Tissue Engineering

Replacing damaged organs with new tissues

By RICHARD LIPKIN

In a housing project on the outskirts of Chicago, a three-alarm fire erupts. Engines rush in, and firefighters valiantly pull a woman and her 6-year-old twin sons from the burning building. One of the boys has third-degree burns over a large part of his body. His condition is critical. Without a supply of fresh skin to cover his wounds, he is likely to die.

Meanwhile, at home in Canton, Ohio, a retired veteran, his ailing liver about to give out, waits anxiously for the phone to ring. His name ranks 127th on a list of potential recipients of donor organs, a list that moves far too slowly for his eroding condition. Without a liver transplant, he may not survive the month.

In a townhouse community in Irvine, Calif., a 38-year-old mother moves groceries into the refrigerator. Suffering from a rare form of arthritis, she finds the mere act of putting away a quart of milk excruciating. The cartilage in her joints has worn away prematurely, and her medications do little to alleviate the intense pain. The solution, her physicians advise, lies in the ability of surgeons to replace tissue in key weight-bearing joints.

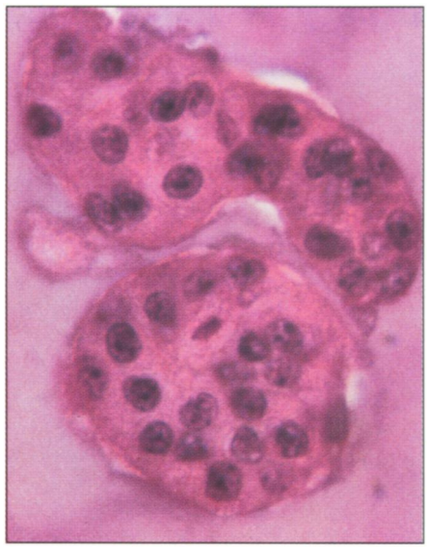
Though these medical cases may seem to have little in common, all three people suffer from the same general problem: Their bodies cannot repair their injured organs. Moreover, their conditions are curable. What they need is healthy, transplantable tissue.

Enter the tissue engineers. These scientists hail from a wide range of disciplines—materials science, chemical engineering, molecular biology, and specialized surgery, to name only a few. Together, they have formed diverse research teams with the aim of learning how to grow new tissue in the laboratory to replace damaged tissue unable to repair itself.

Regeneration of damaged body parts, once considered the province of science fiction, is now moving toward science reality, says Robert Langer, a chemical engineer at the Massachusetts Institute of Technology. Though physicians can by no means regenerate a complete new heart, liver, or kidney, they have grown parts of these and other organs.

For less complicated tissues, such as skin, cartilage, and tendon, several research teams have made substantial headway. They have succeeded, in a number of cases, in growing simple tissues outside the body and then transplanting them into animals. For a few such tissue replacements, clinical trials with human patients are poised to begin.

"There's a tremendous need out there for transplantable tissues and organs," says Gail K. Naughton, chief scientist for Advanced Tissue Sciences in La Jolla, Calif. "When you see the kids, the ones with severe burns, you just want to do something. They keep you going during the long hours.



Robert P. Lanza *et al.*/BioHybrid Technologies

Microreactors filled with insulin-producing islet cells from pigs flourished for 10 weeks in a diabetic mouse without immune system–suppressing drugs.

"There's a large gap between the number of people who need transplants and the number of available organs," she adds. In addition, technical problems and legal threats have caused manufacturers to withdraw from the market some implantable devices, such as artificial joints and breast implants.

"People are only beginning to realize the potential here," says Naughton. "Tissue engineering today is where genetic engineering was 10 years ago."

Organ failure and tissue loss affect millions of people annually, causing premature deaths and immense suffering. Each year in the United States, physicians perform an estimated 8 million surgical procedures to treat these conditions, which require more than 40 million days of hospitalization and cost an estimated $400 billion. Usually, the number of people needing organ transplants exceeds the number of donated organs, sometimes by a factor of 10. In 1989, for instance, liver disease led to 30,000 deaths, though only 2,160 transplants were performed—a shortage brought to public attention by the recent liver transplant of 63-year-old baseball legend Mickey Mantle.

People in need of other organs often fare no better. Many of the 600,000 people with kidney ailments, the 728,000 with pancreas disorders, and the 150,000 with severe burns await new organs. Patients requiring tissue for rarer procedures, such as the 30,000 persons annually who need cartilage for facial reconstructive surgery or the 33,000 in need of tendon repair, find themselves in a similar bind.

"From our point of view, the end goal is to create new tissues to serve as permanent replacements," says Joseph P. Vacanti, a pediatric surgeon at Harvard Medical School and Children's Hospital in Boston. "Ultimately, we want to grow tissue from a patient's own cells to avoid an immune reaction. But to achieve that goal, there's a lot of work to be done."

A major obstacle, says Vacanti, is determining exactly how and why cells differentiate. Most organs include many types of cells, each with its own distinct characteristics. Together, those cells interact harmoniously, producing a whole, functioning organ.

"How do cells know how to reorganize into a new structure?" Vacanti asks. "How do blood vessels know how to grow into new tissue? How does an organ know when to stop growing? Those are basic scientific questions that need to be answered for any tissue under study."

If researchers can discern general scientific principles from a few tissue regeneration models in the laboratory, perhaps those principles could be applied to other organs in the body, Vacanti points out.

"If the experiments continue to look promising, I expect that nearly every human tissue will, at some point, be amenable to tissue engineering," he says.

"That's my vision of the future."

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To handle certain urinary tract problems, Anthony Atala, a surgeon at Harvard and Children's Hospital, has organized a research team to grow replacement tissues for the ureter, bladder, urethra, and kidney. For example, to treat the congenital condition of ureteral reflux, which causes urine to back up into the kidney rather than flow directly into the bladder, the scientists are growing tissue to augment weak ureters and halt the ensuing kidney damage. "Thirty years ago, reflux was the main cause of kidney failure," Atala says. "Now we are treating it with engineered cells."

To strengthen or enlarge weak bladders, Atala's team has developed a method of injecting muscle cells into the walls of a bladder. "Instead of having painful open surgery and a week-long hospital stay, patients can be treated with a relatively simple procedure in a physician's office." To enlarge bladders, the researchers are growing strips of artificial tissue that surgeons can stitch into the organ's wall.

Some of these treatments are ready for testing on humans, says Atala, pending Food and Drug Administration approval. Looking further ahead, scientists are attempting to create artificial kidney tissues. "The kidney is more difficult because it has many tissues with different functions," Atala says. "But if we could replace even one or two of a damaged kidney's missing functions, that would be an improvement."

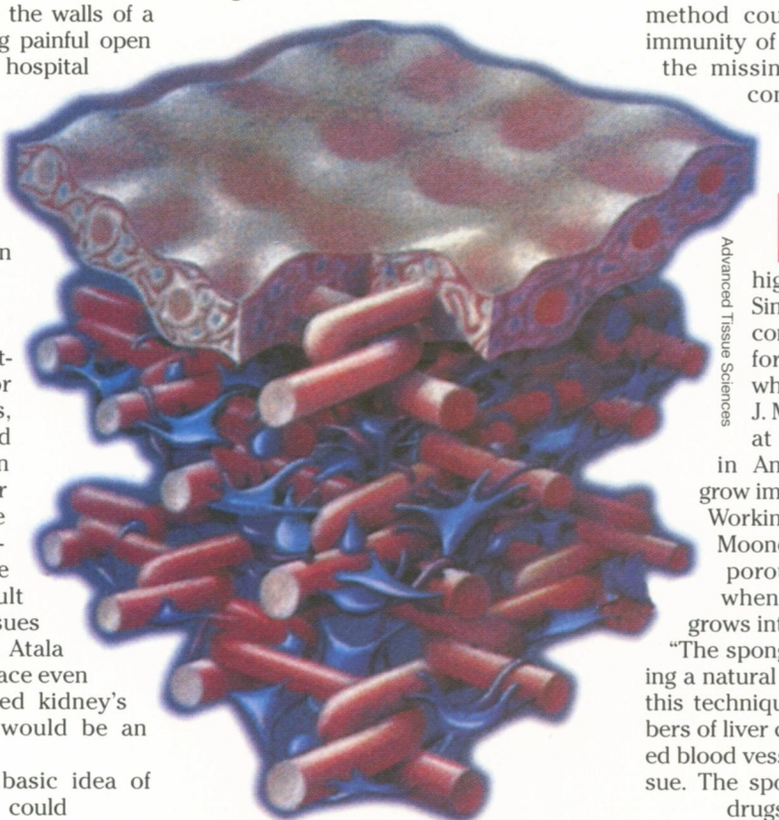
Atala thinks that the basic idea of injecting engineered cells could be used to reconstruct other organs damaged by disease or by surgery for cancer. Several groups in collaboration with Reprogenesis in Dallas are at work on methods of reconstructing breast tissue after mastectomy, he adds. "There's a strong need for this kind of procedure, especially given the problems surrounding breast implants."

Many of the tissue engineering techniques have emerged from a relatively simple concept that originated with Langer and Vacanti more than 10 years ago. The idea is to make gossamer sheets of dissolvable material, seed them with cells, then incubate them in a bioreactor. After several weeks of baking and basting, the cells form tissue. Surgeons can then sew the tissue into a patient, whereupon the polymer matrix, or scaffold upon which the cells grow, dissolves away.

A related method involves encasing individual cells in dissolvable capsules, then injecting them into areas where they are needed. The minuscule cages keep the cells secure until they settle down, take hold, and begin to function on their own. Then the cages, too, dissolve away.

Seeking to treat diabetics with such encapsulated cells, William L. Chick, a physician at BioHybrid Technologies in Shrewsbury, Mass., and his colleagues have devised a system for making injectable insulin-producing cells.

Diabetes, which affects an estimated 2.3 million people in the United States, represents the failure of the pancreas to secrete enough insulin to break down sugar circulating in the bloodstream. Diabetics must inject themselves daily with insulin.



Advanced Tissue Sciences

Scientists place live cells on a dissolvable mesh, which supports the cells as they grow into a full-fledged tissue. A surgeon then implants the new tissue in a person, where the cells take hold and the mesh erodes away.

Chick's treatment strategy involves harvesting insulin-producing cells from pigs, encapsulating the cells in dissolvable "microreactors"—tiny, dissolvable, spherical cages—and then injecting them into the abdomens of people with diabetes, where the microreactors float freely, producing insulin as needed.

"This is a living drug-delivery system," Chick says. "The pancreatic cells have a biochemical mechanism that continuously monitors blood glucose, releasing only enough insulin to keep blood sugar within a normal range. This is a much better system than having to constantly inject yourself with insulin."

The microreactors permit life-sustaining oxygen and nutrients to flow in and wastes and insulin to flow out, keeping cells healthy and nourished. At the same time, they protect cells from antibodies, thwarting an immune reaction. Patients receive an initial injection of cells, to sustain them for 6 months to a year, followed by twice-yearly booster shots. When the cells eventually expire, the microreactors dissolve and the body excretes the waste.

"Using this method, we've successfully treated diabetes in dogs," says Chick, adding that if all goes well, human trials could begin in 2 years. "It's a simple concept. The goal is to make treatment as easy and safe as possible." He also believes that, in principle, the same method could be used to boost the immunity of AIDS patients or to supply the missing blood-clotting factor to control bleeding episodes in hemophiliacs.

Like pancreatic cells, liver cells are finicky, flourishing only under highly favorable conditions. Since a whole liver transplant constitutes the only treatment for end-stage liver disease, which is invariably fatal, David J. Mooney, a chemical engineer at the University of Michigan in Ann Arbor, is attempting to grow implantable liver tissue.

Working with Langer and Vacanti, Mooney has developed a highly porous, spongy material that, when seeded with liver cells, grows into "liverlike tissue."

"The sponges dissolve over time, leaving a natural tissue," says Mooney. "With this technique, we've placed large numbers of liver cells in animals and stimulated blood vessels to grow into the new tissue. The sponge material also contains drugs, which are slowly released, to help the liver cells survive."

The liver of an adult man weighs more than 3 pounds and performs many complicated functions. As the largest visceral organ in the body, it presents "a nontrivial problem" for tissue engineers, says Vacanti.

"We need to get enough tissue transplanted, keep it stimulated, and make sure it has an adequate blood supply and can excrete bile," says Vacanti. "That's a big job."

For people with severely damaged livers, Vacanti would count it a success to replace even one or two of the organ's metabolic functions. "We think we can do that by implanting 10 percent of a whole liver, or about 150 grams of tissue. But that's still a lot of cells."

The research team has succeeded in grafting a healthy portion of liver tissue into several animals. "In Dalmatian dogs, we've shown that implanted cells will replace one liver function for up to 6 weeks," Vacanti

says. "That's a good result, though it's still far from ready for clinical testing."

In general, engineered structural tissues—cartilage, tendon, ligament, and bone—have come closer to clinical application than visceral tissues such as pancreas and liver. Artificial cartilage has probably made the most headway, with wide applicability in the repair or resurfacing of damaged or arthritic joints (SN: 11/12/94, p.318) and in facial reconstruction for victims of cancer or car accidents. Physicians can mold laboratory-grown cartilage into new ribs, noses, and ears for animals and will soon begin testing in humans.

Efforts to generate new bone have also shown encouraging results. Antonios G. Mikos, a chemical engineer at Rice University in Houston, has cultured bone cells inside three-dimensional polymer scaffolds, then implanted the new tissue into animals. As with other techniques, the polymer provides a structure to help the cells get organized, then dissolves away. Mikos believes this technique will perform well for repairing skeletal defects or replacing missing bone sections.

At Boston's Children's Hospital, researchers have replaced the femur in a rat's leg with engineered bone. The implanted material bears weight, integrates into the animal's skeleton, and holds for an extended period of time. In the case of engineered tendon, the newly grown material forms the right shape but has only one-third of a natural tendon's strength. "We're trying to improve the tendon's mechanical properties," Vacanti says. "But the results here, too, look good.

"We believe there will come a day when we can make an entire composite joint."

For people with severe burns or skin ulcers that will not heal, Naughton's team at Advanced Tissue Sciences is engineering off-the-shelf skin patches for emergency grafts. On thin sheets of dissolvable material seeded with dermal cells, the researchers grow the equivalent of living gauze—coverings for open wounds that stimulate the body's own healing mechanisms. For burn victims, the engineered skin provides a temporary live salve that helps keep in fluids and prevent infection, an alternative to the current practice of using skin from cadavers. For skin ulcers, the patch fills in the gap and promotes wound closure.

In a recent pilot study of diabetics with foot ulcers, 50 percent of the patients treated with engineered skin experienced complete wound closure, compared to 8 percent of the control group, Naughton reports. A follow-up study with 200 patients at 20 centers is expected to begin next year.

"For this population of badly injured people," says Naughton, "the potential benefits from engineered skin are great, while the risks are relatively low. If left untreated, these wounds can lead to infections and even amputation."

To generate enough tissue to treat several hundred thousand people a year, the researchers have filled stacks of bioreactors and tissue banks. The seed cells for the skin grafts come from discarded foreskins following "routine circumcisions," Naughton says. In the laboratory, those hearty infant tissues grow readily into patches.

How much skin have they harvested?

"About 250,000 square feet," says Naughton. "That's roughly the equivalent of six football fields.

"I know," she hastens to add. "We've heard all the jokes."

"People are just beginning to see the potential of this field," Naughton observes. "We're getting close to the point where patients will be able to benefit directly from this technology. Researchers are learning from each other's experiences and developing increasingly complex organs.

"During the next 10 years," she adds, "I expect to see worldwide availability of replacement skin for victims of burns and diabetic ulcers, and possibly of cartilage and blood vessels. Soon after that, we'll probably see whole organs, like livers and kidneys, with active metabolic functions." □