NEWS

Wanted: Pig Transplants That Work

A shortage of human organs spurred researchers to look for replacements from animals. They're still struggling to cross the species barrier successfully

In the early 1960s, Keith Reemtsma, a surgeon at Tulane University in New Orleans, transplanted chimpanzee kidneys into six patients and launched the modern era of xenotransplantation. One person survived for a startling 9 months, sparking worldwide enthusiasm for a potentially limitless supply of lifesaving organs and tissue.

Since then, the field of xenotransplantation—the transfer of organs, tissues, and cells from one species to another—has been humbled by a string of false starts and failed procedures. Nearly 4 decades after Reemtsma's transplants, no human recipient of a whole animal organ is known to have survived for as long as that early kidney patient. Twelve-day-old Baby Fae, for instance, received a baboon heart in 1984 but died 3 weeks later. Whole-organ transplants into humans have been largely abandoned in industrialized nations due to massive immune rejection and other safety worries, although researchers hope they may someday be practicable. Clinical trials of cell and tissue xenotransplants, meanwhile, are under way in Europe and the United States, where they are tightly regulated. Thus far, results have been mixed.

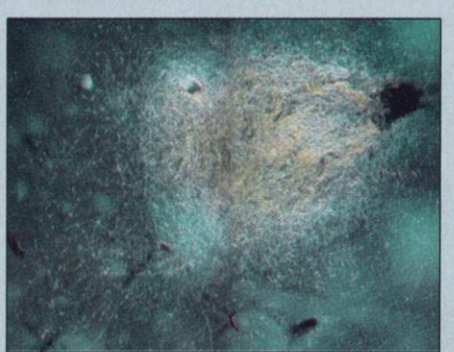
Since abandoning chimpanzees as donors, scientists have turned to pigs, whose organs resemble those of humans in size and function. The one animal-to-human transplant routinely performed worldwide employs pig heart valves. Because the valves are chemically treated to kill living cells, most nations do not regulate their use as xenotransplants.

But living pig tissue is another story. Scientists have known for years about deadly immune responses generated by intact pig organs. So-called hyperacute rejection occurs when human antibodies swoop in on a porcine sugar called α-galactose (α-gal) that studs the surface of pig cells. The antibodies also trigger acute vascular rejection, whereby the host attacks introduced porcine blood vessels. T cells and possibly macrophages also work to thwart the organ, as can happen in same-species transplants.

In January, researchers reported one advance toward preventing hyperacute and vascular rejection: They engineered piglets with just one gene for α-gal instead of the usual two (*Science*, 4 January, p. 25). Pigs with both genes missing, which researchers hope to breed from these animals, could make organ xenotransplants more viable. But "there's a spectrum of opinion" on the subject, says Fritz Bach, a professor of surgery at Harvard Medical School in Boston, who suspects that other antibodies and mechanisms may play a role in immune rejection.

Desperate measures. A baboon heart beat in Baby Fae until she died 3 weeks after receiving it.

Foreign cells and tissues are considered less risky to transplant. Unlike whole organs, they lack blood vessels and can evade some of the immune system's revolt. One convenient target for such xenotransplants is the brain and spinal cord, which are not subject to the same immune system scrutiny as the rest of the body. In clinical trials since 1995, Diacrin, a company in Charlestown, Massachusetts, has implanted porcine neurons into the brains and more recently spinal cords of more than 40 people with neurological disorders; results so far are equivocal. A study on stroke victims was halted after two suffered seizures. Perhaps Diacrin's greatest success emerged from autopsies of two volunteers whose deaths were unrelated to the study: Millions of pig cells that had been implanted in the central nervous system had survived long term. A Swedish study of porcine islet cell implants into the pancreas, however, found that few endured.



Now, get to work. Pig nerve cell fibers (white threads) survived in the brain of a patient with Parkinson's disease.

Another approach to using animal tissue is to avoid transplants altogether. At hospitals in Germany, Italy, the Netherlands, Spain, Belgium, and the United States, patients with acute liver failure have been hooked up to a device that uses porcine liver cells to treat the patient's blood. A phase II/III study of 171 patients recently ended; Circe Biomedical, the Lexington, Massachusetts, company running the trials, reported in November that the treatment prolonged survival for a majority of the patients, buying them more time to find a human donor.

At least as daunting as immune rejection is the concern—fueled by mad cow disease and the apparent emergence of HIV from a primate virus—that xenotransplantation of any type could transmit viruses harmless to pigs but deadly to humans. For instance, all pigs carry porcine endogenous retrovirus (PERV), but its potential effects on people are unknown. Repeated testing, including a 1999 study of 160 xenotransplant patients, has turned up no sign of PERV. Still, no one can prove that PERV or another virus won't jump to humans and cause disease, and health regulatory agencies have reacted accordingly.

The U.S. Food and Drug Administration (FDA) will permit xenotransplant trials on a case-by-case basis, but it requests consent forms warning patients of troubling unknown risks. "The patient consent form makes it sound like they're on the verge of unleashing some plague on the world," says Thomas Fraser, CEO of Diacrin. For instance, the FDA asks that consent forms warn subjects of potential risks to their family, particularly during sexual contact, and inform patients that they must submit to lifelong monitoring (although the agency lacks the legal means to enforce this).

Although stringent, FDA offers more leeway than many other countries. Italy and Germany allow animal tissue to be used outside the body but forbid implants. Japan bans xenotransplants outright, and rules in France and England are so strict that study applications are rarely submitted. Norway and the Netherlands have moratoriums in place. "I find it excessive," says Henri Bismuth, a liver transplant surgeon at Paul Brousse Hospital in Villejuif, France, of the French situation. The intergovernmental Council of Europe is working to establish common standards and include countries such as Russia and China, where cell xenotransplants may have been performed with little government oversight.

Xenotransplantation research continues in labs worldwide, but many agree that stem cells and bioengineering hold at least as much promise. Annika Tibell, chair of transplantation surgery at Huddinge Hospital in Stockholm, Sweden, hopes to see "several different solutions to the organ problem."

—JENNIFER COUZIN

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