Xenotransplantation

The support and opposition to xenotransplantation—the transplant of organs from one species to another—are both based on truth.

It is true that there are far too few human organs available to be transplanted into individuals who will likely die without such a transfer. And it is true that the use of animal organs that have been altered to overcome barriers presented by cross-species rejection is an increasingly enticing solution to the shortage.

But it is also chillingly true that it is impossible to know what is being transplanted along with such organs. The threat of an as-yet-unknown disease making the cross-species jump with a heart, liver, kidney, or other body part alarms experts such as Jonathan Allan, a virologist at the Southwest Foundation for Biomedical Research. In particular, he said, it is difficult to test for the presence of a virus if you do not know it exists. The threat that a new epidemic could spring from such transplants is alarmingly real, said Allan in an interview last fall.

Yet it appears the US Food and Drug Administration, Centers for Disease Control and Prevention, and other federal agencies are ready to issue guidelines that would allow trials of xenotransplants to begin—again.

In truth, xenotransplants have a long history in modern medicine. In early 1964, Keith Reemtsma, MD, of Tulane University oversaw xenotransplantation of kidneys from chimpanzees into six patients, one of whom lived 9 months after the transplant. Other transplants followed, including those by transplant veteran Thomas Starzl, MD, at the University of Pittsburgh. The results, however, were disappointing, and the field fell into disfavor until 1985, when surgeon Leonard Bailey, MD, startled the world by implanting a baboon's heart into an infant known as Baby Fae, who had been born with hypoplastic left heart syndrome. He had hoped that the child's undeveloped immune system would not readily reject the organ, and the child did live for 4 weeks after the transplant. In the early 1990s, Starzl transplanted baboon livers into two patients with advanced hepatitis B. One patient lived 70 days; the other, 26. Both died of infection because of the large doses of immunosuppressive drugs needed to prevent rejection of the primate organ.

In recent years, basic research has led the way to uncovering methods that will prevent the hyperacute immune response that dooms most xenotransplants. Abdul Rao, MD, director of the Section of Cell Transplantation at the University of Pittsburgh, said complement in the circulation is key to this hyperacute response. In our bodies, complement binds to any cell that has a receptor for it. But right next to the complement binding sites are complement inactivators, which stop the action of the chemical.

If a pig organ is transplanted into a human, it binds human complement, which is then activated. "But the pig complement inhibitory protein cannot stop the complement," said Dr Rao. "The human complement gets activated and eventually results in hyperacute rejection."

But there is another level of complexity to the problem, he said. "We humans, because of exposure to a lot of microbial antigens in our lives, have antibodies against what is known as a galactose (1-3)-galactose terminal sugar residue," he said. These antibodies mean that there is such sugar residue, known as Gal for short, in the human system.

"In pigs, on the contrary, the protein is present, but the antibody is not. If you put a pig organ in a human, the antibodies against cells in the pig organ are already present. These carbohydrates are everywhere in the organ. The graft is destroyed within minutes," Dr Rao said.

"How can you prevent this? You endow the pig with human inhibitory protein. This has been achieved by transgenic technology," he said. Both Imutran, a biotechnology company based in the United Kingdom, and Nextran, a US company, have achieved this goal.

Drs Rao and Starzl are collaborating with Nextran on research using transgenic pigs with the transgenic inhibitory protein. In fact, Dr Rao said, there are three transgenic inhibitory proteins in the pigs. "If one misses at one stage of complement activation, another catches," Dr Rao said. "It is more likely to prevent hyperacute rejections. Or we hope it will be. Once the hyperacute barrier is taken care of, these organs become similar to a baboon-to-human transplant. The major barrier is cell-mediated rejection."

Other investigators have attempted to deplete the store of Gal antibodies before transplant by filtering the blood through an external pig organ, which sops up the antibodies. The blood is then returned to the body. However, such depletion is cumbersome and temporary. An alternate pathway can sometimes allow complement destruction to proceed even without antibodies.

In an attempt to block the action of complement proteins, Fred Sanfillipo, MD, of the Johns Hopkins University of School of Medicine in Baltimore, Md, flooded the blood of monkeys with soluble proteins that bind to the complement proteins. Primates treated in this way survived as long as 6 weeks with pig hearts in place. Untreated monkeys reject pig hearts in fewer than 8 days.

There are ethical and scientific questions about the prospect of modifying donor pigs, said Dr Rao. "These pigs have humanized inhibitory proteins. Any ethical committee would refuse to modify a nonhuman primate to make it more human. What, then, is the barrier to creating a superhuman?"

(*Circulation*. 1998;97:1431-1432.)
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But Dr Rao's contention that pigs can be bred virtually "virus free" is being questioned because of findings of endogenous retroviruses in the genomes of even the cleanest pigs. In a commentary in the journal *Nature*, Robin Weiss of the Institute of Cancer Research in London wrote, "Xenotransplantation will potentiate the risk of pig-to-human transfer of viruses not transmitted by the respiratory route. First, the physical barrier is broken by transplanting living porcine tissue organs into humans. Second, the immunosuppression required to prevent xenograft rejection may allow zoonotic viruses to adapt to human infections. Third, the genetic modification of pigs may allow preadaptation of animal viruses for human infection." (*Nature*. 1998;391:327–328.)

As a microbiologist, Weiss warned that there is a risk of setting off a new human epidemic; he pointed out that HIV-1 probably began by cross-species transfer and that HIV-2 almost certainly did. "We need a Hippocratic ethic for community and public health at least to do no harm," he said.

Weiss advised caution, neither prohibiting xenotransplant into humans nor rushing headlong into the procedure. An editorial in the same issue of *Nature* (1998;391:309) called for a moratorium on xenotransplants until international debate on the pluses and minuses has taken place. A host of scientists signed on the moratorium bandwagon in commentary published in *Nature Medicine* (1998;4:141–144).

Guidelines proposed by the FDA that would allow xenotransplant trials to proceed cover everything from the makeup of the transplant team to plans for health surveillance of both animals and human. There are requirements for consent forms, animal procurement, animal screening, and health maintenance of the animals. The guidelines also call for archiving records of both animals and human patients as well as banks of stored serum and tissue samples from each. If a problem arises, the archives will make it possible to identify and contact xenotransplant recipients for testing and alert them to possible health risks.

These guidelines, proposed in the summer of 1996, are still pending. Final rules are expected sometime this year. Yet, as Mary Pender, FDA deputy commissioner, said at a recent meeting of an agency committee studying xenotransplants, the issue has not been easy. "As is painfully evident from the porcine endogenous retrovirus issue you are going to discuss today, the science of xenotransplantation is still evolving, and there is much we do not know about the risks from transplantation, thereby making the creating of a regulatory system different. As usual, there are some who would prefer to have the agency leave their xenotransplantation efforts alone. However, the field will not stand still as we wonder what to do, and we believe that the public will be disadvantaged if we do nothing."

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