Organ Transplant Successes and Failures

It has been over 50 years since the first successful human organ transplant was done—a kidney transplanted from one identical twin to another—and the procedure has become almost routine. The list of organs transplanted includes not just kidneys, but hearts, livers, lungs, and the pancreas. The number of transplants performed is impressive, considering both how complicated the surgery is and how strong a fight the immune system launches against the new organ. More than 325,000 transplants were performed in the United States from 1988 through August 2004. The average number per year is now about 25,000. Kidney transplants account for more than half of all transplants; liver transplants make up about 20%, hearts 10%, and lungs 5%. The number of transplants may seem large, but an even bigger number includes those people who are on a waiting list for an organ—more than 86,000 people right now. Because human beings have two kidneys and can function just fine with only one, kidney transplants can come from living donors. In recent years, methods to transplant just a part of a liver have succeeded because the liver can repair and regenerate itself. A few hundred people each year, often children, receive a lobe of a liver from a family member. All the other organs, however, must come from people who signed a donor card before they died or whose family agrees to the organ donation. The gift of an organ at the sad time of the sudden loss of a family member in an accident is an act of great generosity. Despite these gifts, every year a shortage of healthy organs causes many more sad results—the death of people on the waiting list. In 2003, more than 6,000 people died while waiting for an organ.

Human-to-human organ transplantation has risks. The human immune system is finely tuned to recognize and destroy invaders, and because it carries different forms of transplantation markers from those of the recipient, the transplanted organ is seen as an invader, unless the donor and recipient share exactly the same genes, as in that first successful kidney transplant between identical twins. A major risk exists if antibodies to the donor cells are present in the recipient's blood at the time of transplant. If donor-reactive antibodies are present when the blood connection to the organ is made during surgery, the reaction against the new organ may be so rapid that the blood vessels are blocked and the organ cells die. This rapid antibody reaction to the cells lining the organ blood vessels is called \textit{hyperacute rejection}. Tests for antibodies lurking in the recipient's blood that could cause hyperacute rejection are performed before the transplant to determine who receives a donated organ. The ABO blood group system, critical in blood transfusion, is also important for some, but not all, transplanted organs. An organ donor must be a suitable ABO type for the patient or ABO antibodies in the recipient's blood will cause hyperacute rejection.

After the surgery, new antibodies and killer lymphocytes that cause rejection may develop within days. To prevent this from happening, or at least reduce the chances of it, scientists have discovered and developed a number of \textit{immunosuppressive drugs} that help extend the life of the transplanted organ and, thus, the life of its recipient. \textit{Corticosteroids} and the cancer chemotherapy drug azathioprine were the first drugs used to suppress the immune system for organ transplants. Although their long-term use can have serious side effects, steroids such as prednisone are still widely used. In the 1970s, the introduction of \textit{cyclosporine}, the product of a soil fungus, dramatically improved one-year graft and transplant patient survival. Other widely used chemical immunosuppressive drugs include tacrolimus, mycophenolate mofetil, and sirolimus. Several monoclonal antibodies that remove or shut down T lymphocytes (such as muromonab, daclizumab, and basiliximab) are used to prevent or treat rejection. A preparation of animal antibodies raised against human lymphocytes is still used for the same purpose. Despite all these tools, slow or chronic rejection of the organ remains an ongoing problem.

The success of organ transplantation is measured by organ and patient survival. Over 80% of kidney patients and 65% of their grafts survive for five years. Patient survival is higher than kidney graft survival, because kidney graft failure means that patients must go back onto chronic \textit{dialysis} and usually back onto the waiting list for another transplant. Five-year graft and patient survival rates are lower for other organs. Because there is no counterpart to dialysis that provides long-term support for those with a failing liver, lungs, or heart, patients who need these organs often die without a successful transplant.

Taking Organs from Other Animals
Because the transplant waiting list continues to grow, scientists have explored nonhuman animals as a possible source of organs. Despite the shock and repulsion it sometimes causes, the idea of xenotransplantation, or transplantation of an organ from one species to another, deserves some serious consideration.

**Organs from Primates**

At first, it seemed reasonable to look toward nonhuman primates, such as chimpanzees and baboons, as organ donors. With experience, however, it became clear that nonhuman primates pose significant medical, economic, and ethical problems as alternate sources for organs. Transplants of organs from nonhuman primates would still require the use of immunosuppressive drugs, perhaps at even higher doses than are used for human-to-human transplants. Also, because of our genetic similarity to other primates and because the immune system has been turned off, any unknown virus or microorganism that the organ harbored might jump to humans and cause serious disease. There is strong evidence that HIV, the virus that causes AIDS, originally moved from chimps to humans, so this concern cannot be easily dismissed. Human-to-human transplants do carry the risk of viral infections, but the viruses in question are known (hepatitis viruses, HIV, and cytomegalovirus, among others) and donors can be tested to rule out infections. An unknown virus that does not cause illness in a nonhuman primate might infect a human organ recipient and then go on to infect other people and cause serious human disease. Economic and social factors have also discouraged the idea of using nonhuman primates as organ donors. Nonhuman primates are expensive to breed and care for, and some species are endangered. Many people find the idea of sacrificing these close animal "relatives" as organ sources morally unacceptable because they are so similar to humans.

**Successes and Failures of Primate Organ Transplants**

There have been attempts to use nonhuman primates as tissue and organ donors. In the 1960s, several surgeons transplanted kidneys from baboons or chimps into humans, and the patients survived only a few months. Born with a malformed heart, Baby Fae received a baboon heart transplant in 1984. The procedure, her three-week survival, and her ultimate death were watched by the whole world. After her death, it was learned that a simple ABO incompatibility, rather than the fact that the donor was a baboon, had doomed the procedure.

Two baboon-to-human liver transplants were performed by transplant pioneer Dr. Thomas Starzl in 1992. When both patients died of overwhelming infections within two months, Starzl decided that further organ xenotransplantation should be stopped and more research done.

In 1995, Jeff Getty, a 38-year-old AIDS activist from San Francisco, received a baboon bone marrow transplant from a team from the University of Pittsburgh and the University of California to try to replace his immune system, which had been destroyed by HIV. The baboon cells survived for just a few weeks, but Getty lived for several more years.

**Organs from Non-Primates**

Researchers began to look elsewhere for possible nonhuman donors. The animal that seemed most promising for xenotransplantation was the pig. Pigs are easy and relatively inexpensive to breed, and they produce large litters of offspring. Although the usual breeds of pigs grow to a very large size, tipping the scales at 1,000 pounds (454 kg) or more, breeds of miniature swine grow to about 300 pounds (136 kg) as adults. Their organs are just the right size for humans. The anatomy and physiology of the pig kidney, in particular, makes it especially suitable for transplantation into humans. Whether pig livers would work in humans is unknown. Pigs can be bred and raised in sterile facilities to reduce the risk of infection. However, researchers have recently discovered that pigs harbor in their genome the sequence for several RNA viruses, which, when activated, may infect humans and cause disease.

Another problem with using pigs as organ donors is the very vigorous immune attack that would have to be blunted. Human blood normally contains antibodies to sugar molecules present on the surfaces of pigs' cells. If the antibodies latched onto the cells that line the blood vessels of the pig organ, hyperacute rejection would occur. In addition, several types of destructive lymphocytes are poised to attack organs and tissues from species that are as different from us as pigs are. Some researchers have tried to genetically engineer pigs to reduce the antibody problem. Techniques have included putting human proteins on the surface of the pig cells that prevent activation of complement proteins or disabling the pig gene for the enzyme that puts the antibody-targeted sugar on the cell surface. To blunt the cell-based attack, several researchers have developed methods to replace some of the immune system cells in the potential organ recipient with pig
immune-system cells in an effort to make the recipient better tolerate the pig tissue. This approach has succeeded in experiments with pig-to-monkey transplants. Whether these maneuvers will prevent hyperacute or quick cell-based rejection in humans is unknown, though experiments with pig cells have been encouraging.

A number of small biotechnology companies and academic research teams are working on these problems. However, worries about the pig RNA viruses have cooled enthusiasm for xenotransplantation. Although some laboratory work continues, there appear to be no immediate human xenotransplant studies on the horizon. Some researchers have, however, proposed using pig liver cells in a device kept outside the body to help remove toxins from the blood of patients whose liver has failed, to help the patients survive while they wait for a human liver transplant.

Connections

The shortage of suitable organs for transplantation has led to efforts to see if animals might provide an acceptable alternate source. Despite several attempts—some of them infamous—to use nonhuman primates as organ donors for human patients, medical, economic, and social issues have led researchers to look to other animals. Recently, the pig has become the most promising species for xenotransplantation, although there are serious barriers to using pig organs in people, including the risk of a severe rejection response and the possibility of human infections with potentially dangerous viruses. Research to solve these problems continues, but at a greatly reduced level because of concerns about the potential for a serious viral infection coming from the transplanted pig organ. Meanwhile, the waiting list for organs continues to grow.

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