



Xenotransplantation

XENOTRANSPLANTATION IS THE TRANSPLANTATION OF ORGANS, TISSUES OR CELLS FROM ONE SPECIES TO ANOTHER. RESEARCHERS ARGUE THAT IT IS JUSTIFIED DUE TO THE SEVERE SHORTAGE OF HUMAN ORGANS AND TISSUES AVAILABLE.

The three categories of xenotransplantation are:

Animal External Therapies (AET's) which occur outside the recipient's body. For example, a patient's blood may be passed through a machine (Hepatassist) containing porcine hepatocytes (pig liver cells) to remove toxic substances, and then returned to the patient's own body. Or human skin may be grown in a laboratory over a layer of animal cells and then used as a graft to treat burns.

Animal Cell Therapies (ACT's) involve the transplantation of skin, bone marrow or clusters of specialised cells, such as brain cells (in the search for a cure of Parkinson's disease) or pancreatic islet cells (which produce insulin for diabetics).

Animal Organ Transplants (AOT's) are the most commonly recognised form of xenotransplantation. They involve the transplantation of entire organs, such as hearts, lungs and kidneys, from one animal to another.

Rejection and Immunosuppression

When tissue, cells or organs are introduced to another species they are recognised by the recipient's body as being foreign and are therefore attacked by the immune system. This is one of the major obstacles facing researchers in this field. In order to combat this, recipients must have their immune systems suppressed. Shutting down the body's immune system prevents the foreign matter from being rejected, but it also leaves the recipient vulnerable to disease or infection.

Rejection and immunosuppression is also an issue in human to human transplants (allotransplantation) however this can be assisted by tissue-matching to reduce the severity. In xenotransplantation however, the distant evolutionary relationship between any two species can lead to an extremely strong immune response which sometimes cannot be controlled by immunosuppression. This is referred to as hyperacute rejection.

Rejection is also reduced by genetically modifying the source animal by inserting human genes so that the human recipient's immune system is tricked into not recognizing it as being foreign. Alternatively, the source animal may have a gene removed. The most likely source animal for human transplants is the pig. 'GAL-knockout' genetically modified pigs have been modified to remove a galactose sugar which triggers an immunological response in humans.

Risk of zoonotic pandemic

Viruses can react very differently depending on the species in which they exist. A group of viruses called endogenous retroviruses can remain dormant in its host animal without causing any sign of disease.

If however that virus is transferred to another species, it has the potential to become activated at some time in the future and cause disease in its new host. This type of 'cross-species' infection is known as a zoonosis.

The uncertainty of the risk of disease transmission, particularly across the species barrier, has already been acknowledged by researchers. This is not just a theoretical possibility but a very real threat. AIDS is already believed to have been contracted from chimpanzees. BSE and Ebola viruses originated from cross-species contamination. Some of the major flu epidemics from the start of last century were believed to have originated from pigs, and the current Asian bird flu outbreak has passed to humans who have been in contact with ill birds. Porcine Endogenous Retrovirus (PERV) has already been discovered in the animals intended to be used as a source for organ donors. With continued emergence of new zoonoses from unexpected sources, the inability to diagnose potential xenozoonotic viruses with current tests and their unknown pathogenic behaviour, the chances of cross-species infection seems to be unacceptably high. Even if detected, these viruses are largely untreatable.

Not only would clinical trials of xenotransplantation be exposing the organ (or tissue) recipient to major health risks, but these risks would also be extended to the recipient's carers and families and the wider community. Is Australia prepared to accept the risk of introducing another potentially untreatable human epidemic such as HIV/AIDS or bovine spongiform encephalopathy (BSE)?

Animal Suffering - Diaries of Despair

The 'Diaries of Despair' is a report written by UK group 'Uncaged', about documents that were 'leaked' from the Imutran xeno research in 2000. An example follows of the observations of a baboon who was the recipient of a heterotopic* pig's heart (One typical example from many):

[*Heterotopic organs are those which are transplanted onto a remote part of an animal, such as the neck or stomach, to determine whether it will be rejected rather than whether it will perform its usual function. The animal's original organ remains intact and functions normally].

"X225m was euthanased after 15 days because of an infected haematoma, or swelling caused by clotted blood. On day 3 a 'large volume of bloody mucoïd faeces' had been observed. By day 9 his right arm had become swollen around an injection site, and on day 11 the arm was badly swollen and bruised. Eventually:

Day 12	am	Quite but alert. Right arm still swollen, skin broken and oozing blood.
	pm	Quiet but alert on perch. No faeces seen. Transplanted

heart beating.

Day 13 am Quiet and slightly huddled. Right arm swollen.
 pm Quite and huddled. Right arm swollen with large open wound, heavily bruised, not bleeding. Vomit during dosing. Transplanted heart bleeding.

Day 14 am Quiet but alert, sitting at front of cage. Slow movement. Large open wound on right arm, discharging pus. Normal faeces.
 pm Quiet but alert, moves when stimulated. Wound on right arm larger than observed earlier.

Day 15 am Quiet and huddled, sitting on perch. Reluctant to use right arm. Further wound breakdown.
 Sacrificed for humane reasons."

Also in an interview on FRONTLINE'S "Organ Farm", Dan Lyons, director of Uncaged Campaigns UK stated:

"One of the most unfortunate animals had a piglet heart transplanted into his neck. It was a particularly disturbing example, I think, because for several days he was holding the heart. It was swollen. It was seeping blood, it was seeping pus as a result of the infections that often occur in the wound site. He suffered from body tremors, vomiting, diarrhea. And the animal just sat there. I think living hell is really the only sort of real way you can get close to describing what it must be like to have been that animal in that situation."

For more information about Uncaged and the Diaries of Despair, visit <http://www.xenodiaries.org/>

The above incidents occurred in the UK where animal welfare legislation and regulation of animal research is considered to be of the highest standard.

Alternatives

A number of alternatives are already in various stages of development and/or use. Researchers have acknowledged that allotransplantation (transplants from one individual to another of the same species, such as human to human) is far safer than using materials from a different species. This eliminates the risk of zoonosis and also reduces the chance of the organs being rejected by the recipients body.

Greater availability

In Australia in 2000, 196 deceased people became organ donors. They made up 0.15% of all people who had died during the year. However it is estimated that up to 1% of people who die in a year might

have the potential for organ donation. This would indicate a potential increase of almost 670% in availability.

According to the Australian Bureau of Statistics ¹, there are a number of reasons that may account for the small number of donor organs available.

- Doctors do not ask that organs be donated after a patient has been determined to be brain dead.
- Relatives of the deceased have refused consent.
- Insufficient hospital procedures/equipment available.

In South Australia, intensive care clinicians play an important role in maintaining intensive care patients and requesting donation, and emergency department procedures are also said to have contributed to the highest organ donation rate within Australia².

In contrast to Australia's low donation rate (10.2 per million population), Spain has the highest donation rate (33.9 per million population). This has been attributed to procedures introduced by a national transplant organisation set up in 1989, which included having donation coordinators in hospitals, training medical staff in requesting donation, and closely monitoring potential and actual donation³.

Spain, Belgium, France, Austria and Norway have also adopted a 'presumed consent' system of organ donation. Whilst this has been considered an unethical approach in the U.S.A, the practice does allow everyone the option of not giving consent for their organs, and provides the possibility of saving many more lives. The 'presumed consent' system also negates the need for doctors to intrude on the relative's grievance process - a time at which they may refuse removal of the deceased organs due to their emotional state.

Legislation could also be changed that currently allows objections from relatives, when the donor has previously registered as an organ donor, to prevent the organs from being used. If a person has specifically given consent prior to their death it could be viewed as unethical for another to overturn that decision.

Reducing the demand

The estimate that demand for organs in developed countries is growing at 15% per year⁴ raises the question, why? Many of today's health problems are generated by our choice of lifestyles. Smoking, lack of exercise and consumption of animal products have all been acknowledged as being major contributing factors to such conditions as heart disease, stroke, cancer, diabetes and a range of other ailments. By using our resources to promote healthier life-



styles we would be reducing the number of people who are in need of organ or tissue transplants. Whilst not all those on transplant waiting lists are there as the result of unhealthy lifestyles, with a healthier population, and thus fewer people waiting for transplants, the lower demand for organs and tissue would ensure that those people suffering from genetic ailments have a better chance of receiving a human to human transplant.

Use of organs from 'non-heart-beating donors'

Doctors at University Hospital Zurich have discovered that kidneys transplanted from "cardiac death" donors are just as successful (in some cases more successful) than those transplanted from "brain dead" donors. They have estimated that the use of such organs could increase the availability of donor kidneys by up to 30%. Research currently underway on the liver, pancreas and lungs indicate that these too may be transplanted from a donor shortly after the heart has stopped beating⁵.

Living donors

Donation of organs from living persons is another option for kidneys and (partial) livers. This may also be promoted further by surgeons suggesting this option to patients and their relatives, and by hospitals having the required surgical equipment to perform such operations.

Development of artificial organs

Whilst only in the early stages of development, (as is xenotransplantation), artificial organs do not carry the risk of zoonosis and are considered less likely to cause rejection from the recipient's body, thus eliminating the need for immunosuppression.

The above examples of alternatives to xenotransplantation illustrate that there ARE realistic, safer, less costly (in terms of health risks and finance) and more humane ways to address the current shortage of available human organs. Whilst there may be a high cost involved in instigating and/or expanding the above alternatives, it would be far less costly than to proceed with clinical studies of xenotransplantation - a procedure which causes immense suffering to animals, carries dangerous health risks and has no guarantee of success.

Australian moratorium

In early 2001, the National Health & Medical Research Council (NHMRC) established a working party to determine whether clinical (animal-to-human) trials should be permitted. Note that this has no bearing on pre-clinical (animal-to-animal) studies which were already occurring. A discussion paper was released in July 2002 titled 'Draft Guidelines and Discussion Paper on Xenotransplantation'. The purpose of the paper was to promote community discussion on the issue and encourage feedback.

The decision by the NHMRC was to impose a 5-year moratorium on clinical trials of whole organ transplants, however they required further consideration on cell and tissue therapies. Further consultation and discussion within the Council resulted in a decision to include cell

and tissue xenotransplants in the moratorium. The ban was announced in December 2004.

In December 2009, the 5-year moratorium expired. At this time, the NHMRC issued research guidelines for scientists and ethics committees and recommended that clinical trials involving animal to human transplantation could begin as soon as the Therapeutic Goods Administration could implement the appropriate regulatory and surveillance frameworks. At the time of writing (November 2010), Australia is still not permitted to begin conducting clinical trials, however it is anticipated by the NHMRC that the required frameworks will be established within a couple of years and that the trials will follow shortly after.

Overseas situation

New Zealand

Early February 2005, New Zealand's Bioethics Council released a discussion document regarding xenotransplantation. They called for public submissions over cultural, spiritual and ethical concerns. Restrictions on xenotransplantation were imposed in 2002 with a three-year "sunset clause" so that New Zealanders are not denied access to xenotransplantation if in future it could be shown that the technology was acceptable, safe, and offered the ability to improve health outcomes. The law expired in June 2005 and the New Zealand Bioethics Council recommended that xenotransplantation (animal to human organ, cell and tissue transfer) be allowed to develop in New Zealand.

World Health Organisation (WHO)

The World Health Organisation has recognized the need for tougher controls of xenotransplantation research and, following a meeting of an advisory panel of international experts, issued an action plan to control and regulate the practice. It was concluded that stronger measures were needed by countries to stop the illegal performance of xenotransplantation. The plan includes:

- Updating a compendium of guidelines and recommendations for national health authorities and regulatory bodies to deal with xenotransplantation;
- Improving methods for the collection and dissemination of information on xenotransplantation practices, successes and potential risks; and
- Raising greater awareness among national health authorities and promoting high ethical standards and well regulated practices.

WHO points out that the main risk with xenotransplantation is the transfer of diseases from animals to humans. Several countries have developed rigorous guidelines to prevent this, but xenotransplantation is carried out in countries that lack suitable supervision, have no proof of the quality of the source animal, and no monitoring of the recipient. They consider that international collaboration is paramount to ensure high standards for xenotransplantation across all regions. Without this, efforts will be undermined due to increasing numbers of people traveling to other countries with less stringent laws. For more information, visit www.who.int/transplantation/xeno

References

- 1 The data reported here have been supplied by the Australia and New Zealand Organ Donation Registry. The interpretation and reporting of these data are the responsibility of the Editors and in no way should be seen as an official policy or interpretation of the Australia and New Zealand Organ Donation Registry.
- 2 Totaro, Paola 2001 'Doctors call for organ donation overhaul' The Age July 31 2001
- 3 Australian Donate 2000 Second National Forum on Organ & Tissue Donation, 17-18 July 2000, Best Practises Summary/Outcome paper pp 9-12 Australians Donate, Adelaide.
- 4 Draft Guidelines and Discussion Paper on Clinical Xenotransplantation Research NHMRC, Page 15. 2001
- 5 New England Journal of Medicine. July 25, 2002 . Vol.345, Massachusetts Medical Society.