Animal-to-human transplants: the ethics of xenotransplantation

Summary

NUFFIELD COUNCIL ON BIOETHICS

Introduction

Transplantation is an important and successful procedure in modern health care. It provides significant benefits to patients, both extending life expectancy and improving quality of life. The success of transplantation, however, brings with it the problem of obtaining an adequate supply of human organs for such treatments. The demand for human organs and tissue for transplantation exceeds their availability and the gap between supply and demand is likely to increase.

In these circumstances one possibility is that the imbalance could be redressed by using other animals as sources of material for transplantation into humans. Pig heart valves have been used in human heart surgery for 30 years.[1] Attempts to transplant animal organs into human beings, known as xenotransplantation, are far more ambitious. To date this has not been successful. The best result was recorded in the case of one patient who lived for nine months in the 1960s having received a transplanted chimpanzee's kidney.

The prospect of using animal organs and tissues for xenotransplantation raises important issues, both practical and ethical, which must be debated. This report addresses a range of key questions. What effective alternatives exist? Is it ethically acceptable to use animals for this purpose – specifically primates and transgenic pigs? Will xenografts be safe? How will patients react? What are the implications for the NHS?

Alternatives to xenotransplantation

Debate continues about how to reduce the gap between the demand for transplantation and the shortage of human organs and tissue. Xenografts are only one way of closing that gap. It is therefore important to examine other ways of meeting the demand for organs for transplantation. There are three approaches.

Public health measures aiming to prevent the conditions that currently require treatment by transplantation may go some way towards meeting the demand. However, these are necessarily long-term and of uncertain effectiveness. Increasing the supply of organs from human donors is difficult and, in some cases, not without ethical complications. Mechanical and bioengineered organ replacements, while offering future promise, remain problematical for the time being. This means that attention has turned to the use of animal organs as one potential method of satisfying the demand for transplantation.

Xenotransplantation: prospects

Rare attempts have been made to transplant animal organs or tissue into human beings. However, to date, these attempts have not been successful. There has been some progress in recent years to overcome some of the difficulties in preventing xenograft rejection, but many obstacles remain.

The major hurdle in the way of successful xenotransplantation is preventing the rejection of transplanted animal organs. This is a problem even with human organ transplantation: the recipient's immune system mounts an attack on the transplanted organ, which it sees as foreign. The immune response to organs or tissue from a different species is much stronger.

1 These are treated so they do not cause a strong immune response

The second problem raised by xenotransplantation is whether an animal organ will be able to perform the functions that a healthy human organ does. It is clearly important that the animal organs are about the same size as human ones. Some organs, notably the liver, have complicated biochemical functions that may differ between species. Differences in life span must also be considered. The natural life span of the pig is about 20 years. Would a transplanted pig organ age more rapidly than the human recipient?

Two main approaches are being used to overcome these problems. First, in the United States, the use of baboons is being investigated, on the basis that baboons are closely related to human beings and so the immune response to baboon organs or tissue will not be too strong. The immune response to a primate xenograft is not that much stronger than the response to a poorly matched human transplant. In December 1995, an AIDS sufferer from the US received a transplant of baboon bone marrow in the hope that this would restore the function of his bone marrow.[2] However, the small size of primate organs is likely to cause problems.

The second approach is to use pigs. Since pigs are less closely related to human beings than primates, the immune response to pig xenografts is rapid and severe. However, attempts are being made to modify pigs genetically so that their organs do not cause such a strong immune response when transplanted into human beings. Hearts from these transgenic pigs last longer than unmodified organs when they are transplanted into monkeys. The UK company Imutran Ltd announced its intention to start transplanting hearts from transgenic pigs into human recipients in 1996.[3] In the US, Parkinson's sufferers have undergone xenotransplantation of fetal neural tissue from unmodified pigs in an attempt to treat their condition.

Ethical concerns

Given the recent developments in overcoming the problems associated with xenotransplantation, the moves by companies and researchers to initiate clinical trials, and the amount of interest that has been aroused in the subject, an examination of the ethical issues that arise from xenotransplantation is timely. The following principal ethical concerns arising from xenotransplantation were identified by the Working Party:

(i) Xenotransplantation raises the question of how far, if at all, and in what ways it is acceptable for human beings to use other animals as a source of organs and tissue for transplantation. Even if one accepts in principle the use of animals in medicine and in medical research, their use in xenotransplantation may raise particular difficulties. Are there special concerns about the use of higher primates, or of genetically modified animals?

(ii) If some use of animals for xenotransplantation is considered ethically acceptable in principle, how can the welfare of the animals be adequately protected?

2 He left hospital in January 1996, at which point it was not known whether the transplant had been successful.

3 Imutran was taken over by Novartis in April 1996. No clinical trials with humans have been carried out, but pig-to-primate transplant research continued, attracting some controversial publicity in 2000. Imutran Ltd closed in September 2000 and the technology was transferred to a new company, Immerge BioTherapeutics, set up by Novartis and Biotransplant, Inc in the US. In January 2002 Immerge BioTherapeutics announced that they had produced a litter of cloned pigs, genetically modified to make their organs more suitable for human transplants.

(iii) Xenotransplantation raises the possibility that infectious diseases of animals will be transmitted into the human population. The hazards are remote and unquantifiable. How can this risk be assessed and managed?

(iv) The treatment of early recipients of xenografts may raise serious ethical issues. So far the survival times for recipients of xenografts have been poor, and in effect, early recipients are being used as experimental subjects for the development of the technology. When should clinical trials of xenotransplantation start and how can the welfare and interests of early patients be protected?

(v) Widespread introduction of xenotransplantation could have implications for the health care system. There will be cost implications, and it is possible that xenotransplantation would displace other, perhaps more worthwhile, activities. How should the introduction and provision of xenotransplantation, should it develop into a successful clinical treatment, be managed?

(vi) Xenotransplantation may also have social implications. What attitudes will people have to xenotransplantation and how will individual recipients adjust to receiving a xenograft? What will be the effect of developments in xenotransplantation on the willingness of human beings to donate their organs?

These issues are discussed in the Nuffield Council on Bioethics Report, **Animal-to-Human Transplants: the ethics of xenotransplantation**. The conclusions are summarised below.

Animal concerns: principles

For many people, the principal ethical problem raised by xenotransplantation will concern the relationship between human beings and other animals. The Working Party, as a first step to examining the ethical issues, reviewed the arguments for and against the use of animals for medical purposes in general.

One line of thought holds that when judging whether it is acceptable to use animals for medical purposes, it is necessary to consider whether the pain and suffering of the animals is justified by the potential benefit to human beings. Another line of thought suggests that animals, like human beings, have rights that must be respected when considering their use for such purposes. Whether the argument is framed in terms of the interests or the rights of animals, the crucial point is the extent to which animals share the features supposed to be important to human interests and rights. The feature to which most importance has generally been attached is that of self-awareness.[4] To be self-aware requires a high degree of intelligence, the capacity to make comparisons and judgements, and a language with which to articulate them. It has been argued that suffering and death are uniquely painful to a self-aware being who not only senses pain but can also perceive the damage being done to his or her self and future.

For those who do not accept the use of animals for medical purposes, xenotransplantation will, in principle, be unacceptable. The Working Party does not take this view and considers that some use of animals for xenotransplantation can be justified in principle. The Working Party accepted that some use of animals for medical purposes is "*an undesirable but unavoidable necessity" and that "in the absence of any scientifically and morally acceptable alternative, some use of animals . . . can be justified as necessary to safeguard and improve the heath and alleviate the suffering of human beings*". Not every benefit to human beings

4 This may be described as the consciousness an individual has of his or her own condition and experiences.

will justify the use of animals and, in some cases, the adverse effects on the animals will be so serious as to preclude their use. This conclusion drew on the position set out by the Institute of Medical Ethics towards biomedical research using animals.[5]

The use of primates for xenotransplantation

Even if some use of animals for medical purposes can be justified in principle, their use for xenotransplantation raises specific issues that need further consideration. Particular concerns are raised by the use of primates, such as baboons. The high degree of evolutionary relatedness between human beings and primates both suggests that xenotransplantation of primate organs and tissue might be successful and also raises questions about whether it is ethical to use primates in ways that it is not considered acceptable to use human beings. The characteristics, for example, of intelligence and complex social interactions of these closely related higher primates appear to be so like those of human beings that using members of those species as sources for xenotransplantation might well be seen as ethically unacceptable. The sophisticated capacities of primates suggest that any harm suffered by them should be given great weight. This position is reflected in the principles underlying current practice in the UK.[6] **The Working Party endorses the special protection afforded to primates used for medical and scientific purposes.**

The Working Party would accept the use of very small numbers of primates as **recipients of organs** during research to develop xenotransplantation of organs and tissue from non-primates. In this case, using a small number of primates for research, while undesirable, can be justified by the potential benefits if xenotransplantation were to become a successful procedure.

The routine use of higher primates to supply organs for xenotransplantation on a scale sufficient to meet the organ shortage would represent a new use of primates in the UK. In addition to the special weight given to the harm suffered by primates, other concerns must be taken into account. The endangered status of chimpanzees rules out their use for xenotransplantation. The potential risk of extinction, even to a species like the baboon that is not currently endangered, must be taken seriously. Xenotransplantation using primate organs or tissue may pose particular risks of disease transmission to donor recipients, as discussed later.

Given the ethical concerns raised by the use of primates for xenotransplantation, attention has turned to developing the pig as an alternative source of organs and tissue. As discussed below, in the view of the Working Party, the use of pigs for xenotransplantation raises fewer ethical concerns. To develop the use of primates for xenotransplantation, when there is an ethically acceptable alternative, would not be justifiable. **The Working Party recommends that non-primate species should be regarded as the source animals of choice for xenotransplantation.** However, possibilities for alleviating the organ shortage which do not involve the use of animals, such as increased donation of human organs, and the development of artificial organs and tissue, should be actively pursued.

5 Smith J A and Boyd K M eds. (1991) **Lives in the Balance: The ethics of using animals in biomedical research**. The Report of a Working Party of the Institute of Medical Ethics. Oxford University Press.

6 Wherever possible, primates used for medical purposes must be purpose-bred. Very few licences allowing primate use are awarded: only 29 in 1994. The use of wild-caught primates for medical purposes requires "exceptional and specific justification". NB: the regulations have changed since this Report was published.

The Working Party considered the possibility that, after a number of years of research, it might be found that pig organs and tissue could not be used for xenotransplantation. Would it then be ethically acceptable to use primate organs and tissue for xenotransplantation? The members of the Working Party were agreed that the use of primates would be ethically **unacceptable** if **any** of the following conditions obtained:

- improving the supply of human organs and the use of alternative methods of organs replacement such as mechanical organs and tissue replacement could meet the organ shortage;
- the use of higher primates would result in them becoming an endangered species;
- concerns about the possible transmission of disease from higher primates to human beings could not be met; or
- the welfare of the animals could not be maintained to a high standard.

When considering the hypothetical situation in which the conditions might be satisfied for a species such as the baboon, some members of the Working Party felt that the use of primates to supply organs for xenotransplantation would never be acceptable. Other members of the Working Party felt that, should these circumstances come to prevail, it would be appropriate to reconsider the use of higher primates to supply organs for xenotransplantation. This division of opinion may reflect an ethical dilemma that is currently unresolved for many people.

The use of pigs for xenotransplantation

The main alternative to using primates for xenotransplantation is to use pigs. Attention has focused in particular on pigs, since their organs are comparable in size to human ones, and they breed rapidly and could thus be used to supply transplant material on a large scale. The use of pigs as a domestic animal that is farmed and eaten is long established and many would have fewer concerns about their use for xenotransplantation as compared with the use of primates.

While the pig is an animal of sufficient intelligence and sociability to make welfare considerations paramount, there is less evidence that it shares capacities with human beings to the extent that primates do. As such, the adverse effects suffered by the pigs used to supply organs for xenotransplantation would not outweigh the potential benefits to human beings. In the UK, the breeding of pigs for human use is well established. It is difficult to see how, in a society in which the breeding of pigs for food and clothing is accepted, their use for life-saving medical procedures such as xenotransplantation could be unacceptable. **The Working Party concluded that the use of pigs for the routine supply of organs for xenotransplantation was ethically acceptable.**

If pigs are used for xenotransplantation they are likely to have been genetically modified so the human immune response to the pig organs and tissue is reduced. It is around the transfer of genetic material that ethical concerns turn. Some see the production of transgenic animals as an unnatural act that attempts to change the nature of animals and violates species boundaries. The production of transgenic pigs for xenotransplantation is likely to involve the transfer of a gene or a few genes of human origin. This is a very small and specific change. It is only in combination with all the other genes that make up the human genome that a particular gene contributes to the specification of the characteristics of the human species. Thus, inserting these genes into a transgenic pig would not destroy the integrity of either species. Species boundaries, in any case, are not inviolable but change

through a number of other processes as evolution occurs, for example through selective breeding. **The Working Party concluded that the use of transgenic pigs that have been genetically modified to reduce the human immune response to pig organs was ethically acceptable.** It is important to be vigilant in assessing the effects of transgenesis on animal welfare, particularly because some of the transgenic animals produced to date have suffered from ill affects. Monitoring the welfare of transgenic animals is a high priority, as discussed below.

Should xenotransplantation become widespread, it is possible that surpluses of transgenic pigs may arise, raising the question whether they should be made available on the general agricultural market and used for food. Regulatory mechanisms are in place to examine the acceptability of any proposal to release transgenic animals into the environment or to allow them to enter the food chain.[7]

Animal concerns: practice

In the UK, animals used for scientific purposes are protected by the Animals (Scientific Procedures) Act 1986 (the 1986 Act). Before the use of animals is permitted, the likely adverse effects on the animals must be weighed against the benefits likely to accrue from their use. The Home Office Inspectorate grants licences, in consultation where necessary with the Animal Procedures Committee. The use of animals for xenotransplantation raises questions about their breeding, especially if they are genetically modified, the welfare implications of producing animals free from infectious organisms, and their slaughter. **The Working Party recommends that the convention by which the Animal Procedures Committee advises on project licences in difficult areas should extend to applications for the use of animals for xenotransplantation.** When weighing the harm and the benefits of the use of animals for xenotransplantation, the ethical issues discussed above should be taken into account.

Xenotransplantation research may require the use of limited numbers of primates as xenograft recipients.[8] However, the Working Party recommended that non-primate species should be regarded as the source animals of choice for xenotransplantation and what follows, therefore, refers to the welfare implications of the use of non-primate animals to supply organs for xenotransplantation.

The breeding of transgenic animals is under the control of the 1986 Act. There is no evidence at present that the transgenic pigs developed for xenotransplantation are adversely affected by the genetic modification procedure. Transgenic animals can, in principle, be released from the control of the 1986 Act if there is no significant effect on the animals' welfare after two generations. If they are released, welfare concerns would be covered by the less demanding standards regulating agricultural practice and animal husbandry. Even if it is firmly established, however, that the welfare of the transgenic pigs is not affected by genetic modification, there may be other reasons not to release them from control of the 1986 Act, for example, the procedures required to produce pigs free from infectious organisms.

7 The Advisory Committee on Genetic Modification and the Advisory Committee on Releases to the Environment would advise on such matters. The GMO (Deliberate Release) Regulations 1992 and 1993 would require that consent is obtained from the Department of the Environment before transgenic animals were made available or sold, and the Health and Safety Executive would require notification.

8 Primates are afforded special protection by the 1986 Act

Animals used to provide organs and tissue will need to be free, as far as possible, from infectious organisms in order to reduce the risk that xenotransplantation will lead to the transmission of diseases into the human population. Repeated testing of animals and other procedures may adversely affect animal welfare. Monitoring the genetic composition of animals and screening them to make sure they are free of infectious organisms will require regular blood sampling and tissue biopsy. This would certainly have adverse effects on animal welfare. **The Working Party recommends that, when decisions are made about the acceptability of using animals for xenotransplantation, particular attention is paid to reducing the adverse effects associated with the need to produce animals free from infectious organisms.**

Removal of organs or tissue from anaesthetised animals will come under the control of the 1986 Act. It would be possible, in principle, to remove non-vital organs, or tissues that regenerate, sequentially from animals. This could well result in an increase in animal suffering. The Home Office has stated that the provisions of the 1986 Act regarding re-use of animals would preclude the sequential removal of organs or tissue. **The Working Party recommends that the Animals (Scientific Procedures) Act should continue to be interpreted as prohibiting sequential removal from animals of tissues or organs for transplantation.** It is possible, however, that killing animals and removing their organs without the use of an anaesthetic would not come under the control of the 1986 Act. Any concern revolving around the humaneness of the methods used to kill animals for xenotransplantation would have to be brought within the scope of the Protection of Animals Act 1911.

Important welfare implications are raised by the breeding of transgenic animals; producing animals free from infectious organisms; and removing organs and tissue from animals for xenotransplantation. There is some uncertainty about whether, in practice, all these aspects would be covered by the 1986 Act. In view of the important welfare implications raised by xenotransplantation, **the Working Party recommends that the Home Office should require that all animals used for xenotransplantation are protected under the Animals (Scientific Procedures) Act 1986.** Any reputable company producing animals in order to supply organs and tissue for xenotransplantation would, in any case, wish to be licensed under the 1986 Act in order to reassure the public that their activities were meeting the highest standards of animal welfare. **The Working Party recommends that the standards set by the 1986 Act become the minimum for the industry.**

Transmission of infectious diseases

Xenotransplantation of animal organs and tissue carries with it the potential risk that diseases will be transmitted from animals to xenograft recipients and to the wider human population. Because xenotransplantation involves the direct introduction of animal organs or tissue into the human body, many of the natural barriers to infection are by-passed. Xenograft recipients are also likely to require immunosuppression to prevent transplant rejection, increasing the possibility of infection of a recipient with animal diseases. It is difficult to assess this risk, since it is impossible to predict whether infectious organisms that are harmless in their animal host will cause disease in human xenograft recipients or whether the disease will spread into the wider human population. In this way, xenografting may pose a risk to public health as well as to individual health. There are certain to be infectious organisms of both primates and pigs that are currently unknown, and some of these might cause disease in human beings. There is evidence that infectious organisms of primates, notably viruses, can pass into the human population and cause disease. This supports the recommendation that non-primate species should be regarded as the source

animals of choice for xenotransplantation. The possible risk of disease transmission from pigs, however, also requires careful consideration.

It is not possible to predict or quantify the risk that xenotransplantation will result in the emergence of new human diseases. But in the worst case, the consequences could be far-reaching and difficult to control. The principle of precaution requires that action is taken to avoid risks **in advance** of certainty about their nature. It suggests that the burden of proof should lie with those developing the technology to demonstrate that it will not cause serious harm. **The Working Party concluded that the risks associated with possible transmission of infectious diseases as a consequence of xenotransplantation have not been adequately dealt with. It would not be ethical therefore to begin clinical trials of xenotransplantation involving human beings.** In order to address the risks of disease transmission associated with xenotransplantation, the Working Party suggests that the measures set out below should be taken.

Stringent efforts should be made to assemble as much information as possible about the risks of disease transmission *before* further xenotransplantation goes ahead. This would involve reviewing existing research and undertaking new research where necessary on the infectious organisms of primates and pigs and the possibility of transmission of disease to human beings. Reliable and accurate methods for identifying potentially dangerous infectious organisms in both source animals and human recipients should be in place before clinical xenotransplantation trials are undertaken.

Xenotransplantation should use only source animals reared in conditions in which all known infectious organisms are monitored and controlled. It is ethically unacceptable to use source organs from animals that are known to be infected with infectious organisms (pathogens) which can be eliminated. **The Working Party recommends that a code of practice should be drawn up specifying which organisms should be excluded from specified-pathogen free animals.[9] Xenotransplantation teams should be required to exclude from source animals all the pathogens listed in the code of practice.** Mechanisms should be in place to allow the list of organisms to be updated in the light of experience. The code of practice should recommend the diagnostic tests to be performed by accredited test centres. There is currently no regulatory mechanism that would cover the safety and quality of animal organs and tissue. **The Working Party recommends that a regulatory framework is devised to control the safety and quality of animal organs and tissue for xenotransplantation.**

There should be thorough monitoring of early recipients, with regular testing for signs and symptoms of disease. **The Working Party recommends that standards and mechanisms for monitoring xenograft recipients and for the action to be taken in case of disease transmission should be in place before human trials begin. It should be a requirement of clinical trials that the need for monitoring is explained to the patient and that it is made clear that consent to the operation also implies consent to subsequent monitoring.**

In order to facilitate the recording and analysis of information concerning possible disease transmission, **the Working Party recommends that xenotransplantation teams should be required to record all information concerning individual xenograft recipients in a xenotransplantation register maintained by an independent body.** Suitably anonymised data should be reviewed for evidence of the possible emergence of new diseases. Since,

9 The term specified-pathogen free is used to describe animals from which specified infectious organisms (pathogens) have been excluded.

initially, xenograft recipients are likely to be few, and to be spread across several countries, international co-operation should take place to enable effective review of all the available evidence.

There should be a commitment to suspend, amend or, if necessary, discontinue xenotransplantation procedures at any signs that new infectious diseases are emerging.

Advisory Committee on Xenotransplantation

Implementing the precautions outlined above will require an expert and authoritative body that is independent of the research teams at work on xenotransplantation. In view of the seriousness of the issues and of the public concerns about the technique, **the Working Party recommends that the Department of Health should establish an Advisory Committee on Xenotransplantation.** The proposed Advisory Committee on Xenotransplantation should combine the necessary scientific and medical expertise to examine early protocols with broader expertise to ensure that the Committee keeps in mind the wide range of issues raised by xenotransplantation. It should be open and accountable. There would be a need for close liaison between the proposed Advisory Committee and the Animal Procedures Committee.

Early patients

Many important medical innovations have not been immediately successful. This may well be true for xenotransplantation. This raises two major questions:

- at what stage will it be ethical to progress from using animals as xenograft recipients to the first clinical trials involving human recipients of xenografts?

- How can the welfare of the first patients to undergo xenotransplantation be protected? If it is ethical in principle for them to be offered xenotransplantation as an experimental treatment, what safeguards are needed to ensure that their consent to participation is given freely and with adequate understanding of what will be involved?

Xenotransplants should be offered to human patients only when results using animal recipients suggest that these operations will have a reasonable chance of success. There is currently little consensus within the transplantation community, both in the UK and in the US, as to whether the current data using animal recipients justifies progressing to clinical trials. **The Working Party recommends that no xenotransplantation trials involving human recipients should proceed until the proposed Advisory Committee on Xenotransplantation is in place and has approved the trials.** The proposed Committee would have the expertise to assess the success of xenotransplantation using animal models and to advise on when it is scientifically justified to begin clinical trials. The restriction of xenotransplantation to a small number of centres would allow effective control of the risks associated with the potential transmission of infectious diseases and careful protection of early patients.

Local Research Ethics Committees (LRECs) review, and must approve, all proposals for research involving human participants. All proposals for clinical trials of xenotransplantation will require LREC approval, in addition to the approval of the proposed Advisory Committee on Xenotransplantation.

Even when the results from animal experiments suggest that xenotransplantation involving human recipients is justifiable, the early clinical trials will involve unknown and unpredictable

risks. The question then becomes how best to protect early patients' welfare and interests. It is of the utmost importance that potential patients give free and properly informed consent to participation in the first xenotransplantation trials. **The Working Party recommends that the consent of patients to participation in xenotransplantation trials is sought by appropriately trained professionals who are independent of the xenotransplantation team. The information given to prospective recipients should include an estimation of likely success, attendant risks and subsequent quality of life.** Patients consenting to xenotransplantation should be informed that post-operative monitoring for infectious organisms is an integral part of the procedure, and that their consent to the operation includes consent to this monitoring.

Teams conducting experimental trials on patients are under a scientific and ethical obligation to research and report the subsequent quality of life of recipients, covering not only post-operative length of life, but also such matters as pain, mobility, emotional adjustment and social functioning. **The Working Party recommends that no protocol to conduct a trial should be accepted unless it contains a commitment to a robust description and assessment of the patient's pre-operative and post-operative quality of life.** Quality of life information should be included in any scientific publication.

Special issues arise in the case of children. Xenotransplantation has been proposed as a method of reducing the especially acute shortage of organs for babies and children. Early clinical trials of xenotransplantation will be a form of therapeutic research. Therapeutic research must offer some prospect of genuine benefit for the patient, but it involves greater uncertainties than treatment, and therefore greater caution must be exercised. The British Paediatric Association and the Medical Research Council have advised that therapeutic research should not involve children if it could equally well be performed with adults. It would be difficult to justify the involvement of children in major and risky xenotransplantation trials before some of the uncertainties have been eliminated in trials involving adults. **The Working Party recommends that the first xenotransplantation trials involve adults rather than children.**

The special protection afforded children needs to be balanced with the importance of not withholding potentially beneficial treatment, even if that benefit is offered in the context of therapeutic research. If the first adult trials are successful, and there is greater certainty about the benefits, there would be stronger arguments for offering xenotransplantation to children. The question of consent then becomes important. Children between 16 and 18 may be considered capable of consenting on their own behalf to participate in therapeutic research, although a higher level of maturity would probably be required than that needed for consent to medical treatment. Given the complexity of the ethics and law in this area, a cautious approach would be to obtain the consent of the person with parental responsibility before a child under 18 participates in a major procedure like xenotransplantation. The agreement of any child to participation in therapeutic research such as xenotransplantation should always be obtained.

Similar issues arise for adults who are considered incapable of consenting to participation in therapeutic research because they are mentally incapacitated. The law would appear to be that incapacitated adults may be involved in therapeutic research if this is in their best interests. It would be difficult to justify the involvement of incapacitated adults in the first xenotransplantation trials before some of the major uncertainties have been eliminated in trials involving adults who are capable of weighing the benefits and risks on their own behalf. **The Working Party recommends that the first xenotransplantation trials should not involve adults incapable of consenting to participation on their own behalf.**

Public policy must be able to take account of different attitudes to xenotransplantation. Some people may wish to refuse xenotransplantation as a form of treatment. If refusing a xenograft reduced a person's priority for a human transplant, consent to xenotransplantation would certainly not be freely given. **The Working Party recommends that, at any stage in the development of xenotransplantation, patients who, for whatever reasons, refuse xenografts should remain entitled to consideration for human organs on the same basis as before their refusal.**

What should happen to someone who has accepted a xenograft, but for whom a human organ or tissue at some later date might offer better prospects? In the early stages of development, xenografts are unlikely to be as successful as human transplants, and it is possible that they will only work for a fairly short period of time. **The Working Party recommends that xenograft recipients should remain entitled to consideration for human organ transplantation on the same basis of clinical need as before xenotransplantation.** The Working Party recognises that an implication of this position is that the demand for human organs may not decline, and may even increase, in the early years of xenotransplantation, since xenograft recipients may remain on the waiting list for human organs whereas without a xenograft they might not have survived.

Effects on the health care system

What are the implications for the NHS, should xenotransplantation move beyond the experimental stage and become a routine surgical procedure? It is likely that the major cost implications of xenotransplantation would arise from the larger number of transplants that would be possible. Should xenotransplantation develop into a successful procedure, decisions about its provision would have to be made within the context of wider debate about resource allocation within the NHS.

There are good reasons for introducing new and potentially expensive specialist services in a controlled way. Restricting xenotransplantation to designated centres for the foreseeable future would ensure adequate monitoring of its cost and effectiveness. Already in existence is the Supra Regional Services Advisory Group which is responsible for the introduction and provision of specialist services.[10] **The Working Party recommends that, if xenotransplantation becomes a treatment of choice, the introduction of the treatment into the NHS should be overseen by the Supra Regional Services Advisory Group.**

Personal and social effects of xenotransplantation

Attitudes to xenotransplantation will vary. Some may view it as part of a quest to prolong life, in pursuit of which goal, human beings are prepared to abuse their relationship with other animals. Others may regard it as offering a way of providing organs and tissue for transplantation that is preferable to some of the measures proposed for increasing the supply of human organs. There is a need for transparency and openness in the activities of researchers and policy-makers involved in xenotransplantation, and of full debate about its acceptability.

It is difficult to predict what the effects of xenotransplantation might be on individual recipients and, in particular, how people's views of their body and of their identity might be

10 The Supra Regional Services Advisory Group is responsible for 10 designated specialist services in the NHS, including the Heart, Heart-Lung and Lung Transplant Service and the Liver Transplant Service. The Advisory Group was established as a result of the 1991 NHS reforms.

affected by xenotransplantation. This highlights the need for more research in this area. **The Working Party recommends that counselling of xenograft recipients should include discussion of the possible personal impact of xenotransplantation. The Working Party further recommends that research should be initiated to assess the personal impact of xenotransplantation on potential and early recipients.**

It is highly unlikely that xenotransplantation would eliminate the need for human organs. Xenotransplantation would probably become part of a range of treatments used alongside human organ and tissue transplantation, and the use of artificial substitutes. It is very important to indicate to potential and actual human donors that their gift will be no less precious if it becomes part of the range of available treatments. There is a great responsibility, therefore, on xenotransplant teams, on the media and on those responsible for influencing public opinion to ensure that the reporting of developments in xenotransplantation is as accurate, balanced and unsensational as possible. It should be made clear that, for the foreseeable future, xenotransplantation will not solve the shortage of organs and tissue for transplantation and that there will still be a pressing need for the donation of human organs.

Implementation of recommendations

This report has set out the many ethical issues raised by the development of xenotransplantation. In the view of the Working Party, responding to these issues will require the establishment of an Advisory Committee on Xenotransplantation. **The Working Party recommends that the proposed Advisory Committee on Xenotransplantation should produce guidance on best practice and revise that guidance in the light of experience. The responsibilities of the Advisory Committee should include:**

- **assembling and assessing information about the possible risks of disease transmission, and on that basis making recommendations**
- **establishing a regulatory mechanism to ensure that the appropriate infectious organisms are eliminated from source animals**
- **developing guidance on the monitoring of future recipients of xenografts and maintaining a register of xenograft recipients**
- **approving any xenotransplantation trials involving human recipients and the centres that may undertake such trials**
- **overseeing issues of consent and conscientious objection**
- **assessing the impact of xenotransplantation on individual recipients**
- **facilitating debate and assessing attitudes to xenotransplantation**

No xenotransplantation trials involving human recipients should proceed until the proposed Advisory Committee on Xenotransplantation is in place and the above issues have been addressed.

A particularly wide range of concerns is raised by xenotransplantation, about which people have differing and strongly held views. The Working Party has recommended that the development of xenotransplantation should continue subject to rigorous regulation to ensure protection for potential human recipients and care for animal welfare. Public debate about the ethical issues raised by xenotransplantation will continue. This report is intended to contribute to that debate.