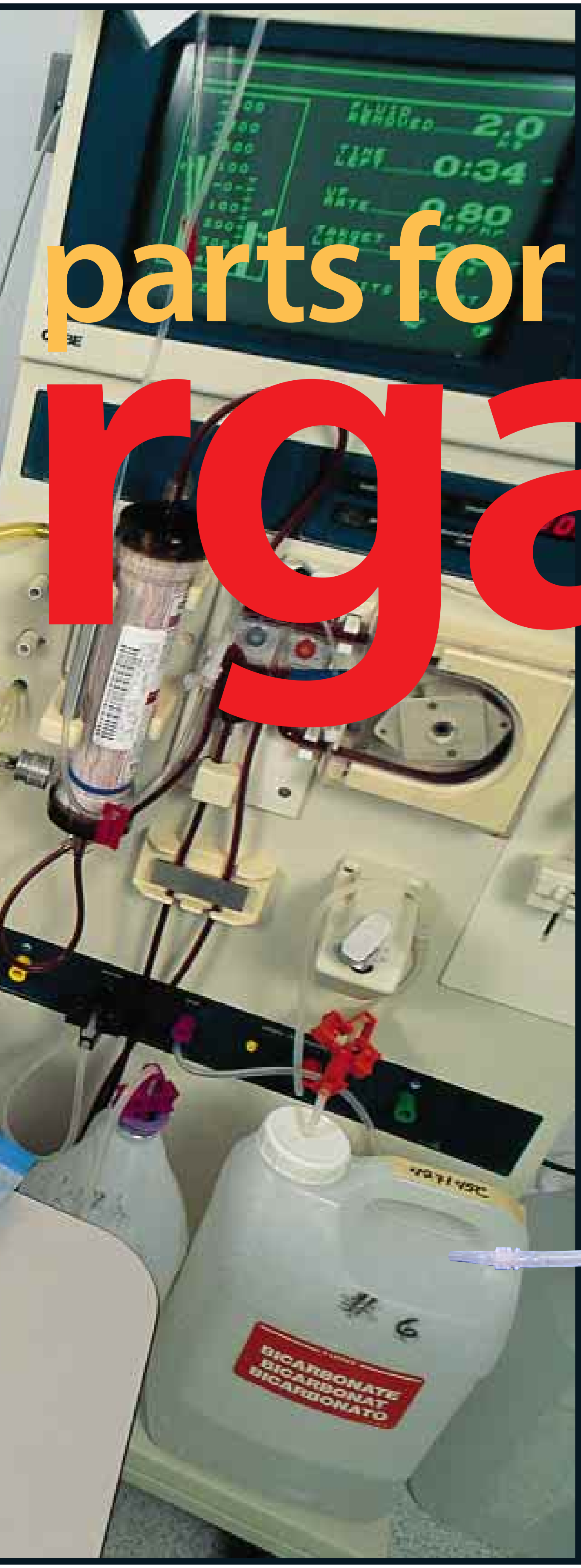
spare o

HOPE: A bioartificial kidney could someday end the exhausting regimen of dialysis. One prototype (*right*) has been developed by the University of Michigan.

MULVEHILL *The Image Works*



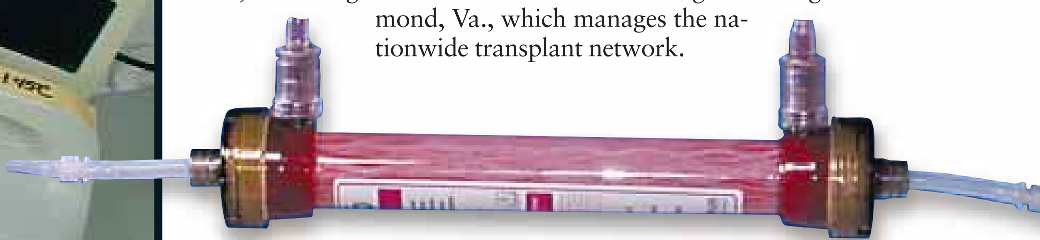
ENGINEERS ARE CREATING ARTIFICIAL REPLACEMENTS FOR FAILING HEARTS, KIDNEYS, PANCREASES AND LIVERS

parts for vital organs

BY DAVID PESCOVITZ

Atherosclerosis, diabetes, cirrhosis, hepatitis and other afflictions kill or disable millions of people every year by ravaging their organs over time. The elderly suffer the greatest toll. Bioartificial organs—a merger of mechanical parts with cells grown in laboratory cultures—could reduce premature death, improve quality of life and serve as vital bridges for seniors waiting for natural-organ transplants.

In the U.S., thousands of people die annually waiting for a transplant, and many thousands more never even make it onto a waiting list, according to the United Network for Organ Sharing in Richmond, Va., which manages the nationwide transplant network.



Engineering whole organs from scratch using pristine stem cells that can differentiate into any kind of body tissue would, of course, be the ultimate solution. But that is a longer-term prospect. For now, bioartificial organs offer the greatest hope for spare parts that can perform the complex tasks of a kidney, pancreas or liver. "We call these the smart organs," says Bartley P. Griffith, director of the McGowan Center for Artificial Organ Development at the University of Pittsburgh. A heart simply pumps blood through one-way valves. Kidneys, pancreases and livers face the arduous task of

VA ANN ARBOR HEALTHCARE SYSTEM

McGOWAN CENTER, UNIVERSITY OF PITTSBURGH

NEW PUSH: The McGowan Center's prototype artificial heart propels blood with a tiny impeller, rather than the power-hungry pumps used in past attempts to replace the organ.

chemically removing waste from incoming fluids and producing key compounds for the body. "If a heart is thought of as a first-grader," Griffith says, "a kidney is a senior in high school, and a liver is a postdoc."

Despite its "simplicity," building an artificial heart has proved difficult. The image of Barney Clark, recipient of the first Jarvik-7 artificial heart in 1982, was telling; his mechanical heart, which replaced his failed natural heart, was connected by hoses to a large, thumping pneumatic bellows outside his body that did the actual pumping. The unit had to be plugged into the wall, limiting Clark's movement. When Clark and a second artificial heart patient, William Schroeder, died within two years as a result of infections and strokes caused by blood clots, the public's hope in the technology died with them.

It took years for researchers to rethink their approach and miniaturize components. Instead of a full-blown replacement, recent devices have attempted to assist a failing heart until a transplant can be found. The left ventricular assist device (LVAD), the foremost example, is now in clinical use. A surgeon implants it into the abdomen, where it pumps blood that has been diverted from the left ventricle, one of the heart's four main chambers that pump blood. The device is powered by a small console or portable battery pack outside the body. The LVAD solves only some heart problems and still requires a power cable that passes through the patient's skin, but it buys crucial time.

LVAD progress has renewed interest in a new generation of artificial hearts. They are smaller and more efficient because they move blood in a fundamentally different manner. Instead of pumping with flexing diaphragms as did the previous generation, they have a tiny spinning impeller that propels the blood like a boat propeller moves water. The McGowan Center uses this approach in its Streamliner artificial heart, designed to be placed in the abdomen and to push blood through the natural heart and arteries using a pair of tubes. Inductive coupling could transfer energy from a coil attached to a battery worn on a belt to a secondary coil and battery implanted under the skin. The subcutaneous battery would then send power to the artificial organ over a thin wire.

The Streamliner may be the Cadillac of artificial hearts. The oblong device, made of titanium, is about four inches long, two inches across and weighs several ounces. It features an impeller suspended internally with magnets. "This eliminates the risk of failure because of bearings wearing out," says Griffith, who adds that the Streamliner faces at least 18 more months of well-funded development before it is ready for testing.

Other leading research teams are using the turbine approach in experimental LVADs. Thermo Cardiosystems is working with the McGowan Center, and Micromed Technology has partnered with the Baylor Medical Center.

Developing a "dumb" organ like the heart is a major engineering challenge, yet it pales in comparison with the complexity of building organs that have biochemical brains. To craft "smart" bioartificial organs like the kidney, pancreas and liver, experts must combine electrical, mechanical and tissue engineering. The strategy thus far is to take organ cells from humans or pigs, grow them in a culture medium, then load them into a bioreactor—a box or tube in which they are kept alive with oxygen and nutrients. The bioreactor is inserted into a larger machine outside the body. A patient's blood is diverted via tubes through the bioreactor, where it is cleansed—similar to the setup of today's kidney dialysis machines.

"Of course, the trick would be to understand the cell culture science and engineer the bioreactor well enough to implant one of these organs," Griffith notes. "I think we're 10 years away from that at least." Closer to fruition, he believes, is a "get out of trouble" bioartificial kidney, worn like a fanny pack, that could keep a patient alive during the wait for a donated human organ.

Beyond the Dialysis Machine

Diabetes and hypertension—the leading causes of kidney disease—plague the elderly. Today there are more than 40,000 Americans waiting for a kidney transplant. They must undergo dialysis or hemofiltration for hours at a stretch, multiple times each week. The regimen is exhausting. Just as vexing is that the machines can do only half the task at hand. While the kidney filters urea waste products from the blood, its tubules must also reclaim 98 percent of the filtrate, returning important sugars, salts and other substances to the body. Dialysis machines just can't pull off the second step.

By combining mechanical devices with engineered tissue, a bioartificial kidney could perform the entire function. Nephrologist David Humes and his colleagues at the University of Michigan have cultured proximal tubule cells, which handle the bulk of filtrate reclamation, from pig kidneys. The cells are enmeshed along hair-thin plastic fibers that line the inside of a polycarbonate filtration cartridge about 10.5 inches long and 1.4 inches in diameter. The cartridge is housed in a larger machine. As the patient's blood is pumped through the bioartificial kidney, the engineered cells filter out urea while returning the useful compounds.

Trials of the new system conducted on dogs last year were successful, and Humes is hoping for approval from the Food and Drug Administration to begin human trials later this year. “At this point, this is a temporary device for acute kidney failure,” he explains. “But we’re working on devices that have both filtration and a tubule element that could be wearable. We’re in a prototype stage.”

According to Humes, the first-generation wearable renal assist device could diminish a patient’s dialysis time by 30 to 50 percent and someday possibly eliminate it entirely. “The first dialysis machine was a huge 10-by-4-foot cylinder,” Humes says. “Our cartridges do the same thing, but you can hold them in your hand.” If fabrication advances make possible even more miniaturization, he adds, he and his team might be able to “devise one of these for implantation.”

SWEET: Now in development, Circe Biomedical’s PancreAssist would automatically monitor blood sugar levels and dispense insulin for diabetics.

CIRCE BIOMEDICAL

An implantable bioartificial device to assist a malfunctioning pancreas would create a similar revolution in the treatment of insulin-dependent diabetics. At present, diabetics must follow a strict daily regimen of self-administered tests to check blood sugar levels and one or more insulin injections to pick up the slack of a weak pancreas. But “because there is no effective feedback mechanism” for the level of insulin required, injection “is done as a best guess,” says Barry Solomon, president and chief scientific officer of Circe Biomedical in Lexington, Mass. The resulting large swings in glucose levels are thought to lead to the major complications of diabetes—vascular disease, retinal disease and heart disease.

The goal is to automate the system. Existing implantable insulin pumps tend to leak, and electronic glucose sensors are notorious for failing after little more than a month inside the body. But the real shortfall is that today’s systems cannot supply the feedback information needed to administer precise and properly timed dosages.

Circe’s PancreAssist system is designed to solve the problem. It is an insulin-on-demand system based on the body’s own chemistry. Now in preclinical development, PancreAssist is an implantable tubular membrane surrounded by insulin-producing islets, all contained in a plastic housing. As the patient’s blood flows through the center of the tube, the islets, harvested from pigs, detect changes in the patient’s glucose levels and respond by producing insulin when needed. The insulin diffuses across the membrane into the person’s blood. The membrane prevents white blood cells and antibodies from attacking the porcine cells, so immunosuppressant drugs are not needed. The unit, half the size of a hockey puck and weighing only a few ounces, will be implanted near the kidney. “Because we’re using cells that not only have the ability to produce insulin but also can sense and regulate that production in response to glucose levels, we’re essentially reproducing what the natural pancreas does,” Solomon explains.

An early version of the PancreAssist proved effective in animals several years ago, but a reengineering of the vascular graft was required before human studies could begin. Solomon hopes the slimmed-down system will be proved on animals and ready for human clinical trials within two years.

Letting the Liver Regenerate

The challenge is greater for a bioartificial liver to replace a natural one damaged by diseases and insults such as hepatitis C and alcoholism. A healthy liver metabolizes toxins, produces bile, regulates the balance of many hormones and manufactures blood-clotting proteins. Designing an organ to accomplish all these complex tasks is daunting. But a device may be needed to replace these functions only for a short time, says Achilles Demetriou, a bioartificial liver pioneer who is chairman of the surgery department at the Cedars-Sinai Medical Center in Los Angeles. “The liver has such a remarkable capacity to regenerate that temporary support could result in complete recovery of the injured organ,” Demetriou points out. If a damaged liver could be relieved of all its duties for just one week, it would have a good chance of repairing itself. There is currently no machine that can take over the organ’s function, however.

The goal, therefore, is a bioartificial organ that can bridge the repair time. Several companies are pursuing state-of-the-art work, including Organogenesis in Canton, Mass., developers of FDA-approved lab-grown skin, and Circe Biomedical, whose HepatAssist system was developed in collaboration with Demetriou.

HepatAssist is undergoing phase II and III clinical trials in liver transplant centers around the U.S. It uses pig liver cells in a bioreactor to remove toxins

the cryonics gamble

No "corpses" reside at the Alcor Life Extension Foundation. Just three dozen "patients" entombed at a rock-hard 320 degrees Fahrenheit below zero who have bet that future physicians will have the technology to "reanimate" them. When each one was at death's door, a friend or family member had phoned Alcor's CryoTransport team. The outfit rushed to the scene. Once a doctor had pronounced the subject clinically dead, the team put the deceased on ice, pumped the body full of medications and solutions and transported it to Alcor headquarters in Scottsdale, Ariz.

The team then circulated glycerol, used as antifreeze, into the major arteries to prevent damaging ice crystals from forming among cells. The patient was then placed in a "dewar"—a tall metal thermos that is filled with liquid nitrogen. The patients stand there today in wait. But don't dare compare them to mummies. Cryonics, Alcor insists, has nothing to do with "bringing people back from the dead."

TIMOTHY ARCHIBALD

YOU BET YOUR LIFE: At her death, Christine Peterson will be frozen in a tank by Alcor, run by Linda Chamberlain (*right*), in hopes she can be revived and repaired.

Freeze now, revive later is certainly one way to attempt to extend your longevity. The first Alcor "member" has been frozen since 1976. "If you're feeling good and you enjoy life, it's not a matter of figuring out why you should do this," says Christine Peterson, a 42-year-old writer and Alcor subscriber. "It's more a question of why you would want to check out."

Nice theory—but there's a catch. Someone someday will have to figure out how to reconstruct your body, mind and soul. And at present neither Alcor nor anyone else knows how to do it. Therein lies the gamble.

Peterson's not worried. She believes a cure for aging will come along before she needs to be frozen. "For people around my age and younger, cryonics is more like backup insurance," she says. If a fix doesn't materialize, then she's betting that nanotechnology will bring her back from the deep freeze. Nanotechnology is one of her life's passions. She has penned a book about it and is married to scientist K. Eric Drexler, a maverick nanotechnology evangelist. The believers say that one day thousands of nanobots—microscopic robots one billionth of a meter long—will be able to travel through your body *Fantastic Voyage*–style, repairing cells to fix whatever ails you. The army of dutiful nanobots would repair widespread cellular damage caused by the freezing, rejuvenate your brain cells and rebuild your tired old body, cell by cell, into something new.

But no one has crafted a single nanobot. And although nanotechnology is all the rage in the popular press, many scientists ridicule molecular robots as little more than the ruminations of science-fiction aficionados.

Peterson has such faith in nanotechnology that she has signed up for Alcor's neuropreservation service—freezing just her head. It'll simply be attached to a more youthful body when it's thawed. Nanotechnology will fix any complications from her recapitation and will subsequently keep her new body youthful forever. Her mother, husband, friends and colleagues such as artificial-intelligence researcher Marvin Minsky will be glad to see it; all of them are signed up with Alcor.

Putting your frozen corpse—er, body—in Alcor's care doesn't come cheap. The flat fee is $120,000. Whether that's enough for the needed half-century of minding isn't clear. Charles Platt, a writer of science fact and fiction and director from the blood of patients, in a technique similar to Humes's bioartificial kidney. A cylindrical plastic cartridge 14 inches long and 2.5 inches in diameter, lined with engineered cells, fits into a larger machine. A patient's blood passes through it for cleansing. Patients undergo six-hour sessions for seven consecutive days. "By then," Demetriou says, the hope is that either "their liver recovers and takes over or they receive a transplant."

HepatAssist is intended to serve solely as a bridge. An implantable liver replacement, Demetriou believes, will probably have to be engineered from stem cells, a venture he asserts will be "orders of magnitude more complex" than those for other organs.

In the meantime, whichever bioartificial organs emerge may face competition from other organ-replacement approaches that are also advancing, notes Peter Stock, associate professor of transplant surgery at the University of California at San Francisco. Most anticipated, perhaps, is xenotransplantation, in which organs harvested from transgenic pigs or primates could be transplanted into humans. The organs would be endowed with certain human genes and engineered to not induce immune rejection. Various attempts to fix faulty organs by altering genes directly are under way, too.

Whether tomorrow's spare organs are built around bioartificial cartridges, pig innards or stem cells will in the end be determined by lab work and by safety and effectiveness questions that get hashed out during the FDA approval process. But no matter which technology beats the organ shortage, the ultimate prize will go to the individual who gets a new lease on life after a visit to the human body shop of the future.

David Pescovitz *writes frequently for* Scientific American *and is a contributing editor at* Wired *magazine.*

Further Information

American Heart Association
(www. americanheart.org).

McGowan Center for Artificial Organ Development
(www.upmc.edu/mcgowan).

IRWIN DAUGHERTY *AP Photo/Mesa Tribune*

of the CryoCare Foundation, which subcontracts freezing, isn't expecting a cryonics patient to be successfully resuscitated for at least 60 years.

If we all could be frozen and defrosted, the earth might become a crowded place. Peterson has an otherworldly solution for that, too: colonize outer space. Her vision of a space-faring society, common among her future-minded peers, is reminiscent of the late LSD guru Timothy Leary's prescription for the human race: SMI^{2}LE, an acronym for "space migration, intelligence increase and life extension."

Indeed, Leary was arguably the most famous advocate of cryonics. (Contrary to rumors, Walt Disney was cremated after his death in 1966, and Michael Jackson has never publicly announced plans to take a liquid-nitrogen bath.) But if, as English scholar Samuel Johnson noted, the prospect of one's imminent demise tends to concentrate the mind wonderfully, then eternity on ice may lose some of its allure. During his final hours of life, Leary abruptly changed his plans for cold storage. His stated reason, according to friends who were at his bedside: "Waking up in the future surrounded by a bunch of men in white lab coats holding clipboards didn't sound like so much fun." *—D.P.*