

ANIMAL TRANSPLANTS: SAFE OR SORRY?

► Amy Otchet

Animal organ transplantation into humans may save many lives or cause untold harm from diseases crossing the species barrier. How should society decide whether or not to go ahead?

Just over 15 years ago, Baby Fae became a household name when American doctors replaced her ailing heart with the heart of a baboon. From Australia to Brazil, millions were riveted by the news reports and followed her progress with baited breath. If they were half-expecting a Frankenstein's monster, they were disappointed. Baby Fae looked like any other wee newborn child. But the sci-fi lullaby turned grim 20 days after the transplant. On November 15, 1984 Baby Fae died. Later her mother angrily maintained that she hadn't been informed about the possible dangers involved. Unbeknownst to the doctors at the time, however, the stakes concerned far more than a single infant's life. We now know there is a possibility that the transplantation of animal organs into humans might unleash infectious diseases similar to Aids.

The scientific community is only beginning to understand the possible risks of xenotransplantation—the use of animal organs and tissue in “spare-part” surgery for humans. Over the past century, there have been about 25 documented cases of such organ transplants, the most recent case being reported in 1993. Kidneys, hearts and livers from baboons and monkeys were the organs of choice. Survival rates were dismal—most patients died within weeks. Today, however, thanks to progress in biotechnology and drug treatments, there is renewed interest in opening another round of human experiments. Scientists in the United States have already begun implanting pig cells to treat patients with Parkinson's disease and diabetes. Others await the green light to begin transplanting organs from pigs into people.

This growing interest is matched by rising fear, however, that an animal virus could jump from the pig to the human patient, spread to others and unleash a pandemic. When viruses cross the species



In Homer's *Odyssey*, Circe the enchantress turns men into swine.

barrier, the results can be catastrophic. At least one strain of HIV is believed to have jumped from monkeys to people after a single infectious event 60 years ago. The influenza epidemic of 1918-19, which killed tens of millions, may have been triggered by a pig infecting one person.

Xenotransplantation thus confronts the whole of society—not just individual patients—with the promise of saving thousands of lives and the possible risk of causing tremendous harm. The lack of scientific data transforms the safety issues into an ethical dilemma which scientists alone cannot answer.

Human transplantation has been a victim of its own success. Surgeons can now transplant about 25 different kinds of human organs and tissue, and survival rates are constantly improving (60 per cent of patients live more than five years). More than one million people worldwide have benefited since 1954, when the first transplant was made. But supply cannot meet demand. In the United States, for

example, 3,900 people died while waiting for an organ transplant in 1996, compared to around 1,500 in 1988.

There are also strong economic arguments in favour of xenotransplantation. About 700,000 patients suffering from kidney disease world-wide are strapped to dialysis machines at an annual cost of about \$19 billion, according to the Organization for Economic Co-operation and Development (OECD). It costs about 60 per cent less to transplant a kidney than to keep the patient on life-long dialysis. Success in xenotransplantation could open up an international market worth \$6 billion plus another \$5 billion in related drug treatments (to prevent the immune system from rejecting the organs). One of the biggest contenders is the pharmaceutical giant Novartis—which not only produced cyclosporin A, the leading drug used in human transplants, but also owns Imutran, a UK-based biotech company famous for genetically engineering pigs for xenotransplantation. ►

► Pigs are the xeno-prize-winners. Non-human primates, like baboons, have been ruled out because their biological similarities to human beings could increase the risk of disease transmission, so brutally highlighted by the Aids and Ebola viruses. Many people also have ethical qualms about using our “cousins” for spare parts, whereas we have been slaughtering and eating pigs for many centuries. Finally, pigs are easier to breed and genetically engineer.

Duping the human immune system

The human body would normally consider a pig organ to be a dangerous “foreign agent” and kill it within minutes by cutting off its blood supply. Imutran and other laboratories are trying to get past this defence (immune) system by lining the pigs’ organs with human proteins through genetic engineering. These proteins endow the pig organ with a kind of human disguise. After a time, however, the human body would gradually realize that the pig organ isn’t acceptable and would launch an attack on it. Imutran is now trying to develop new drugs and may add more human genes to the pigs, says Dr Corinne Savill, the company’s chief operating officer.

These “designer pigs” may, however, make it easier for the animals’ germs to infect people, says Dr Robin Weiss of University College London. About two years ago, Weiss began publishing articles showing how pig viruses could hide behind the human proteins (added to the pigs) and slip past a patient’s immune system. The human proteins might also invite the viruses into human cells. For example, one of the human proteins used by Imutran and other biotech companies is CD55. This protein makes the human body vulnerable to several polio-related viruses. Suppose, says Weiss, that pigs have similar viruses. Ordinarily, they wouldn’t affect humans because of genetic differences. But imagine that the pig viruses learn (through genetic modification) to use CD55 and infect the patient who receives the pig organ. Once a pig disease has crossed over into a single human being, it could mutate further and spread to others.

None of these questions would matter if the pigs could be issued with a “clean bill of health”, says Weiss. Imutran, for example, is trying to breed germ-free pigs in tightly controlled facilities. But even in a hermetically sealed tank all the risks would not be eliminated, particularly those arising from viruses known as PERV retroviruses which are found in the animal’s genes. Weiss has



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Should humans harvest spare parts from animals?

focused on three strains of PERV, which have been described as “second cousins” to HIV or human immunodeficiency virus which causes Aids. Two of them can infect human cells.

Weiss’s findings sent shockwaves through public health organizations and the industry. Researchers immediately set out to survey as many patients as they could find who had been exposed to porcine tissue. Out of about 175 patients screened, none were infected by PERV.

“It’s a relief,” says Weiss, but it’s not conclusive. “This particular virus is not going to be highly contagious but this doesn’t necessarily mean that xenotransplantation is safe.” The patients in question

received porcine tissue not organs, whose sheer volume may increase the risk of infection. Second, they were screened for the three known retroviruses. What about unknown germs? Weiss also wonders whether the retroviruses might be hiding somewhere in the body and become more powerful over time.

François Meslin of the World Health Organization describes a worst-case scenario: a xeno-patient harbours an undetected virus which is passed to others by sexual intercourse, a likely means of transmission. As the virus moves from one host to another, it becomes increasingly dangerous.

“You can take a lot of precautions but you never know how far to go to bring the

risks down to an acceptable level," says Meslin, who points to the case of bovine spongiform encephalopathy—"mad cow disease"—as the closest example of this kind of dilemma. Since Weiss sounded the alert, public health authorities around the world have observed a de facto moratorium on human experiments with xenotransplantation, which doctors describe as clinical trials. This doesn't mean that they are giving up on the research, however. What is happening is that most Western governments are setting up special advisory or regulatory bodies to review any future clinical trials and prepare strict guidelines for monitoring them.

The U.S. and Britain, who are the leaders in xeno-research, are currently finalizing guidelines to monitor not just the patients, but their family-members and health-workers. While the authorities refuse to release the details, it has been said that xeno-patients should refrain from having children, marrying or even travelling internationally. This sounds like a replay of discussions concerning people infected with HIV, says Prof Bartha Maria Knoppers, a Canadian bioethicist regularly called on by OECD to examine the ethics of xeno-research. Close monitoring of patients should not mean trampling on their human rights, Knoppers believes. "Besides," she says, "are we really going to be able to enforce these conditions?" Would it be possible, for example, to take legal steps to prevent a patient from deciding to have a child two years after a clinical trial?

Assessing the risk of viral infections

The sponsors of these trials—mostly biotech companies—will also come under the microscope. Ordinarily, proposals to test new medical procedures or treatments on humans are considered commercial secrets which are restricted to the company involved and the relevant governmental regulatory body, e.g. the U.S. Food and Drug Administration (FDA) which is responsible for approving tests on humans for new medical drugs or procedures. This is not so with xenotransplantation, however. In the United States, a special advisory committee composed of some 15 scientific experts will openly review all requests to test animal organs in people before the FDA renders a decision.

"Absence of evidence is not absence of risk," says Phil Noguchi, director of the FDA's division of cellular and gene therapies. For example, two years ago bio-tech companies proudly insisted that their pigs were germ-free. But when news of the

PERV retroviruses came out, Noguchi says, the companies suddenly "worked a lot harder" to examine the risks. Noguchi also maintains that viral infections are difficult to evaluate. "They may not happen often enough to be a publishable event," he says. "But in a clinical experiment one tenth of a sixth of a chance of infection is a whole lot." This is why the FDA is counting on help from the advisory committee to look in all the "nooks and crannies" where a virus might hide. "We're still in a very difficult position because to a large extent we rely on industry to provide the proof that a clinical experiment is safe," Noguchi notes. "But we also depend on our own scientists."

For Noguchi, the advisory body also

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scores extra points by offering a "public forum" to discuss the ethical issues—from animal welfare concerns to deciding who should receive an animal organ. First, companies might focus on patients with the greatest chances of surviving instead of those most in need of a transplant. Second, it will take years—if ever—before pig organs are effective. For a patient on the verge of death a pig organ could buy a few extra weeks until a human organ becomes available. Should such patients receive priority on the waiting list? There is a third major concern, says John Davies of the U.S. National Kidney Foundation, the world's largest non-profit charity for kidney patients. "We don't want people to stop donating the organs of their loved ones [for human transplants] after the first animal transplant trials," says Davies, "because they think the problem has been resolved." While Davies supports xeno-research, he is not convinced that it will prove successful.

The problem is that these discussions take place between people with vested interests of one kind or another. They fail to include the largest group affected, the public. "It can be argued that there should be some sort of 'community consent'," says Dr A.S. Daar of Oman, who chaired the World Health Organization's consultation on xenotransplantation. "Is the FDA mandate to protect the public enough of a proxy for community consent?" asks Daar. "Until

the public is informed about the issues and is discussing them, I don't think you would want to go ahead with clinical trials."

Daar is looking for ways of stimulating public debate and consent by working with an international committee of "concerned" citizens—mostly scientists and bioethicists brought together by the prestigious Hastings Center, a bioethics think-tank in New York. The aim is to help countries to develop national but non-governmental committees of individuals from various walks of life—economics, law, religion, the media, etc.—who will take time to become informed about xenotransplantation but don't themselves have any vested interests in the matter. These committees would hold "consensus conferences"—what Americans call "townhall meetings"—to spread information about xenotransplantation and gauge the public's response to it.

This idea is the brainchild of Fritz Bach, a scientist at Harvard Medical School who first called for a legal moratorium on clinical trials in the U.S. Bach is often portrayed as a virulent opponent of xenotransplantation and yet he is a leading scientist in the field as well as a paid consultant for Novartis. His corporate sponsor isn't thrilled by his idea of townhall meetings. "You cannot go forward by publicly discussing such complicated subjects," says Imutran/Novartis's Dr Savill. "Now, whether governments have set up the right agencies is another question. Like anything else in society, are the right people in the right place making the decisions? And does the public have confidence in them?"

Bach isn't convinced. "Some insiders think this [moratorium and public consultation] would be a good thing for Novartis," he says. "Just look at the tremendous hullabaloo over genetically modified organisms. If a blue ribbon committee—without any connections to Monsanto—had informed the public that they thought the [GM] food was safe on the shelves, we wouldn't have had this reaction. The scariest thing is always the unknown." ■



- **To find out more or to express your views on ethical and policy issues related to xenotransplantation, contact the electronic discussion group set up by the World Health Organization and Health Canada:**
www.oecd.org/dsti/sti/s_t/biotech/xenosite/country.htm