Building hope: The University of Michigan's David Humes holds his "kidney in a cartridge," a device that could help patients suffering from severe kidney failure.
PHOTOGRAPH BY CHRIS LAKE

SAVING LIVES *with* LIVING ACHINES

For many patients with organ failure, artificial devices like dialysis machines are just not enough. Now doctors are combining the unique properties of human cells with man-made materials to create bioartificial organs, including kidneys and livers, that could save thousands.

BY PETER FAIRLEY

Around a hospital's intensive-care unit it is often called the spiral of death. Chemotherapy or an infection knocks a patient's kidneys out of service, and within a day or two, inflammation spreads throughout his or her blood vessels. Blood pressure crashes, starving the body of oxygen, and in short order the lungs, liver, and other organs begin to fail. Replacing the kidney's most basic function by using conventional dialysis to clear urea and other wastes from the blood is of little help. More than half of those caught in the grip of acute kidney failure die.

But in a small clinical trial completed last winter, a novel treatment offered the first real hope for patients in acute kidney failure. Six out of the 10 critically ill patients beat the odds and survived; all but one had been judged to have no more than a 10 to 20 percent chance of living.

What appears to have saved them is a plastic cartridge the size of a pair of stacked soda cans containing an unconventional active ingredient: one billion human kidney cells thriving inside 4,000 translucent, hollow, plastic fibers. It's called a bioartificial kidney. Developed after a decade of research by University of Michigan internist David Humes, this hybrid of living cells and artificial structure is at the forefront of a pragmatic effort to find an effective treatment for people whose organs have failed. Though the research may not be as glamorous as attempts to develop an all-artificial heart or other completely synthetic organs, the strategy has a distinct advantage: it seems poised to save lives now. "It's clearly a very promising technology," says William Harmon, a transplant physician at Children's Hospital in Boston and president of the American Society of Transplantation.

Bioartificial organs' most compelling use may be for kidney failure patients. While a strictly artificial device such as a dialysis machine can cleanse the blood, it can't replace or mimic the subtler metabolic functions of a large, complex organ like the kidney. Dialysis machines just don't do enough to save most patients in acute kidney failure. Nor, in the long term, do they do enough for the hundreds of thousands of people with chronically diseased kidneys. "Patients who are undergoing chronic dialysis become malnourished, and they sort of wither," says Harmon. The solution, believes Humes, lies in harnessing kidney cells themselves—cells that can rapidly react to changes in the body's environment in a way that machines simply can't.

The kidney-in-a-cartridge, which is being developed by Lincoln, RI-based University of Michigan spinoff Nephros Therapeutics, could be ready for widespread use in as little as three years. And it's only one example of the increasingly popular strategy of using living cells to do the heavy lifting in artificial organs. Several academic labs are developing similar devices packed with liver cells to chew up the toxins that accumulate in the blood when the liver suddenly fails. Already in human trials, these bioartificial livers could help patients in acute liver failure, whose only chance today is a rare organ transplant.

While bioartificial organs offer benefits that purely mechanical devices can't match, they still have some severe limitations. For now at least, they are external devices, and the cells inside them stay healthy for no more than a few weeks. Even such temporary support could be a boon for medicine, sustaining thousands of patients and enabling them to regain the function of their own organs or survive until transplant organs become available. But the real revolution will come with the development of permanent, implantable bioartificial organs. That will require new materials that allow the cells to receive nourishment from the body but still protect them from attacks by the recipients' immune systems. Such devices are years from fruition, but Humes and other researchers developing living temporary devices have started laying the groundwork for them—with the potential for eventually saving hundreds of thousands of lives.

Cellular support: Immature kidney cells harvested from donated organs grow in an incubator, waiting to be seeded into bioartificial kidneys.
PHOTOGRAPH BY CHRIS LAKE

CELL POWER

Life without properly functioning cells can be hell, and no one knows that better than a dialysis patient. People with chronic kidney disease—400,000 in the United States alone—plug into dialysis machines three to six times a week. The machines pump their blood through permeable tubes, squeezing out plasma (the fluid and proteins making up the bulk of blood) and dissolved wastes, which are tossed out. Then the oxygen-carrying red blood cells and the white blood cells of the immune system are mixed with fresh plasma and returned to the body. Such periodic flushing extends the lives of those with diseased or damaged kidneys, but it doesn't make them healthy. Regardless of age, life expectancy for most patients on dialysis is capped at five years. "There's no question that dialysis in its current mode is an insufficient treatment," says Harmon. Dialysis is even less effective for the more than 120,000 Americans every year whose otherwise healthy kidneys are suddenly knocked out by infection, toxins, or strokes. Even with continuous dialysis, 60 percent of those facing acute kidney failure descend into multiple organ failure and death.

There are few if any options. Transplantation of a healthy, compatible kidney is the only reliable means of escape from dialysis. But those in acute failure are seldom stable enough to endure transplants; and while transplants rescue 14,000 people with chronic kidney disease in the U.S. each year, more than 50,000 languish on waiting lists, thousands of whom die waiting. Meanwhile, a fully artificial replacement for the kidney is unlikely any time soon. Bioengineers lack a complete understanding of what the organ does. And compared to cells, even the most ingenious mechanical device is woefully unsophisticated. "Cell therapy is based upon a billion years of Mother Nature's research and development. We're not that bright," says Humes.

The promise of Humes's bioartificial organ is to deliver the full range of kidney functions, even tasks such as regulating the immune system that are barely understood by medical science. Though the fix is temporary, patients who survive acute kidney failure have a good shot at a normal life, free of dialysis. For patients in chronic failure, cellular support could supplement traditional dialysis, arresting their slide into heart disease and infection, improving their quality of life, and increasing their life span.

Ten years ago Humes was one of the few nephrologists who believed that tem-

porary support with living kidney cells was desirable. He was an early advocate of the theory, now gaining ground, that the organ helps to control inflammation and that the loss of this control is what makes acute kidney failure so deadly. In the early 1990s, Humes made the breakthrough that enabled the bioartificial kidney: he found a source of cells. Humes discovered how to isolate the immature cells that form the kidney's tubules—its functional center. Within a few years, he had figured out how to coax these cells to form mature tubule structures in the lab.

To make the devices that Humes and Nephros are testing, technicians harvest immature kidney cells from donor organs deemed unsuitable for transplantation and seed them into hollow, plastic fibers *(see "Bioartificial Treatment," this page)*. There the cells multiply and organize to form a continuous blanket of tissue just one cell thick, transforming each fiber into a living, working kidney tubule. "It's basically what you would see in a kidney," says Humes. "It's their natural architecture."

The first human tests showed that Humes's kidney is safe. What is more exciting is that the device also appeared to pull a few of its first patients out of acute kidney failure, even though the U.S. Food and Drug Administration limited treatments in this initial trial to 24 hours. How such brief support from living tubules could save someone in such desperate condition isn't clear. Humes believes that among the substances that the tubule cells add to blood are molecular signals that instruct the patient's immune system to reign in the inflammation ravaging blood vessels throughout the body. By smothering this inflammatory "forest fire," suggests Humes, the tubule cells stabilize blood pressure, oxygenating and rejuvenating the patient's organs. "We view this treatment as almost like a drenching rain for 24 hours," he says.

LIVING LIVERS

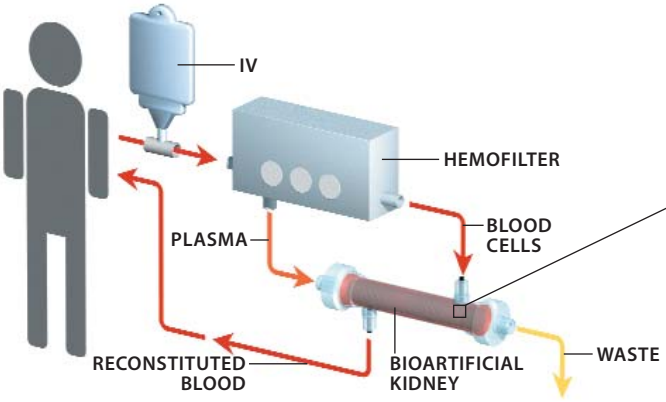
Humes's success is raising hope among corporate and academic researchers who are busy developing similar temporary-support devices for patients in acute liver failure, a rarer yet even more deadly condition. An acute case of hepatitis or a chemical assault (most commonly an overdose of the pain reliever acetaminophen) causes acute failure in about 2,000 people in the United States each year. Without transplants, nearly 80 percent will die, as ammonia and other toxins in the blood degrade the blood-brain barrier, causing the brain to swell out of control. Liver-assist devices analogous to Humes's bioartificial kidney are already in advanced human tests, but despite years of development, definitive success has been elusive.

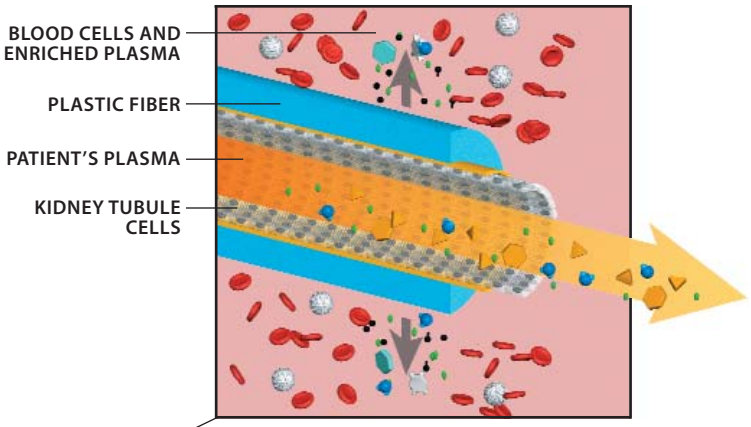
Bioartificial livers employ a cartridge full of liver cells to break down toxins in blood plasma fed into hollow plastic fibers. By taking over liver function, these devices could allow patients' ailing organs to recover—or at least support them until transplant organs become available. George Mazariegos, a transplant surgeon at the University of Pittsburgh's Thomas E. Starzl Transplantation Institute believes such devices might one day do more than carry patients through the most acute phase of liver failure; he hopes that by continuing to support patients for several weeks, bioartificial livers will enable an increasing number to recover the function of their own livers, avoiding the ordeal of transplantation and freeing up donor organs for those in greater need. "Cell-based therapies are going to be part of the mix, for sure," he says.

Finding the right cells may be the key to success. The earliest bioartificial-liver devices used liver cells from pigs to detoxify blood, but concerns over the possible transfer of porcine viruses to humans—unlikely as many researchers considered it to be—frightened investors and dried up financing for these projects. In March, investors pulled the plug on yet another bioartificial-liver company. San Diego-based Vitagen was in advanced clinical trials with a device employing cells cultured from a human liver tumor. These cells had been "immortalized," meaning they could be multiplied ad infinitum—so they were easy to come by. There are risks attached to using tumor-

Bioartificial Treatment

During treatment with a bioartificial kidney, a patient's blood passes from an IV into a "hemofilter" much like a conventional dialysis machine, where the plasma is removed from the blood. Instead of being discarded, the plasma is pumped into the bioartificial kidney's plastic fibers. The reconstituted blood returns to the patient through a second IV while the liquid waste drains out of the ends of the fibers.

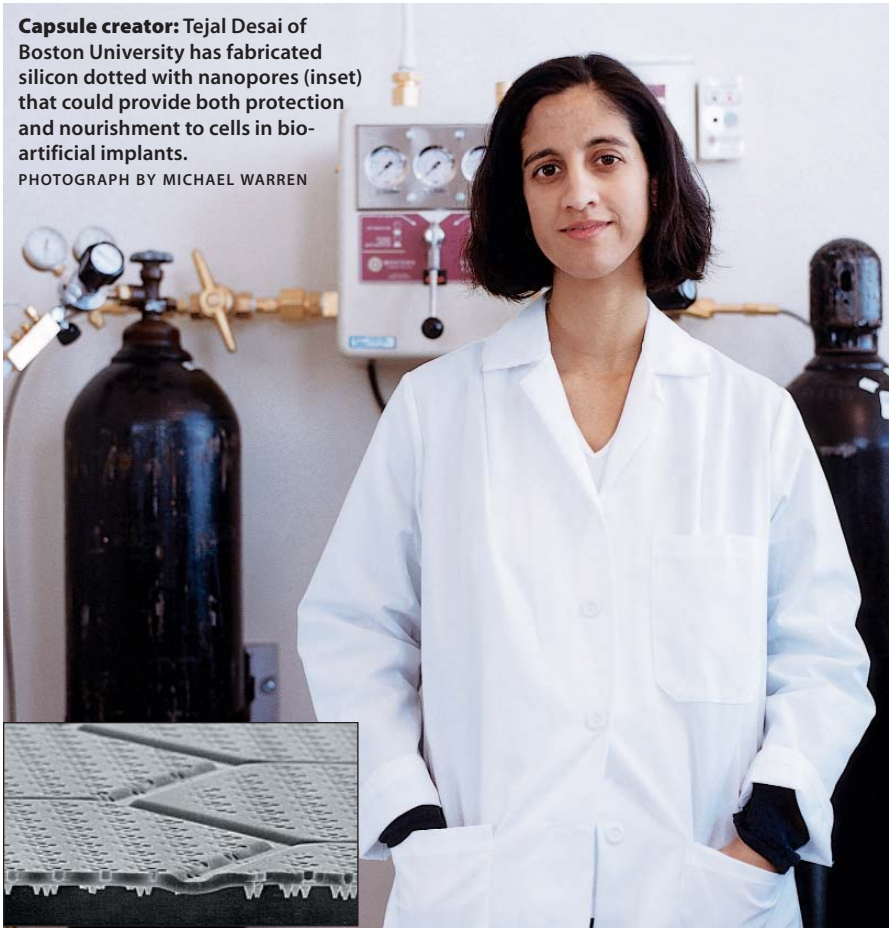




Inside the fibers, tubule cells reabsorb water, sugar, and other nutrients from the patient's plasma and add in supplements such as vitamin D. Blood cells flow past the fibers, which protect the kidney cells from attack by immune cells. The tubule cells pump the enriched plasma through tiny pores in the fibers and back into the patient's blood.

JOHN MACNEILL

Designer liver: In this bioartificial liver created by the University of Pittsburgh's Jörg Gerlach, cells can survive for months.
PHOTOGRAPH BY KAREN MEYERS



Capsule creator: Tejal Desai of Boston University has fabricated silicon dotted with nanopores (inset) that could provide both protection and nourishment to cells in bioartificial implants.
PHOTOGRAPH BY MICHAEL WARREN

derived cells, however, and more significantly, the cells had less-than-normal liver function. Nonetheless, the technology was showing promise in trials, which were halted by the company's demise.

Normal human liver cells clearly would be preferable. Immortalized liver cells retain a youthful capacity for growth because they are frozen in an early stage of development, but as a consequence they have not attained some of their most important detoxification tricks. "Immortalized cells are blocked in their ability to mature, so their ability to support patients is minimal," says Lola Reid of the University of North Carolina at Chapel Hill. Reid says that what is needed are young yet normal human cells, akin to Humes's immature kidney cells, that can grow and develop to populate a bioartificial device. To that end, she is developing cell-handling methods to isolate and amplify immature liver cells from donor organs.

Improvements in device design will help deliver more metabolic firepower as well. Jörg Gerlach, who recently moved to the University of Pittsburgh's McGowan Institute for Regenerative Medicine from Berlin's Charité Institute for Transplantation and Organ Regeneration, has developed a bioartificial liver that employs three types of hollow fibers woven through human liver cells harvested from transplant rejects. One set of fibers delivers oxygen to the living cells, keeping them in metabolic overdrive, while the other two pump plasma respectively to and from the cells, a setup that resembles the natural architecture of the liver. "Our cells spontaneously reassemble into tissue structures. Under these circumstances, the human cells survive for more than two months," says Gerlach, who has already initiated human tests of the device in Germany. Larger trials in the United States could begin within a year.

ADVANCING IMPLANTS

But what of the hundreds of thousands of patients with chronically diseased organs? Bioartificial-organ technology could restore their health as well—if it can make the leap from today's temporary, external devices to long-term implants. Success with extracorporeal devices is inevitably stirring hope for bioartificial implants to treat this much

larger need. Though researchers have pursued the idea since at least the 1970s, the field had been all but abandoned after continual disappointment. The problem: researchers couldn't find a way to fully shield the cells inside an implanted device from recipients' immune systems. Studies of encapsulated liver, pancreatic, and kidney cells have all run into problems due to immune rejection.

In fact, the porous plastic fibers that protect the cells in current bioartificial kidneys and livers from assault have failed in implants time and again. Their minute openings can defend against immune cells, but smaller armaments of the immune system, such as antibodies, can still penetrate the implant and, over time, break down its cells. It's not a problem in temporary external devices, but in an implant, the detritus from dying cells passes out to the surrounding tissues, prompting scarring and blood clots. Eventually this seals off the implant, starving the cells still living inside.

Advances in nanotechnology could provide the solution: a material able to handle the seemingly contradictory tasks of isolating the cells from the immune system while allowing them to actively participate in the body's function. Boston University biomedical engineer Tejal Desai believes nanotech can help fashion capsules with pores that can protect implants from even the tiniest immune invaders. "We can achieve absolute control over what gets into the system, what gets out," says Desai.

Desai is developing a bioartificial pancreas that could extend diabetics' lives and free them from pinpricks. She starts with silicon and etches it full of holes with techniques adapted from microchip production. The holes are 12 to 18 nanometers across, a fraction smaller than an antibody molecule. Desai then shapes the porous silicon into a small capsule or disc and fills it with living, human pancreatic cells. Surgically implanted in rats whose pancreases have been destroyed, these silicon capsules have elicited none of the clotting or scarring that doomed earlier implants. Moreover, insulin produced by the implanted cells maintained the rats' blood sugar levels through the two-week test period, sustaining rats that would otherwise have perished in a matter of days. Within a year, Desai hopes to begin tests in large animals (probably dogs) of a prototype implant for diabetics.

William Fissell, a researcher in Humes's University of Michigan lab, believes that similar silicon membranes could be the key to bioartificial kidney implants. But unlike Desai's pancreatic implants, a bioartificial kidney must filter more than 100 liters of fluid each day. That's easy for a large external cartridge with pumps to do, but filtering that much fluid is difficult in a much smaller implant, especially when nanopores constrain the exchange of fluid. The challenge is to design a material whose openings pass liquid efficiently and can support many tubule cells, yet which still protects the cells from antibodies. Fissell is already testing an elegant solution: stretching nanopores into elongated nanoslits with far more efficient fluid dynamics. If these slits can keep the antibodies out and filter fluids using only the body's blood pressure, bioartificial kidney implants might one day replace dialysis for patients with chronic kidney failure.

But until then, external devices like the kidney-in-a-cartridge are the best hope. Emil Paganini, a leading dialysis authority at the Cleveland Clinic, is convinced of the bioartificial kidney's potential, and the technology has not disappointed him. Five of Paganini's patients were among the first 10 treated. He vigilantly followed their 24-hour treatment and witnessed consistent improvement. In one case, a patient's response to the treatment astounded even this seasoned physician, who has seen his share of against-the-odds recoveries: the young man's kidneys, poisoned by antifreeze, began to function again while his blood flowed through the bioartificial kidney, then shut off when the device was removed. "That blew my mind," says Paganini. The patient's kidneys eventually rebounded, and today the man is healthy.

After decades of frustrating research on purely artificial organs, such experiences are redefining the possibilities of organ replacement, reviving hopes for the struggling field. As Paganini puts it, "The concept of a bioartificial organ is in and of itself exciting." But what's even more exciting to physicians like him is that bioartificial organs, hybrids of the living and the synthetic, could soon be saving thousands of lives. TR

Bioartificial Potential

RESEARCH TEAM	DISEASE TARGET	TECHNOLOGY	STATUS
Nephros Therapeutics (Lincoln, RI) and **David Humes, University of Michigan** (Ann Arbor, MI)	Acute and chronic kidney disease	External and implantable bioartificial kidneys	Human trials (external device only)
Jörg Gerlach, University of Pittsburgh (Pittsburgh, PA)	Acute liver failure	Bioartificial liver using natural liver structure	Human trials
Lola Reid, University of North Carolina (Chapel Hill, NC)	Liver disease	Bioartificial liver using normal human liver cells	Prototype
Amaranth Therapeutics (Cambridge, MA) and **Lawrence Rosenberg, McGill University** (Montréal, Québec)	Diabetes	Pancreatic islet cells in bioartificial organs	Raising funds for animal trials
iMEDD (Columbus, OH) and **Tejal Desai, Boston University** (Boston, MA)	Diabetes	Insulin-producing cells in nanoporous silicon implants	Animal trials
MicroIslet (San Diego, CA) and **Daniel Salomon,** the **Scripps Research Institute** (La Jolla, CA)	Diabetes	Insulin-producing cells in porous organic-polymer implants	Animal trials