

Bioethics Briefing

Number 4: Xenotransplantation

Chris Willmott, University of Leicester

Introduction

Human-to-human transplantation (allotransplantation) has become established as a safe and reliable treatment for diseases associated with a number of organs, principally heart, kidney, liver and lungs. In some ways a victim of its own success, the transplantation service suffers from one major difficulty, a lack of human donor organs. Strategies to address this shortfall have been considered; for example, public health initiatives to reduce demand; changes to legislation to increase availability of organs; and/or the development of mechanical organs. Even if, however, these methods were to make significant strides towards redressing the balance, experts predict that they will never entirely resolve the organ shortage. Where else, then, might we turn for greater supply? The answer may lie in xenotransplantation (also called xenografting), which is the transplantation of animal cells, tissue or organs into another species, in this case into *Homo sapiens*.

The history of xenotransplantation is perhaps longer than might be expected. Appel *et al* (2000) note that surgeons in the 19th century attempted animal-to-human skin grafts using a variety of species as source, including frogs, chickens, cats and pigeons. There are even reports that an attempt was made in 1682 to repair the damaged skull of a Russian nobleman using bone from a dog.

Interest in xenotransplantation rose significantly during the 1990s. In Britain, two key reports, the Nuffield Council on Bioethics' *Animal-to-human transplants: the ethics of xenotransplantation* in March 1996 (see Nuffield, 1996) and the report of the Advisory Group on the Ethics of Xenotransplantation to the Government entitled *Animal tissues into humans* in January 1997 both concluded that

there were sufficient issues associated with the potential use of animal organs to warrant the establishment of a specific regulatory body, and the government responded by establishing the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA, see <http://www.doh.gov.uk/ukxira/>). UKXIRA meets four times a year and has produced some weighty documents, including *Infection risks in xenotransplantation* (Muir and Griffin, 2001), *The physiology of xenotransplantation* (Dobson and Dark, 2002) and *Law and ethics of xenotransplantation: bibliography and abstracts of key articles* (McLean and Williamson, 2003). [Note: in keeping with government practice, *Animal tissues into humans* is sometimes referred to as the 'Kennedy Report', since the advisory body was under the chairmanship of Professor Ian Kennedy. This nomenclature is, however, best avoided since Professor Kennedy was subsequently the chair of a second committee, looking into the retention of organs by doctors at Bristol Royal Infirmary which produced another 'Kennedy Report'].

Xenotransplantation was headline news in January 2002 when PPL therapeutics, a commercial spin-out from the Roslin Institute, announced the birth of five cloned pigs. The pigs had been genetically modified to reduce their expression of a surface antigen responsible for rejection in pig-to-primate transplants (see *The Science of Xenotransplantation*, overleaf). Subsequently, the same team reported a "double knock-out" in which both copies of the offending gene were silenced. At the time of writing, xenotransplantation has rather dropped out of the media spotlight. The BBC News website, for example, has not carried any new xenotransplantation stories since October 2002.

The Science of Xenotransplantation

A suitable organ for transplantation is likely to be a similar size to human organ that it is intended to replace. For this reason, amongst others, xenograft research has focussed primarily on baboons and pigs as the source animals of choice (Nuffield advocates the term 'source' animal rather than 'donor', since the animal has had no say in the matter).

Baboons have been more extensively studied in the USA than in Europe. In addition to relative parity in organ size, the attraction of baboons for xenotransplantation derives from the fact that they, like humans, are primates. As such, it is believed that their organs are less likely to be rejected by the recipient, and greater problems in this regard have certainly been seen with transplantation of pig materials. The very relatedness that makes baboons attractive for research is also, however, the source of objections to their use. Ethically, the use of fellow primates has proven a step too far for some people. Scientifically, the concern is that infectious agents in closely related species might be more likely than infections of non-primates to transfer to humans.

Pigs are now recognised as the most likely source of xenograft organs. Their appeal rests on several criteria. Like baboons, their organs are of a similar size to our own, but they are not so closely related. Pigs reproduce quickly and have a large number of offspring. There are also centuries of experience to be drawn upon in the keeping of pigs, and people are familiar with the use of pigs as sources of material, ranging from bacon and pork as food through to leather garments, in the full knowledge that the pig has lost their life in providing them.

Although use of pig heart valves has been a feature of clinical practice since the 1970s, and certain progress has been made towards the cross-species transplantation of individual cells, the expectant optimism of c.1996 - when Salomon Brothers, the investment firm, predicted that xenotransplantation could be a \$6 billion industry by 2010 (Bach and Iverson, 2002) - has mellowed to hopeful realism.

Scientifically, there are two key hurdles which need to be addressed in order to facilitate xenotransplantation. These are, firstly, immunological problems and, secondly, issues of physiological incompatibility (a third issue, the risks of infection transfer, is considered below, see *page 5 Ethical Arguments Against Xenotransplantation*).

Immunological problems:

At least three distinct, but inter-related, immunological difficulties can compromise a xenograft. These are termed hyperacute rejection (HAR), acute vascular rejection (AVR) and cellular rejection. HAR occurs when the source animal and the recipient are widely divergent species and is initiated by the binding of pre-existing antibodies, known as xenoreactive natural antibodies (XNAs), to surface antigens on the transplanted organ, triggering the so-called complement pathway.

The complement system involves a cascade of protein-dependent reactions similar in organisation to the blood-clotting cascade. In this system, however, the cascade results in the 'puncturing' of endothelial cells lining capillaries and other small blood vessels, which in turn leads to secretion of thrombolytic factors, blockage of the capillaries and haemorrhage of blood into the space between cells. The transplanted organ is rapidly rejected. In the case of pig-to-primate transplants, the particular antigen triggering HAR is usually galactosyl α -1,3-galactose, hence the importance placed by biotech companies on genetic modification of pigs in order to cease expression of this antigen.

Severe and swift as hyperacute rejection can be, a number of successful strategies have been used to circumvent this process in pig-to-baboon experiments. These include; selective reduction of the circulating concentration of XNAs, injection of soluble Gal to neutralise the antibodies, irradiation, immunosuppression or complement inhibitors such as cobra venom (reviewed more fully by Dobson and Dark, 2002). Now, with the additional genetic developments being made, "hyperacute rejection is not

likely to be a barrier to the transplantation of pig organs into humans” (Logan, 2000).

The greatest immunological obstacle to xenotransplantation is currently considered to be acute vascular rejection. These difficulties are, at least in part, due to significant gaps in our understanding of the underlying biology of AVR, though it is believed to be mediated by antibodies (i.e. it is a B-cell response). In contrast, the third type of immune response is cellular rejection and is known to involve direct interaction of T-cells, macrophages and NK (natural killer) cells with the transplanted tissues.

Physiological problems:

Failure to resolve issues of transplant rejection means that animals receiving xenografts have tended to be short-lived. In consequence, there is, to date, relatively little data about the physiological functioning of xenografts. In 2002, Dobson and Dark drew up a thorough review at the behest of UKXIRA. The tone of their review is rather pessimistic; indeed they conclude that “The physiology of transplanted organs and cells is likely to present a significant obstacle to the successful implementation of xenotransplantation” (p.12).

The complexity and diverse nature of the tasks performed by the **liver**, coupled with significant differences in the structure and/or concentration of serum components such as albumin, platelets, creatine and bilirubin render hepatic xenotransplants unlikely for the foreseeable future. Despite the fact that a baboon is reported to have survived for 78 days following receipt of a pig’s **kidney** (Cozzi *et al*, 2000), biochemical problems are also likely to limit the scope for renal xenografts. The relatively straightforward anatomy and function of the **heart** make this organ the best candidate for xenotransplantation. Even here, however, there are concerns that difficulties with the intracardiac nerve supply could result in potentially lethal dysrhythmias.

These difficulties have not stopped a certain measure of success in the use of animal organs as so called “bridging transplants”. Animal organs (and/or mechanical devices) can

be temporarily used to replace or supplement a failing organ whilst a suitable human transplant is sought. A recent clinical trial involving the use of pig livers for extracorporeal liver perfusion (ECLP) reported that nine out of 14 patients with hepatic failure were successfully bridged using pig liver perfusion until transplantation could occur and at the time of reporting seven were still alive (Horslen *et al*, 2000; reviewed by Dobson and Dark, 2002).

Ethical Arguments in Favour of Xenotransplantation

For advocates of xenotransplantation, the attraction of developing cross-species transplants rests squarely on one key fact, namely, that there is a persistent and increasing shortfall of human organs available for allotransplantation. It is estimated, for example, that in the USA there are currently 50,000 patients waiting forlornly for a donor organ and that this shortage is increasing by 5000 to 10,000 each year (see Bach and Ivinson, 2002). This is not, they will point out, a mere statistic; it is recognition that there are people dying whilst they wait in vain for a suitable organ to become available. None of the alternative strategies (e.g. increasing human donation, producing mechanical organs, see ***Ethical Arguments Against Xenotransplantation***) will ever meet this need. It is therefore incumbent upon medical research to develop xenotransplantation as a means of increasing the number of potential organs.

Nor is it not simply an issue of life versus death. The availability of donor organs also has a significant bearing on the quality of life experienced by patients. As *Animal-to-Human transplants; the ethics of xenotransplantation* comments, with reference to allotransplant recipients: "kidney transplant recipients are freed from the necessity of regular, uncomfortable and time-consuming treatment and are restored to a level of health not possible with dialysis. They are able to eat and drink freely, and to travel, in ways that people on long-term dialysis often cannot." (Nuffield, 1996 p. 2)

Consider the manner, too, in which organs currently become available. A potential recipient must spend months, maybe years, on a waiting list hoping for a suitable organ. If and when an organ does become available, its arrival is born out of tragic circumstances for somebody else, frequently a car accident. It is then a race against the clock; the organ and the patient must be brought to the same place within a matter of hours for the operation to take place. There is a mad panic, as domestic affairs - possibly including childcare provision - need to be put in order before the operation. In the meantime, the relatives of the potential donor may decree that the organs are not to be taken away (which

they can currently do, even if the victim carried an organ donor card).

Contrast this, it is argued, with a system where xenotransplantation is available. The operation could be scheduled a long while in advance. The practical and psychological preparations could be made in an unhurried and thorough manner. It might even be possible to grow a genetically modified pig organ to order.

It has also been argued that a steady availability of animal-sourced organs for transplantation would cut back, and perhaps stop entirely, the illegal trade in human body parts, not all of which are provided with the willing co-operation of the donor.

Ethical Arguments Against Xenotransplantation

For many people, concern about xenotransplantation is simply a manifestation of wider concerns about animal welfare. Opponents of xenotransplantation holding this view would likely object in the first instance to model experiments being carried out in which organs are being transplanted from pigs into non-human primates. Fuel for the fire was provided when research documents from Imutran (Cambridge, UK) were leaked to both the Daily Express and the anti-vivisection pressure group Uncaged Campaigns. The concerns raised were two-fold. Firstly, that the experiments had involved unnecessary suffering and secondly, that the internal documents seemed to reveal submission of highly selective and unduly favourable data in the peer-reviewed publication of their findings. For more details, see www.uncaged.co.uk/xeno.htm.

In addition to this, proponents of animal rights arguments would consider it unethical to confine and then kill an animal in order to take only one of its organs. Logically, this particular view could also be held by meat-eating, leather-wearing individuals, who object to waste in the generation of 'spare parts'. It is, however, unlikely that wider use could be made of the remaining carcass, as it will almost certainly have been subject to genetic modification.

At this point we tap into a second stream of worry about xenotransplantation, namely the general public's unease about genetically modified organisms (GMOs). If pigs are to be the source of transplant organs, significant genetic modification will need to be undertaken in order to "humanise" the tissue and hence reduce the risks of rejection. This can involve both modification to reduce the expression of pig-specific proteins, and alteration so that the pig cells produce some human-specific proteins, such as Decay Accelerating Factor, a molecule involved in avoiding the accidental attack of the immune system on "self". Whilst there is evidence of fundamental misunderstanding about genetics and GMOs in the wider population (this is discussed in Bioethics Briefing 1: Ethics and Bioethics), objections to xenotransplantation based on the requirement for genetic modification must be taken seriously.

Perhaps the argument with the heaviest scientific support against xenotransplantation (aside from the technical and immunological issues that have yet to be resolved) centres on the potential transmission of diseases from the donor organ to the recipient and even on to the wider population, a process known as **xenozoonosis**. Of particular concern in this regard are porcine endogenous retroviruses (PERVs). These are viruses encoded within the pig genome and as such cannot be eliminated by stringent hygiene measures (see Muir and Griffin, 2001). The possibility that a novel virus might result from a xenografting procedure is often mooted as a 'nightmare scenario'.

The tensions between the benefits for an individual organ recipient and the risks to wider society have been most clearly articulated by Fritz Bach and colleagues (Bach *et al*, 1998; Bach and Ivinson, 2002). A dying man who has been informed that his only hope is a xenograft has clear reasons to receive such a treatment. If, however, there are potential risks of novel infections spreading to the wider population, then this raises questions about whether the current rules governing informed consent need to be adapted to reflect the possible impact on other people.

Opponents of xenotransplantation sometimes put forward a number of other arguments. These include the potential for psychological effects on the recipient of xenografts as they come to terms with the fact that they are now "part-animal". Even if they themselves are comfortable with this situation, particularly if it has saved them from certain death, it is possible that the patient may suffer as a result of disquiet engendered in their family and associates. Psychological issues are difficult to identify in advance, but the case of Clint Hallam may have some bearing. Mr Hallam was the first in the world to receive a hand transplant, but persistent disquiet about having a dead man's hand led him eventually to having it removed (see, for example, <http://news.bbc.co.uk/1/hi/world/europe/1151553.stm>).

Some generic arguments can be applied in the case of xenotransplantation. One starts from the viewpoint that transplants of this kind are "unnatural" and therefore must be wrong. This is a weak argument, since it applies equally to air travel and to taking pharmaceuticals to treat illness. A related argument, 'the "yuk" factor' may serve as a warning that something is not right but has limited ethical merit. A more substantial sociological argument can be built against novel treatments, including xenotransplantation, on the grounds that it will never be financially viable for many in society and therefore will be yet another example of the 'haves' receiving what the 'have nots' do not.

Finally, arguments against xenotransplantation may advocate alternative approaches to overcoming the shortage of donor organs. Nuffield (1996) focuses on three – reducing demand for transplants (e.g. by public health measures), increasing supply of human organs (e.g. 'opt out' not 'opt in' for donors), developing artificial organs and tissues. To these could be added the potential, should developments in the adult stem cell research go well, for a patient to "grow their own" replacement organ. This would have the advantage that the new organ would be 'self' and would not therefore be at risk of rejection. Such a development is likely to remain science fiction for some while.

Case Study

Carl Jennings is twelve, and he's excited about the prospect of becoming a teenager. That may not seem unusual, but Carl has dilated cardiomyopathy, a heart condition which was expected to cause his death at a much younger age. When he was five, Carl suffered from viral myocarditis, inflammation of the heart muscle caused by a viral infection. After a period of time in intensive care, Carl survived the initial myocarditis, but he has unfortunately proven to be one of the minority who go on to develop prolonged and worsening heart difficulties. He easily becomes tired and is frequently breathless. He cannot walk very far and, in consequence, has to be taken to places in a wheelchair. Carl's heart works inefficiently and has become dangerously enlarged; a heart transplant now offers his only hope of survival.

Carl has been waiting for a suitable heart for several years, but nothing has become available. His situation is now critical and his parents are considering putting him forward for an experimental treatment involving the transplantation of a pig's heart. The pig used for this purpose will have been genetically modified to reduce the immune response. The breeding laboratory is kept as sterile as possible, but there is a theoretical risk of Carl getting an infection and if this was to occur it may be transferable to other people.

Questions to consider

- What **scientific** difficulties can you see?
- What **ethical** objections to this procedure can you see?
- Are there any particular precautions that should be in place before the operation can take place?
- The use of animal heart valves for treating humans is well established; are there really any significant differences in transplanting a whole heart?

Notes for instructors

It is hoped that many of the issues presented earlier in this paper will arise from the discussions. A certain number of leading points have been included (infection risk, GM animal) in order to initiate discussion, but these could be omitted if it was felt that students were likely to be aware of the issues without such prompting.

Carl's youthfulness generates other issues that have not been addressed. For example, as a twelve year old he is not fully-grown – will he require a subsequent transplant when he has matured? If the operation is allowed to proceed there will

almost certainly need to be an undertaking that Carl will never attempt to have children (as a precaution against infection). Is it fair to ask such a young person to make this kind of decision? Would there need to be some other action taken, i.e. sterilisation, to ensure that he is not tempted at a later stage to renege on this?

If you felt so inclined, some additional 'complications' could be introduced. What if Carl is Jewish? What if he is a vegetarian? The most useful purpose served by such "special case" material would be as an illustration of the general rule that 'bad cases make bad laws'.

Heart valves transplanted from pigs are, incidentally, generally washed and subjected to a tanning process in order to render them as biologically inert as possible.

Note: additional case studies focussed around the issue of xenotransplantation are available on the Science for Public Understanding website at www.scpub.org/filelibrary/doc/xeno_case_studies02.doc

Annotated references

Andrews P.A. (2001) Organ farm *British Medical Journal* **322**:1552

Appel J.Z. III et al (2000) Xenotransplantation: the challenge to current psychosocial attitudes *Progress in Transplantation* **10**:217-225

Bach F.H. et al (1998) Uncertainty in xenotransplantation: individual benefit versus collective risk *Nature Medicine* **4**:141-144

Bach F.H. and Ivinson A.J. (2002) A shrewd and ethical approach to xenotransplantation *Trends in Biotechnology* **20**:129-131

Cozzi E. et al (2000) Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts *Transplantation* **70**:15-21

Dobson J.M. and Dark J.H. (2002) The physiology of xenotransplantation (available online at <http://www.doh.gov.uk/ukxira/doh-xeno-trans.pdf>)

Logan J.S. (2000) Prospects for xenotransplantation *Current Opinion in Immunology* **12**:563-568

McLean S. and Williamson L. (2003) Law and ethics of xenotransplantation: bibliography and abstracts of key articles (available online at <http://www.doh.gov.uk/ukxira/law-ethics-biblio.pdf>)

Muir D.A. and Griffin G.E. (2001) Infection risks in xenotransplantation (available online at http://www.doh.gov.uk/pub/docs/doh/76035_doh_infection_risks.pdf)

Nuffield (1996) Animal-to-human transplants: the ethics of xenotransplantation (available online at <http://www.nuffieldbioethics.org/filelibrary/pdf/xenotransplantation.pdf>)

- The Nuffield Council on Bioethics produces thorough and authoritative papers on a number of bioethical issues. Their report on xenotransplantation is one of the oldest (published in March 1996), but still offers a detailed introduction to the topic.

<http://www.doh.gov.uk/pub/docs/doh/ukxporc.pdf>

<http://www.shef.ac.uk/b/bioethics-today/archives/files/Xenotransplantationmain.htm>

Video

In 2001 ITV transmitted the three-part Carlton Documentary *Organ Farm*. These programmes offered “a largely balanced perspective on a fascinating and complex area” (Andrews, 2001) and may be available locally as an “off-air recording”. A 13 minute clip is available online at <http://www.pbs.org/wgbh/pages/frontline/shows/organfarm/etc/video.html> and this gives a flavour of some of the potential benefits and potential risks of xenotransplantation. A book of the series by Jenny Bryan and John Clare is also available (ISBN 184222249X)

News items

<http://news.bbc.co.uk/1/hi/sci/tech/1738730.stm> (January 2nd 2002) Report on the cloning of “knock out” pigs, modified to be less liable to rejection by a xenograft recipient.

Chris Willmott (cjr2@le.ac.uk) is a Lecturer in Biochemistry at the University of Leicester



List of available Bioethics Briefings

The following Bioethics Briefings are freely available at
<http://bio.ltsn.ac.uk/resources/ethicsbrief.htm>

Briefing 1: Ethics and Bioethics

Briefing 2: Genetically Modified Crops

Briefing 3: Pre-implantation Genetic Diagnosis

Briefing 4: Xenotransplantation

LTSN Bioscience is part of the UK Higher Education Academy