grad student and team member Mike Santos. "But instead of focusing on prominent individuals like George Washington, we

Right: When light is bent by its passage around a massive nearby object, an observer—who will perceive the light rays as having traveled along straight lines—can see multiple images (solid circles) of the distant source displaced from its actual location (open circle); the "real" image will not be seen. Below: A Hubble Space Telescope image of the galaxy cluster, Abell 2218, used by Ellis and collaborators in their search for intrinsically faint, very distant star-forming systems. The image pair (arrowed) in the inset represents a single source gravitationally magnified more than 30 times by Abell 2218 and viewed at a distance of 13.4 billion light-years. The object contains only a few million stars, far fewer than a mature galaxy like the Milky Way.

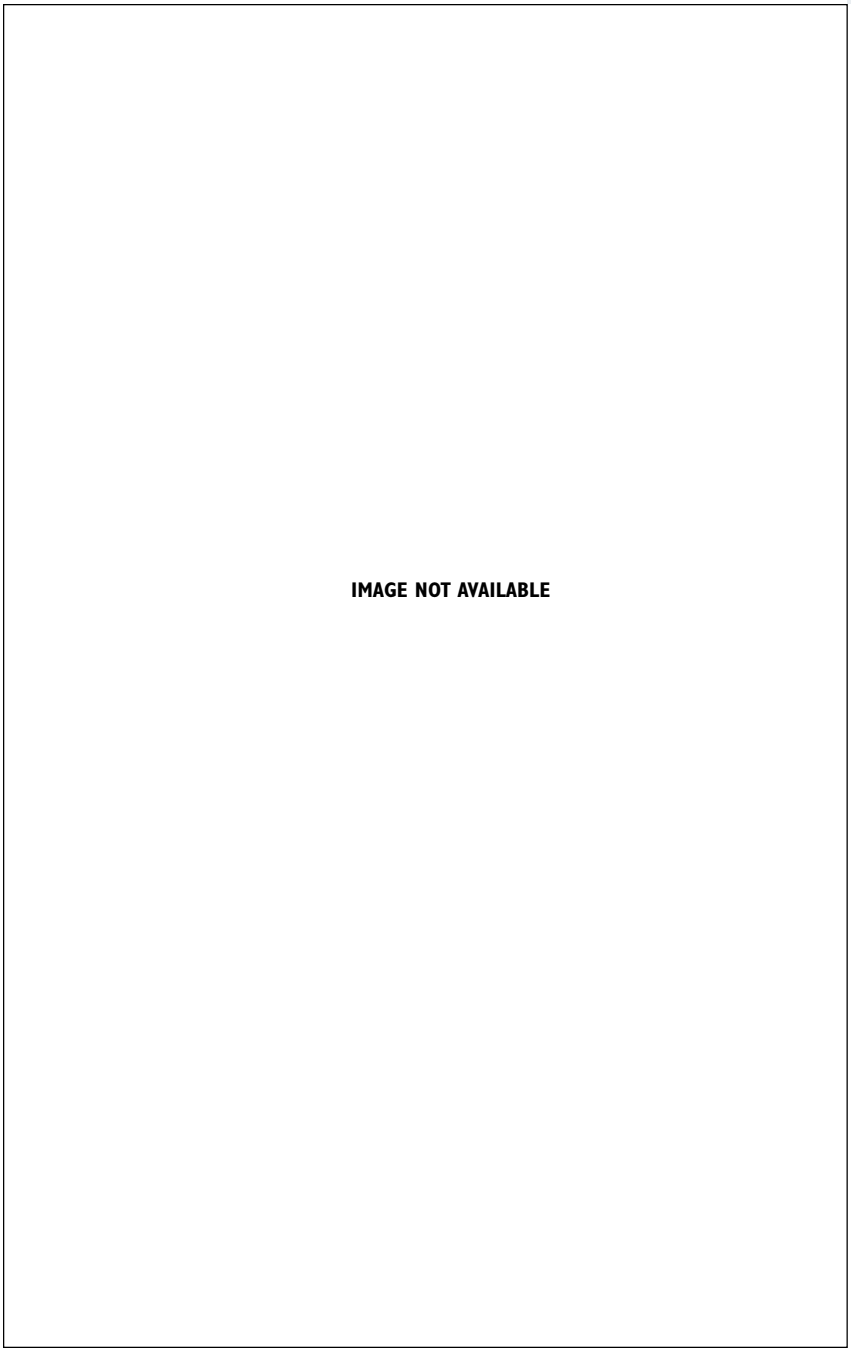




want to know how everyday men and women lived. To really understand what was going on in the early universe, we need to learn about the typical, commonplace building blocks, which hold important clues to the later assembly of normal galaxies. Our study represents a beginning to that understanding."

The team concludes that the star system is remarkably young (by cosmic standards) and thus may represent the birth of a subcomponent of a galaxy. Santos explains, "The narrow distribution of intensity observed with the Keck demonstrates we are seeing hydrogen gas heated by newly formed stars. But, crucially, there is not yet convincing evidence for a well-established mixture of stars of different ages. This suggests we are seeing the source at a time close to its formation." The researchers infer that the stars had been forming at a rate of one solar mass per year for not much longer than a million years. Such a structure could represent the birth of a globular cluster, which are stellar systems recognized today to be the oldest components of the Milky Way galaxy. The work represents part of an ongoing survey to determine the abundance of such distant star-forming sources as well as to fix the period in cosmic history when the bulk of these important objects formed. □—*RT*

The Tangled Web: Communication in



The mysteries of the human brain have inspired countless generations of scientists, poets, and philosophers. Breathtaking in its complexity, the brain is composed of billions of individual nerve cells that are wired together to give rise to thought, emotion, consciousness, and behavior. It is the role of neuroscience to make sense of this complexity—to understand the brain's structure and function. To accomplish this goal, neuroscience draws on many different disciplines, ranging from molecular and cellular biology to cognitive psychology. In my laboratory, we combine chemistry and neurobiology to explore how nerve cells communicate and store information. Our goal is to elucidate the chemical changes that underlie phenomena such as learning, memory, and motor control. And, not surprisingly, the more that we learn about how nerve cells communicate, the more we appreciate the beauty and complexity of the brain.

To understand the workings of the nervous system, one can ask questions at three different levels: organismal, cellular, and molecular. Organismal neurobiology looks at whole organisms, such as flies, worms, and mice, and observes big-picture phenomena such as learning, memory, and behavior. At the next level, cellular neurobiology tries to explain these phenomena in terms of the interactions between cells. We know, for instance, that the process of learning stimulates nerve cells to

This Ramón y Cajal drawing of a brain-tissue section hints at the multitudinous connections made by a mere 11 nerve cells.

Unraveling the Molecular Basis for the Brain

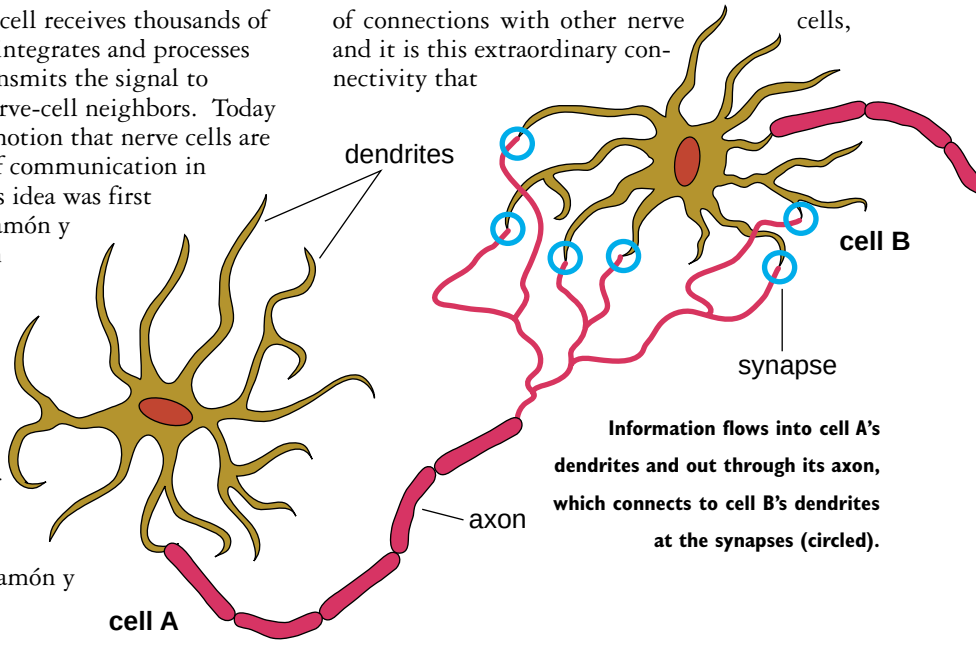
by Linda Hsieh-Wilson

seek out and maintain connections with their neighbors. Finally, molecular neurobiology attempts to explain the interaction and communication between nerve cells at the level of atoms and molecules.

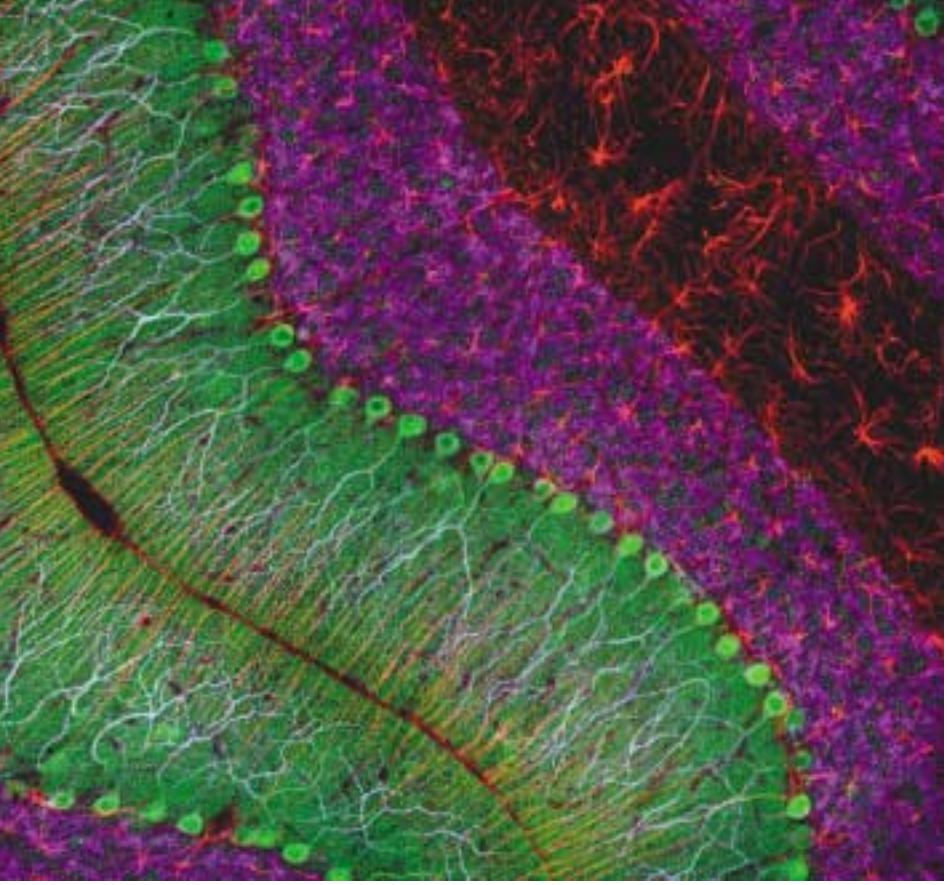
Our group is unlike most other neurobiology labs because of our strong emphasis on chemistry. As chemists, we are trained to think at the molecular level, so we feel right at home at the interface between molecular and cellular neurobiology. In addition, synthetic organic chemistry gives us the ability to design and create molecules in the laboratory. By integrating chemistry and neurobiology, we can synthesize specific molecules and test our hypotheses about their functions in the brain. Ultimately, we hope to relate events at the level of atoms and molecules to the big-picture changes that occur in disease and in normal growth and development.

While the brain is an amazingly complex organ, we can break down the complexity by considering the brain as an organized network of billions of nerve cells. Each nerve cell receives thousands of inputs from other cells, integrates and processes the information, and transmits the signal to thousands more of its nerve-cell neighbors. Today we take for granted the notion that nerve cells are the fundamental units of communication in the brain. However, this idea was first proposed by Santiago Ramón y Cajal, a brilliant Spanish neuroanatomist who examined brain structures using dyes and a microscope. He recorded his observations as sketches in laboratory notebooks—shown opposite is one of his original drawings. Each letter denotes an individual nerve cell. Ramón y Cajal discovered that each cell has branchlike extensions, and realized that these branches would allow it to reach out and interact with other nerve cells. His insight was so fundamental that it forms the foundation of modern molecular neuroscience, and he was honored with the Nobel Prize in 1906.

Building on Ramón y Cajal's observations, neuroscientists have learned that nerve cells have evolved to gather, process, and transmit information. Below is a close-up drawing of two nerve cells. Information flows from one cell to the next, and usually in one direction only. Cell A receives signals through branchlike extensions called dendrites. The cell processes the information and transmits a message that travels out the main extension, called the axon. The far end of the axon then splits into tens of thousands of tiny branches, which contact the dendrites of neighboring cells. While this diagram accurately depicts the flow of information, it is an oversimplification. In reality, each nerve cell in the brain makes thousands of connections with other nerve cells, and it is this extraordinary connectivity that



Information flows into cell A's dendrites and out through its axon, which connects to cell B's dendrites at the synapses (circled).



This microphotographic slice through a rat's cerebellum (a portion of the brain involved in muscular coordination) has been stained with fluorescent tags that bind to specific proteins. The green ovals sprouting blue dendrites are a type of nerve cell called Purkinje cells. Granule cells, another type of nerve cell, show up in the purple layer. The red cells are astrocytes, which are essential to brain function but are not nerve cells. (Image courtesy of Tom Deerinck and Mark Ellisman, National Center for Microscopy and Imaging Research, UC San Diego.)

underlies higher brain functions. Importantly, although Ramón y Cajal made his discoveries more than a century ago, we still don't truly understand how nerve cells talk to one another and keep all of the information straight.

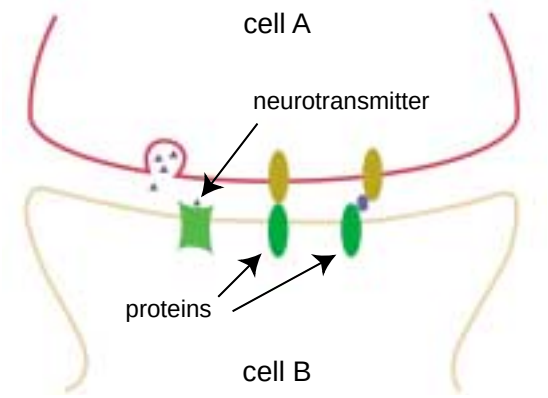
To appreciate fully the power of the brain, we need to consider the nerve cell in the context of billions of other nerve cells. A simple back-of-the-envelope calculation makes the point. The human brain has roughly 100,000,000,000 nerve cells. If each cell makes 1,000 connections with other cells, and each connection processes information at the rate of 100 operations per second, then we're talking about computing power that is still unmatched today. In fact, this simple calculation suggests that our brains are between 10 and 10,000 times faster than the world's fastest supercomputer. At the current rate of development, computing power should surpass the human brain around the year 2015. All this, of course, is little consolation to Gary Kasparov!

Up until now, I've been describing the function of the brain on a cellular and an organismal level. However, we also know something about how communication occurs at the molecular level. Cell A communicates with cell B through a combination of chemical and electrical signals. When cell A sends a message to cell B, an electrical impulse goes zipping down the axon, much like a current through a wire. At the axon's terminal, the electrical impulse reaches a gap, called the synapse, between the two cells. For years, neuroscientists believed that the electrical impulse simply jumped the gap, like a spark between two electrodes. We now know, however, that the electrical signal induces the release of small molecules called neurotransmitters that diffuse across the synapse. Upon reaching cell B, the neurotransmitters initiate a new electrical signal and the message continues on its way.

But there's more to the story than just neurotransmitters. Over the years, scientists have discovered that a variety of molecules—including carbohydrates, proteins, and neurotransmitters—populate the synapse, and the interactions among these molecules control how the nerve cells behave. The modes of interaction vary widely: in one case, for instance, we may find a small molecule that binds to a large protein molecule while, in another case, we may find a small molecule that bridges two large proteins. These binding interactions are highly specific, much like a lock that recognizes only a particular key. It's clear that if we want to understand the flow of information through the synapse, we must study the structure and function of the molecules at the synapse and learn how they interact with one another.

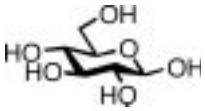
My laboratory focuses on two types of molecules at the synapse: fucosyl sugars and glycosaminoglycans. While both are sugars, they have very different chemical structures. In particular, fucosyl sugars are small and simple whereas glycosaminoglycans are complex polymers, composed of a number of simple sugars strung together like beads on a necklace.

You may recall from organic chemistry that sugars are composed of carbon, hydrogen, and



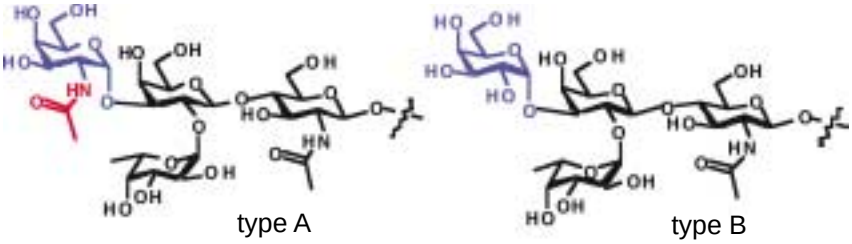
A variety of molecules populate the synapse. The molecules interact in many different ways, three of which are shown here. In addition to the neurotransmitters, which diffuse across the synapse to bind to proteins on the surface of cell B, proteins on the surface of cell A can reach out to bind to proteins on cell B, and small molecules can bridge the gap between two proteins on opposite sides of the synapse. These interactions modulate the strength of the connection between the two cells and are associated with learning and memory.

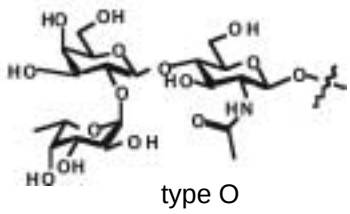
This simple calculation suggests that our brains are between 10 and 10,000 times faster than the world's fastest supercomputer. At the current rate of development, computing power should surpass the human brain around the year 2015. All this, of course, is little consolation to Gary Kasparov!



Above: A molecule of glucose, a simple sugar having five carbon atoms in its ring. (The carbon atoms are represented by the points where two or more line segments intersect; the heavier line segments indicate the part of the ring that sticks out in front of the plane of the page.)

oxygen atoms arranged in a ring. Many people are familiar with sugars as a form of energy, such as glucose or fructose, or as a means of structural support, as in the case of cellulose, which is found in plants. Most people, however, are not aware that sugars also play a critical role in controlling cell-cell recognition. For example, shown below are the three sugars, called blood-type antigens, that determine whether your blood type is A, B, AB, or O. These sugars decorate the surfaces of red blood cells and have very subtle chemical differences. All of them share a basic core structure of three different sugar units, but antigen types A and B contain a fourth sugar unit, galactose, shown in blue. The type-A blood antigen looks a lot like the type-B blood antigen except that it has an *N*-acetyl group, shown in red, in place of a hydroxyl (OH) group. This is a powerful example of how a very subtle chemical change can have a profound impact on human biology—if you have type-A blood and receive a transfusion of type-B blood, this tiny four-atom change can be devastating. Your immune system recognizes the blood as foreign to your body and destroys the offending cells, causing their remains to clump in your blood vessels and wreak havoc.



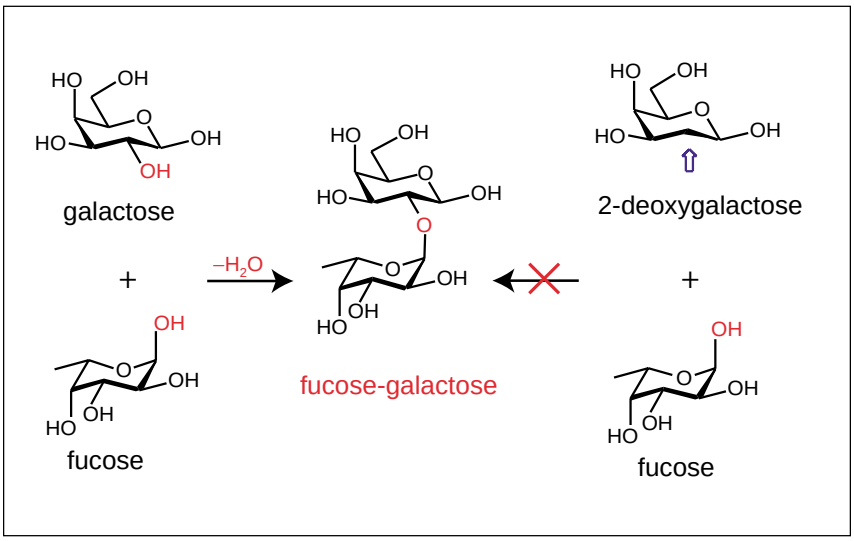


The blood-type antigens share a three-sugar core (black) made of one molecule each of fucose, galactose, and *N*-acetylglucosamine. Type-A blood differs from type-B blood by only four atoms (red), and both differ from type-O blood by one galactose molecule (blue). (People with Type-AB blood have both the A and B antigens.)

In addition to the sugars that determine your blood type, there are hundreds of other sugars that modulate the interactions among cells in your body. For example, sugars control the ability of viruses such as influenza, which causes the flu, to enter and infect your cells. Sugars are also involved in tissue inflammation, which is often a byproduct of injury or disease, and in cancer metastasis. Finally, sugars help nerve cells to grow, establish, and maintain connections—steps that are critical for proper brain development, learning, and memory.

While sugars help to transmit information across the synapse, other molecules also play important roles. In our case, for example, the fucosyl sugars and glycosaminoglycans are chemically linked to large proteins. Proteins are long polymers made up of amino-acid building blocks arranged in varying orders. Tryptophan is an amino acid that you may be familiar with—it is found in high concentrations in turkey, and is the culprit that makes you sleepy after a large Thanksgiving meal. Chemists depict proteins as long, linear chains, but in reality, they fold up into well-defined, three-dimensional structures that endow them with biological functions. For instance, you may have heard of the protein called amylase, which is a digestive enzyme found in saliva that breaks down starches. Another example is hemoglobin, which binds to oxygen molecules and ferries them throughout your blood.

A major project in our laboratory is to understand the role of fucose in the brain. Fucose is a simple sugar that is attached to proteins at the synapse and is frequently associated with other sugar molecules. Several lines of evidence have recently converged to suggest that fucose is important for modulating the transmission



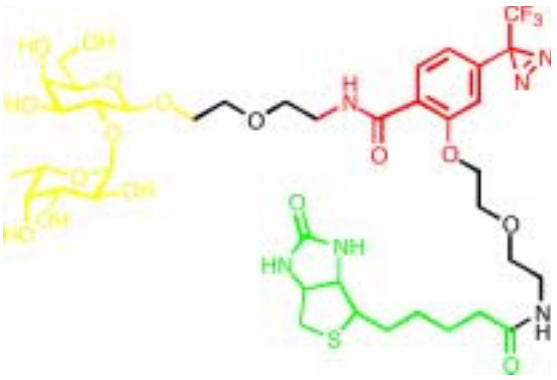
Fucose and galactose (left) link together in the brain to strengthen nerve-cell connections. Each sugar molecule contributes a hydroxyl (OH) group, shown in red, which combine to expel a water molecule and leave an oxygen atom behind as a bridge. Fucose and 2-deoxygalactose (right) cannot link, because the latter is missing the vital OH group at the blue arrow. No linkage, no memory.

of signals between two or more nerve cells. For example, fucose is highly concentrated at the synapse, and repeated nerve-cell firing increases the levels still further. And fucose may be involved in learning and memory because disrupting a critical fucose-containing linkage causes amnesia in lab rats. Fucose is often linked to another sugar called galactose. The linkage, shown in red in the diagram above, is created when hydroxyl groups on the two sugars combine and expel a water molecule. Rats given 2-deoxygalactose (which is identical to galactose in all respects except that it lacks the critical hydroxyl group) cannot form this linkage, and develop amnesia.

You may be wondering how one knows when a rat has amnesia. As it turns out, a number of years ago a neuroscientist named Tassoni and his colleagues at the University of Florence, Italy, conducted a fairly simple memory experiment. The rat was placed in a box whose interior was illuminated on one side and dark on the other. The box was constructed such that the rat received a mild electric shock when it ventured into the dark section. In contrast, the illuminated section did not give shocks. Conditioning the rat taught it to associate the dark section with the shock, so that, after a period of time, the scientists could turn off the shock and the animal would continue to avoid the dark section because it remembered the jolt. The interesting result from our perspective was that rats treated with 2-deoxygalactose (but not galactose, 2-deoxyglucose, glucose, or fucose) after conditioning showed no preference for either section, presumably because they couldn't form the essential fucose-galactose linkage. In another study, rats treated with 2-deoxygalactose were unable to maintain long-term potentiation (LTP), which is a widely used model for learning and memory. Taken together, these experiments strongly suggest to us that fucose-containing molecules at the synapse may play an important role in learning and memory.

My lab has developed a model that may explain fucose's role at the synapse. The figure below shows the synaptic cleft between cells A and B. We know that proteins on cell A's side of the synapse contain fucose, and we believe that fucose is binding to proteins on the surface of cell B, thereby acting as a chemical bridge across the synapse. This binding event should activate the cellular machinery in cell B and instruct the cell to synthesize more proteins. One can envision a positive feedback loop, in which the proteins synthesized in cell B are transported to the cell surface, where they interact with the fucose units from cell A to stimulate still more protein synthesis. This model is consistent with the observation that fucose levels increase at the synapse with repeated nerve-cell activity. The model is also consistent with current theories about the chemical basis of long-term memory. In particular, neuroscientists have observed that new protein synthesis is required to form long-lasting memories. By changing the concentration of specific molecules at the synapse, it is believed that certain connections between nerve cells are

Our model for how fucose could act as a chemical signal: A fucose molecule attached to a protein on cell A's side of the synapse can bind to another protein on cell B's side. This stimulates cell B to make more of the fucose-binding protein, enhancing the cell's sensitivity to fucose and strengthening the connection.



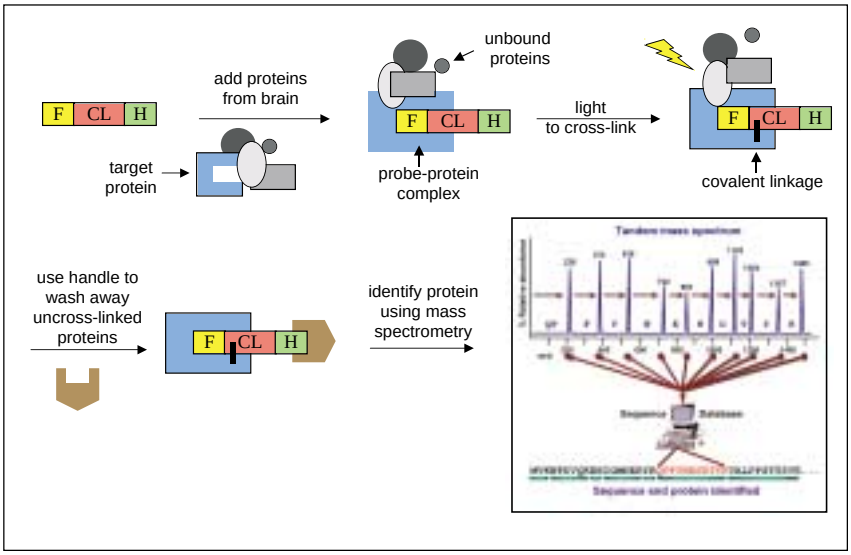
The fucose "harpoon." Upon irradiation with ultraviolet light, the diazarine group (N=N) is converted to nitrogen gas (N_2), which escapes. The molecule left behind is highly reactive and attaches chemically to nearby proteins, allowing us to harpoon them for further study.

enhanced and grow stronger over time.

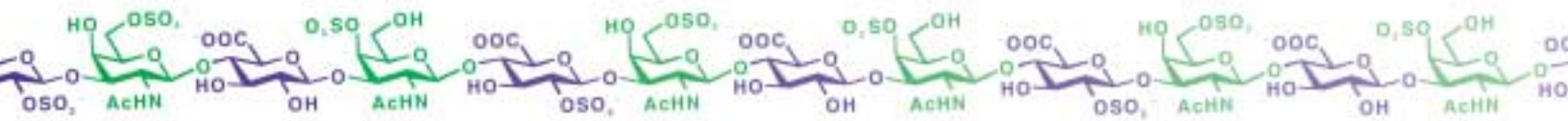
To test whether our model is correct, we need to identify the protein partners that recognize fucose at the synapse. Recently, my research group designed and synthesized a chemical probe that acts as a "molecular harpoon" to help us to isolate and identify these proteins. The chemical structure of our probe is shown above, and it has three basic elements. The first element is a fucose-galactose group (yellow) that interacts with the target protein. The second element is a chemical cross-linker (red), a member of the diazirine family that is the "harpoon" piece of our probe. Diazirine molecules become very reactive when exposed to ultraviolet light. Thus, once the probe is bound to the target, we can zap the solution with ultraviolet light and form a permanent covalent bond between the probe and the protein. The third and final element (green) is what I call a "chemical handle" because it allows us to isolate the protein-probe complex from a mixture of thousands of other proteins. We are using biotin (which, incidentally, is one of the B-vitamins) as the handle, because biotin binds specifically, and very tightly, to a protein called streptavidin. We can buy streptavidin already bound to resin particles that have the consistency of fine sand. So when we want to isolate the streptavidin-biotin-probe-protein ensemble, we simply let the resin sink to the bottom of our centrifuge tube and rinse away all of the other proteins that remain suspended in solution.

Once we have isolated the target protein using our molecular harpoon, we still have the challenge of determining what we've found. Fortunately, there's an instrument, called a mass spectrometer, that identifies molecules based on their size and charge. In the case of very large molecules such as proteins, we must first break the protein up into smaller fragments. Then we use the mass

"Tandem mass spectrum" diagram reprinted from *Current Opinion in Chemical Biology*, Vol. 2000, No. 4, Gygi and Aebersold, "Mass Spectrometry and Proteomics," p. 490, copyright 2000, with permission from Elsevier Science.



How to harpoon a protein and render its identity. The yellow-red-green rectangle is the fucose (F)–cross-linker (CL)–handle (H) probe.



A glycosaminoglycan is a polymer of simple sugars that alternate with each other. Shown here is chondroitin sulfate, which consists of alternating D-glucuronic acid (blue) and *N*-acetylgalactosamine (green). The polymer can be up to 200 sugars long.

spectrometer and a computer to sort the fragments and identify the amino-acid sequence that corresponds to each fragment. As a final step, we compare the amino-acid sequences of our fragments to DNA-sequence databases that contain genetic information for many organisms, including humans, mice, and rats. Once we find a match for our fragments in the databases, we know the identity of our target protein.

Lori Lee, a second-year graduate student in my laboratory, has just completed the synthesis of our chemical probe, and we hope very shortly to learn which proteins at the synapse bind to fucose. We are very excited about this because, if we're successful, we will begin to have a molecular-level understanding of the complex processes by which nerve cells communicate. If you think back to the example of the blood-type antigens, just four atoms meant the difference between a successful blood transfusion and a serious health hazard. With our experiments to unravel the identity of fucose-binding proteins at the synapse, we hope to bring the same molecular-level perspective to our understanding of the brain.

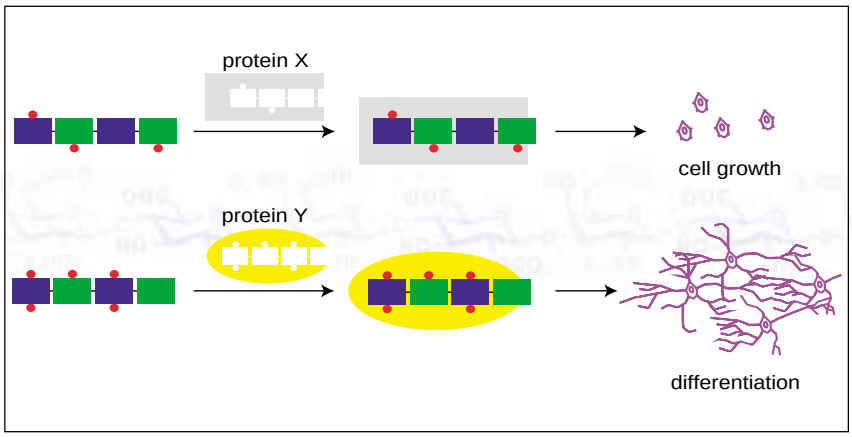
Another area that my lab has been exploring involves a class of molecules called glycosaminoglycans. Glycosaminoglycans play a variety of important roles throughout biology—for example, heparin is a glycosaminoglycan that's used after surgery to prevent blood clotting. Glycosaminoglycans are also involved in Alzheimer's disease, cancer, and angiogenesis, which is the process by which blood vessels develop and link up with one another. Our interest in glycosaminoglycans stems from the fact that, like fucose, they are found at the synapse, are important for proper brain development, and play a critical role in learning and memory. It is believed that, like fucose, glycosaminoglycans are also involved in establishing connections between nerve cells. However, the molecular mechanisms of this process remain poorly understood.

Whereas fucose is a relatively simple sugar, glycosaminoglycans are complex polymers, having a repeating A-B-A-B-A structure composed of alternating sugar units. There are several different kinds of glycosaminoglycans found in nature, and each is characterized by different sugar units. For example, chondroitin sulfate is composed of alternating D-glucuronic acid and *N*-acetylgalactosamine units. Another glycosaminoglycan, heparan sulfate, is composed of alternating L-iduronic acid or D-glucuronic acid and *N*-acetylglucosamine units. Both chondroitin sulfate and heparan sulfate are found in the brain, but they play very different roles. So, at the first level, we see that nature can encode different biological functions by using different sugar sequences.

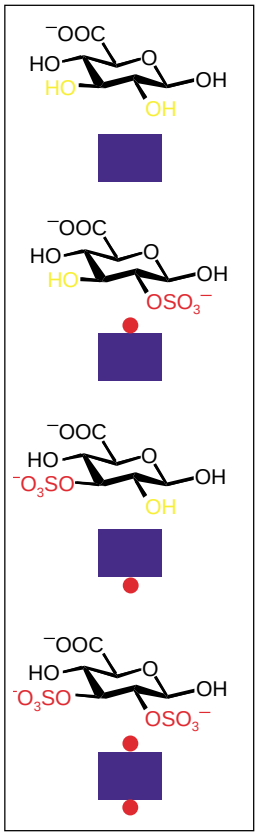
However, nature has taken the chemical diversity of glycosaminoglycans one step further. Even a single sugar molecule can take many different forms. If, for example, we look at a typical simple sugar, we see that there are five different hydroxyl (OH) groups arrayed around a six-membered ring. If we attach a second chemical group to one of these five hydroxyl groups, the resulting molecule is different than if we attach that same chemical group to one of the other hydroxyl groups. These two molecules have the same number of atoms, the same electrical charge, and the same molecular weight. But, importantly, they are chemically distinct. They have different three-dimensional shapes, so they interact with the outside world in completely different ways. A simple example may make the point more clearly: If you look at your right hand and your left hand, you'll see that they have the same number of fingers and are roughly the same size and shape. We all know, however, that no matter how hard you try, you cannot fit a left-handed glove on your right hand. Sugars are much the same and, for this reason, they are both fascinating and challenging to study.

It is useful to keep the image of your right and left hands in mind while you consider the

Different sulfation patterns could be ignition keys, turning on various proteins that control the cell.



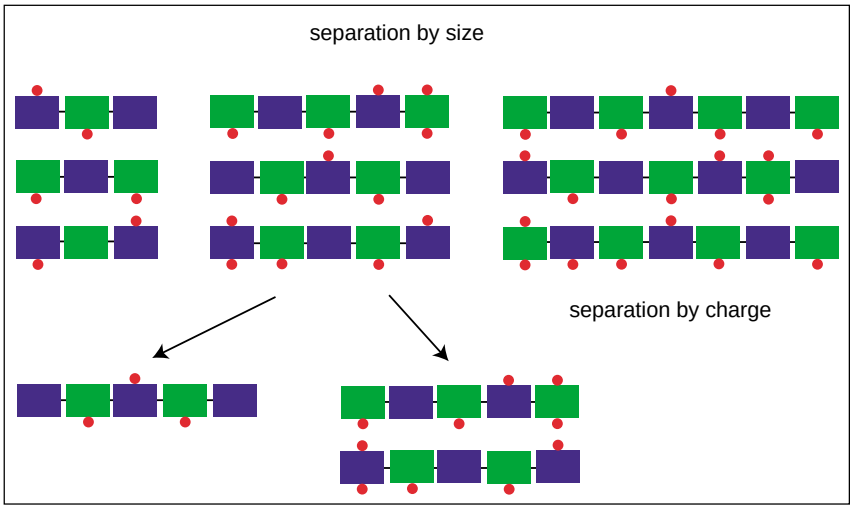
next level of complexity exhibited by the glycosaminoglycans. I have shown the chemical structure of D-glucuronic acid in the drawing below and, for simplicity, as a blue square below the structure. In your body, however, D-glucuronic acid may be chemically modified with sulfate (OSO_3^-) groups at either or both of the 2- and 3- positions, depicted schematically as red circles above and below the blue square. Thus, sulfating D-glucuronic acid generates four different chemical structures: one molecule with no sulfate groups (top), two molecules, each with a single sulfate group at either the 2- or 3-position (middle), and one molecule with sulfate groups at both the 2- and 3-positions (bottom). Similarly, sulfation of *N*-acetylgalactosamine also generates four different structures. The result is that every sugar unit along the polymer chain can have any one of four different chemical structures. So if you consider a simple, four-unit molecule of chondroitin sulfate, you have four possibilities in the first position times four more in each of the second, third, and fourth positions, for a total of 256 different compounds.



Nature has done something remarkably clever here. It's taken a relatively simple polymer and built up diversity by adding sulfate groups along the chain. This strategy has tremendous implications in the body because naturally occurring glycosaminoglycans can be up to 200 sugar units long. Taking into account all the possible ways to sulfate 200 sugars, we end up with a number of possible compounds that is greater than Avogadro's number (6.022×10^{23})!

You may be wondering what is the biological significance of so much chemical diversity. Evidence suggests that the sulfation pattern of a glycosaminoglycan determines whether particular proteins can interact with it. Protein binding, in turn, controls a variety of other downstream biological events, including the ability of cells to grow, communicate, and differentiate into other types of cells. Each of these processes requires the presence of distinct proteins in a defined sequence of events. We and others believe that the "instructions" for these biological events may be encoded, in part, by the sequence and sulfation pattern of glycosaminoglycans. I like to think of glycosaminoglycans as molecular fingerprints because, while they may look similar, no two are identical. Glycosaminoglycans provide a powerful means to encode biological information—nature can use different fingerprints to direct different functions.

There's an intriguing similarity in the way that nature encodes information in the structures of both glycosaminoglycans and DNA. It is well established that nature stores the genetic information of all organisms in the sequence of As, Ts, Cs and Gs, strung along the backbone of DNA's famous double helix. We believe that glycosaminoglycans also encode information through their structure and patterns of sulfation. In particular, we suspect that the position of the sulfate groups along the sugar backbone tells other molecules at the synapse, such as proteins, where to go and what to do. Our goal, of course, is to use chemistry to unlock this sulfation code.



It's easy to separate glycosaminoglycans by their size and then by their charge. However, the two five-sugar sequences at bottom center have equal numbers of sulfates, giving them the same charge. They may be indistinguishable in the lab, but their different sulfation patterns are easily recognizable in the body.

While biochemical studies have clearly demonstrated the functional significance of sulfation, efforts to advance a molecular-level understanding of glycosaminoglycans have been hampered by difficulties in obtaining well-defined chemical structures. Until recently, glycosaminoglycans could only be isolated from natural sources as very complex mixtures of compounds. This was problematic because the same factors that make glycosaminoglycans interesting to study (namely, subtle variations in size, chemical structure, and patterns of sulfation) make them nearly impossible to purify in the lab. Two different glycosaminoglycans that are readily distinguished by a protein in your body may appear virtually identical to state-of-the-art analytical instruments.

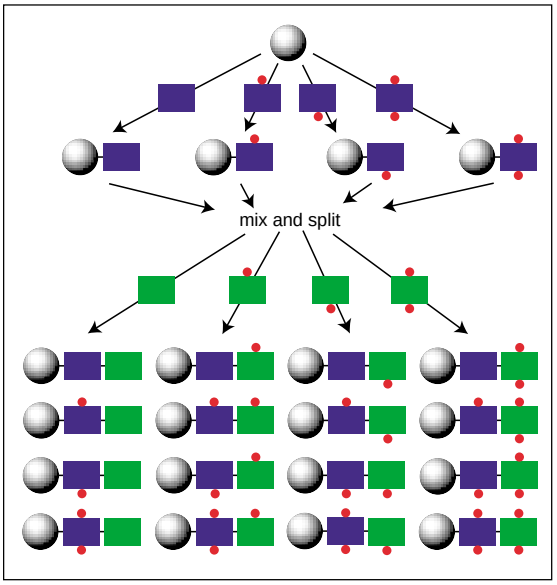
Using the tools of synthetic chemistry, however, we can build predetermined glycosaminoglycan structures in the laboratory. We start with chemically pure building blocks and link them together in an ordered fashion. By choosing the structure of each building block, we can dictate precisely the sequence and sulfation pattern of the resulting polymer. In addition to synthesizing single glycosaminoglycans, we are also developing methods to make large populations of diverse ones. This is important because, in many cases, we have very little structural information about the glycosaminoglycan involved. We may know, for example, that a particular protein binds to a chondroitin sulfate molecule that is at least six units in length, but we do not know which six units are involved or in what sequence. If every unit has four different possibilities, then we have 4^6 or 4,096 different compounds from which to choose. That's a lot of molecules!

Fortunately, chemists have devised two technologies, called solid-phase synthesis and combinatorial chemistry, which allow us to make large numbers of compounds rapidly and simultaneously. To understand the advantage of solid-phase synthesis, it is helpful to understand how chemists ordinarily make molecules. If a chemist wants to create a chemical bond between two molecules, she prepares appropriate building blocks, mixes them together in solution, and may add special solvents, reagents, or catalysts to accelerate the reaction. Once the reaction is complete, she purifies and isolates the desired product. This process of chemical synthesis forms the basis of modern organic chemistry and is the foundation of the pharmaceutical, chemical, and agribusiness industries, among others. The chief drawback is that purifying the intermediates can be time-consuming and expensive.

Nearly 30 years ago, however, Bruce Merrifield of Rockefeller University devised an alternative approach. Merrifield and his coworkers were synthesizing peptides—small polymers of amino acids—and their revolutionary insight was to anchor one end of the polymer to a solid, insoluble support, such as a glass or polystyrene bead. (You can actually see these beads under a microscope, and pick them up with tweezers.) By reacting the growing polymer chain with the right set of chemicals, one could perform a desired reaction and, at the end, the excess reagents and the by-products could be removed by filtering and washing the beads. Merrifield's invention was a fundamental leap forward, and he was awarded the Nobel Prize in chemistry in 1984. Solid-phase synthetic techniques have since been applied to many other molecules, including DNA, carbohydrates, and many classes of smaller compounds.

The second major innovation we use is called combinatorial chemistry—a simple, yet ingenious extension of solid-phase chemistry. If our chemist wanted to synthesize a collection of 16 related compounds using traditional synthetic organic methods, she would need to conduct 16 separate reaction sequences and purify 16 different products. Using a solid-phase approach, however, she can simply divide her beads into four portions and react each portion with a different building block.

Glycosaminoglycans that are readily distinguished by a protein in your body may appear virtually identical to state-of-the-art analytical instruments.



Combinatorial chemistry enables all possible sequence combinations of any given length to be made in a minimal number of steps, as the two-sugar library above shows. (The gray spheres represent the beads.)

PICTURE CREDITS:
15 — Doug Cummings;
16–23 — Linda Hsieh-Wilson

If she were to stop there, the result would be four different compounds. If, however, she pours the four sets of beads back into one flask, stirs them thoroughly, and pours out the mixture into four new flasks that she reacts with a new set of building blocks, then she will generate 4×4 (or 16) different molecules. Accordingly, she would need to run only eight reactions to produce the 16 compounds, and the purification of the final products would be that much simpler.

In chemistry, we call a collection of related molecules synthesized in this way a "library" of compounds. The figure above shows the combinatorial synthesis of a 16-compound glycosaminoglycan library. All the possible sulfation patterns are represented, and each bead contains a unique compound that can be isolated and characterized. In my laboratory, Sarah Tully and Sherry Tsai, two second-year graduate students, and Connie Wang, an undergraduate, have been working on methods to synthesize a chondroitin sulfate library. The construction of this library is a major undertaking, but our group has already successfully synthesized the building blocks. At present, we're optimizing the chemical steps needed to link the blocks to one another and to the beads.

With the library in hand, we can begin to identify the specific sulfation patterns that are responsible for the biological activity of glycosaminoglycans. We've begun to study several proteins whose binding to glycosaminoglycans has been implicated in nerve-cell growth and differentiation, and we expect to find out what governs these interactions. In addition, we want to understand how specific glycosaminoglycans influence cellular behavior, such as nerve-cell growth and regeneration. Finally, we'd also like to correlate specific sulfation patterns with physiological changes in brain function and development. Whether specific glycosaminoglycans are associated with development, aging, and neurodegenerative disease is a wide-open question at this time.

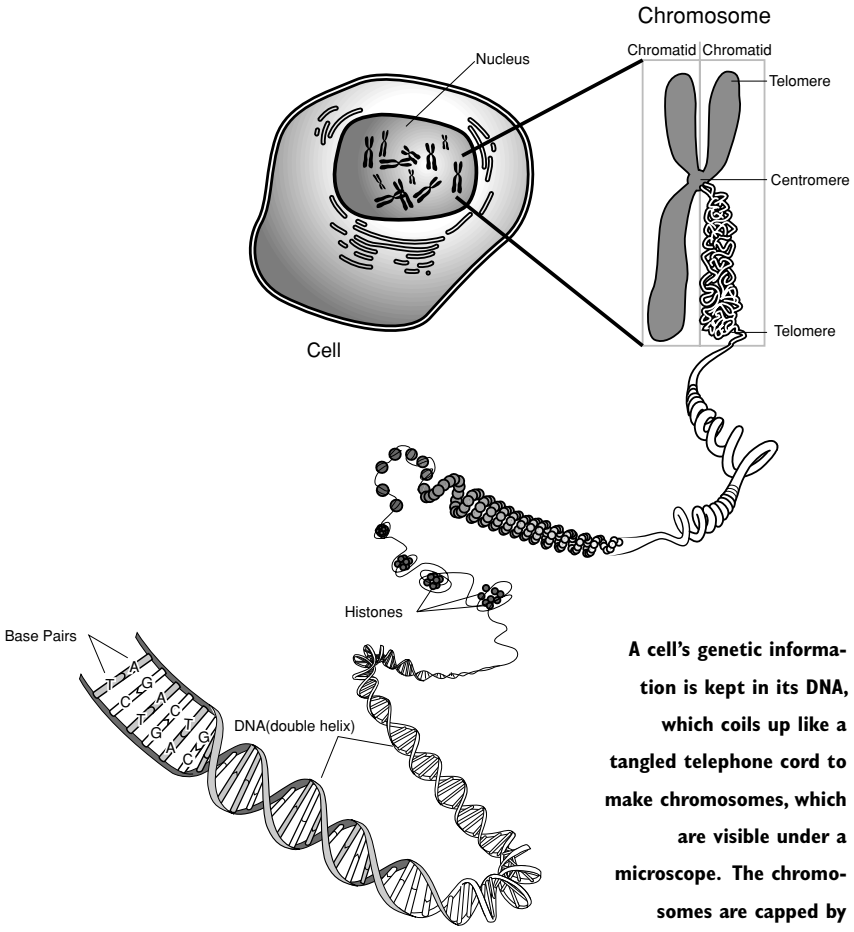
I hope that you'll agree that the intersection between chemistry and neurobiology is an incredibly exciting place to be. As one of the last great frontiers of scientific exploration, neuroscience requires the energy, creativity, and insight of people from a variety of different disciplines. Together, we're working to build a framework of understanding that stretches from molecules and genes to learning, memory, and perhaps even consciousness itself. Unraveling the many mysteries of the human brain will carry us well into the next century. Without a doubt, however, the adventure will continue to captivate the imagination of scientists and nonscientists alike. □

Assistant Professor of Chemistry Linda Hsieh-Wilson earned her BS from Yale in 1990, and her PhD from UC Berkeley in 1996, both in chemistry. After a postdoctoral appointment in neurobiology at Rockefeller University, she joined the Caltech faculty in the fall of 2000. Since then, she has been named a Beckman Young Investigator by the Arnold and Mabel Beckman Foundation, and has received a Research Innovation Award from the Research Corporation. This article was adapted from a 2001 Alumni Seminar Day talk.

The Core 1 Science Writing course, introduced in the winter term of 1999–2000 as an elective, is now required of all juniors. All of the student papers can be found on-line at http://www.its.caltech.edu/~sciwrite/; we present two of the best here.

Immortality Under the Microscope

by Alisa Ching



A cell's genetic information is kept in its DNA, which coils up like a tangled telephone cord to make chromosomes, which are visible under a microscope. The chromosomes are capped by special stretches of DNA called telomeres, which may play a vital role in cellular aging. Graphic by Darryl Leja, National Human Genome Research Institute.

Since the Age of Exploration, the search for worldly riches has coexisted with another quest, for the secret to an eternal earthly life. Some of us fear death. Others fear growing old and not being able to live life. And we dream of being forever young. The fountain of youth seems a silly notion to us today, but only because the conquistadors searched for it across the map of the world, and not through the map of our biology. The search continues, but more profitably today, because today it is directed inward.

Aging, the process that leads inevitably to an organism's death, can be defined as the general decline in the function of organs and tissue over time. In trying to understand the mechanisms of aging of the organism as a whole, many scientists are now looking for explanations on the cellular level. The belief that aging of individual cells leads to aging of the organism was made stronger recently when it was found that a segment of DNA once thought to be insignificant plays a crucial role in cellular aging.

This small piece of DNA is known as a telomere, a name derived from the Greek words *telos* meaning "end" and *meros* meaning "part." Telomeres, also known as chromosomal "caps," are long, repetitive DNA sequences found at each end of every linear chromosome. They carry no information in the genetic sense; however, their physical characteristics provide the cell with vital instructions. By bending back on themselves, they create a loop that may prevent fraying of the chromosome. Therefore telomeres allow the cell to easily differentiate between a chromosome and a broken piece of DNA. But they serve another more vital role. Telomeres can be thought of as cellular biological clocks. During mitosis, or cellular division, the cell is unable to replicate a small portion at the end of the telomere; therefore, these telomeres get shorter and shorter, until eventually the cell is no longer able to divide without losing part of the DNA encoding important gen-

The fountain of youth seems a silly notion to us today, but only because the conquistadors searched for it across the map of the world, and not through the map of our biology.

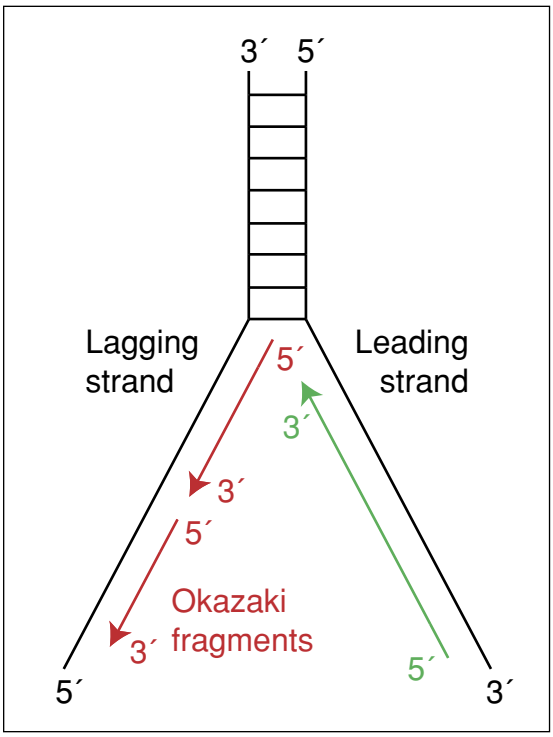
etic information. At this point, known as crisis, the cell simply stops dividing. From crisis, the cell normally enters into an inactive state known as senescence, which eventually leads to cell death.

Telomeres are a relatively recent discovery. In 1881, the German biologist August Weismann postulated that, contrary to the popular belief of the time, cells could only undergo a finite number of divisions. His theory could not be substantiated until 1961, when the biologist Leonard Hayflick, carrying out research at the Wistar Institute in Philadelphia, observed that, in culture, lung cells ceased to divide after about 50 divisions. Even if the tissue were frozen after 25 divisions, upon revival the cells would only divide until the 50-division limit was reached. This indicated that the number of divisions, not elapsed time, determines a cell's mortality. This finite limit to cellular replication has since been known as the Hayflick Limit. Hayflick, however, did not propose a mechanism to explain what he had seen. In 1971, closer observations by Alexi Olovnikov, a Russian scientist, found that telomeres got shorter with each mitotic division. Olovnikov proposed that telomere shortening was somehow related to cellular senescence. Finally, in 1990, Carol Greider and Bruce Fletcher at the Cold Spring Harbor Laboratory in New York experimentally proved that telomere length correlates with cellular aging.

Although many factors contribute to the aging of an organism, evidence suggests that it is directly related to the aging of the cell, and thus to telomere shortening. By understanding these factors' regulation, perhaps someday we will be able to slow or even stop the aging process. Since the length of a telomere determines the number of divisions a cell can undergo, perhaps by extending telomere length we can thereby extend the Hayflick limit, or even immortalize the cell. The implications and possibilities are innumerable.

In order to understand the purpose of telomeres, it is necessary to have a basic understanding of DNA replication. DNA is composed of a series of sugars stacked on top of each other to form the backbone of the strand, and bases attached to each sugar that form base pairs with bases of the adjacent strand of DNA. Each sugar-base complex is known as a nucleotide. In DNA four bases are used; they are abbreviated by one-letter codes: adenine (A), guanine (G), thymine (T), and cytosine (C). Bonds are formed between the bases so that A binds with T, and C binds with G. The two strands of nucleotides wind around each other to form a double helix. The long double strand of DNA condenses to form a very compact structure known as a chromosome.

Each strand of DNA has a polarity associated with it; one end is known as the 3′ (three-prime) end and the other as the 5′ (five-prime) end. The nucleotide strands bind in such a way that they line up antiparallel to each other—the 5′ end of one strand is next to the 3′ end of the other strand, as shown in the figure on the next page. When a cell divides, it needs to make a copy of each chromosome so that each new cell has all the necessary information. An enzyme known as a DNA polymerase is responsible for replicating DNA. The polymerase binds to the 3′ end of one DNA strand, known as the leader strand, and unzips the double helix DNA template as it synthesizes the new strand. However, polymerase can only synthesize DNA in one direction: from the 5′ end to the 3′ end. Since the DNA strands run antiparallel to each other, the other strand, known as the lagging strand, is replicated in segments, known as Okazaki fragments, that later get fused together. Near the end of the chromosome, the polymerase may not have enough room to bind and copy the very last nucleotides on the lagging strand, so therefore the end does not get replicated. This unreplicated portion is known as the 3′ overhang and is eventually lost. Thus chromosome shortening occurs every time DNA is replicated for mitotic division of the cell.



When DNA replicates, it unzips and an enzyme called DNA polymerase "reads" the exposed information from the 3´ end toward the 5´ end. Since the strands are antiparallel, the copy thus produced runs from the 5´ end to the 3´ end. The DNA on the leading strand can be read off in one fell swoop as it unwinds, but DNA on the lagging strand must be copied piecemeal, in so-called Okazaki fragments, which are then reassembled. The last few letters on the lagging strand don't get copied, because the DNA polymerase has nothing beyond them to bind to while copying them, and they are thus lost.

Approximately 50 to 200 base pairs of DNA are lost with each division. In viable cells this process doesn't affect the core DNA, since the overhang is part of the telomeres.

Telomeres, which are simply long repeat sequences of the bases TTAGGG, serve as a buffer to allow the cell to divide many times. After some number of divisions, the telomeres get depleted. The ends of the chromosomes get too close to the genetic material and the cell enters senescence. Compared to the rest of the chromosome, telomeres are relatively small. The average human chromosome is 130,000,000 base pairs long. At conception, telomeres are about 10,000 base pairs long and at birth they have already shortened to about 5,000 base pairs. The age of the human correlates to the length of their telomeres, with the exception that humans with premature aging diseases, known as progeria, exhibit unusually shortened telomeres.

There are several solutions to the end-replication problem. The first solution is to not have any ends at all. This is seen in many bacteria and viruses that have circular DNA. These single-celled organisms can divide forever and never lose any DNA during replication. The second solution is to have special proteins at the ends of the chromosome that specify the starting point for replication, thereby assuring that the ends will be copied. This is seen in some viruses such as adenoviruses. In this way, the ends of the chromosome can be copied. The third solution is to use an enzyme to reextend the end part of the DNA that is lost. This solution is found in all plants and animals.

In humans, certain types of cells do not exhibit a replicative limit. Stem cells (cells that give rise to skin, intestine, and blood cells), germ cells (cells such as sperm or egg that give rise to progeny), and cancer cells (mutant cells that have become immortalized) can all divide indefinitely. The common factor found in all of these immortalized cells is telomerase, a ribonucleic enzyme that synthesizes telomeric DNA (TTAGGG sequences) on the ends of chromosomes, replenishing the material lost to cell division. Telomerase is not normally expressed (or activated) in human somatic tissue (cells that compose the majority of the body, such as skin, intestine, and blood cells—the cells derived from stem cells, in other words) but is expressed in germ cells, stem cells, and cancer cells, where unlimited division is needed.

Studies done on telomeres have all shown that the length of a telomere has many effects on the cell, determining, in particular, the expression of many cellular proteins. It is thought that changes resulting from these processes may contribute to some of the age-related changes of the entire organism. In 1999 a pivotal study was done by Karl Rudolph, Carol Greider, and others at the Dana-Farber Cancer Institute in Boston, in which mice were bred that lacked telomerase. The progeny of these mice contained critically shortened telomeres, which got shorter with each generation. By the sixth generation, the telomeres were so short that the mice could no longer reproduce. It was observed that these mice had much shorter life spans than normal mice, and exhibited symptoms similar to those seen in elderly humans. The mice were graying and balding, they suffered weight loss and ulcers, they took longer to heal wounds, and they experienced an increase in cancer, atherosclerosis, and osteoporosis, as well as a general decrease in their ability to respond to stress. The severity of these symptoms increased with shorter telomere length. The findings from this study demonstrate a direct link between shortened telomeres and aging of the organism.

Still, there are many differences between humans and mice. First, these symptoms are not usually seen in mice at all. Since mice have relatively short life spans and die of predation or environmental stress, they never normally show any of these signs of aging. Also, mice have much longer telomeres than would ever be used in their lifetimes, and express telomerase in somatic cells; therefore telomere shortening does not play a vital role in mice. However, humans do not have telomerase expression in somatic cells and have much longer life spans. Consequently, telomere shortening greatly affects elderly humans, more so than it affects any other organism, since modern medicine perpetually finds ways to prolong human life.

Studies are also being done on humans, especially on humans who exhibit progeroid syndromes—diseases in which children age prematurely. Children with conditions such as Werner's

syndrome and Hutchinson-Gilford's syndrome exhibit faster telomere shortening, decreased cellular divisions, and decreased ability to cope with stress. Some afflicted five-year-olds have telomeres comparable to those of an 80- or 90-year-old. These diseases are rare; their further study could provide valuable insight into the details of organismal aging.

An understanding of how telomerase affects the aging process promises new advances in tissue engineering. Biologists currently look for ways to synthesize organs for transplantation into ill patients. Using telomerase, however, cells within a patient's body could be treated and rejuvenated so that tissue transplants would not be necessary. This has almost an infinite number of applications, including bone-marrow transplants, skin grafts, and cosmetic applications, as well as improving general immunity in older patients, or patients with AIDS or blood disorders.

Such therapies also come with worries. One major concern is that prolonging the life of cells with damaged DNA would lead to further accumulation of mutations and an increase in the possibility of cancer. It is generally accepted that cancer arises from mutated cells that exhibit accelerated growth. Since it takes many divisions for the cell to accumulate enough mutations to become cancerous, cells that can only undergo a finite number of divisions are less likely to become malignant. Runaway cells will quickly come to the ends of their telomeres and die off. In this way the presence of telomeres acts to protect against early development of cancer.

This is also evident in mouse experiments. In the Dana-Farber study, the telomerase-deficient mice also had a high incidence of cancer. It is believed that their shortened telomeres cause a greater instability of their chromosomes, resulting in a higher susceptibility to cancer formation.

But telomerase can also abet cancer if it occurs in the wrong cell at the wrong time. Cancerous cells that find a way to express telomerase can overcome their replicative limit and undergo indefinite growth. Throughout the mid-20th century, many biologists noticed that, from time to time, immortal cells occasionally arose from normal, mortal cell cultures. It is now known that these cells were strains of cancer. When cells reach the Hayflick limit and enter crisis, they normally proceed to senescence and death. However, crisis is a genetically unstable stage where chromosomes, unprotected by telomeres, can randomly break and fuse. A cell in crisis is more prone to random mutation. If a chance mutation reactivates telomerase in such a cell, the cell can continue to divide, and can go on to form a tumor. For this reason, cancer is often found in elderly patients who have shortened telomeres. Most cancerous cells arise in this way, as indicated by the telomerase activity present in 85 to 90 percent of human tumors.

The fact that cancerous cells express telomerase is extremely important. The presence of telomerase in cells where it shouldn't be seen can be used as a tumor marker for early cancer diagnosis. It can also be used as a basis for a cure for cancer. Telomere inhibitors may someday be employed to deactivate telomerase in cancer cells, thereby impeding their ability to indefinitely divide. One potential problem with this method is that it may take too long to terminate a tumor's growth, and the death of the human may occur before the death of the cancerous cells. But current research looks very promising.

Telomeres also play a role in cloning. Observations of Dolly the sheep reveal that her telomeres are shorter than average for a sheep of her age. Dolly was cloned by taking the nucleus, which contains the genetic information, from a somatic cell of a six-year old ewe, and transferring it to an enucleated egg. (An enucleated egg is simply an egg from which the nucleus has been removed.) Since the DNA was from a six-year-old ewe, the chromosomes had telomeres that had already been shortened. This means that Dolly will most likely have a shorter life span. However, Dolly's offspring appear to be normal, and do not exhibit shortened telomeres. This indicates that their telomeres were elongated—most likely in Dolly's germ cells, and not during conception. Cloned mice, on the other hand, do not seem to have this problem. Because of the somatic expression of telomerase in mice, somatic-cell telomeres are not significantly shorter than germ-cell telomeres. There is a possibility that Dolly is simply an exception, and that not all sheep clones will exhibit shortened telomeres. However, if Dolly is not an exception, cloned humans will very likely exhibit shorter telomeres as well.

In short, telomeres and telomerase have several functions. They act to stabilize the chromosomes and prevent them from fraying. They are a solution to the end-replication problem of linear DNA. And, by limiting the number of times that each cell divides, they protect the organism from the accumulation of too many mutations. The consequences are that shortened telomeres result in the aging of the organism. And abnormal cells that find a way to express telomerase can lead to cancer.

Although many researchers seek a simple unified theory of aging, telomeres and telomerase are most likely not aging's only factors. Many theories attribute aging and longevity to meta-

These mice had much shorter life spans than normal mice, and exhibited symptoms similar to those seen in elderly humans... graying and balding, they suffered weight loss and ulcers, they took longer to heal wounds, and they experienced an increase in cancer, atherosclerosis, and osteoporosis.

bolic rate, changes in hormone production, mitochondrial damage, genes that determine longevity, accumulation of toxins, and free-radical oxidation.

One theory is that the number of divisions cells can undergo determines the longevity of the species. (Note that telomere length does not correlate with life span across different species.) It has been found that Galapagos tortoises live an average of 175 years and their cells undergo approximately 130 divisions. Humans have an average life span of about 80 years and human cells undergo around 50 divisions. And mice, which only live for a couple of years, have cells that divide about 30 times.

Another theory bases longevity on the total metabolic potential of the organism, measured as the total kilocalories used per gram of body weight per lifetime. For example, an elephant, which lives about 10 to 20 times longer than a mouse, has an average of 30 heartbeats per minute whereas a mouse has approximately 300 heartbeats per minute. Both species take about 200 million breaths in a lifetime and both species have a metabolic potential of about 200 kilocalories per gram. This figure is much the same for other mammals. Therefore life span simply depends on the rate at which this potential is used up. Humans are an exception, with a metabolic potential of 800 kilocalories per gram.

Another theory bases longevity on a species' ability to reproduce. After reproduction is complete, there is no longer any need for the organism. Therefore, since hormones regulate reproduction, a change in the production of hormones also regulates aging. For women, menopause represents a major change in estrogen levels that is often associated with age-related symptoms such as osteoporosis and a decline in cardiovascular health. For men, there is no one turning event, rather a gradual decline in testosterone levels with age.

Several theories base longevity on the amount of damage accumulated by the cell's DNA. One theory is based on free radicals, which are highly reactive chemical agents that oxidize membranes, DNA, and proteins. This damage accumulates over time and leads to nonfunctional cells. Similarly, toxins can accumulate in cells and disrupt their ability to function properly. Some think that damage done to mitochondrial DNA is more significant than damage done to "genomic" DNA, the DNA of the cell itself. Mitochondria are organelles within a cell that provide the energy for cellular activities. Mitochondria have their own DNA, but there are no mechanisms to repair mutated mitochondrial DNA as there are to repair genomic DNA. Therefore mitochondrial DNA accumulates mutations faster than genomic DNA.

Other theories base longevity on certain genes that help the organism cope with stress. By increasing resistance to stress, the organism can live longer. However, many genes aside from stress genes seem to play a role in longevity.

Despite this multiplicity of theories, it may be possible to indirectly correlate all aging with one specific event that is crucial to the cell's vitality. For example, the telomere theory of aging may apply to many age-related diseases that do not seem at first to be connected to shortened telomeres, such as myocardial (heart) cell death in atherosclerosis. Atherosclerosis is the most common cause of coronary-artery disease and is responsible for approximately one-third of all deaths in the United States. Myocardial cells do not divide; therefore death of myocardial cells in atherosclerosis is not directly due to telomere shortening. However, the endothelial cells of the coronary vessels, which supply the myocardial cells with oxygen-rich blood, do experience telomere shortening and death. The dead endothelial cells build up in the arteries, constricting the blood flow to the myocardial cells, thereby killing the myocardial cells through lack of oxygen.

It could also be argued that the neurons affected by Alzheimer's disease experience a similar fate. It is thought that, since neurons do not divide, their telomeres do not contribute to Alzheimer's disease. However, although there is as yet no evidence to support the possibility, Alzheimer's disease may result from the senescence of neighboring astroglial cells—cells that do divide, and that are necessary in the regulation of the neurons. Similar mechanisms may explain many age-related diseases that affect nondividing cells. More likely, however, there are many intermingled factors that together are sufficient to lead to aging.

In looking for the fountain of youth we look to all the causes of aging. Ultimately what leads to the death of an organism is almost as complex and intricate as what leads to the life of the organism. Even if we never achieve immortality by studying aging, our increased understanding of telomeres and telomerase may extend the life spans of humans and enhance our ability to live out the rest of our years as fully as possible. □

Alisa Ching is a senior in chemical engineering. Her mentor was Bruce Hay, assistant professor of biology, who studies the molecular genetics of cell death. She became interested in telomeres when Hay brought them up in his genetics class one day.

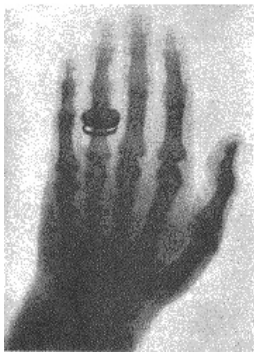
The Promise of Portable MRI

by John Ferguson

Introduction

In the summer of 1881, America's 20th president, James A. Garfield, lay on his bed slowly dying. Somewhere in his body was an assassin's bullet. Over a period of 80 days, 16 different doctors and surgeons tried to locate the bullet. They poked fingers and metal probes into the bullet hole, without success. Even the famous American inventor Alexander Graham Bell tried his hand at locating the bullet by creating a crude metal detector. After some time, he claimed he had found the bullet, and the doctors rushed to operate on Garfield to excise it. However, Bell did not realize that the president's bed contained metal springs. The doctors, of course, could not find the bullet, but created more complications which ultimately led to the president's death.

If this had happened fifteen years later, the doctors would have had no difficulty finding the bullet. A new technology had been discovered that revolutionized the world of medicine. The German physicist Wilhelm Roentgen discovered X rays by observing electric currents in a partially evacuated glass tube. These rays, now known to be high-energy electromagnetic radiation, would pass through objects that light could not. Roentgen experimented with the tube, observing metal and nonmetal objects. He could even see through doors. But more amazing than that were the results when he looked at his wife's hand. In this first medical X-ray image, her bones and metal wedding ring could be seen clearly.



X rays are still very common today. But with the development of computers, 3-D images can be reconstructed from signals received by X-ray detectors that rotate around the subject's body. This technique, known as CT (Computed Tomography) or, more popularly, "CAT scanning" (for Computed Axial Tomography) was introduced in 1972 by Godfrey Hounsfield, who was honored with a Nobel Prize in 1979 and a unit in his name, the Hounsfield, which measures the attenuation of X rays as they pass through tissue. A modern X-ray CT can collect and reconstruct a high-resolution "slice" of the body in half a second. Computers are also used to create images for Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT). Both imaging techniques involve injecting the body with a radioactive tracer and monitoring the emissions as the radioactive substance travels around the body. However,

President Garfield is assassinated at a train depot. From *Frank Leslie's Illustrated Newspaper*, July 16, 1881.

A promising handheld MRI scanner is under development. If successful... [w]e would have a device very similar to the medical tricorder from *Star Trek*; it could measure anything, anywhere.

overexposure to ionizing radiation and X rays has been shown to be dangerous and unhealthy.

Two alternative imaging techniques have become immensely popular due to their mildness and versatility: ultrasound and MRI. These work through sound waves and magnetic fields respectively, which are safe for most people (although MRI scanners cannot be used on patients with pacemakers, cochlear implants, or aneurysm clips). Doctors can prescribe these diagnostic tests as frequently as desired, without concern about the patient's long-term health. However, the largest drawback of these two modalities is their size and their price. A common ultrasound scanner can be wheeled bed-to-bed around the hospital on a cart and costs $150,000, while an MRI scanner needs a shielded room dedicated to MRI and a cryogenic cooling system to operate a superconducting magnet, and costs about $2,000,000.

But on the horizon, two new products show the next direction of medical imaging: portable, nonionizing imaging devices at a fraction of the current prices. A highly portable ultrasound scanner is already being sold; a promising handheld MRI scanner is under development. If successful, the MRI scanner could revolutionize medicine by creating an incredible medical tool. We would have a device very similar to the medical tricorder from *Star Trek*; it could measure anything, anywhere.

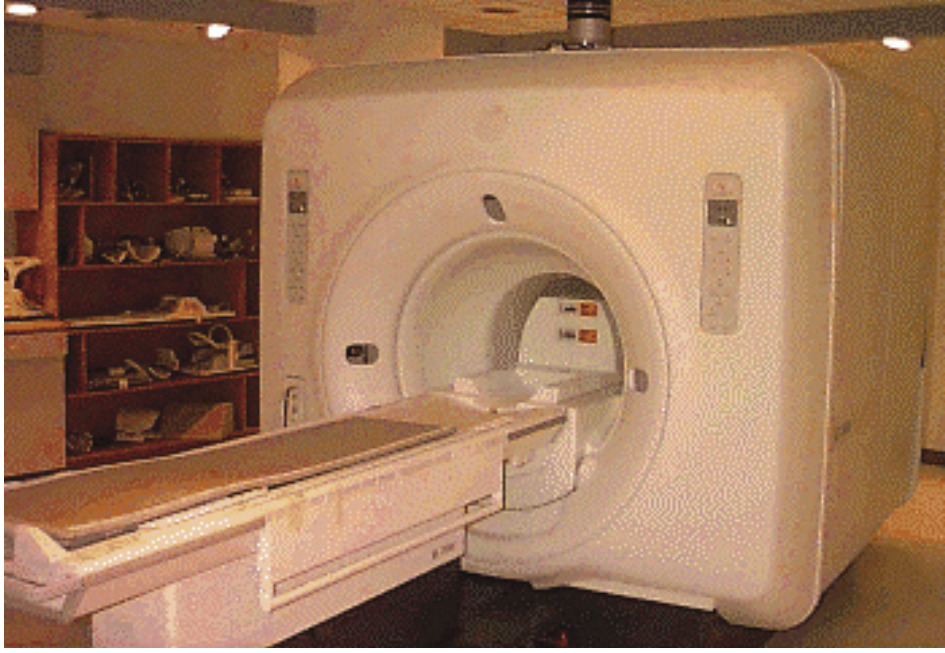
MRI History

But to see how this handheld device works and to realize its possibilities and limitations requires a good understanding of the history of the technology that led to its current state. Thousands of years ago, people in China and Greece independently discovered lodestones and used them for fortune-telling and navigation. However, their useful but seemingly magical motions were not understood until the 19th century. In 1802, the Italian scientist Gian Domenico Romagnosi found that a lodestone would move when a nearby wire conducted current; unfortunately, this result lay unnoticed for nearly 20 years, until Hans Christian Ørsted published the finding. Suddenly the floodgate was opened for scientific discovery. Countless people contributed findings to further the field of electromagnetism, including Ampere, Weber, Faraday, Hertz, Curie, and even the American patriot Ben Franklin. In 1873, James Clerk Maxwell combined all of these results into four simple equations that can be summarized as follows: electricity and magnetism are inescapably tied together. A moving charge (i.e., a current) creates a magnetic field; a changing magnetic field induces a current. The picture seemed complete and fully understood.

However, as in all of physics, the 20th century uprooted many firmly established ideas, giving rise to new possibilities. Quantum mechanics, as described by Wolfgang Pauli in 1924, gave a more complete explanation for the nature of electricity and magnetism. Nuclei of atoms display a property called spin, which is, in a sense, small-scale angular momentum. Normally, the orientation of these spins in a material is quite random. However, in the presence of a magnetic field, the nuclear spins line up parallel and antiparallel to the field, with a tiny excess—a few nuclei per million—lined up parallel. It is these few spins that can be detected, and the way they react to changing magnetic fields gives rise to the predecessor of MRI, Nuclear Magnetic Resonance (NMR).

The official birthday of NMR was in 1946, when a Stanford team led by Felix Bloch and a team from MIT led by Edward Purcell independently discovered that by adding an additional small field to the original magnetic field, interesting results would follow. By adding the second, oscillating, field, known as a radiofrequency (RF) pulse, at the proper frequency for a short period of time, some of the nuclei would absorb the energy, or resonate. After the RF pulse turned off, the nuclei would try to return to their original energies in a process called relaxation, giving off a signal that provided a great deal of information. The information included details of the sample's chemical composition and density, any movement of chemicals within the sample, and, with the use of a third, spatially varying magnetic field produced from gradient coils, the location of the chemicals within the field. Answers to what, how much, when, and where would be given without touching or damaging the sample. NMR remains to this day a premier instrument to investigate chemical structures. But it wasn't until 20 years after the discovery of NMR that the medical diagnostic possibilities were realized.

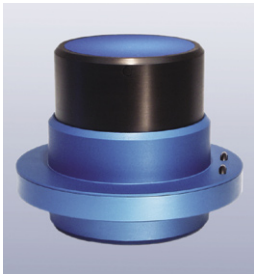
A short time after Bloch discovered NMR, he put his finger inside the magnet and noticed



A normal MRI full-body scanner. The patient lies on the table, which then slides into the hole in the doughnut-shaped magnet. Image courtesy of J. P. Hornak, The Basics of *MRI*, http://www.cis.rit.edu/htbooks/mri/.

a strong output signal. Unfortunately, he did not pursue this result any further. It wasn't until 1972 that a paper by Raymond Damadian, showing that tumors could be distinguished from normal tissue by their relaxation times, woke the world up to the possibilities of medical NMR. Another scientific floodgate opened. Numerous people started noticing all sorts of medically relevant phenomena that could be detected with NMR. In 1978, an imaging device was created based on the differences in relaxation times of different tissues. Instead of naming the new device "Nuclear Magnetic Resonance Imaging," the word "nuclear" was dropped, due to its negative connotations with nuclear warfare and nuclear radiation, and MRI was born. Now MRI scanners can be found in most hospitals and are frequently used to get detailed body images that also contain functional information. Since the first device in 1978, technological improvements in MRI have been true triumphs of both science and engineering.

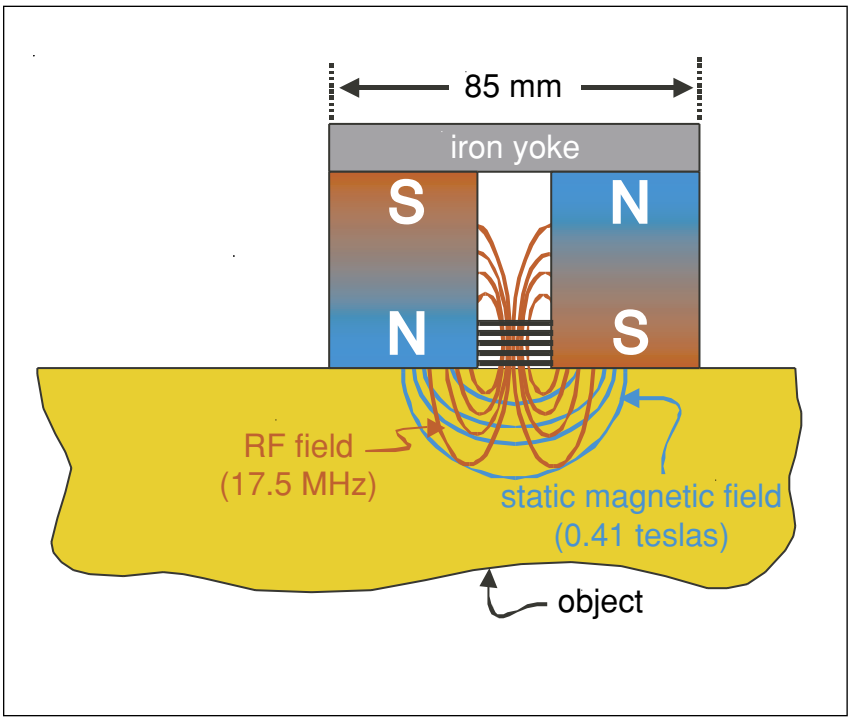
The main magnet, the most vital component of any MRI system, creates enormous design demands. The most common MRI scanner found in hospitals has a strength of 1.5 teslas, 30,000 times that of the earth's magnetic field. To get such a high field strength, a superconducting magnet is used that requires a sophisticated cooling system made from layers of liquid helium and vacuums. Precautions must be taken against a quench, which is a violent expansion of the helium due to insufficient cooling, and a safe-release system must be in place in case a quench occurs. Also, shielding must be constructed to protect neighboring rooms (and adjoining floors!) from the strong magnetic field, which can erase credit cards, affect computer memory and displays, and even kill people who have pacemakers. This shielding can involve about 20 tons of material to block the fields, as well as additional magnets that reduce the outside fields, and sacrifices some of the desired field strength inside the magnet. Other systems that involve complicated design are the shim system, which creates magnetic fields that are homogeneous; gradient systems, which give better spatial resolution and faster imaging; and RF systems that resonate the nuclei within given specifications. All of these issues contribute to the overwhelming cost of an MRI system, averaging $2,000,000 for a new 1.5-tesla installation with about $300,000 in yearly maintenance. In addition, many people believe that the best way to improve the MRI scanner is by increasing the field strength to 3 or 4 teslas. This would improve resolution and scan time, but with a significant increase in the system's size, complexity, protective equipment, and, of course, price.



The NMR-MOUSE is about the size of a prescription bottle. This is not your father's MRI!

The NMR-MOUSE

Enter the NMR-MOUSE (MObile Universal Surface Explorer). This handheld, one-kilogram unit holds promise as a portable MRI device that would cost less than $1,000. Its design is very simple: two antiparallel magnets, held apart by a block of iron and an RF coil, and two gradient coils in the gap between them. The two magnets are made of a rare-earth metal that generates a high magnetic-field strength for their size; the iron block, called a yoke, serves to increase the field strength. The RF and gradient coils serve the same purpose as in a normal MRI scanner—to stimulate the atomic nuclei within a specified region. However, the most important feature in the NMR-MOUSE is the absence of all the extra equipment found in a typical scanner. There are no shim coils, no shielding, and no cryogenic cooling system, since two permanent magnets are used instead of a superconducting magnet. This results from a philosophy entirely different from that of mainstream MRI—namely, that of using a smaller overall field strength, exploiting the stray



A schematic of the NMR-MOUSE being applied to the surface of a solid. The set of parallel black lines between the magnets is the RF coil.

field instead of the main field, and converting the "disadvantage" of inhomogeneity (where the magnetic field is not perfectly uniform) into an advantage.

The inventors of the NMR-MOUSE, Peter Blümler and Bernhard Blümich (both then at the RWTH in Aachen, Germany), were led to design and construction of the NMR-MOUSE in 1993 by two simple realizations: "typical MRI contrast (relaxation, diffusion) doesn't rely on homogeneous fields" and "localization procedures imply inhomogeneous fields." Instead of using the traditional approach of creating a completely homogeneous field and adding systemic variations, they found that a naturally inhomogeneous field with consistent responses would work as well. Unknowingly, they had just entered the world of so-called fringe-field NMR. The first few magnets that were used in NMR had significant inhomogeneities; scientists designed their experiments around this fact. However, as technology improved, the vast majority of researchers looked to bigger and more homogeneous magnets. Even so, a few people, most notably Jasper Jackson, did research with smaller magnetic fields—down to just using the earth's natural magnetic field—and strange combinations of magnets that would create regular fields outside of two magnets. These devices found applications in detecting signals in dangerous places—using the magnet to peer through a wall into a dangerous room, for example—or inaccessible ones, such as logging a well, in which an NMR device is dropped down a very deep borehole to make moisture measurements and detect oil in rocks miles below the surface. These instruments were providing solutions that the larger, superconducting NMR spectrometers could never attempt. So, what seemed like an original idea by Blümler and Blümich—to use a small system to make measurements outside of the main magnetic field—was actually closely related to work done 40 years before. Nevertheless, with the use of more powerful rare earth magnets and efficient computer-aided designs, new possibilities have opened up, most notably in imaging.

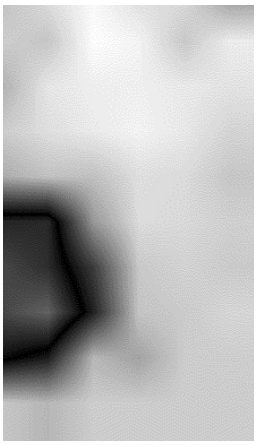
The NMR-MOUSE brings to the table a small yet potent design. With dimensions of 9 × 2 × 2 centimeters and a weight of 1.25 kilograms, it is truly handheld. All it needs to operate is a cable connecting it to a computer, so it is highly portable. The NMR-MOUSE can image an ellipsoid 16 × 1 × 2 centimeters. At the surface, a field strength of 0.5 teslas can be found. Incredibly, as an imaging tool, it can scan with 100-micron (0.1-millimeter) resolution. However, the NMR-MOUSE's biggest limitation is penetration depth; it can only image objects very close by. Currently, the maximum penetration depth is 5 millimeters, with closer objects generating stronger signals. This creates a large restriction on the types of objects the NMR-MOUSE can image, and on its general applications.

Even so, the NMR-MOUSE has found both traditional and novel uses. Blümler and Blümich see applications in nondestructive materials testing, process control, agriculture, food processing, and medicine. Theoretically, any material that contains protons can be detected by the NMR-MOUSE, but polymers (e.g., plastics), elastomers (e.g., tires), and biological materials (e.g., humans) give the best results. And two new applications are possible now, due to the portable and inhomogeneous-field nature of the detector. First, imaging can be done on substances that contain ferromagnetic materials, such as steel-belted tires. An ordinary NMR device would not be able to image such a thing without serious damage and/or signal interference occurring. In fact, strangely enough, the steel cords in tires have been shown to improve the signal for the NMR-MOUSE. Second, because the NMR-MOUSE can be placed in any desired position, directional patterns, called anisotropies, within the material can be measured. Tendons have dense collagen structures that are normally very difficult to measure using traditional NMR. Even so, the NMR-MOUSE has successfully performed accurate measurements on the Achilles tendon in human subjects. This is because the scanner can be manually adjusted to the "magic angle" of 54.7 degrees, where a robust measurement of anisotropies can be made. More experiments are required to develop these measurements into a useful diagnostic tool. Also, the NMR-MOUSE has produced a cross-sectional image of a pork leg, obtained from a butcher, where muscle, bone, and marrow can be easily distinguished. Of course, this is not on a par with modern MRI images, which take incredibly detailed pictures

A prototype of the NMR-MOUSE testing a tire.

of human structures. However, compared to older MRI images produced by multiton machines, the 1.25-kilogram NMR-MOUSE performs quite impressively.

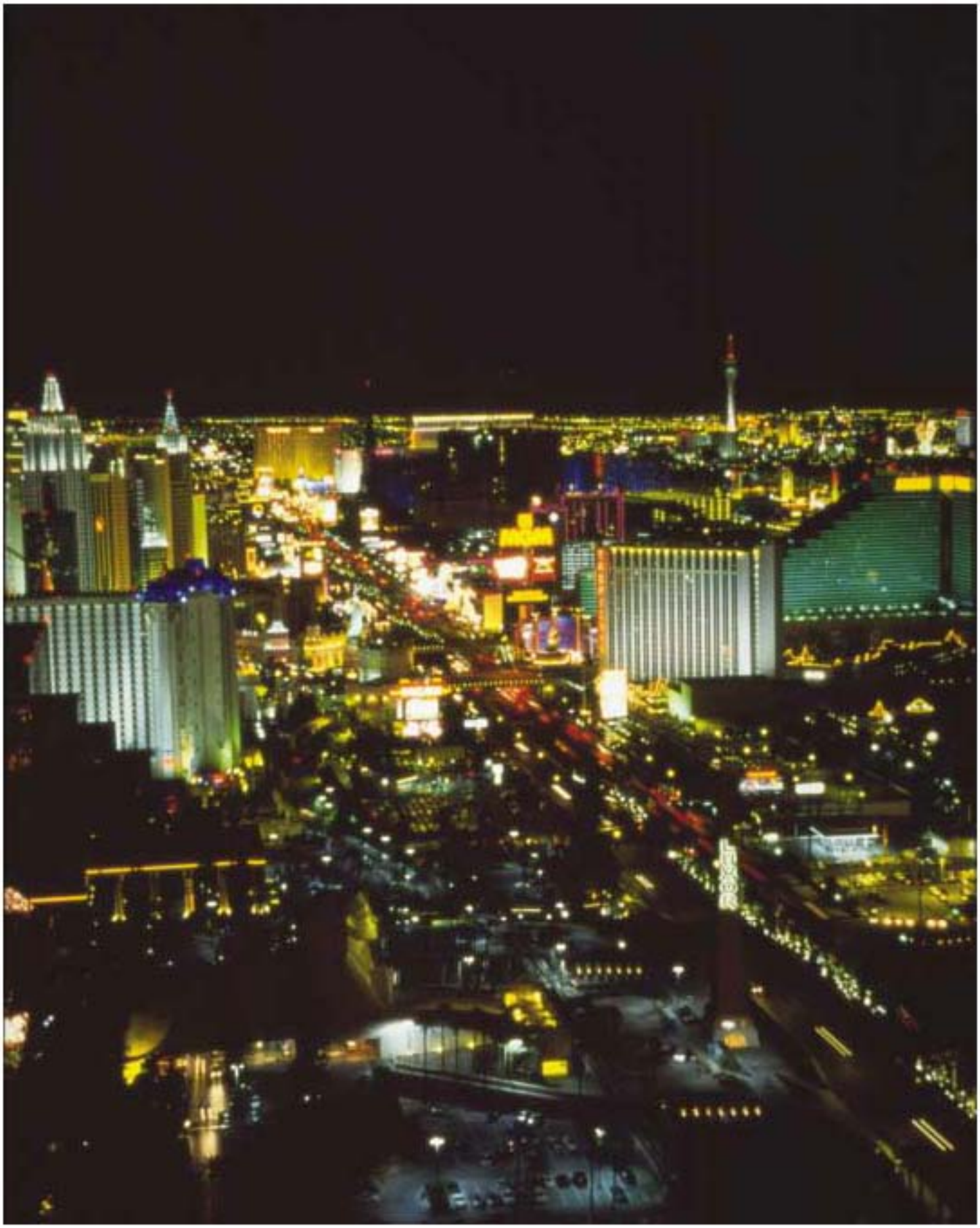
There is another imaging modality that is enjoying success with its portability. Ultrasound has been used as a medical device since the 1950s. Since ultrasound uses sound waves, it is like MRI in being noninvasive and nonionizing. Ultrasound is safe enough to use for viewing the fetus inside a pregnant woman's body without any concern for the baby. It can detect solid structures in the human body and analyze the movements of fluids, such as blood. However, its biggest disadvantage is that it cannot see behind bone or gas—it can't see behind the air in your lungs, for example. A modern ultrasound scanner has two components: a transducer that emits and receives the sound waves and a computer-based data-processing unit. The transducer is handheld, while the computer is normally very large and needs a skilled technician to operate it. However, SonoSite has just developed an ultrasound scanner that weighs 2.5 kilograms for the transducer, computer, and display, is portable, and is easier to operate than traditional systems. Doctors can take the scanner anywhere to make measurements without carrying a large computer-based system. In addition, this new scanner costs only about $25,000, compared to the $150,000 to $300,000 price tag for larger scanners. How can the NMR-MOUSE compete with this new device?



A 5 × 3-centimeter cross section through a pork leg, as seen by the NMR-MOUSE. The black ring is bone; the gray within it, marrow; and the light gray outside it, meat.

At the moment, the NMR-MOUSE cannot compare with the new SonoSite scanner in terms of usage and portability. First of all, it is important to realize that ultrasound and MRI are different imaging modalities; they each have significant advantages and disadvantages. Also, even though SonoSite's ultrasound scanner is much better developed than the NMR-MOUSE, there is a large company behind SonoSite's new system that has provided all of the necessary capital to miniaturize the device. Recall that traditional ultrasounds have handheld transducers and big computers. SonoSite's main contribution has been to make the large computer smaller. They haven't changed the fundamental ultrasound technique. On the other hand, the NMR-MOUSE was developed through the intellectual curiosity of two scientists who had to develop new techniques and designs with minimal funding. They were trying to find alternatives to large and expensive MRI scanners. Fortunately, Bruker, a giant in the NMR and MRI industries, has shown interest in the NMR-MOUSE and has begun collaborating with the scientists. With this corporate sponsorship, the NMR-MOUSE has an opportunity to really blossom. New designs will minimize the penetration limitations that have given the NMR-MOUSE so many restrictions. Maybe in the near future, we will be diagnosed and treated with portable MRI and ultrasound devices by doctors in their offices without having to go to the hospital and be charged a few thousand dollars. Even though physicians will not carry *Star Trek* medical tricorders anytime soon, we are definitely a step closer. Now we just have to work on teleportation. □

John Ferguson is a senior in physics. His mentor was Michael Tyszka, a visiting associate in biology at Caltech and an assistant professor of research at the City of Hope, in whose lab Ferguson worked last summer. This summer took Ferguson farther afield: he was one of four Caltech undergrads to ride the "Vomit Comet" at NASA's Johnson Space Center (see Random Walk).



They didn't build all of those exotic hotels and gilded casinos by letting the players have the edge. Nevertheless, throughout its past 50 years of spectacular growth, Las Vegas has always accommodated an anonymous but thriving culture of successful gamblers.

Vegas Winners

by John Trijonis

When I was asked recently by the Caltech Alumni Association to describe my life as a Las Vegas gambler, the thought struck me that very few people even know that my world exists. Of course, everyone is aware of the immense casino gambling industry in Nevada, but I assume that most people realize that the percentages are set against the players. They didn't build all of those exotic hotels and gilded casinos by letting the players have the edge. Nevertheless, throughout its past 50 years of spectacular growth, Las Vegas has always accommodated an anonymous but thriving culture of successful gamblers ("winners" in the local vernacular).

In describing this culture and my niche within it, I will focus on the following questions: Where in the casinos can you legitimately win? How is my specialty, sports betting, set up? What techniques did I use to derive a successful system? Why is the gambling culture so shadowy and obscure? How did gambling relate to my education and scientific career? Would I recommend this way of life to others?

WAYS TO WIN

Figure 1 portrays a history of the ways to win in casinos over the last half century. The seven curves in the figure represent, in a very approximate fashion, the average yearly winnings for a top-level gambler in seven different areas where the casinos were getting legally beat. Before addressing these areas individually, however, it is useful to understand the assumptions and ground rules for the figure.

First, the curves are really only "guesstimates," qualitatively in the right ballpark but certainly not quantitatively precise. I arrived at them through discussions with various gamblers who I thought were most in the know. The single tick on the left-hand axis should be somewhere around $1 million per year. In order not to understate the great blackjack boom of the 1950s and '60s, I have attempted to represent the winnings in constant dollars (based, say, on the year 2000).

Second, the curves represent earns for the highest level of gamblers, the most successful top few (three to five). In some of the games, most notably blackjack and poker, there were scores of other gamblers winning at a 10th or 20th the rate of the uppermost few.

Third, it is important to stress the qualifier "legal." There have been many schemes and machinations for attacking the casinos illegally: marking cards, having adroitly placed spies peek at cards (for example, the dealer's hole card in blackjack), mechanically fixing dice or slot machines, cooperating with a cheating dealer who is your partner, tossing dice illegally (that is, throwing them short with a special spin just one time when the thrower or his accomplice places a very large bet), or employing hidden computers (for example, to calculate the physics of roulette). I assume, however, that the reader shares my great antipathy for the possibility of prison (or, in the old days, the possibility of the casinos' own brand of punishment).

Finally, at the risk of stating the obvious, when listing ways to win, I am referring to ways of gaining a positive mathematical percentage. Contrary to the advice of the gambling books sold at the Las Vegas airport, you cannot win in the long run with a negative percentage through any sort of bet-timing or money-management scheme. Basically, the winners find a way to be like the casino; they gain a small advantage and play it as often as possible. They remind you of Bill Gates, not Frank Sinatra.

Addressing the games per se, the original way to make a windfall at the casinos was blackjack in the 1950s and early 1960s (first popularized in the book *Beat the Dealer* by Edward Thorp). Using computer-optimized strategies for card counting, bet timing, and card playing, the top players had a

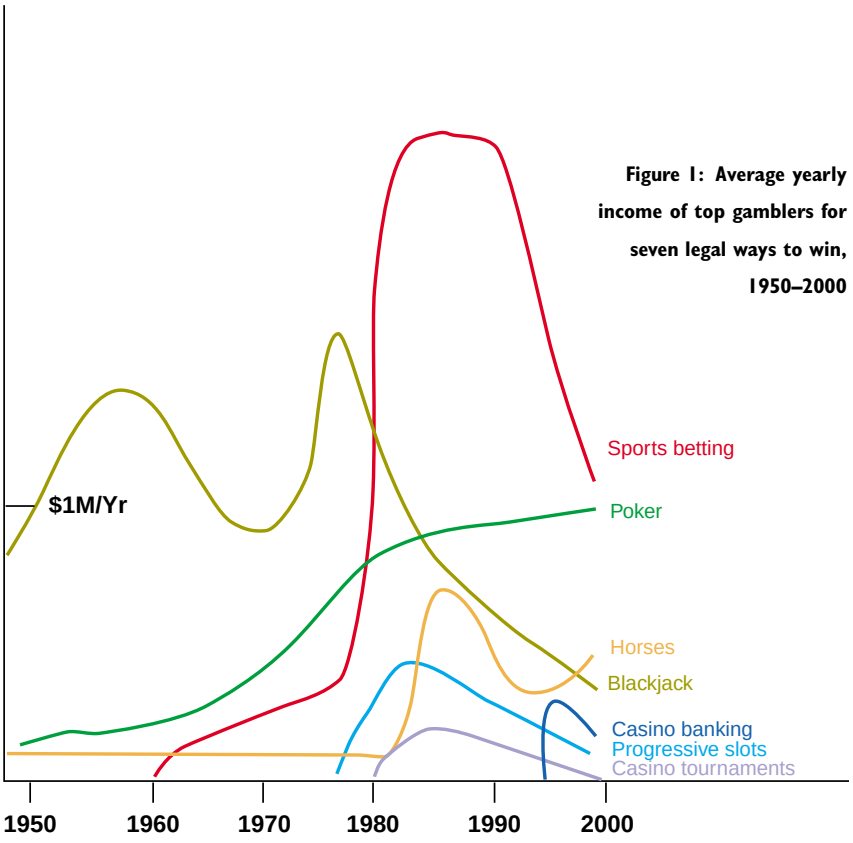


Figure 1: Average yearly income of top gamblers for seven legal ways to win, 1950–2000

> Basically, the winners find a way to be like the casino; they gain a small advantage and play it as often as possible. They remind you of Bill Gates, not Frank Sinatra.

field day up to the early 1960s. At that time, the casinos found tactics to beat back most of the onslaught, specifically by introducing multiple-deck games, restricting play options (that is, changing rules), evicting or harassing suspected card counters, and (allegedly, in the early days) employing cheater dealers. Atlantic City opened in 1978 with a "hand-surrender-option" rule, with a player advantage misunderstood by the casinos, that once again allowed a romp for the best players. When this was corrected by the casinos, and their aforementioned tactics were refined, blackjack became a very "tough beat." In fact, the plus percentages are now so low that an expected income of $100,000 per year requires extremely long hours of play at stakes that risk financial swings of several hundred thousand dollars.

Poker is the other game that has provided solid earnings for winning gamblers for most of the last half century. In this case, the winners are actually beating other players, not the casinos, with the house just charging rent for the table, dealer, and accommodations. Wins have increased over time because of two factors: (1) the casinos have become more diligent about keeping the games honest, and (2) some very rich, very romantic amateurs have been lured by the challenge of tackling the world's best players. The top players owe their edge to familiarity with the scientific poker literature, meticulous notes on opponents, personally funded computer simulations, and many thousands of hours of experience.

Despite the excessive house "take," approaching 20 percent, horse betting has always been profitable for a few astute scientific handicappers (odds-analysts). Historically, however, wins have been severely limited by the amount one could viably bet. Betting large amounts in the "floating odds" pari-mutuel system of horse racing is financially suicidal because the payoff odds are decreased by one's own bet. Also, years ago, when casino race-

books were not tied directly to the racetrack parimutuel pools, casinos tightly limited accepted bet sizes. A trickle for horse players briefly became a flood in the 1980s, when racetracks introduced progressive jackpots, such as Pick-6 pools, in which a bettor must pick the winners of six races or else most of the pool carries over to the next day. (When large Pick-6 pools accumulated, even uneducated random bets would yield positive expectations. This promoted very large bets, in the $10,000s to $100,000s, spread over thousands of horse combinations). Competition among bettors drove earnings down until the mid-1990s, when Nevada casinos, buoyed by the large overall take on horses, offered rebates to horse players to partially cover losing bets (which, of course, greatly helped the few winners).

The biggest wave of player winnings ever to hit Nevada came from sports betting, which was fantastically profitable up to the middle 1990s. . . .This sports wave was set off in the early 1980s when a few high-rolling gamblers (mostly top poker players) discovered three or four analysts performing scientific sports handicapping.

The introduction of progressive jackpots is also the reason that slot machines have been a viable earn since the early 1980s. Winning slot players, often in teams, descend on a group (carousel) of slots when the jackpot becomes large enough to yield a positive expectation. Play typically continues nonstop until the jackpot is hit, with players relinquishing their seats only to partners. If the slot is a game of video poker, the players adopt mathematically optimized card-choice strategies to minimize losses until the jackpot is won. Competition among professional slot players, who vie with each other to catch winning situations at smaller and smaller plus expectations, has driven earnings down in the 1990s.

Casino tournaments, another innovation of the 1980s, allow players to win at games that are otherwise unbeatable, such as craps, roulette, and nonprogressive slots. In tournaments, players pay entry fees that are partly returned as prizes to the most successful entrants. The advantage of the prize money allows the best players to overcome the underlying disadvantage of the game. The winners place their wagers on the play options with minimum disadvantage and employ mathematical game-theory tactics to optimize their chances of emerging as the victor. Profits from casino tournaments, never very large, dwindled in the 1990s because of competition among gamblers and because of waning popularity.

A new opportunity has arisen in the 1990s at casinos outside Nevada—for example, at California card parlors and at Indian reservation casinos. For some games (such as blackjack and Pai-gow poker) in certain casinos, the house is able to charge table usage fees to players but is not legally permitted to book the game. Rather, the dealer or "banker" for the game must be another player. Taking the banker role in such situations can yield a great mathematical edge to the professional gambler. One big problem with banking is that, unlike the situation with its own games, the casino host has little incentive to prevent cheating against a private banker, so that fraud and chicanery have severely pared (and in many cases eliminated) profits.

The biggest wave of player winnings ever to hit Nevada came from sports betting, which was fantastically profitable up to the middle 1990s. Since then, it has been driven back by improved casino odds-making, by reduced casino betting limits, by new regulations restricting organized betting, by real-time publication of casino odds (which allows casino managers to make better adjustments), by consolidation of casino sports books (placing a bet at any of a group of aligned books instantaneously eliminates opportunities at the others), and by intense competition among bettors. This sports wave was set off in the early 1980s when a few high-rolling gamblers (mostly top poker players) discovered three or four analysts performing scientific sports handicapping. As detailed in my story below, I was immersed in the wave as one of the latter.

SPORTS BETTING

Casinos attempt to make a profit in their sports books by using an odds differential for the two sides of a sporting contest. For example, in a baseball game where the true odds on the favored team are thought to be 3:2, the sports book offers a line of 160:140, meaning that a bettor on the favorite must lay $160 to win $100, while a bettor on the underdog would be risking $100 to win only $140. In sports such as basketball or football, with a "point spread" handicap designed to even out the odds (for example, the Lakers were recently favored by 9 points over the 76ers), the bettor lays $110 to win every $100 regardless of which side he takes (the Lakers minus 9 points or the 76ers plus 9 points).

Although this level of odds differential yields a nice casino profit (nearly 5 percent) against unsophisticated or random bettors, it did not—in the past—provide an adequate cushion against scientific bettors. Using the point spread example of an 11:10 odds differential either way, a bettor has a net advantage if he can win at least 11 games for every 10 he loses (11 out of every 21 games), or just 52.4 percent. Up until the last five to ten years, casino point spreads commonly contained

Handicapping analysis may not have been the most lucrative side of the sports-betting wave, but it has always been interesting and challenging. The basic objective of handicapping is to determine the best scientific estimate for the odds of a team winning a game—or in the case of a point spread, the best scientific estimate for the median final score of a game.

substantial errors due to inaccuracies in initially calculating the spreads and inefficiencies in making adjustments as bets were received. During their heyday, the best scientific handicappers were able to use these errors to maintain winning percentages against the point spread of about 57 percent. This translated to a positive return on their bets of about 10 percent (57 percent minus 1.1 x 43 percent, the 1.1 representing the odds differential they had to pay). With an acceptable level of risk, such a handicapper could turn over his bankroll (total capital) about once every three to four weeks, so that the earnings on his bankroll would have been 10 percent every 25 days, which compounds to 300 percent (a quadrupling) per year!

Historically, two major problems confronted scientific handicappers. First, as you might surmise from the previous paragraph, the handicappers had difficulty finding places where they could bet enough money to accommodate their burgeoning bankrolls. People called "followers" exacerbated this problem. As soon as a known winner would bet on a game at one casino, the casino would change its point spread on that game significantly. Furthermore, clerks or other bettors who witnessed the wager would start a chain reaction, betting the hot game at all casinos, so that the advantageous point spread would be eliminated at all casinos within a few minutes. The second problem for the handicappers was to maintain their fundamental advantage over the casino oddsmaker (that is, their 57 percent or so win rate). The casino oddsmaker continually improved his analysis, with much of the improvement coming from ways he devised to anticipate the winner position by learning from previous winner bets. A few handicappers were able to maintain their level of advantage for more than two decades, but this was not without continual advances in their methods, and not without some major bumps in the road. There was always the threat that the casino oddsmaker or the effects of some other winner might, at any time, start making the point spread a trap instead of an opportunity.

Both problems were solved, at least up to the mid-1990s, by the aforementioned union of scientific handicappers and high-rolling gamblers. First, the high rollers promised to bet larger amounts for their scientist friends than the latter had been able to bet for themselves (although there were still limits, of course). The gamblers accomplished this by organized teams of runners and phone persons who would bet at all the casino sports books simultaneously. The gamblers also were able to negotiate high limits at many casinos through various arrangements and connections. They even concocted ways to shake the followers by making phony plays (initially betting on the wrong side). Second, the high rollers eliminated the risk by offering their scientist friends a guarantee. This guarantee, virtually never activated, was that the scientists didn't have to pay their share if the bets showed a net loss for a sports season. The gamblers—with their organization, their large initial bankrolls, their willingness to assume all the risk, and their determination to persevere through all the losing streaks—were amply rewarded. Although they bet considerable amounts for their scientist friends, it was only a fraction of what they bet for themselves. The most successful winners in sports (those represented in Figure 1) were the high-rolling gamblers, not the handicappers.

SPORTS HANDICAPPING

Handicapping analysis may not have been the most lucrative side of the sports-betting wave, but it has always been interesting and challenging. The basic objective of handicapping is to determine the best scientific estimate for the odds of a team winning a game—or in the case of a point spread, the best scientific estimate for the median final score of a game (the scientific point spread). When the casino point spread differs enough from the scientific point spread (typically by at least one and a half points or more), it is worthwhile to bet. The greater the difference is, the more the advantage and the larger the bet.

My own method for deriving a scientific point spread consists, essentially, of adding together numerical values for various factors, such as those listed in Figure 2 for basketball or football. It takes many years of experience to recognize all the relevant factors, and there is a lot of room for creativity in coming up with data and statistical

methods to quantify the factors. The values for each factor are determined using as much data as possible. For example, my own data history for pro basketball covers about 30,000 games. Data for some subjective factors (such as how much a team is typically affected by morale problems) must be collected personally, over the years, game by game.

Figure 2 can also be viewed as a chronology of sports handicapping analysis. In the 1970s, a handicapper would have done very well if he just did a reasonable approximation with the primary factors. By the early 1980s, he needed to perform an exact analysis of the primary factors, along with a rudimentary consideration of the secondary factors. By the early 1990s, a precise analysis of both primary and secondary factors was required for success. Now, even that may not suffice. Today's handicapper needs to invent some secret weapons if he is to remain successful in competition with the casino oddsmaker and other scientific bettors. By a secret weapon, I mean information that is significant yet so arcane or original that few if any competitors are aware of it. For the obvious reason that it wouldn't be secret anymore, I cannot divulge my current arsenal. However, to give the reader a better idea of the concept, I will relate some examples from the past—things that were once secret but are now well known.

Today's handicapper needs to invent some secret weapons if he is to remain successful in competition with the casino oddsmaker and other scientific bettors.

One example concerns betting "totals" on professional basketball games. Totals bets are not on who will win the game, but rather on total number of points to be scored in the game (you bet that the points scored will be over or under the totals point spread). In the early 1980s, a gambler who specialized in the National Basketball Association realized that the casino oddsmaker was doing a reasonable job with the routine statistics of the NBA totals, but that there was a hidden factor dominating the total scores. This factor was the coach's game plan each day—specifically whether the coach intended to have his team run with the opponent (leading to a high score) or slow it down (leading to a low score). The gambler also had an ingenious scheme to obtain the best source for game-plan information—local newspapers. (This was long before daily newspapers became available on the Internet.) He befriended a service contractor who cleaned airplanes at the Las Vegas airport, and his friend's crew collected the local papers for every NBA city from the first flights arriving each morning.

An example from baseball concerns pitcher/hitter matchups. For nearly a century, it has been known that left-handed pitchers perform significantly better against left-handed hitters than right-handed hitters (vice versa for right-handed pitchers). Just a few years ago, however, a scientific handicapper discovered that there is another significant matchup, this one of pitchers and hitters who each have a proclivity to produce either fly balls or ground balls. When a fly-ball

PRIMARY FACTORS

- **team power ratings**
- **overall league home advantage**
- **worth of players**

SECONDARY FACTORS

- **travel distances and days off**
- **emotional influences**
  - **– revenge against current opponent**
  - **– effect of previous game**
  - **– team morale**
  - **– anticipating next opponent**
- **offensive/defensive matchups**
- **special home advantages of individual teams**
- **player substitution patterns**
- **weather (football only)**

SECRET WEAPONS

Figure 2: Factors in predicting outcomes of football and basketball games.

pitcher faces a team loaded with fly-ball hitters, he tends to be successful, achieving many strike-outs and pop-ups. On the other hand, when he faces a team populated with ground-ball hitters, he is apt to yield lots of line drives. With the help of this factor, the handicapper in question was able to capture the vanguard position in baseball betting.

AN UNKNOWN CULTURE

As I noted in the introduction, gamblers tend to shroud their activities. There are two major reasons, the first being fear of competition. Why let rivals know about a positive situation? This idea relates to the struggle against other gamblers and against casino managers. The importance of competition can be seen in Figure 1, where most of the curves show a sharp decline after a peak in winnings. Gambling profits have been razed over time by casino countermeasures and rivalries among winning gamblers.

Concern over competition also explains why there is little decent academic literature on gambling; the winners cannot afford to alert their opponents. (In 1980, Professor of Mathematics Gary Lorden wrote an excellent article for *Engineering & Science* explicating how you can maximize your chances for a windfall in casino games with the percentages against you. There is little or nothing written of comparable quality, however, on how to turn the tables on Las Vegas and get the percentages in your favor.) As to sports betting, I have come across a few articles in the scholarly literature, especially economics journals, but they have all bordered on the nonsensical—with a few far over the border. To paraphrase an old maxim: in gambling (as perhaps in stock and commodity trading), those who can, do; those who can't, publish. The reason I feel comfortable writing this essay is that the competition has already waxed in sports. Handicappers are now commonly heard commiserating with the refrain: "Boy, it's getting brutal out there."

Legal concerns make up the second reason for the furtive nature of gambling. Gambling laws tend to be both expansive and ambiguous. A leading Las Vegas attorney once told me: "With gambling, you can't walk across the street without exposing yourself to at least the possibility of some sort of selective prosecution." Another said: "Some law-enforcement personnel view winning gamblers as akin to pornographers. In their minds, it's just not right." In the 1980s and early 1990s, I heard about several law-enforcement raids on sports betting, usually on the highest-rolling gamblers. The typical scenario seemed to be that a high roller making large amounts of money in sports was mistaken for an illegal bookmaker, that is, a sports bookie accepting bets from others. Fortunately, gamblers that I have personally known who became entangled in such investigations had all been scrupulous about following the law and paying their income taxes, so they were exonerated. Nevertheless, the potential for the unnerving reality of legal trouble is always there.

After my PhD, concurrent with my first 20 years as a gambler, I had a full-time career as an environmental scientist. My specialty was interpreting large sets of air-pollution data. The techniques I used for organizing and analyzing pollution data transferred directly to sports data.

GAMBLING AND SCIENCE

Despite its louche reputation, gambling was always highly complementary with my scientific education and career. Undergraduate and graduate schooling at Caltech taught me how to structure problems sensibly, how to derive mathematical solutions, and how to cross-check results. In the Vegas vernacular, I could think straight. My Caltech curriculum never included a course in probability/statistics per se, but I learned the foundations of that subject during the first month of a hydrology course taught by Norman Brooks (now the Irvine Professor of Environmental and Civil Engineering, Emeritus). He instilled those foundations so thoroughly and so well that, in my entire scientific and gambling career, I never felt second best in being able to understand data or compute odds.

After my PhD, concurrent with my first 20 years as a gambler, I had a full-time career as an environmental scientist. My specialty was interpreting large sets of air-pollution data. The techniques I used for organizing and analyzing pollution data transferred directly to sports data. It might be of interest to note that there was even a specific data set that transferred—weather information. Because of my familiarity with the National Weather Service archives, I decided early in my gambling work to quantify the effect of weather on sporting events (a secret weapon at that time). The most significant impact was on baseball totals (bets on the number of runs scored in a game), where wind speed, wind direction, and temperature proved to be critical.

Personally, it was even more meaningful that gambling had a positive impact on my environmental-science career. In air-pollution research, there are only two significant sources of funding—governmental agencies and private industries (basically, the polluting industries). In my perception, the government agencies essentially want to determine if there is a problem and what can be done about it. The polluting industries, on the other hand, often seem in deep denial. They tend to assert that (1) there is no problem, (2) even if a

problem exists, they aren't the cause, and (3) even if they were the cause, the nature of the problem is too uncertain to try to do anything about it. Being a product of the '60s and a little quixotic, I could only bring myself to work on government studies. Unfortunately, the largest and most lucrative consulting contracts came from industry. This situation not only severely limited my income, but it meant that my research was, in my view, subject to incessant carping from industry scientists and their consultants. (It appeared to me that I was continually trying to defend a simple, reasonable $40,000 government study from red herrings raised by some multimillion-dollar industry project.) The gambling was a godsend, providing me a great income and an objective test that my way of interpreting data was truly correct. As a friend of mine said to me when I first considered putting the effort into sports betting: "Wonderful! It might provide your 'up yours' money!"

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34–41 — Las Vegas News Bureau; 36 — John Trijonis/Doug Cummings

WANT TO TRY IT?

You might be wondering about trying out a gambling avocation. If we were in the early 1980s, with so many of the curves in Figure 1 on the upswing, I would enthusiastically recommend it for any good scientist. It's exhilarating to be living by your wits and a peculiar, thrilling type of fun when you and your colleagues seem to be tapping a boundless money tree. I would issue two general cautions. First, you would need to be objective in evaluating your prospects, diligent in striving for improvement, and receptive to the possibility that competitors might shift the playing field. Second, you would have to be careful about the law. This means paying all your taxes and following the advice of attorneys who are experts on gambling regulations.

In actuality we are beyond the 1990s, a decade that saw most of the winning opportunities in Las Vegas battered by competition among scientific gamblers and by countermeasures from casinos. The notable exception—and the best candidate for a career—is poker, where a high earning potential continues (although it demands an ever-increasing amount of skill). If you are willing to devote a couple of years to perusing the literature, studying computer simulations, scrutinizing players, and gaining general experience, you have a chance to become a solid winner. The major disadvantage of poker, assuming you can be successful, is the interminable time spent at odd hours in crowded, smoky rooms.

Sports betting is a very natural area for scientists familiar with data analysis. Competition is already fierce, however, among experienced mathematical handicappers entrenched with immense historical databases. So, I wouldn't recommend it. That is, unless, you concoct some omnipotent secret weapon! □

Despite its louche reputation, gambling was always highly complementary with my scientific education and career. Undergraduate and graduate schooling at Caltech taught me how to structure problems sensibly, how to derive mathematical solutions, and how to cross-check results.

John Trijonis
***Big T*, 1966**

John Trijonis earned his Caltech BS in engineering and applied science in 1966, his MS in aeronautics in 1967, and his PhD in environmental engineering science in 1972 with the thesis "An Economic Air Pollution Control Model—Application: Photochemical Smog in Los Angeles County in 1975." During his "first life," as an environmental scientist, he was president of the Santa Fe Research Corporation from 1979 to 1993, where, as he says in his article, he "could only bring myself to work on government studies." His main areas of concentration were aerosols and atmospheric visibility, and he published papers on such subjects as "Patterns and Trends in Data for Atmospheric Sulfates and Visibility" (1986) and "Protecting Visibility in National Parks and Wilderness Areas" (1993). For more than 20 years, he pursued a concurrent gambling avocation. As he states in the article, the financial independence provided by gambling had a very positive effect on his environmental science career.

Glen R. Cass
1947 – 2001

Glen R. Cass, professor of environmental engineering and mechanical engineering, died of cancer July 30. He was 54.

Cass received his BS from the University of Southern California in 1969 and his MS from Stanford in 1970. After earning his PhD from Caltech in 1978, he stayed on and taught at the Institute for 24 years. In January 2000, he joined the faculty of the Georgia Institute of Technology as professor and chair of the earth and atmospheric sciences department. He maintained a joint appointment with Caltech.

A prolific scientist with more than 200 published articles, conference proceedings, book chapters, and technical reports to his credit, Cass focused on air pollution, with a particular emphasis on the control of airborne particles, photochemical oxidants, and improved visibility. He was instrumental in identifying the complex mix of airborne chemicals that pollute urban areas such as Los Angeles and the northeastern United States. Of special concern were very fine particles that can be inhaled and stay in the lungs, and that contribute to haze and poor visibility.

Cass initiated a global ozone study at 500 sites around the world in 1999, which continues today. His research group takes airborne particle measurements in many parts of the world. Seven sites in mainland China were monitored for "Operation Blue Sky," which identified pollution sources in Beijing and other cities, and whose results factored into China's 2008 Olympic bid.

He was also interested in the protection of museum collections and archaeological sites from damage due to air pollution. He and his colleagues modeled air quality both within and just outside several museums throughout Southern California, including the new Getty Center in Los Angeles, which was useful in evaluating the effectiveness of various measures to protect works of art.

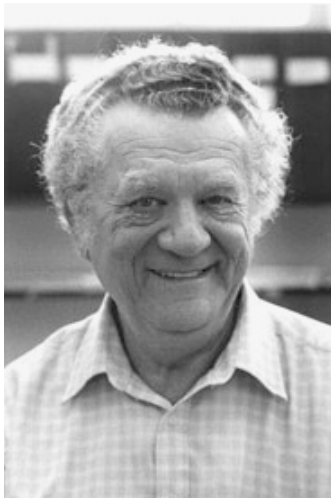
In China, Cass helped design computer-based models that simulated the air flow into the Yungang Grottoes, a collection of man-made cave temples dating from the fifth century A.D., which hold more than 50,000 stone carvings, now deteriorating due to pollution from nearby coal mines. Cass's work contributed to the design of particle filtration systems and ventilation rates for the grottoes.

And in Poland, his work helped save the salt sculptures in the huge Wieliczka salt mine. Miners had decorated the mine with their carved statues over centuries, but in the last century some of the earliest ones had melted into featureless blobs. He contributed to the finding that lowering the relative humidity would halt further deterioration.

Cass is survived by his wife, Jeanie, and son, Rob. A memorial service on campus is planned for January. □

—JP

Samuel Epstein
1919 – 2001



Samuel Epstein, the William E. Leonhard Professor of Geochemistry, Emeritus, died September 17 at the age of 81.

Born near Kobryn, Poland (now Belarus), Epstein emigrated as a child with his family to Canada. He earned his BSc (1941) and MSc (1942) from the University of Manitoba and received his PhD in chemistry from McGill University in 1944.

After working on rare gas fission products for the Canadian Atomic Energy Project, in 1947 he joined Nobel laureate Harold Urey on the oxygen isotope paleotemperature project at the University of Chicago. With-

in several years Epstein and his team made what is widely regarded as the most significant scientific contribution in the history of stable isotope geochemistry: they measured the temperature coefficient of the oxygen isotope exchange reaction between $CaCO_3$ and H_2O and developed astonishingly precise methods to measure oxygen isotope ratios of marine carbonate fossils. This allowed them to calculate the temperatures of the ancient oceans more than 70 million years ago.

In 1952, when Harrison Brown left Chicago to start the geochemistry program at Caltech, he invited Epstein to join him. Over the succeeding years at Caltech, Epstein explored a variety of uncharted scientific terrains, welcoming the prospect of applying the newly developed techniques and principles of stable isotope chemistry to almost every aspect of natural science. He applied oxygen, carbon, hydrogen, and silicon isotope studies to problems of botany, plant and animal physiology, photosynthesis, biochemistry, meteorology, Pleistocene climatology, glaciology, and ore deposits. He wrote many papers on igneous, metamorphic, and sedimentary petrology and carried out important research on the Antarctic and Greenland ice sheets, on isotope geothermometry, on modern geothermal systems, and on the origin of meteorites, tektites, and lunar rocks and minerals.

Epstein was a recipient of the Goldschmidt Medal of the Geochemical Society in 1977, the Day Medal of the Geological Society of America in 1976, the Wollaston Medal of the Geological Society of London in 1977, and the Urey Medal of the European Association of Geochemistry in 1995. In 1976, he was elected to both the National Academy of Sciences and the American Academy of Arts and Sciences, and in 1997, he was elected a fellow of the Royal Society of Canada.

Epstein retired from teaching in 1990, but up until a few months ago, he continued to work full time in the lab every day. He is survived by his wife, Diane, two sons, Reuben and Albert, and three grandchildren. A memorial service will be held sometime in the coming months. □ —*RT*

Honors and Awards

David Baltimore, president of Caltech, has been named a 6th Annual Eddy Award winner for both his and Caltech's "contributions in bringing the fields of education, research and professional employment together" in the Los Angeles County area. He will receive the honor on November 14 from the Los Angeles County Economic Development Corporation, at a dinner and awards program at the Beverly Hilton Hotel.

Kaushik Bhattacharya, professor of applied mechanics and mechanical engineering, and Hideo Mabuchi, associate professor of physics, were both selected to participate in the National Academy of Engineering's seventh annual Frontiers of Engineering Symposium, held September 13–15 at the National Academies' Arnold and Mabel Beckman Center in Irvine, California. "The program brings together outstanding engineers (ages 30–45) from industry, academia, and government to discuss pioneering technical work and leading-edge research in various engineering fields and industry sectors." This symposium featured topics in the areas of aeronautics and aerospace, civil systems, wireless communications, and technology and the human body.

The 2001 ASCIT (Associated Students of Caltech) Teaching Awards have gone to Oscar Bruno, professor of applied and computational mathematics, Dirk Hundertmark, Taussky-Todd Instructor in Mathematics, Edward McCaffery, visiting professor of law, Thomas Neenan, lecturer in music, and Charles Peck, professor of physics. At the same time, George Cheron, lecturer in Russian, and Glen George, lecturer in computer science and electrical engineering, have been honored with ASCIT Lifetime Achievement Awards.

Emmanuel Candes, assistant professor of applied and computational mathematics, has been selected to receive an Alfred P. Sloan Research Fellowship, which carries with it a grant to be used in a flexible and largely unrestricted manner. Sloan recipients are selected on an extraordinarily competitive basis from a group of nominees representing the very best of young scientists.

David Chan, assistant professor of biology and Bren Scholar, has been named a Rita Allen Foundation Scholar. The award carries a $50,000 stipend for up to three years. A graduate of Harvard Medical School and MIT, Chan joined Caltech in

January 2000. He specializes in research on mitochondria, components of the cell that are important in energy metabolism and also in programmed cell death.

Judith Cohen, professor of astronomy, has received the Fullam Award from the Dudley Observatory, in Albany, New York. The award provides up to $10,000 for "encouragement and support for an innovative research project in astronomy or astrophysics."

James Gates, visiting professor of physics, was one of five speakers who participated in the first Isaac Asimov Memorial Panel Debate. Held last February 13 at the American Museum of Natural History, the debate was on the "Theory of Everything."

Steve Gubser, professor of theoretical physics, has received the Gribov Medal, the highest award given by the European Physical Society to young scientists for theoretical work in the field of high-energy particle physics.

Jason Hickey, assistant professor of computer science, has received an Okawa award from the Okawa Foundation for Information and Telecommunications. Carrying a grant of $10,000, the award honors young researchers in areas such as communication networks, computer systems, and artificial intelligence, among others.

Yizhao T. Hou, professor of and executive officer for applied and computational mathematics, has received the Wilkinson Prize from the Society for Industrial and Applied Mathematics.

Nick Nichols, director of Caltech's Industrial Relations Center, has been invited to participate in the Leadership Program on Japan. Sponsored by the Japanese Ministry of Economy, Trade and Industry, the program brings together each year 12 participants from abroad to meet with Japanese business leaders and government officials. The program involves visits to a number of prominent Japanese industries and discussions on the key economic, market, and business issues facing Japan in its international relationships.

John Preskill, professor of theoretical physics, has been named the Andrejewski Lecturer for the fall of 2001. He will travel to Berlin to deliver a series of three 90-minute lectures on quantum computation. □

O'Rourke Named New VP

Robert L. O'Rourke of Pasadena has been named Caltech's vice president for public relations. The newly created position reports directly to President David Baltimore and oversees all of the Institute's public relations operations.

O'Rourke has served as head of public relations at the Institute since 1986, most recently as associate vice president for institute relations, a title he held since 1996.

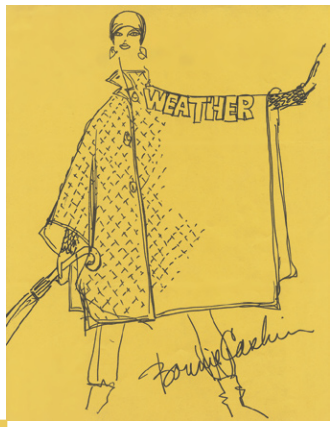
He has had 28 years of experience in the nonprofit public relations field, beginning with the West Allis Memorial Hospital and University of Wisconsin Center for Health Sciences in Wisconsin, the Medical College of Pennsylvania, and later as press secretary to the president at Boston University.

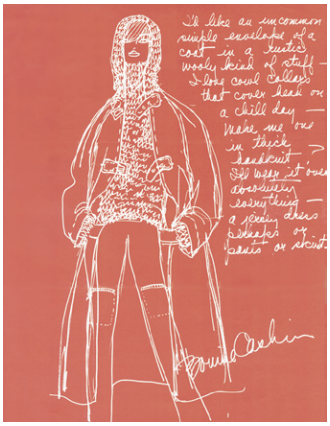
As vice president, O'Rourke is in charge of electronic media publications, government and community relations, media relations, periodicals (which includes *E&S*), publications, public events, and the visitor's center.

He has successfully strengthened the connection between Caltech and the Southern California community by establishing programs that involve Caltech in community activities and that bring the public to campus. He has increased awareness of public events programming at Caltech, established the Institute's first department for web publishing, and introduced the work of Caltech researchers to the external community with such programs as the annual Biology Forum.

President Baltimore made the announcement to the campus October 1. "Since before I had even arrived at Caltech, Bob has been an advisor to me on all questions about public relations. He has been thoughtful in his approach to handling complicated issues and has gone out of his way to make friends for Caltech. It is clear that he loves the place and is able to send its message widely and effectively. Promoting him to vice president will give him greater visibility and authority as Caltech moves forward," he said.

O'Rourke has served in numerous community organizations, including the Pasadena Chamber of Commerce, the Pasadena World Cup Strategic Planning Committee, Pasadena Forward, Los Angeles World Affairs Council, and Breakfast Forum. In 1987 he was a founder of the Pasadena Pops Orchestra. □ —*JP*





Arts and Sciences—Bridging the Gap

Bonnie Cashin was a successful New York fashion designer who defied the high-fashion industry (which she saw as devoted to "hobbling women with its fussy clothes") by creating functional, practical clothes for "women who have something to do." Her simple, elegant styles won a following among such women and also won numerous fashion awards. She designed the first jumpsuit for women, introduced the poncho (after cutting a hole in a car blanket), and first advocated dressing in layers to accommodate changes in weather. Before forming her own fashion firm, she had also created costumes on Broadway and in Hollywood—for more than 60 films.

How did she cross paths with Caltech? Her uncle, James Michelin, a highly respected geologist, had "always wanted to attend Caltech." So Cashin, in his memory, established the James Michelin Scholarship in Geology in 1978. She took a personal interest in her Michelin Scholars, visiting them in California and inviting them to New York. She encouraged their sense of adventure and urged them to encounter creative people in other fields.

Cashin's interest in this kind of creative interaction between the sciences and the arts led her to establish, in 1991, the James Michelin Distinguished Visitors Program by donating to Caltech the oil royalties she had inherited from her uncle. She wanted the program to bring to campus individuals who bridged the gap between the two interrelated worlds. Over the past decade, the Michelin Lectures have been delivered by architectural historian Vincent Scully, artist David Hockney, playwright Tom Stoppard, film director Oliver Stone, opera singer Beverly Sills, architect Frank Gehry, poet Seamus Heaney, and producer/director Jonathan Miller.

In 1996, Cashin made yet another contribution to the Institute, this time in her own name—the Bonnie Cashin Prize for Imaginative Thinking. This gift provides a $5,000 annual award to the freshman at Caltech who writes the most imaginative college-application essay.

Cashin died last year, at the age of 85. The Michelin Lectures were recently endowed through a generous gift from the Bonnie Cashin Estate. This year's speaker will be documentary filmmaker Ken Burns.

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