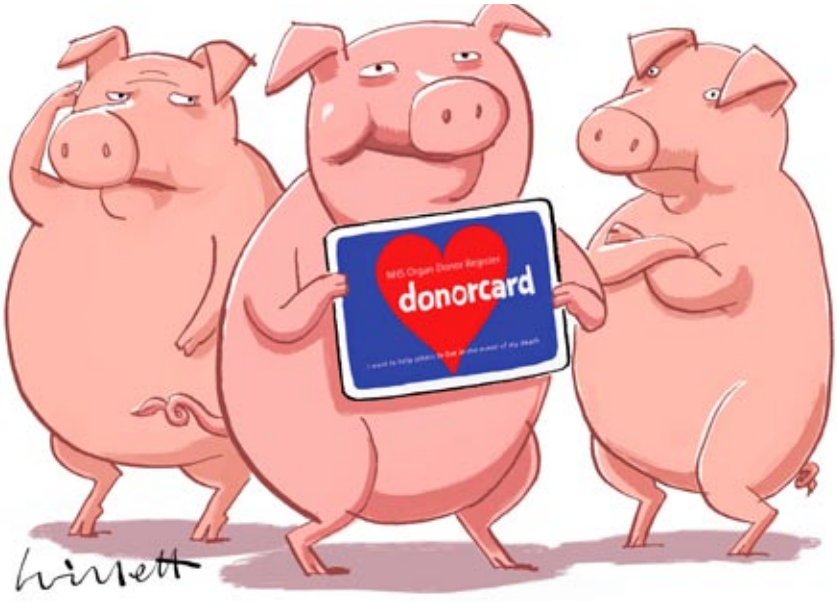
Bit of an animal

Increasing demand for human tissue means that several countries are relaxing restrictions on research into use of tissue from other animals. **Geoff Watts** looks at the challenges



When Australia's National Health and Medical Research Council declared in mid-December that the country's five year moratorium on animal to human xenotransplantation should be allowed to lapse, the move marked another step towards the reacceptance of this controversial procedure. It does not mean, however, that the fears of infection that originally prompted the procedure's fall from grace have been entirely overcome. Throughout the existence of our species, pathogens have periodically crossed the gap separating us from other animals. The microbes have found a new home—but we have been saddled with a new disease, and sometimes with a disaster.

Given this state of affairs it would be foolish indeed to give any microbe a helping hand. If xenotransplantation is to move out of the research laboratory and into routine practice, medical staff will need convincing answers to three questions. Will the animal organ function in its new surroundings? Can measures be taken to prevent its rejection? And is there any risk of transmitting a disease to the recipient? Work during the past couple of decades has not given researchers complete answers to the first two questions, but the findings have been sufficiently encouraging to retain their interest and enthusiasm. That leaves the third concern: the possibility of transmitting an infection. Paradoxically, this may not be a problem at all. The difficulty facing advocates of xenotransplantation is to be certain of this, because their challenge is to prove a negative.

The potential health risks of infection from xenotransplantation take more than one form. Firstly, there is the possibility of transferring an organism that is not pathogenic to (or perhaps even detectable in) the animal donor but is to humans. Then there is the risk of an apparently benign organism becoming pathogenic if transferred into immunocompromised recipients. Finally, there is the possibility of recombination or reassortment of infectious agents to form new pathogens.

Chequered history

The notion of using animal material to treat human disease is hardly new. The 17th century allegedly saw bone from a dog being used to repair the skull of a Russian aristocrat. More recently, the pioneering American transplant surgeon Thomas Starzl implanted baboon kidneys into six patients, one of whom survived for more than 90 days. Perhaps the most celebrated of these exploits featured baby Fae, the Californian infant who in 1984 received a baboon heart. With the help of the newly introduced immunosuppressant drug ciclosporin, she survived for 20 days.

It was in the late 1990s that the clinical bandwagon, hitherto gaining momentum, shuddered to a halt. This was when viral oncologist Robin Weiss of London's Institute of Cancer Research showed that porcine retroviruses could infect human cells in vitro.[1] The finding was a blow to the xenotransplantation enterprise because, with the use of primates increasingly frowned on for a stack of reasons including cost, ethics, and animal welfare, pigs had emerged as the preferred source of donor material. They grow quickly and to about the right size, can be reared under controlled conditions, and can be genetically manipulated to minimise problems of rejection. Moreover, as transplantation researcher Leo Buhler of Geneva University Hospital points out, no harm appeared to have followed from those procedures in which porcine material had actually been introduced into humans. In the early 1990s, for example, a group of Swedish patients with diabetes received pig fetal islet cells in an attempt to control their disease. The experiment was a failure, but the patients—most of whom are still alive—showed no evidence of any infection, recognisable or otherwise. "The other evidence," he adds, "is that insulin from pig pancreases has been used for decades without evidence of viral infections. If something had been transmitted, the argument is that it would have appeared by now."

For all that though, the hypothetical risks remain that immune suppression might allow a virus to replicate more easily in its new host or that the human genes introduced into transgenic pigs to promote the survival of donor organs might also allow pig viruses to infect humans more readily. When Professor Weiss published the evidence that pig endogenous retroviruses could infect human cells, the risk became too real to ignore. Only recently has a cautious

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interest in clinical work begun to re-emerge, says Dr Buhler. So how best to proceed?

Surveillance

The potential public health risk posed by xenotransplantation has been engaging the World Health Organization for several years. As Luc Noel from WHO points out, in May 2004 the 57th World Health Assembly passed a resolution urging member states "to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place," and requesting the director general "to collect data globally for the evaluation of practices in xenogeneic transplantation."[2] In adopting this measure the assembly was acting on a suggestion made years earlier by the Nuffield Council on Bioethics. One of its working parties recommended in 1996 that "teams should be required to record all information concerning individual xenograft recipients in a xenotransplantation register maintained by an independent body. Suitably anonymised data should be reviewed for evidence of the possible emergence of new diseases."[3]

Although most member states took the WHO resolution seriously, according to Dr Noel, the extent to which it was acted on is another matter. Either way, at a consultation meeting held in April the following year, a panel of experts recommended the creation of an inventory of human xenotransplantation activities around the world. It has since been established by the International Xenotransplantation Association and the Surgical Research Unit of Geneva University Hospital in collaboration with WHO.[4] Basic information on procedures (what, when, where, who, etc) is collected through an electronic questionnaire. The information itself has been garnered from scientific publications, conference presentations, internet searches, and reports from members of the transplantation community. A glance at the current 30 or so entries shows that the quality and extent of the information vary considerably.

At the time of writing, 12 countries are on the list, nine of which do not have national regulations. Nor is this the only problem revealed by the inventory. "The scientific community has done its best to make us aware of anything they know," says Megan Sykes of Harvard Medical School, a past president of the International Xenotransplantation Association. "But some of the work is carried out by commercial enterprises that are trying to make money. They're not using proven procedures in any shape or form, and they're not properly monitored. It's quite likely we've missed some in that arena."

Dr Buhler agrees. "We have found a variety of companies, usually in developing countries where there is not much regulation, that try to attract patients and promote animal implants for sleeping disorders, potency, and so on." Even in developed countries, at least in non-academic settings, some work has continued until recently. "This includes countries where you'd think it would not happen. For example, in Bavaria we found a clinic still implanting animal cells. There is no federal law against this in Germany, and Bavaria itself has no law on the matter. In Switzerland there was no regulation until 2003."

Although, as Dr Buhler comments, there has been no serious clinical research for 10 years in Western countries, this is now changing. In October the New Zealand minister of health approved a clinical trial set up by the company Living Cell Technologies to treat eight people with diabetes using pig islet cells. The cells will be harvested from a disease-free population of animals isolated for nearly two centuries on the Auckland Islands and housed in a pathogen-free breeding facility. The work has already begun. And now Australia too has lifted its ban. It's expected that researchers there will soon be using porcine material to research the treatment of diabetes and, perhaps, Parkinson's disease.

Opinions differ on the xenotransplantation procedure that holds the most immediate promise. Dr Noel sees the use of islet cells in treating diabetes as the most likely prospect; Dr Buhler talks of temporary support while patients are waiting for a human organ, particularly in the case of the liver. No matter. In either case, what is abundantly clear is the steadily increasing pressure posed by the conditions that xenotransplantation has the potential to help solve: the continuing shortage of human donor material and, in the case of diabetes, rising prevalence.

Meanwhile, inclusion in the xenotransplantation inventory is not compulsory, and there is no internationally binding set of regulations. So what purpose can the inventory serve? To Dr Noel it's a question of keeping everyone informed. "Transparency in xenotransplantation is of paramount importance," he says. The inventory is a reminder that work is going ahead but should be allowed and encouraged only in so far as whatever risks it may entail have been weighed and judged acceptable in the light of potential gains. Right now that balance may appear to be in favour of xenotransplantation. But the key word there is "appear." The price of abandoning the safeguards prematurely could still be incalculable.

Xenotransplantation[5]

The term xenotransplantation covers a variety of procedures by which non-human cells, tissues, or organs are transplanted, implanted, or infused into human patients. The categories include:

- Transplantation of solid organs such as kidney or liver
- Transplantation of tissues and cells from a source animal without surgical connection of any animal blood vessels to the recipient's vessels
- Extracorporeal perfusion in which human blood is circulated outside the human body through an animal organ or through a bioartificial organ produced by culturing animal cells on an artificial matrix
- Any procedure in which human body fluids, cells, tissues, or organs are removed from the body, come into contact with animal cells, tissues, or organs, and are then replaced in a human

One of Living Cell Technologies' disease free breed of Auckland Island pigs

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2 WHO. *Fifty-seventh world health assembly*. Agenda item 12.14. 22 May 2004. www.who.int/transplantation/en/A57_R18-en.pdf.
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4 International Xenotransplantation Association. Inventory of xenotransplantation practices. www.humanxenotransplant.org/.
5 International Xenotransplantation Association. What is xenotransplantation? www.humanxenotransplant.org/intro2.html.

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