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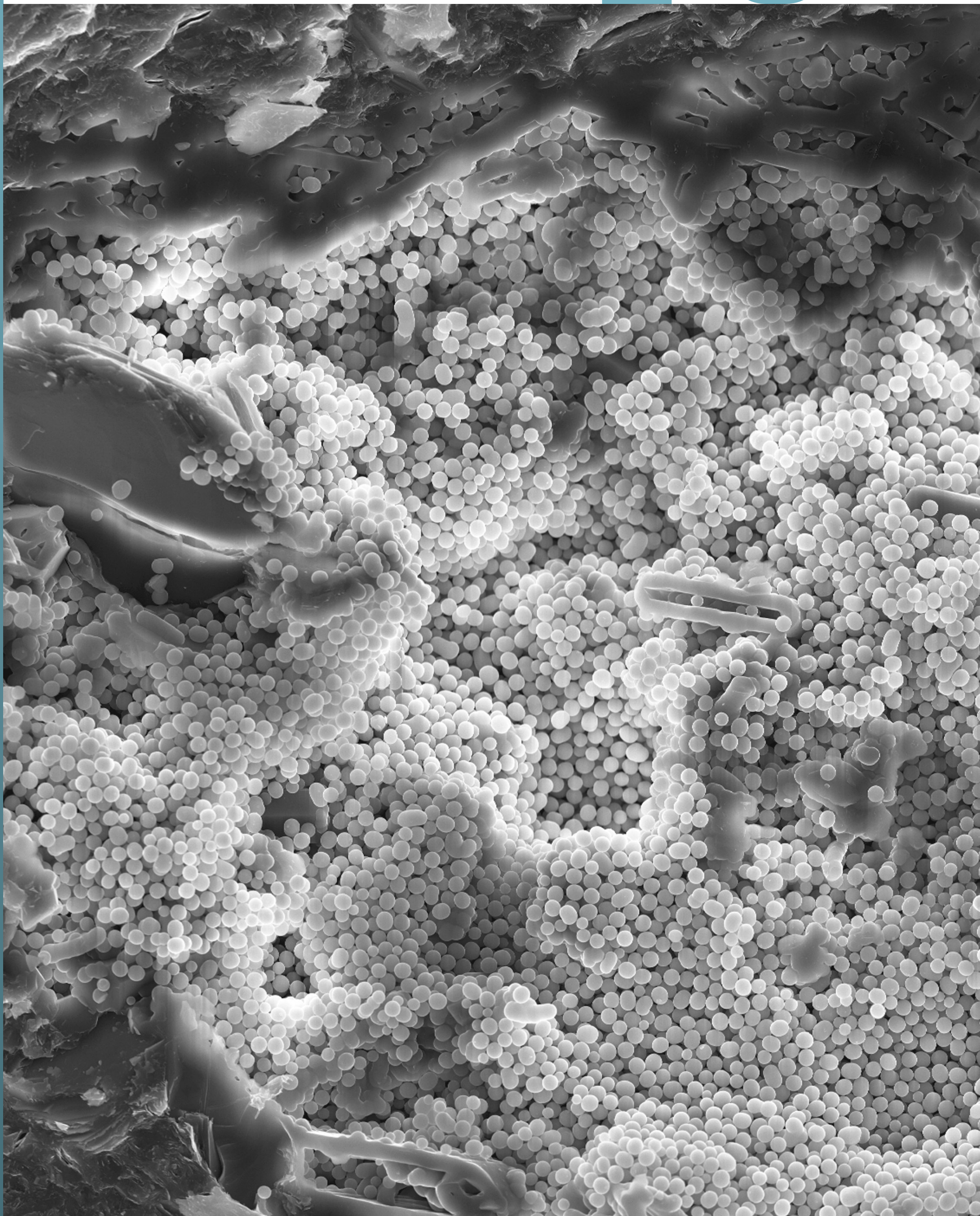

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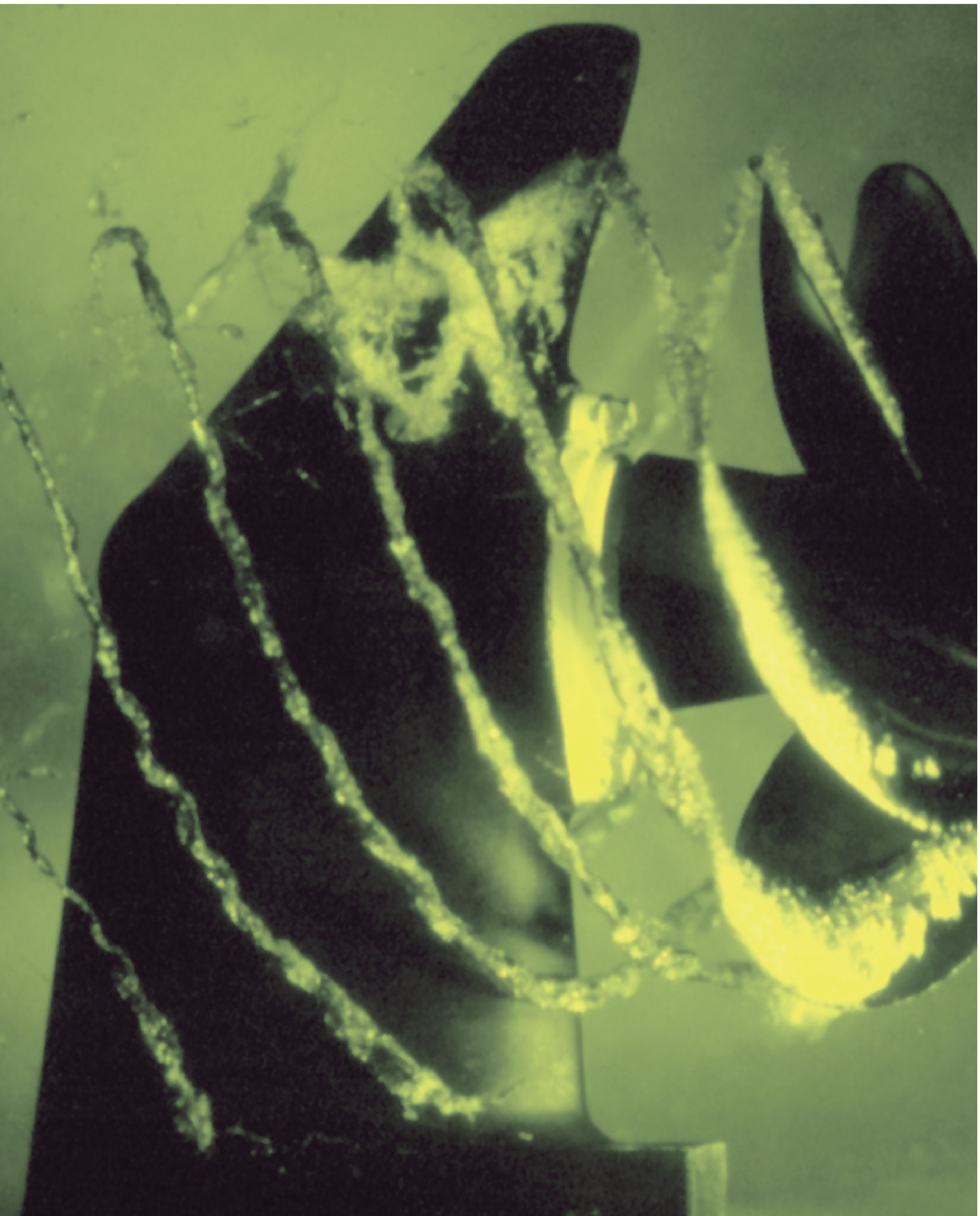

A trail of bubbles can pierce solid steel. Well, no, they can't—but the vorticity generated by a spinning propeller is so strong that where the vortices cross a solid strut they will reform on its far side, and the bubbles will appear to have penetrated. This photo was taken in a Caltech water tunnel by Mark Duttweiler (MS '96, PhD '01); for more on the astonishing things bubbles can do, see the story beginning on page 32.

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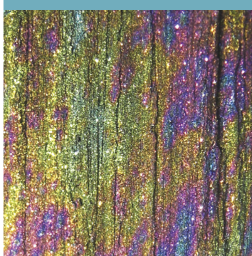

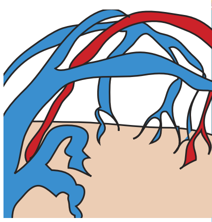

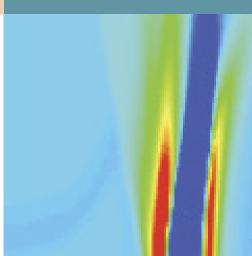

Departments

On the cover: Alien egg colony? Unhealthy intestinal lining? Nope—these are the nanoscale silica spheres that make up opal. When they're loosely scattered as in this image, the resulting opal is creamy. But when they're evenly sized and cemented together, the result is an iridescent gem. See the story on page 10.

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Dark Matter in 3-D

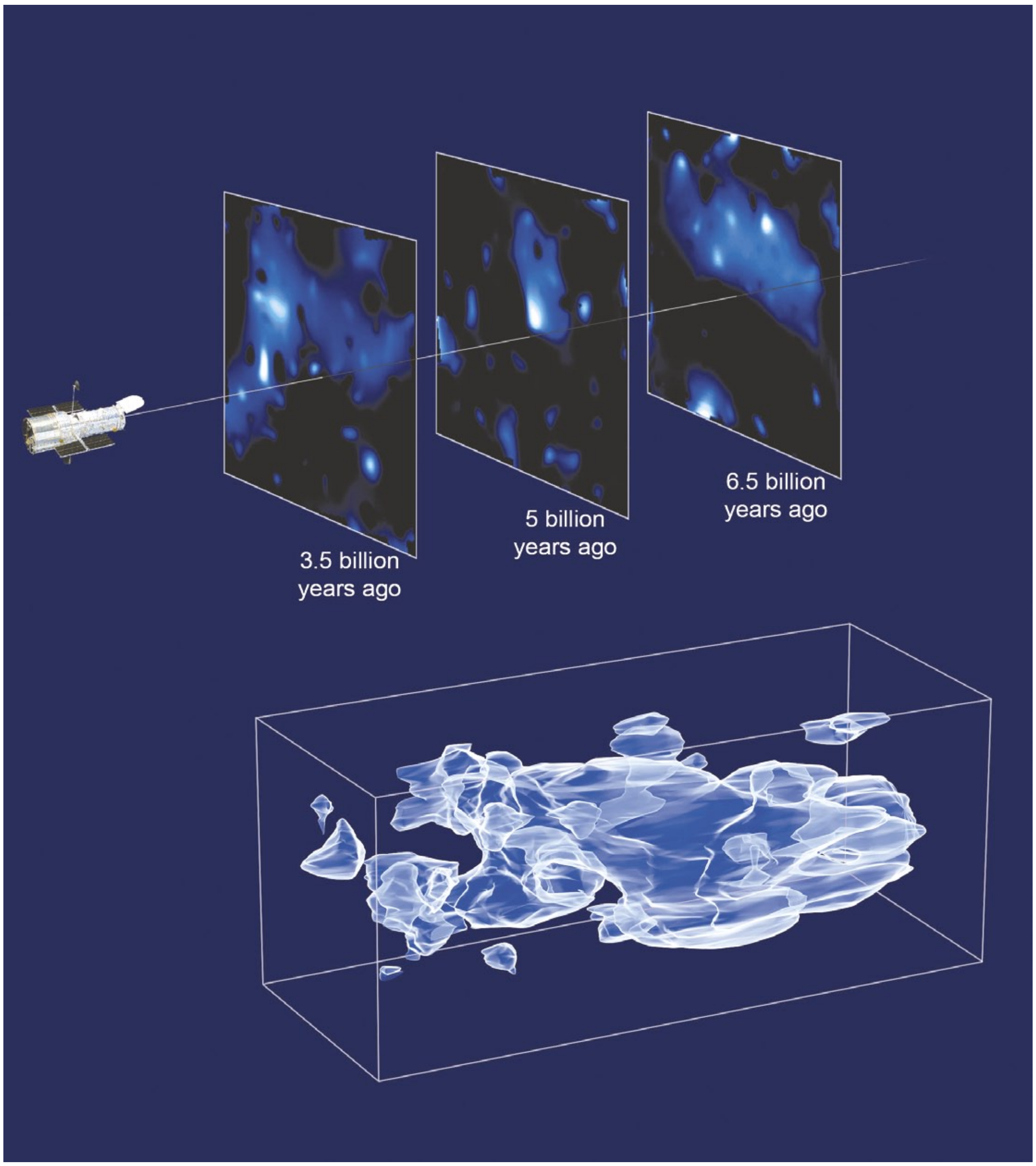
An international team led by Caltech scientists has made a three-dimensional map of dark matter that offers a first look at its distribution. Dark matter, which makes up most of the universe's mass but neither emits nor reflects light, has so far eluded direct detection or even a definitive explanation for its makeup. But a cosmic quirk called "gravitational lensing," first predicted by Einstein, allows the invisible stuff to be traced out.

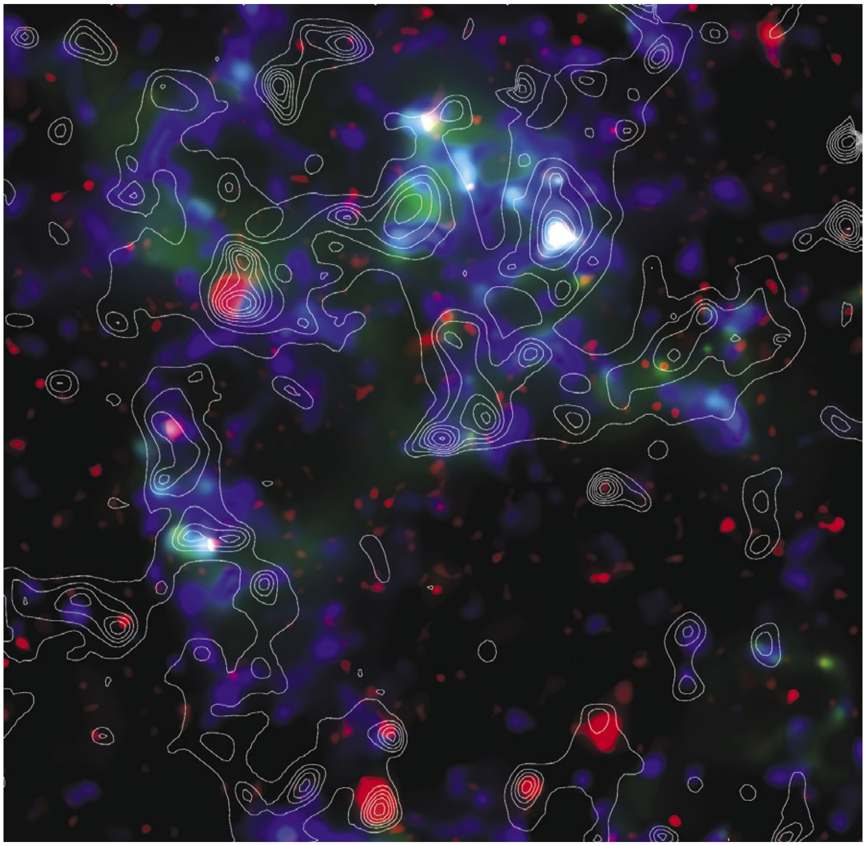
The light rays from distant galaxies are deflected where space is curved by the gravitational influence of dark matter, making the shapes of background galaxies appear distorted. So postdoc Richard Massey and JPL scientist Jason Rhodes carefully measured those shapes to infer the distribution of foreground structures. Since gravitational lensing is sensitive to all mass, it reveals the location of otherwise invisible features—including one concentration of dark matter a trillion times more massive than the sun, around a previously unknown cluster of galaxies.

The 3-D map, which was unveiled at the January meeting of the American Astronomical Society and also appeared in the January 18 issue of *Nature*, reveals a gelatinous network of cosmological filaments that grew over time, intersecting to form massive structures containing clusters of galaxies. According to lead author Massey and coauthor Richard Ellis, the Steele Family Professor of Astronomy, this provides the best evidence yet that normal matter coalesces to form galaxies only inside the preexisting scaffolding of dark matter.

The map was derived from

Below: Light travels at a finite speed, so looking out into the distance is equivalent to looking back through time. Combining a set of slices at fixed distances (top) gives a 3-D map (bottom) that is like a geological core sample of the universe. Evolving over time from right to left, the distribution of dark matter becomes increasingly clumpy.





Above: In this rendering of the entire COSMOS field, the contours show the total mass of both visible and dark matter. Ordinary matter grows inside a dark matter scaffolding: the galaxy mass distribution is shown in blue and number density in yellow; the two combine to become green. Red shows X-ray emission from hot, dense gas in the centers of dense clusters of galaxies. This view covers nearly two square degrees of sky, or roughly nine times the area of the full moon.

the Hubble Space Telescope's widest survey of the universe, led by Nick Scoville, Caltech's Moseley Professor of Astronomy. The Cosmic Evolution Survey (COSMOS) consists of 575 slightly overlapping views of the universe requiring nearly 1,000 hours of observations—the largest project ever undertaken with the Hubble.

Scattered through the COSMOS images are some half-million distorted galaxies whose distances were measured to high accuracy—using color data from the Subaru telescope in Hawaii—as part of COSMOS's research on large-scale structures.

The resulting map stretches halfway back to the beginning of the universe, showing how dark matter started out smooth and grew increasingly clumpy as it continued to collapse. These observations will guide theorists grappling with how large cosmic structures evolved under the relentless pull of gravity, and may illuminate the role of "dark energy"—a sort of negative gravitational force that is believed to influence how dark matter clumps.

According to Scoville, stars in the galaxies in the densest cosmic structures of the early universe are generally found to be older than those in galaxies in more rarified environments, indicating that the galaxies in the denser regions formed first and that the mass accumulated in a bottom-up fashion. By contrast, those galaxies with ongoing star formation today dwell in less populated cosmic filaments and voids.

"Both the maturity of the stellar populations and the 'downsizing' of star formation in galaxies vary strongly with the epoch when the galaxies were born, as well as their dark-matter environment," says Scoville. His team's findings will appear in a future issue of *The Astrophysical Journal*. Other Caltech participants in this COSMOS research on large-scale structures include postdocs Peter Capak and Mara Salvato, Member of the Professional Staff Patrick Shopbell, and Kartik Sheth of the Infrared Processing and Analysis Center. □—*RT*

Delbrück Centennial

A day of science, remembrances, and partying marked the 100th anniversary of the birth of Nobel laureate, molecular biology pioneer, and Caltech professor Max Delbrück. The party, at the Delbrück home one block east of campus, was in keeping with the biologist's penchant for high-spirited shenanigans—until his retirement in 1977, he was known as quite the campus prankster.

"That home became a second home to many of us," recalled Seymour Benzer, the Boswell Professor of Neuroscience, Emeritus, who showed footage of a hike to the bottom of the Grand Canyon in 1949, hosted by Delbrück and his wife Manny. "I had never climbed more than two staircases in my life," Benzer joked. "After 18 miles, I became a unit of tiredness."

Former postdoc Gunther Stent, who went on to establish both the department of virology and the department of molecular biology at UC Berkeley, from where he retired in 1992, recounted Delbrück's early scientific career. Delbrück trained as a theoretical physicist in Göttingen, Germany, but the discipline never fully captured his interest. Just before he came to Caltech in 1937 for a yearlong Rockefeller Fellowship, he was inspired by physicist Niels Bohr to explore the relation of atomic physics and biology, and thus began his foray into the biological realm. Delbrück commenced genetic work on *Drosophila*, a genus of fruit fly that was already becoming a workhorse of molecular genetics, but the forbidding-looking papers categorizing every one of the fly's genotypes turned him off.

By the time he returned to the Institute as a biology professor in 1947, he was fascinated by the question of how viruses infect bacteria, and founded the freewheeling "phage lab," which essentially pioneered the field of bacterial genetics. This work led to a Nobel Prize in Physiology or Medicine in 1969, but according to Stent, accepting it was difficult for Delbrück. He felt the prize contradicted the "Copenhagen Spirit"—an ideal that stressed self-criticism and an egalitarian regard for scientific findings.

Remembrances of Delbrück's early years gave way to today's frontiers of biophysical research. After jokingly referring to himself as an "extinguished" fellow of the Salk Institute, molecular biologist and Nobel laureate Sydney Brenner, an occasional visitor to Caltech since 1960, challenged the audience to tackle biological complexity by returning to phage biology. "The best thing we can do in biology is what we're damned good at: the forward problem. We can't do the inverse problem—I call that the 'low-input, high-throughput, no-output problem,'" he said. Howard Berg (BS '56), now a professor of both physics and molecular and cellular biology at Harvard University, recalled how Delbrück's influence led him to study *E. coli*. Delbrück once told Berg that if he had to do it over again he'd work with bacteria, but he didn't know how to tame them. The word "tame" caught Berg's interest, and the rest, as they say, is history. Berg gave a nod to the Caltech team that took 3-D pictures of a bacterium's flagellar motor (see *E&S*, 2006, No. 3, p. 6); he himself studies the rotary motor of *E. coli's* flagella. Max Delbrück's son Tobi Delbrück (PhD '93) came from Zurich, where he teaches neuroinformatics at the Eidgenössische Technische Hochschule (ETH), and showed off his new toy—a retina built like the human eye's, but in the form of a silicon chip. He had been inspired to his current pursuits during his graduate work with the senior Delbrück's colleague Carver Mead (BS '56, MS '57, PhD '60), the Moore Professor of Engineering and Applied Science, Emeritus.

The celebration resonated even for those who had never met the legend. Rob Phillips, professor of applied physics and mechanical engineering, credited Delbrück for influencing his own career path, which has led to insights into how DNA is packed into viruses—like balls filling a bathtub and locking together to form hexagons. "He's an abstraction, a myth, and a legacy in the same way Feynman or Gibbs might be," Phillips said.

The centennial ended as one imagines it would have in Delbrück's day, with movies and jokes. Professor emeritus and former chair of the biology division Ray Owen recalled the party that marked his last day of chairmanship in 1968. Delbrück presented to Owen an accurate metal sundial fabricated in the astrophysics shop, and then began scribbling on the board a lengthy equation of time demonstrating how it worked.

Finally, under Benzer's direction, the audience joined in with recordings of Delbrück himself, singing a parody by former biology student Sandra Winicur (PhD '71) of *The First Lord's Song* from Gilbert and Sullivan's *HMS Pinafore.* Imagining a Nobel laureate belting out this first verse might amuse many a Caltech grad:

When I was a youth, I wanted to be
A full Professor in Biology.
How I could become one was hard to see
Since my IQ was only ninety-three. □—*EN*

Just Breathe

580 million years ago, the ocean that once covered the present-day Sultanate of Oman was flooded with enough oxygen that the way in which life was constructed was completely changed. This moment, the birth of multicellular organisms, shortly preceded the burst of biological diversification called the Cambrian explosion. Recent evidence indicates that this was the last in a series of similar increases in oxygen availability.

"The presence of oxygen on Earth is the best indicator of life," says John Grotzinger, the Jones Professor of Geology at Caltech who coauthored a recent paper on the subject in *Nature*. "But it wasn't always that way," he adds. "The history of oxygen begins about two and a half billion years ago and occurs in a series of steps. The last step is the subject of this paper."

The study was led by Dave Fike, an MIT grad student who made the move to Caltech in 2006 to stay with his advisor, Grotzinger. Fike uncovered evidence for this final stage in oxygenation at three kilometers' depth in the oil fields of Oman, where the oldest commercially viable oil on the planet is found. He analyzed carbon and sulfur isotope ratios from core samples and drillings to determine the oceanic conditions under which the deposits were originally laid down.

At the time, the ocean covering Oman resembled the modern-day Black Sea, which has a thin oxygen-rich layer on top underlain by an oxygen-starved (what chemists would call a "reduced") environment. "The ocean today is pretty well mixed and thus oxidized at all layers, but the ocean before the Cambrian period must have been very different," says Grotzinger. Different enough to be hostile to complex life—a deep ocean devoid of sufficient oxygen can't sustain multicellular life forms. For this reason, life continued in its single-celled form from its first days, more than three and a half billion years ago, until just before the Cambrian explosion. At that time, according to the team's geologic evidence, deep water began mixing with the shallow ocean, and the result was the first fully oxidized deep ocean. With enough oxygen in the deep ocean came the successful establishment of Earth's first multicellular community, the Ediacara fauna, some of which looked a lot like upright leaves waving on the ocean floor.

Grotzinger says the clarity of the new evidence is persuasive. Geologists have long believed that the rise of oxygen was a key element of the Cambrian explosion, and this discovery certainly seems to confirm it.

The other authors of the paper, which appeared in the December 7, 2006, issue of *Nature*, are Lisa Pratt of Indiana University and Roger Summons of MIT. □—*RT*

CALTECH COPS CRACK CROOKS' COVEY

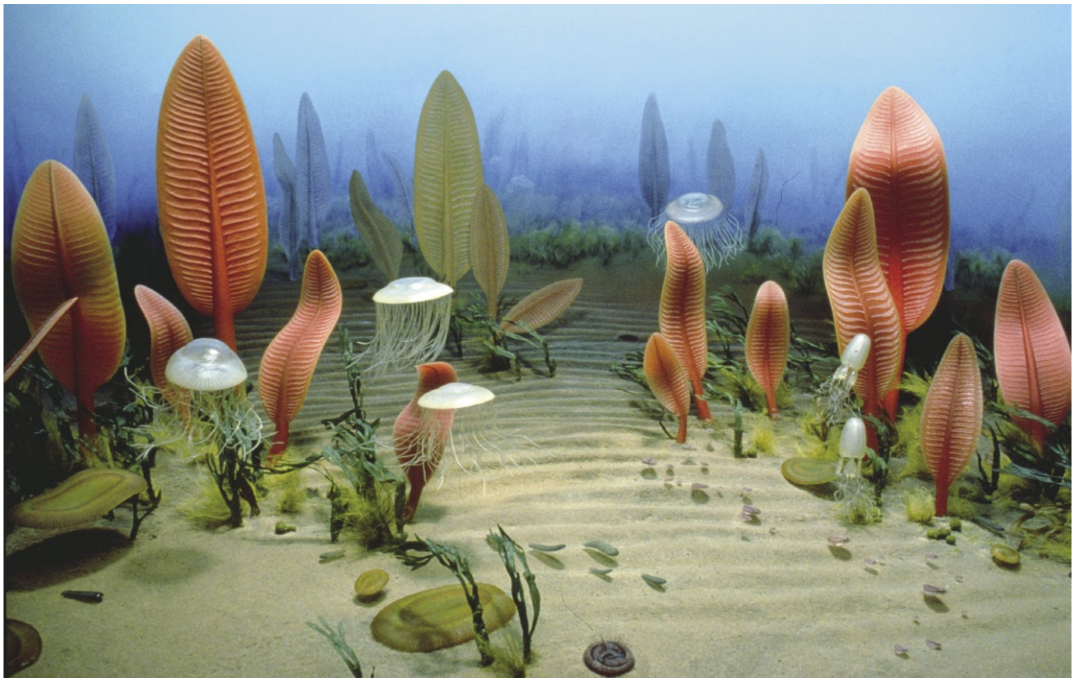
When three unarmed Caltech security officers approached a couple of guys trying to force their way into a campus building, they had no idea that they were helping to crack a Southland burglary ring. For their efforts, Doni Harrelson, Agustin Valadez, and Ivan Gaor will receive the annual Award of Merit from the California College and University Police Chiefs Association at an April 13 ceremony in South Lake Tahoe.

"I'm extremely proud of the entire organization and their commitment to making Caltech a safe place," says Gregg Henderson, head of Caltech Security. "What these three did exemplifies what the entire force does."

The incident unfolded one day last fall when Harrelson spotted two men wandering the campus. Several campus buildings had been burgled recently, some several times, and all officers were on high alert, so she tailed the men and contacted her partner Gaor and Valadez. Minutes later, the three confronted the two suspects as they tried to jimmy open the basement door of the Parsons–Gates building (which had never been hit before), and asked to see their Caltech identification. One of the suspects ran—to be arrested the next day off campus—but the officers caught and held the second until Pasadena police arrived. His parole information linked him to other burglaries around the neighborhood. The police later linked the two suspects, along with a third, to at least 30 burglaries in Monrovia, Arcadia, Pasadena, and possibly as far away as the state of Colorado. □—*RT*

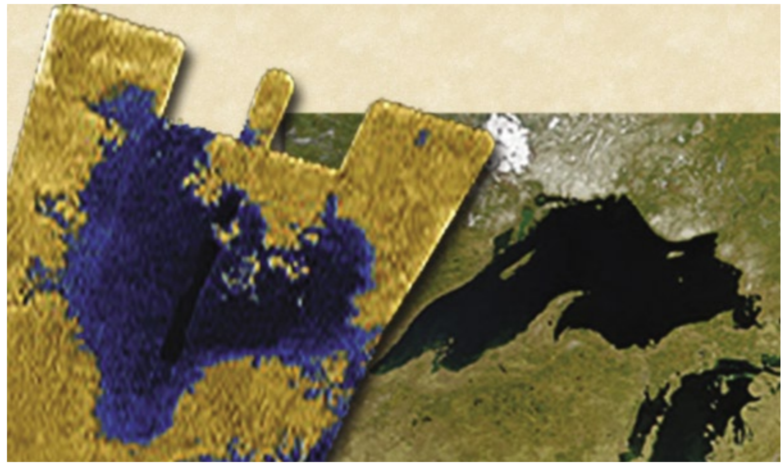
WE'RE ONLINE!

And have been since 1997, but the *E&S* website is pretty deeply buried. The URL (which also appears on our table of contents page) is **http://EandS.caltech.edu**. If you're looking for Feynman's greatest hits, fear not—*E&S* and the staff of the Sherman Fairchild Library have created an online archive starting with Volume One, Number One back in 1937 (yes, we just turned 70) and running up through Volume 36, Number 7, published in June 1973. Feynman articles after that date are also in the archive; the remaining issues will be filled in as budgets and summer interns permit. The simplest way to find anything in either archive is to type the subject or author's name and perhaps a keyword into the search box in the upper right corner of the Caltech home page—the article you're looking for will usually be the fourth hit or above. □—*DS*



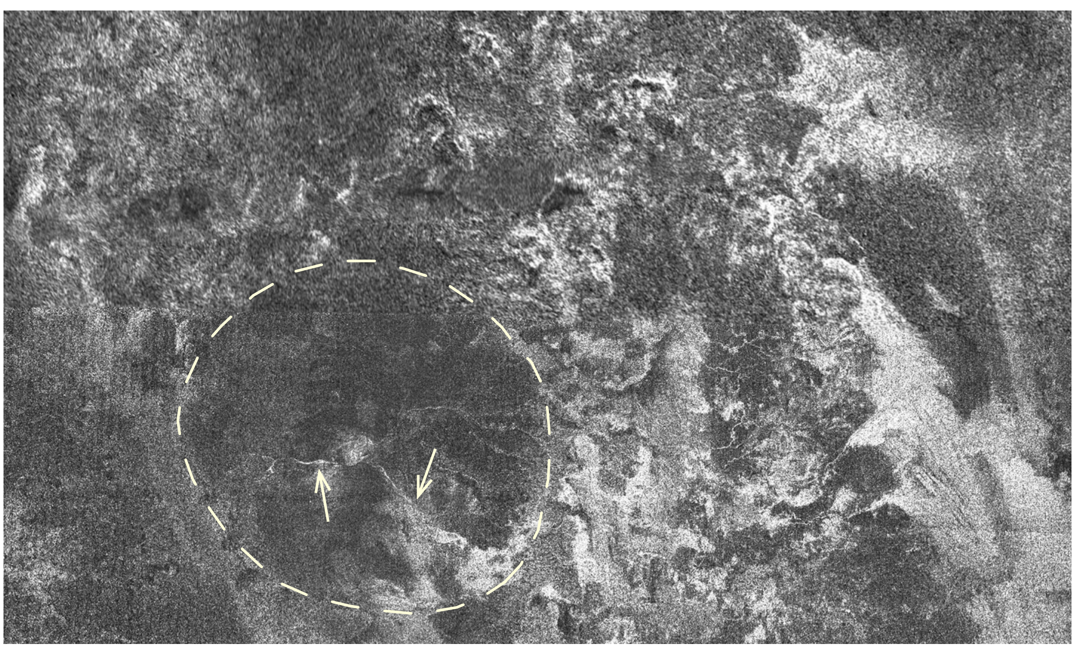
Some of the earliest known multicellular animals, members of the Ediacaran fauna, from about 570 million years ago: *Charnodiscus* (large, orange sea pen); *Ediacaria* (three jellyfish on left), *Kimberella* (tall, skinny jellyfish on right); *Dickensonia* (large, flat, segmented worm), *Spriggina* (small, slender, green segmented worm); *Tribrachidium* (pinwheel-shaped, possibly echinoderm); and *Parvancorina* (lavender arthropod). Image of a diorama from the National Museum of Natural History, courtesy of the Smithsonian Institution.

Rosaly's Volcano



The notoriously foggy city of San Francisco was an appropriate venue for the unveiling of the latest pictures of methane-haze-clouded Titan, shown by JPL's Rosaly Lopes at the annual meeting of the American Association for the Advancement of Science (AAAS). Every February, scientists, journalists, and policymakers from around the world gather to showcase and ogle the year's top science stories. The session devoted to Cassini–Huygens, the JPL–European Space Agency–Italian Space Agency mission that has been exploring Saturn and its moons since 2004, emphasized how closely Titan's surface geologic processes resemble Earth's. According to Lopes, the investigation scientist on Cassini's RADAR team, "Titan is the Earth of the outer solar system."

Indeed, recent views of Titan's northern latitudes reveal the full extent of a volcano that Lopes thinks could be a lot like one of our own. The 180-kilometer-wide Ganesa Macula, endearingly dubbed "Rosaly's volcano" by some of Lopes's colleagues and members of the press, is a large, conical volcano that could resemble either the "pancake domes" of Venus or shield-shaped volcanoes like Hawaii's Mauna Loa. But unlike terrestrial volcanoes, from which molten rock gurgles, Ganesa spews thick slurries of a "cryolava" that had been thought to be made of water mixed with ammonia.



Recent radar images of a region of Titan, the largest of Saturn's moons, reveal a fuller extent of a province riddled with volcanic activity. At 180 kilometers across, Ganesa Macula (shown with base outlined) is so far the largest cryovolcanic feature seen. In this region, bright areas are cryolava. On the volcano, the left arrow points to one of several thin cryolava channels and the right arrow points to where such a channel spills out into a flow. All flows seem directed toward the right (east), suggesting an overall eastward slope to the region.

In other radar-mapping news, the Cassini orbiter has discovered a sea of liquid methane or ethane near Titan's north pole. Since this first-of-its-kind feature extends beyond the mapping swath, its exact extent is unknown, but it is at least 100,000 square kilometers in size—bigger than Lake Superior, which is shown on the right for comparison. And as it is bigger in proportion to Titan's total surface area than the Black Sea, our largest inland sea, is to Earth (at least 0.12 percent versus 0.085 percent), it is, indeed, a sea. The comparison image is from NASA's SeaWiFS, or Sea-viewing Wide Field-of-view Sensor project.

Although Titan's opaque atmosphere hinders spectroscopic analysis of its surface, some clues about the composition of its cryomagma can be gleaned from radar images of individual flows, whose lobate margins are clearly defined. A thick, viscous fluid, like hot tar, would be required to make such lobes—a thinner liquid would simply run off. An isolated flow in another region, around 2,200 kilometers away from Ganesa, is estimated at 300 meters thick, suggesting that the material moves with some difficulty. A water-ammonia slurry would not move that way, Lopes and colleagues argue in a paper in the February 2007 issue of *Icarus*, but adding a dash of methanol to the mix would thicken the cryolava up just fine.

Some individual flows are huge—the newly named Winia Fluctus extends at least 23,700 square kilometers, an area slightly smaller than the state of Vermont.

Despite the multitude of volcanic landforms recently found on Titan's surface, no eruptions in progress have been spied. But this could be because only around 15 percent of the surface has been radar imaged so far, with very little of the overlap needed to show surface changes.

Lopes also thinks that many of Titan's methane or ethane lakes, which so far have been seen only at latitudes north of about 70°, could be housed in volcanic craters, or calderas. Alternatively, she suggests that they could be like karstic lakes on Earth, in which water fills sinkholes formed over pockets of dissolved rock. But it is clear that the Ganesa region, near latitude 50° north, houses an unusually high concentration of recently active volcanoes.

The *Icarus* paper points out that the volcanic provinces on Mars and Venus are associated with large bulges in the crust, presumably caused by the upwelling of magma from below. Whether a similar bulge will be found on Titan remains to be seen. So stay tuned—future flybys could also pick up surface changes from recent eruptions.

The AAAS meeting was especially meaningful for Lopes, as she was the only JPL scientist among the 449 new members elected to the status of Fellow by their peers. At the meeting's close, David Baltimore, professor of biology, Nobel laureate, and former Caltech president, stepped into the AAAS presidency for the coming year. □—*EN*

Surf's Up

If you could not even conceive of a way to answer the question "Is every finite group realizable as a Galois group over the rational numbers?"—if you don't even know what it means—then you might find the odds of someone winning a speaking competition on that topic pretty slim. Yet, at the 2006 Doris Perpall Summer Undergraduate Research Fellowship (SURF) Speaking Competition, sophomore Po-Ling Loh, a math major from Madison, Wisconsin, bagged her second first prize in a row for a math talk. It was a banner year for the subject, in fact: one of the two third-prize winners also talked about math, and this is only the second year since the competition began in 1993 that mathematics speakers have won prizes.

The details of Loh's project, in an obscure but important field of math called Galois theory, seemed to sail above the heads of the audience members. But Loh kept them enchanted with stories, such as how legendary mathematician Evariste Galois died in 1832 at age 20 in a duel with an artillery officer over a woman—but not before recording his ideas the night before. Loh's public-speaking skills are so strong that she needs no show-and-tell props to win over her audience, but she brought some anyway, demonstrating how origami folding can successfully trisect an angle where a simple compass and straightedge fail at the task. (See *E&S*, 2004, No. 1, p. 10 for how to do this at home.)

Mercilessly titled *Q-Admissibility of PSL(2,q)*, the algebraic abstraction that was Loh's project required constructing a polynomial equation with many variables in just such a way that they would factor in a specified pattern. The pattern forms the so-called "Galois group" of the polynomial, and it's part of a fundamental problem that has perplexed mathematicians since long before Galois murkily drafted his thoughts on the matter. Bandying about terms like "Sylow p-subgroup" and "maximal subfield of a Q-division algebra," it was hard to believe Loh's claim that a lack of higher math skills prevented her from solving the challenge. But she will keep plugging away, taking more math classes and attacking another SURF challenge, on a related math topic, this summer. "For now, I'm just focusing on the theory of my research, rather than its applications," she says.

The second prize went to Alex Huth, a senior in computation and neural systems who hopes to pursue further studies in Sweden. His research, which used functional Magnetic Resonance Imaging (fMRI) to mark contrasts in the responses of the visual cortex in the brains of blind and sighted people, was easier to grasp. One subject, a blind man who employs bat-style echolocation to ride a bicycle, also had quite a sense of humor, Huth recalls. "We asked how the train ride to Pasadena had been, to which he replied, 'The view was horrible.'"

Huth's seven sighted subjects responded as one might expect—their visual cortexes lit up when they looked at moving objects. Surprisingly, though, the visual cortexes of the five blind subjects lit up in response to moving sounds, suggesting that this area of the brain keeps working even though its manner of use changes. Huth was lucky enough to work with an additional two subjects who were blind most of their lives but gained vision in their fifties. These fMRI scans seem to have captured brain reorganization in progress—their subjects' visual cortexes responded to both visual and auditory signals. Huth will continue to work on the subject with mentors Melissa Saenz (BS '98), a postdoc in biology, and Christof Koch, the Troendle Professor of Cognitive and Behavioral Biology and professor of computation and neural systems. "In the coming era of sensory rehabilitation—retinal implants for the blind are gaining some traction, and cochlear implants for the deaf are already very advanced—it's becoming increasingly important to study how the brain adapts to such major changes," Huth says.

Tied for third place were freshman Evan Gawlik and senior Arturo Pizano. Gawlik tackled the three-body problem—an infamous conundrum dealing with the motions of three masses in space subject to mutual gravitational attraction—by comparing the accuracy of different numerical methods that try to predict them. In a configuration in which one mass dominates, like the sun in the sun–Earth–moon system, it's relatively straightforward to predict orbits. But when the three masses closely match, their movements are somewhat chaotic and much harder to predict—even when the problem is simplified by considering one mass to be negligible, as Gawlik did.

Pizano studied folding in cytochromes, which are a large family of proteins that, even though their amino acid sequences are similar, all fold their own way. This is a great mystery, as it is the attractions between the amino acids that make proteins fold, so proteins with similar sequences should fold into similar shapes. Within this greater problem lies the subplot of Cytochrome c–b_{562}, the particular class that Pizano studied. While these proteins do have similar folded structures, each accomplishes the task in a different manner. Pizano will continue to pursue the dilemma until he graduates this June.

The runners-up were Matthew Lew, who devised a device for the study of optics, Diana Lin, who tested a model of a signaling pathway in cells, and Andrew Kositsky, who mathematically reconstructed the 20th-century record of slip distribution along the Sumatra fault. □—*EN*

LIGO's Wave Wall Wins Design Award

The Laser Interferometer Gravitational-Wave Observatory (LIGO) Science Education Center in Livingston, Louisiana, has won a 2007 New Orleans Design Award from the New Orleans chapter of the American Institute of Architects.

The Science Education Center was one of 12 winners chosen from over 70 submissions, which is more entries than the chapter has received in any previous year. The award, in the category of "Divine Detail," cited "form and function coming together in an exciting and unexpected way" in the design of the building and its dynamic exterior *Wave Wall*.

Visitors walk into the center under the wall, which is a kinetic wind sculpture consisting of 120 27-foot-long pendulums strung across the entire 85-foot length of the building's façade. *Wave Wall* is activated either by wind or by energetic LIGO guests, who can initiate the wave's motion and propagation via ropes and pulleys. In response, the massive aluminum masts swinging just overhead may trace graceful undulating patterns, or they may break into a chaotic dance with a gust of wind.

Nationally renowned architects Eskew + Dumez + Ripple of New Orleans designed the LIGO Science Education Center, which officially opened in November 2006. *Wave Wall*, commissioned by the U.S. National Science Foundation, was designed by a team of artists that included Shawn Lani, Charles Sowers, and Peter Richards, along with Thomas Humphrey and Susan Schwartzenberg of the San Francisco Exploratorium. They collaborated with scientists and engineers from the LIGO Laboratory, Caltech, High Precision Devices of Boulder, Colorado, and Superior Steel of Baton Rouge.

Fully operational since 2001, LIGO is a scientific facility designed and managed by Caltech and MIT for detecting astrophysical gravitational waves. To visit the LIGO Science Education Center online, go to http://www.ligo-la.caltech.edu/contents/sechome.htm. *Wave Wall* is even on YouTube—check out http://www.youtube.com/watch?v=mIA9zq80hx4. □—*DW-H*

PICTURE CREDITS: 2—NASA/ESA/Richard Massey; 6—NASA/JPL, NASA/JPL/GSFC

Wave Wall **is a linked set of 120 hanging aluminum beams 27 feet long. When set in motion by a visitor or the wind, the interplay of light and shadow, resonance and gravity, makes a hypnotic and ever-changing series of undulations. Photo courtesy of the Exploratorium, San Francisco.**

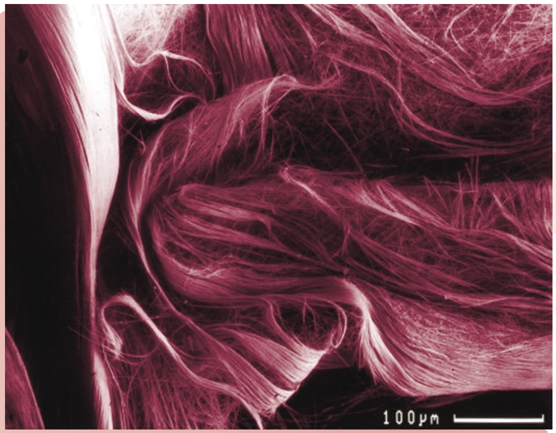
The Secret Lives of Minerals

By Elisabeth Nadin

This rounded and polished rose quartz, mounted in a sculpture by silversmith John Marshall, hosts nanoparticles arrayed to scatter light into a six-pointed star. At 3.6 inches across, it's the world's largest rose quartz star. For over 100 years, scientists assumed both the color and the star pattern arose from inclusions of the mineral rutile. (They were wrong.) To see this and other jewels of gem collector Mike Scott's treasures, visit Orange County's Bowers Museum this summer. To see what really makes it shine, follow the pink path.

Since ancient times, colored stones have been enwrapped in mystery and intrigue, and assigned a worth far greater than their earthy origins imply. Some 4,000 years ago, ancient Egyptians decorated themselves and the walls of their tombs with green beryl—thought to symbolize immortality, and immortalized as emerald by the gem trade. Opal was the gemstone of love and hope for the Romans, who believed it could also render its wearer invisible. Meanwhile, Australian aborigines suspected opal to be a devil luring men to their destruction. Minerals have assumed increasingly complex mythical properties over time. New Age practitioners wield rose quartz not only to treat physical maladies like kidney disease, sexual dysfunction, and migraines, but also to "stimulate the body's love centers" to convert negative emotions to positive ones, calm hot tempers, and improve mental discipline and tranquility.

But these are not the myths that Caltech professor of mineralogy George Rossman (PhD '71) and member of the professional staff Chi Ma, who manages the Geological and Planetary Sciences (GPS) Division Analytical Facility, typically confront. Rather, they seek to dispel less obvious misapprehensions—speculations and inferences on optical phenomena in minerals that have become groundlessly entrenched in the scientific literature. To do so, they pursue the true origins of color, opalescence, and rare patterns like stars, flames, and rainbows. And, if they discover a new mineral while they're at it, so much the better.



Take the rose quartz from the previous page (well, maybe a less attractive substitute), dissolve it in hydrofluoric acid at 100°C, and all that will remain is a nest of pink fibers. What are those fibers made of? Follow the pink to the next page to find out.

A Boyhood Dream

Rossman may be one of very few people who now does exactly what he first dreamed of doing, back when he was a kid picking shiny pebbles from the glacial outwash of the last great Ice Age. His love of nature and rocks in general became a fascination with minerals in particular when a grade-school friend gave him some clear, beautifully colored, glassy minerals. Rossman turned to his teachers for information on these shiny objects, but got no answers. "I knew enough to know that I had to learn chemistry to understand," he says. "It was a hobby interest; I wanted to know where the pretty colors came from."

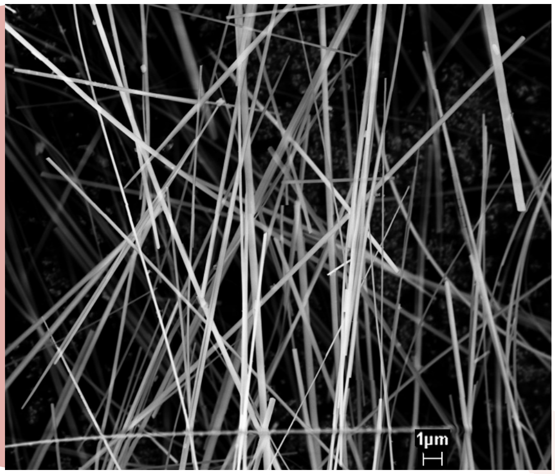
"If you wanted to trivialize George's [PhD] work, you could say he figured out why iron rust is red-brown."

A high-school science project on the response of minerals to a metal detector led Rossman to a summer NSF program during his undergraduate years at the University of Wisconsin–Eau Claire, in which he explored the oxidation state of one particular iron-bearing mineral. After finishing a double major in chemistry and math, he was caught between grad schools when a cult TV show changed the course of his life. "I had already accepted a famous eastern college," Rossman recalls. But then he saw an episode of *The Man from U.N.C.L.E.* in the winter of 1966. It featured the evil agents of THRUSH (Technological Hierarchy for the Removal of Undesirables and the Subjugation of Humanity), who captured young boy geniuses and sent them to a place called Caltech. Rossman knew it was where he belonged. "My professors recommended it [Caltech], of course," recalls Rossman. But "that stupid TV program" had a lot to do with his decision.

Rossman became the first Caltech graduate student of Harry Gray, now Beckman Professor of Chemistry, then freshly arrived from Columbia University. Although his thesis molecule was a molybdenum cyanide, he made a more lasting contribution to a definitive understanding of iron-storage proteins in humans. "If you wanted to trivialize George's work, you could say he figured out why iron rust is red-brown," says Gray. "He laid out the spectroscopy of iron that allowed us to interpret the structure of iron proteins." A model of the structure of ferritin stands in the Beckman Institute courtyard today. In a real molecule, which is colored rust brown, the body stores some five thousand iron atoms inside a spherical cavity.

"One of the best times of my life was being a graduate student at Caltech," Rossman says. "This is where I learned how to be a scientist." While his thesis work was only indirectly related to minerals, he "came over and bugged people in geology to run minerals." That was how the geology department got to know him, and how, soon after his defense in 1971, he came to accept the position offered him by GPS. At the time, most mineralogists were engrossed in crystallography, classifying how atoms are arranged to form minerals. As a chemist, Rossman brought the tools to uncover how those atoms produced colors. According to one member of the hiring committee, professor emeritus Arden Albee, "I became convinced that spectroscopy, in its broadest sense, was the future of mineralogy and petrology. I think that the appointment of George has worked out very well." The students seem to agree—they awarded him the Feynman Prize for Excellence in Teaching in 2004. To this day, Gray's students run experiments in Rossman's lab, and Rossman delivers a special lecture in Gray's inorganic chemistry class on colors in gemstones.

The Rossman of today seems to have retained



At 10,000 times magnification, fibers from the pink mat look like rods. But these rods are about one thousandth the thickness of a human hair, and they are made mostly of silicon, oxygen, aluminum, and boron. Further details on these borosilicate rods follows.

many of the traits of the Rossman of 50 years ago, among which is a bubbling, boyish enthusiasm for minerals. His office is cluttered with rare and common minerals—on shelves, on countertops, on the desk, and on newspapers on the floor. The wide, flat drawers that line one side of the room are crammed with minerals, arranged first in alphabetic order by mineral name, and then, within each drawer, in alphabetic order by locality of origin. "Can we find why G. Rossman became a scientist?" he mumbles while poking through one of these drawers. He's searching for a thumbnail-sized, wedge-shaped slice of watermelon tourmaline also given to him when he was in grade school. He suspects it's from Southern California, but can't be sure. To the glassy wedge is glued the number 23, noting its place as the 23rd collectible of Rossman's youth.

Behind Specimen 23 lie seemingly mythic connections linking the Rossman of yesteryear and today. Rossman's first trespass of the world-famous tourmaline mines of San Diego–based Pala International—a gem mining, trading, and sales operation—in the waning days of his graduate years at Caltech led to the forging of a lifelong friendship and scientific exchange with the company's president, Bill Larson. In the 37 years since they first met, Larson has supplied hundreds of various gem and mineral samples to the cause. "I would give him specific mineral specimens that I knew very well where they came from, and he would slice them and dice them and look at them," says Larson. "A lot of it will go in the collections at Caltech, which will be there for any student that comes after."

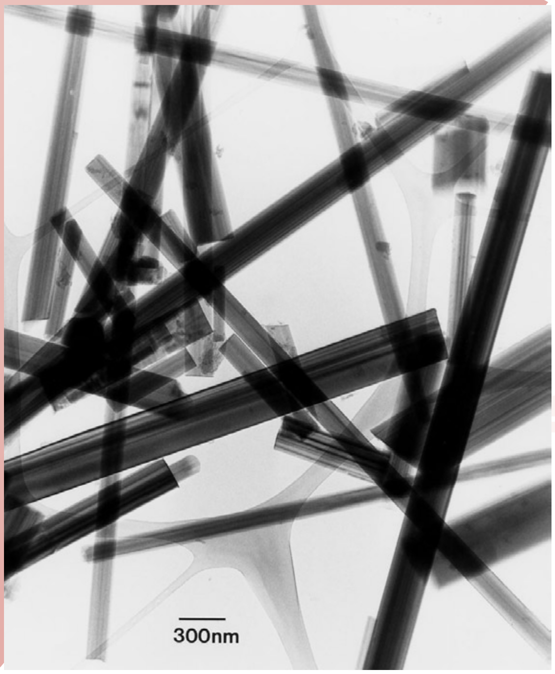
The second uncanny echo between tourmaline and Rossman the mineralogist is the mineral rossmanite. Yes, you read that correctly. Rossmanite is a rare, generally pale pink, translucent variety of tourmaline discovered in the Czech Republic by Canadian mineralogist Julie Selway, and named in honor of Rossman by the International Mineralogical Association in 1998 for his extensive spectroscopic work on this family of minerals. But despite his special affinity for tourmaline, Rossman is loath to name it his favorite. "Don't you love all your children equally?" he retorts.

Although he has handled some of the rarest treasures of the mineral world, Rossman no longer collects. It might raise suspicions that he was angling to pad his private collection, compromising his fairly unrestricted access to unique samples for scientific testing. Instead, Rossman's single-minded scientific curiosity—"I have no personal agenda for these things," he says—has connected him with the world's top mineral and gem traders, from whom he gets many of his samples. While he chooses his requests carefully, he concedes, "Anything I want from the Smithsonian, within reason, I could have." Indeed, his former graduate student Liz Johnson (MS '99, PhD '03) handled the infamous Hope diamond during an extensive spectroscopic study of the Smithsonian's diamond collection.

Rossman's former postdoc Chi Ma says, "If you gave me a diamond, I won't love it. I'd say, 'Let's crack it open and see if there's a defect,'" but Rossman has a slightly more deferential attitude. "He's very cautious not to ruin any good crystals," says Larson. "He knows aesthetics, he knows what a nice mineral specimen is. Now that isn't to say he wouldn't break a piece off the back side, from where it's not seen, and do research on it if he needed it. But he wouldn't destroy a really good mineral specimen just for science." Still, some techniques require destruction. "Let's take one of my beautiful, gem-quality [insert mineral name here], and smash it with a hammer," seems to be one of Rossman's favorite phrases.

Larson considers Rossman to be one of the most intelligent men he has ever met, but Rossman is somewhat modest. Recently, when the two gem lovers were lunching at a symposium celebrating the 75th anniversary of the Gemological Institute of America, the guest speaker challenged audience members to rate their intelligence on a scale from

These borosilicate rods (note the scale bar!) are a rare pink variety of the mineral dumortierite, which underlies both the color and the star pattern in rose quartz. But every spectroscopic test performed by mineralogists George Rossman and Chi Ma yielded an imperfect match to the ideal structure of that mineral. Continue along the path for a view of its crystal structure.



one to 10. "And he said, 'Don't be shy,'" Larson remembers. "I happened to be at the table with George Rossman and George Harlow [Curator of Minerals and Gems at the American Museum of Natural History], and these guys are seriously intelligent. The guy calls out a 10, and we're all staring at Rossman, waiting for him to raise his hand, because no one is going to say they're smarter than George Rossman. He didn't raise it at a 10. He raised his at a nine, so Harlow and I raised ours at eight, being only a little bit less humble than him." As the story goes, after the lunch Larson and Harlow asked why he didn't raise his hand at 10, and to this Rossman responded, "I know Mike Scott."

Which brings us to the final member of a kind of mineral triumvirate. Michael Scott (BS '65), the first president of Apple Computer, has amassed what has been called "the most important private gem collection in the United States." His fascination with colors in minerals led him to Rossman, and his support of Rossman's work led, in part, to the largest mineral spectroscopy and X-ray database on the Internet. Among Scott's collection is what Rossman considers to be the finest specimen of star-patterned rose-colored quartz he has ever seen, and this particular piece spurred Scott to fund an epic investigation of the origins of its optical splendors.

Minerals and Gems

What makes a mineral? It's a fairly simple recipe, for the most part. Take quartz, for example—in this common mineral one silicon atom bonds to two oxygen atoms. SiO_2 molecules bind and repeat, forming interlocking rings that ideally build a hexagonal prism. The silicon-oxygen bond is the building block of 80 percent of all minerals on Earth's surface—to it attach various other ions in orderly ratios and configurations, dictated by the properties of the elements themselves and by the conditions under which the minerals grow. Sometimes they grow with many other minerals to form rocks, and sometimes they fill fissures in these rocks, forming veins of rare composition that are turned by human hands into highly prized gems. Most minerals host trace amounts of rare elements that impart different colors. Garnet, for example, comes in all hues of the rainbow, the rarest of which is a blue-green found only in Madagascar.

Rose Stars, Sapphire Stars

Although colorless quartz is common, its rarer forms come in various hues: gray, purple, pink, or shot through with golden needles. The pink variety is rose quartz, and sometimes a sample of this, when polished and rounded into a sphere, will display a star pattern rising, ghostlike, from its center. The most recent edition of the *Manual of Mineralogy—the* manual of almost every undergraduate enrolled in a mineralogy course—reports "small amounts of Ti^{+4} [titanium] appear to be the coloring agent." Indeed, the origin of rose coloration in quartz has been debated since the 1920s, when mineralogist Edward Holden reported that manganese [Mn^{+3}] was the pigmenting agent. Since then, various oxidation states of titanium and iron have also been called upon to explain the color. As for the star pattern, called asterism, since the 1920s

"When we saw this image, we knew we solved this. Unfortunately, the textbooks haven't been updated yet."

mineralogists have agreed that it arises when light is scattered by inclusions of an oxide of titanium called rutile, which grows as golden needles, arrayed in three crystallographic directions. The *Manual* propagates this idea, and handily ascribes color and asterism to the same source. "It had been assumed, for 100 years, that the inclusions were rutile," says Ma. It seemed like a safe assertion—rutile is observed and verified at macroscopic scales, after all, so why shouldn't it also be present as microscopic inclusions in light-scattering arrays? Case closed.

But in the late 1980s, Kenneth Applin and Brian Hicks of the University of Missouri–Columbia analyzed some pink microfibers they found in rose quartz. Through the technique of X-ray diffraction (XRD), which essentially X-rays a crystal's lattice structure, they established that the fibers were not rutile, but a boron- and aluminum-bearing silicate called dumortierite. This discovery spurred Rossman to reopen the case, which soon heated up. "I knew rutile was not the cause of the color," says Rossman. "When I saw the article by Applin and Hicks, I immediately said 'This has to be it!'" When graduate student Julia Goreva (MS '97, PhD '01) came along, they began to tackle the problem. Together, they dissolved samples from around the world in hydrofluoric acid heated to 100°C, and sample after sample yielded the same thing: a mat of pink fibers.

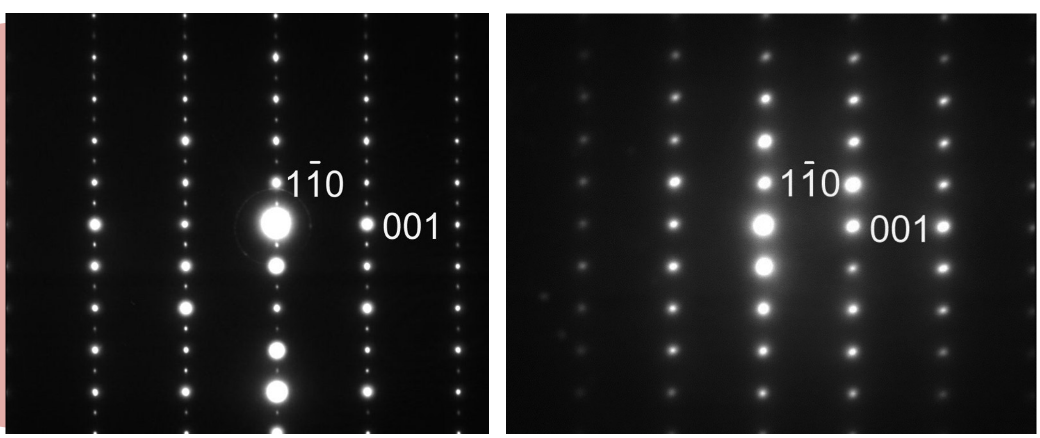
But were the fibers dumortierite? Rossman, Goreva, and Ma hit them with every spectroscopic tool in the arsenal. They imaged them with a Scanning Electron Microscope (SEM) capable of seeing down to 100 nanometers (100 billionths of a meter) in size. To put this into perspective, if you slice a human hair lengthwise into 1,000 strands you are operating at the scale of this instrument. Or, as Rossman puts it, "We're talking things that are really, really tiny in size." The SEM repeatedly pointed to the same thing: borosilicate fibers. Infrared spectra, Raman spectra, optical absorption spectra, and X-ray diffraction patterns all closely matched those of natural dumortierite. But the team was not satisfied—the tests showed a close, but not perfect, match.

Through Transmission Electron Microscopy (TEM), in which a beam of electrons casts a glowing shadow of a specimen's atomic structure onto a camera, they found extra spots in the diffraction pattern and finally established that the fibers' crystal structure was actually bigger than the ideal structure of dumortierite. "We think we've found a global property of common, massive veins of rose quartz," says Rossman, and "a phase previously unrecognized by science."

"When we saw this image, we knew we solved this," adds Ma. "Unfortunately, the textbooks haven't been updated yet."

You are probably wondering at this point why anyone besides a mineral collector might care about the true origin of color and asterism in rose quartz. If you have a cell phone or a TV, you might be interested to know that natural quartz is the source for the silicon wafers in those gadgets' electronic brains. But the quartz must be ultrapure, because carefully controlled impurities, called "dopants," are what make the chips work. Boron is a choice dopant, used to control the depths of junctions between which electricity flows across adjacent semiconductors, so the discovery of boron-bearing dumortierite in rose quartz ruled out this potential source of silicon.

Perhaps the best-known asterated gems are rubies and sapphires—names assigned to red and blue varieties of the same mineral, corundum. (After all, who wants to sport something called corundum on their finger?) Long ago, star sapphires were considered to be portable guide stars, protecting and guiding



The crystal structure of rose quartz's dumortierite (left), as captured by electron diffraction in a transmission electron microscope, is bigger than the mineral's ideal structure (right). It's a new find, which Rossman and Ma nicknamed "dididumortierite." The numbers represent two of the crystal's lattice planes.

A nearly half-carat sapphire from Burma, splayed with rainbowed needles. As with starry rose quartz, needles like these were always assumed to be inclusions of the mineral rutile.

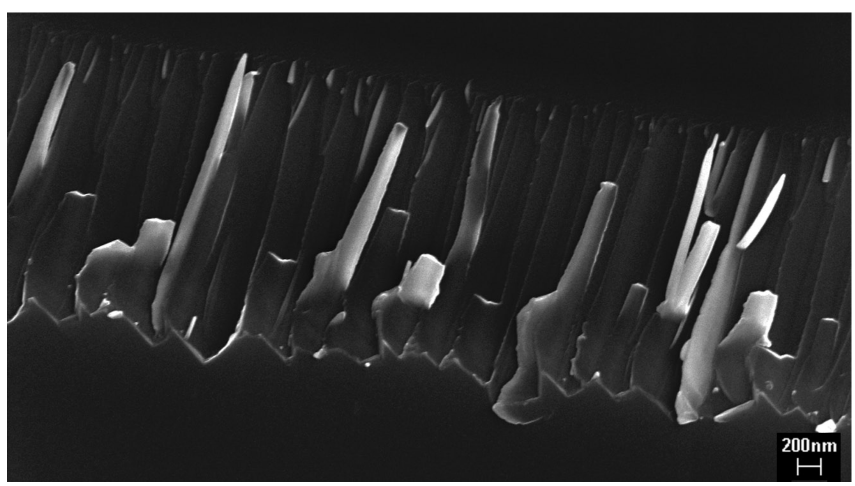
travelers and seekers. More recently, the female supervillain Star Sapphire used the virtually limitless powers of the gem to battle the Green Lantern in the pages of DC comics. But mostly, people prize the jewels for their beauty and rarity. And, as with quartz, rutile needles are found in some corundum. So, says Rossman, "the assertion has been made, time and time and time again, that rutile needles cause asterism in sapphires." Indeed, the online encyclopedia Wikipedia reports that "star sapphires contain intersecting needlelike inclusions (often the mineral rutile) that cause the appearance of a six-rayed star-shaped pattern." After the rose quartz adventure, Ma thought, "Why don't we find a star ruby with the best effect and take a look?"

Corundum, like quartz, has an unassuming formula, consisting of two aluminum atoms bonded to three oxygen atoms. Brilliant reds, greens, purples, or blues arise when ions like iron, chromium, vanadium, or titanium join in. However, corundum is often naturally cloudy and therefore unmarketable. "Until about 30 years ago this stuff was virtually worthless, 50 cents a pound," says Rossman. But then it was discovered that corundum from Sri Lanka clarified upon being heated to around 1,600˚C, and that the oxidation state of the gases in the furnaces could be manipulated to control its color. This led to a flood of cheaper sapphires on the market.

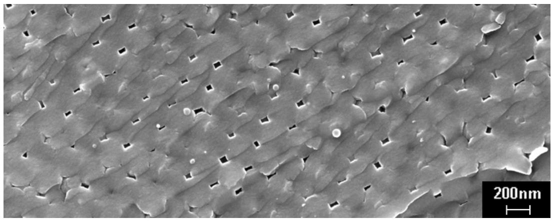
It was presumed that heat treatment dissolved rutile inclusions, thereby destroying any possible hidden asterism. This was plausible for Asian gems, which responded well to heat treatment, but not for African stones, which remained stubbornly turbid. So Rossman and Ma cracked open untreated gems provided by dealers and by the Gemological Institute of America from more than 10 different localities, including Vietnam, Burma, Tanzania, and Myanmar. The largest sample was just under one carat. "Ma Chi and I are destroyers. We take beautiful sapphires, and we smash them to pieces," Rossman says with some glee. "We document it before we crush it," adds Ma. They searched for rutile with the SEM, but found none, even in the samples that bore wispy rainbow trails. Instead, they found nanovoids in the Asian sapphires and nanoinclusions of something else in the African samples.

"Nanomineralogy—I like this term, so I keep using it," says Ma. "We're not like the nanotechnology people, we just use the same tools to look at minerals and find lots of new things," in this case, nanoinclusions of a hydrous aluminum oxide mineral called diaspore. This discovery was made with yet another camera, the Electron BackScatter Diffractor (EBSD), which detects light diffracted by electrons beamed from the SEM and bouncing around the crystal's lattice planes.

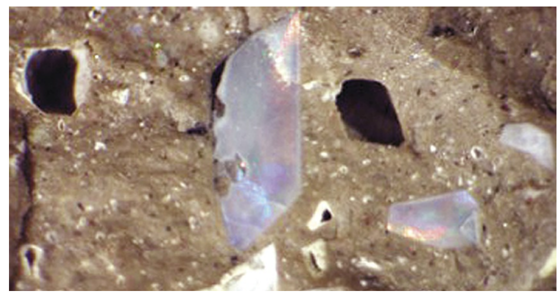
The pair concluded that the 200-nanometer-wide voids in Asian corundum heal, or anneal, upon heating. But in the African stones, the tiny diaspore inclusions persist through heat treatment, an observation that could save African sapphire dealers some money. "The fact that diaspore doesn't redissolve when you heat it, like rutile does, is very consistent with the fact that these African rubies simply do not heat-treat, much to the great disgust of the dealers that mine these things," says Rossman. He hopes this dispels the notion that rutile is the sole cause of optical patterns in gemstones. "To date, we haven't found one single needle of nanorutile in all the material that's been sent to us," Rossman declares.

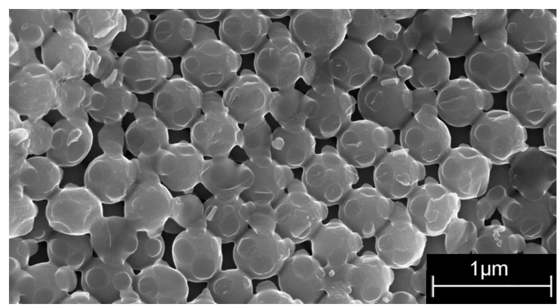


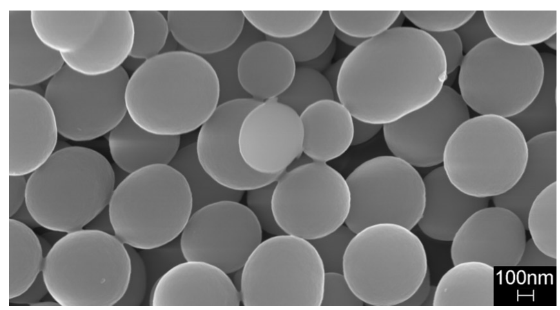
An inclusion-rich corundum, the aluminum oxide better known as sapphire, magnified 50,000 times. The pillar-like forms are nanorods of the mineral diaspore, made of aluminum, oxygen, and hydrogen. Just as with dumortierite in rose quartz, they are sometimes arrayed in a light-scattering star pattern.



Gemmy Australian opal (topmost) and a 50,000-time zoom-in. This magnified view reveals the origins of opal's iridescence. Regions of well-cemented silica spheres disperse white light into colors of the rainbow.
Less commercially appealing opal (below) is found in centimeter-scale pods in ash beds near Tecopa, California. Uniformly sized and regularly spaced silica beads (below middle, at 40,000 times magnification) yield some opalescence. But when the beads are loose and uneven (bottom, magnified 100,000 times), the result is creamy, dull opal.





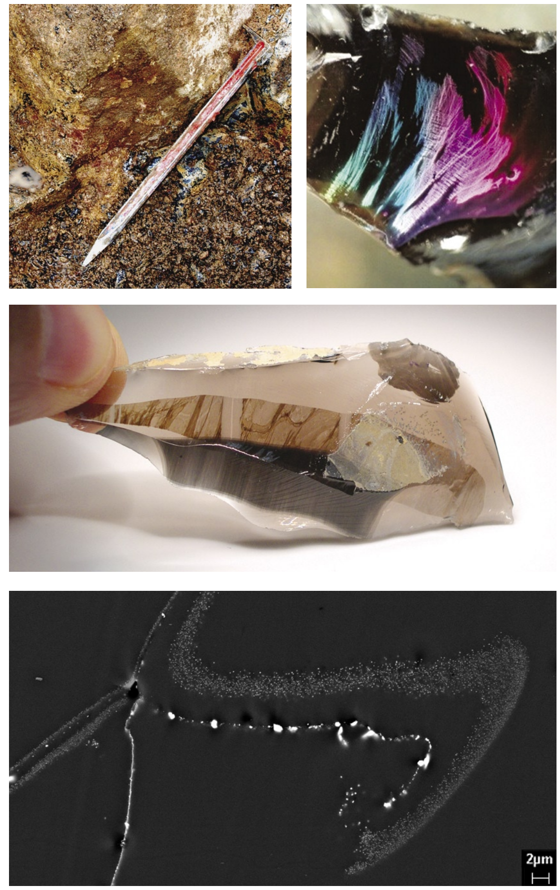


Opalescence

If a crystal arises from a fairly rigid ordering of atoms, what happens when the atoms are disordered? They form a glassy amorphous blob, which is the case for opal, the unruly twin of well-behaved quartz. Both are SiO_2, but opal forms silica spheres with water in its structure. The process begins when silicic acid, which is insoluble in water, quickly polymerizes to form spaghetti-like chains of polysilicic acid. In time, these chains grow wide, forming ribbons, and the ribbons begin to wrap and intertwine to form spheres.

Opal comes in many different colors, and can be clear or creamy, but its most desirable form hosts a resplendent dance. When he was a graduate student in Australia, Ma bought such polychromatic opal earrings for his former girlfriend (now wife), and she lost one. Though he bought her a new pair, the surviving loner didn't last long—he cracked it open and ran it in the SEM at his Australian lab. When he got to Caltech, he showed the photos to Rossman, who wanted to see more. The result was a rigorous documentation of silica spheres in both common and gemmy, iridescent opal. The scientists have also been exploring the properties of the abundant opals in volcanic ash deposits around Tecopa, near Death Valley, which are often creamy but sometimes occur as gemmy centimeter-scale pods.

The play of light in gemmy opal arises when uniformly sized and packed silica spheres are cemented into centimeter-scale domains that act as diffraction gratings, dispersing white light into its spectral colors. In contrast, as Ma describes, "loose beads just give a kind of creamy color," because the light scatters randomly among the irregularly distributed nanobeads of common opal. While this quickly became obvious with some of the first-ever SEM scans, Ma and Rossman recently shot what they are told are the best photos ever taken of opal, providing what Rossman reports as "an eye-opening view of the kinds of things you can see" with the SEM. Through a connection to the Ontario Science Centre in Toronto, Canada, thanks to student Shenda Baker (PhD '92), these images were commissioned for Zoom!, a recent exhibit highlighting views of the micro- and nanoworld.



Most obsidian in the field is pretty unattractive (top left, from Glass Buttes, Oregon), but sometimes a rare find is made. Fire obsidian, which shimmers colorfully under direct light (top right), is streaked with grey and brown "flames" under transmitted light (middle). What makes the flames? Nanoparticles of an iron oxide called magnetite, suspended in waves through the glass (bottom).

Rainbows and Fire

Iridescence is simply the way colors dance about when light hits a surface at different angles. A rainbow emerges from a single drop of oil on a wet street—upon hitting the thin, greasy film, light splits into its individual components, from yellow to orange, red, violet, and blue, because a light wave moves slower in oil than it does in the underlying water. Depending on the thickness of the film, the wavelength of light shifts, so that yellow appears in the thinnest regions of the film and blue in the thickest.

The same process takes place in certain minerals, but the underlying causes have been somewhat mysterious. But Rossman and Ma are open to challenges from anyone who sends them samples, and from these interactions some remarkable discoveries have been made.

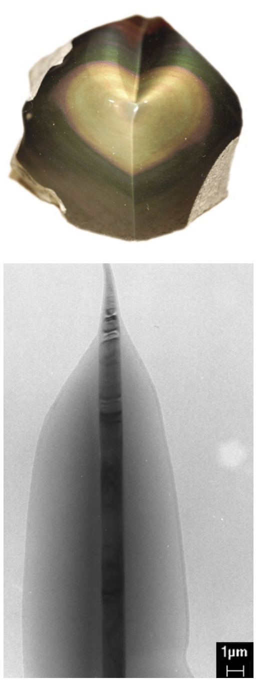
Obsidian

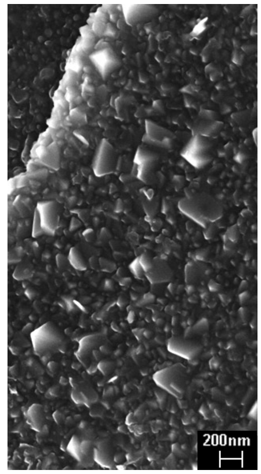
One of their first challenges came in the form of obsidian. Obsidian is a glassy, silica-rich mass that erupts and solidifies almost instantaneously in the earliest stages of an explosive volcanic eruption. Because the material cools so quickly, it has no time to organize its elements into a lattice structure, and forms a noncrystalline glassy mass, which is typically black. But gem and mineral shops often sell worked pieces of Mexican obsidian displaying rainbows of pastel blue, green, purple, pink, and yellow. After SEM and TEM investigations, Rossman and Ma discovered that thin-film interference was at play. Within the glassy matrix of obsidian, nanorods of a calcium- and iron-bearing pyroxene mineral were oriented in just such a way as to set up light-interference.

Their work on the rainbow obsidian sparked the interest of James Miller, a geologist with GeoEngineers Inc., based in Redmond, Washington. Miller is an avid "knapper," meaning he chips stone to make tools, the very old-fashioned way. And during a search for material, he came across some obsidian in Glass Buttes, Oregon, that shimmered colorfully in direct light. It didn't look like rainbow obsidian, but instead hosted flame-like patterns in the glass. Wanting to know more, he sent a few samples to Ma; the result is an upcoming paper in the journal *The Canadian Mineralogist*.

Under bright light, fire obsidian reflects brilliantly colored streaks resembling an iridescent oil slick. When thinned to a translucent blade, dark, wispy flames can be seen through the glass. Rossman suspected the layers of "fire" were made of tiny particles that increased the refractive index in the layer, giving rise to another manifestation of thin-film interference. "Out of curiosity, we said, 'Well, let's take a look at it and find out what it is,'" he recalls. At 100,000 times magnification, they found their answer—a wave of white, snowflake-like nanoparticles were suspended in the glass. EBSD analyses revealed that these flakes were the mineral magnetite, an iron oxide. Prior to these studies on rainbows and flames, it had been assumed that both these effects were produced by bubbles of trapped air aligned in layers. Another scientific myth dispelled.

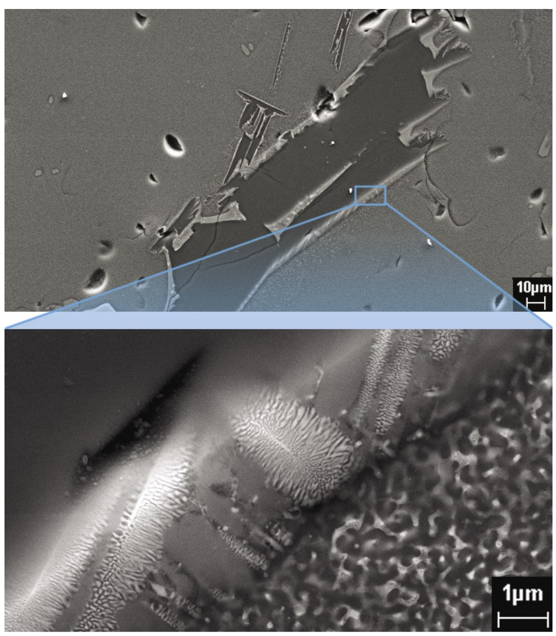
The author's piece of rainbow obsidian, carved into a heart, is just a black blob until light is focused on it (top). The rainbows arise when nanorods of the mineral pyroxene align in just such a way as to set up light-interference.





Iridescence covers basalt from Pisgah Volcano just as an oil slick on water does. The color comes from thin-film interference, in this case provided by 200-nanometer octahedral crystals of magnetite, seen here at 50,000 times magnification.

http://www.where-rv-now.com

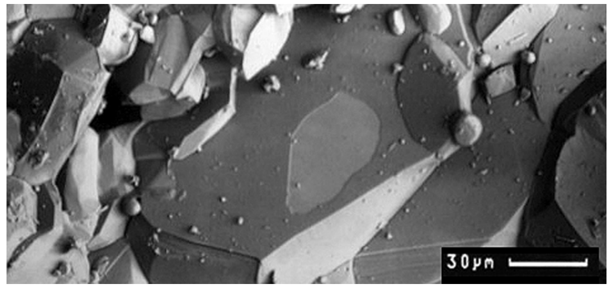


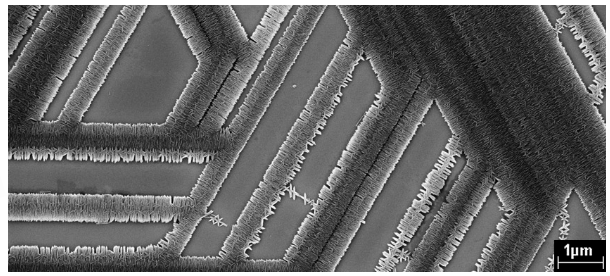
Craters of the Moon National Park in Idaho is home to the rare "Blue Dragon" basalt (top). At 1,000 times magnification (middle), the origin of the blue color appears, in a thin layer coating the sample. Zooming in, to 20,000 times (bottom), reveals the layer consists of branching blobs. These are made of titanium-bearing magnetite, each branch a scant tens of nanometers thick.

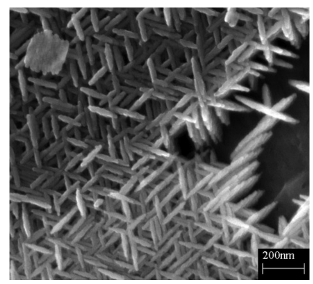
Basalt

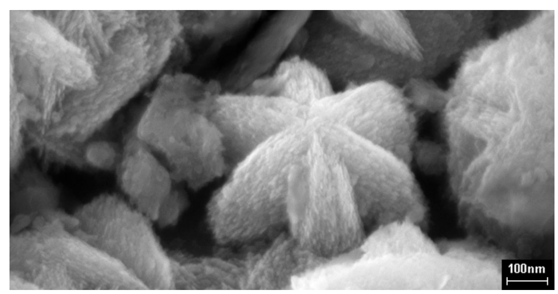
Just last year, during a field trip to Pisgah Volcano in the Mojave Desert, Rossman picked up some solidified lava—called basalt—that was covered with an iridescent sheen. Under the tenfold magnification of his field lens he saw that the color was concentrated in some kind of surface froth coating the basalt. "And layers are what it takes to give rise to iridescent phenomena; layers on the order of a fraction of a micrometer," he thought. So what was in those bubbles? At 50,000 times magnification, and with the help of an X-ray diffraction pattern, he got his answer. They were coated with 200-nanometer octahedral crystals of magnetite.

This discovery led to the next—the origin of the blue color in the "Blue Dragon" basalt of Craters of the Moon National Park in Idaho. At 20,000 times magnification under the SEM, bush-like patterns began to appear in the amorphous glass of the basalt. These proved to be crystals of titanium-bearing magnetite, just a few tens of nanometers thick, arrayed in branching patterns. The blue color arises from a charge transfer between iron and titanium, the same principle that colors sapphire blue. "Again, I've seen nothing comparable to this in the literature," says Rossman. Ditto for the iridescent basalt.









Rainbow hematite (far left) is fairly common, but the root of its iridescence was a mystery, until recently. At fairly low magnification, a hole reveals that the specimen is coated with a very thin layer (top). The layer, magnified 20,000 times, resolves into a grid-like network of nanorods that clump together to form larger rods, sometimes aligned in rows and sometimes arrayed in star-like patterns (bottom, at 200,000 times magnification). At around 10 nanometers long, the nanoparticles are too small to determine an exact chemistry, but their rough compositions indicate a never-before-seen form of aluminum phosphate.

Rainbow Hematite

Hematite, yet another iron-oxide mineral, is the main source for iron, and can also occur in a highly iridescent form. "We got pretty curious—what's going on here?" Rossman recalls. "It's so visually attractive, it was obvious that we should take a look at it." At low magnification, Rossman and Ma found that the crystals of hematite had some sort of coating, with a hole through the coating clearly indicating its extreme thinness. The chemistry of the coating indicated an aluminum phosphate with "a very unusual aluminum-to-phosphorous ratio, unlike anything that's known," Rossman says. "So here we have an interference phenomenon, a thin layer of aluminum phosphate. End of story? No."

At 20,000 times magnification, they found orderly lines of submicron-sized crystals arranged on the hematite like grids on a circuit board. At 85,000 times magnification, the grids resolved into individual rods, sometimes lined up in orderly rows, sometimes crisscrossing each other in star patterns. Their shapes are well defined, but the exact chemistry is difficult to determine, says Ma, because at 10–15 nanometers long and only five nanometers wide, they are "too damn small to get an XRD or EBSD pattern." They have found the same nanocrystal growths in all the samples of rainbow hematite they have tested, from Georgia to Alaska to Brazil. And, says Rossman, "We believe that this is a new phase, previously unknown to science."

Discoveries

Many of Rossman's and Ma's discoveries have been made by pure chance with their powerful tools. "I don't say, 'Today, let's try to find a new mineral,'" says Ma. But looking where no one has looked before often reveals things that have never been seen, and the pair are finding new minerals with geological significance, one after the other. "Nanoscience opens up new possibilities in exploring the natural world," Rossman says. When Ma was navigating the atomic structures of various forms of natural dumortierite in rose quartz, for example, he came across the most barium-rich specimen of a particular variety of the mineral mica. He has also recently discovered a natural occurrence of a mineral—just approved by the Mineralogical Society of America and pending public announcement by formal publication—whose only previously known form was a synthetic one fabricated for use in electronics like ultrasound machines. These discoveries speak to the broader appeal of nanodetectors, and a few years ago the GPS division, in collaboration with the materials science subdivision of Caltech's engineering and applied science division, used part of their $9.6 million NSF Materials Research Science and Engineering Center award to buy a brand new

SEM. One hundred times more powerful than the previous generation—it can see at the scale of one nanometer—and with various analytical attachments scrutinizing the material under observation, the machine is used by more than 200 scientists across the Caltech campus, from more than 40 research groups and from all disciplines except the social sciences and math. Materials scientists are particularly interested in nanodeposition and the study of electrical properties of synthetic materials at this scale.

These tools open all sorts of other intriguing avenues in research. In 1999, the White House invited Rossman to a conference (in the Old Executive Office Building) on "conflict" diamonds—those dubious diamonds that might have funded wars or terrorist activities and recently gained notoriety through the movie *Blood Diamond*. Instead of focusing on tracing techniques that invariably called for the gems' destruction, he and Professor of Geochemistry John Eiler concentrated on looking at the isotopic properties of the dirt caught in microcracks in the stones. Although the program disappeared with the inauguration of the George W. Bush administration, Rossman remains interested in the problem.

But these days he's focused on figuring out exactly how much water is bound up in minerals 100 kilometers below Earth's crust, in the mantle. Scientists have long known that there is enough water down there to have serious implications for processes like how rock is moved around in the mantle and up to the surface, driving plate tectonics, but until now they have avoided tackling the issue of how much water there is. Rossman decided to take it on, and his studies brought him to the nuclear magnetic resonance imager in the subbasement of the Sherman Fairchild Library. There he imaged the structure of miniscule amounts of water in what are considered basically dry minerals. What he found indicates that mantle-bound water could exceed that of all our oceans, which suggests a deep-Earth reservoir for the entire global water system. "I took it upon myself to turn this into a quantitative problem, rather than a 'here it is' problem," Rossman says. And this is, after all, how real scientific adventures begin. □

Chi Ma and George Rossman laugh as they invent fantasy lives for opal's silica spheres, imaged by the scanning electron microscope behind Rossman. Before them is a nanoview of gemmy opal, while the background screen (behind Ma) displays the loose beads of creamy opal.

Mike Scott's gems and minerals will be on diplay from June 2007 until August 2008 at the Bowers Museum of Cultural Art, 2002 N. Main St., Santa Ana, CA 92706. For more information, call them at (714) 567-3600 or visit their website, http://www.bowers.org.

PICTURE CREDITS: 10—Harold & Erica Van Pelt; 11-19—Chi Ma & George Rossman; 17—James Miller; 17, 19, 20—Bob Paz, 18—Teresa Petrykowski & Sterling Udell

Sweet Revenge

By Douglas L. Smith

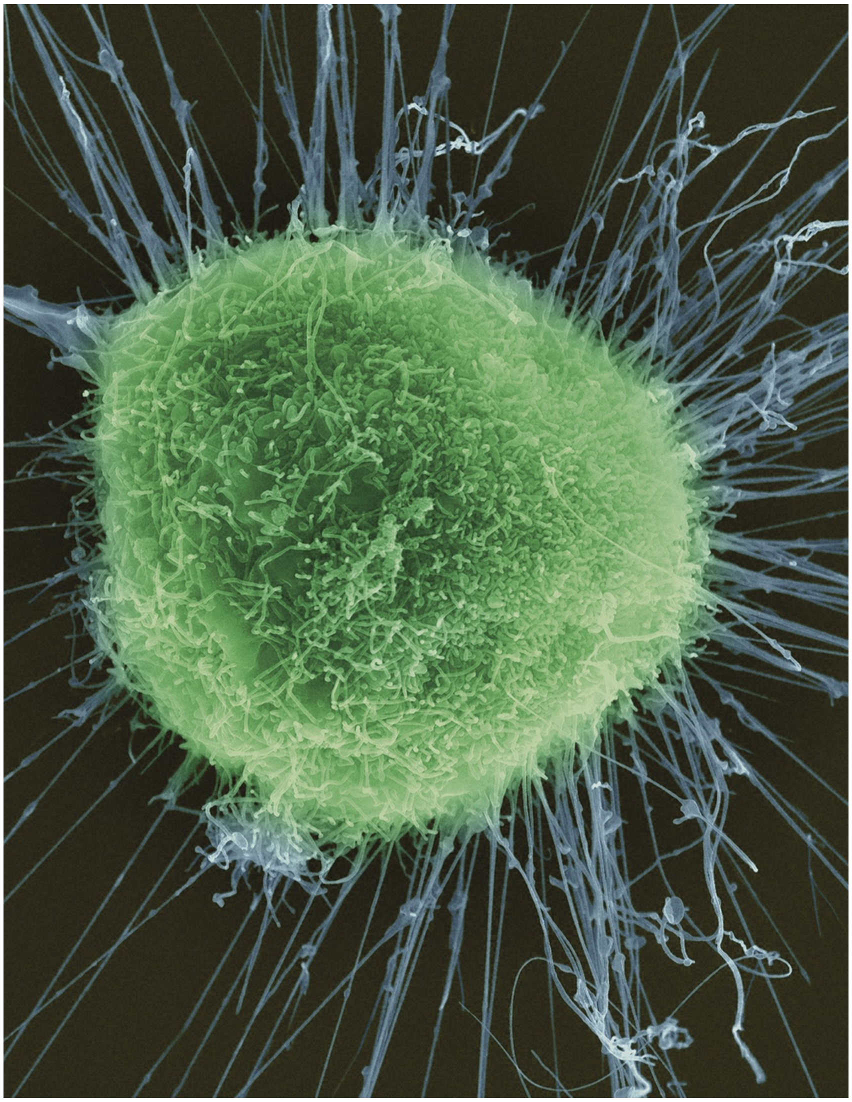


Image © Dennis Kunkel Microscopy, Inc.

A scanning electron microscope photograph of a breast cancer cell, magnified 4,600 times.

Mary Davis was diagnosed with breast cancer at age 36 in April 1995. Her husband, Mark Davis, the Schlinger Professor of Chemical Engineering, began keeping a diary that recorded the nausea, weakness, and hair loss that attended the chemotherapy that followed. In January 1996, the dosage was ramped up. "By Valentine's Day, Mary had lost all her hair for the second time," Davis would write later. "She was unable to eat, was constantly vomiting or felt nauseous, and was given nutrition by IV. She had completely lost her immune system and was in isolation for three weeks. I recall bringing chocolates for all the nurses that day before going in and spending the day in isolation with Mary." Shortly thereafter, she said, "There's got to be a better way—I was feeling fine before the diagnosis, and the treatments are making me sick. Treatments should make you feel better." When Davis replied, "Mary, it's not my field; what could I possibly do?" she fired back, "You people at Caltech are smart, go work on it."

Heavy-duty chemotherapy works by interfering with cell division, which has run amok in cancer cells. But the drugs aren't at all selective, so they also affect cells that are supposed to be dividing rapidly, like those that line your stomach (hence the nausea), and the follicles from which hair grows. Fingernails and toenails can fall out as well, if the cuticle cells succumb. These drugs are given intravenously, and thus permeate your body as they circulate in the blood. At least the few molecules you retain do—most of each and every dose goes straight to urine. Says Davis, "Your kidney is a big filter that removes anything smaller than 10 nanometers in diameter. And most drugs are a nanometer or less."

What we call cancer actually comprises more than 100 different diseases, each with its own characteristics, including survival rates and treatment protocols. But all result from unchecked cell division. Not that cell division is a bad thing: some 50 to 70 billion cells—the equivalent of your

Site	All stages	Local	Regional	Distant
Breast (female)	86.6	97.0	78.7	23.3
Colon and rectum	62.3	90.1	65.5	9.2
Liver	6.9	16.3	6.0	1.9
Lung and bronchus	14.9	48.7	16.0	2.1
Melanoma	89.6	96.7	60.1	13.8
Ovary	53.0	94.7	72.0	30.7
Pancreas	4.4	16.6	6.8	1.6
Prostate	97.5	100.0	--	34.0
Testis	95.5	99.1	95.0	73.1

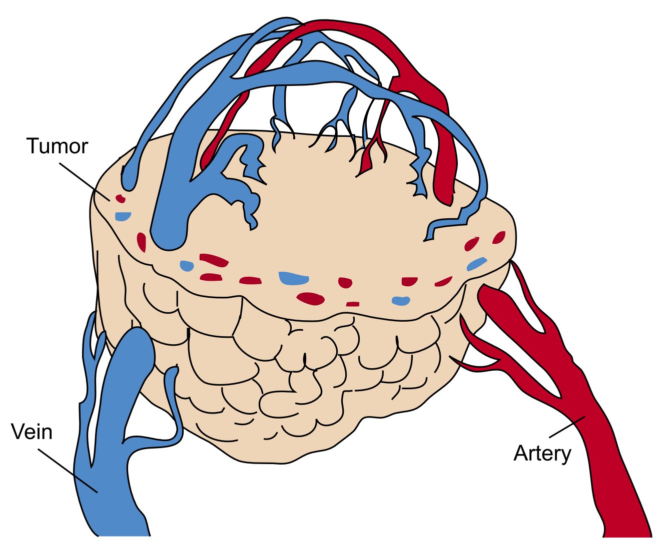
Cancer is really many different diseases, some more lethal than others. This 2004 data from the American Cancer Society shows the five-year survival percentages for various cancers listed against the degree to which they had spread through the body by the time they were discovered.

own body weight—are born within you every year. We'd all look like Eddie Murphy in a fat suit, were it not for the fact that an equal number of cells die at the same time. Some, like skin cells, slough off. Others get tagged for termination for various reasons, usually because they're defective or infected. And some self-destruct when an alarm clock in their DNA goes off. It takes a number of accumulated mutations—some to which we're genetically predisposed, some triggered by environmental factors, and some for no apparent reason—to disable these self-protective systems, and when something is that broken it becomes very hard to fix.

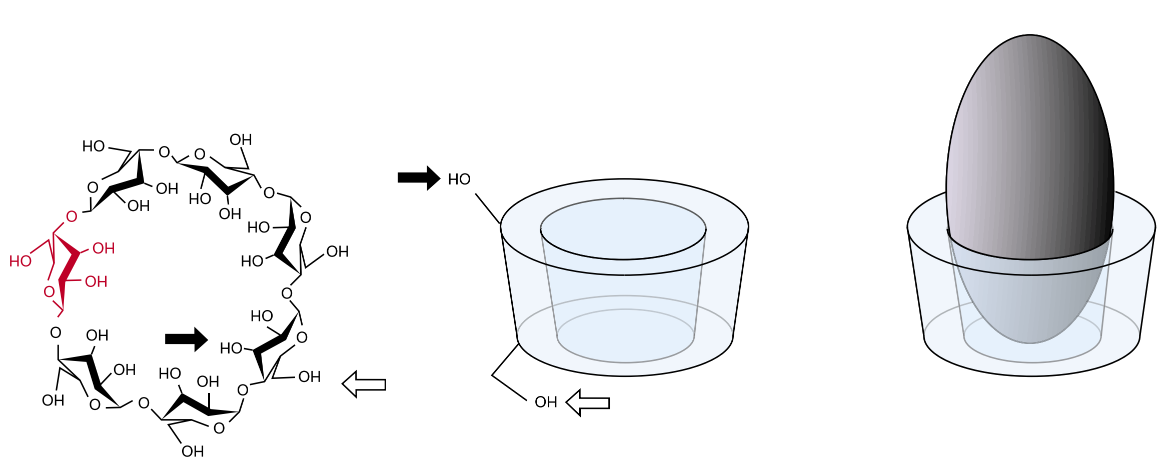
You'd think cancer cells would be easy to find and kill, because they should stand out from the crowd. Alas, they don't. Your cells have molecular tags on their surfaces that prove they are legal residents, and cancer cells, having sprung from your own tissues, still carry a valid ID. Cancer can be invisible to the immune system, unlike foreign cells such as bacteria, or virally infected cells of your own that have begun sprouting foreign markers. A cancer cell's chief difference is its behavior, which is why chemotherapy uses the cell's profligate breeding habits to attack it.

If each cancer confined itself to a single tumor, surgery might suffice. But things go downhill fast when a process called metastasis kicks in. Fast-growing cancer cells tend to be sloppy proofreaders of their own genetic instructions, so mutations continue to accumulate. Eventually some cells acquire the ability to leave the tumor via the blood vessels. Once on the road, every cancer type has its own itinerary: melanomas (skin cancers) move into the lungs, colon cancers head for the liver, and prostate cancer goes straight to the bones. But the new tumors still behave like their original cell types, and need to be treated as such. This can complicate matters immensely, says Davis. "Say you have a bad cough, and you get a chest X-ray, and the doctor sees a shadow in your lung. He might think that it was lung cancer until the biopsy comes back and shows it's a melanoma. And, unfortunately, many different cancers like to go to the lungs—melanoma, pancreatic, breast. . . ."

But wait—there's still more bad news. One of the body's defenses against poisons is a set of molecules called p-glycoproteins that, when summoned into action, sprout on the cell surface and act like little vacuum cleaners, sucking up oily molecules and shooting them back out into the intercellular medium, away from the cell. The newer, more potent anticancer drugs are very oily indeed, and glycoproteins aren't choosy once they get turned on. Says Davis, "These proteins will not only spit out the drug you're using, they'll spit out other drugs you try after that." Multidrug resistance and metastasis frequently go hand in hand, and these cancers are the most deadly.



A fast-growing tumor needs more nutrients and oxygen than the normal cells around it. It commands the circulatory system to grow more blood vessels, stat, and the result is a slapdash network of corkscrewy, leaky plumbing.



A cyclodextrin molecule is a ring made up of six to eight simple sugar molecules, one of which is shown in red. (Davis uses seven-sugar cyclodextrins.) In the top view of the molecule (right), the parts sticking out of the plane of the page are drawn with heavy lines. By convention, carbon atoms are implied at every vertex where two or three line segments meet. The molecule behaves like a hollow, truncated cone, as shown in the even more simplified side view (middle), and other molecules can fit inside it (far right).

Adapted from Davis and Brewster, *Nature Reviews Drug Discovery*, vol. 3, pp 1023–1035, December 2004

Size Matters

When a tumor grows to about a millimeter or so in diameter, it begins to outstrip its food supply. "So," says Davis, "it sends out chemical signals to your blood vessels that say, 'grow some new ones fast, and bring me more blood!'" The vessels oblige, but like many rush jobs, the workmanship is sloppy. "The blood vessels in a tumor are immature. They're weird, they're chaotic, they even form loops. They're also very leaky. They'll let particles as big as 400 to 700 nanometers [billionths of a meter] out into the tumor." What leaks there stays there—like a basement with bad pipes and no sump pump, the tumor lacks proper drainage by the lymphatic system.

It's easy to make drug-laden particles small enough to enter the tumor but too big to be flushed away. But you can't just make them, say, 500 nanometers across, because they will not move throughout the tumor. In the tradeoff between payload and penetration, the trick is to carry as much stuff as you can sneak in—not unlike smuggling watches past Customs. "We think that the 'sweet spot' is about 50 nanometers," says Davis. Particles this size can circulate in the blood for days and days, giving them all ample time to find the tumor, leak out of the new blood vessels, penetrate the entire mass, and enter the cancer cells.

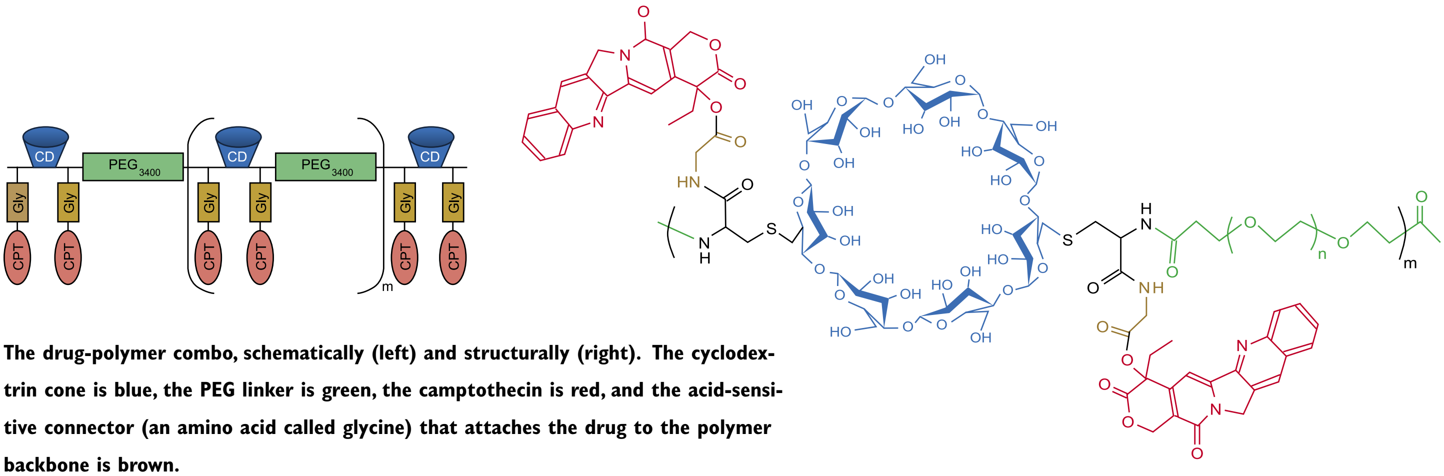
Building a Better Molecule

Davis, the chemical engineer, rose to the occasion. Nanoparticles, which range from 1 to 100 nanometers in diameter, are all the rage in the high-tech community. But they're also a mainstay of the brick-and-mortar economy—when they're suspended in liquid, they're called colloids. Paint is a colloid, as is milk. A particularly handy colloid can be assembled from cyclodextrin, which is a molecule composed of six to eight simple sugars arranged in a truncated, hollow cone—a sugar cone, if you will, with the tip bitten off. Cyclodextrin is made chiefly from cornstarch, and it's nontoxic, water-soluble, and doesn't set off the immune system—after all, it's just sugar. Its cone is a splendid place to stash molecules that are not water-soluble—which, alas, describes those oily anticancer drugs; oil and water don't mix. The first patent on using cyclodextrins to make drugs more soluble was issued in Germany in 1953, and they're still used for that purpose today. But once injected into the body, cyclodextrin molecules quickly release the drug, so Davis needed to find a way to keep the ice cream frozen in the cone, as it were, long enough to enter the tumor cells. And, ideally, once in the cell the ice cream should slowly melt, rather than the entire scoop falling out at once.

Both of these things happened when the cyclodextrin molecules were assembled into chains, using a molecule called polyethylene glycol—PEG to its friends—as a linker. (PEG is used in products from soft drinks to skin creams; on occasion, it's even added to ice cream as a thickening agent.) The resulting polymer looks like a long string of pearls, with round cyclodextrins alternating with linear PEGs.

A drug called camptothecin was chosen to be the payload. Despite its effectiveness against cancer in mice, camptothecin never made it commercially. Besides the usual complaints of being hard to dissolve and highly toxic, it flip-flops between an active and an inactive form. At the blood's slightly alkaline pH, the inactive form predominates. But by reacting the drug and the polymer together, the Davis lab created a chemical bond between the polymer's backbone and the drug, which stabilized it in its active form. The resulting molecule is about 10 percent camptothecin by weight.

This whopping construct still isn't big enough to be refused by the kidneys, so here's the really



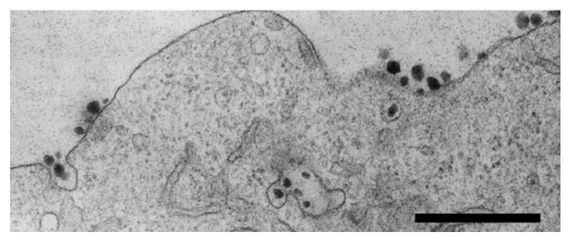
The drug-polymer combo, schematically (left) and structurally (right). The cyclodextrin cone is blue, the PEG linker is green, the camptothecin is red, and the acid-sensitive connector (an amino acid called glycine) that attaches the drug to the polymer backbone is brown.

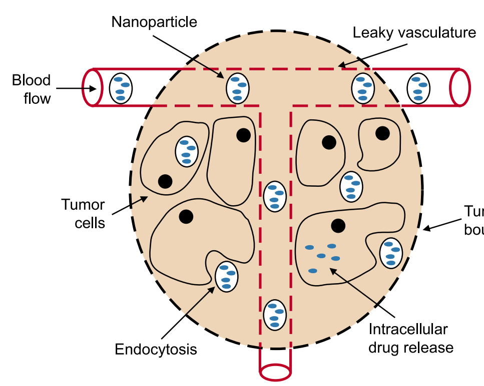
clever part. The combo is packaged as a dry powder. The powder dissolves in water in a couple of shakes, and the camptothecins dangling from the polymer backbone promptly stuff themselves into the sugar cones. Enough of these cones are on other polymer molecules that the whole wad knits itself together into nanoparticles about 40 nanometers across. Says Davis, "We designed this so that it could be kept in any old office, and any nurse can administer it. You don't have to be at a research hospital. You don't need to store it in liquid nitrogen. It just sits on the shelf in a little vial, and you add water to it and stick it in an IV bag."

These nanoparticles elude the oil-repelling glycoprotein pumps because the cancer cell thinks they're food. It engulfs them into little sacs called vesicles that also contain enzymes to digest proteins. These enzymes only work at low pH, so as the vesicle moves into the cell, it slowly fills with acid to activate them. This influx of acid breaks the chemical bond between the polymer backbone and the drug. The camptothecin then works its way free of the sugar cones in dribs and drabs—an automatic time-release mechanism—escapes through the vesicle wall, and sets to work. The empty polymer molecules eventually exit the cell and wind up in the urine.

The nanoparticle was tested on seven varieties of human cancer induced in mice—colorectal (two kinds), pancreatic, breast, non-small-cell lung cancer, small-cell lung cancer, and Ewing's sarcoma. After one dose a week for three weeks, all the non-small-cell lung cancers and most of the Ewing's sarcomas were completely gone, and all the other cancers showed significant reductions. Since one of the forms of colorectal cancer is known to resist irinotecan—an anticancer drug that grosses a billion dollars in sales a year—by activating the glycoproteins, it was clear that the drug-polymer combo was eluding their vigilant vacuuming. By contrast, giving irinotecan to other mice with non-small-cell lung cancer worked for a while and then pooped out. Says Davis, "The tumors came back, and the animals died."

"In all of the animal models that we've done, we've never had one fail yet," says Davis. "No matter what tumor type we use, we've had good results."





Courtesy of Insert Therapeutics.

Top: In this scanning electron micrograph of a cell, the nanoparticles show up as black blobs. At the left of the picture, a vesicle is beginning to engulf some of them—a process called phagocytosis. Another vesicle that has already swallowed several of them can be seen in the middle of the picture. The scale bar is 500 nanometers.

Bottom: A schematic of the whole drug-delivery process.

Besides offering state-of-the-art treatment, at any given time the staff at City of Hope is conducting more than 300 clinical trials, exploring ways to fight cancer, diabetes, HIV/AIDS, and other killers.

The very first vial of the cancer-fighting nanoparticle ever administered to a human subject.

Enter the FDA

There's a long, long road between Caltech and the clinic, and trying to get a drug to market single-handedly is a task well beyond even a Caltech professor's capabilities. So in 2000, after three years of lab work, Davis formed a company called Insert Therapeutics to shepherd things along. Before a drug can be sold in this country, the Food and Drug Administration requires three sets of clinical trials. Phase I is strictly about safety—is the cure worse than the disease? To find out, some 20 to 80 people are treated and then tracked for a year or so to look for aftereffects. Phase II tests efficacy—does it actually work? This involves a few hundred patients in order to gather enough statistics, and at best takes a couple more years unless the results are really spectacular. Phase III compares the new treatment to existing ones, involves thousands of patients, and can drag on for a decade.

The volume of paperwork is absolutely stupefying, and the staggering sums of cash required to see the process through are much easier to get from venture capitalists than university donors. Says Davis wryly, "There are lots of methods in lots of labs and lots of animal studies, but the translation from that into humans is huge, as far as effort and expense. The classic line is, if you could make any money curing mice, we'd all be millionaires by now. And it's true. There are significant differences between mice and humans, and as soon as you get into human studies, you see differences that tell us a lot, from a scientific and mechanistic point of view, about what's going on. But Insert Therapeutics, spearheaded by Thomas Schluep as chief scientific officer, is successfully translating laboratory materials to the clinic."

The nanoparticle, now christened IT-101 (for Insert Therapeutics 101), is midway through Phase I trials under the aegis of Dr. Yun Yen, director of the department of clinical and molecular pharmacology at City of Hope, a research hospital just a few exits east of Caltech on the 210 freeway. Since Phase I trials are the first foray into the human body, they're a treatment of last resort—the participants have already failed other approaches and have nothing left to lose. There are currently numerous patients participating, with a whole spectrum of cancers—lung, pancreatic, kidney, ovarian, and breast. The early results were so encouraging that one patient broke the wall of confidentiality and gave an interview to the *Pasadena Star-News* in September 2006.

This gentleman was diagnosed with pancreatic cancer in 2002, and two-thirds of his pancreas was removed. Two months of chemotherapy followed, but a little more than a year later the cancer returned, spreading into his lungs. "I did another three or four months of chemo, but it didn't work. The cancer began progressing faster, and I quickly reached Stage IV [the last of cancer's four stages]." The chemo "was very tough. I had to lie in bed for four or five days afterward to recover. Just no energy. And I had hardly any white cells left, so I had to avoid people. I couldn't even go to the supermarket. I used to dread every week I had to go in for it." He joined the IT-101 trial in July 2006, and the difference has been like night and day. "I don't notice it much. It doesn't break the immune system, so I don't have to take any supplements for my blood. And the next day I can move around, go shopping. I'm feeling much better, gained some weight." The only side effect he noticed, and he calls it "very tolerable," is that some foods taste a little funny.

Four-Part Harmony

Meanwhile, Davis continues to explore even newer approaches. One particularly promising one uses the cell's own machinery to, in effect, throttle back a runaway gene. RNA is the messenger

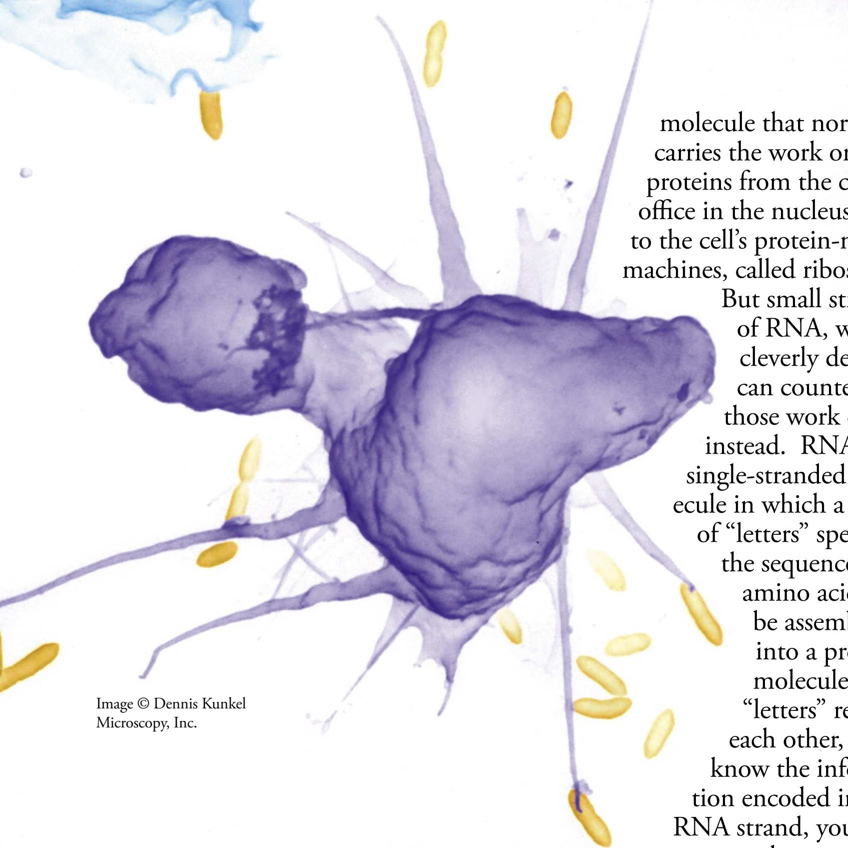


Image © Dennis Kunkel Microscopy, Inc.

A macrophage (blue, and shown 3,900 times its actual size) chows down on some *E. coli* bacteria (yellow) that had managed to sneak into the pleural cavity between the membranes surrounding the lungs.

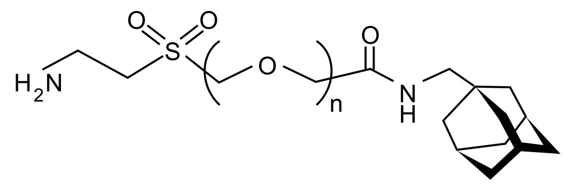
molecule that normally carries the work orders for proteins from the central office in the nucleus out to the cell's protein-making machines, called ribosomes. But small strands of RNA, when cleverly designed, can countermand those work orders instead. RNA is a single-stranded molecule in which a series of "letters" spells out the sequence of amino acids to be assembled into a protein molecule. These "letters" recognize each other, so if you know the information encoded in an RNA strand, you can create another strand that uses the cell's machinery to bring those two RNA strands together and destroy the messenger RNA strand. This phenomenon, called RNA interference, won the 2006 Nobel Prize in Physiology or Medicine for the folks who figured out its workings. If you could get the appropriate siRNA (for small interfering RNA) into a cell, you could essentially turn off a gene that is making it cancerous—just what the doctor ordered. Better still, siRNAs are short molecules that can be made synthetically in bulk.

"We had started trying to use nanoparticles to deliver genes into the nucleus, which is a very hard problem," Davis recalls. "And then you have to control their activity, which is even harder. But when the RNA-interference concept came out in the late '90s, we immediately recognized that this was a much better way to go." But those groundbreaking studies involved injecting a high-pressure, high-volume solution of the siRNA molecules into a mouse's tail vein. Scaled up to human size, the dose would be equivalent to getting shot up with some seven liters of water in the space of a couple of seconds. Malpractice suits would undoubtedly result.

As luck would have it, siRNA molecules have negative charges scattered all along their lengths, and the cyclodextrin polymers can be made with positive ones. Mix the two together, and static cling takes over. The siRNA is woven throughout the nanoparticle, and some of the resulting nearly neutral nanoparticles are safe from the warrior cells called macrophages that roam the body. All cells—your own as well as bacteria, fungi, and viruses—are negatively charged, and macrophages engulf negatively charged entities that don't have proper ID.

In this design, the sugar cones sit empty, so the Davis lab promptly stuffed them with other things. Colloidal particles can agglutinate into glop balls, a process that chemical engineers fight by enshrouding each particle in a "brush layer." The brush's protruding bristles repel other particles, and PEG makes a dandy bristle. So PEG chains were anchored to the nanoparticles by attaching them to molecules of adamantane, which fit neatly into the vacant sugar cones on the nanoparticles' surfaces.

It almost didn't work. "The adamantanes just kept popping in and out, even as the RNA began to bind," says Davis. "But once we got to PEG of a certain size, the brush layer actually imparted an energy of stabilization as it formed, and that keeps the system assembled. It took us forever to figure out what was happening. It's really amazing—without that extra energy, the whole system would just fall apart."



The brush's PEG bristles are attached to molecules of adamantane, whose four fused six-membered carbon rings look like the blades of an eggbeater.

A smattering of the PEG chains end with a molecule of transferrin, an iron-carrying protein that is ingested by rapidly growing cells. Iron atoms are crucial to many enzymes, and cancer cells are gluttons for the metal, so they sprout lots of transferrin receptors on their surfaces. This helps the nanoparticles home in on them. Normal cells have only a handful of transferrin receptors, and the nanoparticles do not compete for these receptors as well as single transferrin molecules do. But a nanoparticle sporting an Afro beaded with a controlled number of transferrins can out-compete the individual molecules for the cancer cell's receptors because its high density of transferrins allows it to bind several receptors at once. "A nanoparticle is the only kind of drug-delivery system with enough surface area to allow you to do this," says Davis. "Multivalency is used by biology everywhere, but trying to do it correctly on a particle is state of the art."

If these nanoparticles lingered in the cell's vesicles, the siRNA would be digested like any other nutrient. So the Davis lab wired in a self-destruct switch. When dunked in acid, an amine group on each end of every polymer molecule picks up a proton, giving the nanoparticle a substantial positive charge that literally blows it apart.

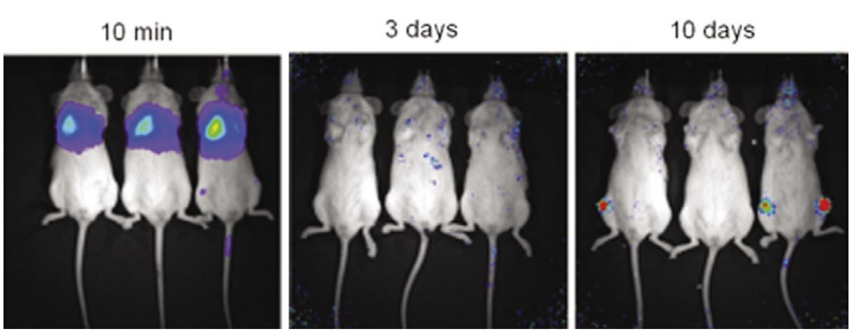
Water simultaneously floods in as osmosis acts to dilute the charge, and the vesicle explodes like an overinflated balloon. The siRNA then gets picked up by molecules that initiate the RNA interference mechanism.

The approach has now been tested in mice with collaborators from Children's Hospital Los Angeles. Cancer cells in 85 percent of patients with Ewing's sarcoma have a genetic rearrangement in which a piece of DNA that normally lives on chromosome 11 somehow winds up on chromosome 22. This "fusion gene," called *EWS-FLI1*, is thought to activate other genes that help the cancer grow, and shutting it down has been shown to retard tumor growth and proliferation. Many cancers, including pancreatic, liver, and numerous intestinal cancers have similar fusion genes. Ewing's sarcoma hides in the bones, and by the time most patients are diagnosed they already have micrometastases—teeny, tiny tumors too small to see and well-nigh impossible to get rid of, even with whole-body chemotherapy. Ewing's is also a nasty bit of business because it frequently develops multidrug resistance.

Ewing's sarcoma hides in the bones, and by the time most patients are diagnosed they already have micrometastases—teeny, tiny tumors too small to see and well-nigh impossible to get rid of.

To mimic these micrometastases and track their spread, mice were injected with Ewing's sarcoma cells that had been modified to include the gene for luciferase—the protein that puts the fire in fireflies. The cells circulated freely through the blood, lodging in all sorts of places, and wherever they wound up, they lit up. Then, for the next five to eight weeks, their travels were followed with an ultrasensitive CCD camera system adapted from astronomical designs by Xenogen, a biological imaging company. Essentially, you strap a tiny gas mask on the mouse, give it anesthesia, lay it on a tray in a dark cabinet, and look for the faintest of glows. Sarcomas turned up in the mice's femurs, lungs, and brains, among other places.

Ten minutes after injection into the tail vein, most of the luciferase-containing sarcoma cells can be found in the capillaries of the lungs. As the cells disperse, the signal scatters and fades until substantial tumors develop.



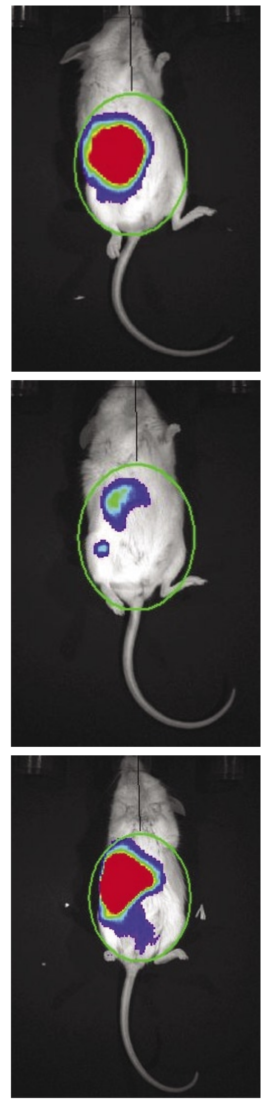
From Siwen Hu-Lieskvan, et al., *Cancer Research*, vol. 65, no. 19, October 1, 2005, pp. 8984–8992.

At about the five-week mark, some of the mice were given a shot—0.2 milliliters of solution, or four drops, a much more manageable dose—of a nanoparticle containing an siRNA against *EWS-FLI1*, that fusion gene mentioned earlier. The intensity of the light they emitted dropped by more than 60 percent for two or three days, then rebounded to pretreatment levels as the cells resumed their unbridled division. "It's a dilution effect," Davis explains. "Each time the cell divides, half of the siRNA goes to each new cell. And these cells divide really fast—much faster than they do in people. So we might only have to dose a patient every few days, or possibly every week. If the cell wasn't dividing at all, the effect would last for a month or so."

Other mice were given a nanoparticle containing an siRNA against luciferase itself. Two days later, the light from the tumors had dropped to less than 10 percent of its original intensity. "And that's the key result," says Davis. "It shows that the nanoparticles are getting to essentially all the cancer cells within the tumor mass." This glow, too, returned to full strength in another three days; the mice, meanwhile, showed no ill effects from either procedure.

And in a long-term study in which mice were given the anti-fusion-gene nanoparticles twice weekly beginning on the day they were also given the Ewing's sarcoma cells, only 20 percent of the mice developed tumors at all.

In 2005, Davis and others started a new company called



Above: These pictures of a mouse with a luciferase-containing tumor were taken, from top, 40, 43, and 46 days after being injected with Ewing's sarcoma cells. On days 40 and 41, the mouse got an injection of the anti-luciferase nanoparticle.

Courtesy of Taka Kawachi.

Calando Pharmaceuticals to bring the siRNA project to the clinic under the scientific leadership of Jeremy Heidel (MS '01, PhD '05). *Calando* is an obscure piece of musical notation that instructs a performer to fade to silence, so Davis chose the name in a nod to Mary, an accomplished flutist—the technology makes a gene go silent. Calando officials plan to start Phase I trials this fall. Calando will supply the polymer and both PEGs in a vial of dry powder, and the siRNA will arrive in a second vial. Once again, all the clinician has to do is add water and fill the IV bag. "It will be the first targeted delivery of siRNA in a human being," says Davis. The hope is that if the right gene is shut down, there will be no side effects whatsoever—not even funky food tastes.

What with its four different molecular components, it will also be one of the most complicated systems the FDA has seen. "They're Porsches, compared to earlier nanoparticles," says Davis—finely tuned machines with a lot of subtle design features. "That's what's really fun about it. There are many, many parameters that had to be understood so they could be engineered to work together."

Davis is keeping his fingers crossed that the trials will go smoothly. "The FDA has been helpful with the Insert trial. But the Calando one is going to be more complicated from a technological and regulatory perspective, due to its four components. Initial interactions with the FDA have been proceeding well."

"We Started from Zero"

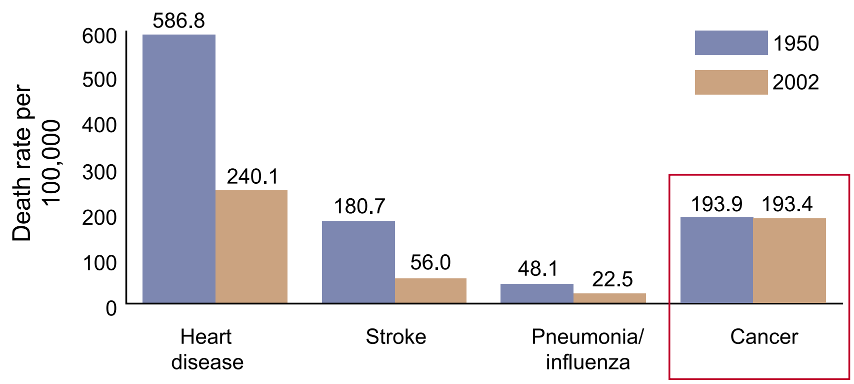
Before Mary's illness, Davis had spent his career improving the workings of zeolites, a class of minerals used as industrial-scale catalysts. While most of his research group continued to mine that vein, he struck out into virgin territory, heading into the mountains that separate chemical engineering from molecular biology. "Basically, we started from zero. We didn't know anything. Hector Gonzalez, an organic-chemist postdoc, started on the synthesis, and Suzie Jean Hwang [MS '98, PhD '01 (now Suzie Hwang Pun)], a grad student in Chem. E., started on the biology. We didn't even know how to culture cells. Suzie learned how to do it, and we just kind of pushed our way through and started building the facilities we needed."

The whole exercise has been a good argument for the tenure system. "It's like everything else—the first couple of years you just can't get anything right, and it was very frustrating," Davis laughs. "The one thing I think that really helped me was that I did it later in my career, so I could actually spend several years without results."

"I have to give credit to Caltech, too. It's very easy to go and talk with people here, and everybody was very helpful getting us started with cells, getting us started with mice. Just mastering the language was difficult—I'd go to medical meetings, sit in the back of the room, and try to battle through the jargon. And the other good thing was I could call up someone and say, 'I'm a professor at Caltech,' and I'd get in to see people that might have been really hard to talk to, otherwise."

Getting the chemical synthesis right in quantities sufficient for use in animals and ultimately in humans was not easy. Their cyclodextrin molecules had 21 chemically equivalent places where the polymerization reaction could occur, and each molecule had to behave like a railroad car, with one coupler on each end. Early efforts yielded cars with one, three, or even more couplers, and the

While death rates from heart disease, stroke, and pneumonia/flu have plummeted in the last 50 years, cancer death rates have remained steady. Data from the American Cancer Society.



polymerization process became a complete train wreck. "When we first started working on this, I was talking with Bob Grubbs [the Atkins Professor of Chemistry and a Nobel laureate], and Bob said, 'Do you really want to start working on sugar chemistry?'" laughs Davis. "I wasn't sure what he meant by that, but after a couple of years, I understood."

They eventually figured out a way to attach two iodine atoms on opposite sides of the cyclodextrin molecule, and built a linker outfitted with a sulfur atom on one end and an amine on the other. The sulfur-iodine reaction was very efficient and very selective, churning out identical cyclodextrin-containing units, called monomers, with exactly two couplers each. "The high-purity, large-scale cyclodextrin monomer synthesis was the killer," says Davis. "Once we had that, everything else was downhill."

Prevention Is the Dream

"I would never have done this without having seen what Mary went through," says Davis. "I was reading cancer-therapy papers from the City of Hope's library while I was sitting in the isolation room with her, wearing a surgical mask so she wouldn't get some bug from me. We were in the middle of a nightmarish situation, but she survived all of it and is fine today. It's been a rough ten years, but when we treated the first patient last summer, that to me was the ultimate. He consented to let me watch the first infusion—the first time IT-101 went into a human being. You just hold your breath, because for the first ten minutes or so you don't know whether there's going to be an allergic reaction or something. Everybody's just standing there, waiting."

Davis is not allowed to communicate with any of the patients, and Dr. Yen can't go into specifics, but he does say that things are good—"the patients' platelet levels and white blood cell counts did go down somewhat, but most of them rebounded on their own. Pharmacology confirms that the drug is staying in the serum, and nobody has suffered nausea, vomiting, or hair loss." By the time the trial ends, he expects to have looked at 20 to 30 patients. Planning for Phase II trials is already under way.

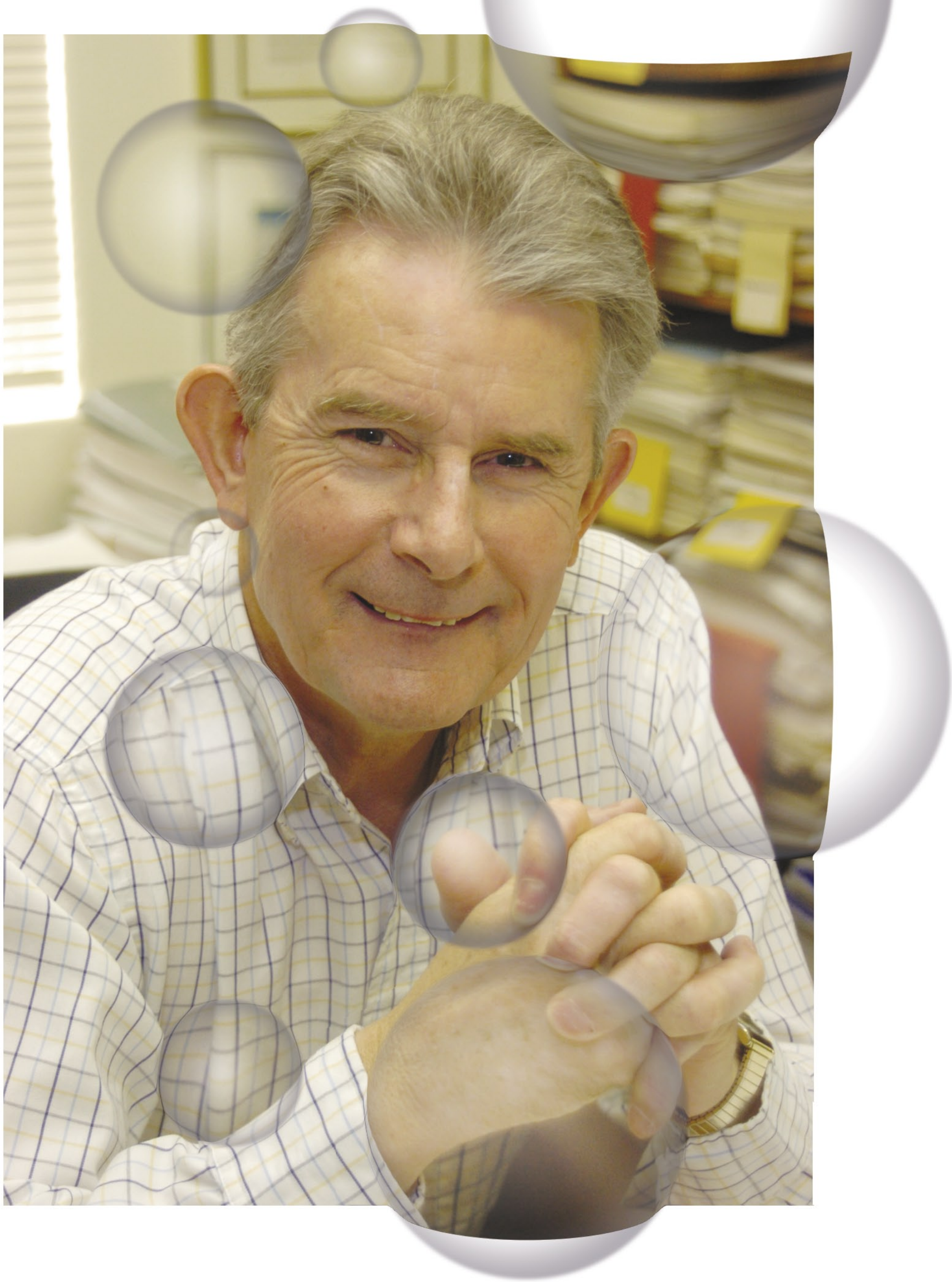
In the meantime, the process has gone from making little bits of powder at Caltech to multi-kilogram lots at Insert and Calando. Even so, production costs have stayed acceptable, Davis says, because the starting materials are so cheap. "Relative to other therapeutics, this is going to be very reasonable."

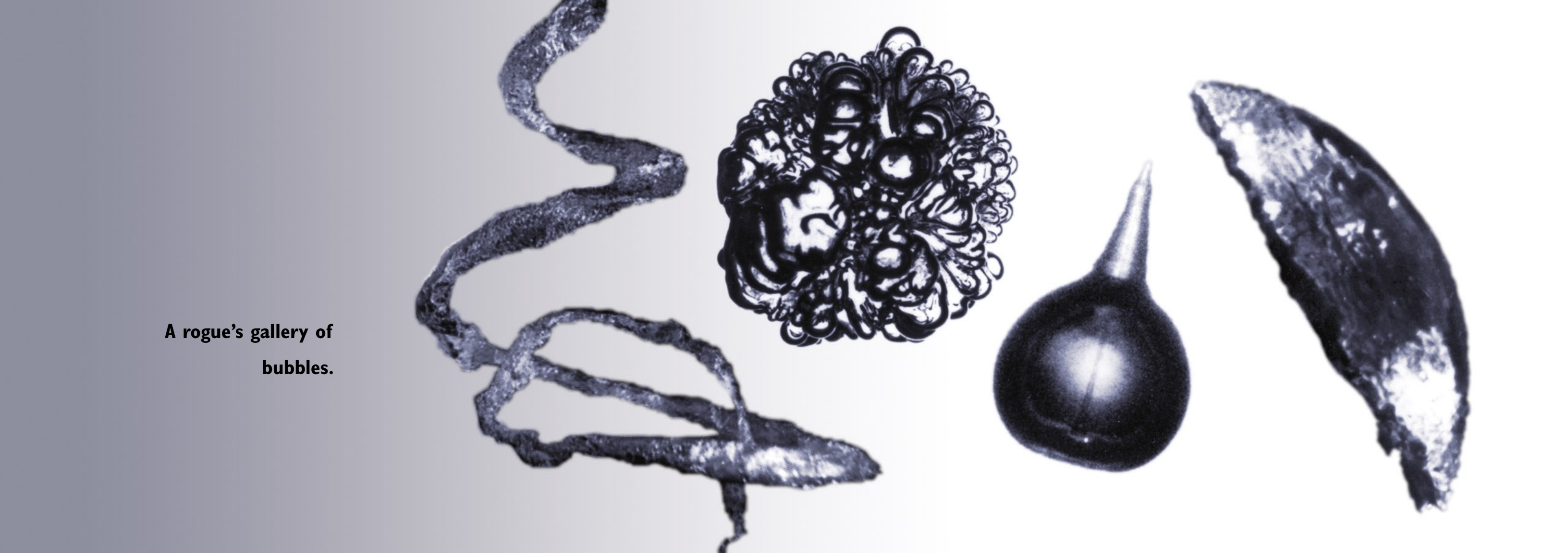
"If we—and others—can create safe, effective therapies with minimal side effects, we're going to change the way in which cancer is treated. It's going to open the door to prophylaxis," Davis says. Doctors routinely prescribe statins—a class of drugs including Zocor and Lipitor—to prevent heart disease by lowering cholesterol. That's likely a part of the reason why deaths from heart disease and stroke have plummeted in the last couple of decades. "Could we do something like this with cancer? Right now, no way. But if you had a set of diagnostic signatures that told you, 'I suspect that there might be something there, but it's so low that I can't yet see it with an imaging agent,' and had a nontoxic treatment without those horrible side effects, why would you not go prophylactic, just to be on the safe side? That's my dream." □

PICTURE CREDITS: 22, 24, 28—Doug Cummings; 27—Mark Davis, City of Hope

The Amazing World of Bubbles

By Christopher E. Brennen



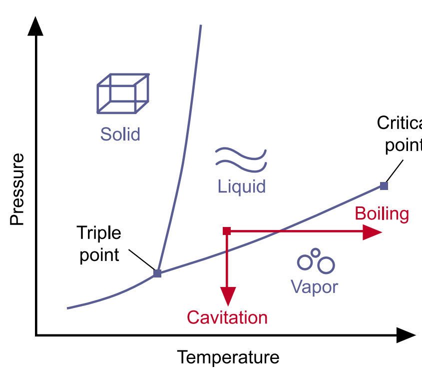


A rogue's gallery of bubbles.

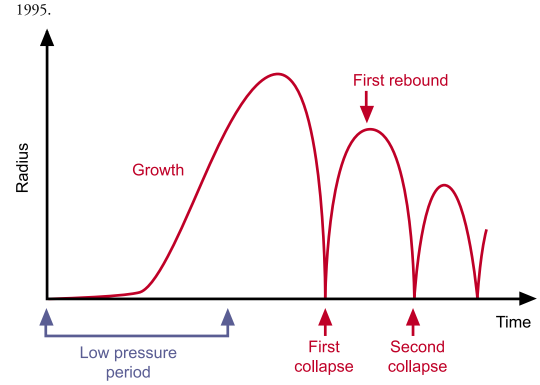
Bubbles come in all sizes, shapes, and forms, but let's begin with a very simple one. A bubble is a small pocket of vapor inside a liquid. This happens because the molecules have crossed the line separating the liquid zone from the vapor zone. Engineers and scientists like to depict this in a phase diagram, which is simply a graph that shows you whether a substance is a solid, a liquid, or a gas—or any combination thereof—at various temperatures and pressures. Increase the temperature, and the liquid boils. It forms bubbles. If you lower the pressure, a phenomenon called cavitation occurs. The resulting bubbles are essentially the same, but the consequences are not—when your teakettle boils, the bubbles don't tear it apart, but cavitation can turn steel into Swiss cheese. The difference is that bubbles formed at high temperatures contain a lot of heat and collapse relatively slowly. But if you cross the line down near the triple point, where solid, liquid, and vapor can coexist, the vapor contains very little heat, allowing the bubbles to collapse quite rapidly and very violently. What matters is not so much *how* you cross the liquid-vapor line, but *where* you cross it.

Back in the 1930s and '40s, Robert Knapp (PhD '29), a professor of hydraulic engineering here at Caltech, built the first camera with a high enough framing rate—about a thousand frames a second—that he could actually see what went on when cavitation bubbles collapsed. He made groundbreaking movies down in the basement of Karman Lab, where he had set up the lab's water tunnel so that the flow went through a low-pressure region in front of the camera. The bubbles grew quite gradually as they entered this region, but they collapsed violently as they exited. The dynamics of this process are highly nonlinear, and that's an important feature. It's also important to note that, to a first approximation, the process is scale-independent, as we shall see—big bubbles behave the same way as tiny ones. When a bubble collapses, it rebounds a few times, as shown in the plot below. A bubble contains mostly vapor, of course, which condenses as the bubble collapses, but there's a little bit of air trapped in there, too. The air can be compressed, but you can't make it go away, and eventually it can't be compressed any further and it springs back. So the bubble rebounds, and it breaks up into a cloud of lots of little bubbles. This, too, is important, because clouds of bubbles have very different dynamics than single bubbles, and I'll return to this later.

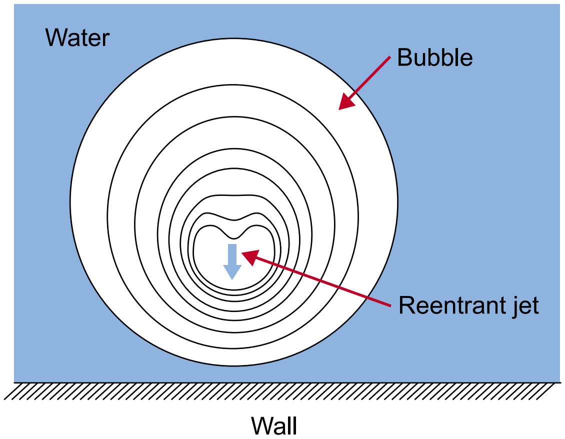
Right: A generic phase diagram. (The triple point marks the pressure and temperature where solid, liquid, and vapor coexist; the critical point is where the distinction between liquid and vapor vanishes.) There are two ways to go from liquid to vapor—raise the temperature, or lower the pressure. The first leads to boiling, the second to cavitation. Far right: The radius of a cavitation-grown bubble in a water tunnel plotted against time.



Adapted from C. Brennen, *Cavitation and Bubble Dynamics*, Oxford University Press, 1995.



When a bubble collapses near a solid surface, the water has a hard time filling the void from the wall side. The collapse, initially symmetrical, becomes directed toward the wall, and a reentrant jet develops.



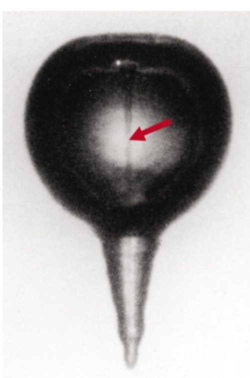
Adapted from M. Plesset & A. Prosperetti, *Ann. Rev. Fluid Dynamics*, Vol. 9, pp. 145–185, 1977.

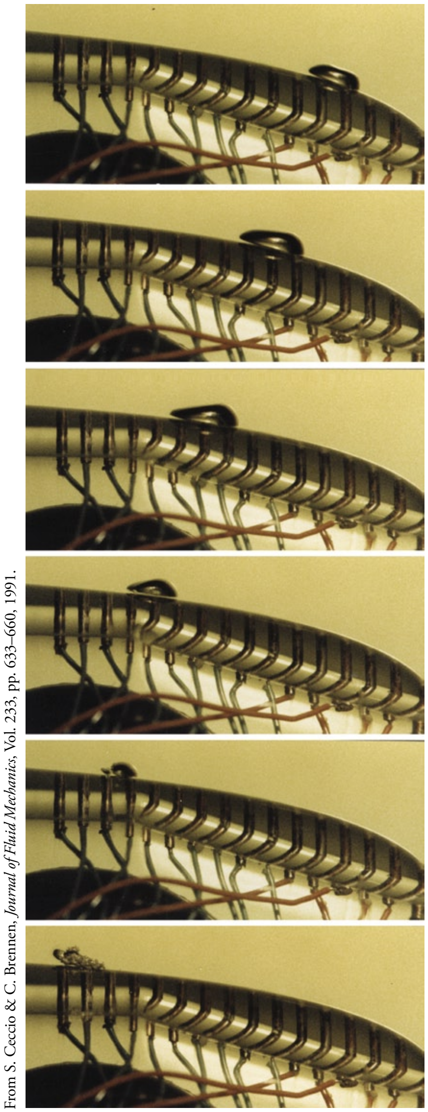
Hitting the Wall

But the most important feature arises when the bubble collapses near a "wall," which could be a steel propeller, a cement conduit, or essentially any hard surface. The side of the bubble next to the wall tends to collapse more slowly than the rest of the bubble, because the inrushing fluid on that side has to first move along the wall and then come in, whereas fluid from any other direction just comes straight in. So a jet of liquid aimed toward the wall rushes into the bubble. The jet can reach very, very high speeds—many hundreds of meters per second—and it blasts right through the bubble and into the wall, producing shock waves and other noisy trauma. (People had known about the noise for a long time, of course—that was the chief way that engineers knew that a pump was in trouble. They'd hear this horrid crackling sound, and when they took the pump apart, they'd find that its impeller blades were all chewed up.) These jets were discovered by another Caltech pioneer, Albert Ellis (BS '43, MS '47, PhD '53), who as a faculty member in the 1950s and '60s developed a number of very important high-speed cameras capable of shooting a million frames per second. He took the picture at left with one of them. The jet, marked with an arrow, is the thin, dark column in the middle of the bubble. The big protuberance is the jet blowing out through the bottom of the bubble.

More recently, grad student Steve Ceccio (MS '86, PhD '90) took the pictures at right of a single bubble growing and collapsing. We make these bubbles by inserting a cylindrical object called a headform into the flow. The cylinder's long axis is parallel to the flow and, as the water goes around the cylinder's blunt end and down the sides, a low-pressure region develops where cavitation bubbles form. Lots of them, and very reproducibly, which allows us to examine the detailed micro-mechanics of their growth and collapse. Sometimes the bubble develops wings, which is a rather curious thing.

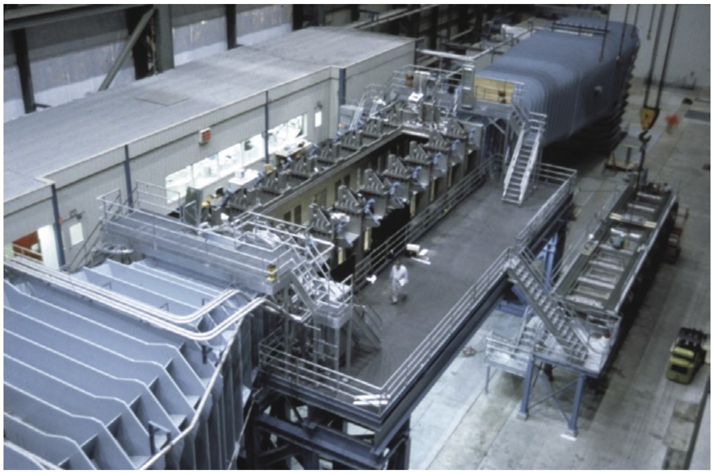
The asymmetric collapse forms a reentrant jet (arrowed), visible as a thin, dark column in the middle of the bubble.



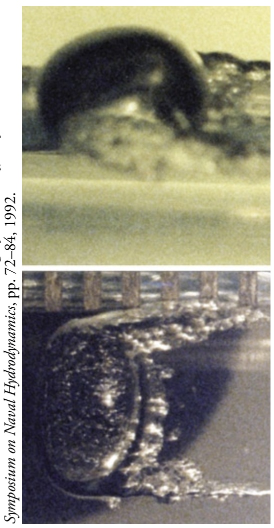


From S. Ceccio & C. Brennen, *Journal of Fluid Mechanics*, Vol. 233, pp. 633–660, 1991.

A bubble grows, splits in two, and breaks up as it travels along a Lucite headform, whose trigger system for the high-speed camera makes it look like a robotic shrimp. The shrimp's segments are a series of silver filaments, set in epoxy-filled holes and machined down to perfect smoothness, that act as electrodes. When a bubble bridges an electrode pair, the resistance skyrockets and "the bubble takes its own picture," says Brennen. "It was the only way we could do it fast enough to catch them." Brennen's second innovation was to hang an underwater mike called a hydrophone in a water-filled cavity in the headform. Water and Lucite have essentially the same acoustical properties, so a hydrophone in the headform picks up only the sounds made by the bubble itself, free of tunnel noise—the first good sound measurements of single bubbles. Brennen calls it "the cleverest thing I ever did."



The Navy's Large Cavitation Channel—catchy name!—is one of the biggest water tunnels in the world. Note the man on the working section's access platform in the middle of the photo.



From Y. Kuhn de Chizelle, et. al., *Proceedings of the 19th Office of Naval Research Symposium on Naval Hydrodynamics*, pp. 72–84, 1992.

Top and side views of a winged bubble made in the Caltech water tunnel. The bubble is about a millimeter long from nose to tail.

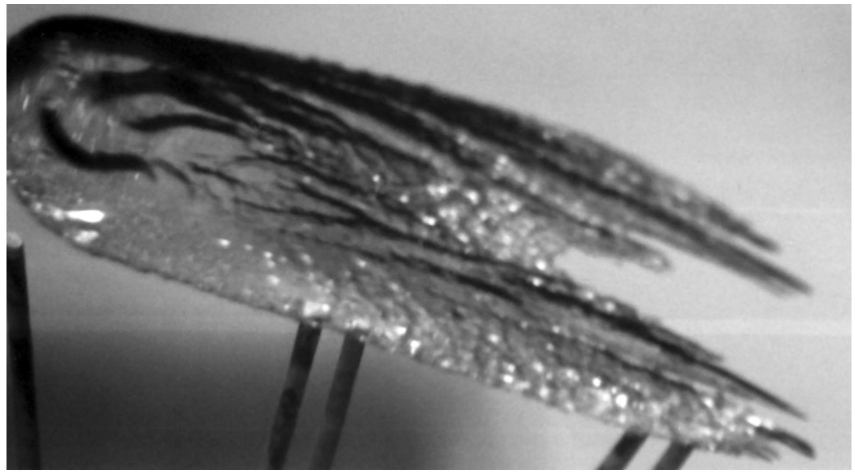
If a bubble interacts with the boundary layer and begins to rotate, the spin can generate a vortex similar to the one that forms on the tip of an airplane's wing. One vortex forms on each side of the bubble, making it look rather like a Viking helmet, or Mercury's hat. The bubble spreads out and the collapse process becomes more diffuse, making it less violent.

We took those photographs for the U.S. Navy, which is interested in making its ships, and especially its submarines, run as quietly as possible. When I showed the Navy our results, that cavitation noise depended upon the geometry of the bubble and how it collapsed, they said, "That's very interesting, but you've done these experiments on this tiny little body. How do we know that they have any relevance whatsoever to a 30-foot-diameter propeller?" Well, often you're asked these kinds of questions you can't answer, but in this instance I was soon able to give a partial reply. This happened in 1991 or thereabouts, just as the Navy was building one of the largest water tunnels in the world—in landlocked Tennessee, of all places. The working section—the part of the tunnel where you do your experiments—is about 10 feet by 10 feet in cross section, with a flow velocity above 40 miles per hour. When this thing is operating, it's like a freight train going by. It draws so much power that we weren't able to run it during the day, because the Navy said the lights of Memphis would dim. (The thought of dimming the lights of Graceland did have some appeal to me, I will admit.) So Steve, Yan Kuhn de Chizelle (MS '91, PhD '94), Douglas Hart (PhD '93), and I ran our little headform again in this tunnel, and then scaled it up to five times and 10 times larger, which is to say we went from a two-inch diameter headform to a 10-inch and eventually a 20-inch one, which we naturally named Big Bertha. This was no mean feat—it's hard to cast pieces of Lucite that big, and a number of our attempts cracked. And the cavitation exerted substantial forces on the model, so much so that I was afraid that it would be torn loose from its mount and ruin their nice new tunnel.

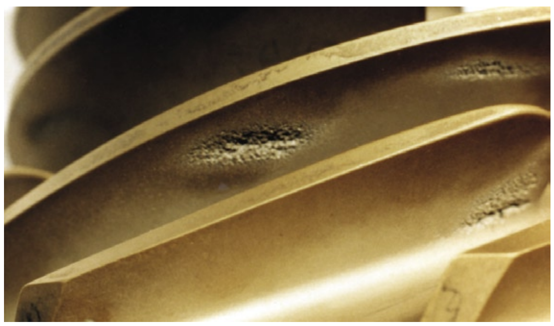
The story has a complicated end because these bubbles were even more distorted than the ones

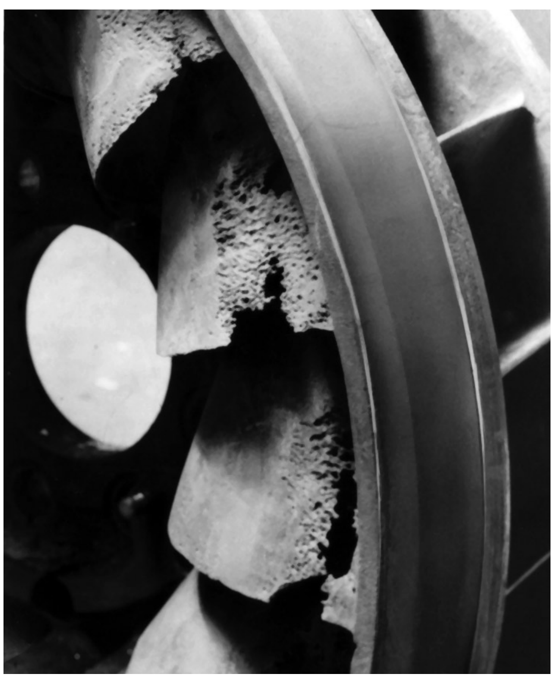
The 10-inch headform being installed in the Large Cavitation Channel's working section.

Big Bertha made big bubbles. This long, stringy specimen is about 10 centimeters long and two centimeters across; the things that look like supporting rods are the electrode pairs in the headform.



From Y. Kuhn de Chizelle, et. al., *Proceedings of the Third International Mechancial Engineering Conference*, Cambridge, England, pp. 165–170, 1992.





Top: The three pitted regions on the undersides of these blades are the early signs of cavitation damage. Bottom: If left unchecked, cavitation can eat through steel.

in the Caltech water tunnel, but we were able to correlate the type of bubble with the noise it produced. We found that the bubbles got bigger as the headforms got bigger, so our little two-inch model made millimeter-sized bubbles, the 10-inch one made centimeter-sized bubbles, and Big Bertha made bubbles 10 centimeters long. The noise is generated as the collapsing bubble compresses that little bit of air trapped within. Each bubble makes a single acoustical pulse, and the accumulation of all the bubbles collapsing makes a sort of crackling sound that can range from a gentle hiss in our little experiments to a deafening BANG!BANG!BANG! BANG!BANG! on a 30-foot propeller blade. All the previous noise calculations had assumed a spherical bubble, and our bubbles were anything but. It turns out that, the bigger the bubble, the more the noise deviates from the spherically calculated result, and the more distorted the bubble, the quieter it is. The bubbles with tails make significantly less noise than those without. So now all the Navy has to do is figure out how to make propellers that generate tailed bubbles. They're still working on that one, as far as I know.

Shocks to the System

The shock waves I mentioned earlier continuously hammer away at any nearby surface. If it's metal, it fatigues and pieces flake off, exposing new surface for the bubbles to continue gnawing away at. It's amazing to think of a bubble eating through steel, but that's what happens. This damage is one of the most serious consequences of cavitation. Above left is the pump impeller in a rocket engine, and the damaged regions have the pitted appearance typical of fatigue failure. If this goes on long enough, it will reduce the blades to Swiss cheese.

But my favorite example is the picture above right, taken inside the conduit leading from the spillway at Hoover Dam, which is on the Colorado

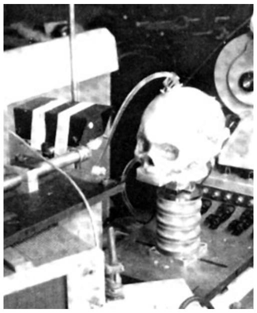
From J. Warnock, *Proceedings of the American Society of Civil Engineeers*, Volume 71, pp. 1041–1056, 1945.

Left: The conduit leading from the spillway at Hoover Dam suffered extensive cavitation damage the very first time it was used.
Below: When Lake Mead fills up behind the dam (top), the water flows over the weir in the foreground and into the spillway (bottom). The bridge crossing the spillway is part of U.S. 93, which connects Kingman, Arizona, with Las Vegas via the dam. If you look closely at the top picture, you can see several vehicles driving along the dam's top.

River out in the desert near Las Vegas. The conduit is a gargantuan concrete tube, 12.5 meters across, and the flow comes down from above at the back of the picture before turning to come straight out toward you. Cavitation has dug a hole 35 meters long, nine meters wide, and 13.7 meters deep at the point where the flow changes direction, which is where the bubbles are most likely to collapse. (By way of scale, there's a man looking into the hole from its left side.) All of that damage was done in less than four months during the winter of 1941, the first time the spillway was used. An aeration system has since been installed in the conduit to cushion the bubbles' collapse.

The spillway runs perpendicular to and behind the dam, as you can see in the top picture at right. If the water level in Lake Mead rises high enough—which can sometimes happen in periods of winter floods, although it hasn't in many years, due to the drought—the water overflows the weir in the foreground and goes into the spillway, disappearing down into the conduit, shown empty at right. It is the most awesome sight. The noise is just enormous, and the mist that rises all around is quite amazing. And everything is constantly cavitating. The pressure oscillations throughout the flow are so large that vapor bubbles are forming and collapsing everywhere.

Cavitation-induced bubbles also play a significant role in head injuries. If you have a container of liquid and you bang it on something hard—and your brain is just a container of liquid, basically, at least from a fluid-mechanics point of view; some have more liquid than others—you're going to generate lots of pressure waves that bounce around in that container. There will be points where the pressure becomes very low and the liquid vaporizes. In serious head injuries, it's almost inevitable. Bubbles will grow and collapse, and the collapse sometimes causes more damage than the blow itself. The problem is that those low-pressure regions where cavitation occurs may be quite remote from the



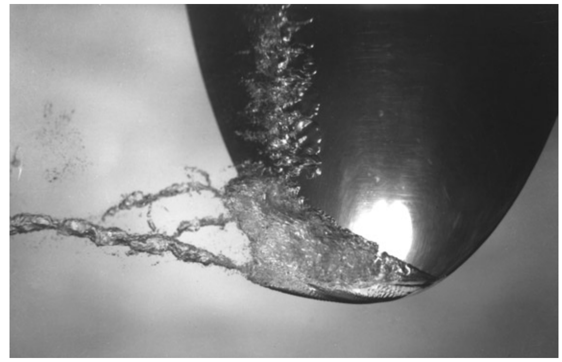
It was Halloween every day in Werner Goldsmith's lab when he was studying the fluid-dynamic aspects of brain trauma. Archival image courtesy of Werner Goldsmith.

actual impact point, so knowing where that damage is going to occur and what form it might take is important in determining how to approach a head injury. Werner Goldsmith at Berkeley spent a significant part of his career examining containers of liquid being banged around, including this one that looks like a skull.

Artificial hearts almost inevitably cavitate, which is a real problem in developing ones that will last a long time. The problem is not so much the damage to the surface of the valve, but the fact that the cavitation bursts red blood cells and destroys them. And obviously, if that happens to too great an extent, the patient is in trouble. I'll focus on one common design, the bileaflet valve, because Mory Gharib (PhD '83), the Liepmann Professor of Aeronautics and professor of bioengineering, and I have both studied it. Any heart valve, be it natural or artificial, is designed to keep the blood from flowing backward, so when the blood starts to flow backward at the end of the so-called diastolic phase, the leaflets pivot closed, as you can see below. Little jets (shown in red) shoot through the gaps between them, and between the leaflets and the walls, forming low-pressure regions that cavitate. This causes hemolysis, which is the word doctors use for busting up a red blood cell.

When surgeons do heart-valve replacements nowadays, they use pig valves. Like the valves we're born with, pig valves are flexible and forgiving, so you don't get the low pressures you do with rigid, mechanical devices. We'd like to build flexible artificial valves, but we don't really know how to make flexible, biocompatible materials that are 100 percent reliable and will last a lifetime.

A singing vortex. The vortex's braided structure is thought to be related to the fact that it sings, but exactly how remains shrouded in mystery.

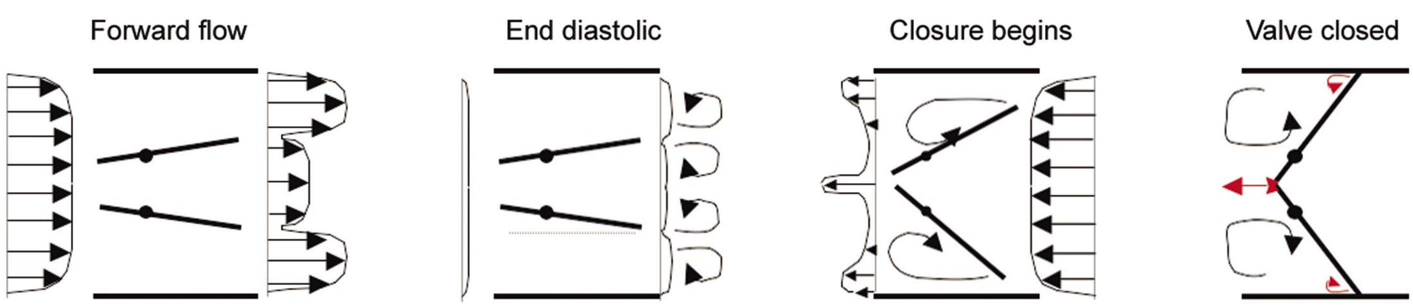


From H. Higuchi, et. al., *Proceedings of the American Society of Mechanical Engineers International Symposium on Cavitation and Multiphase Flow Noise*, pp. 101–106, 1986.

Vortices—What's Not to Like?

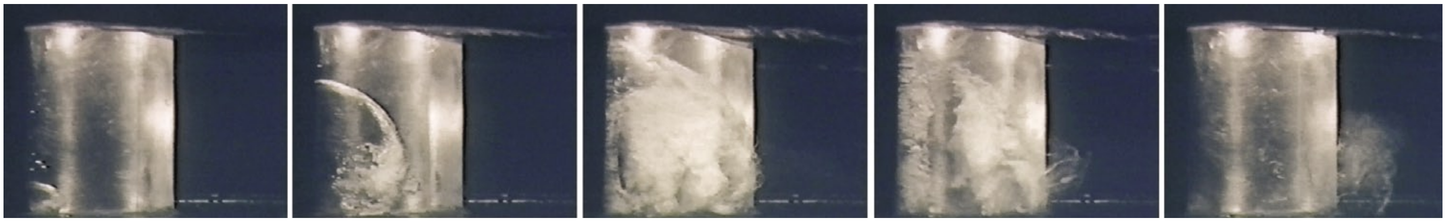
Vortices can also cavitate. (I like vortices.) If you have a rotating flow, say downstream of a propeller, a core of low pressure develops down the middle of the vortex and presto—cavitation! My colleague Roger Arndt, of the University of Minnesota, discovered that this vortex sings. It's the most amazing thing to listen to, and would make a wonderful Halloween sound effect. It's kind of an unearthly "ooooooooooo" sound, not quite a moan. As Roger lowered the pressure, making the vortex grow, the pitch of the singing got lower. Why it sings is not fully understood, but it's an acoustic resonance of the cylindrical structure of the vortex, which oscillates in peculiar ways.

From B. Moines & C, Brennen, *Sixth Annual Hilton head Workshop on Prosthetic Heart Valves*, 2002.



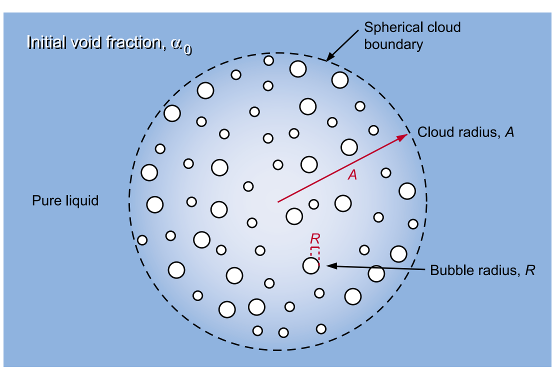
A bileaflet valve is a pair of flat plates mounted on off-center pivots. A reversing flow pushes the plates shut automatically, but also causes high-pressure jets (red) to shoot through the narrowing cracks in the final moments of closure.

Courtesy of Göran Bark.



Top: The places where the paint was eaten off these propeller blades coincided with where the white clouds of bubbles were collapsing. Bottom: This oscillating hydrofoil in Caltech's water tunnel allows collapsing clouds to be studied in detail.

Propellers make *lots* of vortices, one from the tip of each blade, leaving a trail of intertwined helices downstream. And the hub produces a vortex of its own, right down the middle. You can't get away from this—all propellers cavitate, if they rotate fast enough. This is another noise issue for the Navy, because cavitating vortices, that is, vortices with vapor in the middle, are much more stable than normal wingtip vortices and persist much longer. In fact, Mark Duttweiler (MS '96, PhD '01) showed that when one of these vortices impacts the propeller's supporting strut, it reappears on the other side, as though it went right through the strut. That's because of the persistence of vorticity, which is not a Dali painting. The whirling flow pattern is not destroyed by the strut, so the vortex reforms on the strut's far side, which then cavitates also. That's how stable vortices are.



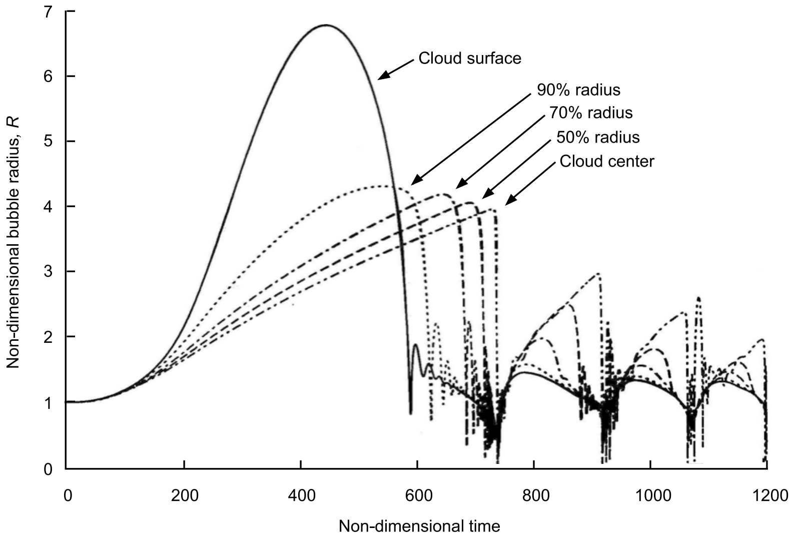
A cloud of bubbles has three important parameters—its radius, *A*; the average radius of its bubbles, *R*; and the proportion of the cloud's volume taken up by the bubbles, α.

We'll Look at Clouds from Both Sides Now

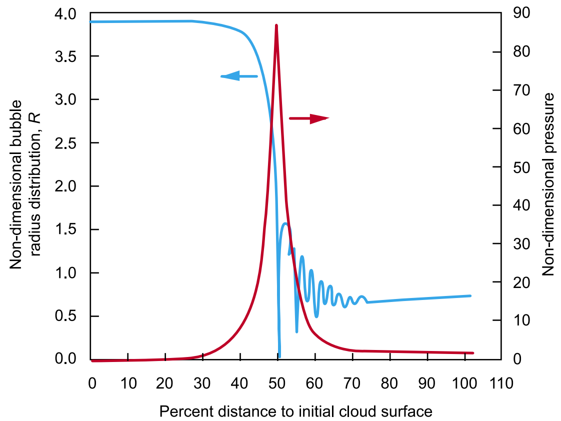
I mentioned clouds of bubbles earlier, and we're now going to turn our attention to them. A colleague of mine, Göran Bark at the Chalmers University of Technology in Göteborg, Sweden, painted a set of propeller blades red. The paint wore away where the damage was greatest, and these regions coincided with where the clouds of bubbles were collapsing. In our lab, grad student Douglas Hart (PhD '93) built an experiment where a hydrofoil's angle of attack oscillated—like driving down the freeway with your hand out the window, and rotating your wrist to vary the wind resistance—to periodically form a cavitation cloud that would then collapse. Beth McKenney (PhD '95), Garrett Reisman (MS '92, PhD '97), and Mark used this setup to try to understand the relationship between the noise generated by the flow—and believe me, it was like a machine gun going off in the lab—and the clouds of bubbles that were formed.

Luca D'Agostino (MS '81, PhD '87) had earlier discovered what's special about clouds of bubbles as opposed to single bubbles. For simplicity's sake, let's think about a spherical cloud. It has three important characteristics: the radius of the cloud as a whole, A; the average radius of the bubbles inside the cloud, R; and the volume fraction of the gas in the cloud, which I'll call α. And there's a special parameter Luca discovered, β, which we call the cloud-interaction parameter for reasons that will be clear shortly. Beta is α_0 times A_0^2 over R_0^2. (The subscript zero means the initial value, because α, A, and R all change as the cloud evolves.) Beta's value is hard to predict, because α is small but A is very much larger than R, but calculating β is of keen interest, because its size determines whether the clouds will be destructive or not.

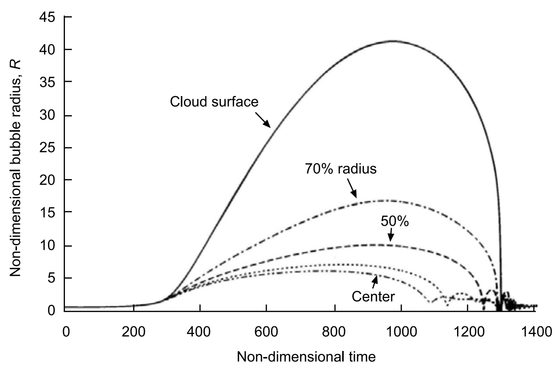
First, let me show you what happens when β is greater than one, which happens when the bubbles are dense enough or the cloud is large enough.



Above: How bubbles grow and collapse at various depths within a cloud that has a β greater than one. The bubbles on the outside collapse first, creating an imploding pressure wave.



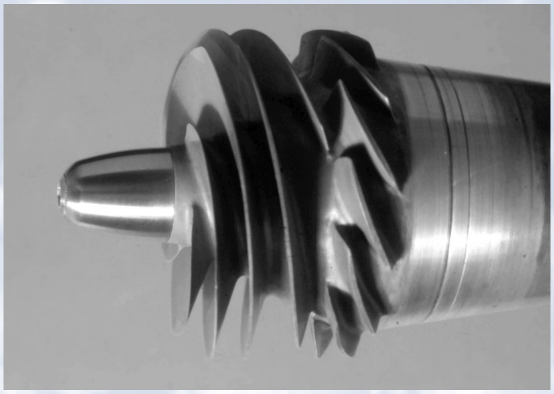
The blue plot shows the bubbles' size (again, for β greater than one) versus their distance from the cloud center at the midpoint of the collapse process. The red curve is the pressure spike associated with the collapse.



When β is small, the collapse begins at the center and moves outward, causing the pressure front to dissipate.

Above left is a plot of the average radius of the bubbles in various parts of the cloud, from the center all the way out to the surface, against time. The cloud goes through the low-pressure region between time 0 and time 400, and the bubbles everywhere in the cloud grow, but the ones on the surface grow fastest. It's as though the growth of the bubbles inside the cloud is blocked by the growth of the bubbles on the surface. The bubbles on the surface also collapse first, and that collapse front, the collapse process, moves inward toward the cloud's center. That's the key—the collapse moves in from the edges. And associated with that is a huge pressure spike, or shock wave, which Yi-Chun Wang (PhD '96) discovered when he did the first nonlinear analyses of these clouds. So this collapse front becomes a shock wave as it moves in. Moreover, because of the geometry of its inward focus, the magnitude of the shock grows at a great rate so that when that shock wave gets to the center of the cloud, it's a *huge* pressure pulse—a surge of 10 atmospheres is not uncommon. This is why a collapsing cloud packs such a wallop—the focusing shock wave generates much more noise, much more damage, than would happen with single bubbles, and having a β greater than one is the culprit.

If β is less than one, which could happen if the bubble density is small, the surface bubbles again grow faster. But now the collapse begins in the center, instead of on the surface, and all that happens is that the collapse front moves outward in a weakening wave of little or no consequence.



A model of the low-pressure liquid-oxygen pump in the Space Shuttle's main engine.

Rocket Science

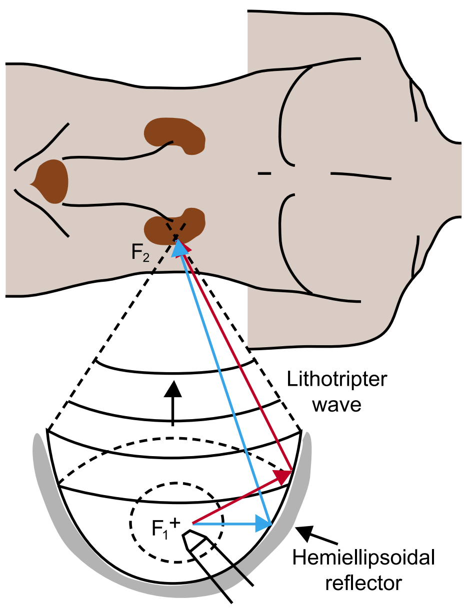
This kind of mathematical analysis has allowed us to analyze complex cavitating flows in devices like the liquid-oxygen pumps in the Space Shuttle's main engines. (For reasons I won't go into, the liquid-hydrogen fuel has very different properties, and the cavitation in it is much more benign.) But the liquid-oxygen pumps cavitate like crazy, because NASA really pushed the design envelope. The high-pressure turbopump runs at 40,000 revolutions per minute, which is almost fast enough to tear itself apart by centrifugal force. The pump is only about eight inches in diameter, and it has to spin that fast in order to move the enormous amount of liquid oxygen the engine consumes. To get the same flow rates at a more reasonable speed would require a pump tens of feet in diameter, and the launch-weight penalty would be prohibitive. Even the more sedate low-pressure transfer pumps, which are a foot across, run at 8,000 rpm. This leads to several problems.

The first and most basic one is a phenomenon called the "pogo instability." A liquid-fueled rocket sitting on the launch pad is essentially two tall, thin tanks of fluid stacked one on top of the other. Now, this structure is very flexible, and after liftoff it may begin to oscillate in a longitudinal mode, a phenomenon first analyzed by Sheldon Rubin (BS '53, MS '54, PhD '56). This causes fluctuations in the pressures going through the pumps, which in turn causes the rocket's thrust to vary, which feeds back into the tanks and makes the oscillations worse. This has been a problem since the early days of the space age, and the first stages of all large rockets have been modified to eliminate it. In 1962, before the role of pump cavitation was recognized, a Titan II rocket had to be destroyed in flight after pogo oscillations of 10 g, or 10 times the force of gravity, led to premature shutdown of the first-stage engines. The second stage of the Saturn V rocket also suffered from pogo instabilities. On Apollo XIII, 33-g oscillations caused one of the five engines in the second stage to shut down prematurely, but the liftoff continued successfully. So when the Shuttle was being designed in the mid-'70s, Allan Acosta (BS '45, MS '49, PhD '52), the Hayman Professor of Mechanical Engineering, Emeritus, and I calculated the dynamic transfer function for the low-pressure liquid-oxygen pumps—that is, we figured out how fluctuations in the flow going into each pump affected fluctuations in the flow coming out. This had never been done before—in fact, the concept of a transfer function for pumps didn't even exist; I borrowed it from electrical engineering. We then verified our calculations experimentally, in an apparatus we built here in the basement of Thomas Lab. NASA used our findings to design an accumulator, a sort of gas-filled reservoir that absorbs the fluctuations, and I am happy to say that the Shuttle has never yet suffered from serious pogo instability.

We revisited the problem several years later, when NASA asked us for help again because the Space Shuttle's main-engine turbopumps weren't operating as expected. Every pump has a critical speed, above which it is whirling so fast that it becomes unstable, like an unbalanced load in the spin cycle of your washing machine. Because the critical speeds on these pumps turned out to be significantly lower than predicted, the engines weren't capable of the designed amount of thrust. We were able to go back and do a more detailed analysis, and discovered that forces within the pump caused by the flow itself affected the critical speed. Once the system's detailed behavior was understood, the engineers found a fix for it. And again, we verified our calculations experimentally. We decommissioned that facility several years ago, since we weren't using it any more, and NASA came in, dismantled it bolt by bolt, and reassembled it at the Marshall Space Flight Center in Huntsville, Alabama, where it is still in use today.

Teeth and Kidneys and Eyes, Oh My!

Now, cavitation and its shock waves aren't always a bad thing. The energy from collapsing bubbles is used to very beneficial effect in a number of medical applications. If you've ever had your teeth cleaned by ultrasound, with that little vibrating probe used by some dental hygienists, you probably think it's the vibration that cleans your teeth. That would be wrong. There's a jet of water surrounding the probe, and it's the collapse of the cavitation bubbles caused by the probe's vibration that cleans your teeth. That's true of any kind of ultrasonic cleaner.

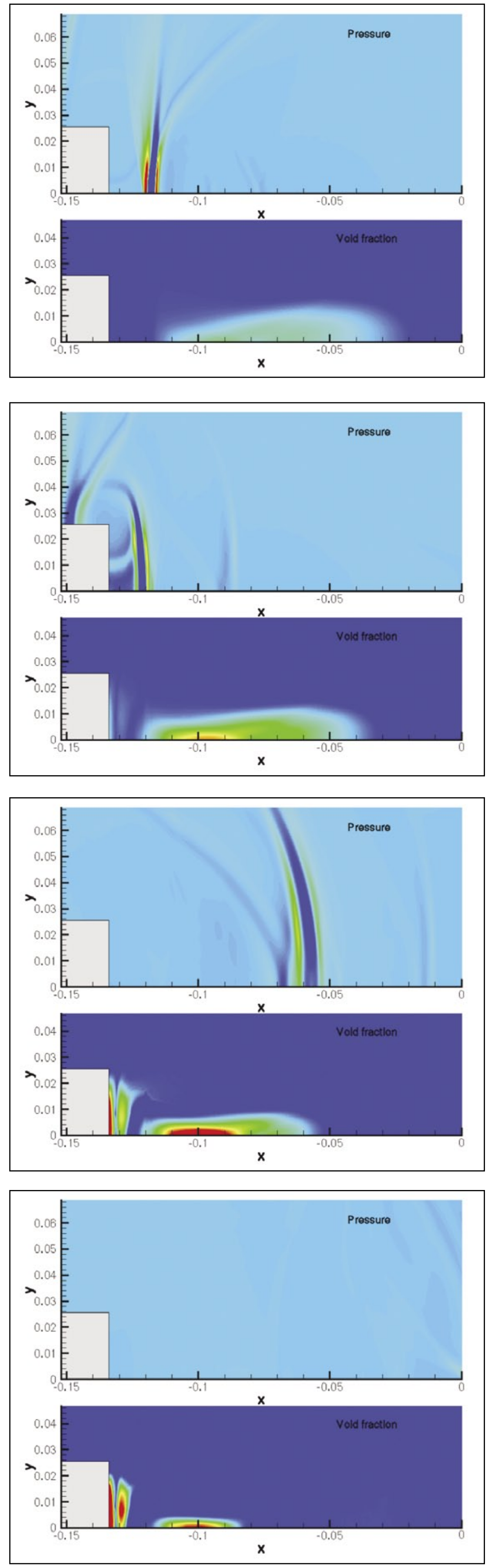


Above: Lithotripsy is a procedure for destroying kidney stones and gallstones inside the body without having to remove them surgically. A water bath conducts a shock wave generated at F_1 and focused by a hemiellipsoidal reflector onto the patient's kidney stone at F_2.

Far right: This computer simulation of a lithotripsy pressure wave and its associated bubble clouds—one at the kidney stone, and one in the surrounding tissue—was part of Michel Tanguay's 2004 PhD thesis work under Tim Colonius.

Cavitation is also the active ingredient in lithotripsy, which is a procedure for reducing kidney stones and gallstones inside the body without any surgical intrusion. The patient lies in a tub full of water, which conducts the shock wave, and a big hemiellipsoidal reflector in the tub focuses a shock wave generated at F_1 onto the patient's kidney stone at F_2. Very large pressure oscillations are generated at F_2 that cause cavitation on the surface of the kidney stone, breaking it up into pieces that can be passed out of the body. But it's very difficult to focus shock waves down to a single point, so some of the bubbles don't form quite on the surface. Guess what happens when they collapse—they damage the surrounding tissue.

It would help to be able to predict this behavior, which is a very hard thing to do, but my colleague, Professor of Mechanical Engineering Tim Colonius, and his students have developed a very nice mathematical model. At right is a set of pictures from a simulation of a shock wave hitting a kidney stone, shown as a gray rectangle. The top panels show pressure (red being high), and the panels below them show the void fraction, which is the density of bubbles created. In these panels red means lots of bubbles. So as the red high-pressure wave crashes into the stone, it creates a red zone of high bubble density on the face of the stone. That's good. But notice that at the same time, another zone of high bubble density forms some distance away, which obviously is not good. Just being able to compute the overall flow has been quite an achievement, because of the many different scales of length and time involved, and we're still decades away from being able to model what goes



on around every individual bubble. Still, these techniques are very helpful in trying to tailor the lithotripter to avoid creating regions of collateral damage.

An alternative way of doing lithotripsy would be to use ultrasound, which can be focused much more tightly. My friend Yoichiro Matsumoto at the University of Tokyo, who has visited Caltech many times and with whom I have worked on many projects, has devised an interesting strategy. He begins by bombarding the stone with fairly weak ultrasound waves, which make a cloud of large bubbles, and then he hits it with a large-amplitude wave, which collapses the bubbles. This would not be so easy to do with shock-wave lithotripsy. And again, the effect of the collapse of the cloud is much greater than the effect of any one single bubble, or of all of them separately. There are still some challenges to be resolved before ultrasound lithotripsy moves out of the lab, but it's an exciting idea.

Cavitation has also led to a better way of doing cataract surgery, which is one of the commonest, most necessary surgical procedures done in the world. Cataracts occur when the lens in your eye turns cloudy with age due to a buildup of opaque proteins in it, and eventually lead to blindness. An eye doctor named Charles Kellman invented a technique called phacoemulsification, in which a small, hollow probe—based on that vibrating dental probe—is inserted into the eye. The probe's tip vibrates, destroying the old, opaque lens, which gets vacuumed away. The new lens is inserted through the same tiny incision that was made to admit the probe, so there's minimal trauma to the eye. Recently, another doctor named Aziz Anis added a clever, literally revolutionary, twist in that he rotates the probe to create a vortex that confines the bubbles to the center of the working surface. This reduces the collateral damage that might be caused by bubbles forming off to the side of the probe.

So the thought I want to leave you with is that cavitation offers a way of focusing energy, noninvasively, from afar. The energies involved can be quite staggeringly large—when that little bit of air inside the bubble gets compressed, it can heat up enough to produce flashes of light, a phenomenon known as sonoluminescence. Experiments by Kenneth Suslick (BS '74) at the University of Illinois at Urbana-Champaign have shown that under some conditions transient temperatures of around 15,000°C can be achieved, more than twice as hot as the surface of the sun. That's the sort of energy you can use to break chemical bonds and do molecular engineering. For example, my colleague Michael Hoffmann, the Irvine Professor of Environmental Science, has been exploring the use of ultrasound and the cavitation it generates to treat polluted water. I could go on, but we're just beginning to understand the positive uses of cavitation, and it's clear that many more lie ahead. □

Although it's generally considered good to immerse oneself in one's subject, this piece of field work on the lower Kern River was a bit too intimate. Brennen was wearing a blue cap and seated in the rear before entering the drink.

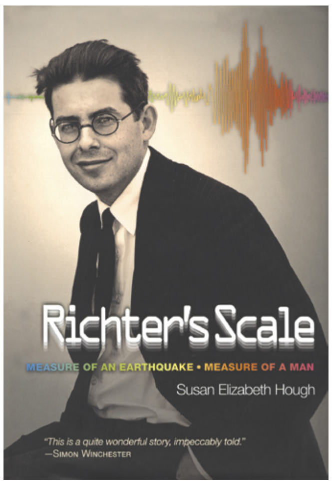
Chris Brennen is a Caltech institution. The Hayman Professor of Mechanical Engineering, he came to Caltech as a research fellow on Fulbright scholarship in 1969, and has been here ever since. He has variously been the Master of Student Houses, Dean of Students, Executive Officer for Mechanical Engineering, and Vice President for Student Affairs. Born in Belfast, Northern Ireland, he earned his BA, MA, and DPhil in engineering sciences at Oxford's Balliol College. His professional accolades include the American Society of Mechanical Engineers Fluids Engineering Award, NASA's New Technology Award, and the Feynman Prize, Caltech's highest teaching honor.

An avid outdoorsman, he received the American Canyoneering Society's John Wesley Powell Award for his contributions to the sport, including his online guide, Adventure Hikes and Canyoneering in the San Gabriels.

This article was adapted by Douglas Smith from a Watson lecture given November 6, 2006.

PICTURE CREDITS: 30—Bob Paz; 40—Doug Cummings; 33, 34, 35, 39—Chris Brennen

Magnitude 10.0



Richter's Scale: Measure of an Earthquake, Measure of a Man
336 pages
Princeton University Press, 2007
$27.95

It's fair to say that the name Charles Richter (PhD '28) rings bells not only in earthquake country, but across the globe. *Richter's Scale: Measure of an Earthquake, Measure of a Man*, by U.S. Geological Survey seismologist Susan Hough, explores how this came to be. In so doing, she describes not only why and how Richter devised the earthquake magnitude scale that bears his name, but also the personal anguish that may have made such an undertaking possible.

According to Hough's book, Richter was an accidental seismologist, meaning that he was an intelligent but aimless guy who happened to have found work in the newly established Pasadena Seismological Laboratory after he finished his PhD in physics at Caltech. In the Spartan concrete building that housed the lab until it moved to the main campus in 1974, Richter managed to harness the mental demons that drove him, years before, to quit his first attempt at a PhD at Stanford University a year after he had begun.

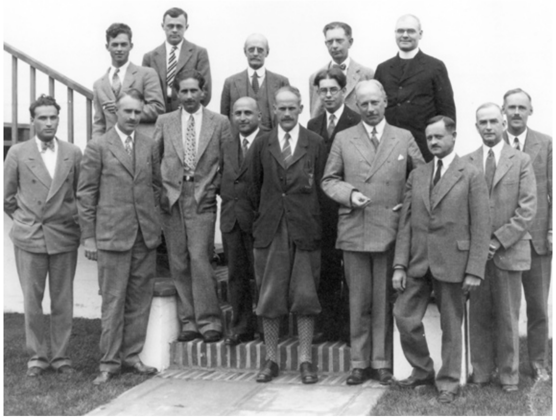
The nature of Richter's demons—and their manifestation in poetical outpourings—constitutes the first four and final few chapters of the book. "Adolescent confusion and near-nervous breakdown, 1921," he wrote in a journal he kept throughout his life, and soon after, ". . . my mother had the good sense to refer me to a psychiatrist." Hough speculates that Richter was plagued by Asperger's syndrome, a form of autism, though there was no diagnosis for this in his lifetime. He was sensitive to light and sound and sought sanctuary in the mountains. But the problems that sometimes unraveled him also made him great. "The laboratory routine, which involves a great deal of measurement, filing, and tabulation, is either my lifeline or my chief handicap, I hardly know which," he wrote in 1949.

It is Richter's scientific contribution and the context in which he devised the Richter magnitude scale that makes his story so incredible. When the 1906 San Francisco quake struck, there was no measure of how it compared to any past or potential future temblor. This disaster motivated the first mapping of the full extent of the San Andreas fault, as well as the founding of seismological laboratories in both northern and southern California. First on the scene in southern California was Harry Wood, who had a background in geology but lacked the PhD necessary to easily gain a position in UC Berkeley's earthquake lab. He recruited physicist cum lab rat Richter and the geologically reknowned Hugo Benioff. Then he coinvented a new seismometer—one was installed at the new lab and another at Mount Wilson Observatory—that Richter used to construct his scale.

Richter began by measuring the amplitude, or height, of seismic waves in southern California as recorded by seismograms—those wiggles that mark the passage of waves generated when land moves along a fault. But amplitudes differ depending on how far away the waves' source is, so he had to apply a distance correction. Then he realized that he had to restrict the scale's numbers to some manageable realm, like one to 10. Richter borrowed the notion from astronomers, who had classified stars by their brightness since time immemorial, but promptly turned their scale on its head—the brightest stars are first magnitude, but small quakes have small magnitudes on Richter's scale. He did this in part so that his scale would have no upper bound. The popular notion that magnitude 10 is the biggest possible quake is wrong—Richter noted that extreme shaking was rare, and 10 might be a natural upper limit, but he never excluded the possibility of something much greater.

Which brings us to the

The Kresge Building, home to Caltech's Seismological Laboratory from 1927 to 1974, when it moved to campus. The back and attached tunnels were carved into granite bedrock, providing a quiet setting for seismometers.

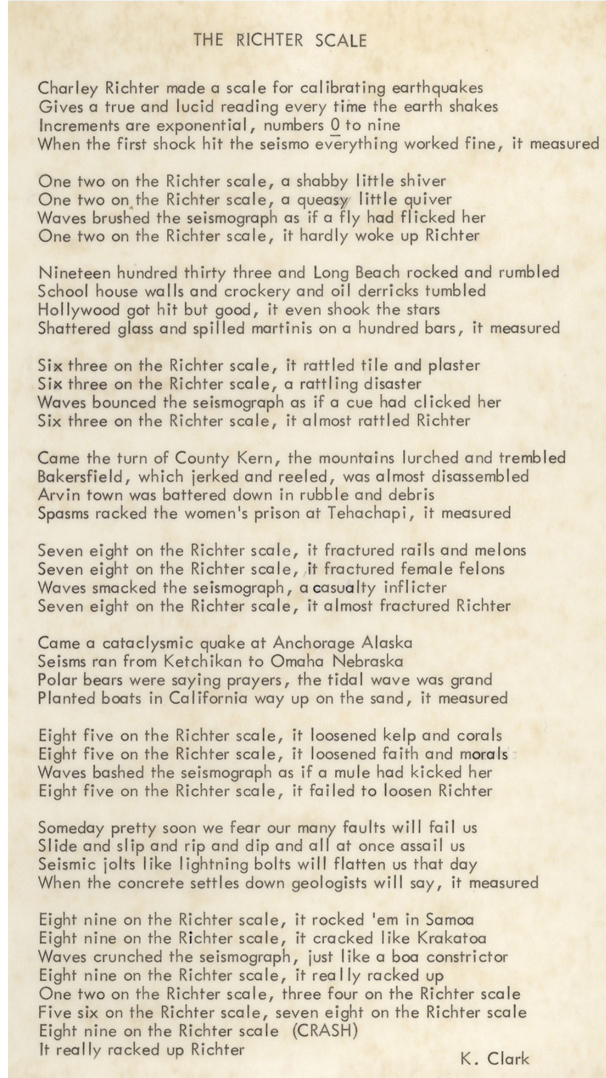


confusion surrounding how multiple, conflicting reports of earthquake magnitudes find their way into the press. For starters, the closer you are to the earthquake's source, the stronger the shaking, but damage is greatest where buildings and people are clustered, and epicenter and population centers don't always coincide. An earthquake *intensity* scale has been around since long before Richter and is still used to report damage. Richter's scale really quantified *magnitude* for the first time, but it still had one major flaw, which has since been corrected—because of the limitations of early seismometers, it was inaccurate for earthquakes larger than around a six on his scale.

It was Richter's colleague Beno Gutenberg who first suggested the scale be extended for worldwide application, and herein lies a great dilemma in Hough's book: Why did the term *Richter scale* stick, when it excluded other scientists who helped Richter develop it? Gutenberg was the one who suggested it would be handy to plot amplitudes logarithmically, meaning that the peak height of a magnitude 5 earthquake is 10 times higher than that of a magnitude 4. (The energy released is 30 times as great, but read the book for more insight on that point.) Indeed, in a 1979 interview Richter acknowledged the term *Richter scale* "somewhat underrates Gutenberg's part in developing it for further use." It was Wood who suggested the term magnitude. And Richter's scale relied on the distance corrections of Japanese seismologist K. Wadati. Hough advances several thoughts on why the homey moniker "Richter scale" is hard to shake. She also points out that seismologists have greatly refined the original formulation of the Richter scale, and use amongst themselves the more universally accurate moment magnitude scale.

Still, Richter's name remains burned into the public consciousness of earthquakes. He became the media's go-to guy of the day, despite his sometimes anticongenial air. During one of many radio appearances, a caller confessed that she was afraid of earthquakes and asked Richter's advice. According to colleague Tom Heaton, Richter replied without hesitation, "Why don't you get the hell out of the state?"

One drawback of Hough's otherwise delightful book is its lack of maps. Keep an atlas on hand as you read, because references to various earthquake regions of the world abound. □—*EN*



THE RICHTER SCALE

Charley Richter made a scale for calibrating earthquakes
Gives a true and lucid reading every time the earth shakes
Increments are exponential, numbers 0 to nine
When the first shock hit the seismo everything worked fine, it measured

One two on the Richter scale, a shabby little shiver
One two on the Richter scale, a queasy little quiver
Waves brushed the seismograph as if a fly had flicked her
One two on the Richter scale, it hardly woke up Richter

Nineteen hundred thirty three and Long Beach rocked and rumbled
School house walls and crockery and oil derricks tumbled
Hollywood got hit but good, it even shook the stars
Shattered glass and spilled martinis on a hundred bars, it measured

Six three on the Richter scale, it rattled tile and plaster
Six three on the Richter scale, a rattling disaster
Waves bounced the seismograph as if a cue had clicked her
Six three on the Richter scale, it almost rattled Richter

Came the turn of County Kern, the mountains lurched and trembled
Bakersfield, which jerked and reeled, was almost disassembled
Arvin town was battered down in rubble and debris
Spasms racked the women's prison at Tehachapi, it measured

Seven eight on the Richter scale, it fractured rails and melons
Seven eight on the Richter scale, it fractured female felons
Waves smacked the seismograph, a casualty inflicter
Seven eight on the Richter scale, it almost fractured Richter

Came a cataclysmic quake at Anchorage Alaska
Seisms ran from Ketchikan to Omaha Nebraska
Polar bears were saying prayers, the tidal wave was grand
Planted boats in California way up on the sand, it measured

Eight five on the Richter scale, it loosened kelp and corals
Eight five on the Richter scale, it loosened faith and morals
Waves bashed the seismograph as if a mule had kicked her
Eight five on the Richter scale, it failed to loosen Richter

Someday pretty soon we fear our many faults will fail us
Slide and slip and rip and dip and all at once assail us
Seismic jolts like lightning bolts will flatten us that day
When the concrete settles down geologists will say, it measured

Eight nine on the Richter scale, it rocked 'em in Samoa
Eight nine on the Richter scale, it cracked like Krakatoa
Waves crunched the seismograph, just like a boa constrictor
Eight nine on the Richter scale, it really racked up
One two on the Richter scale, three four on the Richter scale
Five six on the Richter scale, seven eight on the Richter scale
Eight nine on the Richter scale (CRASH)
It really racked up Richter

K. Clark

Top left: Some notable attendees of a 1929 seismology workshop in Pasadena were (lower row) Hugo Benioff (third from left), Beno Gutenberg (fourth from left), Charles Richter (fifth from right), Harry Wood (third from right), and John Buwalda (far right). Top: Lyrics to "The Richter Scale," written by Kent Clark, professor of literature, emeritus, and sung at Richter's retirement party in 1970. Bottom: Richter and the seismometer installed in the living room of his home. He could estimate an earthquake's magnitude and location from a handful of seismograms, and was thus on call at all hours.

Honors and Awards

Alexei Borodin, professor of mathematics, has been invited to give the 2006–07 Porter Lectures at Rice University. He will give five lectures over two weeks on topics of his own choosing, with the first intended for a general audience and the remaining four for mathematicians.

Jean-Lou Chameau, president of Caltech and professor of civil engineering and environmental science and engineering, has been selected to receive the Prix Nessim Habif from the Société des Ingénieurs Arts et Métiers. The honor brings with it a prize of 3,000 euros. Chameau also has been unanimously elected to the board of directors of the Los Angeles World Affairs Council, which promotes greater understanding of global issues by providing an open forum in Los Angeles for influential figures in world affairs.

Roc Cutri, member of the professional staff and deputy executive director of the Infrared Processing and Analysis Center (IPAC), has been chosen by the National Academy of Sciences to be a corecipient of the James Craig Watson Medal, which includes a prize of $25,000 plus $25,000 to support the recipient's research. He and Michael Skrutskie, an astronomy professor at the University of Virginia, have been honored "for their monumental work in developing and completing the Two Micron All-Sky Survey, thus enabling a thrilling variety of explorations in astronomy and astrophysics."

Roy Gould, (BS '49, PhD '56) Ramo Professor of Engineering, Emeritus, and **Brian Stoltz**, associate professor of chemistry, have been elected fellows of the American Association for the Advancement of Science in the Section on Physics and the Section on Chemistry, respectively.

John Grotzinger, the Jones Professor of Geology, has been selected to receive the Charles Doolittle Walcott Medal in recognition of his "insightful elucidation of ancient carbonates and the stromatolites they contain, and for meticulous field research that has established the timing of early animal evolution." Awarded by the National Academy of Sciences every five years, the honor includes a prize of $10,000.

Sergei Gukov, associate professor of theoretical physics and mathematics, has been selected to receive a Sloan Research Fellowship from the Alfred P. Sloan Foundation. Established in 1955, the fellowships "are intended to enhance the careers of the very best young faculty members in specified fields of science."

Wilfred D. Iwan (BS '57, PhD '61), professor of applied mechanics, emeritus, and director of the Earthquake Engineering Research Lab, has been chosen to receive the George W. Housner Medal, the most prestigious award bestowed by the Earthquake Engineering Research Institute. Housner (MS '34, PhD '41), the Braun Professor of Engineering, Emeritus, is often called "the father of earthquake engineering." The award in his name recognizes "extraordinary and lasting contributions to public earthquake safety."

Marc Kamionkowski, Robinson Professor of Theoretical Physics and Astrophysics, has been named a recipient of the U.S. Department of Energy's Ernest Orlando Lawrence Award. The honor recognizes his work on "how precise observations of the cosmic microwave background radiation can lead to deeper understanding of the origin and evolution of the universe." The award consists of a gold medal, a citation, and an honorarium of $50,000.

Henry Lester, Bren Professor of Biology, has received the Kenneth S. Cole Award from the Membrane Biophysics Subgroup of the Biophysical Society. The award is given annually to an investigator "who has made a substantial contribution to knowledge of membranes."

Olexei Motrunich, associate professor of theoretical physics, has been selected to receive a Sloan Research Fellowship from the Alfred P. Sloan Foundation. Established in 1955, the fellowships "are intended to enhance the careers of the very best young faculty members in specified fields of science." □

Engineering & Science

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