behind photons that took a more direct route. (This problem doesn't afflict long-distance glass fibers because their extremely narrow confines ensure that photons can only travel in one path.)

Since the early 1980s, Koike and other researchers around the world have been trying to get around this problem by experimenting with a type of plastic fiber known as graded index, whose composition changes to create slow lanes for photon travel in the core and high-speed lanes at the perimeter. Although photons that travel from side to side still cover longer distances, they also spend more time in the outer fast lanes than do the straight-flying photons, which plod down the middle. "As a result, there is less dispersion, [because] the different rays of light get to the end at the same time," says Steele. This allows light pulses to be spaced more closely together, boosting the amount of information the fiber can carry.

These fibers create this dead heat among photons because they are made of materials that transmit light at different speeds. This speed is given by each material's index of refraction; the higher the index, the more slowly light travels. In making their early graded-index fibers, Koike and his colleagues started with a hollow tube made from a common fiber polymer known as poly(methyl methacrylate), or PMMA. They then filled the tube with a mixture of two different polymer building blocks, or monomers: MMA, the singlet version of PMMA, and vinylbenzoate (VB), with a slightly higher index of refraction than MMA. When the researchers then shone ultraviolet (UV) light on the tube, the monomers absorbed energy and began to polymerize. And because the concentration of UV light was highest at the periphery, this polymerization progressed from the tube edges into the core. But the monomers polymerized at different rates. MMA polymerized first, producing PMMA, most of which ended up near the edges of the tube. Because PMMA formed first, it squeezed VB into the center before it too turned into a polymer. And VB's slower rate of light transmission created a slow lane for photons.

PLASTIC POWER

Carrier	Bandwidth over 100 m (megabits per second)
Copper wire	100
Step-index plastic fiber	100
Graded-index plastic fiber	2500

Wider wiring. The new plastic optical fibers can transmit huge amounts of data over short distances.

These early graded-index fibers had a serious drawback, however: They dispersed much of the light they were supposed to transmit. The problem, explains Koike, was that "the [polymerized] VB tended to agglomerate" inside the fiber, creating large unruly tangles of polymer chains that scattered most of the light coursing down the fiber. And as a result, the signals transmitted in these fibers quickly faded.

In 1992, however, Koike and his coworkers discovered a new technique for producing graded-index fibers that carry a signal down the line with less scattering. To make their new fibers, the Keio researchers started with the same hollow PMMA tube. But this time they did away with the VB and filled the tube with a mixture of MMA and so-called "dopant" molecules such as benzyl methacrylate and diphenyl sulfide, which have a higher refractive index than MMA. They also used heat instead of UV light to polymerize their monomer. In this case, heating the tube caused a gel layer to form at the interface between the tube wall and the MMA-dopant mixture. In the gel phase, the MMA molecules quickly began to connect themselves to the PMMA chains in the tube wall, pushing the gel layer farther into the core.

At the beginning of this polymerization process, a few of the dopant molecules were trapped in the polymer matrix near the edges, but most were pushed toward the core of the tube. As more polymers formed, they trapped atoms from this more concentrated region while pushing ever-higher concentrations of dopant molecules into the center. At the end, the researchers had a solid PMMA fiber with a continuously graded concentration of highly refractive dopants. And because these dopant molecules don't agglomerate, optical losses in the fibers were reduced.

The new fiber doesn't dispense with the signal degradation problem altogether. Optical signals "still get knocked down by a factor of around 30" after they pass through 100 meters of fiber, says Harry Lockwood, an optoelectronics consultant with the Lockwood Group in Newton, Massachusetts. "But it's still very usable," he adds, because 100 meters is ample for wiring most homes or local computer networks within offices.

Before the new fiber is ready for the market, companies must still work out how to ramp up production to industrial scale. That effort is already well under way among consortia members, such as NEC, Honeywell, Boeing, Sumitomo, Boston Optical Fiber, Packard Hughes Interconnect, and Mitsubishi. And with the new fibers commanding 25 times the bandwidth of both step-index fibers and the fastest copper wires, it's likely this scale-up will be moving fast as well.

–Robert F. Service

BIOPRESERVATION

Putting Proteins Under Glass

Remember Sea Monkeys? Advertised in comic books as a no-fuss, no-muss pet oddity, they come as a package of dried powder. In an aquarium, each powder grain grows within days into a live swimming creature—an embryonic brine shrimp, to be exact. As pets, the miniature shrimp aren't all that exciting, but their phoenixlike resurrection impresses a lot of kids.

And it isn't just kids who are impressed. Scientists and pharmaceutical companies that want to increase the shelf life of protein-based drugs are looking for better ways to store proteins and bring them back to life intact. Freeze-drying, the most widely used method, can bend proteins out of shape. Over the long term, this can lead to degradation of the protein's crucial active sites. "If we have 18 months on a product at room temperature we're delighted," says Michael Pikal, a pharmaceutical scientist with Eli Lilly in Indianapolis, Indiana.

To build a better shelf life, Pikal and other researchers are taking their cues from the Sea Monkeys. Brine shrimp—along with a variety of seeds and micro-organisms—appear to preserve themselves by transforming themselves into a glassy state. Sugars in their bodies encase their cells like sheaths of rock candy, holding proteins nearly immobile. In this "amorphous" condition, the molecules that make up the proteins exist somewhere between the disorder and mobility of a fluid and the orderly immobility of a crystalline solid.

Like the glassy states themselves, researchers' knowledge of these conditions is somewhat amorphous. There is great uncertainty, for instance, over just how the sugars preserve the proteins. In spite of the many unknowns, researchers have, through trial and error, recently found ways to use the glassy state to protect drugs. In the lab, Pikal has used it to keep human growth hormone twice as stable as does Lilly's current process. John Carpenter, a pharmaceutical scientist at the University of Colorado Health Sciences Center in Denver, reports that he and colleagues at Amgen in California have been able to maintain interleukin-1 receptor antagonist protein in a glassy form for 14 months at 50 degrees Celsius, with only 2% degradation. He was even able to bake it at 100 degrees Celsius for 5 minutes with no damage.

The allure of these findings is that phar-

maceutical makers "have to be able to prevent drugs from changing chemically or physically in temperatures as high as a warehouse in Houston at 40 degrees centigrade ... all the way down to subzero when it's being shipped," says pharmaceutical chemist George Zografi of the University of Wisconsin, Madison. The sugar-coated glassy state is stable enough to permit all this.

In spite of these potential advantages, the glassy state isn't common in commercial applications. Sugar preparations that turn some products glassy fail completely with others, a fact that frustrates scientists and makes companies reluctant to take on the technology. "It's not like you call up and buy the magic freeze-drying kit," says Carpenter.

Current freeze-drying techniques are fairly standardized. To preserve protein-based drugs, manufacturers dissolve them in a stabilizing agent, such as an alcohol like mannitol, and place the complex in a freeze-dryer. The liquid is then sublimated away, compacting the protein into a solid. The problem is that as the solution concentrates it can twist the proteins, exposing highly reactive sites that are prone to physical and chemical changes over several months.

To overcome this problem, researchers have been experimenting with sugars as stabilizing agents for half a decade. Carpenter, Pikal, and others have found that if a protein-based drug is mixed with a sugar-based solution and then freeze-dried, the sugars—which turn glassy as they dry—pull the proteins into a stable state. In analyzing the conditions for the process to begin, says Pikal, "there is some common agreement" among researchers. The sugar solution must move easily into the glassy state on its own—sugars do this when dried at room temperature—and it has to mix thoroughly with the proteins. If not, the sugars will turn glassy, but they won't bring the proteins along for the ride.

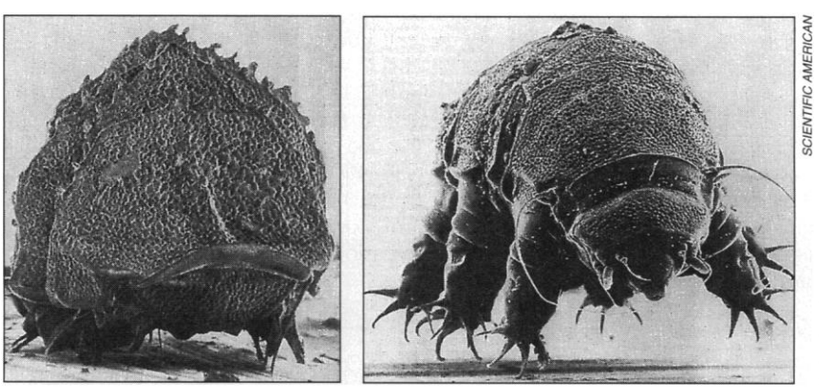
Beyond this area of limited initial agreement, however, researchers have very different ideas about how sugars exert their protective function. "At this point you can say we all agree to disagree on how it works," says Carpenter. Some scientists, such as Felix Franks, a chemist and head of Pafra Biopreservation in Cambridge, U.K., which markets glassy preservation technology, believe it's simply the sugar's glassy state that protects the proteins. In this view, the protein molecules, like ants encased in amber, can't react with anything damaging, such as mold or oxygen.

Other researchers, however, argue that there must be an additional interaction between the sugars and the object of protection. Biologists John and Lois Crowe of the University of California, Davis, have done studies of liposomes (spheres made of fatty molecules that are used to encapsulate drugs) in glassy states. They have learned that unless the fatty molecules are in a liquid phase early in the process, the sugars that subsequently surround the liposome don't exert the effects needed for maximum protection. The liquid phase of the fatty molecules, the Crowes say, may allow a particular type of bonding with the sugars that maximizes protection.

"[We] have to be able to prevent drugs from changing chemically or physically in temperatures as high as ... 40 degrees centigrade."
—George Zografi

The Crowes and Carpenter hold that such bonding preserves proteins and liposomes by keeping them in the same configuration as in their native, watery form. That's important because it keeps proteins from unfolding. According to Carpenter, who has done high-resolution infrared spectroscopy studies of glassy-state proteins, sugars hold the proteins curled, minimizing the area exposed to destructive agents in the environment.

John Crowe suggests that the sugars keep proteins and liposomes in shape by binding to the slightly electrically charged groups—known as polar groups—on the molecules that are normally attached to water. "The sugars hydrogen-bond to the molecules, and they spatially separate like water normally would. We think that it's a specific interaction necessary for preservation," Crowe says.



SCIENTIFIC AMERICAN

Safety glass. A number of animals, including these arthropods known as tardigrades, appear to protect themselves from severe cold or drought by going dormant in a sugar-coated glassy state *(left)*; the glass seems to shield proteins from harm. Rehydration brings the animals back to life *(right)*. Taking a cue from nature, researchers at pharmaceutical companies are experimenting with sugar-derived glass to preserve protein-based drugs.

While this debate continues, a few companies are plunging ahead based on the empirical evidence suggesting that the process, whatever its mechanism, works. One of those companies is Pafra, started by Franks in 1985. He avoids freezing entirely and uses vacuum or spray-drying (in which the protein-sugar solution is sprayed through a stream of hot air). But this is hardly off-the-shelf technology: Pafra has to conduct extensive tests to determine which sugar works best for a particular product before providing each customer with a custom-made solution.

Since 1990, Pharmacia Biotech has been using a Pafra sucrose solution to preserve the DNA manipulation products they sell. Pharmacia is also beginning to market a system to introduce a lambda bacteriophage into bacteria. Most current lambda packaging systems must be stored at -80 degrees Celsius, but Pharmacia has found that by going glassy with a sucrose solution, their system can be stored at room temperature. "Once you receive them you can store them at ambient temperature so it doesn't require deep freezer space," says Brent Burdick, Pharmacia's vice president of R&D. "And it's safer from the environmental standpoint—we don't have to ship it with ice and styrofoam. And that's less capital-intensive."

Despite these initial successes, many firms are taking a wait-and-see attitude. "There are not many commercial pharmaceutical products that use sugars yet," says Pikal. "Most of the work on the sugars has been research work." His lab at Eli Lilly has shown that freeze-drying genetically engineered human growth hormone—which is given to children who aren't growing properly due to a lack of the natural hormone—with the sugar trehalose adds enough stability that Lilly is looking to patent the process. And if Pikal and other researchers can determine why trehalose works better, the knowledge may help them whip this still-amorphous field into more solid shape.

–Karen Celia Fox

Karen Celia Fox produces the radio show Science Report *for the American Institute of Physics.*