INNER ANATOMY
An ingenious use of sugar molds coated with cells may allow investigators to replicate the sturdy internal vessels that are needed to carry oxygen deep within larger organs, such as the kidneys (*shown here*), and to remove wastes.

A Sweet Solution for Replacing Organs

To build large organs that work properly, researchers need to find a way to lace them with blood vessels

By Katherine Harmon

THE AUDIENCES at TED talks are used to being wowed as they learn about advances in technology. Even by TED standards, however, the 2011 presentation by Anthony Atala of the Wake Forest Institute for Regenerative Medicine was amazing. Unseen by the audience at first, various vials and nozzles hummed with mysterious activity behind Atala while he was on the stage. About two thirds of the way through the talk, a camera zoomed in on the device's internal armature and showed it weaving back and forth, depositing living cells grown in a laboratory culture layer by layer on a central platform, basing its activity on highly accurate three-dimensional digital renderings. The process, known as 3-D printing, resembles the operation of ink-jet printers but, in this case, instead of ink the printer uses a solution of living cells. In the end, Atala's machine produced, layer by layer, a life-size kidney made of human cells, much as a personal 3-D printer can spit out, say, a plastic replacement part for a coffeemaker.

A straightforward and quick way to make organs would be a welcome development for the more than 105,000 Americans waiting for organ donations. But the printed kidney Atala demonstrated two years ago was not ready to implant. It lacked two crucial elements: working blood vessels and tubules for collecting urine. Without these or other internal channels, large organs such as the kidneys have no way to get crucial nutrients and oxygen to, or remove waste products from, the cells deep within their interiors, and those cells quickly die. Researchers have tried to print these hollow structures layer by cellular layer into the organ by leaving holes in the right spots on each level, but the method produced conduits that can collapse and seams that can rupture under pressure from the blood being pumped by the heart.

A team of scientists from the University of Pennsylvania and the Massachusetts Institute of Technology has come up with a sweet solution to the problem. Instead of printing an organ and its inner vessels all at once, they print a dissolvable sugar mold of the vessels and *then* build up the appropriate cells around the mold. Later, the mold is washed away, leaving behind the structurally sound passageways that are able to stand up to the varying blood pressure levels found in the body.

AN INSPIRING DESSERT

THE IDEA CAME to Jordan Miller (one of the lead researchers on the project and a postdoctoral fellow at Penn) in two stages. First, while visiting a display of preserved human cadavers and organs at a Body Worlds exhibit, he saw that preparators

had exposed the lacelike structure of a large organ's vessels by injecting silicone into the vasculature and then dissolving away the remaining organic tissue.

Creating a synthetic mold on which to build internal vessels might work, Miller surmised, except that the chemicals needed to dissolve the silicone would be toxic to the living cells that were to be added. The way around that problem hit him when, at a fancy restaurant, he was served a dessert with an elegant hard-sugar lattice. Why not create a mold for an organ's blood vessels and other chambers out of sugar, which could be washed away with water?

Miller and his colleagues modified an open-source 3-D printer called the RepRap to print a carefully proportioned mixture of sugars in filaments of various sizes from about one millimeter down to 100 microns in diameter.

The team used these filaments to create an idealized version of a vascular network and coated the resulting sugar framework in a bio-friendly polymer to prevent the sugar from dissolving too fast. Then the scientists encased the whole thing in a combination of extracellular matrix [see "The Super Glue Cure," on page 52] and endothelial cells of the kind that line blood vessels. Finally, the researchers eliminated the sugar with water, ending up with sturdy blood vessels made up of living cells.

Then it was the cells' turn. Just as they do in the body, they began remodeling the blood vessels in which they found themselves—giving the overall structure more strength and even creating tiny capillaries at the ends of larger vessels. By allowing the cells to fill in some of the details, says Christopher Chen, who runs the Tissue Microfabrication Lab at Penn, "we don't have to perfectly design the architecture." In essence, the body can take over the finer touches on a nearly complete organ, allowing it to become fully functional.

To date, Chen, Miller and their colleagues have created blocks of liver tissue that contain sugar-molded blood vessels and implanted them in rodents to show that they will integrate with an existing vascular system. These slivers of tissue cannot take the place of a whole organ, but it is easy to see how adding liver, kidney or pancreatic cells on a fully developed vascular network could one day lead to the 3-D printing of larger body parts.

Replanting the Brain's Forest

Neurodegenerative disorders devastate the brain, but doctors hope one day to replace lost cells

By Ferris Jabr

INSIDE THE HUMAN BRAIN, branching neurons grow beside, around and on top of one another like trees in a dense forest. Scientists used to think that any neurons that wilted and died from injury or disease were gone forever because the brain had no way to replace those cells. By the 1990s, however, most neuroscientists had accepted that the adult brain cultivates small gardens of stem cells that can turn into mature neurons.

Researchers are still trying to determine exactly how often these stem cells become new neurons and how well these differentiated cells survive and join established brain circuits. Some evidence suggests that the brain's neural stem cells help the organ heal itself in modest ways—helping to replace small populations of neurons that suffocated during a stroke, for example. But this minimal self-repair does not restore the millions of neurons lost to stroke, traumatic brain injury and neurodegenerative diseases such as Alzheimer's and Parkinson's.

If stem cell therapy works for Parkinson's, doctors might be able to treat a wider range of nervous system diseases.

Twenty years ago neurosurgeons tried to overcome the brain's limited regenerative ability by slicing up sheets of fetal brain tissue and grafting them onto a diseased brain to replace dead neurons with new ones. The resulting clinical trials were disappointing, but some investigators think they have now worked out how to make the treatment safer and more reliable. Instead of relying on fetal tissue, scientists can grow millions of young neurons from stem cells in the laboratory and inject the juvenile brain cells directly into patients' brains. Although few expect the therapy to be widely used for another decade or two, early studies toward that end have begun.

The most promising work so far focuses on Parkinson's, which seems to be particularly responsive to grafting. Parkinson's, which affects about 10 million people (including one million Americans) worldwide, results primarily from the death of dopamine-secreting neurons in the substantia nigra, a section of the midbrain important for controlling movement, among other functions. Symptoms include shaking, stiffness and difficulty walking.

In the early 1980s researchers harvested immature brain tissue from rat fetuses and transplanted it into the substantia nigra of rodents whose dopaminergic neurons had been killed to mimic Parkinson's. Despite the transplanted neurons surviving the procedure, they largely failed to form functional neural circuits. Usually, as the brain develops in the womb, neurons in the substantia