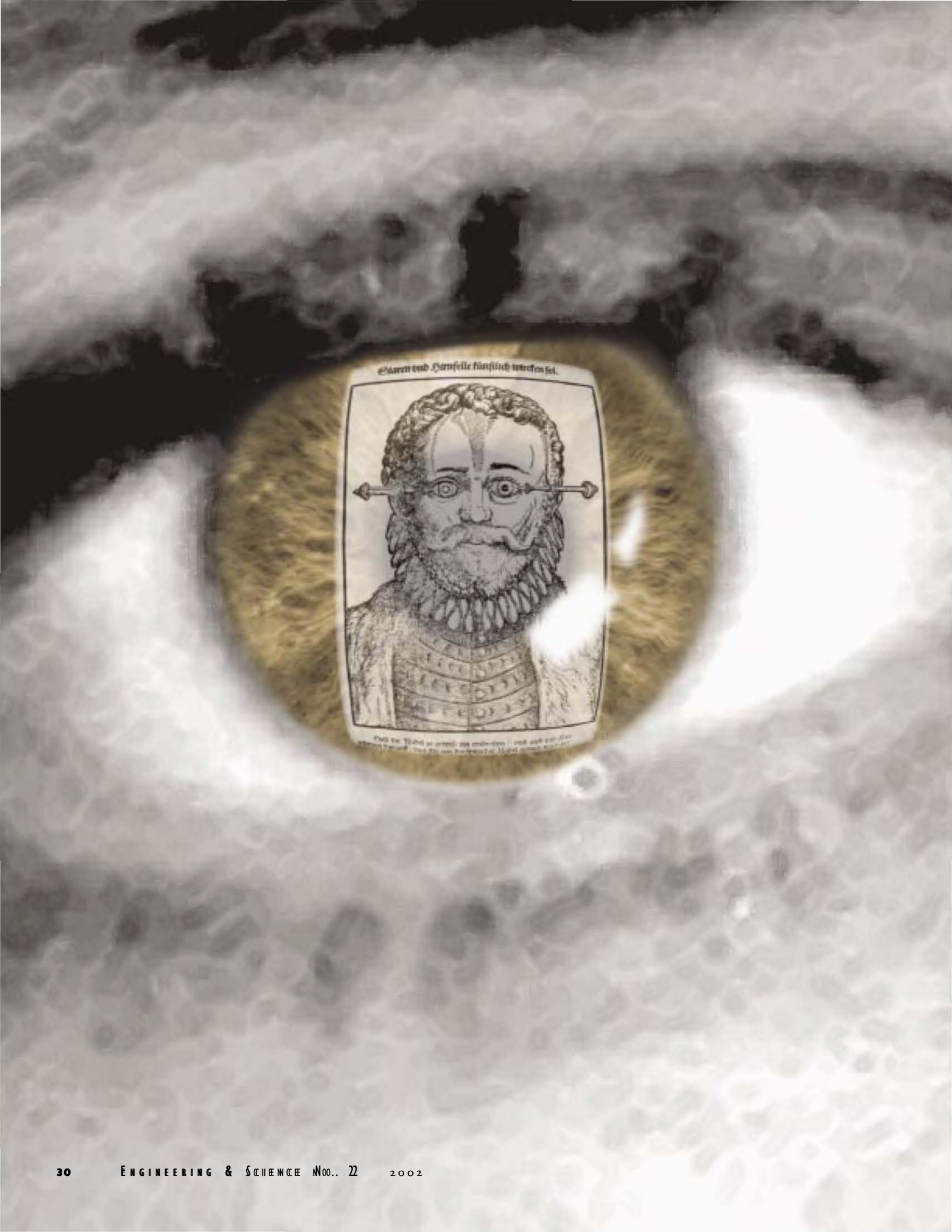


Squishy Is Good

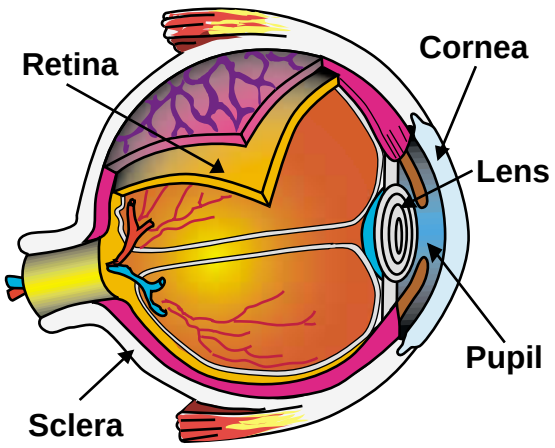
by Douglas L. Smith

Titanium implants are all very well for bones, but soft and pliable is the name of the game for tissues. Professor of Chemical Engineering Julia Kornfield works with stretchy, flexible molecules called polymers. Polymers are long chains of short, simple units, called monomers; plastics are polymers, as are proteins. Kornfield studies how these molecules bend, flow, melt, solidify, and sometimes dissolve, and how you exploit these properties to create everything from squeeze bottles to seat belts. These days, Kornfield, who got bitten by the biotechnology bug as an undergrad, is spending more and more of her time experimenting with gloppy goos for internal use.

One such use addresses a problem that in time comes to most of us—cataracts. So called because it was believed that cloudy material was flowing down through your eyes like a waterfall, they are in fact caused by your eye's lenses losing transparency with age. This can swaddle the outside world in perpetual fog, and in extreme cases leads to blindness. "Most people who are 60 years old have incipient cataracts," says Kornfield. "And by the age of 75, you're a very lucky person indeed if they're not bothering you." The standard treatment calls for replacing the cloudy lens with an artificial one. These lenses are usually made of flexible plastic, which can be rolled up and inserted into the eye through an incision as small as two millimeters—about the diameter of a cooked rice grain. "This is, in fact, the most common surgical procedure for individuals 65 and over. Three million operations a year are performed in the United States; 13 million worldwide."

But it's not an ideal solution: as the eye heals, the accumulating scar tissue changes the position and orientation of the new lens, and even the shape of the eye itself. So a lens that was perfect beforehand generally won't be quite right in the end. There's no way to predict exactly how the scar tissue will grow, and the lenses aren't adjustable, so about one-half of all cataract patients wind up needing glasses or contact lenses. Of course, wearing glasses is infinitely preferable to not being able to see at all, but eye surgeons would love to

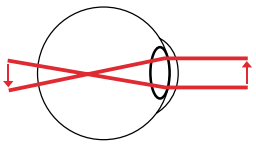
Left: The first known treatment for cataracts was a poke in the eye with a sharp stick. Called "couching," it pushed the cloudy lens aside so that patients could at least see form and color, and was described by the Hindu surgeon Susruta circa the fifth century B.C. Things had not progressed much by 1583, when Georg Bartisch wrote *Augendienst*, from which this woodcut is taken. (The text below the drawing admonishes the surgeon to be careful while screwing the needle into the eye!) Benito Daza De Valdes (1591–1634), an official of the Spanish Inquisition, proposed replacing the lens with an implant—a notion he presumably came up with in his spare time. But these implants, usually of glass, were dismal failures because the body rejected them. During World War II, British ophthalmologist Harold Ridley noticed that airmen showed no adverse reactions to the shards of Plexiglas from bullet-riddled canopies that sometimes lodged in their eyes. Ridley performed the first successful implant, of Plexiglas, in 1949.

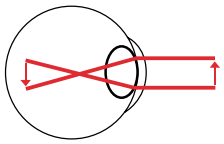


Right: The anatomy of your eye. The sclera is the white part of the eyeball; the cornea, the transparent part where the light enters. The light-sensitive cells live in the retina.

have every patient come out of the operation seeing clearly.

Daniel Schwartz, associate professor of ophthalmology at the University of California, San Francisco, wanted to create a lens whose prescription could be adjusted precisely, without touching the eye in any way, once everything had healed completely and the patient's vision had stabilized. Such a lens would have to be adjustable for nearsightedness, farsightedness, and astigmatism; the adjustment would have to remain stable for years afterward; and, of course, the lens would have to be biocompatible. So Kornfield's phone rang one day, and there was Schwartz, looking for advice. Kornfield, in turn, called Robert Grubbs, the Atkins Professor of Chemistry, whose specialty is making custom-tailored polymers with unusual properties, and who had even ventured into the world of cataract-replacement lenses back in the '80s. Schwartz flew down, and the threesome had a brainstorming session.

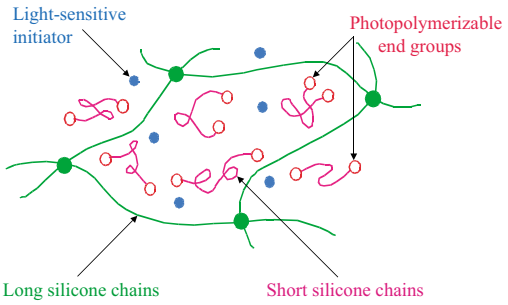




Above: If a lens is too flat, it won't bend the light rays enough to focus them on the retina. Below: But if the lens is too steeply curved, it will focus short of the retina.

There are basically two ways to change a lens's power. One is to change its shape. The more it bulges in the central region, the shorter its focal length. So if an eye is farsighted—that is, the lens is focusing behind the retina—and you thicken the lens up just a smidgen, you can bring the focal plane forward onto the retina; conversely, in a nearsighted eye, you can flatten out the lens to push the focal plane back to the retina. The other option is to change the lens's refractive index. If you have two lenses of the same thickness and radius of curvature, the one made of the higher-refractive-index material will be more powerful. Recalls Kornfield, "Dan said, 'You know, lasers are very frequently used in the eye; eye surgeons feel very comfortable with them.' Bob and I were aware of polymers that had a refractive index you could increase with light—that's how they write holograms on credit cards—so together we envisioned a laser-adjustable lens" made of such a polymer.

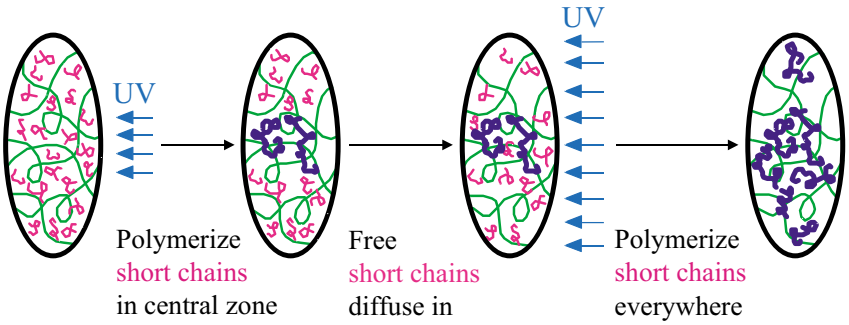
The chemists' first notion was to make the lens from a glassy polymer such as polymethyl methacrylate, better known as Plexiglas, whose chains of 100 to 200 monomers would be connected to one another to form a space-filling, three-dimensional mesh. Swimming through the mesh like minnows through a tuna net would be smaller molecules of only 10 or 20 monomers—too big to be water-soluble and escape into the eye, but small enough to be relatively nimble. The free ends of these molecules would be designed to link up when exposed to strong ultraviolet light, a process called photopolymerization. And a clever choice of monomer would give the short molecules a higher refractive index than the big ones that make up the net. After the eye had thoroughly healed, explains Kornfield, "if we were to shine light at the middle of the lens, all the short guys there would hold hands. Then the free chains on the outskirts would say, 'Hey, there are no short



chains over there!' and they'd diffuse in, raising the refractive index" and correcting residual farsightedness. Alternatively, shining the laser around the lens's periphery would suck the free chains out of the central region, decreasing the refractive index there and fixing nearsighted folk. And astigmatism, in which the lens focuses asymmetrically, could be dealt with by shining the laser along the appropriate meridian. Then, after a thorough vision test to confirm that the lens's prescription was exactly right, flooding the entire lens with UV light would make all the remaining free chains hold hands, locking in the adjustment.

But there's a catch—glassy polymers tend to be very rigid and slow-moving, which is why Plexiglas is stiff. This is no problem if you're writing a hologram on a credit-card sticker, because the holographic elements are less than a millionth of a meter wide. You can create a hologram in a few minutes, but it would take two years for the short chains to permeate across the central three to four millimeters of a lens implant made of the same material. Instead, the chains need to move about as fast as water diffuses through Jell-O—not a blinding speed, exactly, but fast enough to swim into place overnight. (A rigid Plexiglas implant would also require an incision the size of your own lens—about seven millimeters in diameter—that would take much longer to heal.)

"So we asked Dan, 'What polymers are approved for use in the eye?' And he said, "Well, polymethyl methacrylate, silicones, certain acrylics…' and my eyes just lit up when he said silicones. Silicones are some of wiggliest, jiggliest, fastest-moving molecules out there—they just might diffuse fast enough for this to work!" Silicones are made up of alternating atoms of silicon and oxygen, with various side chains dangling from the silicon atoms like charms on a bracelet. Silicones are also old friends to chemists, finding use in everything from lubricants and greases to bathtub caulk, baby-bottle nipples, Silly Putty, and—surprise!—



Left: The adjustable lens' ingredients. The light-sensitive initiator is a separate molecule that triggers the short chains' end groups to link up. Above: The plan for correcting a farsighted lens.

the current crop of flexible lens implants approved for cataract surgery. "So that's how far we got in the brainstorming session. And on the spot, Dan said, 'You've got money for a postdoc!'" It took the postdoc, Jagdish Jethmalani, two years to work through the details, but he came up with a polymer that he calculated could give 98 percent of cataract patients 20/20 vision. "So then Dan said, 'You've got money for a second postdoc! Let's get an optics guy in here and start making some lenses!'" So Kornfield and Grubbs recruited Christian Sandstedt to build a double-convex mold out of concave glass lenses sandwiched together, and they were off to the races.

Making the lenses was relatively easy, but getting them out of the mold wasn't. The silicone kept sticking to the glass, and the lenses refused to peel free once the polymer set. Kornfield was full of advisorly suggestions. "I said, 'In polymer processing, people coat the mold with Teflon spray. Why don't you try that?' They tried every idea I had. None of them worked. So finally one day, Jagdish was patiently waiting for his sister at a beauty parlor. He's the kind of guy who soaks up information from all kinds of things, and leafing through a copy of *Redbook* he saw this new nail polish called Teflon Tough. The ad raved about how smooth it was, and about its tough surface of *real Teflon*. So he ordered some, painted it on the mold, and we've been sailing ever since. We've never found anything that works better."

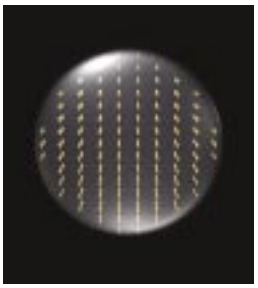
But the serendipity didn't end there. The very first batch of lenses to be treated with ultraviolet light became four times more powerful than they should have. Clearly, the refractive index wasn't the only thing that was changing. After some head-scratching, the chemists realized that making the short chains long enough to stay in the lens had had the unintended consequence of keeping them stretchy after the laser light linked them together. As the free chains shouldered their way into the laser-zapped area, the linked chains had enough "give" to move aside, causing the lens to bulge. (Previously reported photopolymers containing dispersed monomers had actually shrunk slightly.) The effect of the shape change far outweighed the refractive-index change, and is now the basis of the lens design.

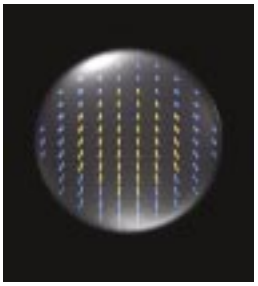
The postdocs assessed the lenses' optical quality by photographing a test pattern through them. If you look at a set of very thin and precisely ruled parallel lines, their uniformity and sharpness of focus will tell you how good the lens is, and their degree of magnification allows you to calculate the lens's power. If the power isn't uniform, the lines will be thicker in some spots than in others, and if the surface isn't perfectly smooth the lines will be grainy. The lines seen through the silicone lenses were crisp and clear. Furthermore, revisiting a batch of lenses left to sit for several days within inches of a fluorescent ceiling light showed that ambient light didn't spur the short chains into action, so a cataract patient could get adjusted one day and come back the next for a final test without ruining the unlocked lens. (But as with vampires, direct sunlight is to be avoided, especially during those two to four weeks it takes for the eye to heal before the adjustment. A good pair of UV-blocking sunglasses will suffice.) Other tests confirmed that the process of locking the changes in didn't itself further alter their power.

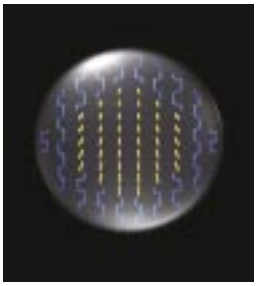
All this has led to the inevitable start-up company, Calhoun Vision, Inc., and the inevitable Web site, www.calhounvision.com. Schwartz is the chairman, and Sandstedt and Jethmalani are among those working on optics and materials research, respectively. The company has built a system to deliver an exact dose of ultraviolet light to a precise location within the eye, and has shown that the lenses respond to different doses in a very predictable manner and that, within batches of lenses zapped with the same dose, the variations are less than humans can perceive. The company plans to begin clinical trials this summer.

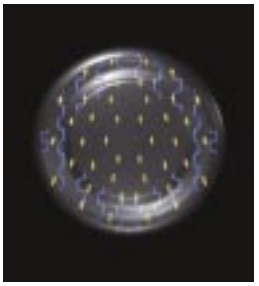
But why stop at cataract patients? Why not fix everyone's vision? Such eye surgeries are already big business, with the most popular method being LASIK, for LAser in-SItu Keratomileusis, which uses a laser to sculpt the cornea—the clear part of your eye in front of the lens, whose shape accounts for roughly two-thirds of the eye's focusing power. "LASIK is a very successful procedure," Kornfield says. "But it has a couple of drawbacks that basically trace back to the nonpredictability of wound healing." Furthermore, LASIK does not work reliably on extremely nearsighted or farsighted people.

To touch up your vision with an implant, the eye's natural lens would be left in place and the implant inserted in front of it. Eye surgeons are already testing nonadjustable implants for this purpose, but are again running afoul of the vagaries of wound healing. So a laser-tweakable version would be the ultimate in extended-wear





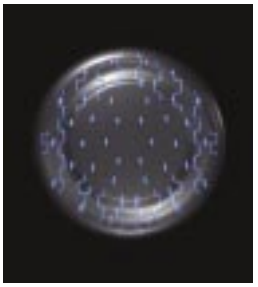


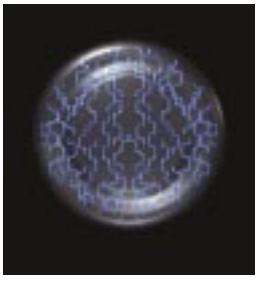


These frames from a Calhoun Vision video show how the nearsightedness correction actually works. The yellow squiggles are the short chains. On activation, they turn blue and link up.

contact lenses. For a while, anyway…. Somewhere around age 45, the eye's own lens loses its ability to bulge on command—or "accommodate," as the eye doctors say—which allows you to focus on nearby objects. "Another really neat breakthrough will be implanting the lenses in such a way that the muscles in your eye that perform accommodation can act on them," says Kornfield. "Perhaps it will be possible for us to enjoy near and far vision into old age."

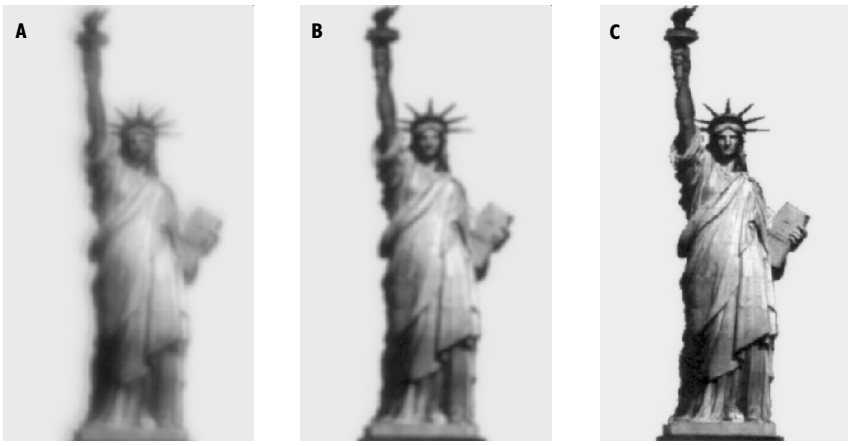
The implant could even be set for "supernormal" vision. Adaptive optics, which astronomers use to take the twinkle out of starlight, employs a system of computer-controlled sensors and mirrors to compensate for changes in the atmosphere's refractive index—the same phenomenon that causes mirages to appear in the middle of the road on hot summer days. A postdoc at the University of Rochester, Donald Miller, with his advisor David Williams and colleagues Jun Zhong and G. Michael Morris (MS '76, PhD '79) adapted that notion to a microscope to give eye doctors the sharpest view yet of the retina. The researchers photographed individual photoreceptor cells in several patients, something that had never happened before because the human lens and cornea aren't precision optical instruments. At the same time, says Kornfield, "the patients looking back out through this system raved about how sharp and crisp their vision was." In theory, Miller says, "electronic spectacles" with adaptive-optics technology could achieve retinal image quality equivalent to 20/2.5 vision, or six times normal. At that point, however, the details being brought into focus are finer than the visual neural system can handle, so





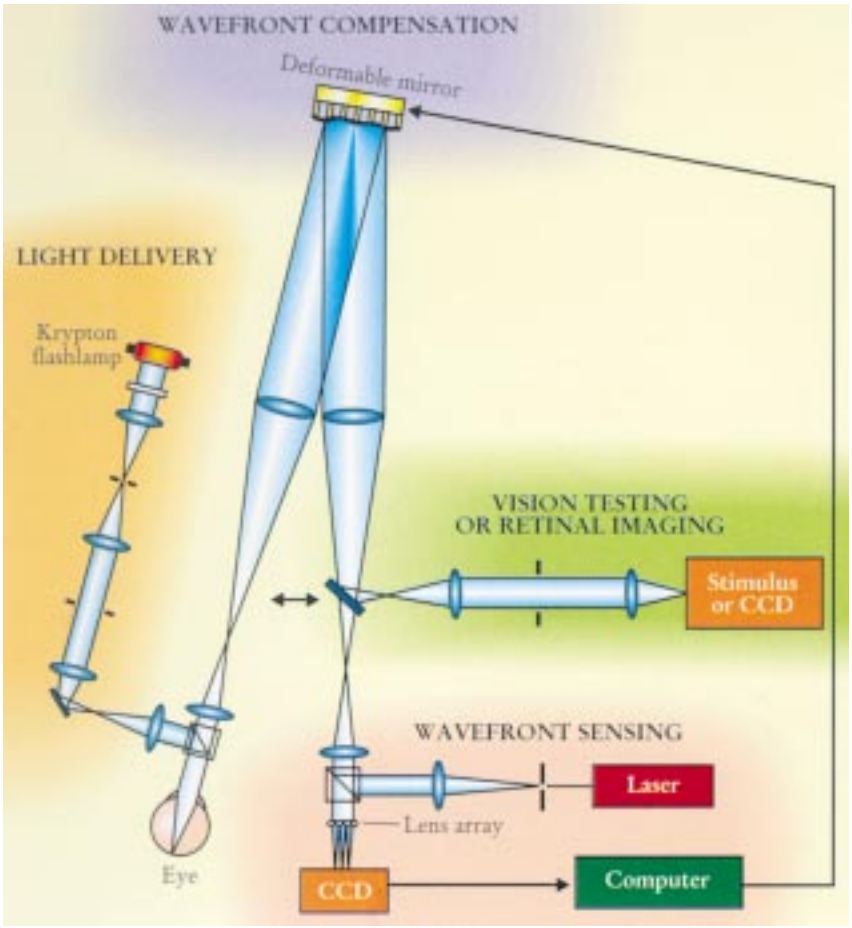
As with vampires, direct sunlight is to be avoided, especially during those two to four weeks it takes for the eye to heal before the adjustment. A good pair of UV-blocking sunglasses will suffice.

The Statue of Liberty, as seen by a person with normal vision standing on a boat three kilometers away, would look like photo A. An adaptive-optic lens that compensated for all the eye's imperfections would sharpen Lady Liberty to look like photo B. Dilating the pupil from its normal daylight diameter of three millimeters to its maximum diameter of eight millimeters would gather more light and sharpen her up even more, as in photo C. On the other hand, simply dilating the pupil without adaptive optics would actually make her fuzzier, as the effect of the imperfections increases with pupil size, which may be one reason why we squint when we're trying to make out highway signs while driving at night.



Donald T. Miller, "Retinal Imaging and Vision at the Frontiers of Adaptive Optics", *Physics Today*, January 2000, Vol. 53, No. 1, p. 36.

Donald T. Miller, "Retinal Imaging and Vision at the Frontiers of Adaptive Optics", *Physics Today*, January 2000, Vol. 53, No. 1, p. 32.



The adaptive-optic system used a Shack-Hartmann wavefront sensor. The light waves of a near-infrared laser (bottom right) reflecting off a point on the retina are distorted by the eye's imperfections. The returning beam passes through an array of tiny lenses that focus pieces of the beam onto a CCD camera. Local errors in the wavefront will move each lenslet's point of focus, allowing a computer to reconstruct what happened to the beam. Actuators behind the mirror then nudge it as needed to bring the wavefronts back into perfect alignment. (The krypton flashlamp is for photographing the retina.)

20/10 vision is a more realistic goal.

Kornfield's lab is also working on implants that can be done on a larger scale. Tissue transplants, for example. Cutting big holes in people is bad, so it would be nice to suspend "starter" cells of the tissue in a liquid polymer that, once injected into the body, would congeal in place. Then the solid would have to pull a slow-motion disappearing act, letting the trapped cells multiply and unite into a tissue. At this early stage in the game people are trying to figure out how to grow simple, undifferentiated tissues, but perhaps someday one could grow a new liver. Or at least a part of one. Meanwhile, back in the real world, a self-destructing scaffolding could act as a timed-release mechanism—for drugs that have to be given as daily shots, or perhaps for blood cells in people awaiting bone-marrow transplants. Or the plastic could simply act as a barrier—an internal bandage, or a support to keep something in place while it heals. Creating such a polymer is a tall order: the liquid would have to harden at the snap of a finger—on command, and so quickly that it can't seep into places you don't want it to go. And the solid would have to be sturdy enough to survive within the body, yet dissolve at a controlled rate.

Several approaches have been tried over the years, each with assorted shortcomings. You can inject short chains that photopolymerize, like the free chains in the lens implant. But it's pretty dark in the rest of the body, so it takes complex fiber-optic systems to get the light where you need it. Alternatively, there are thermosetting polymers that link up at body temperature. Of course, if the material turns solid when cooled to 98.6° F, then the liquid clearly has to be kept warmer. The coolest practical temperature is about 104° F—as high as you can safely set your hot tub—and a fire in the belly should be a literary metaphor, not a side effect of therapy. Furthermore, at least so far, all the solids that form this way aren't very strong

A hydrogel is a gel that likes water. Soaks it up like a sponge, in fact, swelling and getting soft. Which is good for an implant—who wants a stabbing pain every time they bend over?

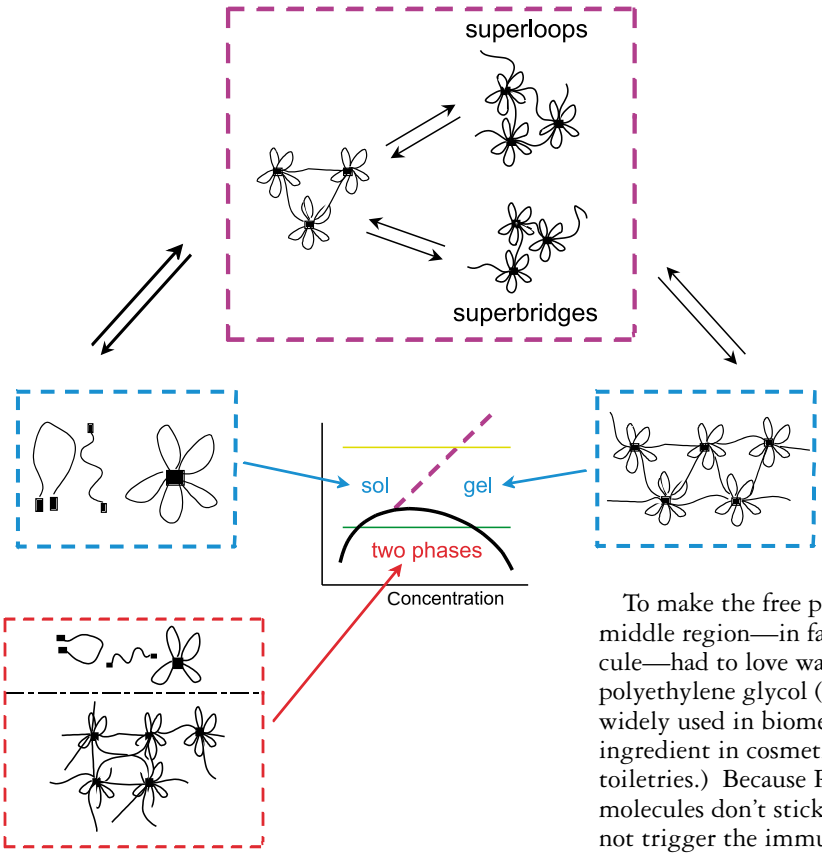
and tend to dissolve too quickly. Another notion is to dissolve the polymer in an organic solvent, and let the polymer precipitate out as the solvent diffuses away. The downside is that the ocean of solvent needed to dissolve the stuff in the first place causes problems of its own, ethyl acetate on your breath being the least of them. And you can't deliver timed-release cells or proteins this way, because the solvent kills the cells and prevents protein molecules from folding into their biologically active shapes. And finally, you can inject two precursor molecules into the body separately, and let them react on site. But the reactions aren't very selective, so you wind up with the internal equivalent of supergluing your fingers together.

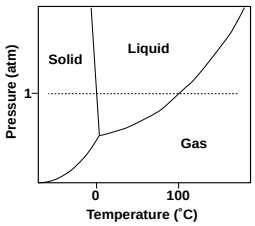
Tissue engineer Jeff Hubbell, then at Caltech and now at ETH, the Swiss Federal Institute of Technology in Zurich, had been thinking that a hydrogel (essentially waterlogged Jell-O) would be just the ticket. Gels, like silicones, are three-dimensional polymer networks, with plenty of room between the chains to fit protein molecules. And a hydrogel is a gel that likes water. Soaks it up like a sponge, in fact, swelling and getting soft. Which is good for an implant—who wants a stabbing pain every time they bend over? A hydrogel is usually more than 90 percent water, so that any embedded cells can easily absorb all the nutrients and other goodies they need. In fact, many tissues *are* hydrogels, including the cornea in your eye. So Hubbell asked Kornfield to design a hydrophilic, or water-loving, polymer that would spontaneously harden—if that's the right word for something so squishy—after injection, and dissolve at a controlled rate thereafter. Kornfield and Hubbell jointly enlisted a grad student, Giyoong Tae (PhD '02), to give it a try.

Hubbell, Kornfield, and Tae wanted a gel that dissolves the way a snowball melts, slowly sloughing off its outermost layer of molecules. That way, a fresh supply of the cells or drug within would be continuously exposed. This is called surface erosion. The trouble is, all the self-assembling hydrogels known when the project began eroded in bulk, dissolving from within, says Kornfield. "If I implanted a slab of one of those gels, it would swell, get softer, swell more, and just fall apart. And at some point, usually in hours or days, the stuff you were trying to release over time would all be dumped at once."

Melting snow is a phase transition between ice and water coexisting at the same temperature. Similarly, this hydrogel needed to make a phase transition between the solid gel and its dissolved state, which is called the sol, coexisting over a range of concentrations. (If you had a vial full of the stuff, you'd see a layer of gel at the bottom and the sol on the top.) So just as the temperature inside a melting snowball "hangs" at the melting point as the air temperature outside continues to rise, the concentration of the sol and the gel inside the lump of polymer remain at equilibrium even if that lump is drowning in enough water to dissolve it fully. The water within the polymer network is saturated with sol-phase molecules that are too big to swim away, preventing further dissolution. The bulk-eroding polymers, by contrast, never reach equilibrium—the material just swells and swells as the trapped water keeps dissolving more and more gel molecules, until suddenly the whole thing lets go.

In order to make the polymer molecules gel in the first place, they're endowed with water-hating, or hydrophobic, ends. Given half a chance, these ends—dozens of them—spontaneously cluster together, each one trying to put its fellows between the body's water molecules and itself. So Tae chose fluoroalkyls, which are notoriously hydrophobic, for the end groups. An ordinary alkyl is made of carbon and hydrogen—it's wax, basically, which is pretty water-repellent already. But replace the hydrogen atoms with fluorine, and you get a fluoroalkyl, like Teflon. And we've all seen water beading up on a nonstick frying pan as the Teflon coating shoves the drops away. As luck (or chemistry) would have it, fluoroalkyls are also more biocompatible than regular alkyls. "We think it's because when you replace the hydrogens with fluorine, you make a molecule that hates water *and* it hates regular alkyl molecules—oils and fats—as well," Kornfield explains. "So it tends not to go into cell membranes and the bloodstream the way that alkyl chains do, which makes the cells very unhappy." Altering the length of the fluoroalkyl would influence how strongly it would want to cluster, and thus how easy it would be to make the polymer gel. Neutron-scattering measurements that Tae did in collaboration with Jyotsana Lal at Argonne National Lab showed that the C_8 fluoroalkyls liked to cluster in bunches of roughly 30, while the bigger and more hydrophobic C_{10} groups preferred to huddle in crowds of 50 or so.



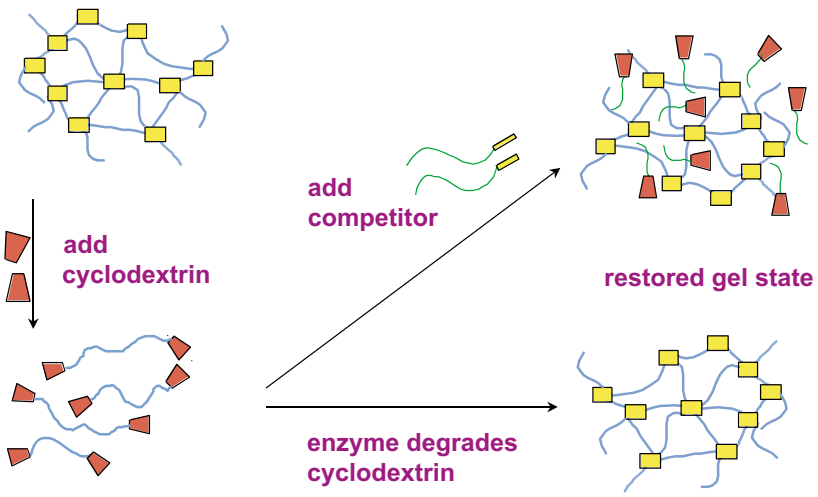


The phase diagram for water (left) shows its physical state at a given temperature and pressure. At constant pressure, say one atmosphere, changing the temperature is equivalent to moving horizontally (dotted line). A phase diagram for Tae's family of polymers (above, center) would be conceptually similar, depicting the transition from sol to gel as a function of concentration. The vertical axis has no label, because it represents a complex balancing act between the many competing forces that act on the molecule's water-loving middle and water-hating ends. A typical bulk-dissolving polymer's behavior is shown by the yellow line. At low concentrations, the molecules tend to bite their own tails as the end groups cling to each other (blue box at left). The scattered flowerlike clusters that do manage to form aren't big enough to fall out of solution. As the concentration rises and it becomes easier for the fluoroalkyls to find one another, the molecules spontaneously begin to assemble themselves into larger structures (purple box). There's no clear-cut transition into a gel, but rather a continuum of coagulation, so the boundary between the sol and the gel is shown as a dashed (purple) line. By contrast, a two-phase system (green line) goes through a well-defined intermediate state (red box) in which the sol and the gel coexist.

To make the free polymer water-soluble, the middle region—in fact, almost all of the molecule—had to love water. For this, Tae chose polyethylene glycol (PEG), a simple molecule widely used in biomedicine. (It's also a popular ingredient in cosmetics, shampoos, and other toiletries.) Because PEG loves water, oily protein molecules don't stick to it. Therefore, PEG does not trigger the immune system nor does blood clot when exposed to it, making it an ideal coating for various kinds of implants. Controlling the length of the PEG region would govern how much water the gel could absorb, and how big a protein could be caught in the mesh.

So Tae made an assortment of materials, with some initial assistance from Thieo Hogen-Esch, a professor of chemistry at USC. The hydrophilic PEG region varied from about 140 to 460 monomers, and the hydrophobic fluoroalkyl groups ranged from six carbons (C_6F_{13}) to 10 carbons ($C_{10}F_{21}$) long. As it turned out, this spanned the entire behavior range, from bulk erosion to sol-gel coexistence, to complete insolubility. But it remained to be seen whether the gel in the two-phase material was really eroding from the surface, and if the erosion rate was slow enough to be useful.

To find out, Tae and Diethelm Johannsmann, at the Max Planck Institute for Polymer Research in Mainz, Germany, applied a coating of the gel to a very thin gold film and immersed it in running water. This experiment is a good example of the roundabout route one sometimes has to take to tease out the piece of data you're looking for. If the film is thin enough, a beam of light hitting it will actually interact with the atoms just beyond it. In other words, light reflecting off the top of the gold film will be "aware" of the gel coating on the underside. Not only that, but the light "sees" the gel-phase molecules to a depth of about one micron, or one millionth of a meter. If the coating is several microns thick, and the gel dissolves



How the uncapping was supposed to work. The yellow boxes are the fluoroalkyl end groups.

exclusively from the exposed surface, then the reflection won't change until the gel has worn down to that last micron, and the time lag until this occurs gives the disintegration rate. But if the stuff is dissolving throughout, the light will see fewer and fewer molecules in the gel state, and the reflection—specifically, its strength as a function of the angle at which the light hits the surface—will also change continuously. The effect is most pronounced at angles near the one at which the light excites the gold's so-called plasmon mode, so the method is known as surface plasmon resonance.

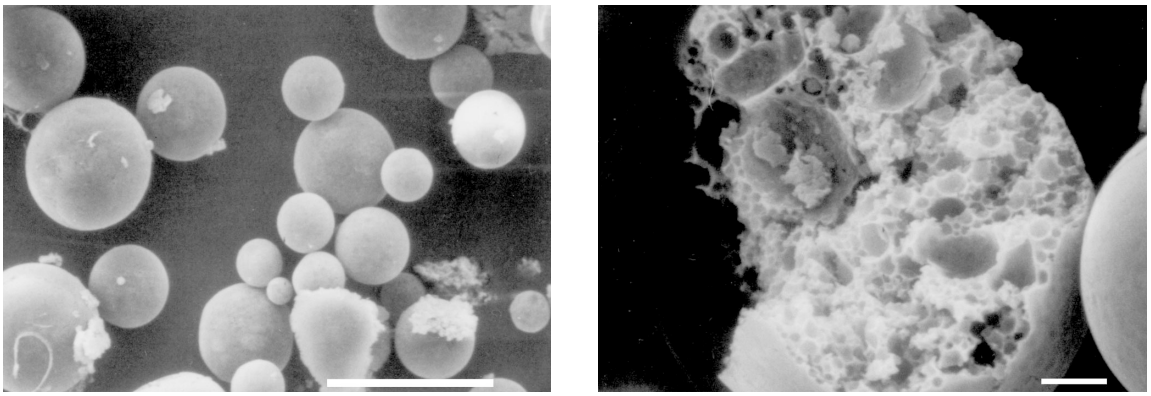
The tests confirmed that the gel was eroding from the surface, and further revealed that the rate was adjustable. Polymers with identical eight-carbon fluoroalkyl groups dissolved at rates controlled by the lengths of their PEG middles, since having more water-loving PEG made the molecule go into solution faster. But for a fixed PEG length, making the fluoroalkyl groups just a little bit longer slowed the erosion rate over a hundredfold. "Imagine each cluster of fluoroalkyl groups is a centipede, and the polymer molecules coming out from it are the legs," says Kornfield. "A cluster of C_8 end groups has 30 legs, and a C_{10} cluster has 50 legs. They all have to let go at once in order for the centipede to wash away. It's really cool, because one of the main parameters that people would love to dial in for use in the body is the erosion rate." By using the fluoroalkyl length and the PEG length as the coarse- and fine-adjustment knobs, respectively, you can tune the time-release setting from days to weeks.

At this point, you may be wondering: if the polymer is concentrated enough to gel in the body, what keeps the sol from gelling in the hypodermic? A good question—that was the final hurdle. "We tried a few ideas that looked really great on paper, but just didn't work out," says Kornfield. "We all pursue dead ends. That's part of science." For example, they tried capping each fluoroalkyl with a flowerpot-shaped molecule called a beta-cyclodextrin. Cyclodextrins are made up of sugar molecules; the beta means there are seven sugars per flowerpot. The sugars are arranged so that the cyclodextrin's outer surface loves water, but the inner surface hates it. The fluoroalkyl can hide inside the flowerpot, which is so cozy that it would rather do that than snuggle with its fellows. This worked really well, and the concentrated polymer dissolved nicely. In fact, it worked a little too well—like grown-ups wrestling with a child-proof bottle, the chemists couldn't get the cap off fast enough. "We tried to use an enzyme to degrade it. What could be better? Maybe it would even respond to enzymes in the body—how cool! Well, we learned that the human body doesn't make any enzyme that's really good at degrading cyclodextrins, and the best ones we could find come from a fungus. But you can't put fungus enzymes into a person without an immune response, which is bad. And even the best enzyme we could find wasn't fast enough." Then they tried to use a competitor molecule—a length of PEG with only one fluoroalkyl end group—to pry the cap off. Just as you would wedge a butter knife under the childproof top to pop it free, a polymer with a C_{10} end should displace a polymer with a C_8 end, because the bigger the fluoroalkyl, the better it likes to climb into the flowerpot. Unfortunately, the competitor molecules were too big to diffuse very fast, so this idea only worked in a test tube, where they could be stirred into the sol with some vigor.

"Giyoong tried all sorts of molecules, and it was very frustrating. Then one day he came into my office and he said, 'Did you know, Julie, that there are organic solvents that are already approved for use in the body?' I said, 'No. You've got to be kidding!' In fact, I probably said, 'That's gross!' But it's true, and it turns out that one of them, called *N*-methyl pyrrolidone, dissolves both the middle *and* the ends of our polymer. Giyoong showed that you could make a solution that's 50 percent polymer and 50 percent solvent and still be runny enough to be injected through a syringe." Furthermore, when exposed to water—or intercellular fluid—the solvent diffuses away within minutes, leaving behind a gel that behaves as if the solvent had never been there. If the solvent molecules had hung around the fluoroalkyl ends, they wouldn't have clustered properly and the polymer wouldn't gel well.

With a workable system in hand, it was time to try it out. Hubbell, Kornfield, and Tae opted to attempt a controlled release of human growth hormone, also known as somatotropin. This protein, made up of 191 amino acids, is released by the pituitary gland. Children lacking the hormone grow less than two inches per year, and in normal quantities the hormone helps kids to grow at the rate of two to three inches per year. Children in the shortest 5 percent of the height

H.K. Kim and T. G. Park, "Microencapsulation of Human Growth Hormone within Biodegradable Polyester Microspheres: Protein Aggregation Stability and Incomplete Release Mechanism," *Biotechnology and Bioengineering*, Vol. 65, No. 6, December 20, 1999, p. 662.



The surface (left) and a cross section through the interior (right) of the glycolic acid microspheres. The scale bar in the left image is 0.1 millimeters; the one at right is 0.01 millimeters.

range for their age and sex are frequently given hormone treatments to help them catch up. This means three-times-a-week or even daily hormone shots, administered year after never-ending year. The shots can be given at home, but it's clearly no fun for the little ones. And even the older kids who have gotten used to needles and are doing their own injections would rather do it just once a month. Which is as infrequent as is practical, because proteins—even in gel storage—can be degraded by hydrolysis or attacked by enzymes called proteases. By the month's end, you can't be sure the protein's any good any more, and it's best to start fresh again.

Human growth hormone presents some particular problems as a timed-release candidate. The pituitary gland stores the stuff in granules, in which pairs of the protein molecule are held together by two zinc ions that stabilize the protein's active form—without the zinc, the molecules aggregate into useless clumps. So the trick is to store the stuff bound to the zinc ions so it won't clump up, and then release it one pair at a time. Many people have been working on this problem, but the only approach that has been approved for clinical use to date encapsulates the zinc-protein dimer inside biodegradable particles made of a molecule called poly(D,L-lactic-*co*-glycolic acid). There are several variations on this theme, but they all suffer from an "initial burst"—as much as half of the hormone escapes in the first day after injection, before the release rate stabilizes. This royally screws up the dosage calculations, and the kids wind up getting less of the hormone than they should. Not surprisingly, children on whom this method was tried did not grow as fast as those who were given the daily injections. And there's a side effect—the biodegradation products of poly(D,L-lactic-*co*-glycolic acid) are, well, acidic, which can lead to a painful inflammation at the injection site.

Tae demonstrated that, at least in a test tube, the hydrogel released the hormone at a nice, even rate with no initial burst. The release could be sustained for two to four weeks, depending on the polymer chosen. And a veterinarian in Hubbell's lab at the ETH injected some into mice to verify that it was biocompatible. Says Kornfield, "Three days later, there was a beautiful, clear, spherical gel under the mouse's skin, and very little inflammation. In fact, the vet said it was quite remarkable how little inflammation there was." However, lots more work remains to be done before these polymers will be ready for clinical trials in humans. But PEG is widely used to stabilize the active forms of various other proteins that are given by injection, so if the trials go well, lots of other applications await.

And goo may be good for you in any number of other ways. Kornfield's lab, and those of a host of other researchers, are just beginning to explore the possibilities of biocompatible polymers. So if your doctor ever tells you that you're in line for an implant, you may wind up with something that owes less to the exotic alloys of the aircraft industry than it does to fifty cents' worth of Jell-O. □

PICTURE CREDITS:
30, 31, 32, 37 – Doug Cummings; 30 – National Library of Medicine; 32, 33, 38 – Julia Kornfield

Professor of Chemical Engineering Julia A. Kornfield (BS '83, MS '84) is also the director of the National Science Foundation's Center for the Science and Engineering of Materials, located at Caltech, which pioneers exotic and futuristic materials. A 1981 Summer Undergraduate Reseach Fellowship (SURF) project involving nerve cells got her hooked on biotechnology, to which her polymer-physics background lends a different perspective. Besides her Caltech degrees, she earned a PhD in chemical engineering from Stanford in 1988. She has been on the Caltech faculty since 1990, earning three teaching awards in that time.

The lens and gel halves of this article were adapted from a Watson lecture given last March and a SURF brown-bag lunch presentation last August, respectively.