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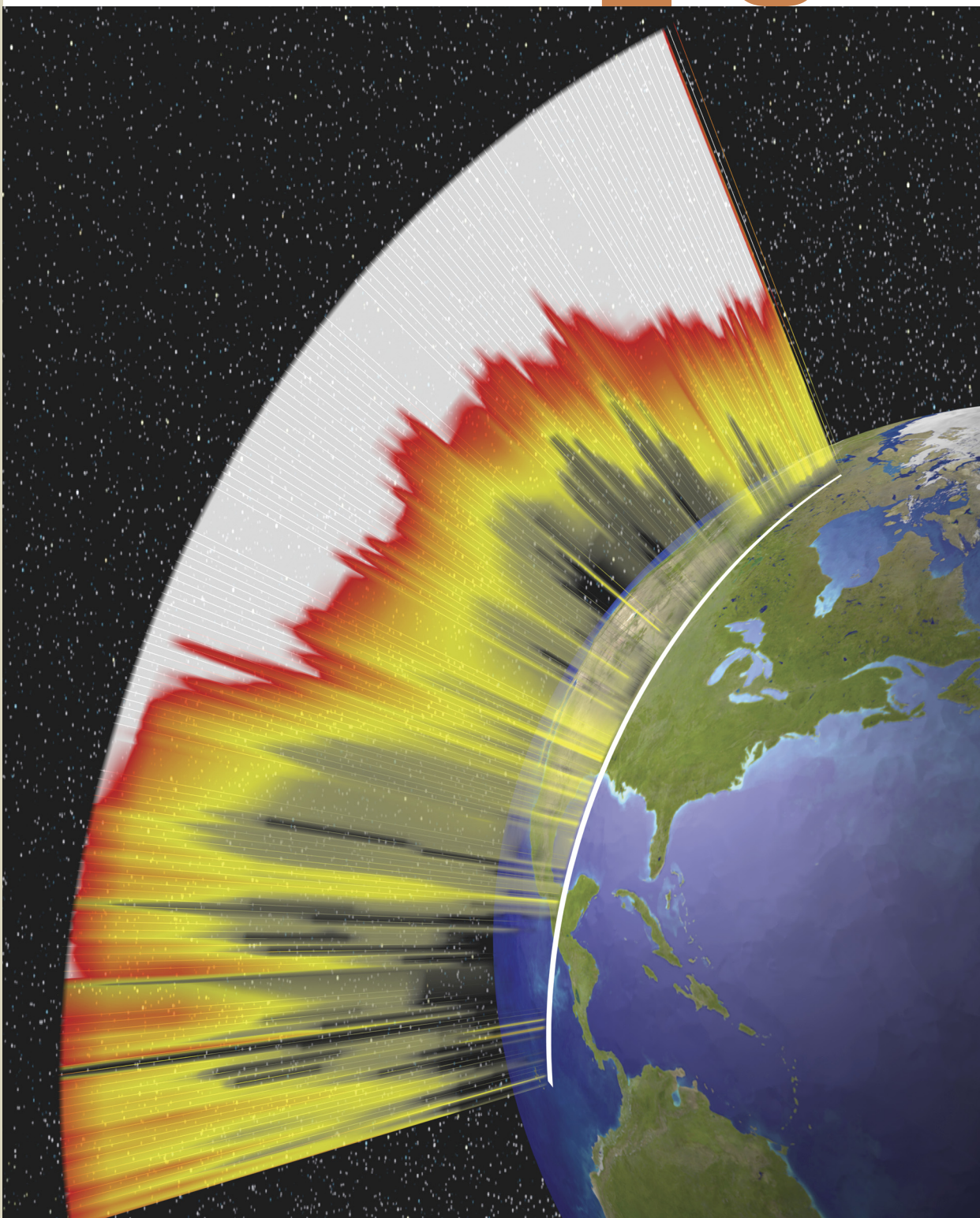

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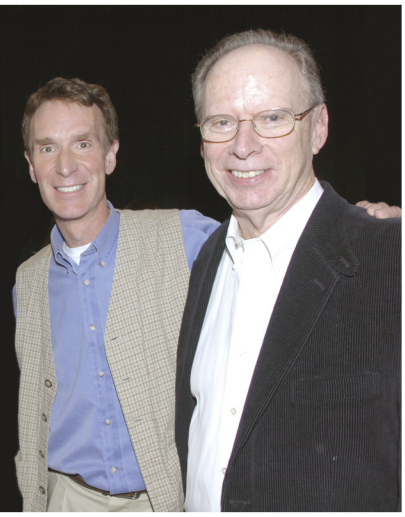

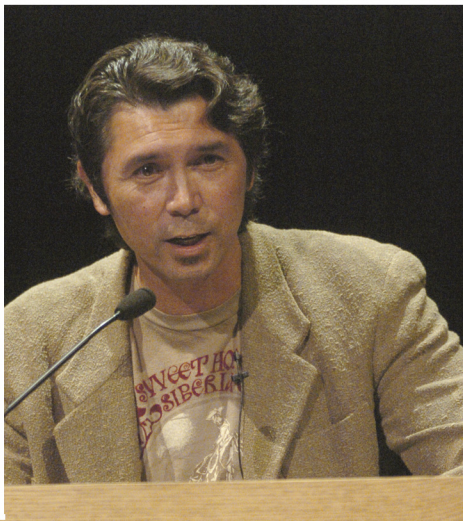

Caltech hosted an informal discussion celebrating the third season of the CBS drama ***NUMB3RS*** at the Beckman Auditorium. Top row: David Krumholz, who plays Charlie Eppes, a mathematics professor at "Cal Sci"; Charlie's colleague and girlfriend Amita Ramajuan (Navi Rawat) and FBI agent Colby Granger (Dylan Bruno, a real-life MIT grad). Middle row, left to right: Bill Nye the Science Guy and Caltech Professor of Mathematics Gary Lorden (BS '62), who consults on the math for ***NUMB3RS***; Charlie's FBI-agent brother Don (Rob Morrow); and agent Ian Edgerton (Lou Diamond Phillips). Bottom row: Series creators Nicolas Falacci and Cheryl Heuton.

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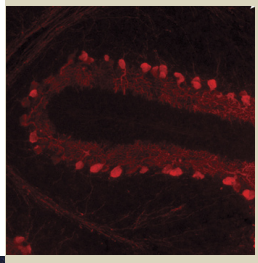

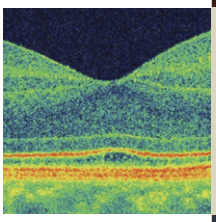

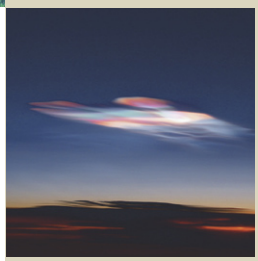

On the cover: This punk Earth's Mohawk is really a "Step and Stare Transect" from the Tropospheric Emission Spectrometer aboard Aura, one of NASA's fleet of Earth-observing satellites. The colors show atmospheric ozone levels from 30 (black) to 100+ (white) parts per billion at altitudes up to about 16 kilometers in early November, 2004. Red marks the bottom of the stratospheric ozone layer. The Mohawk's white bristles indicate the actual measurement locations. For more views from above, see the story beginning on page 32.

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Griffith Observatory Gets *The Big Picture*

When Los Angeles' Griffith Observatory reopens to the public on November 3 after a $93-million and nearly five-year renovation, it will feature the biggest astronomical image ever seen. Twenty feet tall and 152 feet long, *The Big Picture*, a true-color panorama of the core of the Virgo cluster of galaxies, covers an entire wall of the Richard and Lois Gunther "Depths of Space" Exhibit Hall. Data for the image—from a patch of sky roughly the size of your index finger held a foot away from your face—were taken by a team headed by Caltech Professor of Astronomy George Djorgovski using the Samuel Oschin Telescope as part of the Palomar-Quest digital sky survey, a collaboration between Caltech and Yale.

This view of "Markarian's Chain" of galaxies, with the giant ellipticals M 84 and M 86 on the right, and the merging pair of galaxies NGC 4435 and NGC 4438 near the center, occupies 16.7 by 10 feet of wall space.

The full story of this pharaonic undertaking—the enameled porcelain panels will far outlast their creators—will be told in the next issue of *E&S*. □—*DS*

The Breadth of Light

"No, Mr. Bond. I expect you to die," said Auric Goldfinger as a steel-melting laser inched closer to 007's favorite anatomical region. This secret-agent-slicing beam would probably only need to be a few thousand watts of continuous power, according to Martin Centurion (PhD '05), a postdoc in Caltech's Center for the Physics of Information, but the femtosecond lasers he works with routinely put out an unimaginable 10 gigawatts of pulsed power. (For Dr. Evil's benefit, that's ten BILL-ion watts.) It's not that the lasers have gotten bigger—in fact, they're quite a bit smaller these days—but power equals energy divided by time, and a femtosecond is 10^{-15}, or one quadrillionth, of a second.

These ultrafast pulses might be ideal for communications and switching systems, and even optoelectronic computers, but for one serious drawback—the sheer intensity of the light induces a nonlinear phenomenon called the "Kerr effect" that alters the refractive index of the material the beam is passing through. The lasers used in fiber-optic systems are way too weak to be subject to this, but once you cross a certain threshold, the brighter the beam, the more the refractive index changes. The light consequently focuses inside the glass, heating the atoms along its path to a plasma—a fog of free electrons and ionized silicon and oxygen atoms. This might actually be a good thing, in that the plasma's refractive index is negative and prevents further self-focusing, but forming the plasma drains the beam's energy. And, of course, there's the unfortunate side effect of eventually vaporizing the fiber.

A theoretical fix, called "nonlinearity management," has been around for a decade, and now Centurion; fellow postdoc Mason Porter (BS '98); Demetri Psaltis, the Myers Professor of Electrical Engineering; and mathematics professor Panayotis Kevrekidis of the University of Massachusetts at Amherst have actually demonstrated it. The basic idea is to alternate stretches of a material that focuses light of the given intensity with one that causes

Still Going. . .

Voyager 1, humanity's most well-traveled explorer, left the sun 100 astronomical units behind on August 15, meaning it is 100 times farther away than the earth is—9.3 billion miles. The spacecraft has been on the road for 29 years and, moving at a speed of about one million miles per day, could cross the boundary into interstellar space within a decade. It is now in the heliosheath—the outer skin of a bubble of gas called the heliosphere, which is formed by the solar wind—and returns data from these uncharted domains almost daily. □—*DS*

it to spread at that same intensity. As the beam passes through this "Kerr sandwich," it alternately expands and contracts—it "breathes," if you will—and the beam size remains relatively constant overall.

"Basically, the smaller the beam is, the faster it will expand in the air," says Centurion, "and the higher the power, the faster it will focus in the glass, so you can play with these parameters to reach a balance. In our case, the beam diameter doubles after about four millimeters in air."

The sandwich consisted of nine ordinary microscope slides, each about one millimeter thick, placed parallel to one another at one-millimeter intervals. The slides were used not only because they were handy, says Porter, but because "we also wanted to indicate that it didn't need any special materials or circumstances to work." The laser, focused to a beam less than 50 microns (millionths of a meter) in diameter, was shot in pulses of 160 femtoseconds each. If these pulses had gone through solid glass, plasma formation would have kicked in after about two millimeters. Instead, it emerged from the sandwich with essentially the diameter it had when it entered, with no plasma formation. It did lose more than half its power, however, due to internal reflections at each air-glass interface; further studies using slides with a nonreflective coating are already showing better results.

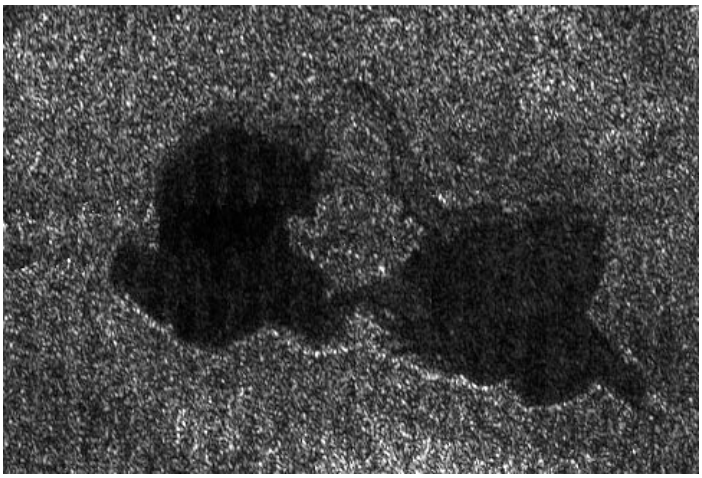
The work was published in the July 21 issue of *Physical Review Letters*. □—*DS*

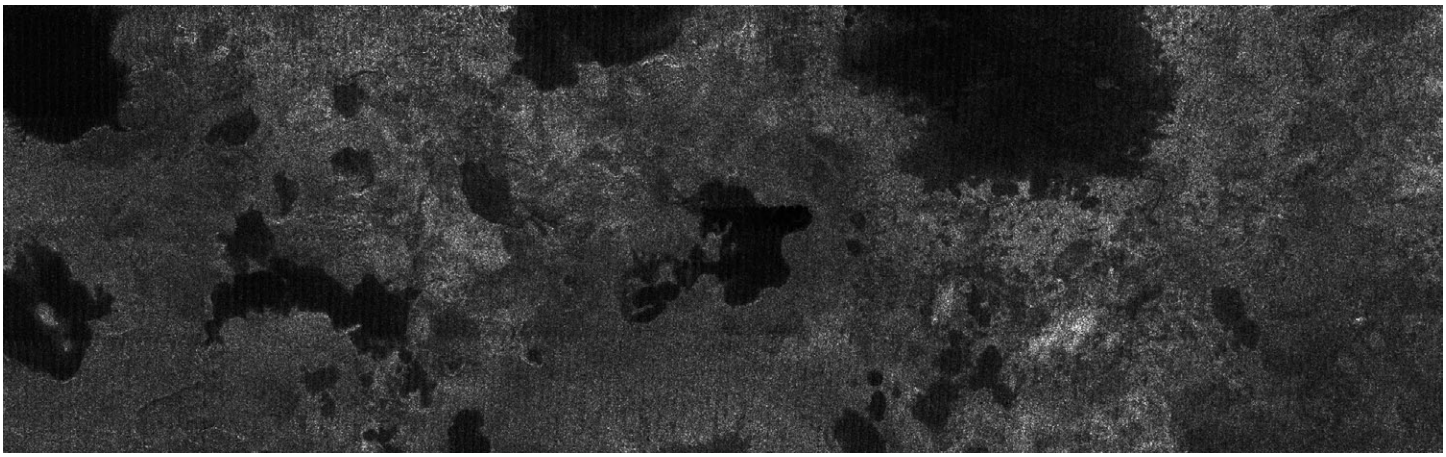
Rockin' with Richter

The Caltech Archives' virtual exhibit in honor of the centennial of the great San Francisco earthquake continues. Module 2 was released on June 22. "The Beginnings of Seismology at Caltech, 1920–1930" chronicles the early work of geologist Harry Wood, instrument builders John Anderson and Hugo Benioff, geophysicist Beno Gutenberg, and the first household name in earthquakes, Charles Richter (PhD '28). Module 3, "Charles Richter and the Earthquake Magnitude Scale," came out on October 4. New features to this module include excerpts of Richter's account of the development of the scale from the taping sessions of his oral history, and an MP3 file of Professor of Literature, Emeritus, J. Kent Clark and Dave Elliot's "The Richter Scale," as performed by the Caltech Stock Company.

The exhibit may be accessed at http://archives.caltech.edu/exhibits/earthquake/index.html. □—*DS*

Cassini's radar may have found lakes of liquid methane or ethane all over the north polar region of Titan, Saturn's largest moon. The patches resemble Earth's lakes in shape, and the black ones reflect essentially no radar signal, meaning they are extremely smooth. The dark gray ones have a slightly rougher surface, possibly due to winds—finding their textures to vary in future passes would strongly support their liquid nature. The image below is centered near 80° N and 92° W and measures about 420 kilometers by 150 kilometers; its smallest visible details are about 500 meters in size. The image at right was taken near 73° N and 46° W and shows two lakes some 20 to 25 kilometers across, or a bit smaller than Lake Tahoe, joined by a relatively narrow channel. The lighter patches in the lake on the right indicate that it may be slowly drying out as summer approaches. JPL built the Cassini orbiter and manages the mission, which is a joint effort of NASA, the European Space Agency, and the Italian Space Agency.





And Speaking of Large Earthquakes. . .

How will Southern California's steel-frame, earthquake-resistant high-rises fare when the Big One hits? That's a very complicated question that a team led by Caltech postdoc Swaminathan Krishnan (PhD '04) has answered with unprecedented specificity using a supercomputer model—the first to combine 3-D seismological simulations with 3-D nonlinear analyses of building motions.

The model "ruptured" a 290-kilometer section of the San Andreas fault between Parkfield, located in the Central Valley, and Southern California. Two magnitude-7.9 earthquakes were simulated—one rupturing southward and the other northward. The model calculated the resulting motions for a grid of 636 points spaced 3.5 kilometers apart and covering the Los Angeles basin, which includes the San Gabriel Valley and Orange County, and the San Fernando basin, which is a geologically separate entity, and applied them to two structures: an actual 18-story building that was designed according to 1982 building code standards and suffered significant damage in the 1994 Northridge earthquake when welds failed, and the same building designed to the stricter 1997 standards. The model predicted each building's "peak interstory drift," which measures the structure's distortion as it sways—for example, for a 10-foot-high story, a drift of 0.10 means that the ceiling is displaced one foot in relation to its floor. Zero-point-one is also approximately the threshold of collapse, while anything over 0.06 indicates severe damage.

Not surprisingly, L.A. fared worse in the south-propagating rupture, where peak drifts for the 1982 building far exceeded 0.10 in the San Fernando Valley, Santa Monica, and West Los Angeles, as well as the areas around Baldwin Park, Compton, and Seal Beach. Peak drifts were in the 0.06–0.08 range in the Huntington Beach, Santa Ana, and Anaheim areas, and in the 0.04–0.06 range everywhere else, including downtown Los Angeles. The 1997 version did better—although peak drifts in some parts of the San Fernando Valley still exceeded 0.10, they were in the range of 0.04–0.06 for most of the Los Angeles basin. In the south-to-north rupture, both buildings scored in the 0.02–0.04 range, suggesting damage enough to close the building but little danger of collapse.

Such hazard analyses could be performed on specific existing and proposed buildings for a range of earthquakes, providing detailed information for developers, building owners, city planners, and emergency managers. "We have shown that these questions can be answered, and they can be answered in a very quantitative way," Krishnan says.

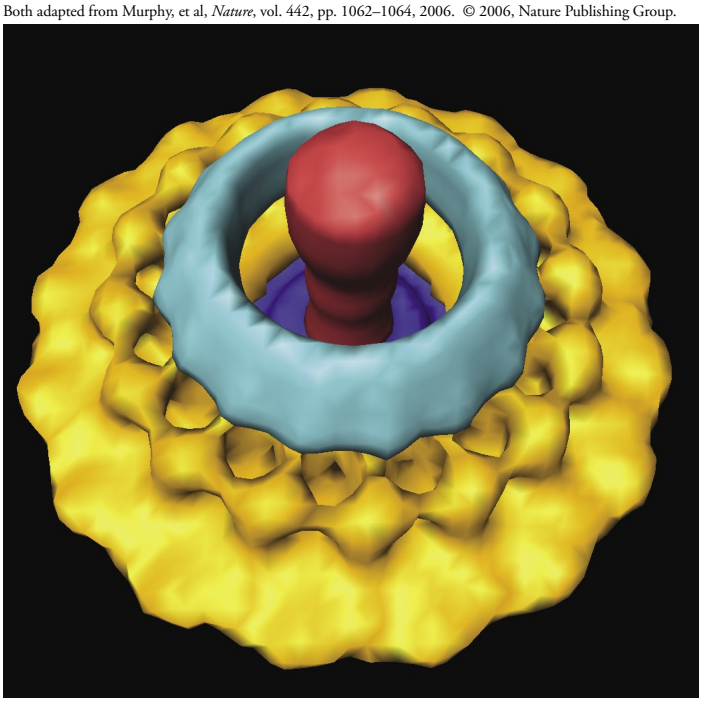
A southward-propagating 7.9 earthquake hit the San Andreas in 1857, and seismologists think an event of that size—propagating in either or both directions—could happen every 200 to 300 years. To put this in context, the Northridge earthquake was a mere magnitude 6.7, yet caused 57 deaths and economic losses of more than $40 billion.

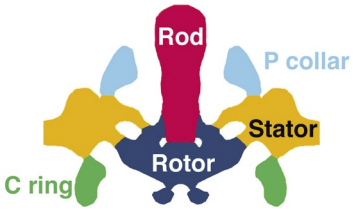
The results were published in October issue of the *Bulletin of the Seismological Society of America*. The other authors are Chen Ji (MS '99, PhD '02), now at UC Santa Barbara, Dimitiri Komatitsch of the University of Pau in France, and Jeroen Tromp, Caltech's McMillan Professor of Geophysics and director of the Seismological Laboratory. Online movies of the earthquakes and building-damage simulations can be viewed at http://www.ce.caltech.edu/krishnan. □—*JP*

Four stamps featuring snowflake photographs taken by Professor of Physics Ken Libbrecht (BS '80) have been issued by the post office just in time for all your holiday-card needs. Libbrecht attended a dedication ceremony for the stamps on October 5 at a major stamp-collecting convention at Madison Square Garden in New York. The snowflake photos are an outgrowth of Libbrecht's work on the physics of pattern formation during crystal growth (see *E&S*, 2001, No. 1). His latest, pocket-sized book on the subject, *Ken Libbrecht's Field Guide to Snowflakes*, just came out as well. Ho, Ho, Ho!

Now They Can Be Shown

Both adapted from Murphy, et al, *Nature*, vol. 442, pp. 1062–1064, 2006. © 2006, Nature Publishing Group.





We couldn't run these images in last issue's electron cryotomography article ("Cellular CAT Scans") because of an embargo by *Nature*. At right is the first-ever high-resolution, 3-D view of a working molecular motor. As coauthor Grant Jensen, assistant professor of biology, remarked in *E&S*, "If he [grad student Gavin Murphy, the *Nature* paper's lead author] thawed the cells out, they'd swim away." The cells in question are a bacterium known as *Treponema primitia*, and the motor spins at about 300 revolutions per second to drive a flagellum that propels the cell.

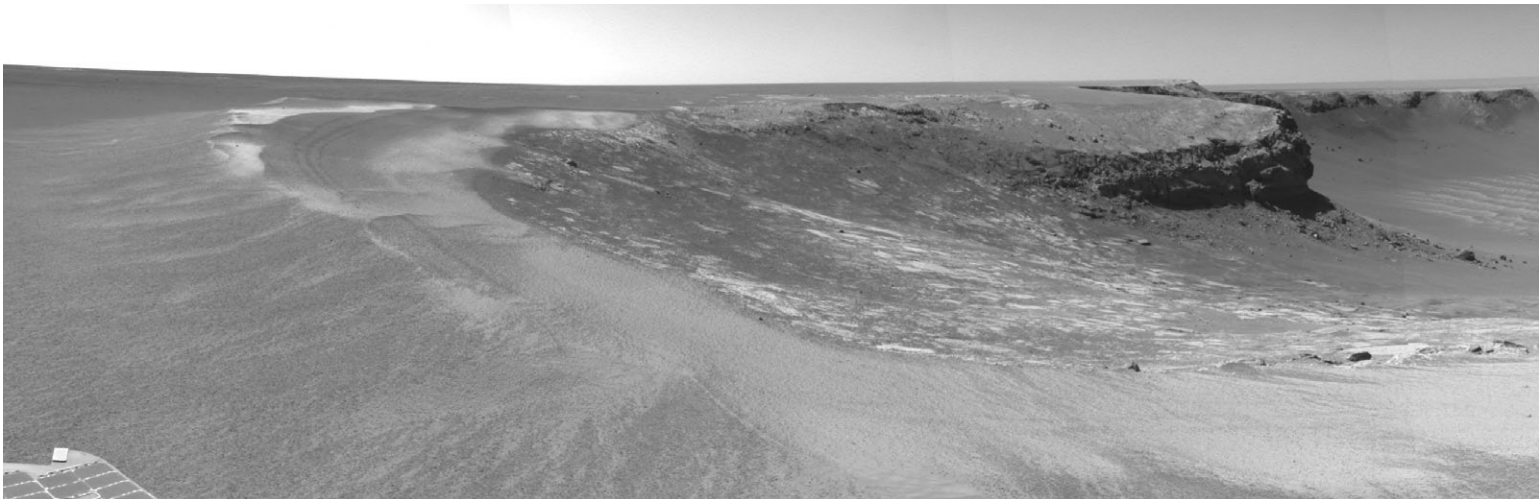
A marvel of complexity, the motor is assembled from molecules of about 25 different proteins. Other researchers had isolated and purified some of them to determine their structures, or had pulled the motor out of the cell to examine it, losing pieces in the process. Seen here for the first time is the ring-shaped torque generator, called the stator (yellow), which is embedded in the inner cell membrane. Nested inside the stator is the moving part, the rotor (dark blue), which is attached to a rod (red) that turns the flagellum. A cross section through the stator (below right) shows that each of its 16 symmetric units grabs the rotor in two places, like a person's two hands gripping the rail of a playground merry-go-round in order to spin it. Also revealed are the stator's connections to the P collar (light blue), which is basically a bushing, and the C ring (green), which acts like a transmission to select clockwise or counterclockwise rotation. The paper, whose third author is Associate Professor of Environmental Microbiology Jared Leadbetter, ran in *Nature*'s August 31 issue. □—*DS*

Opportunity snapped th

frames from the navigati

far side is about 800 meters away, and its rim towers approximately 70 meters above its floor. Victoria's exposures of layered bedrock are 20–30 meters thick—compared to

Eagle Crater, where Opportunity landed—and should reveal a proportionately longer span of local Martian history.



O'Donovan's Giant Planet

We may be down a planet with the recent demotion of Pluto (see box), but the number of giant planets discovered in orbit around other stars continues to grow steadily—around 200, at last count. Now, an international team of astronomers led by Caltech grad student Francis O'Donovan has detected a planet slightly larger than Jupiter that orbits a star 500 light-years from Earth in the constellation Draco. The planet, known as "TrES-2" (pronounced Trace-2) passes in front of a star called GSC 03549-02811 every two and a half days, causing a dimming of its light by about 1.5 percent.

TrES-2 is the first transiting planet—or planet that passes directly between its star and Earth—to be found in an area of the sky known as the "Kepler field," a piece of celestial real estate about the size of your two hands held together at arm's length, or twice the bowl of the Big Dipper. NASA's Kepler mission, set to launch in October 2008, will stare at this patch of sky for four years, and should discover hundreds of planets, both giant and Earth-like. Discovering TrES-2 beforehand allows Kepler's astronomers to plan additional observations of it, such as searching for moons.

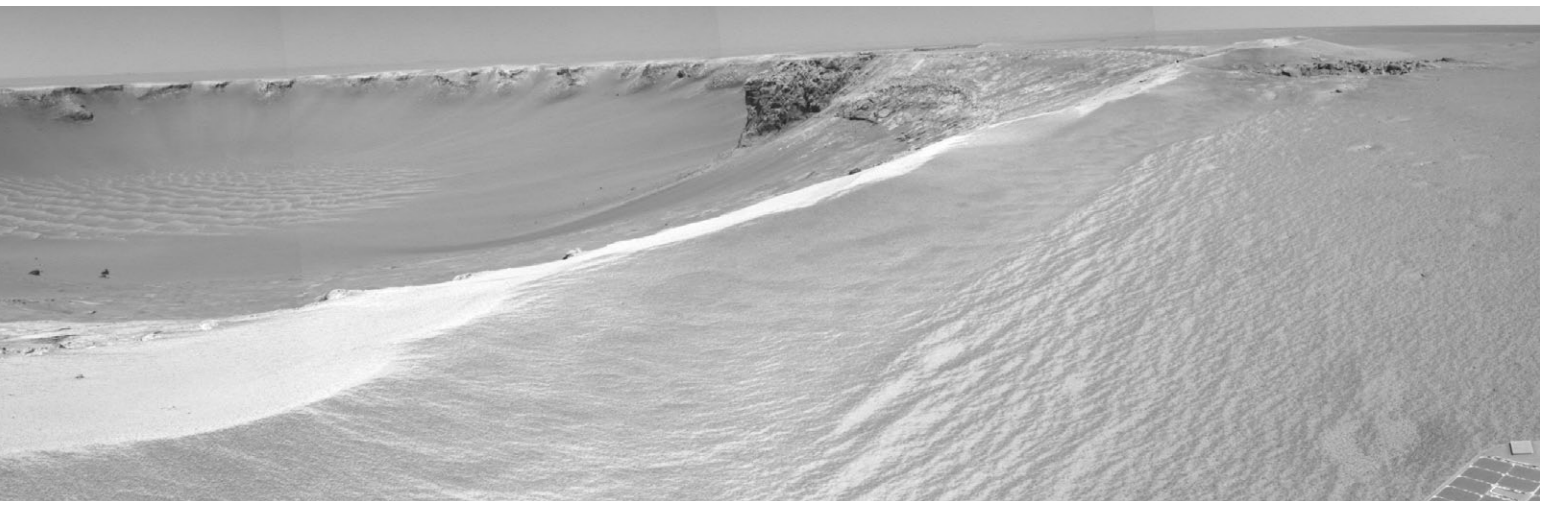
TrES stands for Trans-Atlantic Exoplanet Survey, an effort involving the Sleuth telescope at Caltech's Palomar Observatory, the Planet Search Survey Telescope (PSST) at Lowell Observatory near Flagstaff, Arizona, and the STellar Astrophysics and Research on Exoplanets (STARE) telescope in the Canary Islands—all three of which were built with off-the-shelf camera lenses and mostly from amateur-astronomy components. TrES-2, the second planet to be found by the survey, was first spotted by Sleuth, which was set up by Caltech postdoc David Charbonneau, now at the Harvard-Smithsonian Center for Astrophysics and a coauthor of the paper. The PSST, which is operated by coauthors Georgi Mandushev and Edward Dunham, corroborated the initial detection.

These small, automated telescopes took wide-field, timed exposures covering thousands of stars at a time over a period of about two months per field. When the software detected regular variations in the light from an individual star, it alerted the astronomers. In order to confirm that the dimming was due to an orbiting planet, and not, say, a small, faint companion star, O'Donovan and his colleagues switched to one of the 10-meter telescopes at the W. M. Keck Observatory on the summit of Mauna Kea, Hawaii, to do detailed spectroscopic observations. Says O'Donovan, "All our hard work was made worthwhile when we saw the results from our first night's observations, and realized we had found our second transiting planet."

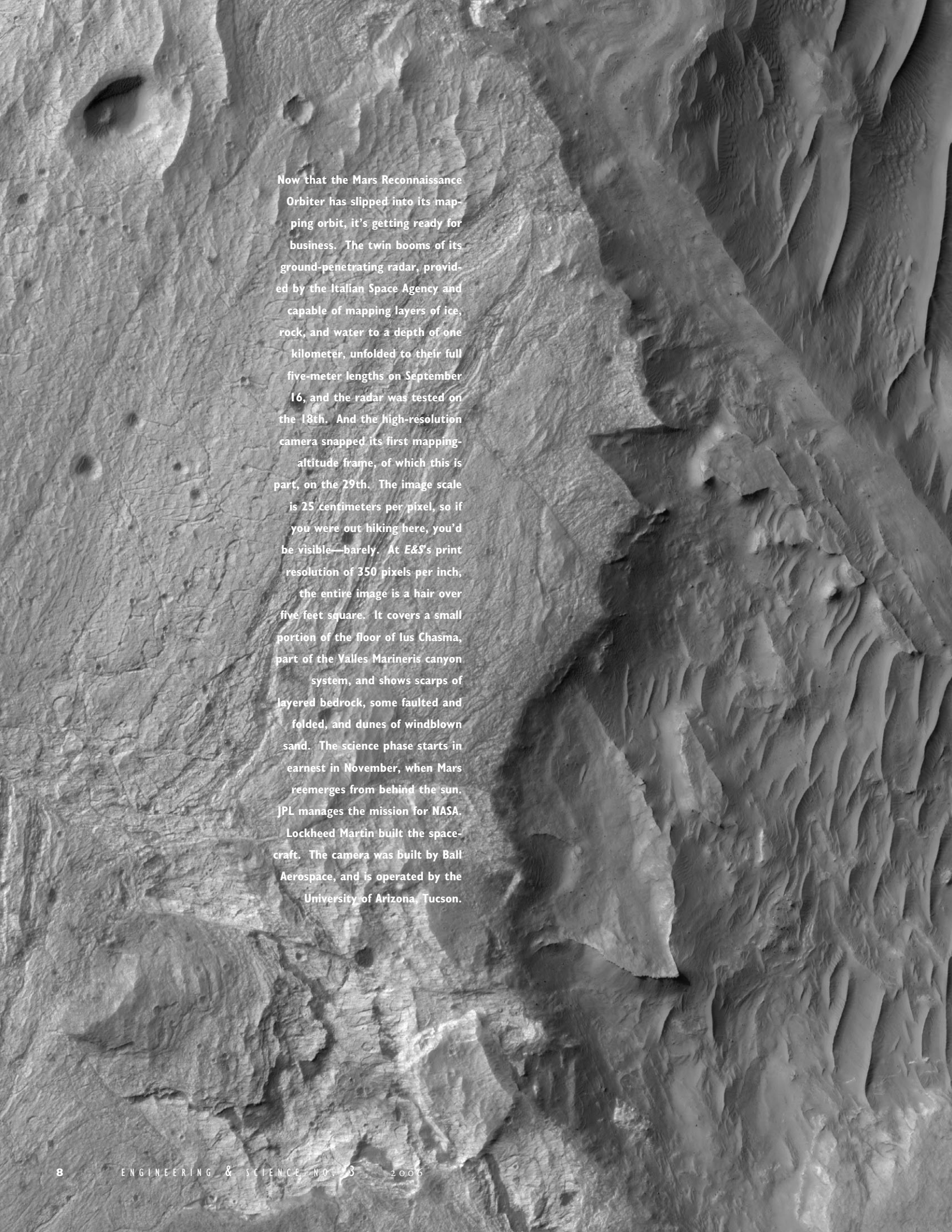
The paper announcing the discovery will appear in an upcoming issue of the *Astrophysical Journal*. The 15 other authors include JPL's John Trauger and Associate Professor of Astronomy Lynne Hillenbrand. □—*RT*

Mike Brown and the Five Dwarfs

As you've no doubt heard by now, in August the body formerly known as "Xena" was denied planetary status by the International Astronomical Union (IAU), which then, for good measure, booted Pluto out of the club as well. These objects, plus the other ones discovered by Professor of Planetary Astronomy Mike Brown and colleagues—Quaoar, Sedna, "Santa," and "Easterbunny"—will henceforth be termed "dwarf planets." The IAU also formally named "Xena" Eris, the Greek goddess of discord; its moon "Gabrielle" is now Dysnomia, Eris's daughter and the goddess of lawlessness. But fans of TV's warrior princess need not despair—Brown notes that Xena was played by Lucy Lawless, and Eris appeared on the show as a recurring character under her Latin name, Discordia. □—*DS*



PICTURE CREDITS: 2-3—Palomar-Quest team/Caltech; 4, 6-7—NASA/JPL; 5—United States Postal Service; 8-9—NASA/JPL/U. of Arizona



Now that the Mars Reconnaissance Orbiter has slipped into its mapping orbit, it's getting ready for business. The twin booms of its ground-penetrating radar, provided by the Italian Space Agency and capable of mapping layers of ice, rock, and water to a depth of one kilometer, unfolded to their full five-meter lengths on September 16, and the radar was tested on the 18th. And the high-resolution camera snapped its first mapping-altitude frame, of which this is part, on the 29th. The image scale is 25 centimeters per pixel, so if you were out hiking here, you'd be visible—barely. At *E&S*'s print resolution of 350 pixels per inch, the entire image is a hair over five feet square. It covers a small portion of the floor of Ius Chasma, part of the Valles Marineris canyon system, and shows scarps of layered bedrock, some faulted and folded, and dunes of windblown sand. The science phase starts in earnest in November, when Mars reemerges from behind the sun. JPL manages the mission for NASA. Lockheed Martin built the spacecraft. The camera was built by Ball Aerospace, and is operated by the University of Arizona, Tucson.

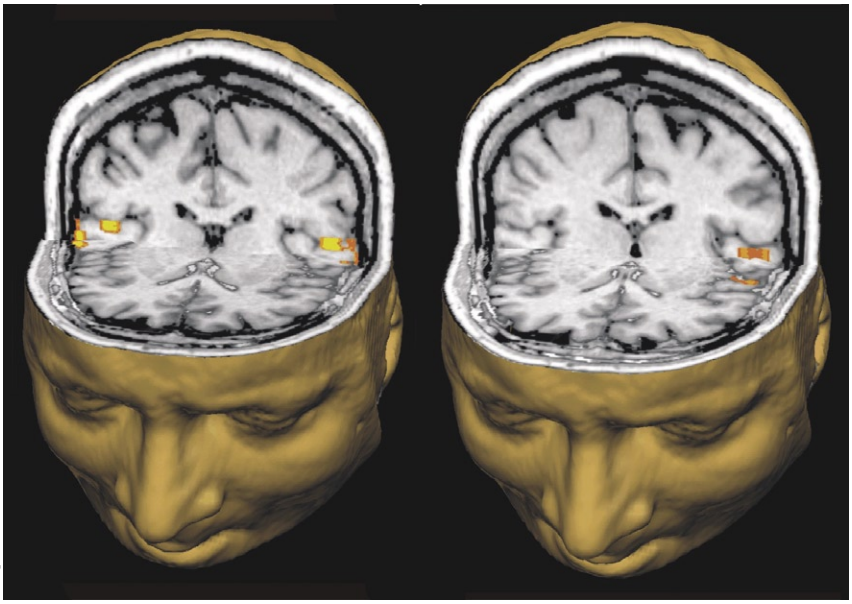
Pregnancy, Immunity, Schizophrenia, and Autism

by Paul H. Patterson

Can something as innocuous as the flu cause schizophrenia? Can a pregnant mom's sniffles have lifelong consequences for her unborn child? Does the brain's own immune system play a role in autism? The answers to these and related questions are indeed surprising, and may suggest new avenues for treatment or even prevention.

As we learn more about the connections between the brain and the immune system, we find that these seemingly independent networks of cells are, in fact, continually talking to each other. As an adult, the activation of your immune system causes many striking changes in your behavior—increased sleep, loss of appetite, less social interaction—and, of course, headaches. Conversely, stress in your life (as perceived by your brain) can influence immune function—the brain regulates immune organs, such as the spleen, via the autonomic nervous system.

Opposite: A detail from *The Temptations of St. Anthony* by Hieronymus Bosch (d. 1516). The fantastic—in the strictest sense of the word—figures portrayed here are not unlike some hallucinations reported by schizophrenia sufferers. Courtesy of the Museu Nacional de Arte Antiga, Lisbon.



Reprinted from Dierks, et al., *Neuron*, vol. 22, March 1999, pp. 615–621, © 1999, with permission from Elsevier.

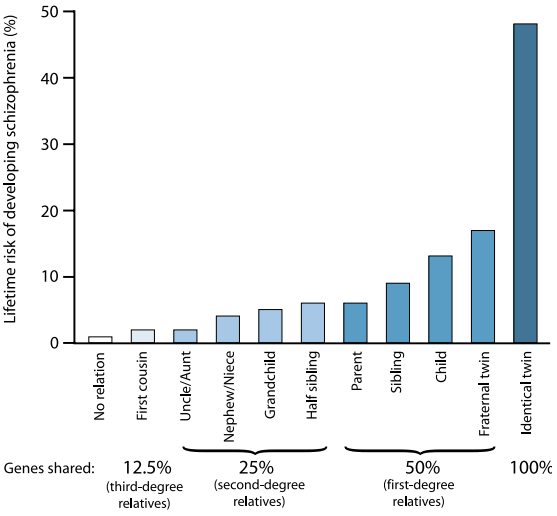
Recent evidence shows that this brain-immune conversation actually starts during the development of the embryo, where the state of the mother's immune system can alter the growth of cells in the fetal brain. As we shall see, such alterations can lead to an increased risk of schizophrenia or autism in the offspring.

First let's consider schizophrenia, which is a progressive disorder whose initial psychotic symptoms usually appear in early adulthood. (For a gripping rendering of how psychotic episodes might appear to the sufferer, see Russell Crowe in *A Beautiful Mind*.) People with schizophrenia can be seemingly quite normal part of the time, and then have very severe problems, which is a huge difficulty for them—people have tended to blame the victim and wonder why the patient doesn't get him- or herself together and behave properly.

In the last decade or two, anatomical and functional differences between schizophrenic and typical brains have begun to emerge. Magnetic resonance imaging (MRI) scans of the brains of identical twins, one with schizophrenia and one without, have shown that in 90 percent of the cases the twin with schizophrenia has enlarged ventricles, which are butterfly-shaped, cerebrospinal-fluid-containing voids in the center of the brain. One explanation for this enlargement is that the gray matter surrounding the ventricles might have shrunk, meaning the brain has fewer or perhaps smaller neurons. Or the neurons might be more densely packed. An alternative hypothesis invokes an infection—encephalitis, for instance, will expand the ventricles. Schizophrenia does not result from a frank infection of the mature brain, but there are other indications, which I'll come back to, that infections might be involved very early on.

MRI shows anatomical details, but functional MRI, which tracks blood flow, shows brain activity. The more blood moving through a particular part of the brain, the more active it presumably is. In these renderings of functional MRI scans of a schizophrenic patient, the head at far left shows, in yellow, that the auditory cortex lit up when a

Heschl's gyrus is the brain's main sound-processing center. A real sound lights it up on both sides of the brain, as seen at far left in these 3-D renderings. The gyrus lights up spontaneously during an auditory hallucination (left), but only on the brain's dominant side.



Right: There is clearly a genetic predisposition to schizophrenia. This chart shows how your chances of developing the disease increase if you have a close relative with it—the more genes you share with the affected person, the higher your susceptibility. Adapted from *Schizophrenia Genesis: The Origins of Madness* by Irving I. Gottesman, W. H. Freeman and Company, New York, 1990.

Separated at birth, the Mallifert twins meet accidentally.

stereophonic sound was played through earphones. The other head shows the brain activity when the patient pushed a button to signal that he or she was "hearing voices." The hallucinations only appear in the dominant hemisphere, so in this right-handed patient, only the left hemisphere's auditory cortex lit up. It used to be said that the voices in their heads were imaginary, but since there is activity in the part of the brain that actually does process auditory information, they really exist, in a sense. Schizophrenics *are* hearing sounds, as far as their brains know, and it would be very interesting to discover what generates this activity spontaneously.

We know that schizophrenia begins in early development. Statistically, children who will later develop psychosis are more prone to disciplinary problems in school, tend to have lower IQs, and are more likely to be beset with emotional and social problems. The differences are too small to be useful for an early diagnosis, but they're there. There's also a surprising delay in the development of motor functions—sitting, standing, walking, and so on.

There's a genetic component to schizophrenia. The most important risk factor for predicting schizophrenia is having a sibling with the disorder. In the general population, the risk for schizophrenia is approximately 1 percent worldwide. If you have a schizophrenic cousin or uncle or aunt, the risk is doubled, which is not very significant. But if you have an identical twin with schizophrenia, the risk is about 50 percent that you will become schizophrenic as well. But it's not 100 percent, so it's not a classical, dominant genetic disease like Huntington's disease, where a single malfunctioning gene gives you the disorder. Rather, people think there are some six to 12 genes involved, each of which contributes a small amount of risk. In the last couple of years, a number of these genes have been identified, including neuregulin, dysbindin, and one called "Disrupted-in-Schizophrenia," or DISC1. Furthermore, each of these genes is well known from animal studies to be very important in early embryonic brain development.

There is also an environmental risk component. Being born in the winter or spring months, or being born and raised in an urban area both increase risk. This is consistent with an infectious hypothesis—we tend to get sick more often in the winter and spring, and we're more likely to sample other people's germs if we live in a crowded area.

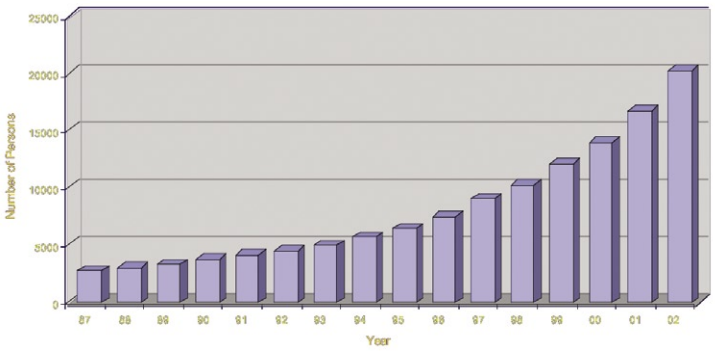
Another important environmental risk factor is maternal infection, which will be one of my major themes. Having a respiratory infection during the second trimester of pregnancy increases the risk for schizophrenia in one's offspring. In the year 2000, Alan Brown and his colleagues at Columbia University in New York studied the medical records of 12,000 pregnant women who belonged to the Kaiser HMO in the Oakland area. Brown found

that there was about a threefold increase in risk if the woman had a respiratory infection during the second trimester, confirming the conclusions of previous studies that had not had access to patient records. The researchers then analyzed frozen serum samples from those women, and found a similar, or even larger—up to sevenfold—increased risk if antiflu antibodies were present during the first half of pregnancy. Moreover, they found a statistically significant association with elevated levels of some members of a group of proteins called cytokines. Cytokines are produced by the white blood cells, and their levels in the blood increase when we get an infection. A calculation of the so-called attributable risk from this data led to the estimate that about 20 percent of the schizophrenia cases would not have occurred if flu exposure had been prevented.

This is a really dramatic piece of information, particularly given that the researchers had to completely ignore the genetic angle. (Even now, we cannot screen for the susceptibility genes that have since been identified.) Thus, the study presumably included a large number of people who will never get schizophrenia because they aren't genetically predisposed, yet it *still* found a three-to-sevenfold risk increase. The actual risk due to maternal infection is therefore likely to be much higher.

Alarmingly, cases of autism appear to be dramatically on the rise. However, it's not clear how much of this actually represents an increase in the incidence of autism, or an increase in the diagnosis of autism rather than, for instance, mental retardation.

Other studies of adult schizophrenic subjects have found cytokine imbalances and elevated levels of white cells in the blood. And antipsychotic drugs such as clozapine, which people take to treat hallucinations and disordered thoughts, are known from animal studies to modulate cytokine levels in the blood. So these drugs might not only be acting in the brain, but on some aspect of the immune system to achieve their effectiveness. I think this is a very interesting observation, but it hasn't made much of an impression on the research community yet, so the possibility hasn't really been investigated carefully.



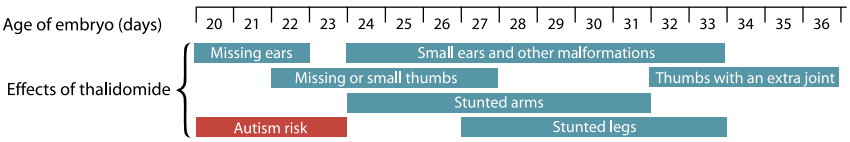
This chart shows how the annual number of people diagnosed with autism who were served by California's Department of Developmental Services began to skyrocket in the mid-1990s. Courtesy of the DDS.

A recent, very impressive paper by William Eaton and colleagues at Johns Hopkins University Medical School analyzed the remarkably comprehensive records of Denmark's health system, which tracks every Dane from the cradle to the grave. The investigators accessed the files on all 7,704 people who were diagnosed with schizophrenia between 1981 and 1998, including the details of every hospital visit those people ever made in their entire lives. It turns out that people who developed any of nine different autoimmune disorders—diseases in which the body's immune system begins attacking one's own cells—had a 45-percent increase in risk for developing schizophrenia.

So there is a link between the immune system and schizophrenia, but we don't know what it is. We know that a genetic predisposition to autoimmune disease exists—are the genes responsible for this predisposition somehow linked to the ones predisposing to schizophrenia? Or is there something about having an autoimmune disorder, such as the creation of antibodies against certain molecules, which increases risk for schizophrenia?

Now let's turn to autism, which was originally described by Leo Kanner at Johns Hopkins in 1943 as a type of schizophrenia. We don't think that way anymore, but there are some interesting similarities—particularly in the withdrawal of patients from the world around them. The hallmarks of autism are, of course, deficient social skills—patients don't read other people's emotions well or respond to them appropriately—and the lack of development of language. Heartbreakingly, about 30 percent of patients actually experience a regression in these areas that starts at about age three. Unlike schizophrenics, however, autistic children frequently display odd, repetitive gestures—banging their heads against the wall, or a flapping motion with the hands that is a classic symptom often used by teachers as a possible indication that a problem may exist. And autistics tend to fixate on objects and rituals. A patient might spend hours playing with a piece of string, for example, or eating her dinner in just the right way. There's also fear of new situations or objects, and oftentimes considerable problems with sensory stimuli—extreme sensitivity to noises, for example. Alarmingly, cases of autism appear to be dramatically on the rise. However, it's not clear how much of this actually represents an increase in the incidence of autism, or an increase in the diagnosis of autism rather than, for instance, mental retardation.

Like schizophrenia, there's a strong genetic component to autism—the single biggest risk factor is having a sibling with it. Autism is also a multi-



Fingers, toes, limbs, and organs all develop in the fetus according to a very strict timetable, and the types of birth defects seen in thalidomide babies correlate very precisely to when the mother-to-be took the drug. Some thalidomide babies are also autistic, revealing a window of vulnerability in early brain development. Autism data from K. Strömland et al. in *Developmental Medicine and Child Neurology*, April 1994; graphic after Patricia Rodier, *Scientific American*, February 2000.

genetic disorder, with six to 10 genes involved, and again, the genes that have been identified thus far (neuroligins 3 and 4, En-2, and Hox-a1) are very important in embryonic brain development. Furthermore, there are environmental risk factors for autism. Valproic acid, which is used to treat epilepsy, causes a dramatic increase in the risk of autism when taken by women before they know they're pregnant. This drug is still commonly prescribed, but people are beginning to get concerned about its use by pregnant women.

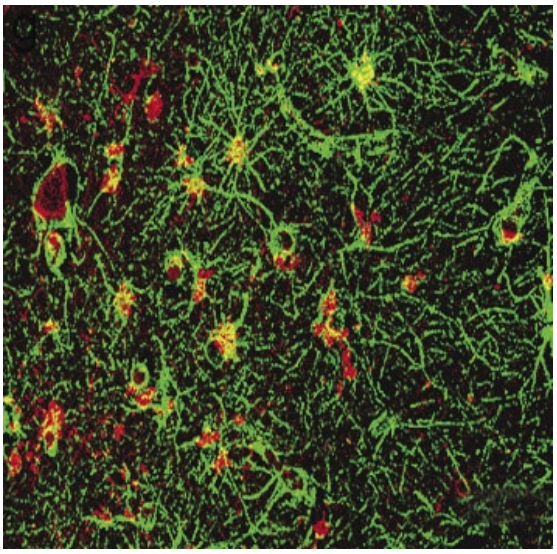
We have a valuable insight into the fetus's period of vulnerability, thanks to the thalidomide tragedy. Those of you who are old enough will remember the use of thalidomide as an anti-morning-sickness drug in the 1960s. Severe birth defects resulted, as did an increased incidence of autism. But what is key here is that the kind of physical abnormality one got—missing ears, stunted arms, stunted legs—was found to depend on how far along the pregnancy was. In other words, the child's deformity told us exactly when, sometimes to within a day or two, the mother took the drug. The window of risk for autism proved to be days 20 through 23 after conception—a very early stage in neural development. At this time, the neural tube is just closing, and the first neurons are just being born. A similar window of risk is found with valproic acid, and with an ulcer-preventing drug called misoprostol. We don't know the cause or causes of autism in most cases, but this window of vulnerability is clearly a very important clue to how the brain is altered in this disorder.

Again, as in schizophrenia, there's a maternal-infection risk factor. A review of the literature by Andrea and Roland Ciaranello at Stanford concluded that "the principal nongenetic cause of autism is prenatal viral infection." This was based primarily on studies of an epidemic of rubella, or German measles, in New England in 1964. On the order of 10 percent of the children born to infected mothers exhibited symptoms of autism, which is really an astronomical increase in risk. Of course, rubella is not common anymore, because we get vaccinated against it, but the point is that maternal infection can increase the risk for autism. Other infections have also been implicated—a paper just came out last week linking genital herpes infection with an increased risk for autism.

Without going into the details, the rates of autoimmune diseases and allergies are higher in families with autism, particularly in the mother. There are also reports of immune dysfunctions in the blood of autistic individuals. These various connections to the immune system are, of course, reminiscent of schizophrenia.

There is also very striking evidence of immune dysregulation in the brain itself. Just last year, a group led by Carlos Pardo at Johns Hopkins found what they're calling a "neural inflammation" in postmortem examination of brains of patients with autism who died between the ages of eight and 44 years. But these people weren't infected—they died of such things as drowning or heart attacks. The study found that the microglial cells, which act as the brain's own immune system, were activated. The study also found amazing increases of certain cytokines in the brain, and of others in the cerebrospinal fluid. This is a landmark paper, in my opinion. It presents the first evidence that there's an ongoing, permanent immune-system activation in the brains of autistic people. It's a subclinical state, because there's no overt infection. But it's there.

To try to untangle how the immune system is intertwined with the development of these diseases, we turned to an animal model. Animals are vital to



In this cross section of the cerebellum of an autistic patient, the microglial cells have been activated, as shown by their absorption of a red dye that binds to an immune-system protein called HLA-DR.

medical progress. If you think a gene is important in a particular disease, you can introduce that gene into a mouse, and note whether it gets something like the human disease. You can also test bacteria, viruses, and environmental toxins. You can study pathogenesis—how the stages of the disease progress, and how it spreads from tissue to tissue—in animals much much easier than you could in humans. And you can, of course, test treatments. By law, you *have* to test drugs on animals first. It's also how we work out the details of new surgical procedures and explore the potential of new therapies, such as those involving stem cells. Without the animal studies that preceded them, such common but highly complex procedures as bone marrow, kidney, and heart transplants would not be available today.

That's all well and good, but what about animal models of mental illness? How do you psychoanalyze a mouse? How can you tell if it's hallucinating? (I think we can, but that's a topic for a future Watson lecture.) And how do we even *model* a disease like autism, which is supposed to be uniquely human? How can you measure an autistic mouse's impaired language skills when—sorry, Walt—they aren't capable of speech in the first place? Or at least not speech that we can understand—they do communicate via alarm and distress calls, and there is even some speculation that they can recognize other mice by their voices. But that, again, is another story.

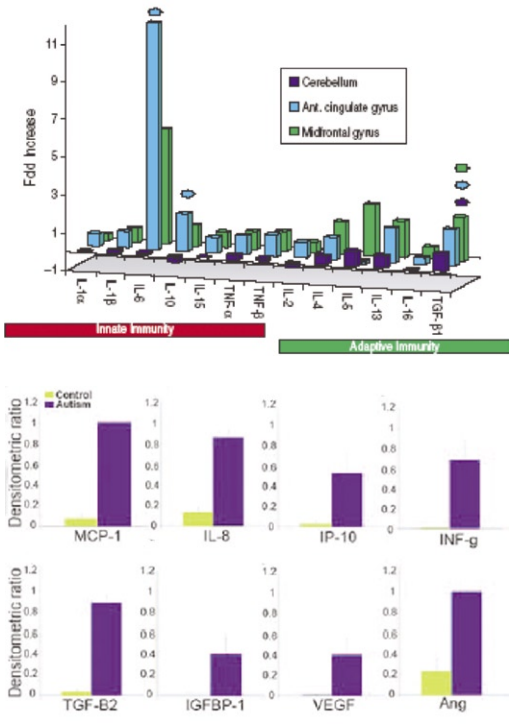
Fortunately, that isn't what we really do with animal models. We don't mimic the *whole* disease in any model—we mimic *features* of the disease. This might be the kinds of neurons that die. It might be some change in the electrical properties of the neurons, or some molecular change such as the cytokine levels. Or it could be the tremors and shuffling gait of Parkinson's disease. In fact, the mouse models of Alzheimer's and Huntington's diseases that are in routine use in labs around the world do not display some of the diseases' key features. The neurons that typically die in human patients somehow survive, for example. So a model doesn't have to be perfect to be extremely useful, even when testing potential human therapies.

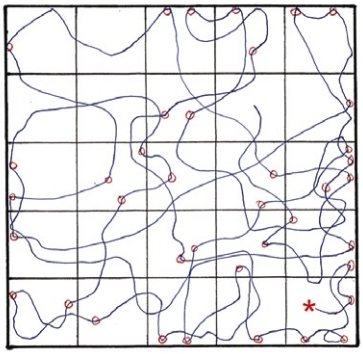
Our laboratory is exploring a model of maternal infection. We give a pregnant mouse the flu by touching a pipette containing a solution of the human influenza virus to her nose, which she then inhales. The mouse gets lethargic, stops grooming herself, hunches in the corner of the cage, and in a few days recovers and behaves normally again. In due time she gives birth, and we study the pups, both as infants and adults. We watch their behavior, and then examine their pathology—what their brains look like.

What types of mouse behavior might be relevant for schizophrenia or autism? People often use what's called an open field test to study anxiety under mildly stressful conditions. The mouse is placed in an enclosure with a camera overhead and grid

A handy guide to deciphering mouse psychology.

Top: Elevated cytokine levels were found in three different parts of the brains of autistic patients. The flat gray rectangle at the bottom of the graph shows the corresponding levels in typical brains. Bottom: Cytokine levels in the cerebrospinal fluid of autistic (purple) and unaffected (yellow) subjects.



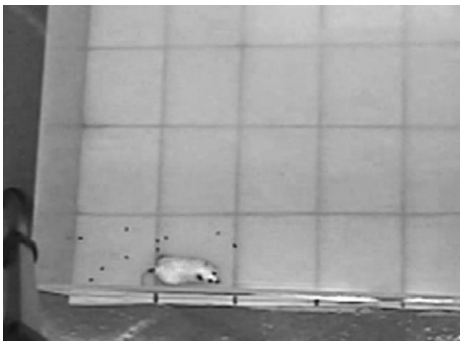


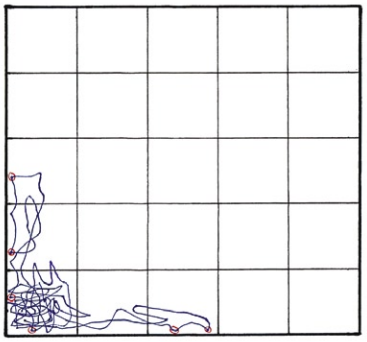
The path followed by a control mouse exploring an unfamiliar place. The asterisk marks where the mouse was placed in the box, and the red circles show where the mouse stood up on its hind legs for a better whiff of its surroundings.

lines on the floor so we can track where the animal moves. A normal mouse usually spends a lot of time creeping along the edges of the box at first, because it's afraid that it's dangerous to go out into the middle—which, obviously, it might be. But it will eventually inspect most of the box, pausing frequently in the process to rear up on its hind legs and sniff the air. Our normal mice, which we call control mice, are born to "sham-infected" mothers who were given a sterile saline solution without the virus. These mice do exactly the same thing—they are timid at first, but they're soon traipsing all over the box.

Below is an example of an adult mouse who was born to a flu-infected mother, and you can tell immediately from the fecal pellets that it hasn't moved beyond its corner very much at all. We would interpret this as excessively fearful behavior, given the mildly stressful nature of the situation, and we can quantitate it by simply measuring the amount of time spent in the center squares of the box. This mouse enters the center many fewer times, and it rears and sniffs much less often as well.

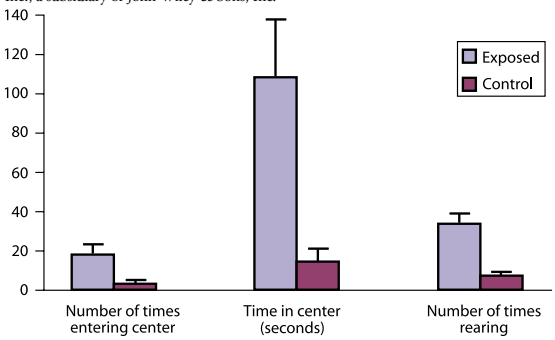
By contrast, a mouse whose mother got the flu tends to stay hunkered down in the corner where it was placed.





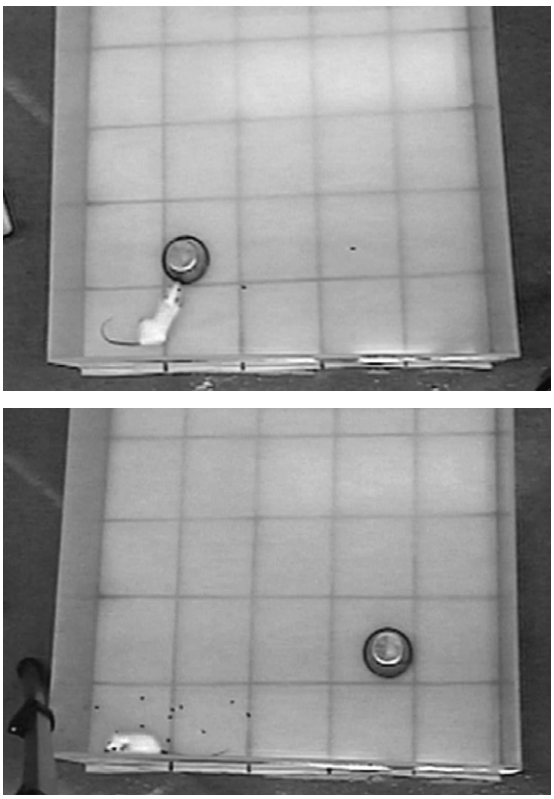
The so-called novel-object test is also relevant. Remember, autistic children are often afraid of unfamiliar things. So when we put something strange and new in the field, say a coffee cup, the control mouse carefully investigates it, touching and sniffing it from all sides, whereas our mouse born to an infected mother is very reluctant to go anywhere near it. In fact, this mouse turns its head away and acts as if the object isn't there. We measure the time lapse before the mouse first touches the object, which we call the latency to first contact, and we count how often contacts are made. Again, the differences are dramatic. The "autistic" mouse waits much longer, and touches the object far fewer times.

We also do simple social interaction tests. We put two mice who don't know each other in the box, and ask how long it takes them to make physical contact, and how often they do so. And not surprisingly, pairs of mice born to infected mothers make contact less than half as often and have more than four times the latency. So clearly they're not socializing properly. Grad student Steve Smith is now following up on that observation by



Mice whose mothers were given the flu virus ventured into the great empty middle of the box much less often (left) and spent much less time there overall (center). They also reared up to sniff less often (right).

At least rodents don't run up bar tabs—biology staff member Limin Shi puts a pair of mice in a three-room box designed to test their social skills.

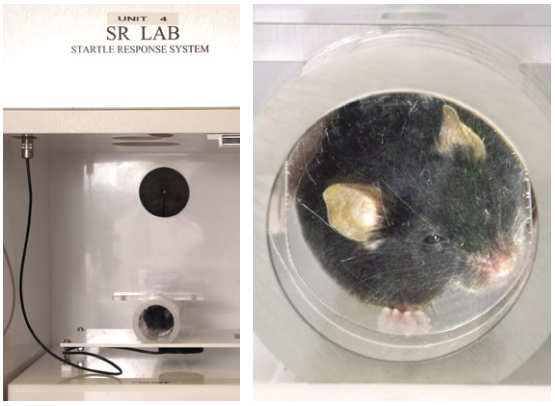


Top: A normal mouse inspects an unfamiliar object with avid curiosity.

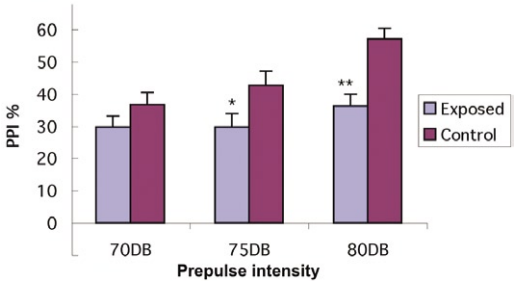
Bottom: An "autistic" mouse ignores it, seeming to act on the theory that if it can't see the object, the object doesn't exist.

using a box divided into three rooms. We put our test mouse in the middle room, and then we put an unfamiliar mouse in one of the side rooms. We leave the room on the opposite side empty in some tests, and in others we put a cage mate of our test mouse in there. Then we sit back and watch where our test mouse goes. Normal mice like novelty, and almost always go to the strange mouse, even when there is a familiar mouse in the other room. Preliminary results with our "autistic" mice, however, show that they prefer to remain in the central chamber regardless of who else is in the box with them.

Another pertinent test is the startle response, which is a lot like sneaking up behind someone with an inflated paper bag and popping it. We put the mouse in a tube inside a soundproof box, and underneath that tube is a motion sensor. There's a speaker in the box, and when a loud sound is played, the mouse is startled, and we measure how high it jumps. But if we precede the loud sound with a softer sound that doesn't startle the mouse—called a prepulse—it doesn't jump so much. This is called prepulse inhibition, or PPI, and when the same type of test is done in people, a striking deficit is observed in schizophrenic and autistic subjects. In other words, they get startled just as much regardless of whether they got a prepulse or not. The loud noise surprises them every time. We think this relates to the attention-deficit issues. On the next page is a plot of the amount of the mice's PPI versus prepulse intensity. As we increase the prepulse intensity, we get a bigger inhibition across the board, but our "autistic" mice have a PPI deficit at every intensity.



Right: The mouse-startling machine. The mouse sits in its comfy burrow—a plastic tube, seen end-on in these pictures, that in turn sits on a platform with a motion sensor (the black unit connected to the black cable) on its underside.



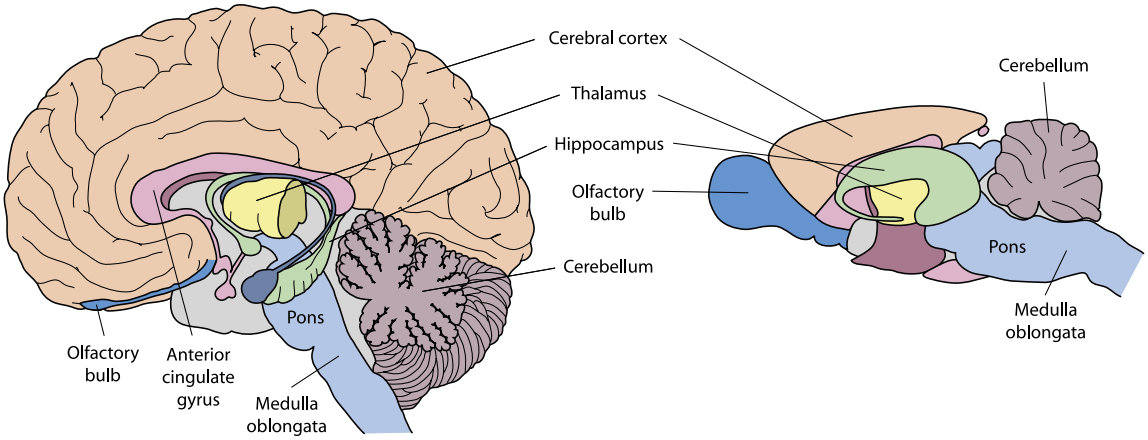
Far right: Regardless of how loud the prepulse was (the numbers are in decibels), the "autistic" mouse was always more startled—that is, had a lower prepulse inhibition (PPI) than a control mouse.

Adapted from Shi, et al., *The Journal of Neuroscience*, vol. 23, no. 1, pp. 297–302, January 1, 2003. © 2002 Society for Neuroscience. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

The PPI is thought to be a measure of sensory-motor gating—the connection between the filtering of incoming sensory information and the creation of motor outputs to the muscles—which is likely to be related to attention deficits and distractibility. In fact, a PPI deficit is also found in attention deficient disorder. Importantly, those antipsychotic drugs mentioned earlier can restore the PPI in schizophrenic subjects, whereas psychomimetic drugs—hallucinatory drugs—disrupt PPI. We have shown the same thing to be true in our mice.

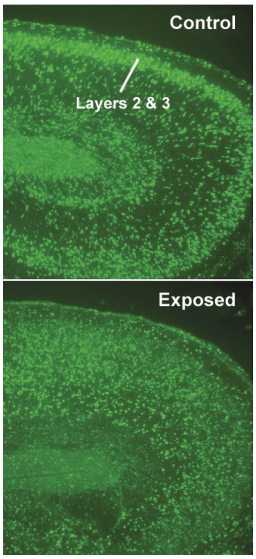
We presume that these behavioral abnormalities are based in brain pathology—changes in the nerve cells, or in their connections. In fact, postmortem examinations of at least some brains of schizophrenia patients have shown nerve cells that are not in their appropriate locations. So recently, biology staff member Limin Shi, postdoc Natalia Malkova, and Steve Smith have been looking at fetal brain development in the mice. For this analysis, the pregnant mice are given the flu at mid-pregnancy, day 9.5 of gestation, which corresponds to the period of very early brain development in humans. In other words, it's similar to the thalidomide window of autism vulnerability. However, because fetal mice develop so fast, the illness also extends through the period corresponding to that second-trimester stage in humans when maternal infections lead to an increased risk of schizophrenia. Five days into the infection, a dye that marks newly formed neurons is injected into the mice, and they give birth six days after that. At right is the brain of a normal pup. The green neurons have taken up the dye, and most of them have migrated out to what neuroanatomists call layers 2 and 3 of the cerebral cortex. This is similar to how a normal newborn human brain would look, too. But this layer is barely present in the pups from infected mothers. Something has gone very wrong, because the green cells have wandered off all over instead of forming the normal, tightly packed layers. We plan to repeat the experiment but let the pups grow to adulthood to see if this disorganization persists, and whether it looks similar to what was found in those few human schizophrenia examples.

Another human pathology occurs in the cerebellum. The cerebellum has lobes, called lobules, which look like a cauliflower in cross section, and contain neurons called Purkinje cells that are pres-



The human (right) and mouse (far right) brains, not to scale.

A 20-month-old child participates in Pierce and Courchesne's current set of exploration studies. The tape grid on the floor helps the researchers map the child's movements. Photo courtesy of Karen Pierce.



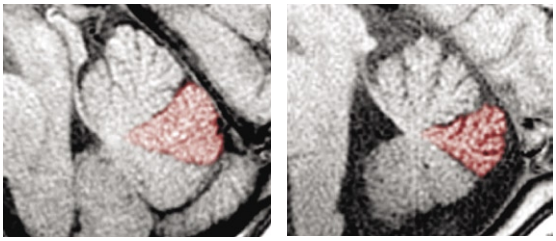
Neurons from an early stage of brain development have been labeled with a fluorescent green dye. These neurons form clearly visible layers in a healthy newborn mouse brain (top), but when the mother was infected in midpregnancy (bottom), the neurons are scattered almost at random.

ent in all mammalian species. Some 90 percent of postmortem autism samples show a substantial reduction in the number of Purkinje cells in lobules VI and VII. In some cases there are even misplaced Purkinje cells. And MRI studies of living autistic subjects reveal that lobules VI and VII are underdeveloped.

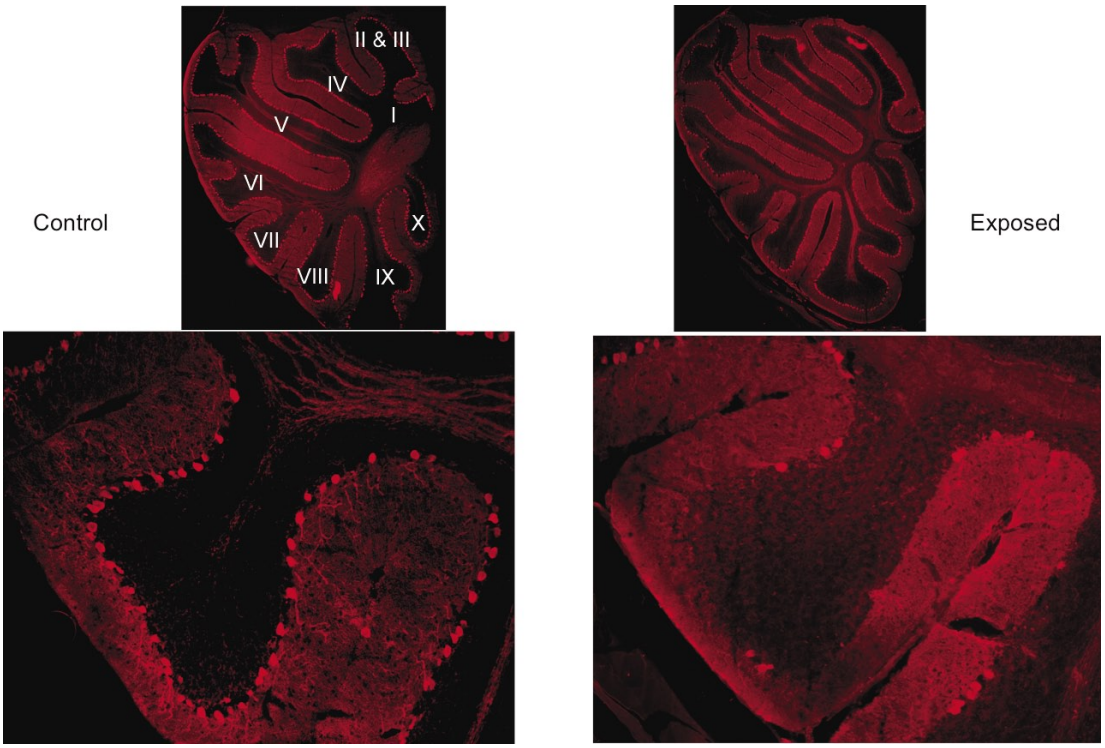
There is a fascinating correlation between abnormalities in lobules VI and VII and children's exploratory behavior. In 2001, Karen Pierce and Eric Courchesne at UC San Diego did a study where they put a child (aged three to eight) in a room with a lot of brightly colored boxes and other intriguing objects, and counted how many of them the child played with in eight minutes. The control kids, on average, explored about 10 of the 14 items. But the autistic children tended to fixate on a few objects to the exclusion of all others—in one extreme example, the child got no further than the very first item it encountered. All of these children had previously had MRI scans as part of another study, and a dramatic correlation popped out—the smaller the autistic child's lobules VI and VII, the fewer objects the child showed interest in.

Because our "autistic" mice were similarly immune to the allure of an unknown object, we wanted to see if they had the same cerebellar abnormality. Treating the cerebellum with a dye that just stains Purkinje cells reveals a consistent difference in these mice, as you will see on the next page. In addition, we occasionally see what we think are misplaced Purkinje cells. The cell bodies are supposed to line up in a neat row along the boundary between the red and the black zones, and not dawdle in the dark interior. We think that this misplacement must have occurred in embryonic development.

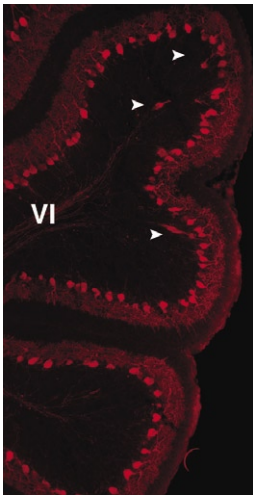
Now let's consider the mechanism for how this works, which is where the animal model comes in very handy indeed. Does the virus actually infect the fetal brain itself, or is it working indirectly through the mother's immune system? We think



An MRI scan of a control child's cerebellum (left) and an autistic child's (right), with lobules VI and VII shaded red.



Control and "autistic" mouse cerebellums stained with a dye that binds to Purkinje cells. The bottom two images are close-ups of lobule VII. The bright red globs are the Purkinje cell bodies, and the dark voids are actually chock-full with other types of cells. The right-hand image—an extreme example from an adult mouse born to an infected mother—shows almost no Purkinje cells.



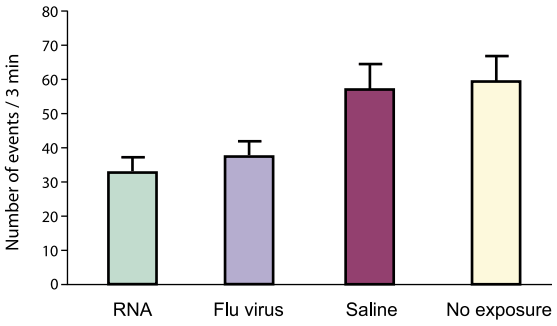
Errant Purkinje cells (white arrowheads) in the middle of lobule VI.

it's the latter, because we can't find the virus in the offspring, either in the embryonic brain or at birth. That's not surprising because, after all, influenza is primarily a respiratory virus. It hardly ever gets out of the lungs, throat, and nose and into the rest of the body. When it does, you have viremia, which is a very serious disease.

Furthermore, we can evoke an immune response in the mother without using a virus, simply by injecting her with a piece of double-stranded RNA. Mammals don't make double-stranded RNA but many viruses do, so the immune system knows that when it sees double-stranded RNA, it needs to swing into action. It starts secreting cytokines and in general mounting a vigorous antiviral response, even though there's no infection. Tellingly, the offspring of mothers whose immune systems have been artificially activated in this way display the same PPI deficit that we saw before. So we don't need the virus; activation of the maternal immune system is sufficient to alter the behavior of the offspring.

A second example of "autistic" behavior brought on by maternal immune activation was discovered by Natalia Malkova. Anecdotal evidence suggests that autistic human infants may be less bonded with their mothers. When Natalia removes the mother mouse from the family cage, it normally induces considerable crying in the control pups, although since mouse pups vocalize at ultrasonic frequencies, we have to use a special microphone to hear them. So Natalia counted how often the pups cried in three minutes, and the mice born to a double-stranded-RNA-exposed mother cried less than pups born to a normal mother.

We think that maternal immune activation alters brain circuits. Besides that dramatic abnormal layering Limin finds in the mouse cortex, and a loss of Purkinje cells that's been seen in the human cerebellum, there's that permanent, subclinical, altered immune state in the autistic brain—those increased cytokine levels. Are those cytokines an irrelevant, residual footprint—a fossil, if you will—of some earlier event, like a maternal infection? Or are they actually interacting with the brain in an ongoing fashion, with consequences visible in the patients' behavior? I favor the latter hypothesis.



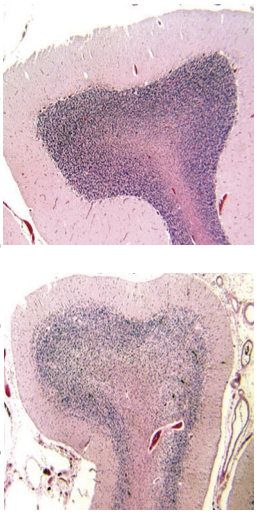
Mouse pups born to uninfected mothers (yellow bar) cried about 60 times in three minutes, or once every three seconds, when separated from Mom. So did control pups (purple) whose mothers had inhaled a sterile saline solution. Pups whose mothers' immune systems had been activated, either by a virus (lavender) or a piece of double-stranded RNA (green), cried much less often.

In some clinical trials where cancer patients were given cytokines in the hopes that these molecules would attack their tumors, dramatic differences in behavior and mood became apparent—up to severe depression, in the worst cases. And other researchers have found that high levels of cytokines in animals can alter learning and memory.

If this hypothesis is true, what would happen if we changed the brain's immune state? Antipsychotic drugs are known to suppress the immune system. Is that relevant to psychotic behavior? We are very interested in this possibility. In fact, Carlos Pardo of Johns Hopkins and I are organizing a meeting with the Cure Autism Now and Autism Speaks foundations to examine the possibility of immune intervention in autism. People take anti-inflammatory drugs such as aspirin to modulate their immune response all the time—is this a strategy worth exploring in this context?

We are just starting to explore the interactions between the immune system and the developing brain. Cytokines aren't the only possible conduit from a mother's infection to the fetus's developing brain—there are other changes brought about by corticosteroids, which are released following an infection or sickness, that also have effects on the fetus. And don't forget the genetic component—on what are those genes acting to increase the susceptibility? They might affect fetal brain development directly, or they might affect the brain's susceptibility to such other factors as cytokines, or the response of the placenta to the mother's immune activation, or they might even be acting in the mother, to affect her response to infection. We should be able to sort these possibilities out eventually, using this animal model.

Finally, I want to ask a question that's come up in the literature in the last few years—should we really be promoting universal maternal vaccination? The flu vaccine has been recommended routinely to pregnant women in the United States since 1957. The official policy of the Centers for Disease Control states that "administration of vaccines to women seeking prenatal care is an opportunity for preventative intervention that should not be wasted." Now you might say, "Well, of course, you don't want to get the flu if you're pregnant!" But remember that double-stranded RNA experiment—we activated the immune system, and it caused all these downstream effects on the fetus. And what does a vaccination do? It activates the immune system. That's the *point* of vaccination. In practice, not all pregnant women receive flu shots, and I think that universal vaccination of pregnant women could get us into a whole new set of problems. I'm hoping, therefore, that a way will be found to intervene somehow and repair the damage or reregulate the immune system. This mouse model is an excellent place to start. □



Vargas, et al. *Annals of Neurology*, vol. 57, no. 1, pp. 67–81, 2005, © 2004 American Neurological Association. Reprinted with permission of John Wiley & Sons, Inc.

Top: Purkinje cells (purple-blue dots) in a normal human cerebellum. Bottom: Nine of the 10 autistic brains analyzed showed patchy Purkinje cell loss.

Postdoc Natalia Malkova and friend.

Paul Patterson, the Biaggini Professor of Biological Sciences at Caltech and a research professor of neurobiological surgery at the Keck School of Medicine at USC, got his BA in biology at Grinnell College in Iowa in 1965, and his PhD from Johns Hopkins in 1970. He was a professor of neurobiology at the Harvard Medical School before coming to Caltech in 1983, following in the footsteps of his uncle, the late Professor of Geochemistry Clair Patterson. This article was adapted by Douglas Smith from a Watson lecture given May 17, 2005, at which Patterson was introduced by Caltech trustee Ted Jenkins (BS '65, MS '66), who has a schizophrenic son, and who with his wife, Ginger, underwrote the cost of the mice for the beginning of this work. Other support came from the late Ruben Mettler (BS '44, MS '47, PhD '49), the Cure Autism Now and Autism Speaks foundations, the Stanley Medical Research Institute, the McKnight Foundation, and the National Institute of Mental Health.

Mouse limos.

PICTURE CREDITS: 17, 18, 21—Bob Paz; 14, 18 — Doug Cummings

New Sight for Old Eyes

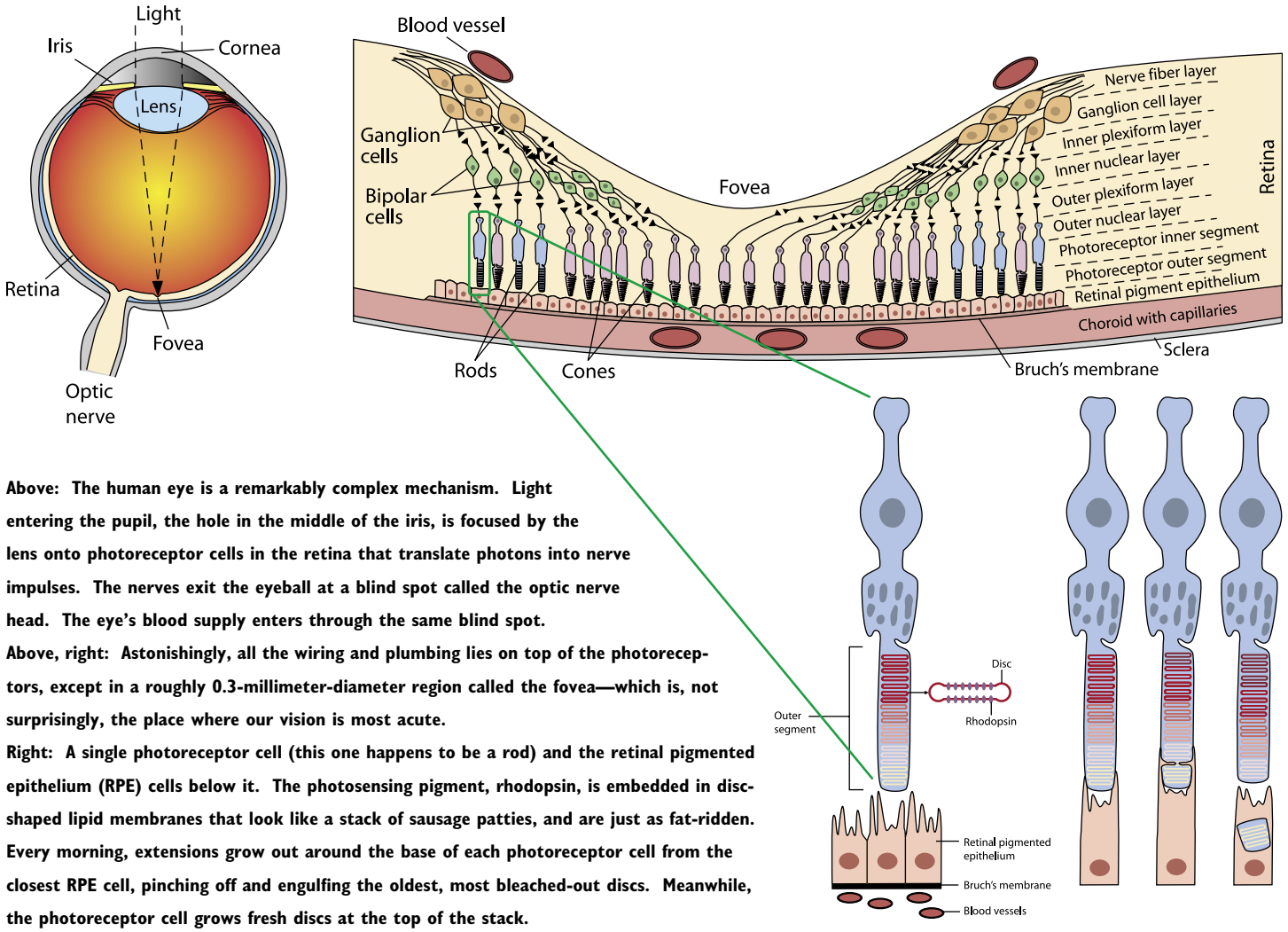
by Scott E. Fraser

Our research team as we might appear through the eyes of someone with advanced age-related macular degeneration, or AMD. Back row, from left: Assistant Professor of Electrical Engineering and Bioengineering Changhuei Yang, biology staff member Changjun Yu, Professor of Chemical Engineering Julia Kornfield (BS '83, MS '84), and grad student Jeff Fingler (MS '03). Front row: Member of the Professional Staff Mike Tyszka, biology staff member Jon Williams, Fraser, and Dan Schwartz, an associate professor of ophthalmology at UC San Francisco. Obscured in the AMD fog: Nobel Laureate Bob Grubbs, the Atkins Professor of Chemistry.

My mother leads a very active life, and she has near-perfect vision. In a few years, however, she may be forced to give up driving, and eventually even reading, as what is now just sort of a fuzzy zone in the middle of her field of view becomes a black hole. Like many of her friends, my mother has age-related macular degeneration, or AMD, a progressive eye disease affecting the area of the retina that gives us our clearest, most detailed vision. AMD begins by distorting and blurring what we see, and can lead to the loss of sight in the center of the field of vision. While none of us will die *of* AMD, a huge fraction of us will die *with* it. It's the leading cause of vision loss in people over 50 in the Western world. As many as 10 million Americans have AMD now, but the numbers will reach staggering proportions as the baby boomers reach their 60s and 70s. So a couple of years ago a group of us here at Caltech, and Dan Schwartz, an ophthalmologist at UC San Francisco, assembled a team to tackle this problem.

AMD affects a region of the retina called the macula, the "bulls-eye" where the lens focuses the light rays. The macula is densely packed with light-receptor cells in order to give very sharp vision. It seems odd, but the photoreceptors are actually at the back of the retina, so before any light reaches them it has to first pass through several layers of nerve cells, blood vessels, and other tissues. To minimize the effects of the intervening cells on our highest-resolution vision, there is a small sunken area in the center of the macula where many of the nerve cells are pushed to the side and there are no overlying blood vessels. This area is called the fovea, and it is packed tight with "cones," the photoreceptors that sense colors. But, as you can see in the diagram below, there is a complication to this arrangement—the fovea's blood supply must come from the back of the retina, and that's perhaps the key to understanding what goes wrong in macular degeneration.

The photoreceptors are the retina's most metabolically active cells. Their outer segment is basically a stack of thousands of discs containing a pigmented protein called rhodopsin, and when this pigment absorbs light, it sends a signal through the inner segment and then, via other nerve cells, to the optic nerve that leads to the brain. Being a photoreceptor is rough, because it's bombarded with light all day long—each rhodopsin molecule absorbs count-

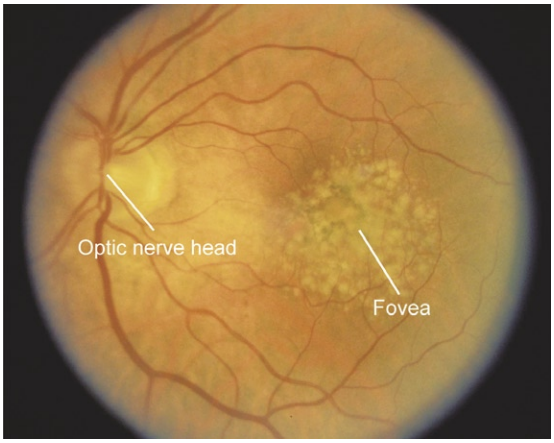


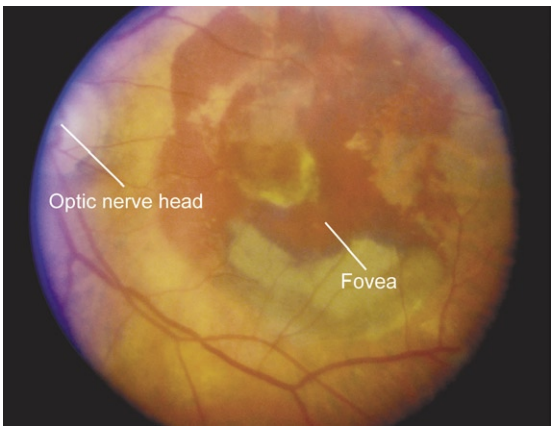
Above: The human eye is a remarkably complex mechanism. Light entering the pupil, the hole in the middle of the iris, is focused by the lens onto photoreceptor cells in the retina that translate photons into nerve impulses. The nerves exit the eyeball at a blind spot called the optic nerve head. The eye's blood supply enters through the same blind spot.

Above, right: Astonishingly, all the wiring and plumbing lies on top of the photoreceptors, except in a roughly 0.3-millimeter-diameter region called the fovea—which is, not surprisingly, the place where our vision is most acute.

Right: A single photoreceptor cell (this one happens to be a rod) and the retinal pigmented epithelium (RPE) cells below it. The photosensing pigment, rhodopsin, is embedded in disc-shaped lipid membranes that look like a stack of sausage patties, and are just as fat-ridden. Every morning, extensions grow out around the base of each photoreceptor cell from the closest RPE cell, pinching off and engulfing the oldest, most bleached-out discs. Meanwhile, the photoreceptor cell grows fresh discs at the top of the stack.

While none of us will die *of* AMD, a huge fraction of us will die *with* it.



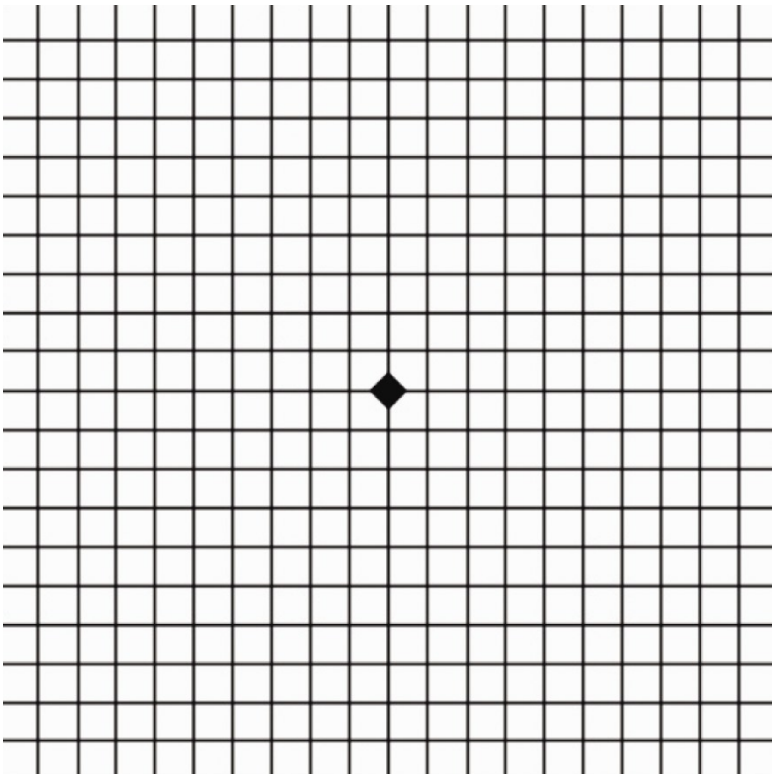


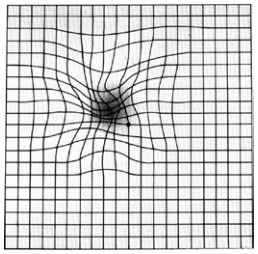
Top: The central part of a retina in the early, or dry, stages of AMD. The yellow spots are fatty deposits called drusen. Bottom: A retina with wet AMD in an advanced stage. The red regions are leaking blood, and it's likely that many of the the photoreceptors therein have died. This person would retain his or her peripheral vision, yet be legally blind—whenever this eye focused on an object, it would disappear into a black hole. These images were made with a fundus camera, which is essentially a low-power microscope designed for looking into the eye.

less photons each hour and must regenerate itself after each photon with fresh retinal, a derivative of vitamin A, before it can absorb another. With time, this huge influx of light bleaches the visual pigment in the same way that a brightly colored piece of fabric laid out in the sun loses its color, so every morning the oldest discs—about 10 percent of the outer segment—are pinched off the back end of the photoreceptor and eaten by the cells of the retinal pigmented epithelium (RPE), while new discs are added to the inner part of the segment. The RPE cells do more than take out the garbage; they also deliver nutrients and the molecules of retinal needed to regenerate the visual pigment, so they're important support cells for the photoreceptors and need to be in close contact with them.

There are two forms of AMD. In the early, or "dry," form, cream-colored plaques called drusen are deposited in the macular region. Drusen are located within Bruch's membrane, a crucial matrix at the base of the RPE cells that separates the retina from the blood vessels. These fatty deposits build up naturally with age, and many people over 50 have some. But if they get out of hand, they can block the diffusion of nutrients, and even potentially oxygen, from the underlying blood supply to the retina. Usually, patients with dry AMD are able to read just fine; however, many have difficulty with night vision and give up driving under dimly lit conditions.

With time, the disease can advance to "wet" AMD, which is much more serious. It begins when new blood vessels start to grow into the retina to try to resupply the starving photoreceptors. To understand where these new blood vessels come from, we have to go back to the early 1970s. Judah Folkman, a surgeon at the Children's Hospital, Boston, realized that when tumors were first forming, they didn't have a very good relationship with the blood vessels around them, and so they grew very slowly. After a while, vessels did grow out to supply the tumor with blood, and as soon as that happened,





Above: An Amsler grid to self-test for AMD. (The small grid at right shows what an AMD sufferer might see.) To use the grid, hold the magazine 12 inches away, and cover one eye with your free hand. Look at the central dot with the other. Repeat the test with the other eye covered. If you cannot see all four corners of the grid, or if some of the lines are blurry, wavy, or missing, call your eye doctor.

the tumor grew explosively. Folkman proposed that the tumor cells' need for oxygen was causing them to give off a growth factor that spoke to the nearby blood vessels and caused them to grow, and he identified it as vascular endothelial growth factor (VEGF), which, as we now know, also plays a major role in wound healing. The new blood vessels that grow in response to VEGF are more fragile, thinner, and less organized than normal ones, and they leak. This is useful if we want to deliver a chemotherapeutic agent into a tumor—the agent is injected into the bloodstream and leaks out around the cancerous cells—but it's very bad when such blood vessels grow up through Bruch's membrane to underlie the RPE cells. These abnormal vessels leak blood and fluid that damage the macula, inevitably replacing it with scar tissue.

What can you do if you're in the early-onset stage of dry AMD and want to protect yourself from wet AMD? The best advice is to avoid strong sunlight by wearing sunglasses, and to give up smoking, because heavy smoking has been shown to increase the chance of developing wet AMD. Certain patients with larger drusen, or who are already noticing some visual loss, can benefit from multivitamin tablets containing high levels of antioxidants and zinc, which are available in drug stores. In a 10-year Age-Related Eye Disease Study (AREDS) sponsored by the National Eye Institute, such tablets significantly reduced the risk of advanced AMD and vision loss. A number of other, ongoing, clinical trials are showing promising signs that multivitamin tablets containing the antioxidant lutein may also be effective. Lutein is found in dark-green leafy vegetables such as broccoli, kale, and spinach, but it's not easy to eat enough greens to have any effect on AMD—tablets are better.

Regular self-testing is also a good idea, so that you'll spot differences in vision when they first occur. The brain combines information from both eyes to generate our visual scene, and uses details viewed by one eye to fill in for missing or distorted vision in the other. Thus it's sometimes easy to miss that there's something wrong, so to self-test for the earliest defects, you have to check one eye at a time. A simple test to detect AMD, the Amsler grid, was developed by eye doctors who noticed that people with the undiagnosed condition were coming in and saying that their venetian blinds suddenly looked wavy. We've provided one on this page so that you can do the test right away, but there are also plenty of websites on AMD that feature them. If you do see wavy lines, you might want to book an early appointment with your ophthalmologist.

At present we don't have any foolproof method for preventing the earlierst blood-vessel growth in patients with AMD. The AREDS-formula multivitamins are the only early-stage treatment available, and their effectiveness is limited. Treatment of the later-stage wet form requires repeated injections of drugs that block the VEGF pathway and make the new blood vessels regress. These injections have to go directly into the eye, which

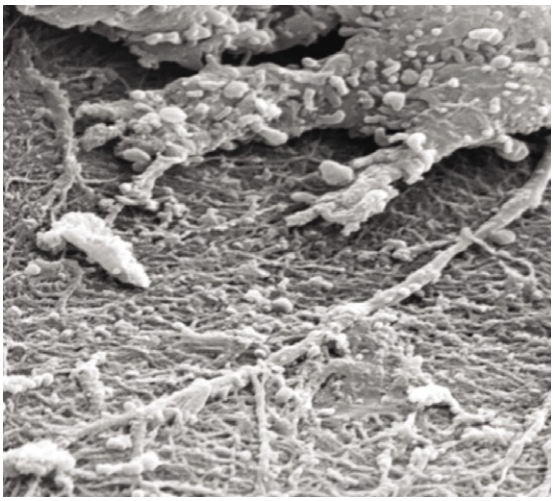
If we could catch people in the early stages of wet AMD while their sight is still good, these drugs might save their reading and driving vision.

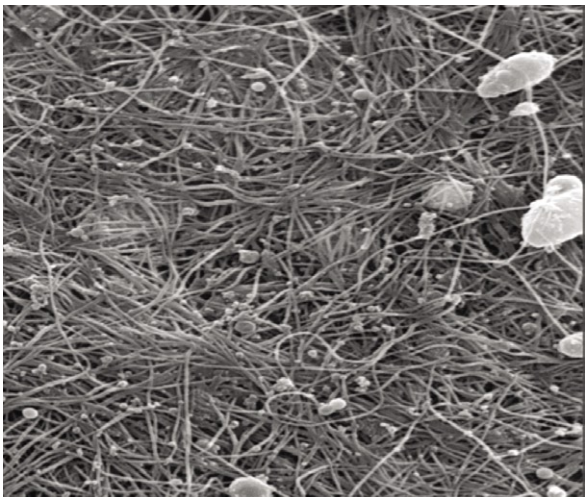
can be painful and may cause complications such as infection, hemorrhaging, and cataracts. The drugs used are either very high-affinity antibodies that bind to the VEGF and remove it, or anti-VEGF aptamers, which are short chains of RNA that grab the VEGF and inactivate it. People are looking at other delivery methods, such as putting little minipumps inside the eye to dose it continuously. But once retinal cells have died, injecting anything is unlikely to bring them back, so these treatments are best thought of as a means to arrest rather than reverse the vision loss. This makes early detection of AMD a critical component of the treatment plan.

Studies of the anti-VEGF drugs shows that they stabilize vision in 90 percent of the cases, and that the earlier the treatment begins, the better the outcome—about 30 percent of patients even see modest improvement. Therefore, if we could catch people in the early stages of wet AMD while their sight is still good, these drugs might save their reading and driving vision. Unfortunately, there are no means for early detection of the abnormal blood vessels, and most people with wet AMD don't see their eye doctors until they've had significant visual loss. So our group is developing an instrument to help find those abnormal vessels in the earliest stages of wet AMD, often before the patients are even aware of any visual problems. I'll return to that subject later.

There's still a lot of dispute about the underlying cause of AMD. Some people argue that the drusen are to blame, citing the similarity of their protein components to the protein plaques seen in the brains of Alzheimer's patients. However, those plaques have not been proven to be a cause of Alzheimer's, and could simply be one of its effects. Other people, including our team, believe that AMD is the result of fat accumulating in Bruch's membrane—the support and filter system I mentioned earlier.

This fat comes from those light-sensing discs in the outer segments of the rods and cones. Each disc has its rhodopsin embedded in a fat-based, or lipid, membrane. When 100 to 200 of those discs are pinched off each photoreceptor every morning,



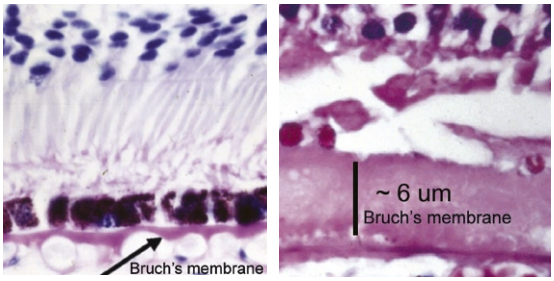


Right: A scanning electron microscope image of an elderly Bruch's membrane. Fat drips off the collagen fibers like rusticles from the *Titanic*'s deck rails. The large RPE cell at the top of the image is pulling its feet away in disgust. Far right: After the membrane has been bathed in alcohol, all the fibers are clean again, forming a nice open mesh for nutrients to pass through. Images courtesy of Ilene Sugino.

the nearest RPE cell has to eat this fatty breakfast. And with thousands of individual photoreceptors in the macula area, it's worse than being on Elvis's bacon diet. The RPE cells then have to clear this fat out into the blood vessels running behind the retina, and they have to do it through Bruch's membrane.

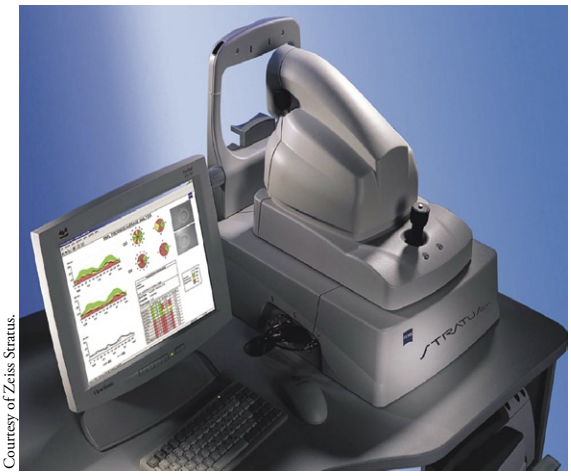
This membrane is a very thin matrix made of the sort of connective tissue that makes skin tough, and in some ways it resembles the stacked layers of multi-ply toilet paper. The theory is that some very small fraction of the lipid molecules get stuck as they pass through it, so that by middle age a good amount of fatty goo will have built up. And that's a problem, because this membrane is the meeting ground for all the retina's nutritional and waste-clearance activities. Once the mat is clogged with fat, it can't do its work as well. In fact, in the photo at far left on the opposite page, you can see that one of the RPE cells is pulling back its processes, as it's not happy touching the membrane any more. As dry AMD progresses, as seen in the photo on this page at far right, Bruch's membrane gets thicker and thicker and creates a barrier between the blood supply and the RPE cells. This fatty barrier may cause the overlying retinal cells to become oxygen-starved, secrete VEGF—triggering wet AMD—and slowly start to die.

When our collaborators, Marco Zarbin and Ilene Sugino of the University of Medicine and Dentistry of New Jersey, dissolved the fat away from Bruch's membrane with ethanol, a healthy-appearing membrane was restored—a nice mat of open fibers that oxygen, water, and all the other nutrients can move through easily. But before you think this is another good reason to drink red wine, you should know that a very high concentration of alcohol was used, and it was done on a cultured membrane from an excised eye. It's not a treatment many people would want. That's why our group is working on a better way of assessing the health of Bruch's membrane and treating the fat deposits.



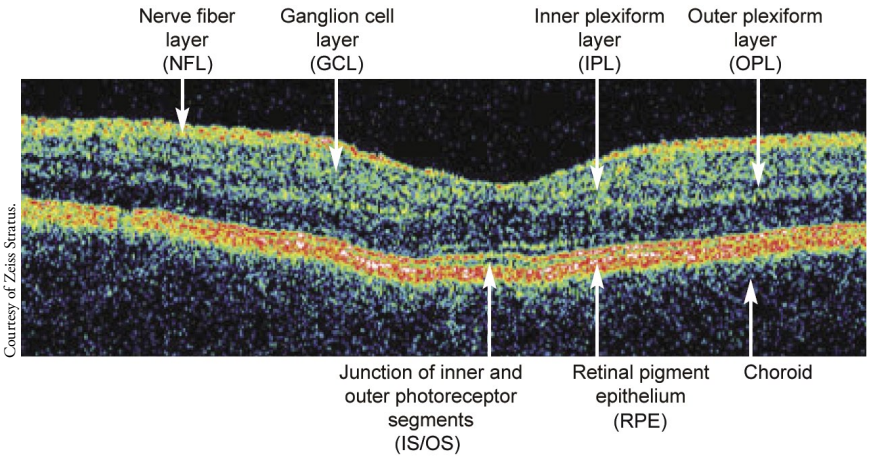
A healthy Bruch's membrane, seen above left as the purple-red layer below the very dark RPE cells. (Another function of the RPE cells is to absorb any light that gets past the photoreceptors. If the RPE cells begin to die, people can actually be bothered by the glare of light bouncing off their own retinas!) This membrane is one or two microns (um, or millionths of a meter) thick. In advanced cases of AMD, the fat-swollen membrane is several times thicker, as seen above right. Images courtesy of Dr. W. Richard Green at the Johns Hopkins Medical Institute.

To develop better imaging instruments for eye doctors to use, Member of the Professional Staff Mike Tyszka, biology staff member Changjun Yu, and I began by looking into the eye of a mouse with our magnetic resonance imaging (MRI) machine. MRI detects the nuclei of hydrogen atoms, so we could see the water moving in and out of the retina, and we could see the fluid in the eyeball because of its molecules' random movements. We also showed that with the right sort of MRI machine, it's possible to look into the eye and tell if there's a defect in retinal permeability. But since the chances of an eye doctor having a $3-million machine in the office to screen for AMD are zero, we decided to use a different approach and adapt a machine that's already used to look for retinal



Courtesy of Zeiss Stratus.

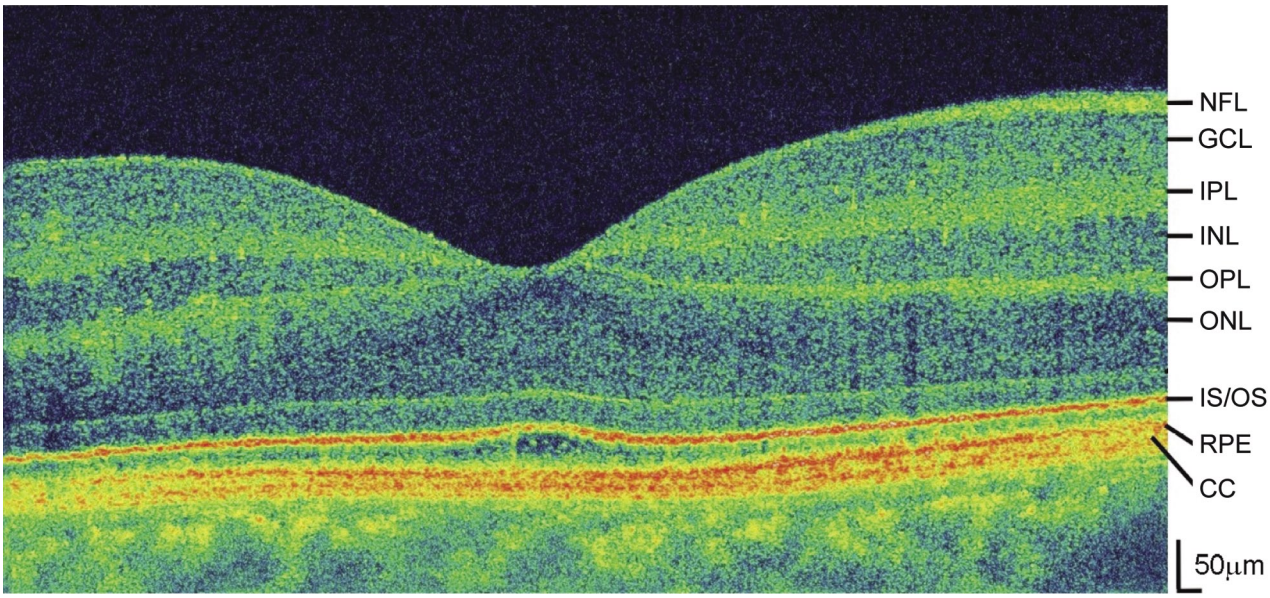
The Stratus optical coherence tomography (OCT) machine, above, produces images like the one below, in which the retinal layers with the highest reflectivity appear in red. (The central dimple is the fovea.) An OCT image from a half-million-dollar machine built at MIT gives much better resolution, as seen at bottom. INL stands for inner nuclear layer, ONL is outer nuclear layer, and CC is the choriocapillaris, a layer the Stratus could not distinguish from the RPE cell layer.



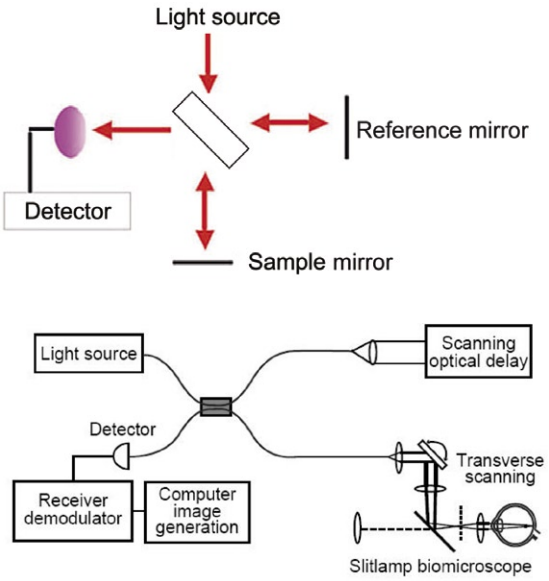
Courtesy of Zeiss Stratus.

holes, swelling, and detachment—the Stratus OCT. Made by Carl Zeiss Meditec, this machine uses optical coherence tomography (hence the OCT) to image the retina.

An OCT such as the Stratus is basically a modified Michelson interferometer. A laser's light is split into two beams that are bounced off mirrors and recombined at a detector, where they create interference fringes. Because these fringes depend on the relative distances the two beams have traveled, if one of the mirrors is moved, the fringes change. This exquisitely sensitive method detects a movement by either of the mirrors of even a fraction of the wavelength of light. To turn the interferometer into an OCT system, the laser is replaced by a light source with a broad bandwidth, usually a superluminescent diode. These diodes emit light of many wavelengths, so the "coherence"—the width of the region of space where all



M. Wojtkowski, et al, *Optics Express*, Vol. 12, No. 11, 2004, © 2004 Optical Society of America.



Top: How interferometry works. Light from a single source passes through a partially silvered mirror that reflects some light and transmits the rest. One beam bounces off a reference mirror a fixed distance away, while the other travels a varying distance to the sample mirror. When the two beams are recombined, the interference fringes tell you how much the sample mirror has moved. Bottom: The same idea can be adapted to your eye.

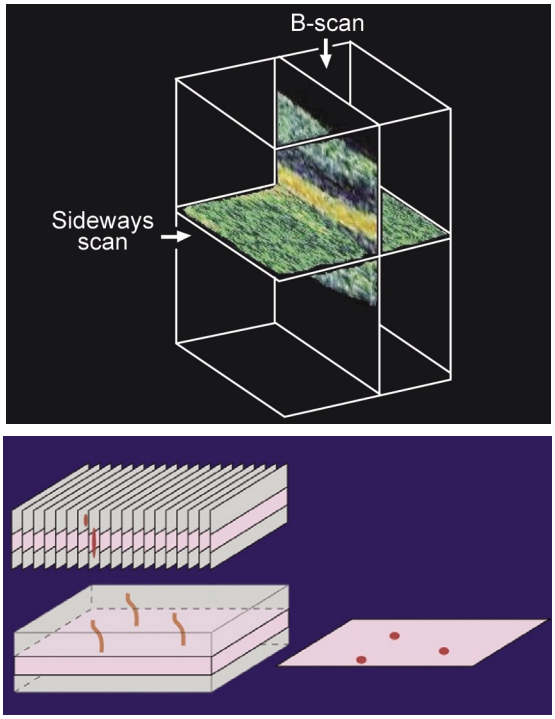
the peaks and troughs can align to make interference fringes—is quite narrow. (Most lasers, by contrast, have a coherence length that can be measured in meters, and so give fringes over a very broad range of mirror movements.) The diode only produces interference if the path difference between the reflected beams is less than half the coherence length—about 15 microns, or 15 millionths of a meter—producing an image with very high depth resolution.

If we replace one of the mirrors with someone's eye, we can record the light that reflects off the different retinal tissues at different depths and build up a 3-D image. It's almost like having an ultrasound machine, but one based on light instead of sound.

The Stratus produces images good enough to see if the retina is swollen or has a shallow retinal detachment, but we're aiming to do better. Some university labs working on OCT can already generate images with much higher resolution, but their usefulness is limited because the instruments cost as much as half a million dollars. We're trying to make a very inexpensive version that can generate images that are just as good, and two members of my lab, grad student Jeff Fingler (MS '03) and biology staff member Jon Williams, working with Assistant Professor of Electrical Engineering and Bioengineering Changhuei Yang, have already created systems that give comparable resolution for one-tenth the money. It's looking very promising.

Most OCT systems take images of slices through the depth of the retina, so if we want to identify blood vessels growing through a particular retinal layer, we have to take a lot of slices and examine each one for a blood vessel. Although the fastest systems can take as little as one second for a scan, the procedure usually has to be repeated many times before getting a well-focused image, because most people aren't very good at keeping their eyes still for that long. It's not their fault—eyes are always darting about and can't fixate on one spot for an entire second. But by turning the slices on their sides and taking an image of an entire retinal layer all at once, we can speed things up. Instead of imaging one small slice of the retina at different depths, then imaging the slice next to it, and so on, we scan from one side of the retina to the other all at one depth and then repeat the process at different depths, which creates an image more than 100 times faster. With colleagues Dan Petersen and Richard Haskell at Harvey Mudd College, we've developed a microscope that can image such constant-depth slices,

Simply injecting something that binds to fat and dissolves it won't work. There's a lot of fat in our body that we wouldn't want to be rid of, like the fatty sheaths around our nerve cells.



Top: A variable-depth scan, called a B-scan in a term borrowed from ultrasound, versus a constant-depth scan. Bottom: It's much easier to find blood vessels when you are scanning across them rather than along them.

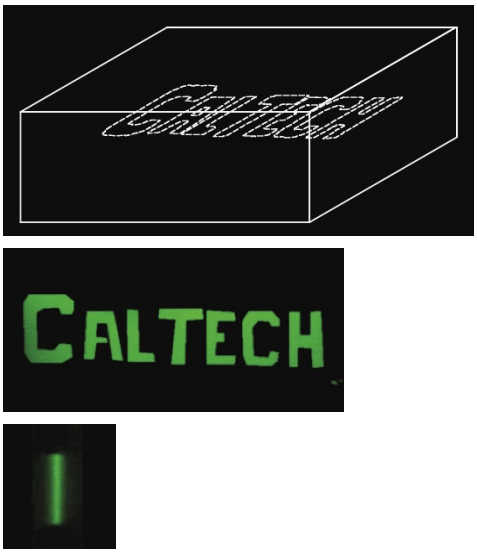
which we're now refining for medical use as part of a Stratus-like instrument. The eye examination will be much quicker, and if there are just a couple of blood vessels coming through, we'll have a good chance of seeing them.

Even so, blood vessels don't really show up well in standard OCT images. We're going to improve that by putting the machine into Doppler mode, which sees moving particles, such as those in the blood. It works very much like a radar gun, analyzing the changes in frequency of the fringes between successive scans. The blood vessels really jump out, and it's even possible to tell the direction of flow.

So we're coming close to developing an inexpensive system that will let doctors see those tiny new blood vessels that are the tell-tale signs that you have an early form of wet AMD and need to get treatment. Better still, while looking at the retina with our Doppler OCT, we've seen that fat-clogged tissue actually moves in a different way than normal. The healthy fibers are in constant motion, buffeted by the water molecules around them, and the entire membrane undulates like a sheet of tissue paper in a light breeze. As fat builds up, the tissue becomes stiffer. So the same machine should be able to tell us whether fat is building up in Bruch's membrane.

Of course, knowing where this fat builds up is only going to be useful if we have a way to get rid of it, and this is something we've been working on with Caltech's latest Nobelist, Atkins Professor of Chemistry Bob Grubbs, and Professor of Chemical Engineering Julia Kornfield (BS '83, MS '84). Simply injecting something that binds to fat and dissolves it won't work. There's a lot of fat in our body that we wouldn't want to be rid of, like the fatty sheaths around our nerve cells. Curing someone of macular degeneration while dissolving their brain is not going to be a great treatment. A better solution would be a targeted drug that only dissolves the "bad" fat in the membrane.

Finding a fat-dissolving chemical that will only



The AMD team put Caltech's name up in lights, albeit very tiny ones. At top is a schematic of the fluorescein-laden epoxy slab showing where the activating laser was focused. At center is the result, as seen from above, and at bottom is a side view showing how thin and uniform the fluorescein uncaging was.

bind to that particular region of the body is proving to be very difficult, so we've chosen another approach, called photoactivation, in which the drug is kept inside a chemical "cage" until hit by a light source that disintegrates the cage and frees the drug. The idea is to inject a patient with a caged molecule, then shine a laser light through the eye onto selected areas of fatty deposits in Bruch's membrane, using our Doppler OCT machine to see exactly where those deposits are. To ensure that no "useful" fat is accidentally dissolved near the target area, we'll use a technique called two-photon activation. To open the cage, two photons have to be absorbed by it simultaneously, something that only happens when a huge number of photons are concentrated in one place. While single-photon activation would uncage the drug anywhere along the beam path, two-photon activation will be localized at the focal depth of the incoming light.

We've tried this technique on a solid slab of epoxy with a caged fluorescein dye in it, and focused the two-photon uncaging laser on different positions at constant depth to spell out "Caltech." As you can see, the shapes of the letters look pretty good. But the impressive—and very important—thing about this is that, when looked at from the side, we've only activated a very, very thin sliver of the dye—in this case approximately five microns thick. Bruch's membrane in older people becomes that thick or more, so this technique can be used to target only the fat in the membrane, and no other tissues above or below it.

By removing the barrier fats, we aren't going to be able to give you the Bruch's membrane of an 18-year-old, but we really don't have to. All we need to do is to restore the membrane's permeability to the point where there's good nutrient and waste flow. If we can change the permeability of a 70-year-old membrane back to the way it was at 50, it will be good enough to nip AMD in the bud. □

Scott Fraser is the Anna L. Rosen Professor of Biology and professor of bioengineering. He is also the director of Caltech's Biological Imaging Center. Fraser earned his BS in physics from Harvey Mudd College in 1976, and his PhD in biophysics from Johns Hopkins University in 1979. He and his hyphenate, Marianne Bronner-Fraser, the Ruddock Professor of Biology, have coauthored two children, much to the delight of his mother, who can see them just fine so far.

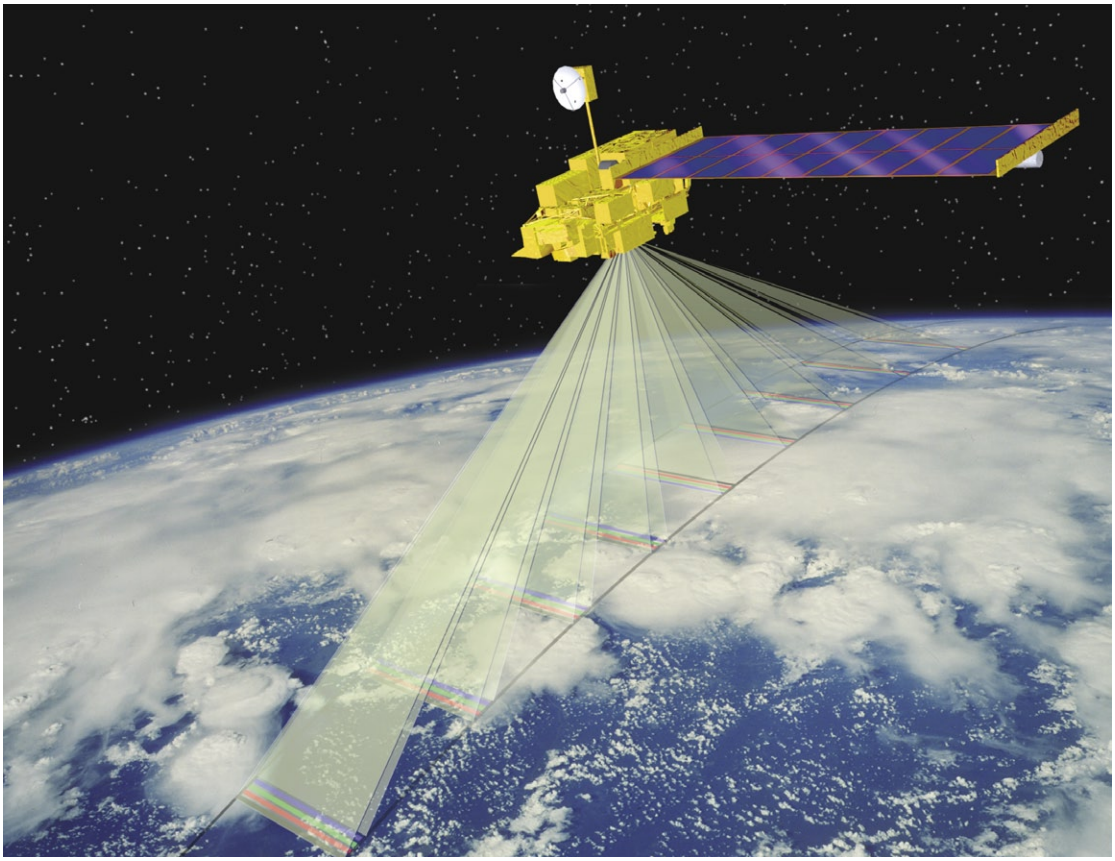
This article was adapted by Barbara Ellis from Fraser's Seminar Day talk last May.

Bob Grubbs, the missing member of the macular degeneration team.

PICTURE CREDITS: 22, 31—Bob Paz; 23, 30 — Doug Cummings

Our Atmosphere: The View from Above

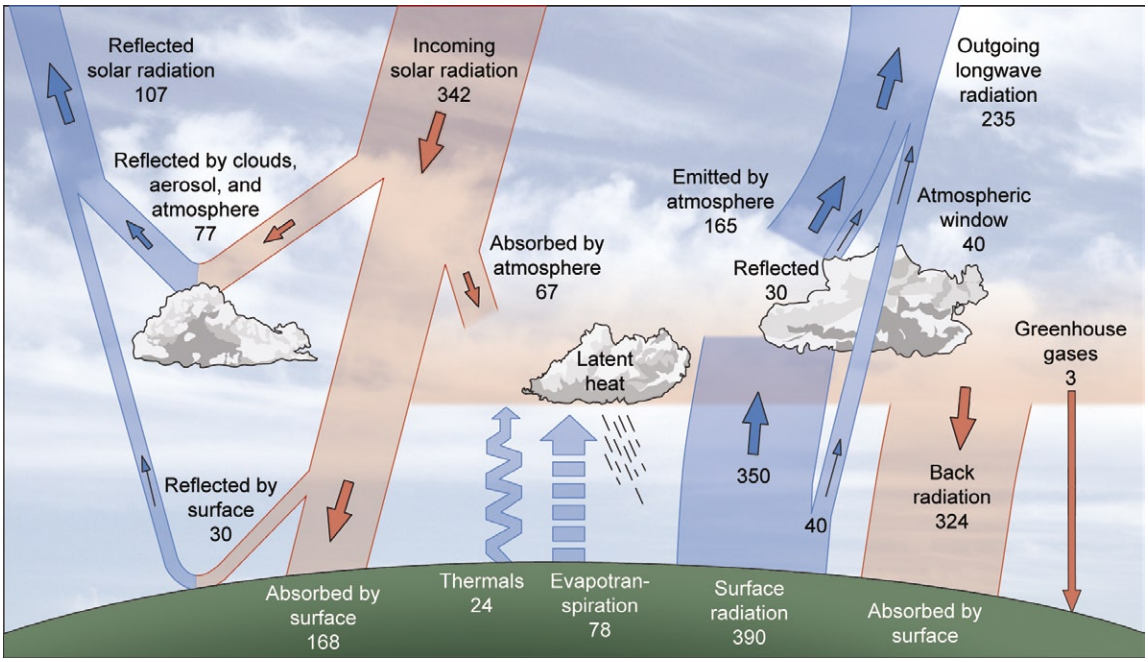
by Eric J. Fetzer



The Multi-angle Imaging SpectroRadiometer (MISR), built and managed by JPL, flies on the Terra satellite. MISR's nine attached cameras each point in a different direction, and each takes images in four different wavelengths. These images are used to track atmospheric smoke, dust, ash, and pollution, which play key roles in climate change.

This view from space is brought to you by several of the latest generation of satellite instruments viewing our atmosphere. Climate science is about simple concepts playing out in a very complex system. It has been said that the art of physics is judicious simplification; I would say that the art of atmospheric science is actually judicious complication. So what we can learn about this system using satellite observations? And, of course, why does all of this matter?

There are clearly some outstanding issues in the climate sciences. One is greenhouse gases, and their several attendant issues, among which is global warming—each of us in the United States alone produces several tons of carbon dioxide per year, contributing significantly to a greenhouse effect that has important implications. Pollution and dust also have an impact on climate, not to mention air quality. Then there is the granddaddy of all pollution problems, the Antarctic ozone hole. But I predict the big issue of this century will be how global warming affects future water supplies.



The climate cycle is a complicated system of components that absorb and reflect solar radiation. Around 342 watts per square meter (W/m²) of solar radiation enters Earth's atmosphere, and the same amount reradiates back from the planet, but this radiation takes many detours along the way. It can get trapped in clouds or reflected by clouds, absorbed by Earth's surface in some places and reflected in others. Each path taken must be tracked and understood in order to understand the entire system. Anthropogenic greenhouse gases, despite amounting to a measly three W/m² of the radiation budget, are an important factor in climate change.

The outstanding issues in the climate sciences primarily have to do with how the climate system maintains an energy balance. Into this balance are thrown complications like clouds, water vapor (which is actually the number one greenhouse gas), and pollution. These things, unfortunately, are all tied together, with no easy way to disentangle them. Like the legendary Gordian knot, they form an inextricable tangle with no ends. But, unlike Alexander the Great, who began his ascent to the throne of Asia by slicing the knot in half, we don't have a sword. We can't hack this knot into pieces, so we have to disentangle it very carefully through approaches like analysis, observation, and computer modeling—all of which are based to a large degree on satellite observation.

Let's begin our exploration of the atmosphere with a trip to your driveway. When you stand on a very hot driveway in the full sun, you feel intense heat on your skin, which happens to be a very good sensor of infrared radiation. You are feeling the very simplest case of radiative balance: sunlight comes in and infrared radiation goes out. The atmosphere behaves in a similar manner, conceptually. The sun heats Earth's surface at 342 watts per square meter. That's essentially one toaster for every three square meters, at a thousand watts per toaster. And there are about 342 watts per square meter, on average, reradiating back from the planet into the atmosphere. So there is a long-term balance between what goes in and what comes out.

Unlike in the driveway model, solar energy's many paths to the planet and back through the atmosphere are a little more complex. Clouds and Earth's surface can both reflect sunlight and absorb it. Snow is a very strong reflector, while bare dirt or sand absorbs solar energy. Water also absorbs almost all the sunlight that hits it. Some of this energy is reradiated as heat, which is visible from space as infrared radiation. Several of the instruments we work with at JPL "see" this infrared radiation. In tracing the various paths of solar energy, we face the complexity of the climate system, which involves variable reflectivity and reabsorption from clouds and Earth's surface, as well as a number of other effects going on inside the atmosphere. Understanding the atmospheric part of the climate system is all about understanding these internal exchanges.

Water vapor is a big player in this energy balance. We hear a lot about carbon dioxide and other anthropogenic gases as the important greenhouse gases, and they are definitely linked to our warming climate, but they don't have nearly as great an impact on climate as water vapor, a naturally occurring greenhouse gas. Clouds are even more important than water vapor. The presence of different types of clouds, some that lead to cooling and some to warming of the atmosphere, will probably have a much greater impact on climate change than the small but positive effects of carbon dioxide. The magnitude of the carbon dioxide–induced warming is reduced or amplified by cloud feedbacks. Because we don't know some basic things, like the actual distribution of different types of clouds globally, understanding these feedbacks is especially challenging.

Keep in mind that human-produced greenhouse gases amount to only a few percent at most of all these numbers coming in and going out of the atmosphere in a somewhat confusing way. To understand the climate system better, we need to understand how this small number, the amount of greenhouse gases in the atmosphere, can be so important in the face of these larger numbers.

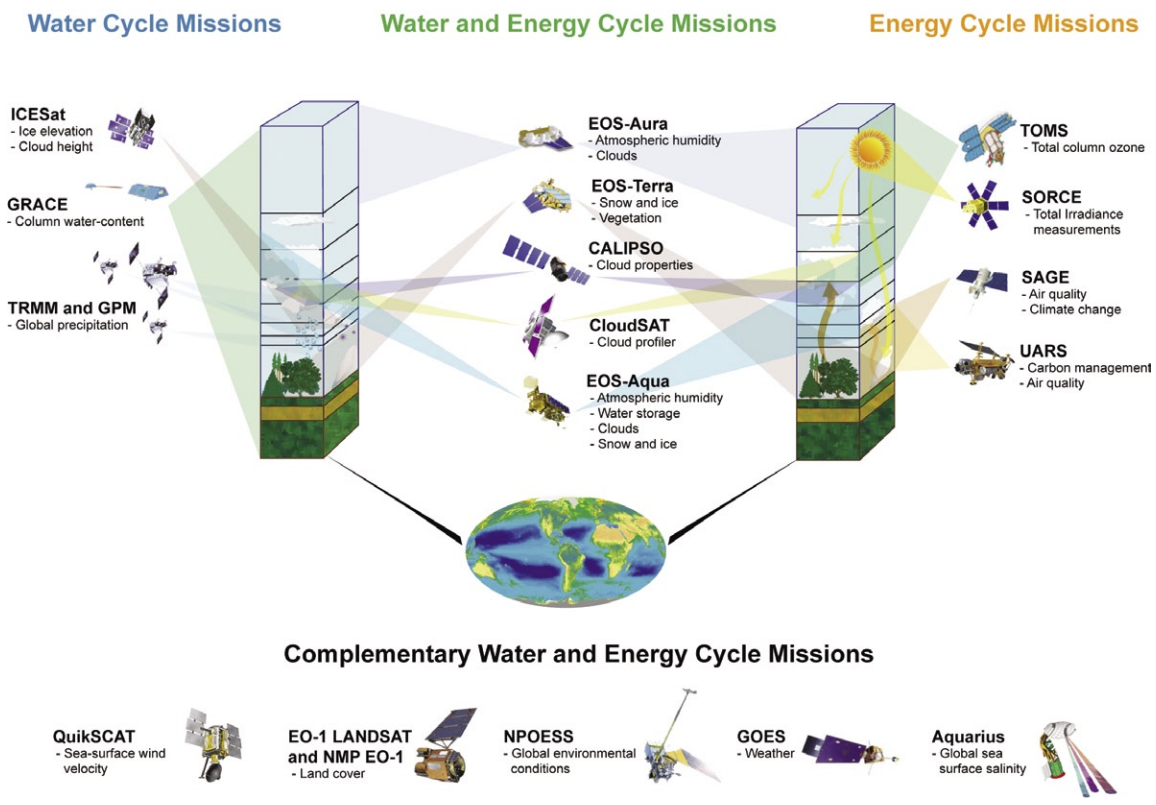
Finally, atmospheric motion is also critical to the whole picture of energy transport. Much of the year, Antarctica receives no sunlight, yet it radiates energy to space. That heat has to come from somewhere, and this is where the atmosphere and ocean come in. They take heat from the tropics and redistribute it to the poles and to higher latitudes. This redistribution of heat, in a broad sense, is the climate system.

You might think measuring thermal radiation from a piece of land is trivial, but this apparently trivial problem is something we still don't understand in detail. The world is a lot more complex than a driveway, and we don't fully understand the properties of everything that the sun shines on.

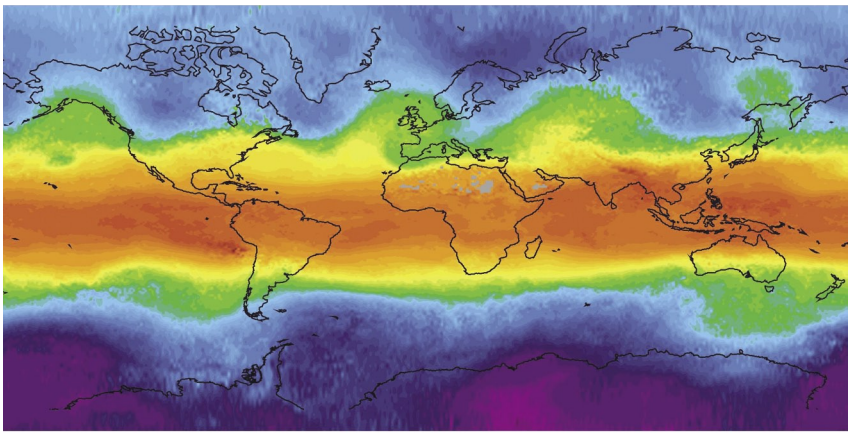
Why observe this all from space? Because we get near global coverage, with gobs of data pouring in. We have the potential to see detailed pictures of many processes. But there are challenges that come with this. Rather than directly observing many components of the atmosphere, we make inferences about them based on some prior understanding. For example, we don't actually observe temperatures from space, we infer them based on observations of radiation. Returning to the driveway example, we can't simply take a thermometer reading of the driveway's temperature from space. Instead, we measure the intensity of infrared radiation from the driveway, and then infer a temperature for it based on the known physical properties of the driveway. And there are parameters that might be fundamental to radiative balance that we can't observe from space, like back radiation from the atmosphere to the ground, so we have to infer these in other ways. There are also certain climate states that we can't observe. Very few instruments can observe deep into hurricanes, for instance.

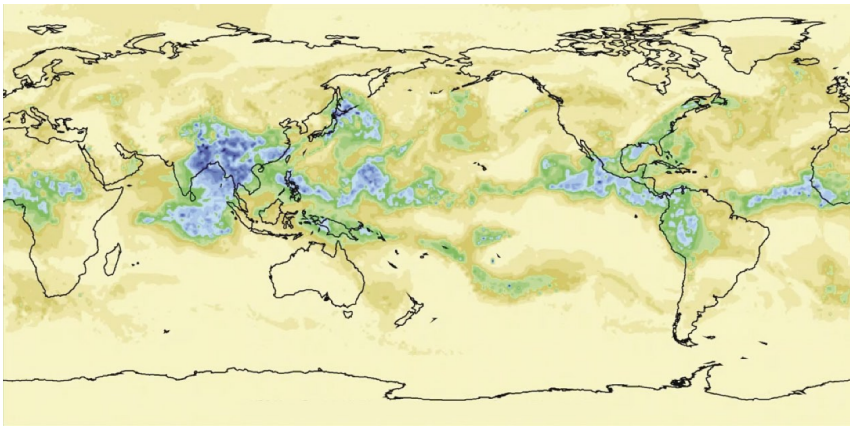
You might think measuring thermal radiation from a piece of land is trivial, but this apparently trivial problem is something we still don't understand in detail. The world is a lot more complex than a driveway, and we don't fully understand the properties of everything that the sun shines on. Furthermore, we don't understand the details of all the data we do have. Data is not information, and information is not knowledge. How do we transform data into information, and then use that information to gain insight into the atmosphere? Finally, once we get through the process of inferring from observations, we have to look at our inferences to make sure they make sense. Part of the job is knowing where and when those inferences could be wrong.

Much of the data that we analyze come from instruments carried by one or another of the satellites of NASA'a Earth Observing System, or EOS. All 17 satellites employed in EOS missions are devoted to making myriad observations related



NASA's Earth Observing System, or EOS, comprises 17 satellites launched periodically over the past two decades. Each satellite carries instruments designed to monitor various components that contribute to the climate cycle. The satellites follow either polar-orbiting or low-inclination tracks, repeating their observations regularly and thus improving our understanding of Earth as an integrated system over the long term.





Top: Temperature is distributed fairly smoothly at around five kilometers' altitude, ranging from hottest near the equator (reddish hues) to coldest near the poles (purple). People living in the midlatitudes experience winter storm systems that arise along the wavy front where hot air meets cold high in the atmosphere. This image shows an eight-day average temperature distribution in May 2004. Bottom: In contrast, water vapor in a layer from five to fifteen kilometers' altitude is unevenly distributed. The wettest places on Earth are above the tropics (as shown in blue), but moisture isn't spread evenly *throughout* the tropics. This image averages two days of data from late August 2004. Images by Stephanie Granger, JPL.

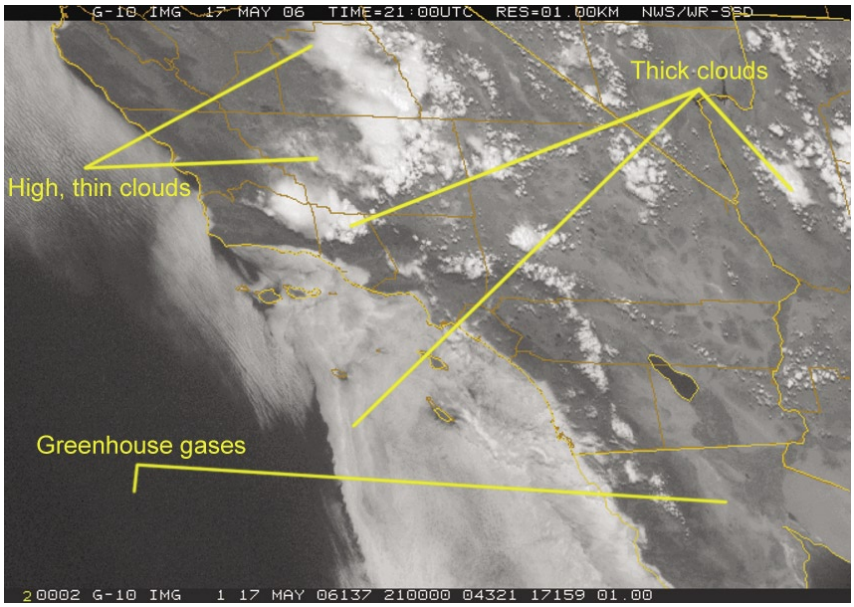
to Earth's water and energy cycles, and many of those instruments are built and operated by JPL. For example, we are constructing highly accurate temperature profiles of Earth's atmosphere from measurements made by the Atmospheric Infrared Sounder (AIRS), a JPL instrument launched on the Aqua satellite on May 4, 2002.

Let's continue our exploration of the atmosphere, with data from AIRS, by considering temperature distribution at a pressure of 500 hectopascals, or 500 millibars, which occurs some five kilometers above Earth's surface. Some things are expected: it's warm at the tropics and cold at the poles. But the interface between the cold polar air and the warm tropical air is wavy. Over the span of 11 months of temperature inferences, at some altitude well above the surface, waves of warm and cold air roll along this interface. We live in these rolling "waves" in the wintertime here in North America. These are the so-called midlatitude storm systems, and they are the mechanisms by which heat is transferred by the atmosphere from equatorial regions to the poles. The waves slosh along, generally from west to east, changing from day to day, which is why today's weather can be quite different from yesterday's weather. What these waves do at five kilometers' altitude is coupled to what we experience on the ground. It becomes clear, then, that the day-to-day view of global temperatures entails a lot more complexity than what we saw in the static view of radiative balance in the driveway model.

The next quantity we'll look at is water vapor, the fundamental greenhouse gas, which is also measured with the AIRS instrument. At roughly the same altitude of five kilometers and on up to 15 kilometers or so, the so-called upper tropospheric water vapor is distributed in a complex way. While temperature varies fairly smoothly from hot to cold across the globe, water vapor masses are scattered and disorderly, with filaments and blobs. Cloud distribution is even more spatially variable. As we saw earlier in the radiative balance example, these water vapor and cloud masses contribute to the energy balance of the planet. Upper tropospheric water vapor amounts, while small, are important in determining the radiative balance of cloud-free regions.

Although some of the wettest places on Earth are in the tropics, some of the driest parts of the upper troposphere are also there. So, while water vapor is generally more abundant in the tropics, this is not necessarily the case *throughout* the tropics. In the upper troposphere, as water vapor moves around, carrying temperature changes with it, it also changes its state to form clouds or ice. These changes add up to a poorly understood climatic system in one particular part of the atmosphere. But it is in the lower altitudes where much of the atmospheric water cycle is dictated, because most of the atmospheric water vapor lives here. There are other factors at play in the lower atmosphere, like surface evaporation, that help determine its water vapor abundance.

Into this already complicated scenario float the clouds. Water vapor, temperature, and clouds are all interrelated in the climate system: temperature depends on whether clouds are present, and clouds are present depending on the temperature and availability of water vapor.

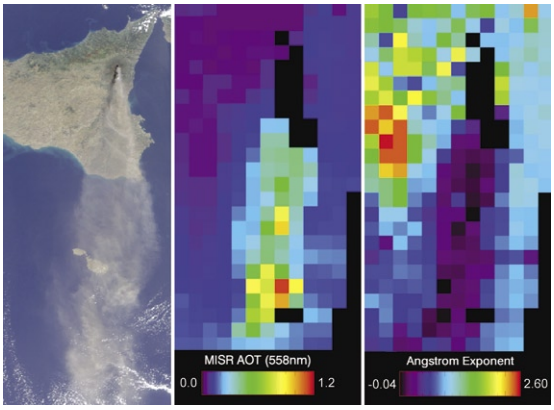


A typical May day in Southern California. This weather satellite image shows various kinds of clouds and a marine fog coming off the Pacific Ocean. These, along with greenhouse gases, play different roles in reflecting or trapping incoming solar radiation.

You may now be sensing the challenges of trying to understand clouds. Satellites are our best hope for doing this because they give us lots and lots of detailed information. However, complications arise in our understanding of the role of clouds in the climate system. Let's consider as an example a satellite photo from NOAA's Los Angeles forecast office, of weather in Southern California in May 2006. There were thunderstorms inland in northern Santa Barbara County and vicinity, and, along the coast, low-lying, thin fog known as the marine layer coming off the Pacific Ocean. This is not too atypical of Southern California in summer. High, thin clouds act as a thermal "blanket," transmitting sunlight but trapping heat radiating back from the ground. Thick clouds reflect sunlight from above back into space, thus helping to cool the surface. Low, thin clouds may be present, but they neither heat nor cool. And in regions with no clouds, greenhouse gases warm the planet. All of these factors, distributed across only a couple hundred miles, have to be taken into consideration in the radiative balance of this scene. Now consider the whole planet, which is a lot bigger than that!

Some other recent work, by senior research scientist Ralph Kahn at JPL and his colleagues, is focused on understanding aerosols, which are tiny particles suspended in the atmosphere. Desert dust, wildfire smoke, and volcanic ash are all aerosols, and their impact on surface and atmospheric temperatures make them an important factor affecting climate. Most aerosols actually cool the planet by blocking sunlight that would otherwise reach Earth's surface—for example, ash from the volcanic eruptions of El Chichon in 1982 and Mount Pinatubo in 1991 significantly cooled the planet for a year or two. Kahn heads a research team working with data from the Multi-angle Imaging SpectroRadiometer (MISR) instrument, which was built and managed by JPL and launched on December 18, 1999, on Terra, the flagship of EOS's advanced instrument-carrying satellites. The MISR instrument has nine attached cameras, each pointed in a different direction and each taking images in four different wavelengths, so it is set up, in part, to monitor the brightness, contrast, and color of sunlight reflected back to space by aerosols.

Looking at the ash cloud from the October 2002 eruption of Mount Etna, Kahn's team came up with a quantitative measure of aerosol optical thickness—or how well you can see through the particle cloud—and how that visibility varies with the wavelength of light. An image taken from directly above Mount Etna by one of MISR's cameras, at a resolution of 1.1 kilometers, is compared with a compilation of similar images from the other cameras. In the optical depth image, each pixel is 17.6 kilometers on a side, and color-coded by the difficulty of seeing through the aerosols in that region. The volcano itself is opaque, and parts of the plume have a high optical thickness. For reference, smoggy air typically has an optical depth of around 0.5 to 1.0, and it is impossible to discern most objects behind a haze that has



Ash erupted from volcanoes can significantly cool the planet by blocking sunlight from reaching Earth's surface. MISR images from the 2002 eruption of Mount Etna helped determine the aerosol optical thickness (AOT, middle panel), or how difficult it is to see through the ash plume. In the Angstrom exponent map (right panel), which shows the distribution of particle size, the ash plume is easily discerned.

an optical depth greater than three. Another property, the Angstrom exponent, relates the change in optical depth with wavelength to the particle's size. Generally, the larger the Angstrom exponent, the smaller the particle size, so something like an ash plume can be easily distinguished from background air particles. Combined with images that show the elevations of different materials, from sea level on up, optical depth and particle size calculations can help map the true distribution of aerosol amount and type in the atmosphere.

We can use MISR to quantify other sources of dust in the atmosphere, like desert dust or smoke from fires. In Southern California, the Santa Anas, which are dry, hot winds channeled out of the desert in winter, can play a significant role in moving dust through the atmosphere. Similar and larger dust plumes are generated in the dusty expanses of the Sahara and the Gobi deserts, from where they are blown out to sea and sometimes cross entire oceans. While volcanic ash in the upper atmosphere can cool the planet by blocking sunlight, dust in the lower atmosphere absorbs sunlight and reradiates it as heat. So pure dust in the air can become a significant component to local atmospheric heating. This is just one more thing we have to think about.

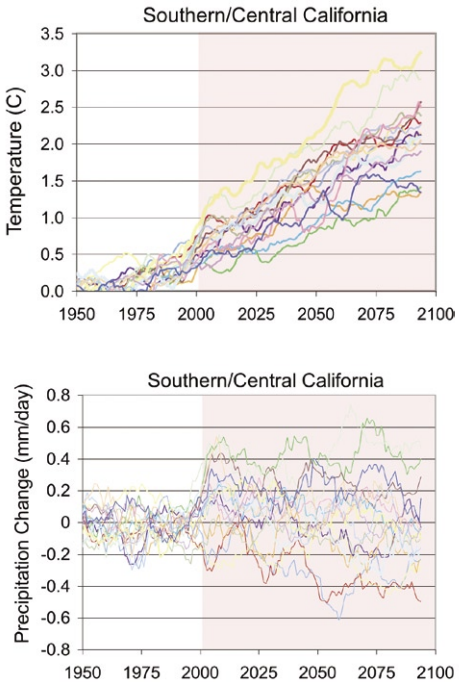
As opposed to ash in the upper atmosphere, dust in the lower atmosphere absorbs sunlight and can warm the atmosphere. These dust clouds off of Southern California are mapped using the optical depth determinations of the MISR instrument.

Why should we care about climate-related issues? The answer is simply that we need to know what is going to happen to the planet, because these issues affect everyone. Right now, though we don't have a detailed understanding of many climate processes, we do have many climate models, which come from computer predictions based on several variables. Those include equations of motion for the atmosphere, our best estimates of interactions of cloud particles with each other and with aerosols, and a description of how radiative balance is maintained. Seventeen climate models designed to predict the long-term temperature, whose outputs were analyzed specifically for Southern California and project through the year 2100, all show that we expect warming. Similar agreement is seen for most places on the planet. So why do we need to keep studying this question? Sure, there are some minority voices saying this is not true, but the overwhelming scientific consensus is that we will see global warming, and it is a consequence of anthropogenic greenhouse gases. This is acknowledged by everyone from Greenpeace to the Bush administration.

Global warming is a problem we will have to deal with, so the question becomes, "How does one deal with this?" The answer is critical to our future management of resources like water. If we look at forecasts of rainfall in Southern California, we see that our ability to make predictions diminishes rapidly. This is due mostly to the feedback between temperature, water vapor, and clouds. Because the atmosphere can hold more water as it warms, increasing temperatures may lead to more water vapor and even more warming. But there are many other feedback mechanisms potentially at work, some of which lead to cooling. As we saw earlier, low, thick clouds cool the planet by reflecting sunlight, even as other clouds warm by transmitting sunlight but blocking infrared radiation escaping the lower atmosphere.

The California climate models each treat cloud feedbacks and the associated water cycles slightly differently, leading to different long-term predictions of rainfall. So, as opposed to the consensus on global warming trends, there is wide disagreement about what will happen to the water cycle. Will the future bring more rainfall or less?

When considered on a global level, the impact of changes in precipitation could have dire consequences. Further drought appears likely in Africa and in the Middle East, where the climate is already fairly dry. Shrinking of mountain glaciers in the Himalayas could disrupt the water supply to the



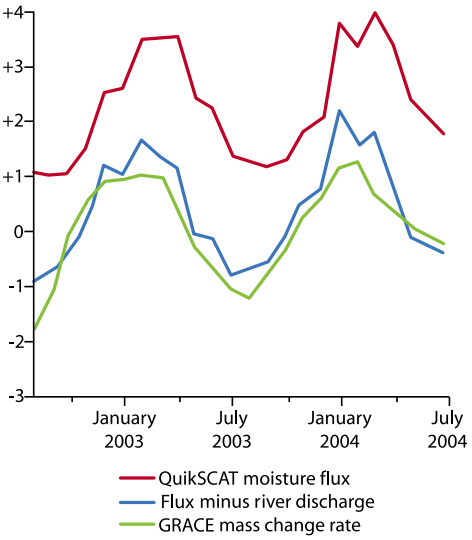
Despite our confidence in long-term climate models that predict warming for most places on Earth, predictions of precipitation are all over the place. As you might imagine, this has serious implications for future water supplies. Analyses by Duane Waliser, JPL.

more than one billion people in India and China who depend on runoff from those mountains. The geopolitical implications of changes in the hydrologic cycle as a result of global warming are significant.

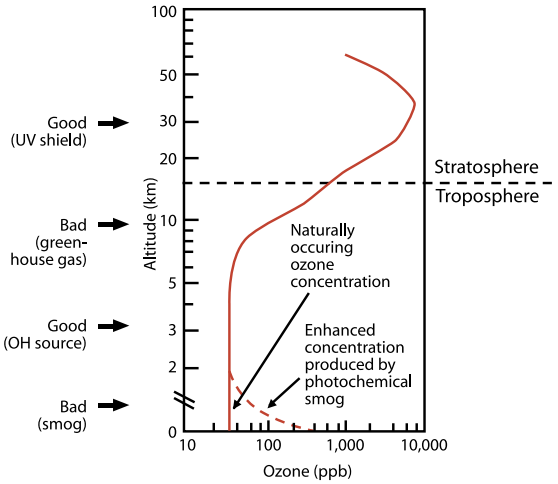
It is clear that atmospheric scientists need to understand the water cycle, and this understanding will primarily come from observation. Timothy Liu, a senior research scientist at JPL and leader of the NASA Ocean Surface Vector Wind Science team, uses space-based observations to study how surface winds distribute heat and water vapor between the ocean and the atmosphere. These observations are made with three more of the EOS satellites. The Quick Scatterometer (QuikSCAT), built by JPL, was launched in June 1999 to measure ocean surface winds. The Gravity Recovery and Climate Experiment (GRACE), which carries JPL instruments, measures changes in Earth's gravity field over time, including those caused by changes in groundwater storage on land. And, finally, the Tropical Rainfall Measuring Mission (TRMM) measures how much rain falls over the tropics and how much heat is released with it. The measurements made by these three satellites quantify the influx of water through precipitation, and the distribution of water by winds. These quantities are then compared to the amount of water lost from the oceans by evaporation and the amount of water leaving the continents and flowing into the oceans from rivers (based on years of data collected by ground-based river gauges). Liu's studies of South America recently established the first reliable space-based water budget for a whole continent. It shows that the total water budget of South America (gain by precipitation minus loss by rivers) matches both in magnitude and in phase the mass change from gravitational pull measured by GRACE. But this is only a beginning. We would like to understand the water budget of the entire planet, down to individual river basins.

Two final climate-related issues worth mentioning are air quality and the ozone hole. We still have widespread problems with pollution, even though air quality in Los Angeles has greatly improved since 30 or 40 years ago, in part through work by people at Caltech. But many large developing-world cities have air pollution issues that make ours pale in comparison. The pollution in these cities is a consequence of burning fossil fuels for heating, cooking, transportation, and industry. Also, the burning of forest and grassland for agriculture, and overall deforestation in general, are other persistent issues related to global warming. This burning of what we call "biomass" releases ozone, whose role shifts between good and bad depending on how far it lies above Earth's surface.

Ozone is beneficial in the upper atmospheric layer called the stratosphere, which extends from about 10 kilometers to about 50 kilometers above Earth's surface. In its most concentrated layer, 20 to 25 kilometers above Earth's surface, stratospheric ozone protects us from ultraviolet rays, which cause skin cancer. Descending into the lower atmosphere, called the troposphere, at 10 kilometers above the surface, ozone is a greenhouse gas, contributing to global warming. Then at three kilometers above Earth's surface, ozone is good again, helping to remove many chemical pollutants. But at ground level, ozone in the air we breathe is harmful, causing premature lung aging.



Above: Space-based measurements of the moisture flux over South America (red line) are tracked from space by the Quick Scatterometer. From these measurements is subtracted the water loss from the continent measured with ground-based river guages. The resulting water balance (blue line) matches both in amplitude and phase the mass changes (green line) measured from space by the Gravity Recovery and Climate Experiment (GRACE).



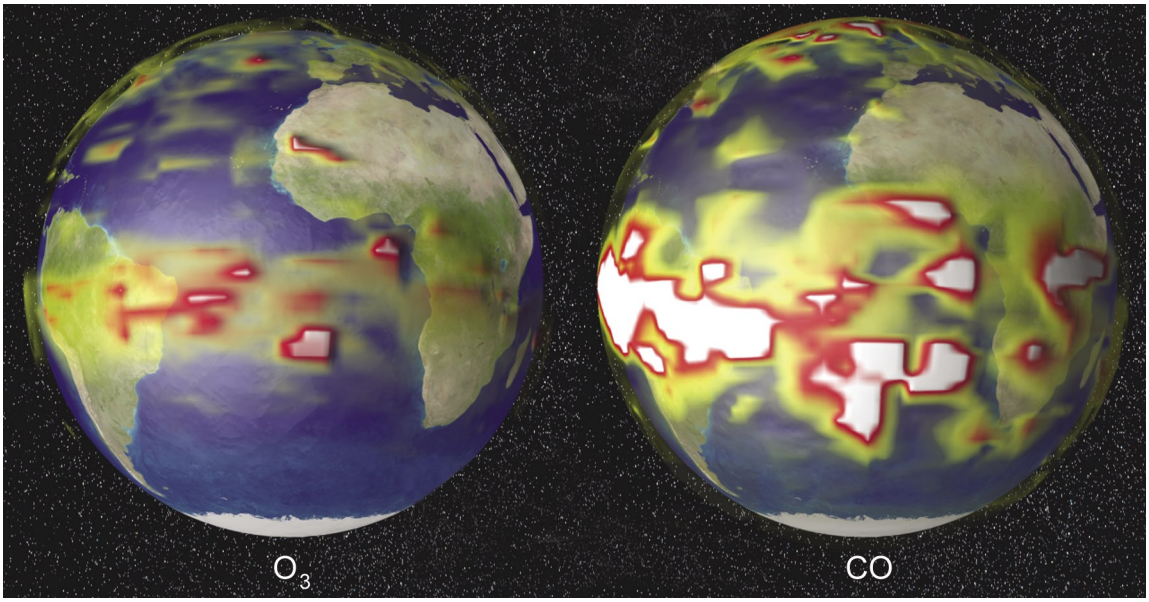
Ozone plays roles that alternate between good and bad (for us!) at different levels of the atmosphere. Ozone levels are in parts per billion.

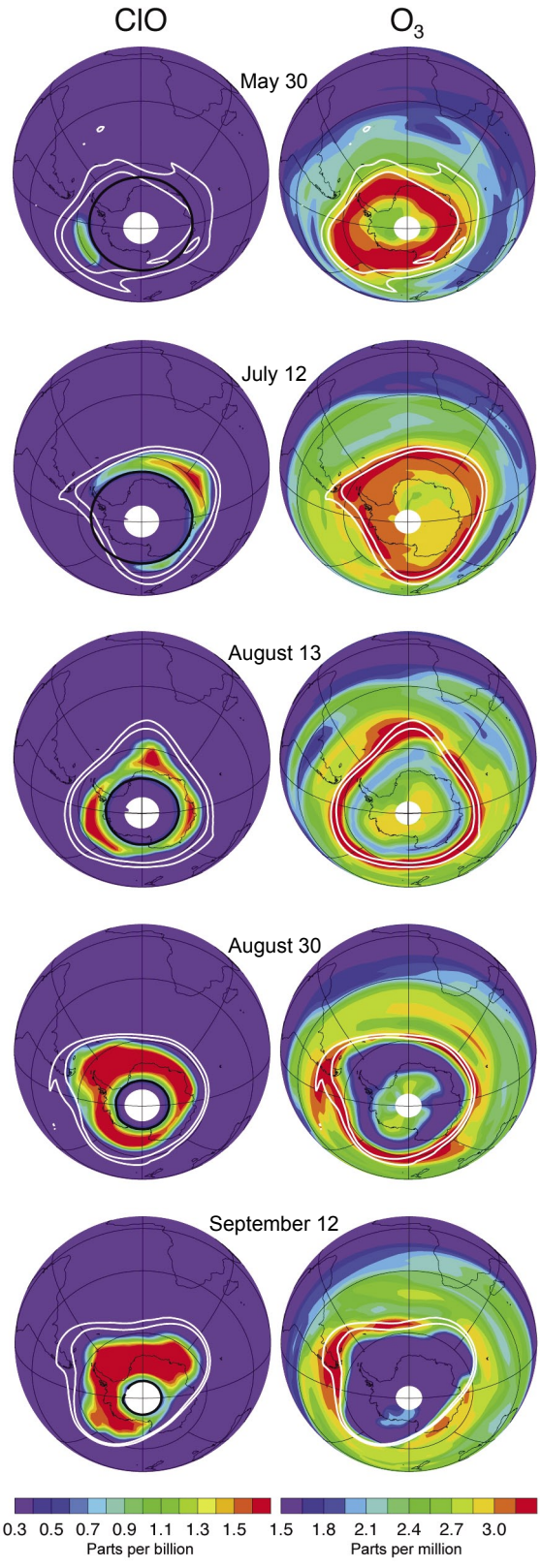
If we look at the presence of carbon monoxide and ozone as measured by the Tropospheric Emission Spectrometer (TES)—launched on July 15, 2004, on the EOS satellite Aura—we see that these gases appear and disappear over time. The images from Aura show that carbon monoxide is abundant in our atmosphere, and yes, that is the carbon monoxide that kills people when they don't ventilate their heaters properly. It is created by incomplete burning of vegetation. People in the tropics commonly burn grasslands in the dry season before summer rains begin, to improve forage. Ozone is created in this process as well, both by burning and by chemical processes in polluted air.

A year of TES data shows that Africa and South America are the major sources of these gases during the burning season. Atmospheric processes then pump ozone and carbon monoxide from these regions into the sky over the southern Atlantic Ocean. There is also some carbon monoxide and ozone in the Northern Hemisphere, due in most part to low pollution emission standards in China and Eastern Europe. As the year progresses toward winter, higher and higher levels of carbon monoxide and ozone appear in the high northern latitudes, because people heat their homes with fossil fuels, primarily coal. Incidentally, while big SUVs contribute some greenhouse gases, most are emitted through home heating.

Some of the most interesting atmospheric chemistry data coming from space are from JPL's Microwave Limb Sounder (also on Aura), which remotely senses atmospheric gases, temperature, pressure, and cloud ice. In a view of the globe centered on

Space-based measurements by the Tropospheric Emission Spectrometer (TES) show that Africa and South America are major contributors of the ozone (O_3) and carbon monoxide (CO) that then blow across the southern Atlantic Ocean from June–September. Relative concentrations range from lows shown in black, to intermediate values in yellow, to highs shown in red–white.





Antarctica, winter 2005. As chlorine monoxide (ClO, left column) builds up from early July to mid-September, ozone (O_3) disappears in the atmosphere 20 kilometers above Antarctica. In the darkness of polar night in the South Pole (the region *inside* the heavy black circle), clouds of frozen nitric acid host reactions that activate chlorine as soon as sunlight returns. Increasing sunlight as winter progresses leads to a increasing ClO abundances and greater destruction of ozone, until mid- to late September, when the icy clouds disappear. Descending air in the winter polar vortex (the pair of heavy white lines), a wind tunnel that isolates a region above the Antarctic through the winter (May-September), also helps replenish lower-altitude ozone from higher abundances above. After ozone reaches its minimum in mid-September, the vortex starts to shrink and eventually breaks down, and chunks of the "ozone hole" float northward. Maps of data from the Microwave Limb Sounder (MLS) by Michelle Santee, JPL.

Antarctica, we can track temperature, nitric acid, hydrogen chloride, and chlorine monoxide, which all play a role in ozone chemistry through the year. From this data, provided by principal scientist Michelle Santee (MS '89, PhD '93) of JPL's Microwave Atmospheric Science Element, we see a rather complex chemistry that is fairly easy to interpret. I say "easy" with two caveats. First, it took years for the mechanisms at play in ozone destruction to be identified and understood. Second, the loss of ozone is still only easy to quantify in the Antarctic; the dynamics of ozone is much more complicated in the Arctic, because several competing factors there compensate for the chemical destruction of ozone.

The disappearance of ozone begins with the release of chlorine from chlorofluorocarbons, or CFCs, in the presence of sunlight. (That chlorine, by the way, comes from the CFCs that we all used back in the 1950s–1970s. While generally extremely long-lived, CFCs are broken down by intense ultraviolet light in the stratosphere. Many CFCs are still floating around up there, and they continue to be released today from countries where they are not banned.) Chlorine is anathema as far as ozone goes: a single atom of it destroys ozone and survives, going on to destroy many thousands more ozone molecules before being neutralized by some other reaction.

The chlorine released from CFCs becomes destructive only after it is activated; this activation begins in May on the surfaces of nitric acid particles that condense to form clouds in the very cold, early winter stratosphere over Antarctica. Early May is also polar night at the South Pole, so full-time darkness reigns. The reaction of activated chlorine with ozone begins only when sunlight returns to the Antarctic in July. These reactions create chlorine monoxide, which is the smoking gun signifying the destruction of ozone. The series of globes shown at left track the demise of the ozone and the rise of chlorine monoxide at 20 kilometers' altitude, and you can see that there is no chlorine monoxide in the polar night. So the ozone is fairly safe in mid-May, in the absence of sunlight, especially as it is being replenished in the lower stratosphere by descending winds from the upper stratosphere, where abundances are higher.

But as the sun returns in July, destruction eventually overcomes replenishment, and we start to see the ozone values in the lower stratosphere decline. The ozone loss accelerates as winter progresses, sunlight increases daily, and more and more activated chlorine reacts with ozone. By mid-September, chlorine monoxide is at its highest, and a region the size of the entire Antarctic continent is almost completely depleted of ozone. This is what we call the "ozone hole." (By the end of September, the Antarctic air is too warm to host the icy clouds, and chlorine monoxide disappears.)

Fortunately for us, the deepening and widening ozone hole is kept confined to a region over

the Antarctic by the "polar vortex," a region of air isolated from its surroundings by strong encircling winds. Until late spring, that is, when the vortex begins to break up, and chunks of the hole split off and float away to places like southern South America, New Zealand, and Australia. New Zealanders, as a result, are very concerned about their increased skin cancer risk. By late December, the ozone hole has vanished, and everything gets reset until the austral fall, when in the darkness of polar night the temperatures drop again, another winter polar vortex spins up, and the whole process starts all over again.

Our challenges in understanding the climate cycle have just begun. We need to integrate all our observations in some meaningful way. There are a lot of things we do not understand about how the climate system works. For example, while we now understand the mechanisms forming the Antarctic ozone hole, and treaties since the 1980s have sought to diminish ozone loss, global warming is a far more complex issue. Furthermore, a lack of complete observations leaves the water cycle not fully understood, especially over land. Our eventual understanding will help us address issues of water supply. There are also persistent questions about how clouds and aerosols cool the planet, and even about how both those quantities interact. All of these open questions carry serious implications for our future quality of life.

What happens to the climate because of widespread burning of cow dung for fuel in India, for instance? The resulting soot particles can act as condensation nuclei for clouds, which reflect sunlight and actually cool the planet. In this case, aerosols indirectly cool the planet, and appear to counteract some of the anthropogenic warming caused by increased carbon dioxide and other greenhouse gases. We need to understand exactly how this happens. Some people have pointed out that global warming, ironically, can be counteracted by dirty air.

But could that counteract the classic feedback mechanism at work in global warming: rising temperatures leading to increasing water vapor, which will lead to a heightened greenhouse effect? The magnitude of that effect is still not understood, and there are many, many other mechanisms that we need to understand in order to make reliable predictions in the face of climate change. The real challenge lies in improving climate forecasts, and I think the societal benefit of this should be apparent to all of us. □

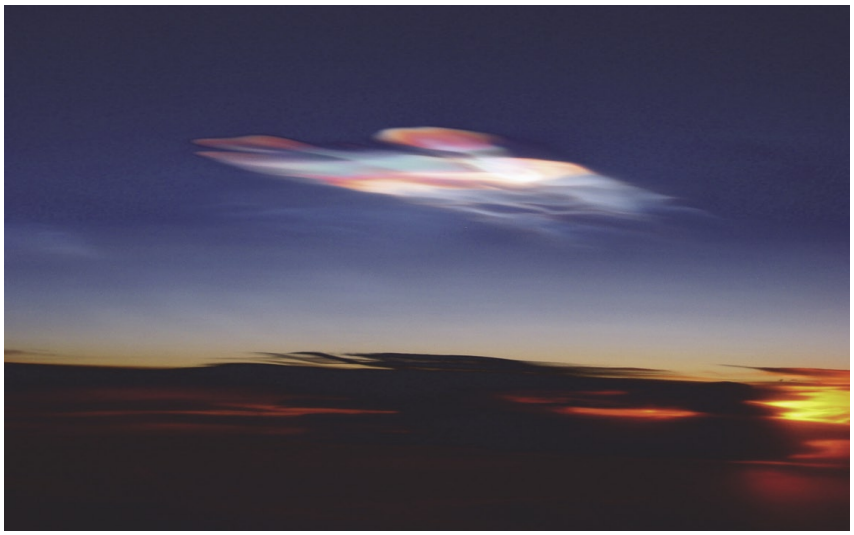
Eric Fetzer arrived at the Jet Propulsion Laboratory in 1991 as a postdoc, and is now a senior member of the technical staff. He earned a bachelor's degree in physics from the University of California, Berkeley, and a PhD in atmospheric science from the University of Colorado, Boulder, where he studied waves in Earth's stratosphere. He has worked since 1994 on the Atmospheric Infra-Red Sounder (AIRS) instrument, and also leads an effort to characterize water vapor and clouds using several other satellite instruments. His group won a NASA Group Achievement Award in 2004. In his spare time, Eric gets in loads of trouble while hiking, mountain biking, and rock climbing with Caltech alumni.

Fetzer thanks those colleagues mentioned in the text for their research results and assistance, and Brian Kahn, Stephanie Granger, and Sharon Ray for their help.

This article was adapted by Elisabeth Nadin from an Alumni Seminar Day lecture given on May 20, 2006.

PICTURE CREDITS: 32, 36, 37, 39, 40 — NASA/GSFC/JPL; 34, 38—NASA/JPL; 33 — Doug Cummings; 36—NOAA

Below: Clouds of frozen nitric acid, sulfuric acid, and water vapor form the substrates for chemical reactions that activate chlorine to destroy ozone. These clouds form when temperatures drop below -88°C, and are present usually between the end of May and end of September over Antarctica. Photograph over Iceland by Mark Schoeberl, NASA.



Honors and Awards

Barry Barish, Linde Professor of Physics, Emeritus, has been awarded a Laurea ad Honorem in Physics by the University of Bologna. A workshop, "Beyond the Standard Model," was held at the Bologna Academy of Sciences on October 2 in honor of Barish and his fellow recipient, Nobel Laureate Sheldon Glashow of Boston University.

Jacqueline Barton, Hanisch Memorial Professor and professor of chemistry, received the 2006 Willard Gibbs Award from the American Chemical Society's Chicago section on May 12; she is the second woman to have received the honor in its 95-year history, the first having been Marie Curie. She and **Peter Dervan**, Bren Professor of Chemistry, who won the award in 1993, are the first husband and wife to be so honored. Barton was cited for her "elegant, vitally important work" on "the molecular chemistry of DNA and its relevance to the development of a variety of diseases and inherited abnormalities."

Warren Brown, associate professor of history, **Nathan Dunfield**, associate professor of mathematics, **Ali Hajimiri**, associate professor of electrical engineering, **Niles Pierce**, assistant professor of applied and computational mathematics and bioengineering, and **Brian Stoltz**, associate professor of chemistry, have been named as faculty recipients of 2006 ASCIT (Associated Students of Caltech) Teaching Awards. The Teaching Award for research mentor has gone to **Preston McAfee**, Johnson Professor of Business Economics and Management and executive officer for the social sciences, and awards for teaching assistant have been received by grad students **Bob Pelayo**, in mathematics, and **Christine Thomas** (PhD '06), in chemistry, and by **Po-Ru Loh**, undergraduate in mathematics, class of 2007.

Charles Elachi (PhD '71), Caltech vice president and professor of electrical engineering and planetary science, and director of the Jet Propulsion Laboratory, in May received the Order of the Cedars, officer grade, from Émile Lahoud, president of Lebanon. Elachi's return to his native country included, among numerous events, giving a lecture at the American University of Beirut on "The Challenges and Excitement of Space Exploration." He also won the 2006 Royal Society of London Massey Award, which "recognizes outstanding contributions to the development of space research," and was named one of "America's Best Leaders" by *U.S. News & World Report* and the Center for Public Leadership at Harvard University's Kennedy School of Government.

Wolfgang Fink, visiting associate in physics and senior member of the technical staff at JPL, has won first prize in the Congress of Evolutionary Computation 2006 Huygens Probe Competition, which was held at the World Congress on Computational Intelligence 2006, July 16–21, in Vancouver, British Columbia. The competition involved creating algorithms for evaluating fractal landscapes representing the surfaces of moons.

Peter Goldreich, DuBridge Professor of Astrophysics and Planetary Physics, Emeritus, has been awarded the Grande Medaille of the Académie des Sciences of the Institut de France. Created in 1997, the award is given annually, rotating among the disciplines relevant to each division of the academy. Recipients have "contributed to the development of science in a decisive way, both through the originality of their personal research and by their international presence and stimulating influence."

Judith Hall, lecturer in creative writing, has received a 2006 Guggenheim Fellowship. Associated with Caltech since 1999, Hall is a widely published poet, the author of several books, and the poetry editor for the *Antioch Review*. Her fellowship will support the composition of a new book. Fellowships "are awarded on the basis of distinguished achievement in the past and exceptional promise for future accomplishment."

Paul Jennings (MS '60, PhD '63), provost and professor of civil engineering and applied mechanics, is the Earthquake Engineering Research Institute's George W. Housner Medalist for "extraordinary and lasting contributions to public earthquake safety." Housner (MS '43, PhD '41), often called the father of earthquake engineering, is the Braun Professor of Engineering, Emeritus.

Jeff Kimble, Valentine Professor and professor of physics, garnered the 2006 Berthold Leibinger Zukunftspreis. He is the first recipient of the prize, which is to be awarded every two years for milestones in laser research, and was cited for "his groundbreaking experiments in the field of cavity quantum electrodynamics."

Jerrold Marsden, Braun Professor of Engineering and Control and Dynamical Systems, has been named a Fellow of the Royal Society, which cites "his fundamental contributions to a very wide range of topics," including plasma physics, general relativity, and solar-system mission design. Established in England in 1660, the Royal Society is the world's oldest scientific academy in continuous existence and has counted Isaac Newton, Charles Darwin, and Albert Einstein among its members.

Marsden has also received the 2006 Graduate Student Council Mentoring Award. **Robert Sherman**, professor of economics and statistics, received the GSC Teaching Award, and **Ryan Turner** (MS '06), graduate student in chemical engineering, the award for teaching assistant.

Barry Simon, IBM Professor of Mathematics and Theoretical Physics, has been invited to give the 2006–07 van Winter Memorial Lecture in Mathematical Physics at the University of Kentucky, on March 20 of next year.

The **Two-Micron All Sky Survey (2MASS) Team** has been named to receive the Astronomical Society of the Pacific's 2006 Maria and Eric Muhlmann Award, which recognizes "the development

Caltech Shares Both Balzan Prizes in Science

Lange (far left) and Meyerowitz (left).

Andrew Lange, Goldberger Professor of Physics, has been selected to be a corecipient of the 2006 Balzan Prize for Observational Astronomy and Astrophysics, with BOOMERANG colleague Paolo de Bernardis. The BOOMERANG experiment, utilizing a microwave telescope suspended from a balloon over the Antarctic, has provided important new images of the early universe. A second Balzan Prize, for Plant Molecular Genetics, went jointly to **Elliot Meyerowitz**, Beadle Professor of Biology and chair of the biology division, and Christopher Somerville of Stanford University, for "their joint efforts in establishing *Arabidopsis* as a model organism for plant molecular genetics."

The prizes will be personally presented by the president of the Italian Republic, Giorgio Napolitano, on November 24 in the Palazzo Corsini in Rome. Each prize is worth one million Swiss francs (about $810,000), which is shared equally among the winners, who in turn must allocate half of their award to research projects to be carried out by young scholars in their respective fields.

The Balzan Prize is almost as lucrative as the better-known Nobel, and is one of the highest world honors for science, culture, and humanitarianism. Established by Angela Lina Balzan, heiress of Italian newspaper magnate Eugenio Balzan, who had invested his assets in Switzerland and then left Italy to protest the rise of fascism, the International Balzan Foundation gives two prizes annually in various fields of science and two in the humanities. It also awards a two-million-franc Prize for Humanity, Peace, and Brotherhood among Peoples at longer intervals. □

Honors and Awards, Continued. . .

of innovative research instruments and techniques." Based at the University of Massachusetts Amherst, the project includes team members from Caltech's Infrared Processing and Analysis Center (IPAC) and from JPL. The Muhlmann Award is given annually "for recent significant observational results made possible by innovative advances in astronomical instrumentation, software, or observational infrastructure."

Ahmed Zewail, Nobel laureate, Pauling Professor of Chemical Physics and professor of physics, has been selected to receive the "Albert Einstein" World Award of Science 2006 for his development of the new field of femtoscience and his "valuable contributions to the revolutionary discipline of physical biology." The honor is awarded by the World Cultural Council, which was founded in Mexico in 1982. □

Nelson Leonard
1916 – 2006

Faculty Associate in Chemistry Nelson J. Leonard died of cancer at his home in Pasadena on Monday, October 9, barely a month after his 90th birthday. Although Leonard did not join Caltech until 1992, at the ripe old age of 76, "he played a very important role in the life of the division," says David Tirrell, the McCollum–Corcoran Professor and professor of chemistry and chemical engineering, and division chair. "He mentored many younger faculty members, participated in all our divisional decisions, and was an active member of the Freshman Admissions Committeee for many years."

Leonard was born on September 1, 1916, in Newark, New Jersey, and earned a BS from Lehigh University in 1937, a BSc as a Rhodes scholar at Oxford University in 1940, and a PhD from Columbia University in 1942. He moved to the University of Illinois at Urbana-Champaign as a postdoc and remained there until he retired in 1986.

A synthetic organic chemist with an interest in biochemistry and plant physiology, Leonard helped develop a method for mass-producing the antimalarial drug chloroquine in time for it to be used in the Pacific Theater during World War II.

DEAN E. WOOLDRIDGE
1913 – 2006

With his longtime collaborator Folke Skoog (BS '32, PhD '36), a plant physiologist at the University of Wisconsin, Leonard did groundbreaking work on the substances that initiate plant growth and flowering. He also developed a host of the indispensible fluorescent "markers" used to trace DNA, RNA, and other biochemicals within cells. He published more than 400 papers and held eight patents.

At the same time, Leonard was a critically acclaimed singer, soloing with the Chicago, Cleveland, and St. Louis symphony orchestras. After joining Caltech, he served on the board of the Pasadena Symphony.

Leonard is survived by his second wife, Peggy Phelps, whom he married in 1992; daughter Marcia, of Maplewood, NJ; sons Kenneth, of Agoura Hills, CA; James, of Olympia, WA; and David, of Seattle, WA; and seven grandchildren. His first wife, the former Louise Vermey, died in 1987.

A memorial service is planned for November 13 at All Saints Episcopal Church in Pasadena; memorial donations may be made to the Nelson J. Leonard Fund at the Pasadena Symphony. □—*DS*

Dean Everett Wooldridge, a leading scientist and technological industrialist, died on Wednesday, September 20, in Santa Barbara, California, after a brief illness. He was 93.

Born in Chickasha, Oklahoma, on May 30, 1913, Wooldridge graduated high school at age 14, and received his bachelor's and then master's degrees from the University of Oklahoma before the age of 20. In 1936, at age 23, he received a doctoral degree in physics (with the rare designation of "summa cum laude") from Caltech. He then joined the staff of Bell Laboratories and achieved a worldwide reputation as a leading expert in the theory of magnetism basic to modern electronics. When World War II began, Wooldridge became the head of a group developing the first airborne computers to guide missiles.

In 1946, he left Bell and joined classmate Simon Ramo (PhD '36) to build a unique electronics and missile corporation now known as Hughes Electronics. In five years that company concentrated the largest number of engineers and scientists in the U.S. devoted exclusively to military technology. It was the premier company producing airborne radar, computers, and guided missiles to counter a possible bomber attack on the U.S., with the Hughes apparatus equipping every American interceptor airplane.

In 1953, Wooldridge and Ramo founded the Ramo-Wooldridge Corporation with the backing of Thompson Products, Inc., which manufactured parts for Hughes's Falcon missile. Mathematician John Von Neumann picked Wooldridge and Ramo to join a government-initiated committee that formed the nation's Intercontinental Ballistic Missile (ICBM) program. Wooldridge and Ramo were then awarded the prime contract for overall systems engineering and technical direction of the ICBM, to which President Eisenhower assigned the highest national priority and which became the largest single weapon systems program in U.S. history. In 1958, the Ramo-Wooldridge Corporation was the first corporation to build and launch a spacecraft, Pioneer 1. One of its later spacecraft, Pioneer 10, was the first to leave the solar system, transmitting back outer-space data for well over 30 years.

Ramo-Wooldridge merged with Thompson Products in 1958 to form TRW, Inc. With Dean Wooldridge as its president, TRW became one of the world's largest high-technology companies. After he retired in 1962, Wooldridge traveled with his wife for 10 years and then took up the study of neurology. From these studies he authored two highly respected books, *The Machinery of the Brain* and *The Machinery of Life*, which were widely recommended in postgraduate courses in leading universities.

Wooldridge served as a trustee of Caltech and a consultant to the President's Science Advisor. He received a number of honors, including membership in the National Academy of Sciences.

Wooldridge married Helene Detweiler in 1936. She passed away in 2001. He leaves three children, Dean E. Wooldridge Jr. of Las Vegas, Nevada, Anna Lou Eklof of Bailey, Colorado, and James A. Wooldridge of Basking Ridge, New Jersey, and three grandchildren, Michael Andrew, Jonathan David, and Lisa Michelle Wooldridge. □

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