California Institute of Technology

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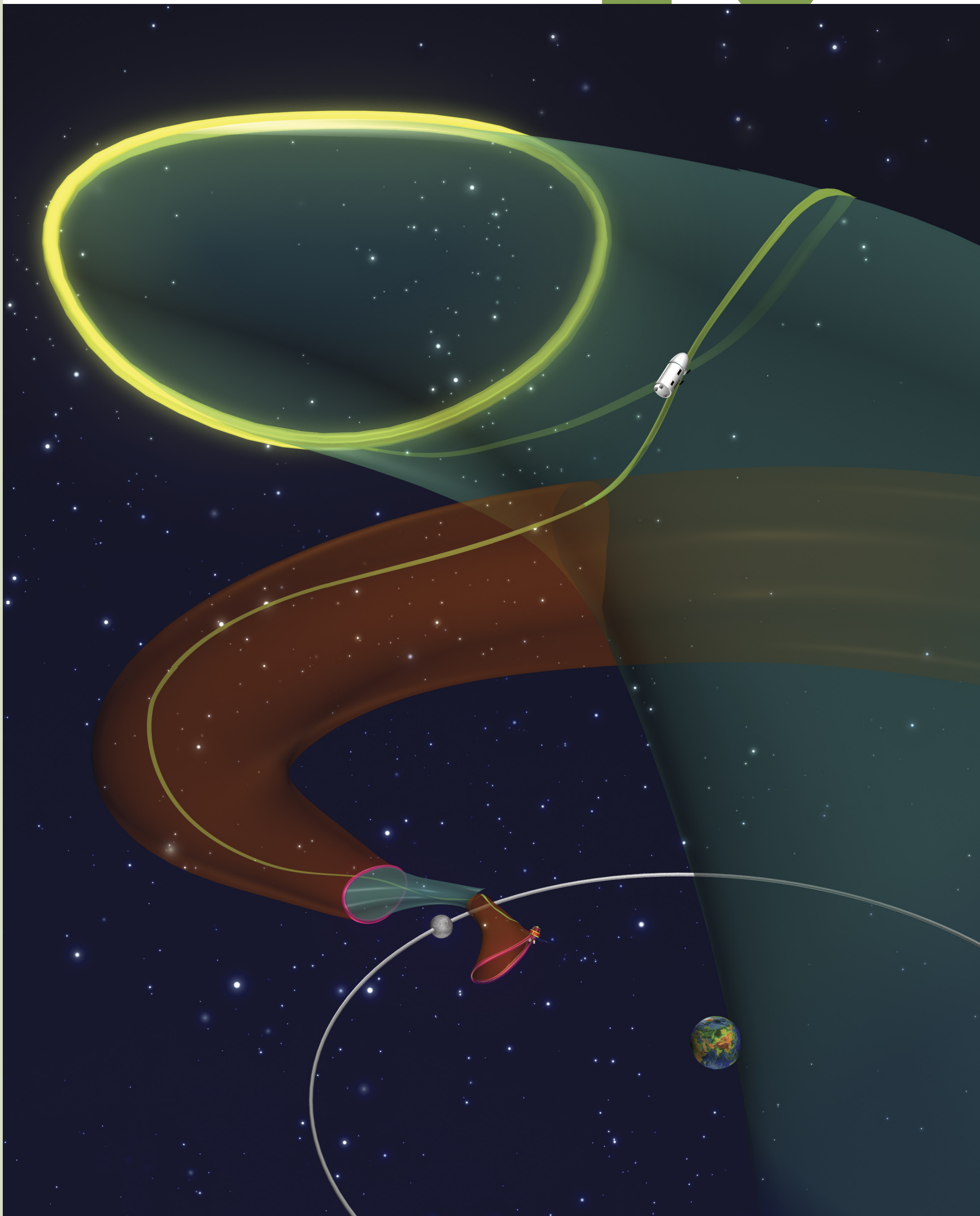

IN THIS ISSUE

As of January 1, the CT scanner (like this InVision CTX 5500 DS), which can peer into checked luggage for hidden explosives, is becoming standard equipment in U. S. airports. How these instruments, and others still in the research laboratory, work is explained in an article beginning on page 26.

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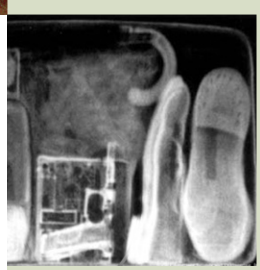

On the cover: Built at a staging area between the earth and moon, a telescope en route to a parking orbit in deep space could ride the surfaces of a series of "tubes" between gravitational balance points. Such a trip takes relatively little fuel; the trick is making the segue from tube to tube. For more on this low-cost way of getting around the solar system, see the story on page 6. Art by Cici Koenig.

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Neutrino Mine Hits Pay Dirt

In the subatomic particle family, the neutrino is a bit like a wayward stepson. Neutrinos were long ago detected—and even longer ago predicted to exist—but everything we know about nuclear physics says there should be a certain number of them streaming from the sun, yet there are nowhere near enough. Now an international team, including Professor of Physics Robert McKeown, has revealed that this deficit is real, and not merely an observational quirk or something unknown about the sun's interior. The team used the KamLAND detector deep in the Kamioka mine in Japan. Thus shielded from background and cosmic radiation, the detector is optimized for measuring the neutrinos from all 17 nuclear power plants in the country.

Solar neutrinos are produced when two protons fuse together to form a deuterium nucleus, a positron, and a neutrino. The positron eventually annihilates both itself and an electron, while the neutrino, being very unlikely to interact with matter, escapes into space. Therefore, neutrinos should flow from the sun like photons from a light bulb—radiating evenly in all directions, as if the surface of a sphere were being illuminated from its center. And because a sphere's surface area increases as the square of its radius, an observer standing 20 feet away would see only one-fourth the photons of an observer 10 feet away.

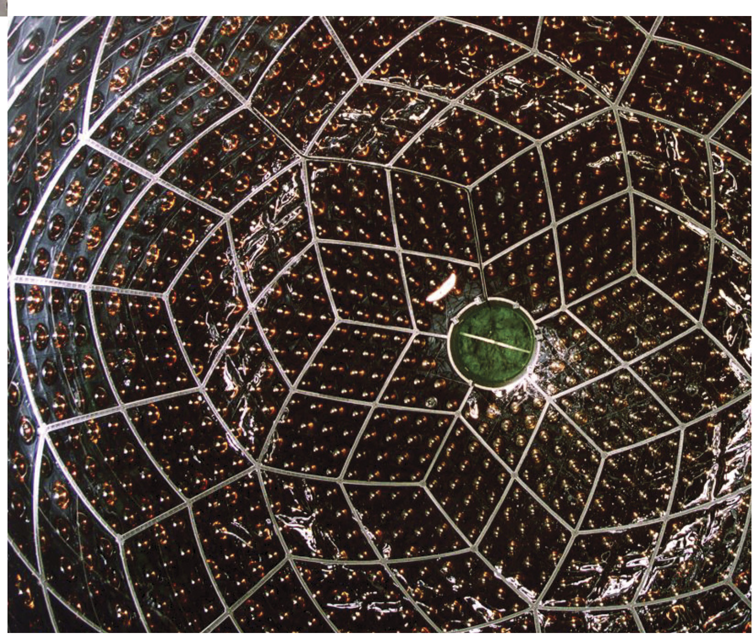
Thus, we expect to see a given number of neutrinos coming from the sun—assuming we know the proton-fusion rate—just as we can predict the luminosity of a light bulb at a given distance if we know the bulb's wattage. But carefully constructed experiments have found far fewer solar neutrinos than there should be.

One explanation is that the neutrino "flavor" oscillates between the detectable "electron" neutrino type, and the much heavier "muon" neutrino and maybe even the "tau" neutrino, neither of which can be detected. Quantum-mechanical calculations predict that the number of detectable electron neutrinos oscillates steadily, from 100 percent down to a small percentage and back again. Therefore, the theory says, we see only about half as many neutrinos as we should because about half of them are at that moment in one of the undetectable flavors.

At KamLAND, physicists can, for the first time, observe neutrino oscillations without making assumptions about the properties of the source of neutrinos. Because power plants have very precisely known amounts of material generating the particles, it is much easier to determine with certainty whether the oscillations are real. Power plants run on nuclear fission, in which an atom breaks apart to form two smaller atoms, an electron, and an antineutrino (the antimatter equivalent of a neutrino). But matter and antimatter are thought to be mirror images of each other, so power-plant antineutrinos should behave exactly like solar neutrinos.

"This is really a clear demonstration of neutrino disappearance," says McKeown. "Granted, the laboratory is pretty big—it's Japan—but at least the experiment doesn't require the observer to puzzle over the composition of astrophysical sources."

In addition to McKeown's team at Caltech, other partners in the study include the Research Center for Neutrino Science at Tohuku University in Japan, the University of

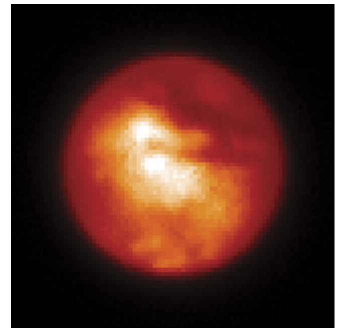


Professor of Physics Robert McKeown (above) scrubs the inside of KamLAND's neutrino detector—a stainless steel sphere (right), 18 meters in diameter and lined with about 2,000 photomultiplier tubes to catch the elusive flash of a neutrino hitting 1,000 tons of what is essentially heavily doped baby oil. So sensitive is the detector that a single speck of dust within it could emit enough natural radioactivity to queer the readings.

Alabama, the University of California at Berkeley and the Lawrence Berkeley National Laboratory, Drexel University, the University of Hawaii, the University of New Mexico, Louisiana State University, Stanford University, the University of Tennessee, Triangle Universities Nuclear Laboratory, and the Institute of High Energy Physics in Beijing.

The project is supported in part by the U.S. Department of Energy. □—*RT*

The Methane Rain Falls Mainly on Titan



This Keck image of Titan shows several small, bright clouds of methane near the south pole (bottom), as well as the large, bright "continent" at the equator.

Teams of astronomers at Caltech and UC Berkeley have discovered bright clouds of methane near Titan's south pole. The observations were made using the W. M. Keck II 10-meter and the Gemini North 8-meter telescopes atop Hawaii's Mauna Kea volcano. Titan is Saturn's largest moon, larger than the planet Mercury, and is the only moon in our solar system with a thick atmosphere. Like Earth's atmosphere, Titan's is mostly nitrogen. But Titan's lack of atmospheric oxygen and its extremely cold surface temperatures (–183° C) make it inhospitable to life. Titan's atmosphere also contains a significant amount of methane.

Earlier spectroscopic observations hinted at the existence of clouds on Titan, but gave no clue as to their location. These early data were hotly debated, since Voyager spacecraft measurements of Titan appeared to show a calm and cloud-free atmosphere. Furthermore, previous images of Titan had failed to reveal clouds, finding only unchanging surface markings and very gradual seasonal changes in the haziness of the atmosphere.

The Keck and Gemini telescopes are outfitted with

Shear Stress Is Good for the Heart

In a triumph of bioengineering, an interdisciplinary team at Caltech has seen, for the first time, the blood flow inside the beating hearts of embryonic zebrafish. The results reveal that high-velocity blood flowing over cardiac tissue is important for proper heart development, which could have profound implications for future surgical techniques. The team obstructed the blood flow through the hearts, which are finer than a human hair, and followed the action on very-high-resolution videos. The reduced "shear stress," or friction imposed by the flowing fluid on its surroundings, led to serious heart defects.

Thus, says co-lead author Jay Hove, more detailed studies of shear force might illuminate human heart disease. Congestive heart failure, for example, causes the heart to enlarge due to constricted blood flow, so a precise understanding of the flow could lead to ways to counteract the enlargement. And exploring the genetic factors involved with blood flow in the heart—a future goal of the team's research—could aid in the diagnosis of prenatal heart disease. "Our research shows that the shape of the heart can be changed during the embryonic stage," says Hove. "The results invite us to consider whether this can be related to the roots of heart failure and heart disease."

Hove, a bioengineer, along with Liepmann Professor of Aeronautics and Bioengineering Morteza Gharib (PhD '83), teamed with Scott Fraser, the Rosen Professor of Biology, and co-lead author Reinhardt Köster, a postdoc in Fraser's lab. Gharib, a specialist on fluid flow, has worked on heart circulation in the past, and Fraser is an authority on the imaging of cellular development in embryos. The effort is thus a marriage of engineering, biology, and optics.

The researchers used zebrafish because their one-millimeter eggs and the embryos inside them are nearly transparent. The embryos were treated to block the formation of additional pigment, and "optically dissected" via confocal microscopy, which allows the imaging of a layer of tissue. The two-dimensional images are "stacked" to make a three-dimensional reconstruction.

Köster microsurgically inserted beads into the embryos' hearts to block the blood flow, nearly eliminating the shear forces. The obstructions had a profound effect—when observed two to three days later, the tiny hearts had not formed valves properly, nor did they "loop," or form an outflow track properly. Because the early development of an embryonic heart is thought to proceed through several nearly identical stages in all vertebrates, the effect should also hold true for human embryos.

The researchers will now attempt to see how slight variations in the shear force affect structural development, and explore how gene expression is involved in embryonic heart development.

The team also includes grad students Arian Forouhar and Gabriel Acevedo-Bolton (MS '99). The work appears in the January 9, 2003 issue of *Nature*. □—*RT* adaptive optics, in which a flexible mirror compensates for distortions caused by turbulence in Earth's atmosphere. (These distortions cause the stars to twinkle.) Details as small as 300 kilometers across were distinguished on Titan, a stupendous 1.3 billion kilometers away—the equivalent of reading a car's license plate from 100 kilometers, and finer than the details seen by the Voyager spacecraft at their closest approach.

"We see the intensity of the clouds varying over as little as a few hours," said postdoc Henry Roe, lead author for the Berkeley group. "The clouds are constantly changing, although some persist for as long as a few days."

Titan experiences seasons much like Earth, though its year is 30 times longer due to Saturn's great distance from the sun. Titan is currently in the midst of its southern summer and its south pole has been in continuous sunlight for over six Earth years, which may explain the clouds' location.

"These clouds appear to be similar to summer thunderstorms on Earth, but formed of methane rather than water. This is the first time we have found such a close analogy to the Earth's atmospheric water cycle in the solar system," says Caltech grad student Antonin Bouchez.

In addition to the clouds above Titan's south pole, the Keck images, like previous data, show a bright, continent-sized feature that may be a large icy highland, surrounded by linked dark regions that are possibly ethane seas or tar-covered lowlands.

"These are the most spectacular images of Titan's surface we've seen to date," says Michael Brown, associate professor of planetary astronomy and lead author of the Caltech paper. "They are so detailed that we can almost begin to speculate about Titan's geology, if only we knew for certain what the bright and dark regions represented."

In 2004, Titan will be visited by JPL's Cassini spacecraft, which will look for clouds on Titan during its multiyear mission around Saturn. Cassini carries a probe named Huygens, furnished by the European Space Agency, which will parachute into Titan's atmosphere and land near the edge of the bright continent.

The results were published by the Caltech team in the December 19 issue of *Nature* and by the Berkeley team in the December 20 issue of the *Astrophysical Journal*. The Caltech team includes Brown, Bouchez, and Caitlin Griffith of the University of Arizona. The Berkeley team consists of Roe, Imke de Pater, Bruce Macintosh of Lawrence Livermore National Laboratory, and Christopher McKay of the NASA Ames Research Center. The research was

A Letter to the Editor

It was a pleasure reading Doug Smith's profile on Charley Kohlhase, a man of remarkable and varied talents. As the former media relations representative for the Cassini mission, I will always be grateful to Charley for saying "yes" to my design idea and funding the development of Cassini's "Amazing Saturn" poster.

The inspiration was provided when JPL's former education head Phil Neuhauser gave me a color copy of an old *Amazing Stories* magazine cover. It featured a painting of ice skaters on the imagined surface of Mimas, one of Saturn's moons. The ringed planet dominated the horizon. It seemed a natural starting point for a poster to depict the Cassini mission, replacing "Amazing Stories" with "Amazing Saturn." Fortunately, Charley was enthusiastically receptive to my idea and crude sketch. He provided the resources and oversight, and we were able to adapt already-commissioned artwork to the vertical poster design.

I'm also grateful to the classroom teachers who advised the Cassini education outreach team, telling us we'd garner more student interest if we designed a poster with inspiring, mind-opening artwork. Hence, the eye-catching "Amazing Saturn" poster, with the curriculum-friendly information about the Saturn system and Cassini mission printed on the back.

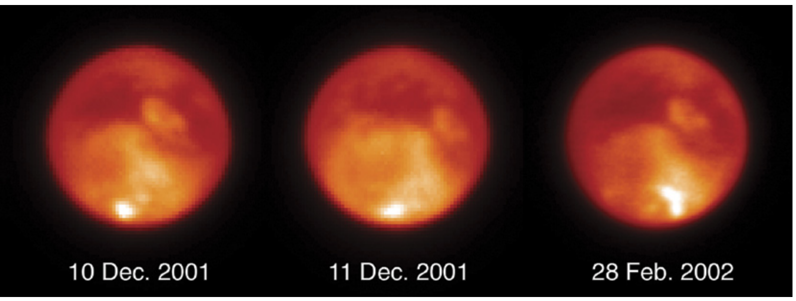
Sincerely,
Mary Beth Murrill

Interfering RNA Keeps the HIV at Bay

Caltech and UCLA researchers have developed a new gene therapy that is highly effective in preventing the HIV virus from infecting individual cells in the immune system. While not curative, the method could reduce the number of HIV-infected cells in the bodies of people who have the virus. Reporting in the January 7, 2003 issue of the *Proceedings of the National Academy of Sciences*, Caltech president and professor of biology David Baltimore and collaborators used a disabled version of the virus as a "Trojan horse" to smuggle a disruptive agent into human T-cells, thereby reducing the likelihood that a potent HIV virus will be able to successfully invade the cell. Early laboratory results show that more than 80 percent of the T-cells may be protected.

"To penetrate a cell, HIV needs two receptors that operate like doorknobs and allow the virus inside," says Baltimore. "HIV grabs the receptor and forces itself into the cell. If we can knock out one of these receptors, we hope to prevent HIV from infecting the cell." The receptors are called the CCR5 and the CD4. The human immune system can't get along without the CD4, but about 1 percent of the Caucasian population is born without the CCR5. These people are known to have a natural immunity to AIDS. Therefore, the researchers disrupted the CCR5 receptor with a special double-stranded RNA known as "small interfering RNA," or siRNA, engineering a disabled HIV virus to carry it into the T-cell. (The disabled funded in part by grants from the National Science Foundation and NASA. □

These Keck images of Titan show essentially the same face in all three shots. The bright storm cloud in the February 28 image is over 1,400 kilometers long.



virus has no disease-causing ability.) Once inside the T-cell, the siRNA knocked out the CCR5 receptor. When the T-cells were put in a petri dish and exposed to HIV, less than 20 percent of them became infected.

"Synthetic siRNAs are powerful tools," says Irvin Chen, an author of the paper and director of the UCLA AIDS Institute. "But scientists have been baffled at how to insert them into the immune system in stable form. You can't just sprinkle them on the cells."

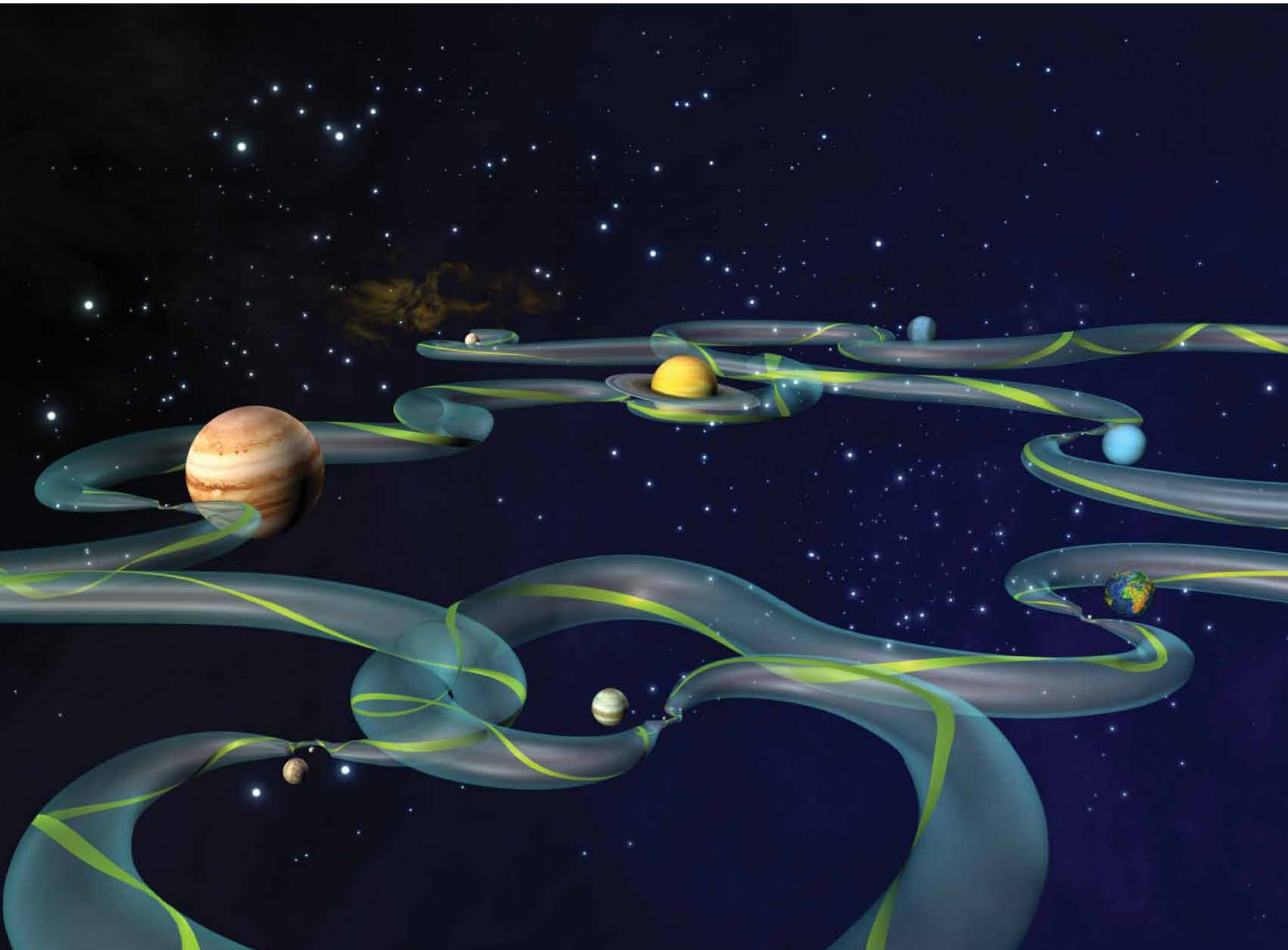
"Our findings raise the hope that we can use this approach or combine it with drugs to treat HIV in people—particularly in persons who have not experienced good results with other forms of treatment," says Baltimore. The technique can also potentially be used for other diseases when a specific gene needs to be knocked out, such as the malfunctioning genes associated with cancer, Chen says. "We can easily make siRNAs and use the carrier to deliver them into different cell types to turn off a gene malfunction." It could also be used to prevent certain microorganisms from invading the body, Baltimore adds.

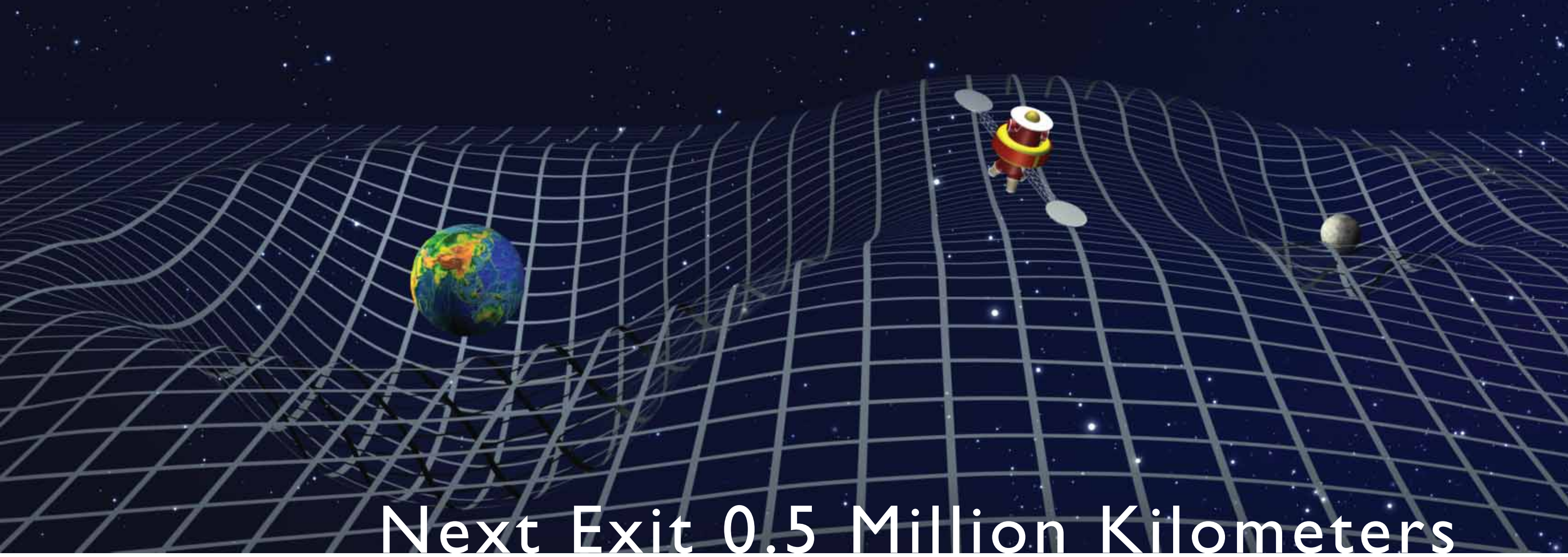
The paper's other two authors are Caltech postdoc Xiao-Feng Qin and UCLA postdoc Dong Sung An. The two contributed equally to the work.

The research is supported by the National Institute of Allergy and Infectious Diseases and the Damon Runyon–Walter Winchell Fellowship. □

Image credits: NASA, Jayanne English (U. of Manitoba), Sally Hunsberger (Penn State), Zolt Levay (STScI), Sarah Gallagher (Penn State), and Jane Charlton

The Hubble Space Telescope's Wide Field and Planetary Camera 2, designed and built at JPL, caught this close-up of a galaxy cluster known as Stephan's Quintet. It reveals that the upper two galaxies collided violently, bedecking themselves with a diamond necklace of star-forming regions. A gentler side of the quintet is seen in the opening scenes in Frank Capra's *It's a Wonderful Life*, in which they play the heavenly bureaucrats who dispatch the bumbling Clarence to George Bailey's aid. Caltech is honoring Capra, who graduated in 1918, with a film festival that includes four of his movies (although not this one). Details can be found at http://events.caltech.edu.





Next Exit 0.5 Million Kilometers

by Douglas L. Smith

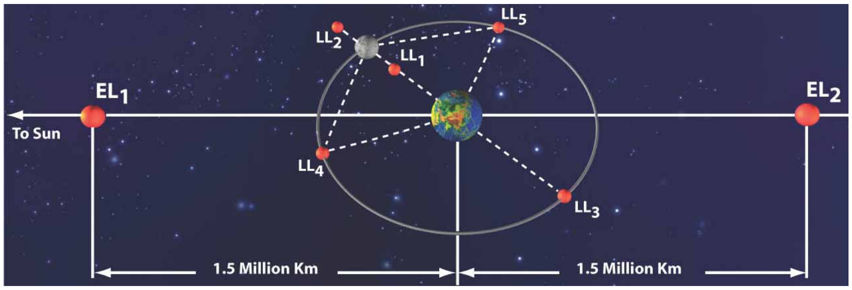
The year is 2020. Under a crescent Earth, the assembly crew at the Lunar Gateway Service Area some 62,000 kilometers above the moon's surface installs new electronics on an infrared telescope and sets it moving, at the speed of a Ford Pinto climbing an on-ramp, off to park itself deep in Earth's shadow, where a little cryogenic coolant goes a long way and where Earth is always directly overhead for high-speed data downlinks. This spacecraft has, in fact, just entered what Martin Lo (BS '75), a member of the technical staff at JPL, calls the Interplanetary Superhighway—"a vast network of winding tunnels in space" that connects the sun, the planets, their moons, and a host of other destinations as well. But unlike the wormholes beloved of science-fiction writers, these things are real. In fact, they are already being used.

The Genesis mission, for example, is following a route that a team of scientists led by Lo plotted through the sun-Earth interchange of this freeway system. (In fact, this low-energy route helped JPL win the mission.) Genesis, of which Caltech professor of nuclear geochemistry Don Burnett is the principal investigator, is collecting samples of the solar wind—the torrent of charged particles that emanates from the sun, and whose makeup reflects that of the disk of gas and dust from which the sun and the planets condensed. In 2004, Genesis will bring its booty home the same way. (Well, technically not the *same* way, as it will return through the other side of the cloverleaf, as it were.)

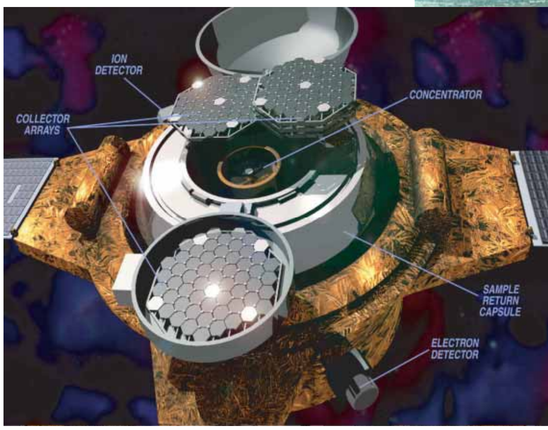
Lo, together with Caltech's Jerrold Marsden, professor of control and dynamical systems (CDS), and their coworkers Shane Ross (BS '98, a CDS graduate student) and Wang Sang Koon (a CDS senior postdoc) have begun a systematic mapping effort of what is more properly known as the Interplanetary Transport Network. As a freeway system, the network is more akin to the Pacific Coast Highway and other scenic routes than to interstates like the I-5—a collection of meandering byways for leisurely travel, not the fastest, most direct routes between points. But the quickest paths in outer space are all toll roads (it costs a lot of rocket fuel to use them), while you can ride the Interplanetary Superhighway almost for free. Gravity does the driving, so the system is really more like an elaborate set of Hot Wheels tracks. All you have to do is let go of the car at the right place. (It's a lot more complicated than this, because the tracks are in constant motion, but we'll get to that later.)

Think of a planet as a bowling ball sitting on a taut rubber sheet; the depression the ball makes is its gravitational well. To hoick a marble (the spacecraft) up out of that well takes thrust—often quite a lot of it. But what if the marble was balanced on a cusp, such as where Earth's well and the moon's well meet? The gravitational (and sometimes rotational) forces would balance one another, and the slightest sneeze, a mere feather touch, would nudge the spacecraft in the right direction.

A set of five of these balance points, called Lagrange or libration points, exist between every pair of massive bodies—the sun and its planets, the planets and their moons, and so on. Joseph-



Left: The planets are connected by a vast network of low-energy "tunnels" in space that run between the solar system's Lagrange points. Above: The Lagrange points are the regions where the gravitational forces between a pair of massive bodies balance. Right: Wheels within wheels—this diagram shows the five Lagrange points of the Earth-moon system (marked as LLs, for Lunar Lagrange) and the two closest sun-Earth Lagrange points, marked as ELs. Images courtesy of Khrysaundt "Cici" Koenig, Caltech department of computer sciences, graphics group.



Launched on August 8, 2001, Genesis is sweeping up specks of the sun—individual atoms of the solar wind—on five collector arrays the size of bicycle tires and in an ion concentrator. The sample-return capsule will parachute onto the Air Force's Utah Testing and Training Range in September 2004. Because the samples are incredibly fragile, the capsule will be snagged in midair. The sample, consisting of several milligrams of hydrogen and helium and some 20 millionths of a gram of heavier elements, will be the only extra-terrestrial material brought back to Earth from deep space since the Apollo landings, and the first to be collected from beyond the moon's orbit.

Louis Lagrange (1736–1813) discovered the existence of the two points now known as L_4 and L_5, each of which is located in the orbital plane at the third vertex of an equilateral triangle with, say, Earth at one vertex and the moon at the other. So L_4 is 60° in advance of the moon, and L_5 60° behind it. Ideally, a spacecraft at L_4 or L_5 will remain there indefinitely because when it falls off the cusp, the Coriolis effect—which makes it hard for you to walk on a moving merry-go-round—will swirl it into a long-lived orbit around that point. Comet debris and other space junk tends to collect there, and Jupiter has accumulated an impressive set of asteroids that way.

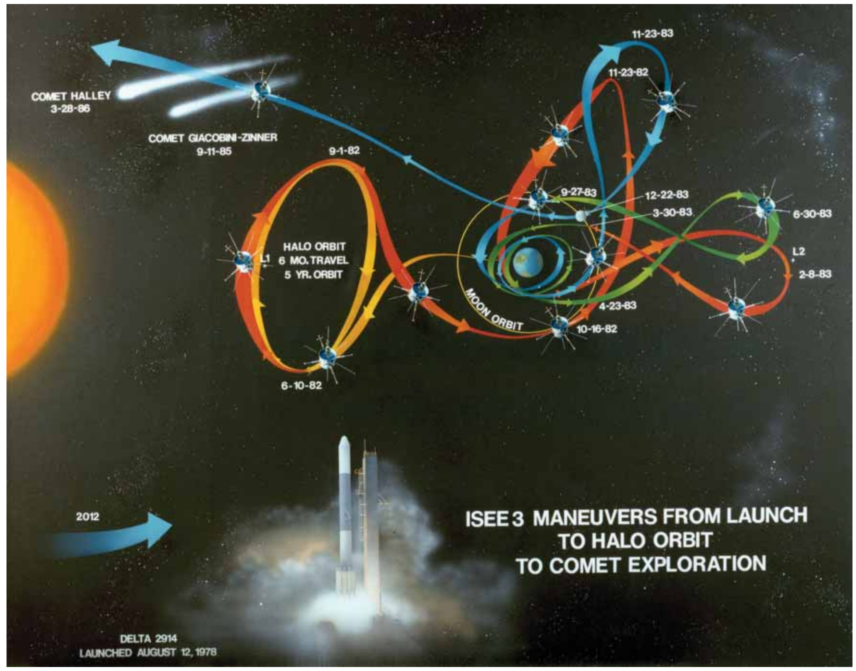
Leonhard Euler (1707–1783) rounded out the assortment with L_1, L_2, and L_3, where the rotational forces don't balance out and nothing stays put for long. (Euler actually discovered L_1, L_2, and L_3 first, but Lagrange had a better press agent.) For the sun-Earth pair, L_1 lies on a line between them, about 1.5 million kilometers from Earth. Genesis is parked in a halo orbit around L_1, so called because, as seen from Earth, the flight path follows a halo around the sun. (Sitting right on L_1 isn't a good idea, as the spacecraft's radio signals would be lost in the sun's glare.) Since orbits around L_1 are unstable, Genesis needs a small boost every 60 days or so to keep it on station. Because of its unobstructed view of the sun, L_1 is a popular place these days—the Solar and Heliospheric Observatory (SOHO), a joint project of the European Space Agency and NASA, and NASA's WIND and the Advanced Composition Explorer (ACE) are also there. (Ed Stone, the Morrisroe Professor of Physics, is ACE's principal investigator, and two of its nine instruments were built on campus.) L_2 is a similar distance from Earth as L_1, but in the opposite direction, and L_2 orbits are also unstable on a 60-day scale. NASA's MAP, the Microwave Anisotropy Probe, has been in orbit around L_2 since October 2001, mapping the variations in the leftover heat from the Big Bang. And finally, L_3 lies hidden from our view directly behind the sun. We haven't found any reason to keep a spacecraft there, but it's proven a dandy place for science-fiction writers to conceal inhabited, Earthlike planets—despite the fact that all these anti-Earths and Planet Xs would, if left unattended, fall out of orbit in 150 days or so.

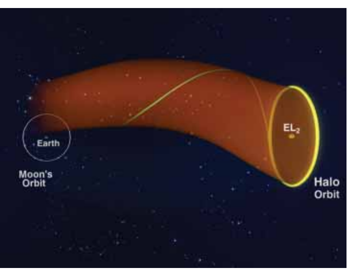
"Historically, L_1 and L_2 were not interesting," says Koon. "People were interested in L_4 and L_5, because they are stable. But instability can be a good thing, because a little force achieves a big result." Adds Ross, "You, walking around, are dynamically unstable. You keep falling forward." Without your inner-ear balance system constantly sending signals for your body to right itself, you'd be flat on your face in an instant. (Watch a toddler learning to walk some time.) But this imbalance is good, as it allows a little forward impetus to move your mass.

The tools to deal with this celestial instability were developed by Jules-Henri Poincaré (1854–1912) in the 1890s. Poincaré was working on the infamous three-body problem, which has bedeviled mathematicians since the days of Isaac Newton. The problem is simplicity itself: calculate the orbits of three masses whose only interaction with one another is through their gravitational pulls. Building on Kepler's foundational work, Newton solved the two-body version—Earth going around the sun, for example—but throwing a third mass into the mix gives a complex interplay of constantly shifting forces. Says Marsden, "You can fit the equations for the three-body problem in a corner of the blackboard somewhere, but the subtleties in it are very interesting. Many computational scientists like working on it because it's one of the simplest problems that's complicated enough to test out computational theories." And trying to do all nine planets at once? Fuggedaboudit.

Poincaré simplified the mess by organizing similar orbits into "manifolds." A manifold is any nice, smooth surface: a sheet of paper is a manifold, as is the surface of a sphere; or the crust of a donut, also called a torus. Poincaré saw that families of orbits lay on "invariant" manifolds—"No matter where it goes, a particle that starts on that surface will remain on that surface forever unless you give it a knock," Lo explains. "So that surface is invariant." These manifolds sit inside what is called six-dimensional phase space, because it includes the three dimensions of normal space plus a dimension for the particle's velocity in each direction. Thus particles that have the same location but different velocities will appear at different points in the 6-D phase space. (Marsden and Lo are working with Alan Barr, professor of computer science, on ways to visualize such higher-dimensional objects, but, fortunately, there's a lot that's easy to see in two dimensions.)

Poincaré noticed that if an unstable orbit is periodic—that is, if it returns to its starting point, A well-traveled spacecraft. The International Sun-Earth Explorer 3 (ISEE3) was put in a halo orbit around L_1 to study solar flares and cosmic gamma-ray bursts. It was later renamed the International Comet Explorer (ICE) and dispatched to comet Giacobini-Zimmer by way of L_2. (The wildly looping orbits, like the bow on a Christmas package, are typical of a route through the tubes.) ISEE3/ICE flew through Giacobini-Zimmer's tail on September 11, 1985, and went on to become the only U.S. representative in the international fleet of spacecraft that greeted Halley's comet in 1986. It is now plying its original trade in a 355-day sun-centered orbit, and will return to Earth's vicinity in August 2014. Image courtesy of the Goddard Space Flight Center and the National Space Science Data Center.





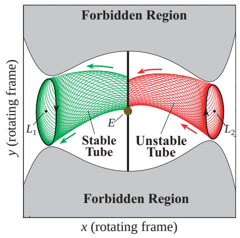
A spacecraft falling out of orbit around Earth's L_2 point would describe a path on this tube. Image courtesy of Cici Koenig.

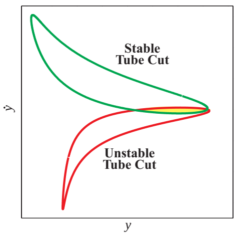
like a circle or an ellipse does—it generates a tube-shaped manifold containing all the paths one could take to fall out of that orbit with no change in energy. So if you were to plot the path of a spacecraft drifting out of orbit around Earth's L_2 point, for example, you'd see it slowly unwind into a spiral wrapped along the surface of the tube. This tube is called the "unstable" manifold of that orbit. Furthermore, another manifold contains all the paths that wind *on*to the original orbit—the movie can run backward as well as forward. Just to muddy the waters, the manifold leading to the unstable orbit is called the "stable" manifold.

And there the matter stood for nearly 100 years, waiting for computers to plot the manifolds and for spacecraft to ride them. In the late 1960s, Charles Conley and Richard McGehee (BS '64) noticed that the sun-Earth system has, for any energy level in a fairly broad range, only one periodic orbit about L_1 (and another about L_2) that lies entirely in the plane of Earth's orbit. Called a Lyapunov orbit after its discoverer, it is unstable. Conley and McGehee were able to classify all the orbits winding onto and off of the Lyapunov orbit, as well as all the orbits that entered its vicinity, and found that these orbits completely controlled the paths of bodies near Earth's L_1 and L_2 points. In other words, a slow-moving asteroid near L_1 or L_2 can only approach or leave Earth via a Lyapunov tube.

But the pioneers of spaceflight weren't particularly interested in the Lagrange points—as Gertrude Stein once said in another context, there is no there there. And there's a much more straightforward way to get spacecraft into low-Earth orbit, or to the moon, or to the other planets. Newton and Kepler left behind the tools for constructing flight paths from simple conic sections—bits of parabolas, hyperbolas, ellipses, and the ubiquitous circle—and their use is now a highly developed art. However, a visionary named Robert Farquhar persuaded NASA to fly the first mission to a Lagrange point—the International Sun-Earth Explorer 3, launched to orbit Earth's L_1 in 1978. (Farquhar also coined the term "halo orbit.") Farquhar's team found a path to the halo orbit with the aid of numerical searches. Says Lo, "Because the dynamics of the tubes are so strong, when you search around the halo orbits for a transfer trajectory from Earth, your path will invariably be controlled by the halo orbit's stable manifold." (In fact, it takes a prohibitive amount of thrust to avoid the manifold.) Then a group led by Carles Simó at the University of Barcelona explicitly proposed riding the stable manifold as a cheap and easy way to get SOHO out to Earth's L_1, and developed software tools to compute the flight path by using segments of trajectories on the manifold to "seed" the calculation. SOHO wound up taking another path, but people started dusting off their Poincaré. "Farquhar's pioneering methods required lots of human interaction," Lo recalls. "On the Genesis team, we used his group's tools to compute the initial trajectory" back in the mid-'90s when the mission was first proposed.

"So we've known about halo orbits since the '60s," says Lo, "and in the '80s the Spaniards reintroduced Poincaré's tube theory. And the question I began to ask was: If you continue these orbits out, where do they go? Is it possible to go from one planet to the next?" In other words, would the unstable outbound tube from, say, Earth's L_2 point intersect the stable inbound one to Mars's L_1 point? If so, you wouldn't need a big engine and a massive fuel tank to get there and a great deal of money might be saved.



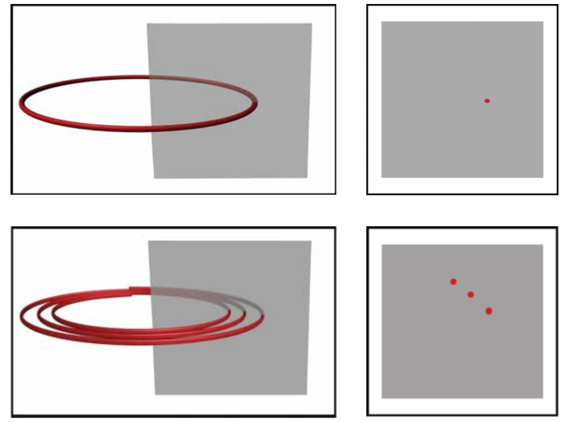


Top: A close-up of the plane of Earth's orbit in our immediate neighborhood, looking down from above. The sun is waaay over to the left. The plot rotates around the sun at the same speed that we do, keeping Earth frozen in the center. A spacecraft at a given energy can make a halo orbit (black arrows) around L_1 or L_2. A portion of some of the paths winding onto the L_1 orbit is shown in green, and the corresponding portion of the paths leaving L_2 is in red. The gray "forbidden region" is inaccessible to a spacecraft at the given energy—you can't get there from here without firing the rocket. Bottom: A Poincaré cut passing through Earth in the *y*-direction. The top plot's vertical axis is now this plot's horizontal one, and this plot's vertical axis is the velocity in the *y*-direction. You can cross from one manifold to the other at the points where they intersect.

1995 was the summer of Shane Ross's freshman year. A physics major, he had signed up for a SURF (Summer Undergraduate Research Fellowship) with Andrew Lange, a physics professor who was working on a competitor of MAP, the Big-Bang heat-mapper currently at L_2. Recalls Ross, "When I saw the trajectory that the spacecraft was going to do, I was more interested in that than the physics. So Andrew directed me towards Martin." Says Lo, "I was trying to find out whether the invariant manifolds of different planets intersected, but I was also interested in the behavior of the regions around Earth's L_1 and L_2 because of the Genesis trajectory-design project. As a freshman, Shane didn't have the math to develop the tools to compute the manifolds of halo orbits, so I thought maybe the manifolds of the Lagrange points themselves might tell us something. If you think of the tubes of a set of concentric periodic orbits as the layers of a leek, the manifold of the Lagrange point is a line down the leek's middle. So if the manifolds of two Lagrange points intersect—or even just come very close—then the tubes probably intersect as well. And if the manifolds intersect in space, even if they're at different energies, they're useful. You can bridge the energy difference by firing a rocket, so long as the paths connect." The exercise bore fruit almost immediately. Says Ross, "In July, I noted [in my lab book] that the invariant stable and unstable manifolds for the sun-Earth L_1 and L_2 visually appeared 'close to intersecting.'"

As Earth orbits the sun, the tubes are lashing through space like water from a demented lawn sprinkler. So when you plot a tube, you do it in a rotating reference frame, meaning that the two massive bodies are plotted at fixed points on the *x* axis. Now the manifolds are frozen in space, and the only thing moving is the spacecraft. (See the drawing at upper left.) You also hold the spacecraft' velocity constant, because you'd need a fresh sheet of paper for each new velocity. Drawing a pair of halo orbits, or rather drawing their two-dimensional projections in the (*x*, *y*) plane, gives the bean shapes around L_1 and L_2. They aren't ellipses, explains Ross, because "in 3-D, a halo orbit looks like the edge of a potato chip." But they're periodic, and that's the important thing. The unstable manifold coming off L_2 is shown in red, and the stable manifold leading to L_1 is green. Now, if you take a cross section through the manifolds parallel to the *y* axis, as shown by the heavy line, you can make a second plot of the spacecraft's position (*y*) versus its velocity in the *y*-direction (*y-dot*), as shown in the lower left drawing. This is called a Poincaré section (above right), and the intersections of the red and green lines mark the locations and speeds at which one can segue from manifold to manifold for free.

But if you're trying to get from, say, Earth's L_2 point to Mars's L_1 point, you suddenly have a four-body problem, which is truly a computational

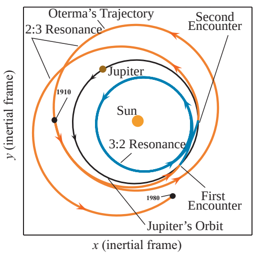


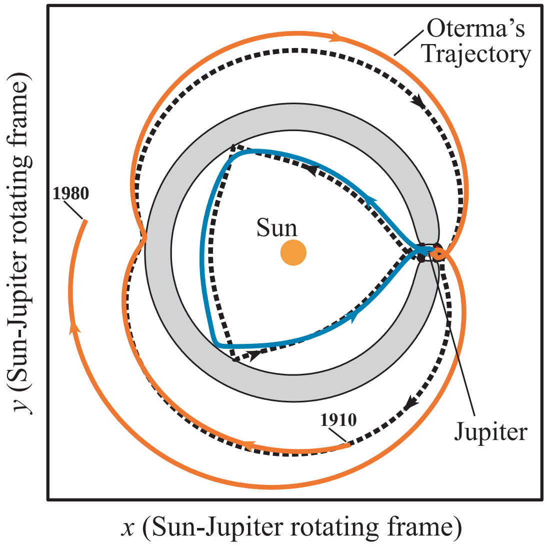
A Poincaré primer. Poincaré invented a general method for classifying orbits by plotting any two parameters against each other—in this case position versus velocity. If you have an elliptical orbit (top left), a Poincaré section taken perpendicular to it (gray) will plot as a single point (top right) because the orbit always returns to the same spot with the same velocity. But if you have an orbit that is gradually spiraling inward (bottom left), the Poincaré cut will show a set of points trending to the left as the radius decreases, and up because objects in lower orbits move faster. Courtesy of Cici Koenig.

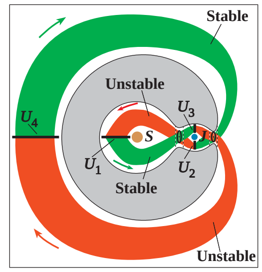
swamp. So you make two simplifying assumptions: everything lies in one plane (from Earth on out, all the planets except Pluto are within 2.5°) and all planetary orbits are circular (again pretty much true except for poor old Pluto). Now you can treat the system as two three-body problems (sun-Earth-spacecraft and sun-Mars-spacecraft) coupled together through their common members.

Says Lo, "Originally, I wanted to find the intersections of the manifolds between Mars and Earth. When that proved too difficult, we switched to Jupiter-Saturn, which yielded an immediate result" the summer of Ross's sophomore year. Adds Ross, "The manifolds of Jupiter's L_2 and Saturn's L_1 intersected in position within a short time—a few decades." Further work showed that you could go between any of the outer planets for free. It might take a few hundred years, however—possibly a couple of thousand. Earth to Mars just happened to be the worst-case example, taking tens of thousands of years.

Still, the Voyagers took a mere two years to get from Jupiter to Saturn using conic sections and gravity assists, so a free tube ride that "only" takes a few decades may not seem like an exciting prospect. Comets and asteroids, however, have all the time in the world. Could they be roaming the freeways from planet to planet, like celestial retirees in their motor homes? Yes, they could. For example, at the time of its discovery in 1943, a comet named Oterma was in a 3:2 resonance







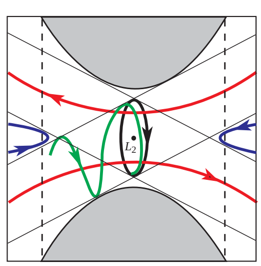
Above: The path of comet Oterma from 1910 to 1980, plotted in a non-rotating reference frame. Above, right: When plotted in a sun-Jupiter rotating frame, Oterma's orbit matches the tube trajectories (dashed line) almost perfectly. Note that in the rotating frame, Oterma moves clockwise relative to a stationary Jupiter, even though the planets—and Oterma—orbit the sun counter-clockwise. Far right: The patched-together sections of Jupiter's tubes that Oterma used. U_1 through U_4 are the Poincaré cuts.

inside Jupiter's orbit—that is, Oterma made three laps around the sun for every two that Jupiter did. But it hadn't been there long—in 1958 Liisi Oterma back-calculated the orbit of her find and discovered that it had been in a 2:3 resonance *outside* Jupiter's orbit until 1937, when a close encounter with the giant planet had flung it onto the inside track. Then in 1963 Oterma suddenly changed lanes again without signaling, nose-diving past Jupiter like the driver in the left lane who suddenly realizes he's about to pass his exit, to once more lie in a 2:3 resonance outside Jupiter. The two nearly traded paint in the process—Oterma only missed Jupiter by 14.7 million kilometers. It turns out that the 3:2 resonant orbit passes very close to the sun-Jupiter L_1 point, while the 2:3 orbit (surprise!) sideswipes L_2. Says Lo, "Oterma's trajectory almost followed a cookie-cutter" path along the manifolds.

Recalls Lo, "This was before we went to Jerry [Marsden], so I didn't have the full theory of *how* this transport occurred, and Jerry suggested the possibilities that he knew about." It turns out that just missing the manifold was the key, as Conley had discovered for the sun-Earth combo some 40 years earlier: if you ride the manifold in, you get trapped in an orbit around the Lagrange point, but if you pick a point in the Poincaré cut that lies inside the tube, you'll plunge toward the planet. What happens next gets very complicated—chaotic, in fact—but you can emerge at either Lagrange point, or you can wind up in orbit around the planet. (Conversely, if you skirt the tube's mouth without entering it, you'll head back out where you came from without crossing over.) Says Marsden, "Back in the '60s, Conley and McGehee discovered a lot of the bits and pieces of this that were very important, but we developed the mathematical underpinnings that established the big-picture framework."

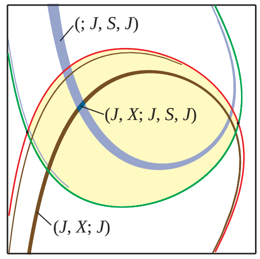
Koon, Lo, Marsden, and Ross proved that you could pick any itinerary you liked for *any* set of Lagrange points, and a trajectory existed that would follow it. So, in principle, you could set a course for a comet that would swoop in from the outside, whirl around Jupiter three times, cross to the inside track, make fifteen orbits around the sun, cross over to the outside track again, make three more orbits around the sun, and then get permanently captured by Jupiter to take up a new life as a Jovian moonlet. The software Ross adapted to do these computations was provided by Gerard Gómez of Barcelona University and Josep Masdemont of the Polytechnic University of Catalunya, also in Barcelona, members of Simó's SOHO team.

Koon et al. also devised a notation system for plotting the itinerary and keeping track of where you were in it, allowing them to classify paths based on what points were visited, even if the details of course and speed were wildly different. Koon calls this "the most amazing thing. Dynamical systems theory—symbolic dynamics—allows us not only to prove the existence of all these complicated trajectories, but also to keep



Conley and McGehee's bestiary of orbits is based on the periodic (black) orbits, in this case a Lyapunov orbit—an ellipse that lies in the plane of Earth's orbit and is easy to deal with mathematically. Asymptotic (green) orbits wind onto or off of the Lyapunov orbit, and collectively define the stable and unstable manifolds. Transit (red) ones pass inside it and enter one of its tubes. Nontransit (blue) ones shy away from the tube's mouth and return to the region of space from whence they came.

Right: A Poincaré cut in Jupiter's plane, like the one on page 10. The green and red lines are the stable and unstable manifolds. The region where they intersect (light yellow) contains the crossover trajectories. The blue strip labeled (; *J*, *S*, *J*) winds around and around, approaching the green line but never actually touching it, and contains particles that are in the Jupiter region and will slip inside to visit the sun before returning. The brown strip (*J*, *X*; *J*) approaches the red line in a similar manner and contains trajectories that have returned to Jupiter after having been out beyond its orbit. The strips' intersection (*J*, *X*; *J*, *S*, *J*) gives the paths where a particle began near Jupiter, ventured outside, and is now back at the planet, but will plunge toward the sun and later return to Jupiter.



fuel means less mass, which means more payload—more bang for the buck, and fewer bucks for the mission.

Says Lo, "I grew up with the picture of the solar system we inherited from Kepler and Copernicus—a series of planets isolated in stately, concentric, nearly circular orbits. And you're always surprised when things like comets intrude." But the tube model provides an easy way for comets and asteroids to get into the inner solar system. As a tube sweeps through the outer reaches, every now and then some debris will fall into it and be whisked in toward the center. In fact, it's almost a circulatory system, with space junk for blood cells and the tubes acting as blood vessels. And while the sun pumps the system, it's not built to the mammalian plan but rather, with the planets, is more like an earthworm, which has multiple hearts.

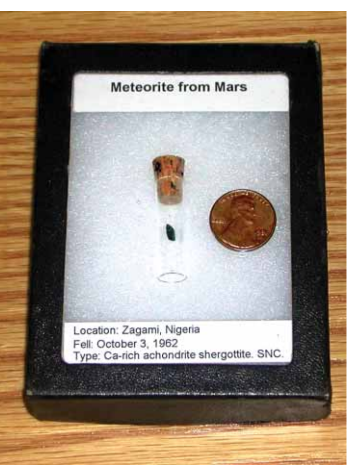
Seen from this cardiac point of view, the dinosaurs could be considered to be victims of a blood clot—the asteroid that whacked them was traveling down an artery that happened to be obstructed by the earth. (Yes, the tubes can pass through planets as well as going around them.) Marsden once gave a presentation to an audience that included physicist Richard Muller and geologist Walter Alvarez, who have brought the asteroid extinction theory from crackpot sci-fi to mainstream science over the last 20 years. Says Lo, "They told Jerry that they wondered if that asteroid used our orbits, because it had a very low impact velocity. You can infer that from the huge deposit of iridium it created. If it was a hot, fast impact, the iridium would have been vaporized and destroyed."

But an even better circulatory analogy might be the world's wildest water park. "Imagine a set of water slides winding downhill every which way," says Marsden. "Now, imagine that the slides are in constant motion, moving up and down and passing through one another unhindered. You can go anywhere in the park by hopping on the nearest slide and then switching from slide to slide as they rise and fall." Eventually, a slide will pass by your destination, and you hop off. Says Marsden, "Sliding is naturally dynamic and requires very little active control, unlike a car whose motor is always running and which has to be steered. And proper timing is critical, which is a key ingredient to the whole methodology—you have to jump from one tube to another at just the right moment, while a freeway interchange is static."

The fluidic analogies are not far off the mark. Says Marsden, "I inherited postdoc Chad Coulliette and grad student François Lekien from Steve Wiggins [a Caltech professor from 1987 to 2001]. They are working on fluid mixing and transport of materials in the ocean, which turn out to have basically the same mathematical infrastructure as dynamical astronomy." In other words, whether you're dropping dye overboard in

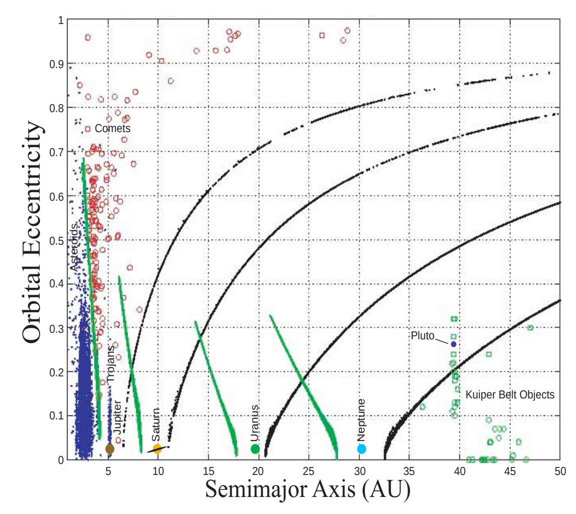
track of them. Otherwise there would be almost no way to think about them." The notation system divides the space in the neighborhood of any moon or planet into three regions—the region beyond its orbit, abbreviated *X* for exterior; the region between the L_1 and L_2 points, abbreviated *E* for Earth, *J* for Jupiter, and so on; and the region within the body's orbit, abbreviated *S* for sunward. So the itinerary described in the previous paragraph would be written as (*X*, *J*, *S*, *J*; *X*, *J*), with the semicolon showing that the comet is currently in its brief venture back outside Jupiter's orbit.

All this work, beginning with the Earth L_1-L_2 analysis, was published in a massive paper in *Chaos* on April 12, 2000. Says Marsden, "The real understanding of the tubes—using the ideas of transport through the tubes or bouncing back, as well as how the tubes navigate the neck region—was motivated by the Genesis return orbit and is a critical ingredient to understanding the whole picture. It is an enabling set of ideas that builds on what Conley and McGehee did, but goes well beyond it. This was the most important contribution of the *Chaos* paper."



This sliver of Mars probably rode a tube to Earth.

Poincaré had, in fact, been dabbling in chaos theory, although he didn't know it because he was in the process of inventing the field. Chaos theory, a branch of dynamical systems theory, studies systems like the three-body problem that can be completely described by a few simple equations, but whose behavior alters dramatically depending on very small changes in one's choice of initial conditions. The various tubes emerging from a set of periodic orbits around L_1 and L_2 wrap around one another in a very complex way. The Poincaré cut winds up looking like the chocolate swirls in marble fudge ice cream, and adjoining points will take you to wildly different destinations. And that's why the theory is so powerful—it doesn't take much exertion to move a smidgeon in any direction along the cut, making a large number of tubes accessible at a very low energy cost. Less



A different kind of Poincaré section of the outer solar system, plotting orbital eccentricity—how far out of round the orbit is, with 0 being a circle—versus the orbit's semimajor axis, i.e., the maximum distance it gets from the sun. (The average sun-Earth distance is defined to be one AU, or astronomical unit.) The green lines are the L_1 manifolds and the black lines are the L_2 manifolds. The Trojans are the family of asteroids caught at Jupiter's L_4 and L_5 points.

Jupiter's four biggest moons, from the outermost in: Callisto (top), Ganymede, Europa, and Io.

Monterey Bay and letting the submarine currents carry it out to sea, or tracing a family of asteroids back to a single source, the rules are the same. "The fluids people are a little bit ahead of the dynamical-astronomy people, and François and Chad came up with some very clever tricks that allow us to compute transport quantities for much longer times than were known before. That leap would not be possible unless you have a mathematical framework, in this case dynamical systems theory, that encompasses both fields."

In yet another leap, the collaboration includes a pack of chemists—Charles Jaffé of West Virginia University, Turgay Uzer from Georgia Tech, and Utah State's David Farrelly. "Suppose an asteroid hits Mars and throws up a bunch of debris," Marsden asks. "What's the probability of some of it reaching Earth? Being bound in Mars orbit and then escaping is mathematically analogous to a molecule breaking apart. Jaffé, Uzer, and Farrelly brought in all sorts of techniques from chemistry, because chemists have really been worrying about those problems."

It's useful to know how material sloshes through the solar system, drifting on gravity's currents, but no man will wait for that tide. A mission a grad student would consider a good career move needs to get where it's going in only a few years at most. You can do this if you stay in the vicinity of one planet—taking the beltway rather than the interstate, as it were—and a Japanese spacecraft named Hiten was the first to do just that. Launched in January 1990, it was placed into a highly elliptical orbit around Earth, from which it was supposed to release a small probe named Hagoromo into lunar orbit. Hagoromo's radio failed before deployment, however, and Hiten didn't have enough fuel to get to the moon itself on a conventional path. So JPL's Edward Belbruno (now affiliated with Princeton) and James Miller proposed gradually nudging Hiten's orbit into a very long ellipse extending some 1.4 million kilometers from Earth. (You may recall that the sun-Earth L_1 point is about 1.5 million kilometers out.) In this region, which Belbruno and Miller called the Weak Stability Boundary, a carefully timed rocket burst sent Hiten looping into lunar orbit.

The same trick will work in other planetary neighborhoods. The gulf between Jupiter's moons Ganymede and Europa is only about 400,000 kilometers—about the distance from Earth to the moon. So a mission could fly to Jupiter on conventional conic sections, then slip into a "petit grand tour" of the Jovian system. Based on the method developed in the *Chaos* paper, Koon, Lo, Marsden, and Ross created a proof-of-concept flight plan in which a spacecraft took one loop around Ganymede before settling into a permanent orbit around Europa—a moon that planetary scientists are dying for a long look at, as it may have oceans of liquid water beneath its frozen surface. "Most previous applications of dynamical systems theory to mission design focused on the surfaces of the invariant manifolds," says Koon. "We showed that the regions inside and outside the manifolds can be used to advantage as well as the manifolds themselves." Recent, more ambitious itineraries include Callisto and Io, and go on for a hundred or so orbits. Says Ross, "I think 100 is sort of the limit of predictability. Like you can only predict the weather for so many days into the future, we can only predict what's going to happen up to some finite horizon in any chaotic environment." So you still need to fire the maneuvering thrusters every now and then, just as Genesis needs a nudge every couple of months to keep it in orbit around L_1. But you'll use a lot less fuel if you work with the manifolds rather than trying to punch through them.

Nowadays, these calculations for space missions are done using a software package called LTool, which can actually handle an *N*-body problem using positional data from JPL's elaborate model of the solar system, called an ephemeris. LTool grew out of a set of computational tools developed by astrodynamicists at Purdue over the last 20 years, and which Lo borrowed from longtime collaborator Kathleen Howell, a halo-orbit expert there. Lo, Howell, and her grad student Belinda Marchand used these tools on a Jupiter-resonant comet called Helin-Roman-Crockett (codiscovered by JPL's Eleanor Helin), meticulously matching the comet's orbit with the appropriate segments of Jupiter's tubes—the model's first use of the real motions of actual celestial bodies instead of idealized circular orbits. In 1998, Lo assembled a JPL team to develop and expand the software, calling on Larry Romans (PhD '85), George Hockney, Brian Barden and Roby Wilson (both Howell alums), Min-Kun Chung (BS '81), and James Evans.

LTool got its first real workout on the Genesis mission—the spacecraft that's now sampling the solar wind at L_1—for which Lo served as mission-design manager. Lo, Howell, Barden, and Wilson came up with a trajectory that carries the spacecraft from liftoff through five orbits around L_1 before the craft drops out to make a single pass around L_2 in order to touch down in Utah's Great Salt Desert during daylight. When the launch date slipped from February to August 2001, the team was able to completely redesign the working orbit in a week—a task that would normally have taken months.

More recently, LTool calculated the first formation flight around a Lagrange point, an option being considered for the proposed Terrestrial Planet Finder (TPF), which will look for Earthlike planets around other stars. A fleet of several small spacecraft flying in formation could act as a single large telescope, and one convenient place to deploy such a thing is L_2. Lo, Gómez and Masdemont (the boys from Barcelona), Romans, and Caltech's Ken Museth showed that the gravitational balance at L_2 would make it very easy for such a fleet to stay in formation even as the individual ships maneuvered to point the virtual dish in any direction.

And refinements to the transport theory could narrow the list of stars for TPF to look at. Our solar system is filled with a diffuse cloud of "zodiacal dust" fed by cometary tails and the dandruff from asteroid collisions. As Earth and its sister planets swim through the dust, they leave wakes. Similar exozodiacal clouds have been seen around other stars, and "as telescopes get sharper and sharper, you can identify more and more features in them," says Lo. Many astronomers hope to be the first to spot an Earthlike planet by its wake. Looking for signs of life, of course, is much more difficult—you'd need to keep the telescope focused on the planet for some time in order to try to discover, say, oxygen and methane spectroscopically. You could cull some duds in advance by calculating whether the planet was in the habitable zone—the proper distance from its sun for water to be liquid. But it's generally agreed that many of the carbon-rich molecular building blocks of life get delivered to newborn planets by asteroid and comet impacts, and the rate of this fusillade changes with time as the planets sweep up the debris. "If you have too many bombardments, life never takes hold, but if you have too few you don't get enough raw materials. What is that happy medium, and when does it occur?" Lo asks. Says Marsden, "We are hoping that our transport theory will enable us to better understand the process, and do the calculations more efficiently." You could plug various star and planet combinations into the model and find out which ones seem conducive to life, and then predict how their wake patterns would look at various stages.

So. The Lunar Gateway Service Area we began with—is it pie in the sky, or perhaps castles at the Lagrange point? Well, the long-term vision put together by the NASA Exploration Team (NExT) sees the Earth-moon L_1 point as a way to get humanity beyond the low-Earth orbit occupied by the International Space Station. No timetable and budget has been set, however, and operations at the space station are set to run through at least 2017. But the lunar L_1 point would be "a very attractive location if [NASA] decides to send advanced robots or even humans to the surface of the moon. The entire surface of the moon is accessible with moderate ease. It's an excellent staging area for deep-space missions, human or robotic, and maybe for one day sending humans to Mars," Harley Thronson, the NExT team science chief, told the *Houston Chronicle* at the 2002 World Space Congress in October, where the plan was widely discussed. "This is really where you learn to drive around the neighborhood and develop your capabilities."

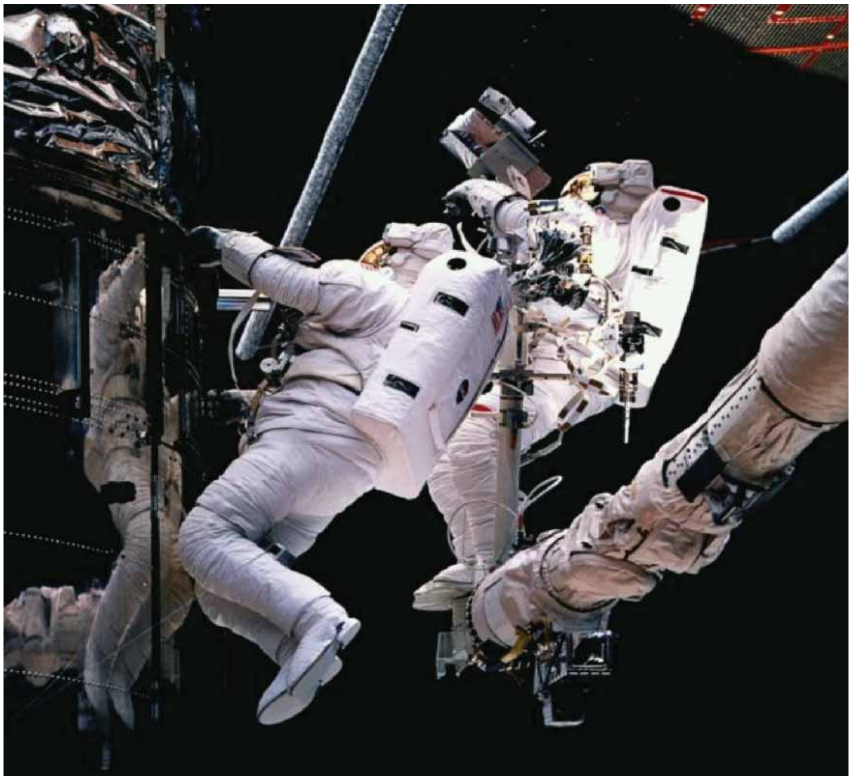
"You don't have to fight against Earth's gravity," says Lo. "When you lift off from Earth, you have to build your spacecraft to withstand a lot of G forces. But if you were launching it from space, you could have a much lighter structure." And you could build things at the Gateway that couldn't be built on Earth at all—thin-film mirrors, for example, incapable of supporting their own weight. The same holds true at the space station, but it would cost a lot more fuel to launch from there, and there's no cheap path back if the telescope needs service. And the Gateway would also widen the very narrow launch windows for some planetary missions. You could keep the spacecraft hanging around in the neighborhood until the time is ripe, revving it up in the meantime with multiple Earth flybys like David whirling his sling around his head before letting fly at Goliath. It could take weeks to get to the moon's L_1 from Earth by tube, which might prove a bit too leisurely for impatient humans but would be fine for freight—food, toilet paper, and spacecraft parts. People would probably prefer to hop a fast rocket on a conic section. It would be like crossing the Pacific today—cargo goes by ship, but most people take a plane.

But right now Lo, Marsden, and company are a long way from compiling a Rand McNally–esque road atlas of the entire system, much less a detailed street map. The work they've done so far is more of a point-to-point nature—the equivalent of having a bunch of people just hop into cars and drive, and seeing where everyone winds up. To do this, they pick a large number of initial conditions and let the computer run the paths out to wherever they go. They can make informed choices of the starting points to set the machine off in the right direction, but the final destinations remain the luck of the draw. What they need is enough computer power to make the equivalent of time-lapse aerial photographs of all those flailing tubes. Furthermore, there are whole families of periodic and quasi-periodic orbits that haven't even been catalogued yet, much less explored—you can have an orbit that lies on the surface of a torus, for example, so that it looks as if you had soldered the ends of a Slinky together. The manifolds winding onto and off of this orbit look like hairy donuts. And Randy Paffenroth, staff scientist in applied and computational math; Eusebius Doedel, visiting associate in applied math; Herb Keller, professor emeritus of applied math; and Don Dichmann of the Aerospace Corporation have discovered even weirder orbits that are impossible to describe in simple terms.

But what if you aren't anywhere near the tube you want to take? Lo, Marsden, and company, in collaboration with a group headed by Michael Dellnitz at the University of Paderborn in Germany, are also working on an extension of the theory they call "lobe dynamics." Lobe dynamics allows you to begin at a distant point on the Poincaré cut and, over many successive passes, hop chaotically between orbital resonances until you arrive in the vicinity of the proper tube and fall in. It's kind of like starting in the middle of a grassy paddock and bouncing your way over the rough ground to reach a paved road.

"Exactly how three-body dynamics can be used to help solve Galileo-type trajectories is a real-life research problem," says Lo. "How this connects up to conventional conic orbits is not entirely clear. They're not separate, not clearly distinct, and we would like to be able to use elements of both. Ultimately, this will enable us to do missions we can't even conceive of now. The rational numbers didn't replace the integers, they just increased the number of things we could do. And who knows what lies ahead? Beyond the rationals are the irrational numbers, and beyond them the imaginaries." Says Marsden, "Since the foundation of the Interplanetary Transport Network we have laid is so broad and fundamental, it helps us understand many different, otherwise disparate phenomena at multiple scales, from the trajectories of spacecraft to the chaotic motion of comets and the transport of zodiacal dust particles."

Says Marsden, "We'd really like to establish a formal joint Caltech/JPL center to carry on this research, perhaps in collaboration with Caltech's Center for Integrative Multiscale Modeling and Simulation. But we need a donor—someone who thinks this stuff is really cool." Adds Lo, "It's a large-scale project. Maybe not quite as horrendous as, say, the human genome, but a lot like those star catalogs. It's going to take some time, because there are a lot of theoretical underpinnings that are still not really understood." The center would take advantage of Caltech's supercomputer facility and draw faculty from a wide range of disciplines. And the work done at the center would redound to other fields in return—perhaps the celestial dynamicists will ultimately teach the chemists a thing or two. □



Above: Space Shuttle astronauts replace a gyroscope on the Hubble Space Telescope in low-Earth orbit. Future telescopes at L_1 and L_2 could be brought into the Lunar Gateway Service Area for repairs.
Below: The planets' stately, isolated orbits are really connected parts of a larger whole, like the labyrinth in Chartres Cathedral. Courtesy of Cici Koenig.

PICTURE CREDITS:
8 – Genesis; 10-13 – Shane Ross; 12 – Doug Cummings; 13, 15 – NASA

Smoke Gets in Your Brain

by Henry A. Lester

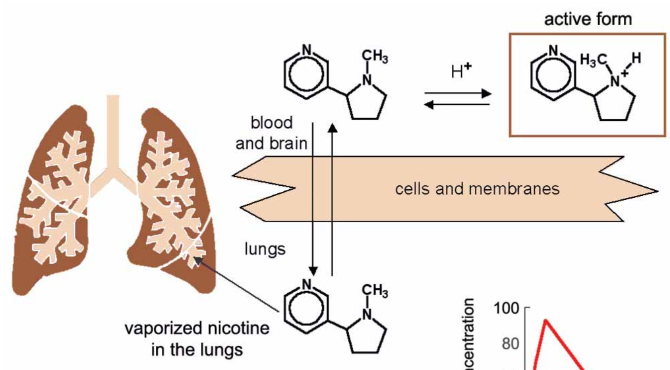
If smokers are self-medicating with nicotine, what does this tell us about the brain? To understand just what nicotine is doing to our nerve cells at the molecular level, and why it is so addictive, my laboratory has designed mice genetically altered to be hypersensitive to it. I'd like to tell you about our first results with these mice, and what we're learning from them. It turns out that these mice also have implications for other human conditions, such as Parkinson's, Alzheimer's, alcoholism, epilepsy, and pain.

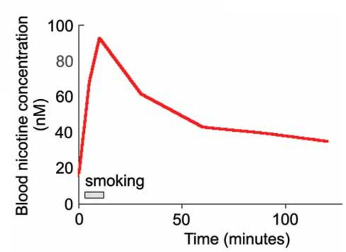
Let's start with a person who has taken a puff on a cigarette and now has vaporized nicotine in his or her lungs. How does the nicotine get to the brain? On this journey, nicotine must cross a number of cells and membranes, such as those separating the lungs from the blood and the blood from the brain. Nicotine accomplishes its journey rather well, because in the uncharged form membranes are very permeable to it. But the form that is active on cells does have a charge, because it has picked up a proton (H^+). This is a common theme with drugs of both therapy and abuse such as morphine, heroin, and cocaine: they enter the bloodstream and get to the brain fairly rapidly, then take on a slightly different form—typically by gaining a proton—in order to act on each drug's specific receptor in the brain. If the nicotine molecule gained a proton too early, it wouldn't be able to pass through the lungs and into the blood.

Cigarette manufacturers know this. A typical Marlboro, for example, has many ingredients in addition to tobacco (including licorice extract, glycerol, carob beans, and cocoa), and one additive, simple ammonium hydroxide, that increases the pH of the fluid layer lining the lungs. This prevents the average nicotine molecule from becoming protonated, keeping it in the uncharged state appropriate for crossing the lungs. South American Indians know this trick too, and chew their coca leaves with a dash of powdered lime to keep the cocaine solution nonacidic.

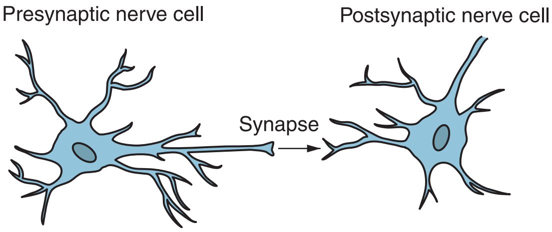
Nicotine concentrations in the blood (and presumably in the brain as well) increase within minutes after just a few puffs, and they also decrease rapidly after smoking stops. In ways we don't yet fully understand, this rapid pulse of nicotine is probably important for some of the subsequent events, including addiction. A nicotine patch is not addictive, because it releases a steady, much lower concentration that partially blunts the response to these pulses. Although the pulse of nicotine is brief, on a time scale of minutes, it appears as quite a high concentration over a long period of time to the actual cells and synapses involved.

Nicotine gets into almost all areas of the brain, but the brain cells I'd like to emphasize first are

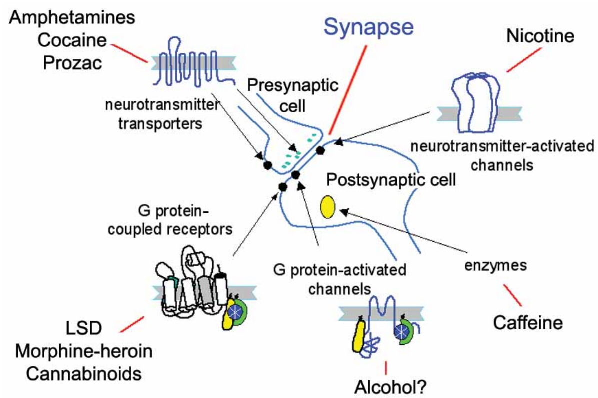




Levels of nicotine in the blood rise quickly after just a few puffs on a cigarette, right, because the uncharged molecule can pass across membranes with ease. Once it reaches the brain it activates by taking on a charge.

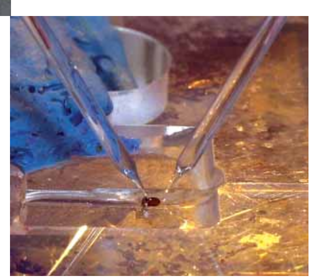


Signals between nerve cells are carried across the synapse by neurotransmitter molecules.



Some recreational drugs work by taking the place of neurotransmitters as they cross this gap; others work on nearby molecules.

Left: A patch-clamping rig set up to record the flow of ions through receptor channels in the large immature egg cell (oocyte) of the frog *Xenopus.*



Right: The egg is bathed in one type of chemical while glass pipettes doubling as electrodes inject it with another type. As receptor channels open and close in response to these chemicals, the electrodes measure the currents set up by the flow of ions.

those in the so-called pleasure/reward system deep within the midbrain. Some of these, the dopaminergic cells, respond to acetylcholine or nicotine by releasing dopamine.

In the brain, impulses move between two nerve cells across a gap called the synapse. It's a miniature chemical jump. The signal is electrical while it propagates within the presynaptic cell toward the synapse, but it's transformed into chemistry, in the form of a molecule called a neurotransmitter, in order to pass across the synapse. Once the neurotransmitter has got to the other side and reached special receptors on the outer membranes of the postsynaptic cell, the impulse continues on its way as an electrical signal.

Acetylcholine is the normal transmitter used in many synapses in the brain, and is received by acetylcholine receptors on the postsynaptic nerve cell. This starts the firing of an electrical signal, and triggers the release of dopamine. Having completed its task, acetylcholine is rapidly broken down by an enzyme called acetylcholinesterase.

A typical acetylcholine synapse is a wondrous biophysical machine, specialized to act on a time scale of a thousandth of a second over a distance scale of just a couple of microns—about two millionths of a meter.

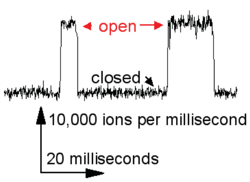
The nicotine molecule mimics acetylcholine in certain key ways that we are now beginning to appreciate, and binds to the same receptors. But because it can't be broken down by acetylcholinesterase, it persists at the synapse for minutes rather than milliseconds, and excites the postsynaptic neurons to fire rapidly for long periods, releasing large amounts of dopamine. This induces a feeling of pleasure (which is what smoking's all about), although we don't really know *how* the pleasure arises.

The synapse is also the site of action of many other recreational drugs that mimic neurotransmitters. LSD, morphine, heroin, and cannabinoids act on molecules called G protein-coupled receptors; amphetamines and cocaine (as well as some therapeutically useful drugs such as Prozac) act on neurotransmitter transporters; and caffeine and alcohol act partially in this neighborhood as well. Nicotine acts on a neurotransmitter-activated receptor bearing the full name of nicotinic acetylcholine receptor (because acetylcholine is the usual transmitter, and nicotine can mimic it), so let's take a closer look at one of these.

The receptor straddles the cell membrane. The part that senses nicotine or acetylcholine molecules is on the outside of the cell, and other key parts are inside the cell. It is partially an electrical machine: current flows through it, but not as electrons or protons. In a cell, current flows as ions, primarily sodium and potassium, moving through a channel down the middle of the receptor, and past a constriction that acts as a gate to control the flow.

For many years, neuroscientists have pursued two goals: first to record individual currents through an ion channel, and second to visualize the structure of an ion channel at the atomic scale. The first goal was made possible by an idea that occurred simultaneously to Richard Feynman at Caltech and Erwin Neher in Germany in the 1970s. I didn't believe Feynman, so I didn't follow this up, and Neher did the experiments himself. He perfected the single-channel recording technique between 1976 and 1980, receiving the Nobel Prize with his partner Bert Sakmann in 1991. The clever circuit Neher developed, called a patch clamp, allows us to measure the currents that flow through an individual channel in response to acetylcholine or nicotine (the traces are so similar, it's hard to tell the difference).

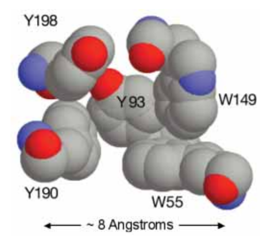
Right: The acetylcholine binding site at atomic resolution has five aromatic amino acids. Red represents oxygen; blue, nitrogen; gray, carbon. Below: A recording from a nicotinic acetylcholine receptor channel.



The patch clamp enables us to measure a channel opening even if it lasts only about a tenth of a millisecond, and even if it does so only once every 20 minutes or so. That's about 1 part in 10 million; very rarely in biology does one have the chance to work with such precision. In the recording shown on the left, the nicotinic acetylcholine channel gate is initially closed and no current flows. It opens when exposed to acetylcholine or nicotine, and a current of about 10,000 ions per millisecond flows through, corresponding to about one picoampere. It typically stays opens for between one and two milliseconds.

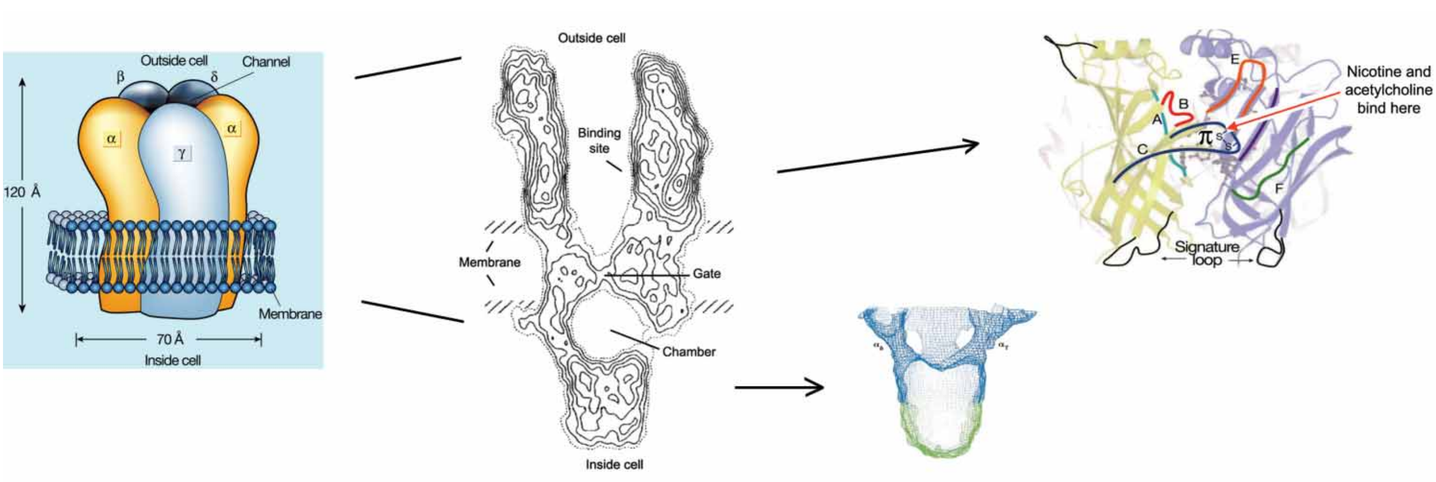
The receptor has five subunits arranged around the channel on the axis of symmetry, two made of one kind of protein (yellow in the diagram below left) and three of other, very similar proteins (blue). The part that receives the acetylcholine or nicotine molecule is outside the cell. We've recently learned the X-ray crystallographic structure of a molecule that's so very much like this external part of the receptor that we can use it as a guide for our experiments. For instance, the region labeled π is where the actual binding takes place. We don't yet have such good resolution for the region of the receptor inside the cell, but we think that the bottom of the channel has a little barrier on the axis, so that the ions must pass out the sides through five rudimentary "windows."

When the structure of the external part at atomic resolution was published, many people were surprised that the binding site was a box lined by aromatic (benzene-containing) amino acids and open at one end. In this arrangement, the amino acids lacked negative charges to attract the positively charged acetylcholine molecule. But this aromatic box was not a surprise to us at Caltech, because my colleague and collaborator Dennis Dougherty, the Hoag Professor of Chemistry, had been hypothesizing for the last 10 years that acetylcholine binds to aromatic rather than negatively charged groups.



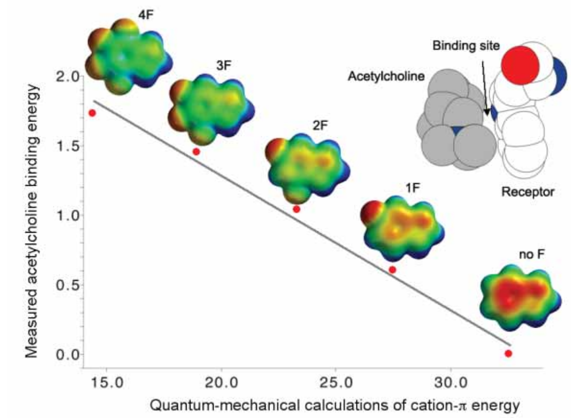
Dougherty & Lester, *Nature* 411: 252 (2001) © Macmillan Publishers Ltd.

Even the resolution of about three angstroms in the X-ray image shown here isn't good enough to tell us where in the box acetylcholine or nicotine actually binds. But the Dougherty and Lester groups have also done a series of experiments to specify this binding, using a combination of quantum mechanics and biological measurements



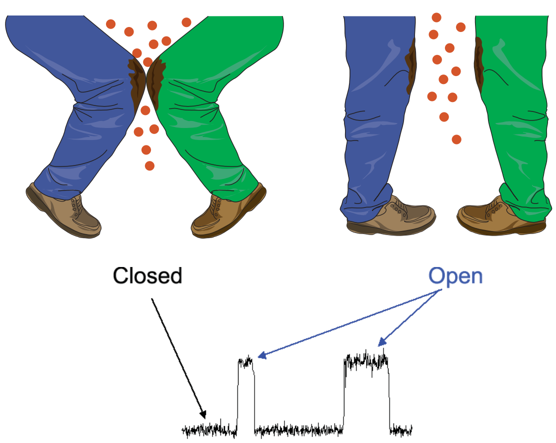
Dougherty & Lester, *Nature* 411: 252 (2001) © Macmillan Publishers Ltd. Miyazawa et al., *JMB* (1999) vol. 288, p.765. ©Elsevier Science Dougherty & Lester, *Nature* 411: 252 (2001) © Macmillan Publishers Ltd.

Building up a picture of a nicotinic acetylcholine receptor, from left to right: Five subunits arranged around a central channel make up the region that sticks out of the cell; an X-ray composite view through the central axis of the whole receptor; another composite view of the region inside the cell, showing the chamber and some of the windows; the protein structure of the α (yellow-green) and β, γ, or δ (lavender) subunits at the level of individual proteins, showing the position of the acetylcholine or nicotine binding site (π).



Acetylcholine binding energy was measured in frog eggs with unnatural receptors incorporating one to four fluorine (F) atoms, and plotted against the theoretical binding energy of these modified amino acids.

on immature frog eggs. In the eggs, we produced a series of acetylcholine receptors in which the side chain of a particular existing amino acid, number 149, was replaced by unnatural side chains that are like benzene except that either one, two, three, or four fluorine atoms have taken the place of some of the hydrogen atoms. The face of a benzene ring has a negative charge, so that it can attract the positive acetylcholine molecule, and fluorine makes this face less negative. Dougherty's group calculated the energy of the interaction between a positive charge and the modified benzene rings. When we plotted this calculated binding energy against an experimental measurement proportional to the binding energy obtained in our modified frog eggs, we noted a straight line. This is always exciting for a scientist, because it tells us we've guessed correctly what's happening. In this particular case, we're satisfied that we know to a precision of roughly half an angstrom where the acetylcholine molecule binds. It is near the face of the benzene ring that is part of the side chain at amino acid 149. We think that we will need this level of resolution to design better drugs for nicotinic acetylcholine receptors, and the so-called cation-π experiment that I've just related describes the best data presently available.

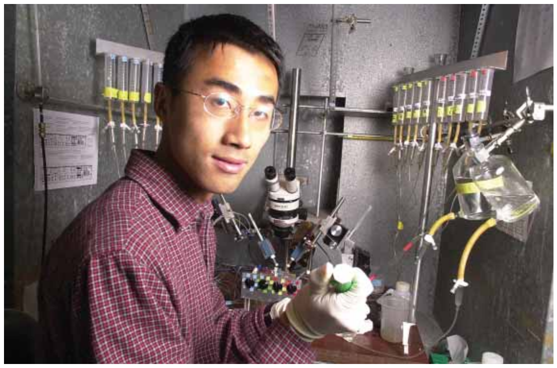


The gate of the receptor is made up of five rods, one from each subunit. When the channel is closed, left, the rods are bent like oily knees into the center of the channel. When acetylcholine binds they straighten out, right, allowing ions to flow through the watery gap that opens up.

About 50 angstroms below the acetylcholine binding site is a gate that opens and closes to stop the flow of ions on the axis of the channel, which you will remember is composed of those five nearly symmetrical subunits. Nigel Unwin of the Laboratory of Molecular Biology in Cambridge believes these subunits are shaped like five bent rods on the axis of the channel—rather like five Caltech professors standing in a circle with their knees sticking into the middle. When the channel is closed, the "knees" are quite oily and therefore won't let sodium and potassium ions through. But when acetylcholine binds, these five knees act with a coordination that might prove uncommon for professors: all five rods rotate, removing the oily knees and revealing a watery stripe in the channel. The sodium and potassium ions now face an environment resembling water rather than oil, and they obligingly flow through. The flow of sodium into and potassium out of the cell is an electrical current that provides the little ramps of voltage change that, in turn, eventually trigger nerve impulses in the postsynaptic cell. When the acetylcholine or nicotine leaves the binding site, the knees snap back into place, closing the channel again.

How do these angstrom-level movements, ion flows, and other biophysical events govern the biological process of nicotine addiction? Let's think first about what addiction actually is. Addiction means that someone will self-administer a drug

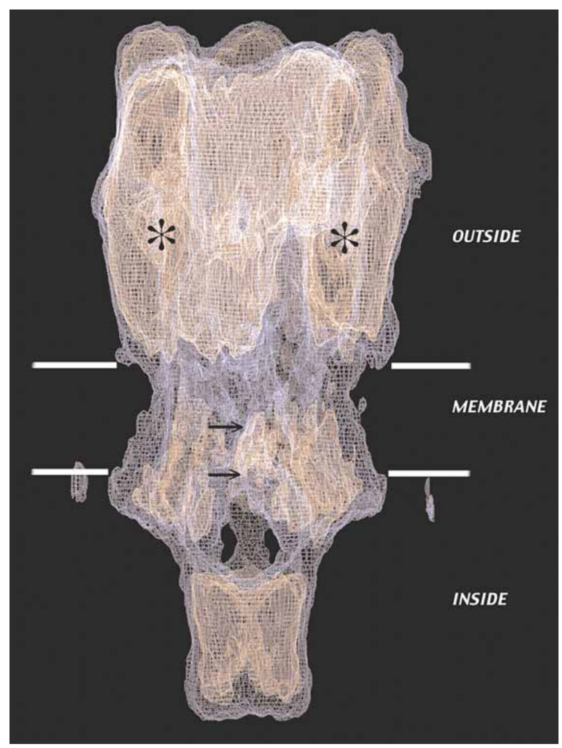
Graduate student Tingwei Mu recording the electrophysiology of a frog egg with unnatural amino acids incorporated into the receptors.



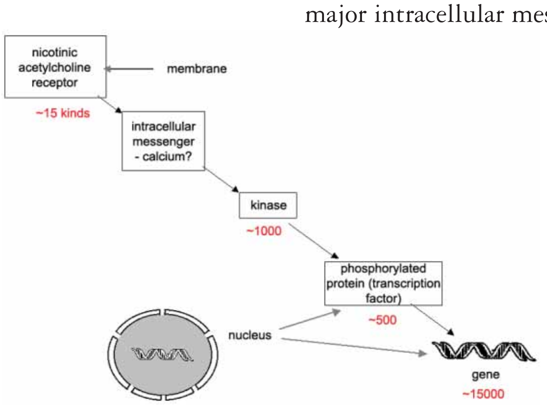
even though it might not be good for them, or at the expense of positive beneficial actions. A similar definition applies to animals. The gold standard for studying nicotine addiction in animals is an experiment called self-administration. A rat or mouse will press a lever to administer nicotine to itself, even though there might be food, or some other pleasurable activity, available. What physiological changes occur during these addiction processes, and how can we study them in molecular terms?

Biologists now believe that, like many other changes in an organism's behavior, addiction is caused by a process that links events at the surface of a cell to events at the level of the genes. This is called a "signal transduction pathway." Such pathways often lead to changes in the repertoire of genes expressed by the cell (each cell normally expresses a subset of the 30,000 or so genes in the human genome). "Changes in gene expression" is nearly synonymous with "new proteins are made," and these new proteins lead to changes in the cell's function. In the case of nicotine, the community has worked out some of the pathway. We know that a nicotinic acetylcholine receptor is activated, and that this leads to a small molecule that acts as an intracellular messenger. We don't know which one it is yet, but most researchers bet that the major intracellular messenger in this pathway is calcium, because when the channel opens up, some calcium flows into the cell along with sodium. Calcium then activates another kind of protein called a kinase, which (sometimes indirectly) adds phosphate to, and activates, a protein called a transcription factor. This binds to the DNA and changes the type and amount of genes expressed. It's a complicated pathway that still needs to be broken down into individual steps before we can understand it fully, but it's my personal bet that nicotine addiction will be the first addiction to be solved, because we already know so much about it. Knowing which molecules are involved will help us to design better pharmaceuticals that could interfere with or change the addiction.

Which nicotinic receptor starts the pathway? There are, in fact, about 15 different kinds of nicotinic acetylcholine receptors. How do we find the one involved in most of the responses to nicotine? Biologists approach this problem by using "knockout" mice. They identify a molecule that might be a good candidate, then isolate the DNA corresponding to the gene that codes for this molecule. In test tubes and cultured cells, the candidate gene is interrupted (knocked out) with another, easily detectable, marker protein, which is often a jellyfish protein that fluoresces green under

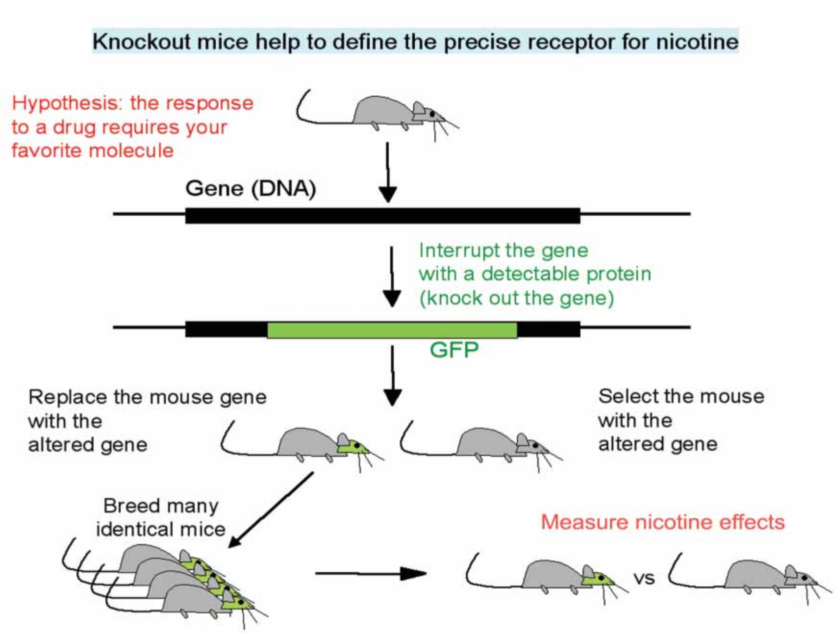


N. Unwin: The Croonian Lecture 2000. *Phil. Trans. R. Soc. Lond. B* (2000) 355 p.1813. ©The Royal Society.



Left: The probable signal transduction pathway for nicotine. Above: A neuroscientist's view of the entire nicotinic acetylcholine receptor. Asterisks indicate the sites where acetylcholine (or nicotine) binds. Within the membrane, the upper arrow points to the best guess of where the "knee" is, and the lower arrow points to the narrow part of the channel when it is open. Below this are the five windows through which ions flow into the cell.

UV light called green fluorescent protein. A strain of mice is then constructed carrying the altered gene and many identical mice are bred. This takes one to two years, so it requires a real commitment to do these experiments. Then—in the present case—they compare the effects of nicotine on the knockout and normal (wild-type) mice. This was done in several laboratories throughout the world in the 1990s, and the firm conclusion was that, of



the 15 or so nicotinic acetylcholine receptors, the most important receptor for nicotine addiction was the one with the classy name of $\alpha4\beta2$. (There are about 10 types of nicotinic α subunits, and about seven types of receptor β, γ, or δ subunits, and the full brain receptor may have two $\alpha4$ subunits and three $\beta2$ subunits, adding up to the five-subunit structure we discussed earlier.)

Can we go further in working out the pathway of nicotine addiction? We begin to have a problem when we try to do that, because there are about 1,000 kinases, 500 transcription factors, and 15,000 genes expressed in the brain. Sorting through these pathways by generating one genetically altered knockout mouse at a time would obviously be impractical. Therefore my research group, and other groups around the world, have adopted a different way of addressing the problem. We reasoned that instead of *eliminating* the response to nicotine, we would *accentuate* the response by making a hypersensitive nicotinic acetylcholine receptor that might emphasize the pleasure pathway, and allow us to find behaviors and molecules that are easily observable. By making changes to that oily knee, we set about designing an $\alpha4\beta2$ receptor that was hypersensitive to acetylcholine. We found that the less oily we made the knee, the longer it wanted to stay open rather than closed, so that we were able to design receptors that stayed open not for the normal 1 or 2 milliseconds, but for 20 or even 200 milliseconds. We produced a series of receptors with progressively less oily, more watery knees. Designing these and testing them in frog eggs is quite quick, only taking a month or so, but the next step, generating a mouse strain with the receptor, takes about two years. In contrast to the knockout procedure, these mice are called knock-ins.

What is the behavior of these hypersensitive knock-in mice? They are rather anxious, for a start. There are some classic tests for anxiety, and one is to put the mouse in a box with mirrors—mice like to be alone, and avoid such boxes. The hypersensitive mice avoid the mirrored box more than usual. They're also sedated by nicotine injections some hundredfold smaller than those that sedate normal mice. In a sense they act as though they're already addicted to their own acetylcholine, though it's not an analogy I'd pursue at the moment. When they're given slightly larger amounts of nicotine, an interesting behavior occurs. If you have a cat, you may have noticed that when you open a can of cat food, it sticks up its tail, and the tail quivers a little. This is a response associated with pleasure called a Straub tail, and it's a very nice response to score in a mouse because it doesn't hurt it. Our hypersensitive mice display an abnormally strong Straub tail response in response to low quantities of nicotine.

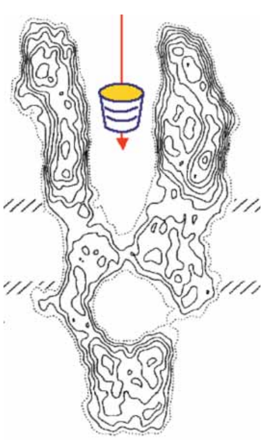
Do these hypersensitive mice self-administer extremely small amounts of nicotine? It's a bit embarrassing to admit this, but we don't know yet. Giving a seminar about your own research is a bit like buying a new computer—you'd always rather wait another six months. Although we don't know the answer to the question yet, these hypersensitive mice have already revealed a lot of other interesting characteristics.

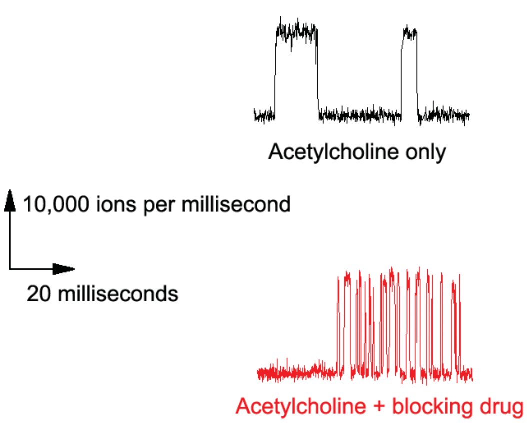
A hypersensitive mouse sports a Straub tail after a small amount of nicotine.

A knock-in mouse that might have the same mutation in one of the receptor subunits that causes ADNFLE epilepsy in humans.

While we were working on generating these strains of hypersensitive mice, neurologists in Melbourne, Australia, were defining a newly recognized human disease called autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The name basically says it all: autosomal means it's inherited through one of the chromosomes other than X and Y; dominant means that only one copy of the altered gene is enough to cause the disease; nocturnal means that these seizures occur at night; and frontal lobe means they start in the forebrain. Seizures arise during non-REM sleep, and begin with the sensation called an aura that many epileptic patients describe, which is why they're often confused with nightmares rather than diagnosed as seizures, especially in children. As you may already have guessed, some ADNFLE patients carry a mutation in the $\alpha 4$ subunit of the nicotinic acetylcholine receptor, and others have a mutation in the $\beta 2$ subunit. Furthermore, the mutations occur very near the oily knee that holds the channel open or closed for varying amounts of time.

Channel blockers work by binding in the receptor channel and desynchronizing the electrical signals in the cell.



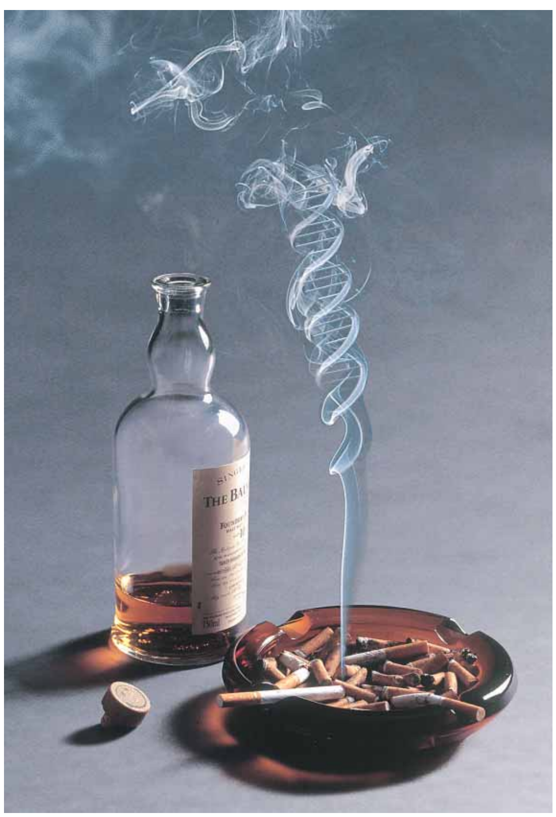


Are the receptors of ADNFLE sufferers like knockouts—nonfunctional nicotinic acetylcholine receptors—or are they like hypersensitive knock-ins and excessively functional? We had one big clue: although ADNFLE can be controlled only partially in children, it *can* be controlled in adults with channel blockers. These are drugs that enter the receptor and bind in place of acetylcholine, like a cork plugging a drain, and prevent current flow. This desynchronizes the electrical signal in the cell, so that it can't efficiently activate nerve impulses further on down the line. A channel blocker would block a hypersensitive receptor, which opens for too long, but wouldn't have any effect on a knockout receptor, which would never open, so this is an indication that ADNFLE patients have probably got hypersensitive nicotinic acetylcholine receptors.

So are our hypersensitive knock-in mice prone to nicotine-induced seizures? There's no doubt they are, as my postdoctoral colleague Carlos Fonck has shown. About 40 percent of human epilepsies are inherited, and many can't be controlled by drugs, so it would be a wonderful opportunity to have an animal model for one form of epilepsy that begins with an understood mutation in a gene, which leads to a change in the function of a membrane protein, which results in a change in the function of a nerve cell, and ultimately gives us an understanding of what's happening in the neuronal circuit. We've already generated knock-in mice that have the precise mutations that cause ADNFLE and we're looking forward to working with them.

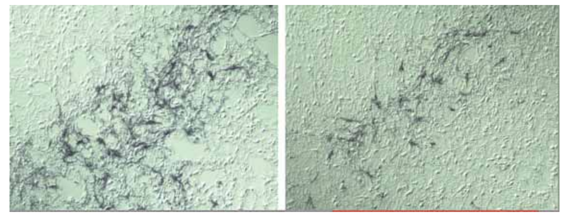
Our knock-in mice could also be useful for research into Alzheimer's disease. Nerve cells degenerate in this disease, including some that make acetylcholine directly. The most successful Alzheimer's drugs now on the market are cholinesterase inhibitors. These block acetylcholinesterase, thereby helping to prolong the action of any acetylcholine still being secreted by the remaining nerve cells. Allan Collins of the University of Colorado suggested to us that if our hypersensitive mice were very sensitive to acetylcholine, they ought to respond to the increased amounts present when treated with these drugs. So we administered galantamine (Reminyl) and tacrine (Cognex), and the mice did indeed respond quite sensitively in the Straub tail assay. But I doubt that we'll make major progress on Alzheimer's disease using these particular mice, because the present research on this disease is concentrating on the way to prevent or decelerate cell death.

Now let's turn to alcohol. Some 80 percent of alcoholics are smokers. What's the common link? At this point, even the most enlightened people are tempted to shrug and invoke either moral or psychological phenomena. But psychology and moral reasoning both occur in the brain, and are now actively being investigated by neuroscientists. And there are multiple reports of genetic links between smoking and alcoholism. It's also probable that alcohol affects the same dopamine pleasure system as nicotine, opium, and amphetamines. We were interested to find that our hypersensitive mice are "cheap drunks"—they respond quite sensitively to alcohol, although they were generated by manipulations of *nicotinic* receptors. For instance, a much lower dose of alcohol is needed to calm a startled hypersensitive mouse than a startled normal mouse. We're interested in pursuing this link.



Eighty percent of alcoholics are smokers. What's the link? Photo illustration by Larry Harwood and Julianne Snider for the *Coloradan*, of the University of Colorado at Boulder.

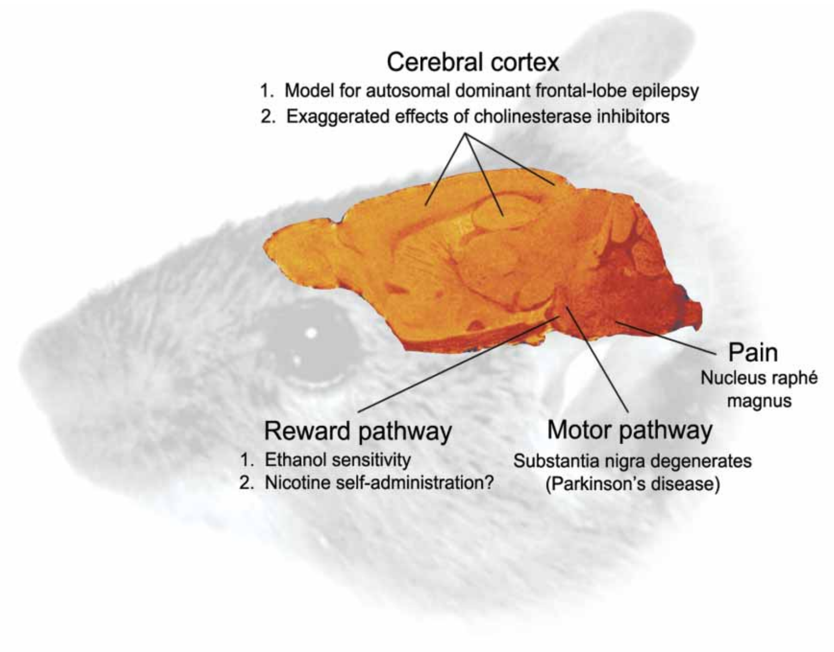
The most hypersensitive mice also have fewer nerve cells that make dopamine (stained black, right panel) than normal mice (left panel).



Labarca et al., *PNAS* (2001) 98, p.2786 © The National Academy of Sciences.

In addition to the dopamine-producing cells of the pleasure/reward system, the only other major group of nerve cells that produce dopamine is located nearby in an area called the substantia nigra. The dopamine-producing cells of the substantia nigra help to set the activity level of a motor pathway that controls movement, and it's these nerve cells that degenerate in Parkinson's disease. The causes of this degeneration are still unknown, but there is no obvious genetic link, as only a very small fraction of cases are inherited. A persistent finding is that smoking appears to protect against it (yes, you *have* read correctly). Caroline Tanner of the Parkinson's Institute in Sunnyvale, California, has reported on a set of 43 identical pairs of twins distinguished by the fact that only one member of the pair had Parkinson's disease. In the 33 of these so-called discordant twin pairs containing at least one smoker, the twin without Parkinson's disease smoked an average of 10 pack-years (if a person smokes half a pack per day for four years, he has added two pack-years to his total; and so on) more than the twin that did not. We don't even know whether the protective effect of smoking involves nicotine itself or another component of smoke. However, on the theory that a nerve cell's adjustment to slight excess stimulation underlies the protective effect of smoking, a couple of drug companies are already working on drugs for Parkinson's disease based on derivatives of nicotine.

Our most hypersensitive mice—the ones that have the most watery amino acid at the knee and keep their channels open the longest—are born with few if any of the nerve cells that make dopamine. They seem to have degenerated even before the mice were born. These mice thus have a neonatal form of Parkinson's disease. We've traced this effect to the fact that the dopaminergic cells die from overstimulation. They're so sensitive to endogenous acetylcholine that their channels are constantly open, allowing sodium,



Mice hypersensitive to nicotine could help research into a variety of medical conditions affecting different parts of the brain.

calcium, and potassium ions to flow in and out. The cells completely exhaust their energy stores trying in vain to restore these ions, and as a result, they die. This phenomenon, called excitotoxicity, is thought to underlie several degenerative diseases. To study it further, we'd like to adjust the system. We don't want a mouse that never succumbs to Parkinson's disease; that's not a disease model. We don't want a mouse that dies at birth; that's not an appropriate model for Parkinson's disease. We want a "Goldilocks mouse," one that would acquire Parkinson's disease as an adult.

Finally, I'll note some work relevant to pain done by John Daly and his colleagues at the National Institutes of Health. Nearly 10 years ago, they studied the skin secretion from a poisonous South American tree frog, *Epipedobates tricolor*. This extract induces the Straub tail in mice, and Daly tracked the effect down to one particular molecule in the secretion, called epibatidine. Epibatidine has a structure similar to nicotine; it is the most potent known activator of some of the nicotinic acetylcholine receptors, including the $\alpha 4\beta 2$ receptor; and, most interestingly, it is a very effective painkiller (nicotine is also an analgesic). This story caught the attention of several drug companies, who are testing painkillers based on nicotine derivates. Sure enough, our hypersensitive mice are also exquisitely sensitive to the analgesic effects of nicotine.

I have been studying nicotinic receptors at Caltech since 1973, with colleagues born in 36 different countries. The research has been supported by the National Institutes of Health, the Sidney Stern Foundation, the Plum Foundation, and the Keck Foundation, as well as by California's 25-cents-per-pack tax on cigarettes. But a couple of years ago, the epibatidine story caught the eye of Paul Simon, whose song "Señorita with a Necklace of Tears" has the following verse:

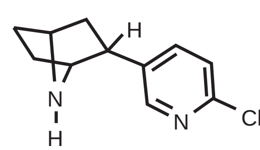
> Nothing but good news
> There is a frog in South America
> Whose venom is a cure
> For all the suffering that mankind
> Must endure
> More powerful than morphine
> And soothing as the rain
> A frog in South America
> Has the antidote for pain
> That's the way it's always been
> And that's the way I like it *

We need to brainstorm about endowing this research with the royalties from a song. □

Bren Professor of Biology Henry A. Lester came to biology from a background in the physical sciences. After a degree in chemistry and physics from Harvard followed by a PhD in electrophysiology from Rockefeller and two years of research at the Pasteur Institute in France he came to Caltech in 1973 to continue in this field, but over the last 20 years he has also embraced biochemistry, molecular biology, and, more recently, neurogenetics. On campus, he is one of the few professors known to all the undergraduates, because every year he introduces another 180 or so freshmen, many of whom have no previous knowledge of biology, to the required course "Drugs and the Brain." This article was adapted from a Watson Lecture given in October 2002.

PICTURE CREDITS: 16, 18, 20, 25 – Doug Cummings; 18, 20 – Dennis Dougherty; 18, 21-23 – Bob Paz; 25 – Russell Jacobs; 25 – J. De Leeuw, Belgian Herpetological Society

The South American tree frog *Epipedobates tricolor* secretes epibatidine, a powerful painkiller with a chemical structure similar to that of nicotine.



* "Señorita with a Necklace of Tears" was written, arranged, and produced by Paul Simon, and is on the album *You're the One*, © Paul Simon Music (BMI), 1999, 2000.

Countering Terrorism: The Role of Science and Technology

A Personal Perspective

IMAGE NOT LICENSED FOR WEB USE

Los Angeles Times photo by Luis Sinco

by Jesse L. (Jack) Beauchamp

On January 1, airports all over the country began sprouting SUV-sized CT scanners to screen passengers' checked baggage for explosives, part of a federally mandated plan to beef up aviation security. Los Angeles International Airport was up and running, with 58 of the new CT screeners and 270 smaller scanners to detect traces of explosives, on the first day of the new year. The lines at the Tom Bradley Terminal stretched out the door (above). Jack Beauchamp's October Watson Lecture foreshadowed this next level of security and explained the research that went into these machines (and subsequent instruments still in development)—and how they work.

The terrorist threat is a real one. The ease of travel and the access to explosives technology make the terrorist's job a fairly easy one, especially when he's willing to die to accomplish his objectives. And there's a broad spectrum of financial supporters for terrorist activities, which gives factions the ability to strike at any desired target.

In countering such threats, we have so far been mainly reactionary—responding to wake-up calls when terrorists strike. It would be better if we could get out of this mode, if we could anticipate the bad guys and prevent them from carrying out

It's clear from the intentions of Congress and the White House that we're embarking on an enormous program with an R&D budget of around $36 billion to do the best we can.

their intended activities. This is a tall order, but it's clear from the intentions of Congress and the White House that we're embarking on an enormous program with an R&D budget of around $36 billion to do the best we can.

We have had several wake-up calls already. In 1988, an explosion blew Pan Am Flight 103 out of the skies, killing everybody on board. Forensic work, including careful reconstruction of the aircraft, determined the amount of a common type of explosive that was able to destroy the plane. This information has helped define some of the parameters that are used in the certification of explosive-detection systems in airport security today.

A second alarm went off in February 1993, when a first attempt to bring down the World Trade Center failed. Ramzi Yousef, the mastermind behind this scheme, was also implicated in a complex plot to blow up as many as 11 U.S. aircraft simultaneously over the Pacific Ocean. This wasn't even a suicide mission (nor was Pan Am 103). The terrorists practiced on a flight in Southeast Asia; the bomb was to be planted by a passenger flying a short leg of a flight before the aircraft's departure to either Hawaii or the continental United States. Those involved with the plot were aware of the security precautions and planned their attack to avoid detection. They carried the components on board and assembled the bomb in the bathroom; it was then left in the life preserver under a seat. On the next leg of the flight it exploded, killing a Japanese businessman. But the aircraft was not destroyed, and the larger plot was discovered and thwarted.

Another significant event occurred in 1995, when the Aum Shinrikyo group planted sarin gas, a nerve agent, on five Tokyo subway trains. Only a dozen people died, but several thousand were hospitalized, and it's fortunate that the event did not lead to far more deaths than it did. But we also need to note that this group experimented with a variety of biological agents, as well, and carried out one anthrax attack. Aum Shinrikyo was even able to finance a group of doctors and nurses to bring back the Ebola virus from Africa. It's not known whether or not they succeeded, but this is pretty scary stuff.

When the Murrah Federal Building in Oklahoma City was destroyed by a truck bomb in 1995, 168 died. And in 1998, terrorists were able to mount a coordinated attack, ramping up the stakes in this game by simultaneously bombing two United States embassies in Africa and killing 224. Then terrorists attacked the USS *Cole* while it was refueling in Yemen in 2000.

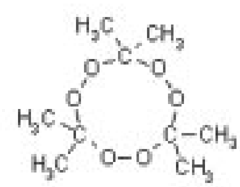
And then came September 11, 2001. About 2,800 people died (compared to 2,400 at Pearl Harbor). I think this event is going to continue to have an impact on the way we live for the next few decades. Potential targets are abundant.

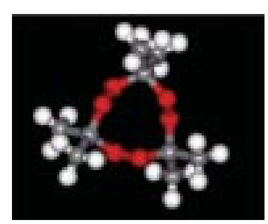
All involved with security have their own favorite list of targets. I have some of my own that I won't even mention here; they would be so disastrous and so easy to do that I'd feel terribly responsible if someone actually went out and did one of them. Among potential objectives already widely known, big buildings will continue to be tempting, easy targets. The Federal Aviation Administration (FAA) provides a conveniently downloadable map on the Internet of numerous other sites, called "temporary flight restrictions." They include nuclear power plants, national laboratories, even the president's ranch. Then there are dams, large airports, the air-traffic-control system, large public gatherings, public figures, the banking and economic sector (remember *Goldfinger*?), energy supplies (for example, the unprotected pumping stations along the Alaska pipeline, a map of which you could find on the Internet until a year ago), and last but not least, the Internet itself.

As for the latter, we're becoming increasingly dependent on the Internet for absolutely everything. Unfortunately, "everything" includes material that actually aids terrorism. If you want to read what the bad guys read, you can search for *The Terrorist's Handbook* and download a copy of it. It will tell you how to build bombs and how to make the explosives that go into them (if you can't acquire them elsewhere). It will also tell you *how* to acquire them elsewhere: just walk over to the chemistry laboratory at any nearby university, go into the stockroom, and load up your backpack with all the ingredients you need to make high explosives.

What brought this to everyone's attention was the shoe bomber, Richard Reid, who claims that he used a recipe from the Internet to fashion his infamous sneaker bomb. It has been reported that the molecule he prepared—we'll do a little chemistry now—is triacetone triperoxide (TATP). It can be made from hydrogen peroxide, which you can buy from the local pharmacy; acetone—not the type for fingernails, but the paint-thinner

Triacetone triperoxide, or TATP, the shoe bomber's explosive of choice, is easily concocted at home.





Above: The author and his wife, Patricia (also a pilot), love to fly to remote places. Here they camp under the wing of their Cessna 172 in Alaska's Denali National Park. Below: The virtual cockpit of a Cessna 172 on Microsoft Flight Simulator, which can teach you how to fly a plane with your feet still on the ground.

variety available in any hardware store; and a small amount of hydrochloric acid (sulfuric acid will also do). Then you can log onto the Internet and easily find several procedures for combining these ingredients to synthesize TATP. Some are, I would say, quite a bit safer than others, so you might want to consult with your chemist friends. So you don't need a Caltech degree in chemistry to make a compound that has essentially the same power as RDX, the principal component of plastic explosives. What Richard Reid didn't know, as he tried to strike a match to ignite his TATP-lined shoes, was that it's very shock-sensitive. If he had simply stamped his foot, he and the plane might have been history.

I find it interesting that the Bureau of Alcohol, Tobacco and Firearms (ATF), which has responsibility for classifying explosive materials, added this chemical to its list of explosives only this past year, even though it's been used by terrorists and others for nearly two decades and has been known for more than a hundred years. But they finally admitted that, yes, this is a dangerous explosive.

If science and technology are, to some degree, at the terrorist's disposal, what can science and technology contribute to *prevent* or mitigate future terrorist attacks? This is a broad field that I can't begin to cover here, so I'm going to limit myself to the threat to commercial aviation, in which I have some experience.

How did I get involved with aviation security? I'm a chemist. Right now my main interests lie in developing advanced methods for sequencing proteins in the gas phase. But my wife and I are both pilots. We love to fly, and we keep our little airplane at the El Monte Airport.

So, how hard is it to actually fly an airplane? Can anybody—a terrorist, say—just climb into an airplane and learn to fly it? Well, if you'd like to give it a try without the expense of buying a plane or even renting one, you can get yourself a copy of Microsoft Flight Simulator. This is advertised as being as real as it gets, and it's extremely good. The behavior of the "airplane," when you "fly" it, is very close to the real thing. And the simulator gets terrific gas mileage compared to my plane.

One of my graduate students accompanied me on a trip from Pasadena to northern California for a meeting. He had never been in a small plane before, but he had played with Microsoft Flight Simulator. He got in the plane, took off, and flew it all the way to Monterey, performing the navigation as well. And the flight simulator isn't just based on a Cessna 172 like mine, but also includes large aircraft such as a Boeing 737.

Are small planes tools for terrorism? We've seen that a 757 can cause significant damage, but what might one do with a small aircraft? A 1993 Office of Technology Assessment report published a study of the dispersal of 100 kilograms of anthrax spores, which a crop duster could carry on a single flight. The researchers estimated about half a million deaths would result from spraying that amount of anthrax over Washington, D.C. So the answer is yes. The news media reported that four of the hijackers involved in the September 11 attack actually applied for a loan—I think it was from the Department of Agriculture for about half a million dollars—to modify a crop duster. I've never seen a copy of that loan application, but I'd be interested in what they said they were planning to do with it and what the modifications were.

In the early 1990s, having been a pilot for a decade and interested in aviation and the air-traffic-control system, I got involved in developing new mass-spectrometry methods for the detection of explosives. (I'll tell you more about this later.) This combination led to my nomination as chairman of the National Research Council Committee on Commercial Aviation Security, a post I held (succeeding John Baldeschwieler, the Johnson Professor and Professor of Chemistry, Emeritus) from 1993 to 1997. When the explosion on TWA Flight 800 was initially thought to be a terrorist event, President Clinton formed the White House Commission on Aviation Safety and Security, also known as the Gore Commission, after its chairman. I was also appointed to that group, which focused on three specific areas: improved

The National Research Council Committee on Commercial Aviation Security (Beauchamp is in dark shirt, bottom row, left), established in the early '90s, convened here in Atlanta during the 1996 Olympic Games.

aviation security, improved aviation safety (reduction in fatalities due to pilot or crew error and air-traffic-control failures), and improved aircraft reliability (reduction in failures of components and systems). On the whole, aircraft are extremely reliable. Pilot error is a problem; over the last 20 years, pilots have actually killed more people than terrorists have, including all the deaths at the World Trade Center and the Pentagon. But aviation security was our most urgent focus.

We spent six months traveling all over the world, studying what other countries do to protect their aircraft. I spent a week in Israel learning what they do. Theirs is a very different problem, but they have a lot of experience and know-how that we have been able to benefit from.

Early in 1997, the White House Commission submitted its report to the president, who asked the secretary of transportation to implement the recommendations. There's a lot of inertia in Washington's bureaucracy; things get done slowly, if at all. One of the recommendations was to complement technology with automatic passenger profiling. The idea is that most passengers, frequent fliers and families, can be easily defined as being of little or no risk, leaving just a small group of people who merit additional attention. For the most part, this can be done using computer databases. Although progress has been made on this recommendation, the system was not to my knowledge implemented on September 11.

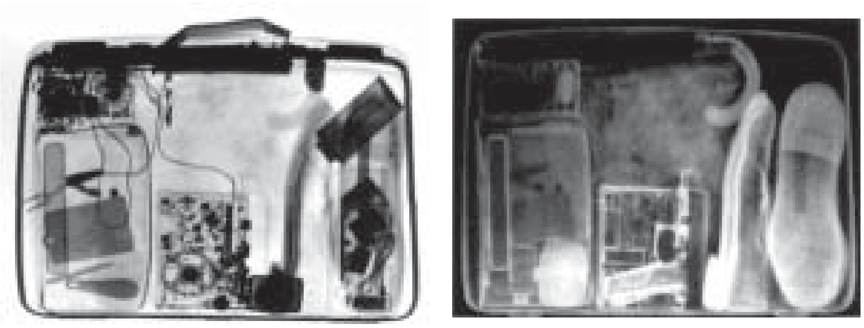
If science and technology are, to some degree, at the terrorist's disposal, what can science and technology contribute to prevent or mitigate future terrorist attacks?

Another of the recommendations was to give properly cleared airport security personnel access to classified information that they need to know. Airlines have been told what to do and not why they're being asked to do it. There needs to be something in between to provide airlines with more information about the nature of a threat so that they can design more effective responses. And that's still a problem.

Let's take a look at aviation security, some of the issues involved, and some of the newer technology. I'll try to explain how some of the security equipment works so that you can impress your friends the next time you're in line at the airport. Aviation security mainly involves screening passengers, their carry-on bags, and checked luggage. Each poses different problems. We need to screen passengers for weapons or explosives. Passengers and carry-on luggage need to be checked rapidly because people tend to board aircraft at the last minute. Checked luggage offers the best opportunity to put a large explosive device onto an airplane. There are a lot of issues associated with checked luggage that I'm not going to discuss here. One of the most important is determining that every suitcase belongs to someone who is also on the plane. Referred to as bag-matching, this is a very difficult problem. Cargo and mail carried on an aircraft also need to be checked.

Detection of explosives in the airport environment presents two distinct problems: bulk detection and trace detection. You need some means to detect a big chunk of explosives and to say, "Yes, there is very likely a bomb there. Let's not let that suitcase or that person on board the plane." Trace detection, on the other hand, involves looking for evidence of bomb making, such as small bits of explosives remaining on a person's hands or clothes. And we'd like to be able to detect chemical and biological weapons as well.

What are the recent scientific and technological developments that enhance aviation security? We are all familiar with the monitors that have been x-raying our carry-on bags ever since airport



Most x-ray scanners currently in use in airports employ an x-ray source on one side of a bag and a detector on the other to generate what is called a transmission image (left). X-rays bounced back (backscattered) through the same bag to a second detector provide much more information, in this case a plastic gun (right).

Backscattered x-rays aren't used on airline passengers in the United States (most people would object to an instrument that can essentially strip them naked), but they can illuminate hidden weapons very clearly, as the man above demonstrates—a metal gun and and a scalpel blade in the front view and a metal file, plastic knife and plastic gun (a Glock 17) in the back. Backscattered x-rays can also pick out illegal aliens being smuggled in a truckful of bananas (right). (Images on this page courtesy of American Science and Engineering.)

screening procedures were established as the result of the hijackings in this country in the '70s. The screeners look at a bag in a single-view x-ray image in *transmission*. This means you have an x-ray source on one side of the bag, a detector on the other, and you look at the transmitted x-rays, just as with a chest x-ray.

Technology has brought a lot of improvements in x-ray equipment. We now have inexpensive, high-resolution displays and also false-color images. The latter doesn't display a greater amount of information, but it's less boring to look at and helps keep the screeners on their toes. Another technique to maintain operator alertness is called TIP—Threat Image Projection—in which an image of, say, a gun, is inserted into a bag electronically, just to see if the operator is awake. The system allows the operator to determine that the object is not real (a green light flashes when a button is pushed) before he calls the security guards over.

Monitoring equipment can also use x-rays of two wavelengths, which allows you to discriminate based on atomic number. It's more complex, but you get more information out. This would be useful, for example, for finding a detonator based on a lead salt. Unfortunately, you can now buy organic detonators that don't even have metal housings. They're made of paper.

Backscattered x-rays are extremely useful to augment the information you get in an x-ray image. Instead of looking at the x-rays transmitted through the bag, you look with a second detector at the x-rays that are bounced back through the bag again. If you look at the bag with a transmitted x-ray (far left), you can make out various things—a radio, a shoehorn, shaving cream. But can you see a gun? If you look at the same suitcase with backscattered x-rays (left), you can see a plastic pistol. More information is always a good thing. We will start to see more of these scanners in airports soon.

The backscattered technique can also be used to examine large things, such as cargo pallets. Typically, unless you have very high-energy x-rays, you can't penetrate a truck or cargo pallet sufficiently to look inside for the presence of bombs or weapons. But backscattered images can be quite revealing. The image below is from an x-ray system installed at a border-crossing checkpoint between Guatemala and Mexico. The driverless truck has moved through the scanner on a conveyor belt to give it a smooth transit speed past the x-ray source and the detectors. Hidden in the load of bananas in the truck, you can see compartments containing people being smuggled across the border and unknowingly receiving a dose of x-rays.

You *can* use backscattered x-rays on people at very low intensity. They're reflected by the skin and penetrate clothing reasonably well. They're used in prisons to prevent the importation of drugs and weapons, but we haven't yet put them in airports in this country. Since the scanner can see through your clothes, there's a privacy issue to be considered. But in the image at left, you can see that this person has a gun on his thigh; he has a file on the back of his thigh; and in the small of his back he has a Glock 17—a favorite plastic weapon used to avoid metal detectors. Other technologies provide similar imaging capabilities without employing x-ray exposure, which would likely not be accepted by the general public. One such approach generates an image using millimeter waves, but it's expensive and still in development.

Luggage is easier to bombard with radiation than humans are, and suitcase scanning has seen many improvements in the last decade. After Pan Am 103, the FAA Technical Center began investing $20–50 million per year in research and development, doing some of it in-house but mainly providing grants to small businesses and to university researchers to develop the technology and equipment for detecting explosives and weap-

ons. What came out of all this is based on medical technology, specifically CAT scans.

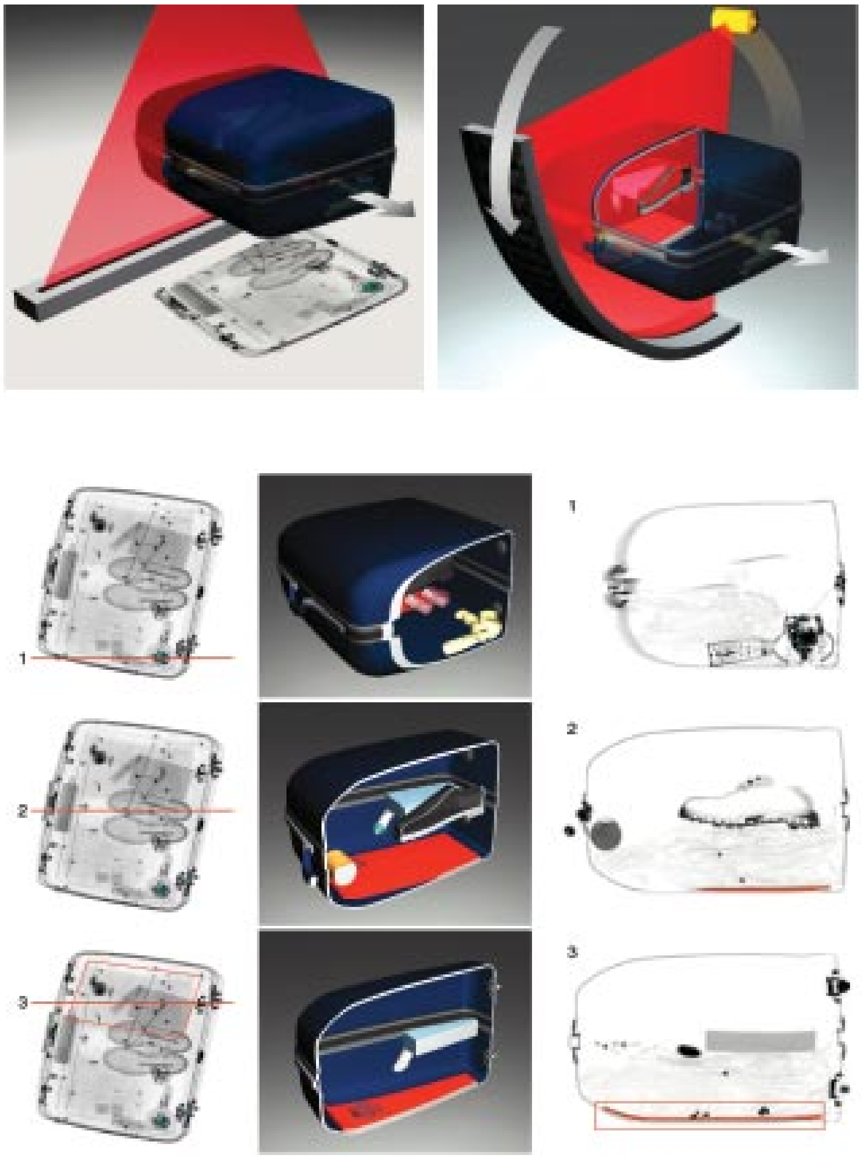
The InVision CTX 5500 x-ray scanner, an automated explosive-detection system, gives the operator a red light if it observes what might be a bomb in the suitcase. This could be a false alarm. For certification of automated explosive detection equipment for checked baggage, the FAA requires high throughput; a high probability of detection for different explosives in different configurations (some are very easy to detect, while others are difficult); and a low probability of false alarms. If you crank up the probability of detection, you're also going to increase the probability of false alarms. If you want to reduce false alarms, you pay the price of a lower probability of detection.

This scanner weighs about a ton and has a gantry that rotates at 60 rpm. It has an x-ray source and a series of detectors that allow it to look at the absorption of x-rays simultaneously over a broad fan. The instrument is rotated around the target, recording data as a function of angle; then you use that information in a fast computer to reconstruct an image of the object, just like a medical CAT scan looking at cross sections of a brain. The quantity of interest is actually the linear attenuation coefficient of the object, which you can obtain for each "voxel," or volume element.

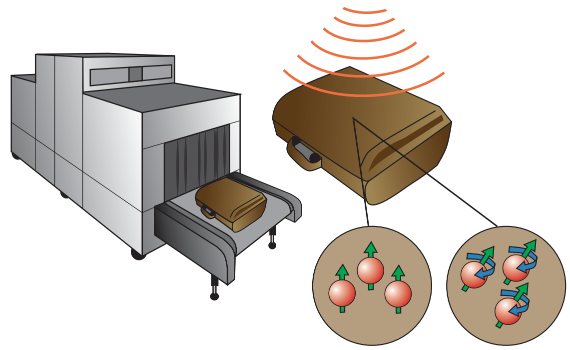
These coefficients are then used to calculate what is known as the CT number—an arbitrary definition that just gives you a scale. Some common CT numbers are: air, –1,000; water, 0; dense bone and metal would have CT numbers of around 3,000. You can determine certain types of bone disease by looking at the CT number. Explosives also have specific CT numbers, which I'm not allowed to tell you here, but they fall in a fairly narrow range. We would like it very much if these CT numbers didn't overlap with the CT numbers of any other common substances.

At left are CT images of a suitcase, showing cross-sectional slices of it as it moves through the CT scanner. You can see a sheet of plastic explosive in the bottom. This is one of the most difficult types of explosive to detect, because it usually conforms to the shape of the suitcase and it's sufficiently thin that it doesn't attenuate x-rays to any significant amount in a transmission image. Once you have identified a suspicious object, you can go back and take many more slices and reconstruct the full shape of the suspected explosive.

The latest version of the CT scanner is the InVision CTX 9000. This particular instrument has been certified at 542 bags per hour, to my knowledge the world's fastest. That means that it has about six seconds to detect a bomb reliably. I know it's been certified for this speed, but I think it's unlikely that this performance will be achieved in actual airport use. One of the reasons I'm doubtful is that the bags the FAA uses at their test center are lost luggage kept in storage lockers. As



A transmission x-ray image of a suitcase (left) produces a flat, two-dimensional view of the contents and cannot detect the sheet of explosives lining the bag. In the InVision CTX 5500 scanner, the x-ray source and detectors are rotated around the suitcase (top, right), creating multiple slices of data that a computer can reassemble into a three-dimensional image. These data also deliver information on the composition of the bag's contents; the characteristic "CT number" of plastic explosive exposes the hidden sheet of this material on the bottom of the piece of luggage (red). (Illustration courtesy of InVision Technologies.)



Left: A quadrupole resonance scanner, a variant of an MRI scanner, bombards a suitcase with radio frequency pulses, which excite the quadrupolar nuclei (among them nitrogen and chlorine, common in explosives) and cause them to align and precess at a particular frequency. When these relax back to equilibrium, an echo signals a receiver coil. Each explosive's signal is unique (left, below), as is that of heroin.

you might guess with unclaimed luggage, they don't contain a lot of consumer electronics. This removes much of the clutter that makes it difficult to tell whether an object that has been flagged as a bomb is, in fact, a bomb. In a real situation, you're looking for components—the detonator, the timer, the power supply for the detonator—and when you have electronic clutter, it's difficult and more time-consuming to pick out those components.

Another thing removed from these lost suitcases is food. Unfortunately, it turns out that a number of food products have CT numbers similar to common explosives. Clearing false alarms from, say, smoked salmon from the duty-free shop, may mean significant delays.

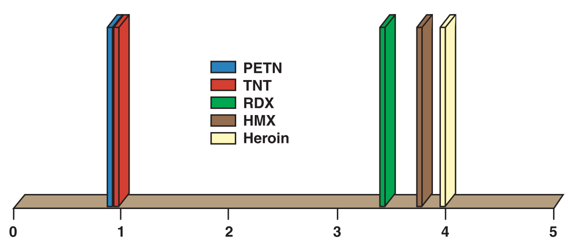
There are also other technologies that could be employed, but there are problems of practicality with all of them. One that still looks promising (although it requires a controlled temperature-and-humidity environment to function well) is a device called a quadrupole resonance scanner. It doesn't make an image like an x-ray scanner; it detects the total amount of substances that have quadrupolar nuclei. That includes nitrogen and chlorine, chemical components of numerous explosive materials. The instrument bombards the bag with radio frequency signals at a particular frequency, causing the alignment of quadrupolar nuclei. An echo occurs as these relax back to a thermal population distribution, inducing a signal in a receiver coil. You can see resonances (right) associated with a fairly wide range of explosives, including PETN, TNT, RDX, and HMX. Certain drugs, such as heroin, can also be detected—a convenient byproduct of numerous explosive-detection technologies.

Another method, impractical for a variety of reasons, involves coherent x-ray scattering, which gives information on molecular structure that can then be used as a fingerprint to characterize different explosives. This might turn out to be quite useful for resolving false alarms.

Neutron scattering is very appealing, especially to physicists, because it would likely provide employment for a PhD physicist in every airport in the country. But for practical reasons, you don't want to have neutron sources in airports because they are large and require shielding. And the quality of the images and the information is still not quite good enough to be useful.

One simple solution is just to contain a potential explosion in checked luggage with containers made of high-tech polymers instead of the flimsy containers that you see being pushed around airports today. This would significantly increase the cost of the containers, but it's a one-time investment that could save lives.

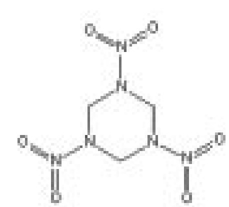
I don't think dogs are very practical for detecting explosives in airports. It remains controversial what they actually "smell." I think, though, that they have a tremendous deterrence effect, and for that reason alone it's probably worth having them. Now, if you could figure out the olfactory process and mimic it with an electronic nose, you'd save a lot on dog food. And electronic noses would work 24 hours a day without trainers. Nate Lewis, Argyros Professor and Professor of Chemistry, is working on just such a device, but an airport model is still on the horizon.

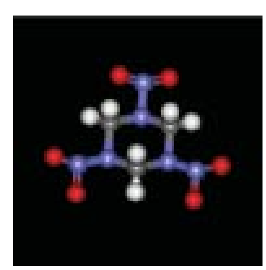


An electronic nose might also be useful in screening passengers for trace amounts of explosives. A trace amount doesn't necessarily mean that a person has been involved with making an explosive device that he's trying to sneak on board. He might be a law-enforcement agent or somebody who loads his own shells for hunting; plastic explosives are also used in some mining operations.

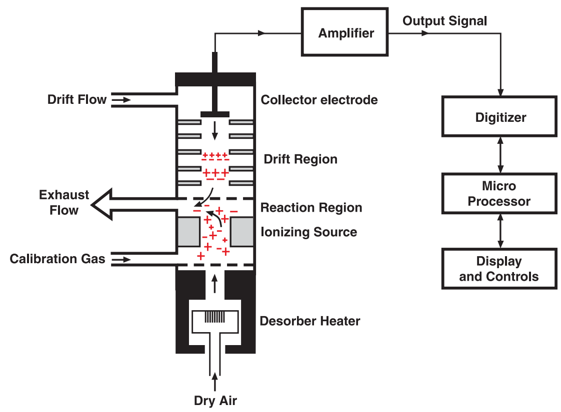
Now, in trace detection there's one molecule that's important to target: RDX, or cyclonite, which is the main component of plastic explosives. It's very involatile. In air at room temperature, it's only one part per trillion, so you have to have a very sensitive detector to be able to spot it. What's used in airports is an ion mobility spectrometer. It works incredibly well in detecting and identifying both explosives and narcotics. A pad that's been wiped on your computer or your suitcase is then heated to release the sample into

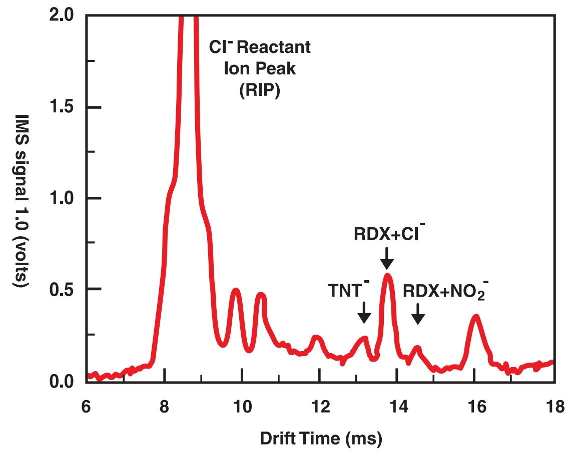
RDX, or cyclonite, $(CH_2)_3N_3(NO_2)_3$





Right: An ion mobility spectrometer can detect traces of explosives. The sample, wiped from a suitcase, is heated, ionized, and sent through a drift tube, which sorts the ions by size. The data from the detector (far right) show the presence of RDX, which attaches a chloride ion in the ionizing source.

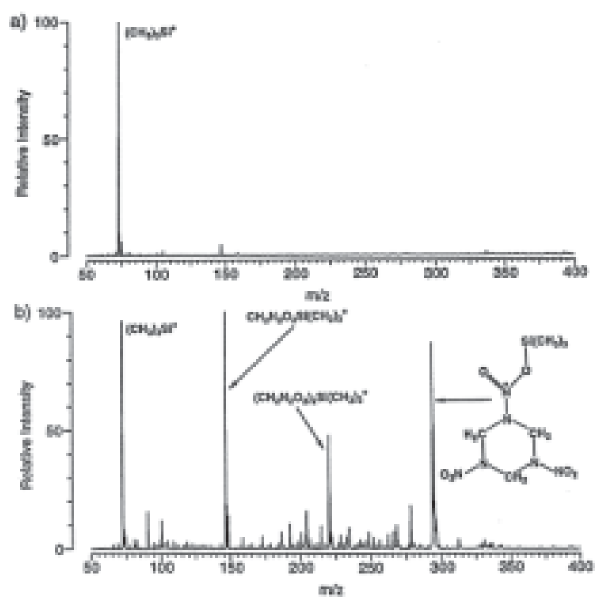




the instrument. The molecules enter a region where they become ionized; they then move through a drift tube under a constant electric field. The small ions encounter less resistance from the gas, so they arrive at the detector first, and the heavier ions arrive later. So the instrument sorts things out at the detector based on their size. You can see above what the data look like, as a function of drift time. The particular experiment above shows the presence of RDX, which attaches a chloride ion in the ionizing source and gives rise to the characteristic peaks in the spectrum. The technique does have its limitations. The resolution is not very good. It's subject to contamination and to interferences, creating a lot of unidentified peaks. For example, a perfume might overlap the main RDX peak. But it does work and is widely used.

A better method for trace detection is mass spectrometry. Earlier this fall, John Fenn, professor of analytical chemistry at Virginia Commonwealth University, shared the Nobel Prize in chemistry. Fenn made very important contributions to the use of mass spectrometry for looking at biological molecules—the molecules of life. In his own words: "Mass spectrometry is the art of 'weighing' individual atoms and molecules to determine their masses or molecular weights. Such weight information is sometimes sufficient, frequently necessary, and always useful in determining the identity of a species." There you have it from this year's Nobel Prize winner in chemistry. And it just happens to work really well for explosives.

I'll give you an example of work that we've done in my lab developing sensitive, selective methods for mass-spectrometric detection of explosives. RDX has oxygens that just love to bind to silicon, so if you use trimethylsilyl cations as an ionizing reagent, they selectively attach to the RDX, leading to characteristic peaks in the mass spectrum that can be used to identify explosive material. In the experiment below, the reactive ion is stored in a device called an ion trap. After many collisions with gas molecules passing through the trap, eventually the reactive ion finds the RDX and sticks to it. So, after one second of reaction time, you see the spectrum on the bottom instead of the one on the top. You can see the RDX and you can see two fragments that come from cleavage of the ring. These data provide forensic evidence for the presence of RDX.



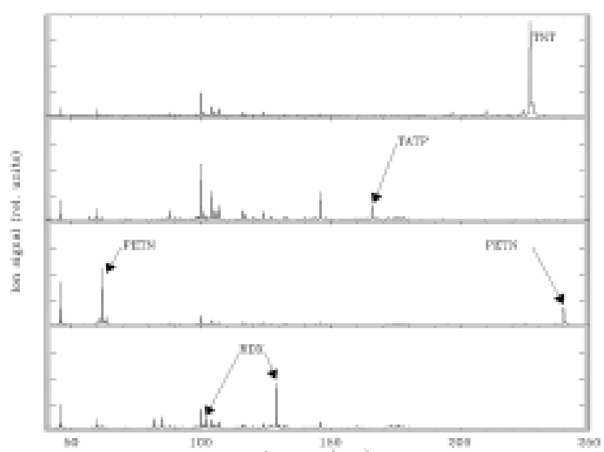
In mass spectrometry work done in the author's Caltech lab, RDX is chemically ionized with trimethylsilyl cations—$(CH_3)_3Si^+$. When these collide with trace amounts of RDX, a stable compound forms, which can be characterized using mass spectrometry, giving the spectrum in the lower graph. Within a second, you can see the RDX at the right, with peaks of the two dissociation products in the center.

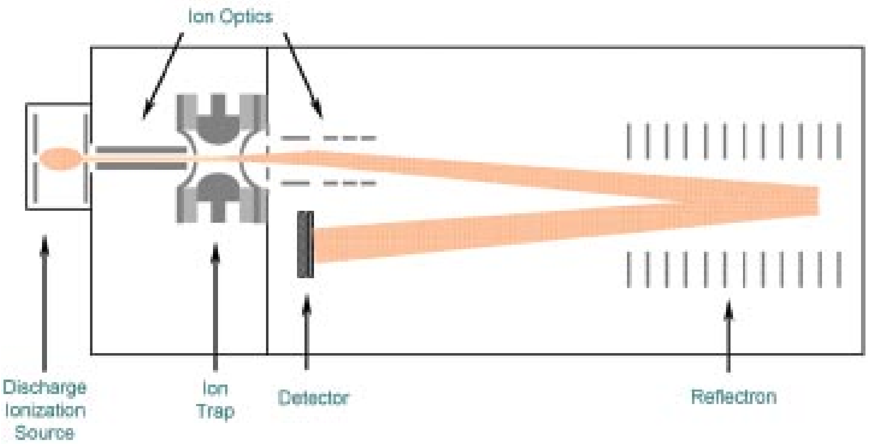
[We should] continue to support research and development related to new technologies for the detection of weapons, explosives, and chemical and biological weapons. I have to say this because I'm a research person, right?

The typical portals to screen passengers aren't designed to sniff for explosives on a person; they failed, for example, to detect the shoe bomb on Richard Reid. One advanced system has been developed by Syagen (a Tustin firm founded by Jack Syage, who was a postdoc at Caltech with Pauling Professor of Chemical Physics and Professor of Physics Ahmed Zewail) and Sandia National Laboratory. Syagen's expensive portal can screen people for traces of explosives, chemical weapons, and narcotics without direct contact or x-rays. One of the first such systems for an airport, it's now undergoing testing at Idaho National Laboratory. This super-high-tech device uses mass-spectrometric detection. When you're standing in the portal, it takes your picture so that it has a record of every individual passing through (that's the easy part). In the picture at right, laminar flow of ionized air is shown by the red arrows; the blue arrows indicate other air flows from pulsed nozzles that ruffle your clothing to dislodge particles; and the white arrows indicate injection of ionized air to assist in collecting the particles. Once collected, the particles are passed into a mass spectrometer with an atmospheric-pressure discharge ion source. Ions are extracted and accumulated for a short period of time in an ion trap and then injected into a time-of-flight mass spectrometer. All the ions here initially have the same energy, causing the light ones to arrive at the detector first and the heavy ones last, providing a mass spectrum. In addition to having excellent sensitivity to explosives, the portal can also detect chemical agents such as VX, a potent nerve gas.

In addition to chemical weapons, much progress has been made on rapidly determining the presence of pathogens, or biological agents. For example, the Ebola virus has a particular protein in its coat that can easily be detected and analyzed with mass spectrometry. Depending on how the analysis is performed, you get not just the molecu-

Above: In the Syagen portal, the main stream of air flows past the subject (red arrows), as pulses of air (blue arrows) puff his clothing to liberate particles, while other jets of ionized air help collect them (white arrows). Next the particles pass into a time-of-flight mass spectrometer (opposite page), which delivers the mass spectrometric fingerprints for several common explosives (below). (Illustrations courtesy of Syagen Technology, Inc.)





Above: After the particles are collected in the portal, they are heated to release explosive vapors, which are then ionized and collected in an ion trap, before being ejected into a time-of-flight mass spectrometer. The lighter ions arrive at the detector first and the heavier ones later, producing a mass spectrum. The orange band indicates the path of the ions; the reflectron enhances the mass resolution of the device.

lar weights but the actual sequence of amino acids, which are unique signatures. Scott McLuckey, professor of analytical chemistry at Purdue University, is one of the leading researchers working on this technology.

In closing, I'll give you my 10 recommendations for countering terrorism. They're not too different from some of the conclusions of the recent National Academy of Sciences report.

- Make effective use of intelligence information.
- Make effective use of deterrence. Nobody holds up a doughnut shop with a police car in front, even if there's no policeman around.
- Promote coordination and communication between agencies responsible for security at all levels. People need to talk to one another.
- Promote public education and vigilance. If I were flying a plane out of some small airport and saw a guy taking out his backseat and loading in cases of TNT, I'd call the police and then see what I could do to stop this guy from leaving the airport. If you see somebody unloading canisters of gas at 3 a.m. into a neighbor's garage, call somebody to come take a look at it.
- Support the public-health infrastructure and research related to infectious diseases. I think the best thing we can do in response to the threat of biological attack is to start doing a better job of protecting ourselves from known diseases.
- Equip and train first-response teams to deal with emergencies. The faculty at Caltech spends a lot of time doing K–12 education; the National Science Foundation requires us to do it. I think the NSF and other agencies should require us to spend a certain amount of time working with hazmat teams. We can do a lot to help these teams learn how to use the equipment they already have and to help make some of the newer technologies available for their use.
- Avoid complacency by recurrent training of airport screeners. Pay attention to human factors, such as boredom. I don't think it matters whether the screeners are private or federal; it's performance that's important.
- Continue to support research and development related to new technologies for the detection of weapons, explosives, and chemical and biological weapons. I have to say this because I'm a research person, right? But I also think that, more than tomorrow's detectors, we need to implement in the field the technology that's already available right now.
- Restrict access to materials likely to be employed in terrorist acts. I know it's a free country and we can't keep stuff off the Internet (although we can try to stifle information on how to make explosives). But we should take measures to limit access to, say, chemistry-department stockrooms at Caltech and other universities.
- Do what we can to restrict access to tempting targets. Sometimes this can be accomplished by some pretty simple means. □

Jesse L. (Jack) Beauchamp earned his BS from Caltech in 1964. After graduate school at Harvard and a PhD in 1967, he returned to Caltech to join the faculty. He has been professor since 1974 and was named the Ferkel Professor of Chemistry in 2000. For his decades-long work on the structure and reactions of molecules and ions in the gas phase, he has been recognized with numerous awards, including three from the American Chemical Society: the ACS Award in Pure Chemistry and the Peter Debye Award in Physical Chemistry, and he will be receiving the 2003 Field and Franklin Award for Outstanding Achievement in Mass Spectrometry. He is a member of the National Academy of Sciences—and the Aircraft Owners and Pilots Association.

PICTURE CREDITS:
28-29 – Jack Beauchamp;
31 – InVision Technologies

Genes, Aging, and the Future of Longevity

by Colin Rundel

We present another undergraduate paper that caught our attention from among the many excellent papers to come out of this year's Core 1 Science Writing course.

The woodcut *Oedypus Sphynge*, above, is from the 1687 edition of *Atalanta Fugiens*, a book of alchemical emblems by Michael Maier first published in Frankfurt in 1617. Each emblem is accompanied by a piece of music, making this book one of the first attempts at a multimedia production. By permission of the Huntington Library, San Marino, California.

The Sphinx's riddle, "What is it that has four feet in the morning, but two at midday, and three, when the evening comes, and has only one voice; when it has most feet, it is the weakest?," to which Oedipus answered, "Man," illustrates the natural progression of life from the development of childhood, to the strength of adulthood, to the final decline of old age. This progression is not at all unique to humans. All life undergoes some form of aging, slowly deteriorating over time until finally succumbing to the inevitability of death. The common signs that most people recognize as aging, such as the appearance of a wrinkle or a slight creakiness when getting out of bed, are larger manifestations of the aging process as it occurs in every cell of the body. In the scientific world the aging process is defined as the general deterioration over time of the cells, tissues, and organs of an organism, ultimately reducing normal function and increasing the probability of death. Aging is a complex process that involves a multitude of both environmental and genetic factors that result in the determination of an organism's life span. But why does aging happen? All life is the product of evolution and, as such, all natural processes in one way or another have developed as a result of natural selection. This implies that, as deleterious as it might seem, aging serves some beneficial function.

Aging, Evolutionary Biology, and You

While the arguments about the evolutionary sources of aging are far ranging and highly speculative, there are two predominant theories. The first suggests that aging evolved as a process of planned obsolescence. Much like a car or a flashlight, organisms are thought to have been designed to wear out over time and eventually need replacing. While such an argument seems counterintuitive at first, it does have some grounding in evolutionary biology. Within a population, it is important that there be at least a small amount of turnover, with older members of the group dying and being replaced by newborns. While this borders on a group selectionist argument, it still has important implications. Firstly, it is important that new individuals are born into the population so that natural selection has something on which to operate. Without the mixing of genetic material that occurs with sexual reproduction, the gene pool stagnates and the population's ability to adapt to new conditions is diminished. Secondly, turnover allows the population to maintain a more stable growth rate and a more evenly distributed demographic. For example, a population in which there is no loss of individuals due to old age increases the stress on the population, as the ever-increasing population must waste limited resources on post-reproductive individuals who are not contributing in any significant way to their offspring's reproductive success. This implies that aging plays a role in creating turnover within a population in order to promote genetic diversity and limit the rate of population growth.

A second line of reasoning for the evolutionary basis of aging is that the forces of natural selection are weaker for organisms that have reached a post-reproductive stage of life. The simple idea behind this is that natural selection is mostly focused on producing an organism that can successfully produce as many offspring as possible, thereby spreading its genes as widely as possible. So once an organism has passed the reproductive age, any mutations that negatively affect survival are not subjected to the same rigorous selective pressures as early-acting deleterious mutations. Therefore, over the billions of years of the evolution of life there has been a tendency for the accumulation of late-acting mutations that negatively affect survival. Given enough of these mutations, an organism will exhibit rapid deterioration after the reproductive stage of life; that is, it will age. While these two theories are presented separately, they are not

All over the world, laboratories of renowned scientists are studying the processes and diseases associated with aging, and still no clear picture has emerged of any single "aging pathway."

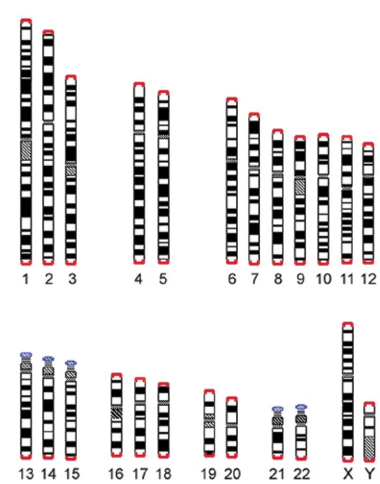
mutually exclusive and have probably both played a role in the evolution of the aging process.

Aging in a Nutshell

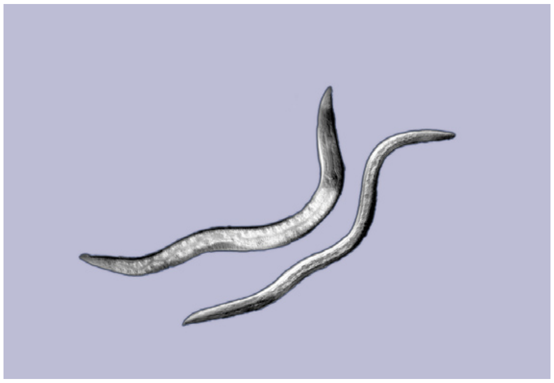
Speculation about the evolutionary reasoning behind aging does little to address the proximate causes of aging. Aging is an amazingly complex process in which a multitude of different factors act over time to slowly reduce viability. All over the world, laboratories of renowned scientists are studying the processes and diseases associated with aging, and still no clear picture has emerged of any single "aging pathway." Much noise has been made in recent years by the popular press about the role of telomeres in aging. Each time a cell divides it is necessary that it make copies of its chromosomes, but every time this duplication occurs, a small portion of DNA at the end of the chromosome is not copied, due to the nature of the replication mechanism. To combat this, organisms have evolved telomeres, stretches of junk DNA at the tips of their chromosomes, portions of which can be lost without any ill effects. The problem is that the telomere is only so long, and after a certain number of cellular divisions the chromosome will have shortened to the point where pieces of critical genes will be lost. At this point most cells will simply commit suicide or be destroyed by the immune system. This fits nicely with one of the theories of aging, since the older we become the greater the number of divisions our cells have undergone. Therefore, as we reach old age, more and more of our cells die because of telomere shortening. Yet this programmed cell obsolescence is not enough to explain the majority of degeneration associated with aging. And the argument implies that as the shortening occurs, it should remove pieces of the same genes on the end of each chromosome in everyone. Such a process cannot possibly explain the seemingly random way in which aging affects each individual in a unique way.

So what might be a more fundamental and inclusive theory of aging? The surprising answer seems to lie in free radicals, small reactive molecules that surround us every day of our lives. They are in our food, they are in the air we breathe, and even our bodies produce large quantities of them. This theory was originally proposed by Denham Harman in the 1950s as the "free-radical theory of aging" and has subsequently gathered support from numerous sources throughout the scientific community. The basic principle of this view of aging is that throughout our lives, our cells are bombarded by various free radicals, which bind to and damage a whole host of critical cellular factors like DNA and proteins. Over time this damage accumulates and reduces the functioning of the cell, which will subsequently reduce the organism's ability to function as more and more cells are damaged. Therefore, what we recognize as the aging process is the gradual accumulation of this cellular damage.

Although generated in a variety of ways, the majority of free radicals have an unexpected source—the cells' mitochondria, which release reactive species of oxygen. So the production of these radicals occurs as an accidental by-product of normal respiration. During the final stages of respiration the chemical energy derived from the breakdown of sugars is used to synthesize ATP, the basic unit of energy used in the cell. However, during this process electrons can be inappropriately transferred to molecular oxygen, thereby generating superoxide, a highly reactive species of oxygen. Whether this occurs due to an inherent flaw, or as part of some greater evolutionary design is unclear, yet it seems to fit within the context of



Map of the 23 human chromosomes, with the telomere caps shown in red or blue. Courtesy of the Human Telomere Mapping and Sequencing Project.



The well-fed roundworm on the left will age faster than the skinny dauer larva on the right.

the evolutionary necessity of aging. The implication is that through the process of living we are slowly poisoning ourselves with each breath we take. While this paints a somewhat bleak picture of existence, it at least identifies who the enemy is and offers some hope that in the future something could be done to postpone the inevitable without reducing the quality of life.

The connection between aging and oxidative stress due to superoxide agrees nicely with previous connections drawn between aging and metabolism. It has long been known that life expectancy and metabolic rate are inversely related, as animals with high metabolic rates tend to have very short life spans, whereas larger animals with lower metabolic rates can expect to live far longer. For example, the average mouse kept in captivity can expect to live about two years, while a captive elephant in a zoo has an expected life span of upward of 70 years. Regardless of the medical attention administered, or how carefully the mouse is treated, at present there is no medical treatment available that can extend its life span much beyond those two years. In light of the free-radical theory of aging this makes sense. The mouse simply has a far higher metabolic rate than the elephant and therefore the rate of superoxide production is increased. The net effect of this is that the mouse's tissues will accumulate damage at a far greater rate than those of the elephant and as such will display a more rapid onset of aging. Yet, like most models, there are also certain marked exceptions to the rule that complicate the explanation. In particular, some birds and bats exhibit life spans that far exceed what would be expected for their metabolic rates. This would imply that the basic tenets of the free-radical theory are correct, but that the effects of the stress are modulated by certain genes that can increase the life spans of some organisms. Once again, evolution has taken a very heavy hand in determining how and when the aging process occurs.

Genetics of Aging: The Beginning

It is evident that within different organisms the levels of free radicals produced must be regulated in some manner. Therefore, if there are factors that directly affect the amount of reactive oxygen species present in the body, they should have an indirect effect on life span. The implication is that there are specific genetic factors within an organism that have been programmed by evolution to set a specific life expectancy, one that is most beneficial for reproductive success. Experimental confirmation of this has come out of Michael Rose's laboratory at UC Irvine, where researchers were able to selectively breed fruit flies (*Drosophila melanogaster*) for extended life span. Just like eye color and height, aging must therefore be at least partially under the control of certain genes, which can be selected for, just like an animal breeder can select for increased size or a gentler disposition. This opens up a whole new world of possibilities for studying the aging process. Through genetic dissection, it becomes possible to identify genes that affect an individual's life span and to fit them into an overall picture of the aging process.

Suddenly, the study of aging is switched from a top-down view of the effects of aging to a bottom-up approach, where causes can be determined. Now individual genes can be identified as contributors to the aging process and their products characterized, opening the door for the creation of drugs that can slow aging. However, there is one problem with Rose's work. By selectively breeding his flies, Rose has significantly altered the genetic diversity of the new long-lived population. It is therefore impossible to differentiate between the genes that extend life span and the genes that were selected for, due to the population of flies he bred for the experiment. This then leads us to the current state of genetic aging research, the analysis of single-gene mutations that have a significant impact on an organism's life span. The benefits of such an approach should be immediately apparent, as the alteration of the properties of a single gene should give a definitive answer as to its effects on aging.

Enter the Worm

Single-gene aging research is still a relatively new field and, at the present time, only a handful of genes that affect aging have been identified in a variety of model organisms. It was not until 1988 that the first aging gene was identified, *age-1*. This is a gene in the nematode (roundworm) *Caenorhabditis elegans* or *C. elegans*, one of the model organisms commonly used in genetic research. The effect of reducing the level of *age-1* expression in a nematode was a 110 percent extension of maximum life span at 25°C, while also reducing reproductive output.

This discovery was followed by the identification of a variety of other nematode genes that made a direct connection between stress response, mating, and aging. One of the surprising results to come out of this work was the discovery of the connection between aging and a molecular pathway known as the insulin signaling pathway. Everyone has heard of insulin, the protein that regulates the level of blood sugar and plays a central role in diabetes. But how does it connect to aging? The basic role of insulin within a cell is to measure the amount of sugar that is present in the blood at any given time, and then to instruct the body how to respond appropriately. This has one useful feature that has been latched onto by aging. Since this molecule is constantly measuring the amount of sugar present, it could also be used to measure the amount of food being consumed by the organism at any given time. So it is believed that a pathway has evolved that is capable of reporting on the level of food availability in the environment. In combination with other signals, it allows the organism to monitor biochemically if it is undergoing food stress.

Transgenic fruit flies bred by Colin Rundel to investigate the genetics of aging.

This connects to aging and reproduction in a somewhat subtle way. By constantly monitoring whether food supplies are plentiful, an organism can decide if it is a good time to mate or not. The general strategy is that during times when food is plentiful an organism should make the energetic investment in reproduction and produce as many offspring as possible, but when times are not so good, it should batten down, save most of its energy, and hold out until a better opportunity presents itself. This type of strategy is beautifully demonstrated by *C. elegans* in its ability to form dauer larvae. For those not familiar with the development process of *C. elegans*, the worm goes through several larval stages, much like a butterfly (without the cocoon). During one of these early stages there is the potential for the worm to adopt a dauer form, which is an alternative type of larva whose formation occurs under stressful conditions, most notably when food is scarce. These dauers have several amazing properties, the first of which is that, as soon as food is available, the worm is able to continue development and become a fully functional adult. What is more interesting to the study of aging and free-radical stress is that during the dauer period, the worm exhibits a dramatically slower aging process and increased resistance to stress. It is because of this connection to dauer formation that several of the most notable aging genes, *daf-2* and *daf-16* for example, were found in worms. As an interesting side note, it has also been shown that the genes linked to dauer formation can be altered in such a way that they no longer cause dauer formation but still impart the benefits of stress resistance and longevity.

What Good is a Fly?

It is now time to return to the organism that is at the center of so many other genetic stories, the fruit fly, *Drosophila melanogaster*. Research into aging in flies got off to a far slower start than one would expect. The first single-gene mutant that extended life span in the fly was not identified until 10 years after the discovery of *age-1*. This mutant came to be known, appropriately, as *methuselah (mth)*, and while the extension in life span was less than that seen in *age-1*, only a 35 percent increase, it was still significant because the mutation exists in an organism another step closer to humans. There has been only one problem with *mth*: it shows no significant similarities to any other known gene. After four years, its cellular function has yet to be characterized. It is known that the gene negatively influences longevity and stress resistance but is critical for the survival of the fly.

In the last few years, the rate of discovery of new aging genes has sped up considerably, but the number is still hovering around a half-dozen or so published mutants. While this is certainly progress, the numbers available are simply too small to construct any type of detailed biochemical pathway. One interesting finding, however, has been the identification of a gene involved in insulin signaling that also affects aging, implying that the system originally found in worms is conserved, and that related genes may prove to extend life span in higher organisms.

Aging and Mammals

So, you are probably asking yourself, what is the point of all this? While to a geneticist it is wonderful that the life of a worm or a fly can be extended, I am certainly not either of those, so how is this going to affect *my* life? The truth of the matter is

> . . . one surefire way to extend your life span without having to do anything at all to your genes, or having to take any drugs . . . is known as caloric restriction, and all that is involved is limiting the amount of caloric intake to approximately 60 percent of the normal amount.

that at the moment it is not going to in any significant manner. Progress is being made on a variety of fronts, but for now the field is too new, and there is much more that remains to be discovered about the genetics and biochemistry of the aging process. Two recent discoveries do show a great deal of promise for the future of a direct application of aging research to the human population. The first of these is the identification of the first known single-gene aging mutant in a mammal, $p66^{shc}$, found in mice in 1999, only six years after the journal *Nature* published an April Fools' Day article on just such a long-lived mouse. The second encouraging finding is the recognition of a link between a group of French centenarians and a region on the fourth human chromosome, implying that there may be a gene in that area responsible for longevity.

While there is little hope of any kind of genetic treatment in the near future, there may be some opportunities for a more pharmaceutical approach. Before discussing the chemical compounds that seem to affect aging, it is important to mention one surefire way to extend your life span without having to do anything at all to your genes, or having to take any drugs. The process is known as caloric restriction, and all that is involved is limiting the amount of caloric intake to approximately 60 percent of the normal amount. The amazing part of this process is that it seems to exist universally in all organisms, from mice to worms, and everything in between. The conclusion that can be drawn from this takes us back to what we first saw with the worms: our bodies can pick up on when food is in short supply and respond by increasing all of our molecular defenses to better survive until a period of greater abundance.

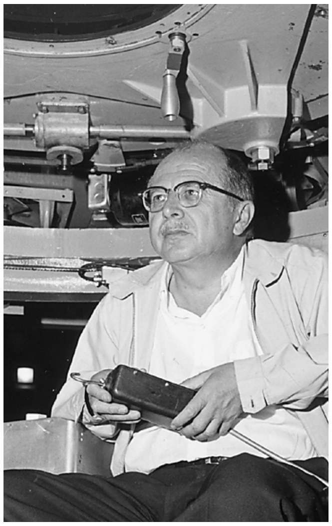
For those individuals who do not find this prospect appealing, there appear to be other options, but it will be a long time before they become available as antiaging therapies. For example, a drug known as PBA (4-phenylbutyrate) has been shown to extend the life span of *Drosophila* flies when mixed into their food. It is thought to function by inhibiting enzymes responsible for winding up DNA and packing it together into chromosomes. This alters gene-expression levels because regions of the DNA that would typically have been inaccessible become available to express their genes. How this causes an increase in life span is very unclear. However, the drug seems to achieve a goal similar to that of a protein known as sir2, which has also been shown to increase life span in worms and yeast. But we are once again confounded by our lack of understanding of how the aging process works, and any possible use of PBA is thus limited. It is hard to appreciate how complex biological systems are, and even the slightest alteration can cause far-reaching effects that are amazingly difficult to predict.

Where This Leaves Us

At the present time, doing research into aging is like trying to do a jigsaw puzzle with half the pieces and the box missing. You do not know what it is supposed to look like or where everything is supposed to go, but connections are being made and new pieces are being found all the time. Aging is a complex and intricate process that is entangled in a multiplicity of other systems in unexpected ways. The genetic approach to aging holds great promise, but it needs to shift from the question of what will extend life to the more important question of how life is extended. Society also has to investigate how slowing the aging process may influence our demographic, economic, and environmental conditions before any therapy is made available for human use. With an ever-expanding world population bringing us ever closer to the earth's carrying capacity, extending life span may have disastrous consequences for humanity and the planet as a whole. □

Colin Rundel is a senior majoring in biology. He has spent the last two years attempting, with some success, to extend the lifespan of fruit flies in the laboratory of Seymour Benzer, Boswell Professor of Neuroscience, Emeritus. His science writing mentor was Paul Sternberg, professor of biology and Howard Hughes Medical Institute Investigator. Colin is planning to go to graduate school and continue "forcing helpless insects to do his bidding."

Jesse L. Greenstein 1909–2002



Jesse L. Greenstein, the DuBridge Professor of Astrophysics, Emeritus, died October 21 at the age of 93. Greenstein came to Caltech in 1948 to organize a new graduate program in optical astronomy in conjunction with the new 200-inch Hale Telescope on Palomar Mountain. The Caltech astronomy program quickly became the premier academic program of its kind in the world, with Greenstein leading it from 1948 to 1972. His research interests largely centered on the physics of astronomical objects. The next issue of *E&S* will carry excerpts of the memorial service, which will be held February 11 at 3:30 in Dabney Lounge.

Wheeler J. North 1922–2002

Wheeler J. North, professor of environmental science, emeritus, died December 20 at the age of 80.

He earned two bachelor's degrees from Caltech, one in electrical engineering in 1944 and another in biology in 1950, and had been a member of the faculty since 1962.

North studied kelp, proving that the ocean's kelp beds are part of a complex marine ecosystem providing food and shelter for hundreds of underwater species. He pioneered scuba diving as a basic tool for marine scientists.

A memorial service, which will be reported in *E&S*, will be held February 22 at Dana Point.

Satish Dhawan 1920–2002

Satish Dhawan, who was director of the Indian Institute of Science (IISc), chairman of the Indian Space Commission and the Indian Space Research Organization (ISRO), and president of the Indian Academy of Sciences, received his engineering degree from Caltech in 1949, his PhD in aeronautics in 1951, and a Distinguished Alumni Award in 1969. He returned to Caltech as a visiting professor in 1971-72, when he reportedly asked to delay Indira Ghandi's summons to return home to head the ISRO until his course was finished. Hans Liepmann, Theodore von Kármán Professor of Aeronautics, Emeritus, was his thesis adviser.

Remembering Satish Dhawan

by Hans Liepmann

In January 2002, Satish Dhawan, my friend for more than half a century, whose personality and friendship had an important and lasting effect on me and my understanding of India, died at his home in Bangalore, India. Roddam Narasimha (Caltech PhD '61, Distinguished Alumni Award '86), also a professor at the Indian Institute of Science, has written a complete and beautiful history of Dhawan's life, the man and his contributions to society—a story so well presented and complete that there is little I could have added to it, even at a time when I was a great deal younger and a better writer than now, in my 89th year. All I can add are a few reminiscences of our first meeting and our work together—a time for which there exist now few living witnesses—and glimpses of our contacts over all these years.

I have often mused about the bifurcation points in one's life, the times when a small and sometimes even unwelcome choice of alternatives results in major changes in one's future. One of these bifurcations (in, I believe, 1946) resulted in my meeting Satish Dhawan. I wrote about the occasion a number of years ago in a memoir.

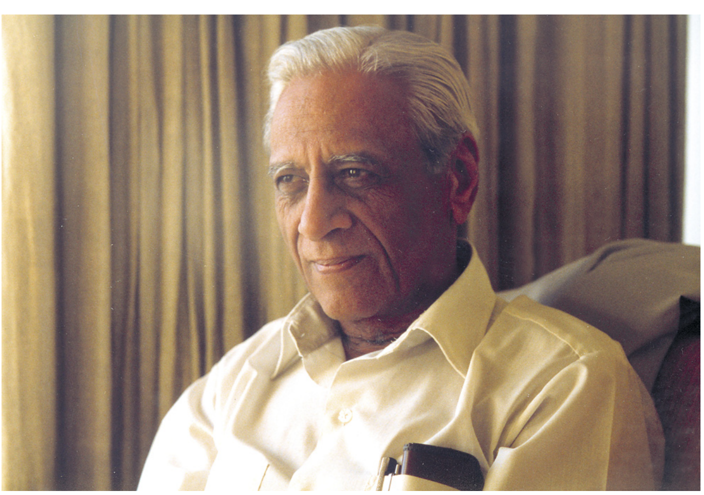
Ernie Sechler, one of the original members of the GALCIT (Graduate Aeronautical Laboratory of the California Institute of Technology) faculty, was an excellent engineer, but his most outstanding quality in my opinion was an uncanny feeling for the potential of students. Ernie handled the graduate admissions. Looking back now, I realize that on every occasion where we disagreed on potential student behavior and performance, he was right and I was wrong.

Sometime in the mid-'40s, I worked with two Indian graduate students (both, I believe, from upper-crust, wealthy backgrounds) with whom I could not work well. They both seemed to have a reluctance to perform the sometimes unpleasant and boring chores necessary in experimental research. I was, of course, not stupid enough to consider this a general characteristic of Indians, but I felt that perhaps the select group that came to Caltech from India had prejudices against manual labor and essential, but not highly intellectual and glamorous, routines. In any case, I told Ernie that I'd like a rest from Indian students.

Within days he called me with

the news that he had a new student from India who wanted to work with me. At first I wouldn't even agree to come down to the second floor to talk to the student, but Ernie insisted, and knowing him and his instincts about students, I finally did walk downstairs, where I met Satish Dhawan. Later he was to become the director of the Indian Institute of Science in Bangalore, the Indian institution probably closest in scope and aim to Caltech. Ever since then, we in GALCIT have had close contacts with the Indian Institute of Science, and thus a calibration station for admissions, leading to some excellent Indian graduate students at GALCIT.

Satish did join my research group, and it soon became evident that we had acquired an outstanding new member. From his previous scholastic records, we expected excellence in scholarship and class work, but there was so much more. Satish was immediately accepted and respected by this highly competent and proud group of young scientists. He showed an unusual maturity in judging both scientific and human problems, a characteristic that today is called "leadership quality." I usually hate using terms like this to pigeonhole a person, but here it fits. Satish could be tough without having to get mad first—a trait that I envy. He was a natural mentor for younger people. Finally, he had a very good sense of humor, a quality that I think is necessary, but not sufficient, to keep one from becoming pompous in old age. I still remember our Ping-Pong games in the lab. When Satish won, he would crack: "See, I am a crafty Asiatic!"



Anatol Roshko (now Theodore von Kármán Professor of Aeronautics, Emeritus), Satish, and I worked together on a problem in shockwave–boundary-layer interaction. This was Satish's first participation in active research. It was a marvelous time! Almost everything we touched was new and exciting. Our equipment was modest, even for the standards of the time, but with some ingenuity it could be made competitive; this was an additional stimulus. The three of us worked easily and well together and laid the foundation for our lasting friendship over the next half century. After this work was done, Satish started his thesis work on the direct measurement of skin friction. This was actually a classical problem in low-speed flow of both fundamental and direct technical importance. The aim of Satish's effort was the development of a new technique capable of making similar measurements in supersonic flow possible. It was the beginning of a lasting research effort and a great success. In addition, Satish cooperated with Anatol on the design and construction of an ingenious flexible nozzle for our research in supersonic flows—another example of ingenuity substituting for large amounts of grant money.

Finally bureaucracy intervened, and Satish had to return to India in such a hurry that he could not even finish the introduction to this thesis, which, like any good researcher, he had left to be done last. So I finished it for him, which led to a funny incident: One faculty member reading the rough draft of the thesis called me up complaining that in the introduction Satish had not acknowledged me as his thesis supervisor. So I had to add a remark to this effect. After the report came out, it happened that the great Sir Geoffrey Taylor visited GALCIT, and I showed him Satish's work. He happened to have a leaking fountain pen with him and managed to make a spot on the title page. I asked him to sign the spot with his name and send the signed report to Satish. I wonder what became of it.

In 1964, I took my family with me for a term at the Indian Institute of Science. It was certainly no accident that Bangalore was the only place for me to spend a term away from my many years at Caltech. It was not nearly as easy to get there as now. Bangalore had not yet developed into the Silicon Valley of India. We got stranded for a few days in Delhi, and the long-distance telephone worked only sporadically.

At this time Satish had been director of IISc for only a few years, but the place was already humming, full of young, eager students and obviously endowed with a new confidence in the future. We lived on the campus. Some evenings Satish would come to our "hutment," and the two of us would walk around the campus and talk about anything that we considered a university should do and be. At other times we gathered together in the director's place for tea in the evening, where we learned much about Indian life and aspirations. Nalini, Satish's wife, we met there for the first time, and she and their children became part of our extended family. I know now enough of university life and problems to realize how immensely difficult it was for Satish at his young age to reform time-honored curricula and professor-student interaction, and to instill the self-confidence necessary to reach for new research vistas. That he succeeded beyond all expectations was evident to me on my later, shorter trips to Bangalore.

Many years ago Satish told me that accurate weather prediction could improve India's economy decisively. With the flock of satellites he helped organize, Satish did indeed do something about the weather. Now future geophysical satellites will be launched from the Satish Dhawan Space Center, named in his honor last September. □

Faculty File

Charles Steidel

Paul Wennberg

Two New MacArthurs Named

Charles Steidel, professor of astronomy, and Paul Wennberg, professor of atmospheric chemistry and environmental engineering science, have been named MacArthur Fellows, a prestigious honor bestowed each year on innovators in a variety of fields and commonly known as the "genius grants." The John D. and Catherine T. MacArthur Foundation of Chicago named 24 recipients of the award this year, each of whom will receive a $500,000 "no strings attached" grant over the next five years.

Steidel's expertise is cosmology, a field to which he has made numerous contributions in the ongoing attempt to understand the formation and evolution of galaxies and the development of large-scale structure in the universe. In particular, Steidel is known for the development of a technique that effectively locates early galaxies at prescribed cosmic epochs, allowing for the study of large samples of galaxies in the early universe.

Access to these large samples, which are observed primarily using the Keck telescopes on Hawaii's Mauna Kea, allows for the mapping of the distribution of the galaxies in space and for detailed observations of many individual galaxies. These are providing insights into the process of galaxy formation when the universe was only 10 to 20 percent of its current age.

Steidel did his undergraduate work at Princeton (BA '84), earned his PhD from Caltech ('90) and has been a faculty member at Caltech since 1995.

Wennberg, who is a specialist in how both natural and human processes affect the atmosphere, is particularly interested in measuring a class of substances known as radicals. These radicals are implicated in processes that govern the health of the ozone layer as well as the presence of greenhouse gases.

Wennberg has earned recognition in the field for developing airborne sensors to study radicals and their chemistry. One of the early scientific results from these measurements demonstrated that conventional thinking was incorrect about how ozone is destroyed in the lower stratosphere, affecting assessments of the environmental impacts of chlorofluorocarbons and stratospheric aircraft.

A graduate of Oberlin College (BA '85) and Harvard University (PhD '94), Wennberg joined the Caltech faculty in 1998. □—*RT*

Honors and Awards

Frances Arnold, the Dickinson Professor of Chemical Engineering and Biochemistry, has been selected by the Delaware Section of the American Chemical Society to receive the 2003 Carothers Award, for her "outstanding contributions and advances in industrial applications of chemistry."

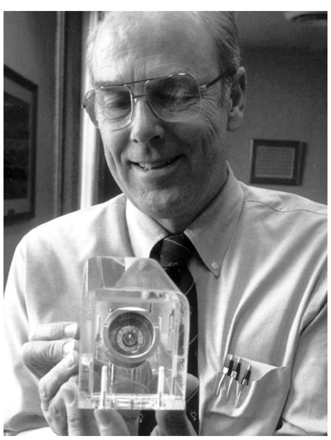
Barry Barish, the Linde Professor of Physics and director of the Laser Interferometer Gravitational-Wave Observatory (LIGO), has been nominated to the National Science Board by President George W. Bush. The National Science Board was created in 1950 to "promote the progress of science; advance the national health, prosperity, and welfare; and secure the national defense."

Jacqueline Barton, the Hanisch Memorial Professor and professor of chemistry, has been chosen by the American Chemical Society to be the 2003 recipient of the Ronald Breslow Award for Achievement in Biomimetic Chemistry. Sponsored by the Breslow Endowment, the award recognizes "outstanding contributions to the field of biomimetic chemistry" and consists of $5,000 and a certificate.

Pamela Bjorkman, professor of biology at Caltech and investigator of the Howard Hughes Medical Institute, was one of 11 international researchers to be awarded the Max Planck Research Prize by the Max Planck Society in Germany for her work in determining how the human immune system fights disease at the molecular level. She has also been elected a member of the American Philosophical Society.

Noel Corngold, professor of

Charles Elachi



Tom Everhart

applied physics, has been selected to receive the 2002 Wigner Award from the Honors and Awards Committee of the American Nuclear Society "in recognition of his outstanding achievements in the field of nuclear reactor physics."

Charles Elachi, director of JPL and a vice president of Caltech, has received the 2002 Takeda Award for his work in developing space-borne radar instruments to monitor the global environment. The award, established last year by the Takeda Foundation of Japan, honors individuals who demonstrate outstanding achievements in the creation and application of new engineering knowledge to benefit human needs. Elachi shares half the approximately $800,000 award.

Richard Ellis, Steele Family Professor of Astronomy and director, Caltech Optical Observatories, has been elected a Fellow of the American Association for the Advancement of Science for his "seminal work in observational cosmology that has provided insight into the origin and evolution of galaxies and the distribution of the unidentified dark matter."

Thomas Everhart, president emeritus, has been awarded the Okawa Prize of approximately $80,000 from the Okawa Foundation for Information and Telecommunications, "for distinguished accomplishments in the development of scanning electron microscopy and microfabrication technologies; and for outstanding contributions and leadership in the development of science and technology, engineering education, and progress of the information industry." The Okawa Foundation was established in Japan in 1986 and began awarding the Okawa Prize in 1992.

Leroy Hood, BS '60, PhD '68, visiting associate in biology, will receive the 2002 Kyoto Prize in Advanced Technology "for outstanding contributions to biotechnology and medical technologies," according to the Inamori Foundation. The approximately $400,000 prize was awarded November 10 in Kyoto, Japan.

William Johnson, Mettler Professor of Engineering and Applied Science, has received several honors. He has been elected a fellow of ASM International, the Materials Information Society, "in recognition of his distinguished contributions to the field of materials science and engineering," particularly being noted for the invention of bulk metallic-glass-forming alloys and for the development of bulk metallic glasses as structural materials. He has also been selected to receive the 2003 Fellow Award and the 2004 Robert Franklin Mehl Award, both from the Minerals, Metals and Materials Society (TMS) in recognition of his contributions to materials science. In addition, he has received a Highly Cited Researchers Certificate from the Institute for Scientific Information in honor of "his accomplishments as one of the most highly cited and influential researchers in his field."

Joseph Kirschvink, BS, MS '75, professor of geobiology, has been elected a 2001 fellow of the American Association for the Advancement of Science for his "unique capabilities in producing innovative ideas for linking geologic events and biologic evolution through a study of rock and paleomagnetism and biomagnetism."

James Knowles, Kenan Professor and Professor of Applied Mechanics, Emeritus, has received the Warner T. Koiter Medal from the American Society of Mechanical Engineers, which is honoring him for "seminal contributions in nonlinear solid mechanics."

Lee Lindblom, BS '72, senior research associate in theoretical astrophysics, has been elected a fellow of the American Physical Society "for his fundamental, ground-breaking analyses of many microscopic aspects of the equilibria, oscillations, stability, evolution and gravitational radiation of relativistic rotating stars."

Shirley Malcom, member of the board of trustees, has been awarded the Public Welfare Medal, the most prestigious award of the National Academy of Sciences, established in 1914 to "honor extraordinary use of science for the public good." Malcolm is head of the Directorate for Education and Human Resources of the American Association for the Advancement of Science.

Carver Mead, BS '56, PhD '60, Moore Professor of Engineering and Applied Science, Emeritus, is being inducted as a Fellow of the Computer History Museum in Mountain View, California. The chairman and founder of Foveon, Inc., Mead is being recognized for his "many pioneering contributions in solid-state electronics."

Paul Patterson, professor of biology, was awarded $300,000 over three years by the McKnight Endowment Fund for Neuroscience for his research on mental illness. □

$1.4-Billion Campaign Launched

Charlie Rose plays master of ceremonies at the campaign kickoff celebration.

On October 25, under a festive tent erected on the athletic field, 400 Institute friends, donors, and supporters kicked off a five-year, $1.4-billion campaign with the motto: "There's only one. Caltech." The evening of dining and dancing also featured Charlie Rose, Emmy award-winning host of the PBS interview show, as master of ceremonies. President David Baltimore, board of trustees chairman Ben Rosen, and trustees vice chairman and campaign chairman Wally Weisman also spoke at the event, and a video specially commissioned for the campaign, *Infinite Possibilities*, was shown.

On the following day, Rose also served as moderator for "A Celebration of Caltech Science" in Beckman Auditorium, which highlighted the Institute's interdisciplinary research.

More than half of the campaign goal is already in hand thanks to a $600-million commitment from Gordon and Betty Moore and the Moore Foundation, and $200 million raised during the "quiet" phase of the campaign. During the kickoff dinner, JPL director Charles Elachi announced the naming of an asteroid in the Moores' honor.

Of the $1.4 billion, the most ambitious campaign goal in Caltech's history, $810 million is slated for the endowment, which will support the people of Caltech: its faculty and students. Included here are new professorial chairs; faculty reinvention funds (to change research direction) and discovery funds (for innovative research ideas); new faculty startups; visiting scholars; the President's Fund for enhanced JPL/campus interaction; graduate and postdoctoral fellowships; and undergraduate financial aid and the Summer Undergraduate Research Fellowships (SURF) program.

A campaign goal of $400 million is dedicated to buildings—some new ones and renovation and expansion of some old ones. Among the new structures Caltech would like to build are an astrophysics lab, an information science lab, a chemistry teaching/research lab, and a campus center for student activities in the arts. Plans are also under way to renovate Dabney Hall for the Humanities, Robinson Lab (to reinvent it as a home for global environmental science), some biology labs, and the student houses. Expanding the Children's Center is also on the wish list.

New equipment needs are also encompassed by the campaign, with a goal of $190 million. These funds will be used to support the design of CELT (the California Extremely Large Telescope—30 meters in diameter); establish a Center for Plate Boundary Studies; relocate the Owens Valley Radio Observatory, along with a second array, to a higher site; and acquire a synchrotron beamline for studying macromolecules, imaging magnets for brain studies, nanofabrication facilities, and a variety of other essential instrumentation and computation equipment.

"In today's competitive environment, it has become more and more expensive to deliver the kind of research and education for which Caltech is renowned," said Baltimore. "To remain preeminent, we must bring to bear on our mission increasing resources."

For more information on the campaign, visit the web site at http://one.caltech.edu.

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