

The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-Human Transplantation

A DISCUSSION DOCUMENT

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We would like to thank the New Zealand Ministry of Health for permission to use its material on international approaches to xenotransplantation regulation, which is included here as an appendix.

We express our grateful thanks to those people in different parts of New Zealand who discussed these issues with various Council members, giving us their time and the benefits of their knowledge and experience in xenotransplantation, human diseases, animal welfare and ethics, and risk analysis.

Our thanks go also to those who generously gave their time to peer review this document. Notwithstanding that valuable assistance, the responsibility for both the content and style belongs to Toi te Taiao: the Bioethics Council.

Foreword

Toi te Taiao: the Bioethics Council was established in 2002 to consider the cultural, ethical and spiritual issues raised by biotechnology. To carry out this role the Council provides information, engages people of New Zealand in dialogue and gives advice to government.

This discussion document is about xenotransplantation - the transplantation of living cells, tissues or organs from one species into another. The focus here is on animal-to-human transplantation, looking at what the process involves and the related cultural, ethical and spiritual concerns.

The ready supply of animal organs has long roused interest in their potential for use in xenotransplantation, but the problems with immune system rejection of these foreign organs seemed insoluble. However, in recent years the focus has shifted away from the transplantation of organs towards the use of cells and tissues, which have less severe rejection problems and which some people find more acceptable. The possibility of genetically modifying source animals to lessen the chances of rejection has helped create new interest in the area, spurred by a rise in the need for donated cells, tissues and organs.

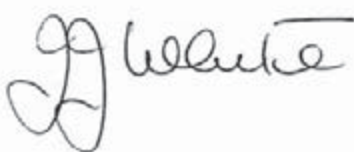
In 2002 the Government passed an amendment (Part 7A) to the Medicine Act 1981 to provide interim regulation while the safety and ethical, cultural and spiritual issues associated with xenotransplantation were considered. Part 7A allows xenotransplantation trials to be considered and approved by the Minister of Health, but requires strict criteria to be met before an approval is given. No applications have been made to the Minister of Health under this provision. This amendment is due to expire in June 2005, when new provisions for regulating xenotransplantation will need to be in place.

As part of its consideration of the cultural, ethical and spiritual aspects of xenotransplantation in New Zealand, the Bioethics Council is seeking public involvement in a dialogue process. This process will complement the review of human tissue regulation being undertaken by the Ministry of Health, and will provide valuable input into the recommendations which the Council will make to the Government on xenotransplantation.

Those who are familiar with the work of the Royal Commission on Genetic Modification will be aware that xenotransplantation involving genetic modification was the subject of one of the recommendations of the Commission. This discussion document and the dialogue arising from it have a wider focus and relate more particularly to the pending legislation on all aspects of xenotransplantation.

One of the key tasks of Toi te Taiao: the Bioethics Council is to consult and engage with Maori, as part of its commitment to the Treaty of Waitangi. The Council's approach to dialogue with Maori continues to evolve and is outlined in Chapter 6.

Xenotransplantation raises important questions about what it is to be human, how humans should treat animals, and how advantages and risks should be weighed when it comes to saving individual lives. We invite you to read this discussion document and join the discussion.



Jill White

Chair

Toi te Taiao: the Bioethics Council

January 2005

Join the Discussion

Toi te Taiao: the Bioethics Council is considering the cultural, ethical and spiritual aspects of xenotransplantation and wants to hear from a wide range of New Zealanders. Your thoughts, feelings and questions are valuable.

The Council will be conducting a dialogue on xenotransplantation in 2005, involving an open submissions process, an online forum and a series of dialogue meetings. The Council will then produce a report, which will describe the views put forward during the dialogue and will also state the Council's own position after reflecting on what was heard during the dialogue and its own research.

This document aims to inform the dialogue and submissions process by providing information about the nature of xenotransplantation and the cultural, ethical and spiritual questions it raises.

Have your say

To have your say about xenotransplantation, please do consider becoming involved in one or more of the following activities.

- **Visit the website** for background information and links to more detailed background research: www.bioethics.org.nz
- **Join the online discussion forum**, which will run from **1 March 2005**. To register, log on to www.bioethics.org.nz/dialogue/forum/
- **Attend a dialogue event**. Details of where and when will be posted on our website.
- **Make a submission** by mail, email or online. In Part Two of this document there are questions to help guide you to make a submission. There is a submission form on our website, or just send us a letter or email.
- **Get together with whanau, friends or workmates** and have a discussion. We want people thinking and talking about these topics, even if you do not end up writing anything down. Our website has links to ideas on running dialogue groups.

Note: submissions close 20 May 2005.

For more information

Email: xeno@bioethics.org.nz

or write to: Bioethics Council
PO Box 10-362
Wellington.

INTRODUCTION

Introduction

The term ‘xenotransplantation’ derives from the Greek word *xenos*, meaning foreign, and all the issues surrounding this procedure spring from the notion of associating something ‘foreign’ with a human body.

In recent years the transplantation of human cells, tissues and organs (allotransplantation) has dramatically improved the survival and health prospects for people suffering from life-threatening illnesses. Xenotransplantation involves transplanting living cells, tissues or organs between species, and in particular, from animals to humans. It is being considered because worldwide the demand for human cell, tissue and organ donation far exceeds the supply. This would be true even if everyone agreed to donate their cells, tissues or organs when they die. Furthermore, the world’s population is ageing, which will place increasing demand on donation as more people suffer from chronic degenerative diseases. Currently there just are not enough human donors to go round, and as a result people on waiting lists are dying.

The body’s immune response is serious enough with donated human organs and tissues, but it is so severe with animal organs and tissues that xenotransplantation has not been seen as a viable option. However, interest in xenotransplantation has been rekindled as a result of recent advances in the genetic modification of animals to make their tissues less likely to be rejected. The development of increasingly sophisticated anti-immune drugs and the accelerating need for cells, tissues and organs have also contributed to an intensification of research into the possibilities of xenotransplantation.

Along with the promise of a potentially unlimited supply of organs and tissues there are risks in xenotransplantation, especially from the transfer of diseases across species - as is thought to have happened with HIV. There are also questions as to whether we should be performing these procedures on animals and humans, with respect to the effects on animals’ lives and the ‘mixing’ of different species. The Government wants these issues to be publicly debated and the full implications of xenotransplantation to be clarified before decisions are made about its use in New Zealand.

Toi te Taiao: the Bioethics Council is engaging in a dialogue with New Zealanders to find out what they think about xenotransplantation, and this document is aimed at informing this dialogue. This is not intended as a technical document. The Council’s concern is specifically with the cultural, ethical and spiritual aspects of xenotransplantation. We are not directly concerned with assessing the safety and effectiveness of xenotransplantation, the extent of the public health risk it causes, the best ways of dealing with the risk, or the extent of the demand for xenotransplantation treatments. These matters are being considered elsewhere by the Government. However, we do not want to exclude these topics from our dialogue because obviously they give rise to many of the cultural, ethical and spiritual concerns about xenotransplantation.

For example, someone who believes there is something wrong with mixing material from different species may be willing to tolerate this procedure if it would do a great deal of good - such as saving a child’s life. Clearly such a decision depends on an assessment of the safety and effectiveness of xenotransplantation. This discussion document briefly covers these topics, and we expect and welcome discussion on these and any other matters relating to the cultural, ethical and spiritual judgements about xenotransplantation.

The document is divided into two parts. In Part One we begin by looking at what xenotransplantation is, taking some care to define the different types and their uses, given that we may decide that there are both justifiable and unjustifiable applications of the technology. Chapter 2 asks why xenotransplantation should be seriously considered, followed by a chapter on how well the procedure actually works. Whether a procedure works or not will also be judged in terms of the risks involved, and these are addressed in Chapter 4.

Having established the technical groundwork, in Part Two we directly address the cultural, ethical and spiritual issues relating to xenotransplantation. Chapter 5 looks at spirituality, culture and need. Chapter 6 then considers Maori and xenotransplantation. This is followed by an overview of the ethics of using animals for human benefit, and a chapter that looks at how we might balance individual benefits with public risks, especially in terms of infringing on human rights. The final chapter outlines the legislative situation in New Zealand and the decisions to be made. How other countries are handling these issues is covered in the appendix.

There are obviously other questions that need to be addressed about the use of xenotransplantation, not least being the question of cost: what resources would be required to raise the animals, perform the procedures and monitor the recipients afterwards? How do these compare with the costs of alternative procedures? Would such an allocation of resources move funding from other areas of greater need, including research? And if the operations were not government funded, would there be equity issues of who receives this new treatment? These are important questions if xenotransplantation is to be considered in New Zealand, but they are beyond the scope of this document.

Face-to-face dialogue

The Bioethics Council has been charged with promoting ‘dialogue’. Often ‘dialogue’ is used in the sense of government consulting with the public along traditional channels of input into policy decisions (e.g., submissions to government and regulatory authorities, select committee hearings, consultation on proposals). However, the Council is determined to engage in dialogue that genuinely seeks to build understanding, rather than persuading people to adopt a position.

This kind of dialogue works on the assumption that agreement on a way forward often requires not simply more information, or tighter arguments, but a deeper understanding of how others understand a situation.

Dialogue provides a ‘space’ in which participants can, without fear of ridicule or personal attack, examine their own and others’ deeply held convictions in such a way that all parties respect the nature of those values and try to understand what shapes and gives meaning to other people’s lives.

The value to government of dialogue about biotechnology is that:

- the public has an opportunity to better articulate and understand the values and beliefs they and other citizens think should underlie government policy
- government can get a better understanding of what is at stake for the public, the factors that shape public responses to developments in policy and technology, and the values the public wish to see expressed in political and economic decisions.

PART ONE >
XENOTRANSPLANTATION: SCIENCE, SAFETY AND EFFECTIVENESS

PART ONE >

Xenotransplantation: Science, Safety and Effectiveness

1. What is Xenotransplantation?

Many people know of someone who has received a cell, tissue or organ transplant. The donor is usually a person who has died as a result of brain damage, for example through a stroke or accident, but it may also be a living donor who has donated, for example, a kidney or some bone marrow. This type of transplant, where the donor and the recipient are both of the same species (in this case human), is called **allotransplantation**.¹

In recent years another type of transplant technology has hit the headlines - **xenotransplantation**. In human medicine, xenotransplantation means using living non-human animal cells, tissues or organs to treat humans. It is not a new idea - animal organ and tissue transplants have been tried a number of times over the centuries, but with little success. Now, however, researchers are working on this technology again. Chapter 2 explains why.

The different types of xenotransplantation

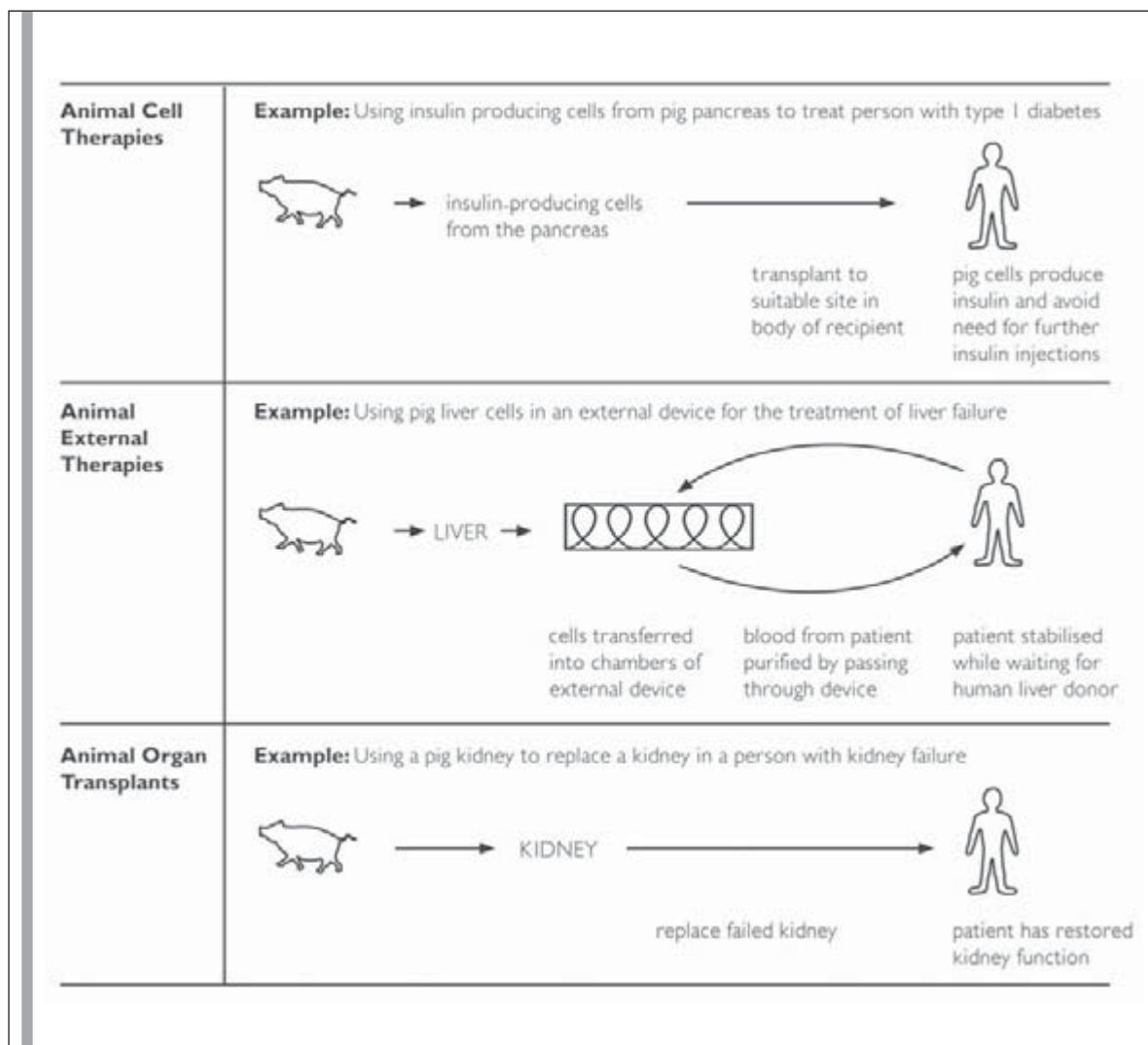
When we hear about transplantation, we usually think of **organ transplants** such as hearts or kidneys. However, it is important to stress from the outset the sheer variety of ways of doing xenotransplantation. Transplantation can also involve tissues, such as bone marrow, or clusters of specialised cells, such as **pancreatic islet cells** (which produce insulin). These transplants are called **cell therapies**.

Transplants can also involve different types of procedures. Most involve putting living tissue, cells or an organ into a patient to replace diseased or failing parts of the body. Less well known are **external therapies**, which occur outside the body of the patient. An example is when blood from a patient with liver failure is passed through a machine containing animal liver cells to remove toxic substances (a procedure similar to kidney dialysis). Another external therapy involves growing human skin in the laboratory over a layer of animal cells and later using the skin as a graft to treat burns.

Figure 1 shows the different types of procedures that are defined as ‘xenotransplantation’.

¹ There is a glossary at the end of this guide to provide more information about technical and other key terms used. The first time words that are described in the glossary are mentioned in the guide they are printed in bold (like this: **allotransplantation**).

Figure 1 > What is xenotransplantation (animal-to-human transplantation)?



Some types of xenotransplantation are relatively advanced and close to moving beyond research into treatment; others - particularly the transplant of whole organs - are a long way from being used clinically. Some types aim to improve on current treatments, as with diabetes; others aim to provide treatment where currently there is none, as in external therapies (mentioned above). Some types use cells, tissues or organs that are **genetically modified**; others do not. Some types use relatively few animals or need not inflict great suffering; others use a variety of animals, including primates, and may involve considerable suffering for animals. Some types use organs that are central to many people's sense of identity, such as hearts or eyes; others involve parts that are likely to be less central, such as pancreatic islet cells.

The point of stressing this variety is that concerns about one type of xenotransplantation may well not apply to another type. For example, an objection to the genetic modification of animals would not apply to xenotransplantation that does not involve genetically modified animals. So our cultural, ethical and spiritual discussions of xenotransplantation need to be discriminating. It could be that no kinds of xenotransplantation should be allowed, or that all should, but we should be careful not to rule it out or rule it in through thinking that all types are the same.

The process of developing xenotransplantation

Researchers around the world are working out the science of xenotransplantation step by step. They start with laboratory studies on cells and tissues to work out the underlying science. Then they conduct studies on small animals (such as mice, rats or rabbits) to test possible procedures. The same approach is used in other medical research, such as cancer research or the development of new drugs. If these early studies are successful, further thorough research is needed to develop procedures that can be used to treat humans. This research covers two main areas.

- **Animal-to-animal studies**, in which the source and recipient animals are as similar as possible to the proposed human treatment (for example, from pig to baboon). These **preclinical studies** are needed to make sure a procedure can be conducted safely and effectively on animals before it is tried on humans.
- **Animal-to-human trials**, in which animal cells, tissues or organs are used for human treatments in closely monitored **clinical trials**. These trials, which are most likely to involve pig-to-human transplants, would be attempted only if animal-to-animal studies showed a high likelihood of benefit to humans.

Clinical trials can be either **therapeutic** (the people participating are expected to benefit from their involvement in the study) or **non-therapeutic** (the study is designed to obtain further knowledge, but may not directly benefit the participants).

Because of the potential risks involved, only research with some prospect of helping people is considered to be acceptable for clinical trials of animal-to-human transplantation. As with other medical technologies, the process of testing new therapeutic procedures through clinical trials can take many years and involve several phases.

2. Why is Xenotransplantation Being Considered?

A victim of success

Human-to-human transplantation has become a successful way of treating various human diseases and conditions, such as heart disease or kidney failure. However, human tissue and organ transplantation usually depend on donations from people who have died, most often as the result of brain damage through stroke or accident. Over the past 20 years transplants have become more frequent and successful. The number and scope of transplant procedures have also increased to include a broader range of tissue, cellular and organ transplants, such as transplants of insulin-producing pancreatic islet cells for treatment of diabetes.

Unfortunately, this medical success story is beset by a major problem: the need for donations is accelerating but the number of donors has not risen to the same extent. As a result, New Zealand, like the rest of the world, already has a severe shortage of donors. This includes donations of eyes for corneal transplants, heart valves, skin and bone, as well as whole organs. The problem is only going to get worse because, like most other developed countries, New Zealand has an ageing population with an accompanying accelerating rate of chronic medical conditions such as diabetes. And the rate of diabetes, in particular, is predicted to rise and to affect increasingly younger age groups due to rising levels of obesity. Ironically, our success in reducing the number of road traffic deaths has reduced the number of potential donors further.

The need is disproportionately spread in New Zealand's population, however, with rates of Maori diabetes almost three times those of European/others.² Maori are also over-represented in cases of diabetic renal failure, with rates up to 10 times those of non-Maori,³ yet the rate of renal transplantation in Maori (0.4 cases per 10,000 population) is not significantly different to that for Pakeha (0.3 per 10,000). The rate of donation is also low. For example, a statistical analysis by the National Organ Donor Co-ordination Office showed that only six Maori families consented to organ donation between 1988 and 1996 (from a total of 290 families).⁴ Given the prevalence of kidney disease in this population group, and potential issues around tissue matching, this low rate of organ donation may seriously disadvantage Maori. This makes it imperative that we understand the issues Maori have with donation and xenotransplantation.

The overall shortfall of donors will be difficult to overcome. This is not a minor hiccup that can be easily solved by greater efforts or funding; it is extreme and it is increasing. Many people suffer and some die while on a waiting list for a suitable transplant.

The costs to society of these shortages can be measured in the deaths and illness of patients; in emotional, social and economic costs to their families; and in direct and indirect economic costs to the wider community. As a result, medical researchers face two challenges. The first is to keep people alive while they wait for a suitable organ or tissue donation. The second is to find suitable alternatives to human donations for repairing or replacing damaged or diseased tissues and organs. Animal external therapies, such as liver perfusion, may help to overcome the first challenge, while transplants of animal tissues, cells or organs may offer a solution to the second. This is why xenotransplantation is being seriously considered.

² Prevalence of self-reported diabetes, 2002/03 New Zealand Health Survey (Maori: 8.0%; European/other: 2.9%).

³ Discharges from public hospitals in 2003 for renal failure in people with diabetes, Ministry of Health (Maori 70.7 per 100,000; non-Maori 7.2 per 100,000).

⁴ National Transplant Donor Co-ordination Office figures; cited in Te Puni Kokiri, *Hauora o te Tinana me Ona Tikanga*, Te Puni Kokiri, Wellington, 1999.

In some cases it is not just a matter of getting an improved supply of tissues and organs. Xenotransplantation could be of great benefit in treating people with diseases for which there is currently either inadequate treatment (as with severe diabetes) or no treatment at all (as with Huntington's disease or Parkinson's disease). Xenotransplantation for severe diabetes involves transplanting insulin-producing pancreatic islet cells from pigs. This procedure is closer to the clinical stage than other forms of xenotransplantation, and it also responds to a disease that is both serious and common in New Zealand and other developed countries, and is predicted to increase.

Scientists are working to overcome several major obstacles to xenotransplantation, including rapid **immune rejection** (see Chapter 3) and structural or functional incompatibility of the animal transplant (it simply doesn't work properly in the human recipient). With the rapid development of **genetic technology** over the past decade, some scientists believe that it might be possible to overcome these problems by genetically modifying the source animals to make their tissues and organs more compatible with humans. Hence, the shortage of human donors, combined with developments in genetic technology, has further stimulated interest in xenotransplantation.

What are the possible alternatives?

Some people question the need for xenotransplantation. In their view, there are alternatives into which it would be better for society to put its efforts and resources.

Alternative therapies

At the same time as xenotransplantation research is progressing, researchers are exploring other new therapies to overcome the shortage of donated tissues and organs, and to treat an increasing range of diseases and conditions that have not been treated before.

One such area of work is on human stem cells. Stem cells are unspecialised cells that have the capacity to mature into specialised cell types (such as those that make up the heart, liver, brain and pancreas). It is hoped that these cells will have the potential to repair human organs and to treat a similar range of diseases to those proposed for animal cell therapies. However, human stem cell technology raises a number of ethical issues of its own, and its development will require the use of animals in preclinical studies similar to those required for xenotransplantation research (including **non-human primates**). Also, some stem cell techniques cannot be regarded as an 'alternative' to xenotransplantation because the stem cell lines are grown on a layer of animal cells, which brings them within the definition of animal external therapies.

A second area of research is into the use of mechanical or artificial organs, either for short-term 'bridging' procedures for people waiting for an organ to become available, or for longer-term replacement or repair. The development of artificial devices may provide solutions to some conditions and diseases that currently require transplants - but not all.

Like xenotransplantation, research in both these areas is in the early stages and it is not clear whether they will be more or less successful than animal therapies across the wide range of diseases and conditions involved. Only further work will determine the best form of therapy for each condition. At present we simply do not know what therapies will be safer or more effective.

Increasing the number of human donors

It has been suggested that xenotransplantation would not be needed if the number of human donors could be increased. This would require an increase in the number of organs and tissues retrieved after death and/or from the living.

Retrieval from people who are dead is limited by the number of suitable potential donors. As we saw in the previous section, organs, in particular, are usually removed only from those who are declared brain dead, and they are only a very small number of those who die. Moreover, retrieval is limited by the rules governing consent. In New Zealand, families must, in practice, give consent before organs and tissues can be retrieved. The Ministry of Health is currently reviewing the regulations governing retrieval of tissue and organs from the dead and the living, and one option could be to introduce a system of **presumed consent**, where it is presumed that people are willing to donate unless they or their families explicitly refuse. However, the ethics and effectiveness of presumed consent are matters of controversy.⁵

Other suggestions include increased support for emergency care professionals in their work with the relatives of potential donors, the adoption of a donor registry, payment to families, and increased advertising to the public. Some of these measures are ethically controversial, and no matter how successful they might be it is unlikely they would provide enough of a supply to meet demand.

Some organs and tissues - such as kidneys, parts of livers or bone marrow - can be removed from living people and transplanted. This is becoming more common, but again there are limits. One is the number of people willing to undergo the removal of parts of their bodies. Living donors have often been relatives or friends, but there are suggestions to try to increase the number by allowing payment. The payment of money is, however, considered ethically difficult by many. Furthermore, some organs (such as hearts) will not be removed from the living, and removal of other organs (such as part of a liver) is controversial because of the risks that major surgery carries for the donor.

Preventive measures

It has often been suggested that preventive programmes and healthy lifestyle education on topics such as exercise and good nutrition could help to reduce the need for transplants. However, many conditions treated by transplantation, such as kidney failure, are not necessarily related to lifestyle. They can occur in young, otherwise healthy people because of an infection or some other factor. **Type 1 diabetes** and Parkinson's disease - both active areas of research on animal cell therapies - are not related to lifestyle. Type 1 diabetes is usually diagnosed in children and young adults and its cause is unknown. The cause of Parkinson's disease is also unknown.

Sceptics about xenotransplantation reply that even if these alternatives would not solve the whole problem, they would at least reduce the need for using animals. So one set of questions is about whether the demand for transplants could be better met in other ways. Again, the answers in a given case might depend on which type of xenotransplantation is under discussion. A further set of questions concerns whether xenotransplantation would be a good way of meeting demand for transplants. Part of the answer to this question hinges on how well xenotransplantation works - or might be expected to work - and we turn to this next.

⁵ Refer to the Discussion Document on the Review of Human Tissues and the Summary of Submissions www.moh.govt.nz

3. How Well Does Xenotransplantation Work?

Research on xenotransplantation is still developing. The focus is on finding out whether it can work and, if so, whether it is safe for use in humans. Because of rejection and other problems such as size and shape, animal organ transplants will be the hardest procedures to perfect and may never be successful. Instead, researchers predict that in the short-to-medium term animal cell therapies (such as brain or pancreatic islet cells) or animal external therapies (such as devices using animal liver cells, or skin grafts) are more likely to be successful. This is because cell transplants and external procedures cause less immune rejection than organ transplants and present fewer structural and functional problems. These kinds of procedures are already being tested in limited clinical trials overseas. It is therefore these procedures, rather than organ transplants, that are likely to be the subject of the initial research proposals considered in New Zealand.

The following summary briefly describes the current state of research on each of the three types of animal transplantation procedures described in Chapter 1.

Animal external therapies

The use of external machines containing animal liver cells to treat acute liver failure has been tested in many animal-to-animal studies, with some promising results. The Food and Drug Administration in the United States and the relevant authorities in Europe have therefore allowed clinical trials of pig liver dialysis procedures. Although not conclusive, these animal-to-human trials have shown some success with ‘buying time’ for patients with liver failure who are waiting for a suitable liver transplant from a human donor. Importantly, the use of pig liver cells in this way has not caused any significant adverse effects. Some bigger trials are now planned overseas to obtain better information about the effectiveness of the procedure.

There have also been encouraging results from both animal studies and clinical trials of techniques to grow human skin on feeder layers of animal cells, then using the skin to repair burns.

Animal cell therapies

Animal cell therapies involve the transplantation of isolated animal cells or cell clusters. They have the potential to treat diseases, such as type 1 diabetes, Parkinson’s disease and Huntington’s disease. They may also be able to be used to repair damaged tissues or organs, thus avoiding the need for more invasive surgery.

Research on animal cell therapies is at an early stage, although some islet cell transplants for Type 1 diabetes was trialled in New Zealand in the mid-1990s. Some success has been achieved in animal-to-animal studies, with good survival of the transplanted cells and minimal side-effects. Based on these results, agencies in the United States and Europe have approved a number of animal-to-human trials of animal cell therapies. Some of these have already been carried out. For example, promising clinical outcomes have resulted from the implantation of neural cells from foetal pigs into the brains of patients with Parkinson’s disease. Others are either planned or are in progress.

So far, these clinical trials have included very few patients and the results obtained do not clearly show that animal cell therapies are effective. However, in many cases the cells survived well in the recipient and did not cause unwanted side-effects. Further animal-to-animal research is now being carried out to discover how to promote the function of the cells as well as their survival.

Animal organ transplants

There are major obstacles to the transplantation of whole organs between species. This was shown by a succession of failed attempts from the 1960s to the early 1990s. For animal organ transplants to be successful, researchers need to prevent the transplant being rejected by the recipient's **immune response** (because it recognises the transplant as 'foreign' and attempts to destroy it) and also to ensure that the organ functions properly. Rejection occurs in three ways: hyperacute rejection, delayed organ rejection and cellular rejection. The physiological processes involved are extremely complicated, and they present huge challenges to the success of xenotransplantation.

In recent years researchers have been using **gene** technology to genetically modify pigs to overcome the most severe forms of immune rejection. As a result, the survival times of animal-to-animal organ transplants have increased from minutes or hours, to days or weeks. Researchers think that these times may continue to improve as the science is better understood, new modifications are made to the source animals, and improved **immunosuppressant drugs** are developed and tested. Another approach has been to encapsulate the **xenograft** in a membrane that allows some molecules to pass through but keeps out the large molecules (such as antibodies) that are responsible for the immune response. Once again, there are a variety of technical problems that must be overcome. However, South Korea announced at the beginning of 2004 a 10-year plan to mass produce genetically altered pig organs for human transplants.

In summary, although animal-to-animal studies are being carried out in various countries, there is clearly a long way to go before such transplants can be tested in humans.

Which animals work best?

It would seem obvious, when searching for ways to reduce the rejection reaction to xenografts, to use animals as physiologically close to humans as possible, such as old world monkeys and the apes (for example, chimpanzees). However, this very closeness creates complex ethical problems as well as an increased likelihood of cross-species infection. There are strict regulations in New Zealand about the use of non-human primates in research, so it is unlikely that these species would be used for xenotransplantation research in this country.

At present the pig is the favoured animal for research into xenotransplantation, because they grow quickly to about the right size, produce large litters and can be reared in specific pathogen-free conditions (where some but not all micro-organisms are excluded). In terms of ethical concerns, the fact that pigs have long been used as a source of meat reduces - but certainly does not eliminate - the concerns of many people, especially when weighed against the possible benefits.

However, recently it has become clear that there is also the possibility of cross-species infection from pigs. This takes the issue of whether to perform such a procedure out of the realm of an individual decision to take a personal risk, usually for the sake of a therapeutic effect, into the realm of the safety of the xenotransplantation recipient's **close contacts** and the community at large. The spectre of **HIV** and **AIDS** hangs over discussions on the possibility of cross-species infection, so we will now turn to look at the risks involved with xenotransplantation.

4. What are the Risks?

Cross-species infection

The main risk for a person receiving animal transplant therapy is that the transplant might not function properly. However, there is also a risk that one of the wide range of viral, bacterial and other infections known to occur in the source animals will infect the transplant recipient, causing disease (sometime called **xenosis**). Some cross-species infections are caused by bacteria, viruses and **prions**, that move from animal to animal and then across to humans. HIV is one example, being a human version of **SIV**, which is caught from infected chimpanzees. The same problem occurs for human-to-human transplantation, and transplant recipients have contracted infectious diseases from donor organs and tissues.

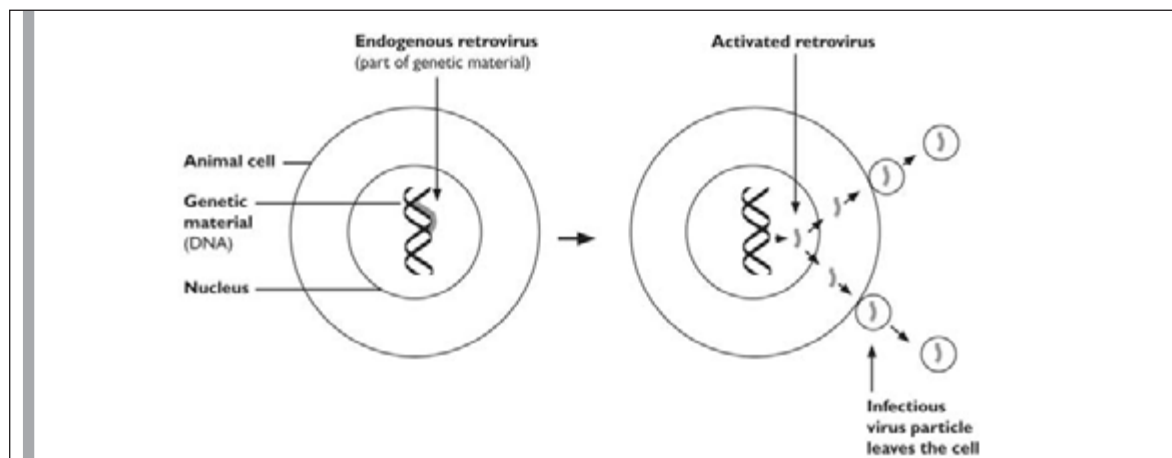
Unfortunately, for both human-to-human and animal-to-human transplantation, the potential for an infection to occur is increased by the drug treatment that transplant patients receive to suppress their immune systems and help prevent rejection of the transplant. However, researchers believe that the risk of infection by pathogen-caused animal diseases would be minimised in the same way as for human infections: by rigorous screening of source animals and appropriate treatment of transplant recipients if an infection occurs.

While known animal infections may not pose a serious problem, xenotransplantation does carry another potential risk that has more serious implications for both the individual patient and the wider community. This is the risk that a previously unknown disease, or a new form of a known disease, might emerge and infect recipients of animal transplants and subsequently spread to close contacts and the general public, causing a serious new epidemic. It is for this reason that consideration of the risks of the procedure need to go beyond an individual's assessment of the personal risk they are willing to take.

ERVs

A group of viruses called **endogenous retroviruses** (ERVs) are of particular concern. Instead of actively causing infections like other **retroviruses**, the endogenous retroviruses remain dormant in their host - embedded in the **genetic material** - not causing any obvious signs of disease. However, they may be activated occasionally, and it is possible they could then infect other animals, including different species. Little is known about what might make endogenous retroviruses become active but, if an **animal transplantation product** contains an endogenous retrovirus, there is the potential for it to activate at any time in the future and infect the transplant recipient (see Figure 2). Such an infection could spread to close contacts of the recipient (for example, medical staff, family, friends) and, in the worst case, to the general population. These ERVs cannot be screened out.

Figure 2 > Possible activation of an endogenous retrovirus



PERVs

Most pigs have a retrovirus called **porcine endogenous retrovirus** (or PERV). In 1997 researchers reported that when they mixed pig cells with human cells in the laboratory, some human cells became infected with PERV.⁶ The first evidence of cross-species transmission of a retrovirus during a transplant occurred in 2000, when a study found transmission of a PERV from pancreatic pig cells into immunosuppressed diabetic mice.⁷ This raises the possibility that the recipient of a pig transplant may be infected with PERV, or with another, currently unknown, infectious disease agent. Some retroviruses have been associated with cancer.

Many researchers consider that the risk of a new infectious disease emerging as a result of xenotransplantation is very low. More than 200 human patients have received pig transplant therapies and none have become infected with PERV or other new infectious agents. However, such an event cannot be completely ruled out and the consequences, were it to happen, could be serious.

Such risks must therefore be assessed and weighed against the potential benefits of xenotransplantation. It is impossible to generalise the level of risk associated with xenotransplantation research, which must be assessed over the long term. The precise risk will vary from one procedure to another, depending on a range of factors including the following:

- *The amount of direct contact between animal and human tissues* - this may be zero for some external procedures, such as liver perfusion devices, where the animal liver cells are contained within the device and separated from the patient's blood by a membrane. It may also be minimal in some cell therapies where the cells are contained in an organic capsule, such as collagen. However, in the case of organ transplants, direct contact would be considerable. The immunosuppression required following whole-organ transplants following such procedures also increases the risk of infection, due to the weakening of the recipient's immune system.
- *The length of time the animal and human tissues are in contact* - this may be very short for external therapies, and long term for cell and organ transplants.
- *Detailed information about any retroviruses or other infectious agents that the source animal carries.*

Informed consent

As we have seen, the risks to the recipient are that the transplant will not work, or will worsen their condition, and that the transplant will infect them. The existence of risks does not in itself mean that xenotransplantation should be rejected. Most standard surgical operations, especially those performed under general anaesthetic, carry some risk. So long as the recipient is aware of the risks, and there is sound evidence that the risks are outweighed by the potential benefits, the familiar idea of informed consent can be applied.

In New Zealand, the Code of Health and Disability Services Consumers' Rights establishes the rights of the consumer to make informed choices about the delivery of health services - including clinical trials. For informed consent to be obtained, information on the procedure, including any known risks, needs to be provided to the subject. In the case of xenotransplantation, the patient would need to be informed of the risks of cross-species infection, even if these risks were not quantifiable.

⁶ C Patience, Y Takeuchi, RA Weiss, Infection of human cells by an endogenous retrovirus of pigs, *Nature Medicine*, 1997; 3(3); cited by S Jessamine, Certain peril: a risk evaluation of xenotransplantation in New Zealand, paper presented at the New Zealand Risk Management Association Conference, 2002.

⁷ Public Broadcast Service, *A History of Xenotransplantation Experiments*, 2001.

It is highly likely that any xenotransplantation research carried out in New Zealand would be therapeutic (expected to benefit the subjects) rather than done on healthy subjects. Before being permitted, there would be a scientific review of the pre-clinical data by an expert group, and then review by one of New Zealand's seven new **Health and Disability Ethics Committees**.

Public health risks

If the xenotransplant procedure involves a risk not only to the recipient but also to close contacts - and in the worst-case scenario of an epidemic, a risk to everybody - individual consent becomes insufficient. The ethical question then becomes: is it right to impose risks on people without their consent? Are the risks of xenotransplantation so great as to make the procedure wrong without the consent of the whole community? How are we to weigh the risks of potentially saving the life of a person with kidney failure against the unknown risks of an epidemic?

There is also the question of how far the need for consent should extend. For example, should it extend to clinical staff involved with the procedure? If they refuse to be involved and the patient dies as a consequence, what would this mean? Should close contacts of the potential recipient also be asked to consent?

It is obvious from these questions that, unlike the situation with other new medical procedures, the risks of xenotransplantation potentially include the whole community. It is for this reason, in particular, that it is crucial that people have the chance to think about the benefits and risks, to discuss their feelings, and to be kept informed and involved in decisions made about xenotransplantation. In Part Two we turn from descriptions of the more technical aspects of xenotransplantation to look at the cultural, ethical and spiritual aspects, and then in a later section we return to the problem of weighing individual benefits with public risks.

PART TWO >
XENOTRANSPLANTATION: CULTURAL, SPIRITUAL AND ETHICAL ISSUES

PART TWO >

Xenotransplantation: Cultural, Spiritual and Ethical Issues

Introduction

Xenotransplantation raises serious ethical issues, such as respect for the integrity of humans and whether it is morally wrong to use animals for medical procedures to benefit humans, including whether it is acceptable to genetically modify animals. Xenotransplantation also raises some unique issues about the rights of individuals and the common good of all members of society.

People have widely differing views on these issues. These views are often influenced by their cultural and spiritual background, their personal or family members' medical conditions, their understanding of the technologies involved, and their views about the rights and the welfare of animals.

As we have seen, transplantation - and therefore xenotransplantation - is an important issue for Maori to consider, and the Bioethics Council looks forward to receiving input from Maori. Within ethnic and cultural groups there is usually a range of opinions and beliefs, often relating to the extent to which individuals affiliate with Western culture or with their culture of origin. This diversity may well be present in views put forward by Maori, which will enrich and deepen the discussion for all participants.

One of the primary aims of this document is to encourage people to think about xenotransplantation in relation to their cultural, ethical and spiritual beliefs. Part One provided information about the technology and its potential uses. In Part Two we detail some of the cultural, ethical and spiritual issues involved, and outline different views people may have about xenotransplantation. These views represent only some of the possible ethical, cultural and spiritual perspectives. You may identify with one or more of them, but you may also have another perspective. The Bioethics Council is interested in the views that strike a chord with your own beliefs, and ideas you might have about ethical, cultural and spiritual issues that are not touched upon here.

5. Spirituality, Culture and Human Need

One objection to xenotransplantation is that it contravenes the appropriate relationship between humans and nature, or between humans and God.⁸ Beliefs about these relationships may come from a cultural background, involvement in a particular religion, or from a spirituality that is not derived from a particular culture or religion.

The Royal Commission on Genetic Modification referred in its 2001 report to “world views”, which give rise to the cultural and spiritual values that guide our individual decision-making. They identified as a major issue the problem of “how to link cultural and spiritual values (such as the sacredness of nature) with specific decisions (such as whether to approve the development of a transgenic cow)”.⁹ We could easily substitute xenotransplantation here for the development of a transgenic cow, because the same issue emerges when we consider how, and to what extent, cultural and spiritual beliefs should influence our decision-making about the use of animal-to-human transplants.

For many people human need is the factor that most incisively challenges cultural or spiritual beliefs that might otherwise prevent the use of a particular biotechnology. A life-threatening condition, whether in oneself or a loved one, may see some cultural or spiritual beliefs give way to the need to preserve life or improve health. The preservation of life may itself be the spiritual or cultural value that carries the greatest weight. The intersection of cultural and spiritual beliefs with human need is always an area where complex issues arise, not only for individuals but for society as a whole.

Religious viewpoints

As an indication of religious viewpoints, the Australian public consultation on xenotransplantation received submissions from representatives of the Christian, Jewish and Islamic religions, who agreed that xenotransplantation does not contravene the order of creation, and that the use of animals for human benefit is acceptable. A review of world religions found that xenotransplantation is acceptable in most of the major religions.¹⁰ Both Islam and Judaism forbid the eating of pork, but accept xenotransplantation on the basis that humans have a higher place in the world and therefore have the right to use animals for their welfare, as long as the animals are treated with respect.¹¹ A number of religions that do object to transplantation, such as the Hindu or Buddhist faiths, still allow the individual to make a choice.¹²

Nature

Many people who feel that xenotransplantation is ‘unnatural’ will not be thinking from within a religious framework. Some believe that species have an integrity that should not be transgressed by mixing parts of one species with another. Species have evolved to occupy their own ecological niches, to be functioning parts of a whole, and therefore there is something fundamentally wrong with xenotransplantation. The

⁸ Committee on Defining Science-based Concerns Associated with Products of Animal Technology, Board on Agriculture and Natural Resources, Board on Life Sciences, et al, *Animal Biotechnology: Science-based concerns*, National Academies Press, Washington DC, 2002.

⁹ Royal Commission on Genetic Modification, *Report and Recommendations*, 2000, p.16.

¹⁰ AS Daar, Ethics of xenotransplantation: animal issues, consent, and likely transformation of transplant ethics, *World Journal of Surgery* 1997; 21: 975-82; cited by Jessamine.

¹¹ F Rosner, Pig organs for transplantation in humans: a Jewish view, *Mount Sinai Journal of Medicine* 1999; 66 (5) & (6); cited by Jessamine.

¹² Steering Committee on Bioethics, *Report from the Working Party on Xenotransplantation*, Council of Europe, Strasbourg, 2000; cited by Jessamine.

idea that species have value in themselves as they are, quite apart from their usefulness to humans, is a strong theme in the conservation movement. This can give rise to strong clashes of belief systems, as when a proposal to develop an area could endanger the survival of a species valued by conservationists but not valued by developers.

Certainly feeling part of an overall system of being, life or nature is an important part of the ethical and spiritual beliefs of many people, which often carries with it responsibilities for caring for other parts of that system - a concept often referred to as 'stewardship'. We will be looking further at this stewardship relationship in the next section when considering the interests of animals.

We do, however, need to be careful when rejecting something purely on the basis that it is 'unnatural'. On the face of it, the term 'unnatural' could be seen to cover any medical intervention, or the selective breeding of animals and plants, or for that matter wearing clothes, driving cars and flying in aeroplanes. Also, the objection in terms of unnaturalness can merge imperceptibly with what has been called the 'yuck factor' - an intuitive reaction that something is disgusting and therefore wrong. Such a reaction is perfectly valid but in the context of xenotransplantation it could be accommodated, by individuals having the right to refuse their personal consent for a xenograft (see Chapter 4 for further discussion on informed consent). If someone feels strongly that they could not tolerate having parts of another species in their own body, this would be seen by many to be a justifiable response. Denying a medical procedure to others purely on the basis that one finds it personally distasteful may be much harder to justify.

Identity

In Part One, when we were discussing the different types of xenotransplantation, we noted that some organs (especially) and tissues are more related to an individual's sense of personal identity than others. Would - or in fact should - the particular tissue, cells or organ involved alter our thinking about xenotransplantation? Consider the transfer of a number of pig pancreas cells to a person suffering from diabetes. Compare this to a person who has been given a pig's heart, or perhaps even a pig's eyes. Is there a point at which the person receiving the transplant, or other people, would feel that he or she was now less human? That somehow their personal identity had been compromised?

Some tissues and organs appear to be more integrally related to the sense we have of ourselves as human beings. These are likely to be tissues and organs that are most readily visible, are related to reproduction and the continuance of our lineage, or that we traditionally associate with our thoughts and social interaction. For example, according to the Catholic Church, "the implantation of a foreign organ into a human body finds an ethical limit in the degree of change that it may entail in the identity of the person who receives it."¹³ Both Pius XII and John Paul II have clearly upheld the moral legitimacy of the therapeutic use of xenotransplantation, as long as "the transplanted organ does not affect the psychological or genetic identity of the person who receives it", and the procedure balances benefits over risks.¹⁴ In particular, the Church refers to the head and sexual organs as "indissolubly linked with the personal identity of the subject".

Some may argue that concerns about identity are simply another version of the 'yuck factor'. Just as, for cultural and historical reasons, it may seem more unethical to use dogs or chimpanzees rather than pigs for medical procedures, it may seem more unethical to use eyes rather than a kidney. This is a complex area, and for many people issues of personal identity and mixing the identities of different species will be significant when weighed against the potential medical benefits.

¹³ Pontifical Academy for Life, *Prospects for Xenotransplantation: Scientific aspects and ethical considerations*, http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html, p.9.

¹⁴ Pontifical Academy for Life, p.10.

Xenotransplantation and human need

For some, the arguments about nature and identity are beside the point when set against the needs of potential recipients. The most obvious reason for xenotransplantation research is that it offers the prospect of treating people in serious need. If xenotransplantation were actually to work, it would be used for people who would otherwise die or else suffer from less effective treatments for serious conditions. For some, the chance of meeting these health needs is sufficient reason to go ahead with such research. Meeting needs - saving life especially - is considered by some to be a basic principle of humanity. It might also be a requirement of a just society that it do its best to help its members when they are severely ill and can be helped. Some believe it would be a dereliction of duty to fail to exercise our ingenuity as humans to solve or at least ameliorate such central problems of the human condition as disease and premature death.

An argument that sometimes accompanies the ethical plea to help people suffering from disease is that those who object to xenotransplantation are free to reject a xenograft in their own case, but they should not be able to impose their views on others, and in particular not those who desperately need treatment. What's more, it is sometimes said, when people are touched by real cases - and especially when they need treatment for themselves, or a loved one, - cultural or spiritual concerns about nature or identity will seem irrelevant abstractions.

Responding to serious needs, particularly saving lives, matters for many people. For others it must be balanced against or limited by other factors. Later sections discuss how xenotransplantation affects the interests of animals and how it poses a potential risk to public health. But even setting those topics aside, some people believe that we can go too far in trying to defeat death and disease, and for them xenotransplantation might be going too far. Death, it is said, is a fact of life: humans have a natural life cycle, but modern humans have a tendency to ignore death or refuse to face up to it.

Questions >

1. What spiritual or cultural perspectives influence your view of xenotransplantation?
2. What concerns do you have about the effect of various types of xenotransplantation on the recipient's identity?
3. To what extent should cultural and spiritual views about xenotransplantation be taken into account when the Government is making decisions about the use of this technology?

6. Maori and Xenotransplantation

There are several reasons why Maori must be accorded particular consideration when decisions about biotechnologies such as xenotransplantation are being made. Firstly, the Crown has a special relationship with Maori as tangata whenua and Treaty partner. Secondly, Maori have poorer outcomes in many areas and some biotechnologies have the potential to either widen or close these gaps. Thirdly, New Zealand is the only country where Maori culture, Maori knowledge systems and the Maori world view matter and have been accorded protection.

The Bioethics Council has an explicit requirement in its Terms of Reference to seek out and consider Maori views. However, Maori are likely to have a range of views: some views will be similar to those of other New Zealanders, some will differ and some will be unique, but all will be Maori views. In trying to distil out Maori views some unique factors need to be taken into consideration.

- To form their views, Maori, as with other people, may require clear, accurate and relevant information on matters that may seem abstract or irrelevant to others.
- Full disclosure by Maori of relevant Maori knowledge may be an unreasonable expectation, because some knowledge may be sacred or private, or only articulated adequately in te reo Maori. The Council respects Maori decisions about the degree of disclosure that Maori choose to make.
- No advice to the Crown/Government will be acceptable unless it explicitly considers Maori positions.

The Council considers that its advice to the Government would be inadequate without explicit consideration of Maori positions. The Council undertakes to make Maori positions on xenotransplantation explicit in its report to the Government.

A range of Maori views

Three scenarios that may represent possible Maori views are presented below. These scenarios may assist Maori readers determine where their own position lies. Maori readers may agree with all or part of any of the scenarios, or a combination of them.

Scenario 1 >

Technologies that meddle with the natural order of te ao Maori are wrong. Irrespective of the possible positive consequences of xenotransplantation, the risks to te ao Maori are just too great to contemplate. Maori lore must be adhered to.

Maori expect that their Treaty partner, the Crown, will protect te ao Maori and heed our advice in this regard.

This view resides at the more conservative end of Maori opinion.

Scenario 2 >

Maori should benefit from every modern advantage; no-one has the right to make decisions for individuals – Maori or otherwise. The fact that Maori do not feature as significant donors means that xenotransplantation offers an alternative pathway to the benefits of modern medical advances. There could be real advantages for whanau, hapu and iwi in this approach.

Maori should enjoy all of the rights and privileges available to a modern world and should be able to rely on scientific safeguards to protect us all. Whanau would still have the right to decline treatment if they wanted.

This scenario resides at the more liberal end of Maori opinion.

Scenario 3 >

A cautious approach which judges risk in Maori terms should be adopted. While some Maori may also adopt other cultural stances (for example, religious or philosophical), decisions should principally balance Maori priorities with Maori concerns.

In a health setting, concepts of hauora and whanau ora are key. Maori should be involved in a collective sense.

As a bottom line, though, unacceptable ‘Maori-risk’ should determine decisions without question. A Maori ‘no’ is a ‘no’ for New Zealand.

Questions >

Maori readers may like to use the following statements to focus their thinking on xenotransplantation. What are your views on each statement?

<i>My personal view would be:</i>	<i>Agree</i>	<i>Neutral</i>	<i>Disagree</i>	<i>Do not know</i>
If xenotransplantation were able to offer reduced disparities for Maori, and improvements in health and hauora, then I would support its use.				
Because xenotransplantation uses animal tissues or organs, I could not accept its use in Maori.				
Maori views should be paramount in making decisions for New Zealand as a whole.				
Maori and whanau should be at liberty to make their own decisions about xenotransplantation.				
Concern for the protection of the public should outweigh individual benefits (or in Maori terms, iwi, hapu and whanau protection should outweigh individual benefits).				
Because xenotransplantation is such an abstract, complex technique, we should be able to rely on the Government to determine if it could be used safely or not.				

7. The Interests of Animals

In this discussion we have been talking about using animal tissues, cells and organs in medical procedures involving humans. As we have seen, there are an enormous variety of possible uses for xenotransplantation, utilising a range of different animals. Before looking at the ethical aspects of using animals for xenotransplantation it will be worthwhile to see which animals are likely to be used and for what reasons.

Animals likely to be used in xenotransplantation

Non-human primates

Researchers, research sponsors and the wider community generally agree that **non-human primates** (such as baboons and other monkeys) are not a suitable source for any of the proposed animal therapies (external therapies, cell therapies or organ transplants) because of the risk of infections to the recipient and the wider community. The US Food and Drug Administration has effectively prohibited the use of non-human primates in animal-to-human xenotransplantation since 1999.

The use of non-human primates in medical research also raises serious ethical issues. Non-human primates are highly intelligent animals with complex behavioural and social needs that are difficult to meet in a medical research environment. However, baboons are considered the most suitable species for animal-to-animal studies (such as pig to baboon) to obtain important information on the effectiveness of a procedure before it can be tested in an animal-to-human trial.

Pigs

At present, pigs are considered to be the most likely and appropriate non-human source of organs and tissues. The anatomy and functioning of pigs are very similar to those of humans. Pigs are domesticated animals that are easy to breed, and, importantly, pigs are suitable for genetic modification.

Other animals

Animal-to-animal transplantation studies would use a variety of animal species in the early stages of the research (such as mice, rats and rabbits). If these studies show promising results, researchers will need to trial the procedure in an animal study that is as much like the future clinical use of the therapy as possible. This will usually involve the use of non-human primates (specifically baboons) as transplant recipients, as noted above, but fish and cattle might also be used for some procedures, such as helping to grow skin. Researchers are also considering the use of other species (such as cattle, fish and mice) for cellular transplants.

Genetic modification of animals

Researchers predict that immune rejection of animal-to-human transplants may be avoided by genetically modifying the source animals, as well as by treating the human recipient with drugs to suppress their immune response (immunosuppressant drugs). Genetic modification of source animals involves inserting some human genes into the animals to make their cells, tissues and organs behave more like human-to-human transplants.

This raises some difficult ethical issues about the rights and welfare of the animals, such as whether the insertion of human genes may make the animal in some way 'human', or whether inserted genes cause unexpected side-effects in the animals. One view may be that these issues need to be considered case by case to ensure that the proposed modification does not alter the animal in any other significant way. The aim would be to ensure that the animals retain the essential characteristics of their species.

Animal welfare and ethics

Virtually everyone believes that mammals, at least, have some ethical significance, in that it is wrong to hurt or kill them, especially if this has no benefit to humans. People who believe that human benefits outweigh the harm caused to animals often argue that these benefits are potentially very large, in terms of lives saved and suffering alleviated. This argument is often based on the belief that humans in some sense have a moral status superior to that of animals, and that therefore the needs of humans outweigh the rights of animals.

Some think it is wrong to cause suffering to or kill animals even if this has major benefits. Such an argument might be based on the belief that humans and animals have the same moral status, but it is not necessary to take this position to argue against the exploitation of animals. Some opposing the exploitation of animals maintain that the benefits to humans of xenotransplantation are often overstated and the suffering of animals understated. In this view, many animals will have to die or suffer in research for gains that are purely speculative.

It is a matter of controversy how much suffering xenotransplantation experiments and rearing would cause. For example, some types of xenotransplantation involve killing young pigs under anaesthesia, whereas others involve the destruction of a chimpanzee's immune system through chemotherapy and radiation. To minimise the risk of cross-species infection, source animals for xenotransplantation would probably need to be bred and raised in monitored, biosecure facilities. The adverse effects on animals could give rise to particular concern, especially since these source animals would need to be raised in isolation.

The Animal Welfare Act 1999 regulates the use of animals for research or testing through Institutional Animal Ethics Committees, each of which includes a representative of an animal welfare organisation. It is likely that the physical care and health of source animals would be high, because of the need to minimise the risks relating to transplantation, but as we have seen this does not eliminate ethical concerns about the treatment of animals. The Animal Welfare Act provides no guidance on balancing the harm to animals against the human benefits of the research.

The primary question seems to be how we ought to weigh the interests of animals against those of humans. The answer to this could depend on the animal in question - whether apes, pigs or mice - and how much the animal suffers in rearing and experimentation. It may also depend on the benefits to humans, in terms of exactly how safe and effective xenotransplantation will be.

Xenotransplantation involving genetic modification

One of the reasons there has been renewed scientific interest in xenotransplantation is the possibility that genetic modification will greatly reduce the immune response that is currently a major barrier to the use of animal-to-human transplants.

Pigs have a molecule on the surface of their cells called the Gal antigen, which triggers an acute immune response in humans. Genetic modification has made it possible to 'knock out' the Gal gene that produces this molecule in pig cells. Cloned piglets have now been born with the Gal gene deleted, which removes the molecule that causes the human immune system to reject pig cells, tissues and organs. Research is still being carried out on this and other aspects of the human immune response to pigs to see to what extent genetic modification can solve the problem of rejection. While immunosuppressant drugs may still be needed, the genetic modification of pigs to deactivate or delete molecules that trigger human immune reactions significantly improves the chances of successful xenotransplantation.

People with strong objections to genetic modification may accept the transfer of an animal organ or animal tissue if it has not been genetically modified, but oppose the use of xenotransplantation if it involves genetic modification of the source animal.

Questions >

4. What is important to think about when deciding whether or not xenotransplantation is an acceptable use of animals?
5. How should we weigh the welfare of animals against that of humans?
6. Does it matter which animals (for example, primates, domesticated farm animals, mice, fish) are being used for xenotransplantation. If so, why?

8. Individual Rights, Public Risk?

The restrictions on xenograft recipients

In Chapter 4 we looked at some of the risks of xenotransplantation. While the risk of cross-species infection was always known (for example, from retroviruses such as HIV), the discovery of endogenous retroviruses that hide in the genetic material of animals and may suddenly be ‘switched on’ has increased concerns. Raising pigs in pathogen-free environments will not eliminate the risk of porcine retroviruses (PERVs) being transmitted from the xenograft to the human recipient. More seriously, the recipient may then pass the infection on to close contacts (medical staff, family and friends, co-workers), which in the worst-case scenario could result in a pandemic.

There is a serious problem in assessing this risk and weighing it as a factor. On the one hand, there have been no reported instances of cross-species infections in the hundreds of xenotransplantations carried out. On the other hand, the consequences of getting it wrong are so serious that it would seem morally irresponsible to simply assume that because there have been no reported problems so far everything will continue to be fine.

One solution to this dilemma could be to do everything possible to ensure that the source animal is pathogen free, and then, given the problems of PERVs, closely monitor and restrict the activity of the recipient - indefinitely - to deal with the possibility of PERVs being transmitted. Subjects of clinical trials might have restrictions placed on them, including undergoing compulsory **monitoring**, being confined in quarantine in the event of a public health emergency, and restrictions on travel and physical contact. This raises ethical issues different to those discussed so far, involving the application of public health measures that override an individual’s rights.

Understanding such restrictions would have to be part of the process of giving informed consent. But how could we be sure that a recipient will honour these restrictions after many months or years? It has been suggested that written consent to xenotransplantation would need to resemble a contract, but the ethical and legal implications of this are such that public health legislation is probably a more promising means of enforcing compliance. Currently, under section 70 of the Health Act 1956, medical officers of health have special powers for preventing the outbreak or spread of any infectious disease. These powers include requiring people to submit themselves for medical examination.

The reason post-xenotransplant monitoring is legally problematic is that it would involve the ongoing monitoring of individuals who are apparently healthy, on the off-chance of detecting pathogens that may not even exist and may not be communicable if they do. It is unclear whether the current legislation can justify this kind of ongoing testing, so it may be that specific xenotransplantation legislation would be needed. Such legislation could grant greater powers to officials to perform ongoing monitoring and examination of asymptomatic individuals, and could also cover arrangements for the consent of clinical staff, family members and close contacts of recipients. There are questions as to whether this would be justifiable.

One very important question is whether legal compulsion would be morally justifiable - something we raise in the following section. Also, would such compulsion be effective?

Experience overseas with notifiable infectious diseases that are covered by legislation and that require ongoing monitoring and medication over an extended period (such as tuberculosis) has shown that people willing to concur at the start of the process will often eventually tire of the restrictions this imposes on their lives and will attempt to opt out, law or no law.

Perhaps this is all too much trouble. Would it not be simpler to prohibit xenotransplantation and be done with it? Unfortunately this would not eliminate all the public health risks because of what has been termed ‘xenotourism’.

Xenotourism

If the New Zealand Government prohibits all research into, and the medical use of, xenotransplantation on the basis of public health risk, there is still the problem of xenotourism. **Xenotourists** are New Zealanders who, in desperation, travel overseas to countries that do allow xenotransplantation, undergo the procedure and then return to New Zealand, *or* people from overseas who have had xenografts and then visit New Zealand. Because this may be done covertly there would be no possibility of even minimal monitoring of such people.

As a result, the management of these risks needs to be considered even if xenotransplantation is prohibited in New Zealand. Indeed, xenotransplantation is already occurring in other countries, perhaps without the careful selection and husbandry of source animals needed to reduce the risk of cross-species infection.

The kinds of public health measures needed to manage the movement of xenotourists (both those wishing to visit New Zealand and New Zealanders wishing to travel overseas) would be ethically controversial, and could include:

- a requirement to disclose information about xenografts to medical authorities
- a register of recipients
- regular checks on the health of recipients, including taking blood samples
- informing the recipient's relations and close contacts that they have had xenografts
- restricting the travel of recipients
- (in extreme cases) quarantining recipients.

Many of these measures would involve a severe infringement of an individual's right to confidentiality, to refuse medical treatment, and to freedom of movement (including not being imprisoned). And, of course, anyone who has previously received an animal transplant will need to be excluded from donating any of their organs or tissues in the future. This rule will need to apply in all countries, including those that operate a presumed consent system for organ donation. These measures might be justifiable if the recipients accepted these as conditions for undergoing xenotransplantation, but should people be required to restrict their freedom in this way? In any case, xenotourists would often not have consented to these conditions, so would it be acceptable to infringe their rights in this way?

One response would be to have an international agreement or regulations covering xenotransplantation, including the appropriate questioning of entrants and the registering of xenotransplantation recipients with a national authority (similar to the process for notifiable diseases). There is a much greater global awareness of the need to co-ordinate responses to newly emerging diseases. For example, the clinical, epidemiological, laboratory and infection control responses to the recent outbreak of severe acute respiratory syndrome (SARS), which were co-ordinated by the World Health Organisation and government agencies, were effective in controlling the outbreak.

Some believe that, given the difficulties of regulating xenotourism, it would be better to have well-regulated xenotransplantation here than to take the risk of people going to less well-regulated countries for xenotransplantation and bringing disease back.

It should be noted that the proposed government approach of preventing xenotransplantation from taking place in New Zealand until the implications are fully considered does not specifically address the issue of xenotourism. Xenotourism is therefore the aspect of xenotransplantation that most urgently requires regulation.

Questions >

7. How should the interests of the individual be weighed against those of the public?
8. What is your view about exposing non-consenting third parties to the risks that xenotransplantation might create? Does it make a difference which type of xenotransplantation is involved?
9. What would be your response if a family member living with you wanted to undergo xenotransplantation?
10. What public health restrictions would it be right to impose on the recipients of xenografts performed in New Zealand? Does it make a difference which type of xenotransplantation is involved?
11. What public health restrictions would it be right to impose on xenotourists? Does it make a difference which type of xenotransplantation is involved?

9. Decisions about Xenotransplantation in New Zealand

In 2001 an application was made to the Ministry of Health to conduct an animal-to-human transplant clinical trial in New Zealand. This application created concern about clinical safety, and about the adequacy of regulatory review processes for the ethical issues involved in xenotransplantation. The application was ultimately declined on clinical safety grounds.

In 2001 the Royal Commission on Genetic Modification released its report, which included reference to xenotransplantation. The Commission recommended that the Bioethics Council develop ethical guidelines for xenotransplantation involving genetic modification.

In response to these events the Government passed an amendment (Part 7A) to the Medicine Act 1981. This amendment allows xenotransplantation trials to be considered and approved by the Minister of Health, but requires strict criteria to be met before an approval is given. No applications have been made to the Minister of Health under this provision.

Part 7A expires in June 2005.

During 2004 the Ministry of Health has been carrying out a review of all legislation relating to human tissues, with a view to developing new legislation. This review includes transplantation of human organs, and it is logical to ensure that new legislation also covers animal-to-human transplants.

New Zealand needs to make decisions about xenotransplantation during 2005.

Question >

12. What decisions do you think the New Zealand Government should make about xenotransplantation?

GLOSSARY & APPENDIX

Glossary

AIDS: acquired immune deficiency syndrome.

Allotransplantation: transplantation of living tissue, organs or cells between individuals of the same species (for example, from human-to-human).

Animal-to-human trials: xenotransplantation research in which organs, cells or tissues are transferred from an animal species (such as pigs) to a human (see also Clinical trial).

Animal transplantation product: a live cell, tissue or organ from an animal that is used in a xenotransplantation procedure.

Cell therapies: transplants involving the use of living tissues (such as skin or bone marrow), or clusters of specialised cells (such as brain cells or insulin-producing pancreatic islet cells).

Clinical trial: a research study that tests how well new medical treatments or other interventions work in people.

Close contacts: family members and other close associates of an animal-to-human transplant recipient. The precise definition varies according to the type of procedure and other factors, and would be included in the clinical trial protocol.

Endogenous retrovirus: a retrovirus that is incorporated in the genetic material in every cell in the body of its host, and is passed down from generation to generation. Normally an endogenous retrovirus does not cause any obvious signs of disease.

External therapies: therapies that occur outside the patient's body, such as when blood from a patient with liver failure is passed through a machine containing live animal liver cells, to remove toxic substances (a procedure similar to kidney dialysis).

Gene: a section of genetic material that codes for a specific characteristic of the organism.

Genetic material: a molecular structure in living organisms that contains all the information about the structure and function of the organism (commonly a molecule called deoxyribonucleic acid, or DNA).

Genetic technology: a term used to describe the methods used by scientists to modify the genetic material of living organisms.

Health and Disability Ethics Committees: of which there are seven, are established under section 11 of the New Zealand Public Health and Disability Act 2000 to provide independent ethical review of health research and innovative practice to safeguard the rights, health and wellbeing of consumers and research participants, and, in particular, those persons with diminished autonomy.

HIV: human immunodeficiency virus.

Immune rejection: an immunological response by a person's body when it refuses to accept substances or organisms that it recognises as foreign; as in 'the transplanted liver was rejected' (see also Immune response).

Immune response: the body's mechanism for distinguishing 'self' from 'other' and eliminating invading micro-organisms or other foreign material from the body. In transplantation, the immune response can lead to rejection of the transplanted organ, tissue or cells.

Immunosuppressant drugs: drugs that suppress the natural immune response to foreign material. These drugs are usually given to transplant patients to help prevent rejection of the transplant.

Monitoring (of transplant recipients and contacts): regular testing for infectious disease status, including blood and other testing for any signs that an infection is either present or has occurred.

Non-human primate: mammals of the primate order apart from human beings (for example, apes, baboons, monkeys).

Non-therapeutic research: a clinical trial in which the study is designed to obtain further knowledge but is not expected to be of direct benefit to the participant(s).

Organ transplants: transplants involving the use of whole living organs, such as hearts or kidneys.

Pancreatic islet cells: cells from the islets of Langerhans, which are specialised areas within the pancreas that produce insulin (see also Type 1 diabetes).

PERV: porcine endogenous retrovirus.

Preclinical study: a study carried out using animals or laboratory methods to test the effectiveness or safety of a procedure before clinical trials are carried out on human patients.

Prion: a fragment of protein that acts as a disease-causing agent.

Porcine endogenous retrovirus (PERV): an endogenous retrovirus found in the genetic material of pigs. A variety of PERVs are endemic in almost all breeds of pigs (including New Zealand herds), making it impossible to remove them by selective breeding. This is a serious issue for xenotransplantation, because pigs are the most likely source of organs and tissues.

Presumed consent: in the context of transplantation, the principle that if a person has not specifically requested that their tissues or organs not be used for transplantation, their consent can be presumed.

Retrovirus: a family of viruses defined by their particular genetic structure. The family includes the lentiviruses (such as human immunodeficiency virus, HIV), oncoviruses (such as human T-cell leukaemia virus) and endogenous retroviruses (which exist as sequences embedded in the genome of their host).

SIV: simian immunodeficiency virus.

Type 1 diabetes: a condition characterised by high blood glucose levels caused by a lack of insulin. This occurs when the insulin-producing islet cells in the pancreas are destroyed by the body's immune system. Type 1 diabetes typically develops in young people (i.e., is not related to life-style factors), and is treated by injections of insulin.

Type 2 diabetes: a condition characterised by high blood glucose levels caused by (stage 1) the body's inability to use insulin effectively and (stage 2) a lack of insulin. Type 2 diabetes usually occurs in middle-aged and older people.

Therapeutic research: clinical trials in which participating patients are expected to benefit from their involvement in the study.

Xenografts: organs, tissues or cells that have been transplanted from one species to another.

Xenosis: the transfer of infections by transplantation of xenogeneic tissues or organs.

Xenotransplantation: transplantation of living cells, tissue or organs from one species to another (for example, from pigs to humans). Xenotransplantation procedures include animal organ transplantation, animal cell therapies and animal external therapies.

Xenotourists: recipients of xenografts who travel internationally, and who are of concern because of the potentially reduced ability to monitor their health, especially in the context of spreading a disease caused by xenotransplantation.

Appendix: International Approaches to Xenotransplantation Regulation

The World Health Organisation

On 22 May 2004 the Fifty-Seventh World Health Assembly adopted a resolution on allotransplantation and xenotransplantation.¹⁵ This included urging member states to:

- allow xenotransplantation only when effective regulatory control and surveillance by national health authorities are in place
- co-operate in the formulation of recommendations and guidelines to harmonise global practices, including protective measures in accordance with internationally accepted scientific standards to prevent the risk of potential secondary transmission of any xenogeneic infectious agent that could have infected recipients of xenotransplants or contacts of recipients, and especially across national borders
- support international collaboration for the prevention and surveillance of infections resulting from xenotransplantation

and requesting the Director-General of the World Health Organisation to:

- facilitate communication and international collaboration among health authorities in member states on issues relating to xenotransplantation
- collect data globally for the evaluation of practices in xenotransplantation
- proactively inform member states of infectious events of xenogeneic origin arising from xenotransplantation
- provide, in response to requests from member states, technical support in strengthening capacity and expertise in the field of xenotransplantation, including policy-making and oversight by national regulatory authorities
- report at an appropriate time to the Health Assembly, through the Executive Board, on implementation of this resolution.

The Council of Europe

The Committee of Ministers of the European Council, in preparation for adopting a resolution on xenotransplantation, published a report on the state of the art in xenotransplantation¹⁶. This report included a survey of 27 states' legal, regulatory and scientific approaches to xenotransplantation and found that legal and regulatory frameworks specific to xenotransplantation were incomplete in many states.

Only 13 to 22 percent of these states had laws relating to:

- clinical or experimental xenotransplantation
- importation/exportation of tissue specifically for xenotransplantation

¹⁵ Hazardous Substances and New Organisms Act 1996.

¹⁶ Schedule One Prohibited Actions of the Human Assisted Reproductive Technology Bill 2004 bans the development of hybrid embryos for reproductive purposes and their implantation into animals and humans.

- environmental and public health protection from xenotransplantation risks
- xenotransplantation infection risks controls
- indemnity and compensation in the case of cross-species infection.

With regard to regulatory and administrative arrangements, 67 percent of states require that specific authorisation be obtained before xenotransplantation research is carried out; 80 percent require such authorisation before clinical trials on humans are carried out. Research application guidelines have been drafted in approximately 34 percent of the states.

Initiatives for public debate on xenotransplantation had occurred in 34 percent of states.

Clinical trials of xenotransplantation were planned or underway in eight states, with 12 states performing xenotransplantation research on animals.

The Committee of Ministers of the Council of Europe adopted a recommendation to member states regarding xenotransplantation in June 2003. The recommendation includes 34 articles and aims to protect public health and all those individuals involved in xenotransplantation in the short and long term. It also ensures that xenotransplantation procedures comply with relevant animal welfare regulations.

The United States

The United States Food and Drug Administration (FDA) regulates xenotransplantation products and oversees xenotransplantation clinical trials. A Xenotransplantation Product Reviewer Working Group has been established, which:

- discusses application of the principles set forth in relevant FDA regulations
- reviews and discusses current scientific and medical data and literature relevant to xenotransplantation
- reviews and discusses the current status of xenotransplantation applications submitted to the agency
- discusses the unique issues that these products may present
- highlights areas of concern where further expert advice may be needed.

A number of clinical trials of xenotransplantation are currently underway in the United States, with regulatory approval.

The United Kingdom

The British Government is assisted in the consideration of xenotransplantation by the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). The Authority was established in May 1997 following the Government's acceptance of the recommendations made in *Animal Tissue into Humans*, the report of the Advisory Group on the Ethics of Xenotransplantation.

The UKXIRA's role is to:

- provide a focal point for xenotransplantation activity in the UK
- provide a means of regulating xenotransplantation and, in particular, to provide a process through which applications to undertake xenotransplantation in humans can be considered
- consider the underlying evidence about xenotransplantation developments and to consider whether clinical trials can be justified.

According to its Fourth Annual Report (2000/01), there were no applications to undertake clinical trials in xenotransplantation in the UK, and there were no trials underway.¹⁷ The UKXIRA reviews applications for clinical trials of xenotransplantation on a case-by-case basis.

Australia

In 2001 Australia's leading health advisory body, the National Health and Medical Research Council (NHMRC), established a working party to look at whether xenotransplantation research should go ahead in Australia. A discussion document, including draft guidelines, was released in 2002. Following a high level of feedback from the community on the discussion document, a second round of public consultation on the NHMRC's response to the initial consultation was completed in March 2004. In September 2004 the NHMRC announced that there should be a five-year moratorium on any clinical research into animal-to-human whole organ transplants in Australia.

The NHMRC also ruled that non-human primates (for example, baboons) should never be considered as source animals for any future clinical trials of animal-to-human transplantation.

The NHMRC in further considering issues surrounding animal cellular therapies and animal external therapies, issued a statement in December 2004 that there should be no clinical trials in Australia using animal cellular therapies or animal external therapies for five years.

Canada

Xenografts are considered therapeutic products and are subject to the requirements of the Food and Drugs Act, and the Food and Drug Regulations or the Medical Devices Regulations. Clinical trials of xenotransplantation cannot proceed without the approval of Health Canada.

Public consultation on xenotransplantation has also occurred in Canada. Health Canada provided funding to the Canadian Public Health Association to form a Public Advisory Group (PAG) to consult with the public and report back to the Minister of Health. The PAG reported back to the Minister of Health in January 2002, recommending that xenotransplantation involving humans should not proceed in Canada until critical issues have been resolved. The Group also recommended that stringent and transparent legislation and regulations be developed to cover all aspects of xenotransplantation clinical trials.¹⁸

¹⁷ United Kingdom Xenotransplantation Interim Regulatory Authority, *Fourth Annual Report: December 2000 - December 2001*, Department of Health, London, 2002.

¹⁸ Canadian Public Health Association, *Animal-to-human Transplantation: Should Canada proceed?* Canadian Public Health Association, Ottawa, Ontario, 2002.

