Chapter 7

Early patients

7.1 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?

When will xenotransplantation trials involving human beings be justified?

7.2 As discussed in Chapter 3, there are significant scientific hurdles to be overcome before xenotransplantation can be clinically successful. Progress has been made in controlling the rejection of xenografts by the immune system, as indicated by the increasing lengths of time that xenografted organs or tissue survive when transplanted into animals used as experimental recipients (paragraph 3.29). The question is: at what point will the results from experiments using animals as recipients justify clinical trials involving human beings?

7.3 Experience with other major developments in medicine, such as human organ transplantation, the use of mechanical organs and, indeed, the few xenotransplants already performed, suggest that early xenograft recipients will not have a good chance of survival (Table 3.1). To an extent this is inevitable since, by their nature, trials of new treatments involve unknown and unpredictable risks. It will be impossible to predict, for example, whether a pig kidney will function properly in a human body, until the first transplants into human beings are performed. Thus, even when the results from animal experiments suggest that xenotransplantation involving human beings is justifiable, these will be major and risky operations. Because of this, it is important not to perform xenotransplants on human recipients prematurely. Advocates of early clinical trials of xenotransplantation point to the desperate situation of patients waiting for human organs for transplantation, many of whom will die before suitable organs become available. It is certainly crucial to ensure that

no unnecessary obstacles are put in the way of treating these patients. But it should also be remembered that the first heart transplant, performed by Christian Barnard in South Africa in 1967, was followed by a worldwide spate of unsuccessful attempts to perform heart transplants. The reaction to these operations, which were seen as ill-judged and premature, slowed the subsequent development of successful heart transplantation. This disadvantaged the group of patients that it had been intended to benefit.

7.4 While recognising that medicine has made huge strides as a result of experimentation, members of the Working Party felt that these had sometimes been achieved at the expense of the first patients to be given the new treatment. These first patients might sometimes have been better served by an approach more accepting of death: an approach that preserved dignity and reduced suffering to a minimum. In some cases, it has been cruel to offer a possible life-saving procedure that resulted in a long drawn-out, painful death, instead of a relatively peaceful end. The offer of such a procedure in itself puts pressure on patients to accept - and may distort judgement.

7.5 Yet there will be many patients for whom the chance of making a contribution to medical research will provide a motive for accepting a xenograft. Indeed, respect for individual choice argues that people should be able to offer themselves as experimental subjects, provided that adequate safeguards are in place to ensure that consent is free and properly informed.

7.6 Procedures, which are experimental but offer the chance of genuine treatment for the patients, are termed **therapeutic research.** The important issue is that medical teams should not compromise the care of the individual patient in the interests of scientific research. Rather they must see themselves as using an experimental procedure for which there is evidence that the benefits will outweigh the adverse outcomes. Since clinical trials will take place within the context of a doctor-patient relationship, the doctor is legally obliged to act in the best interests of the patient. Thus, there must be grounds for believing that the treatment will be effective and will offer some benefit to the patient.[1]

7.7 Xenotransplants should therefore be offered to human patients only when results using animal recipients suggest that these operations will have a reasonable chance of success. But it is difficult to say when that stage will have been reached, as a member of a UK team researching xenotransplantation himself has pointed out.[2] 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

[1] Kennedy I and Grubb A (1994) **Medical Law: Text with Materials**, Second edition, pp 1042-3. London: Butterworths.

[2] White D (1995) Letter to **Nature**, 378:434.

to clinical trials.[3, 4] Given the difficulty of making this decision, and the importance of not putting patients at unnecessary risk, it would seem advisable that xenotransplantation trials involving human beings should not proceed until there has been an opportunity for consensus amongst the transplantation community to develop, based on discussion of the evidence as published in peer-reviewed scientific and medical journals. Nevertheless, xenotransplant teams have proceeded with trials involving baboon bone marrow in the US.[5] The UK company Imutran Ltd has indicated its intention of starting clinical trials of xenotransplantation using pig organs and tissue in 1996.[6] In contrast, Thomas Starzl, the US transplant surgeon who headed the xenotransplantation of baboon livers into two patients in 1992-3, has argued for a moratorium on further clinical trials of xenotransplantation on the basis that more research is needed before xenotransplantation will be clinically successful.[7]

7.8 The Working Party has recommended the establishment of an Advisory Committee on Xenotransplantation which would regulate xenotransplantation with respect to concerns about the possible transmission of disease-causing organisms (paragraphs 6.38 - 6.41). The proposed Advisory Committee on Xenotransplantation would also 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 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.**

7.9 Local Research Ethics Committees (LRECs) review, and must approve, all proposals for research involving human participants.[8] As such, all proposals for clinical trials of xenotransplantation will be referred to an LREC and will require LREC approval, in addition to the approval of the proposed Advisory Committee on Xenotransplantation.

7.10 This combination of safeguards offered by the proposed Advisory Committee on Xenotransplantation and LRECs would provide a two-fold system for regulating early xenotransplantation trials. This type of system has been successful in regulating gene therapy trials, which require approval from the specially established Gene Therapy Advisory Committee and from LRECs. The Working Party consider that such a system is equally desirable for the regulation of xenotransplantation.

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3 No cheers for baboon to AIDS patient xenotransplant (1995) **Lancet**, 346:369-70.
4 New ways to avoid organ rejection buoy hopes (1995) **Science, 270**:234-5.
5 AIDS patient given baboon bone marrow (1995) **Nature, 378**:756.
6 Pig-to-human heart transplant slated to begin in 1996 (1995) **Nature Medicine**, 1:987.
7 Starzl T (1995) Comments made at Institute of Medicine conference on Xenograft transplantation: science, ethics and public policy, Washington DC.
8 Department of Health (1991) **Local Research Ethics Committees**, London.

7.11 As set out above, the initial trials to xenotransplant organs will be major and risky procedures. This suggests that it would be justifiable to offer organ xenotransplantation only to patients for whom there is no alternative form of effective treatment. This would apply to many heart patients, whose lives are at risk and for whom the shortage of human organs is acute. The lives of most kidney patients can be maintained, albeit uncomfortably, on dialysis. For some people with renal failure, however, accessing the vascular system becomes extremely difficult and, eventually, dialysis may no longer be possible. The potential, albeit small, risk that xenotransplantation will transmit new infectious diseases to the population at large must also be considered (paragraphs 6.16 - 6.19). It would be hard to justify posing any potential public health risk unless the first xenografts were used to save the lives of people with no alternative possibilities of treatment.

7.12 Another issue is whether it would be unethical to transplant certain types of animal organ or tissues into human beings. One respondent drew a distinction between material "*of a 'mechanical' (for example, heart muscle) rather than 'personal' (for example, neural material) character*".[9] Xenotransplantation of neural tissue has been proposed as a possible treatment for Parkinson's disease. In the US, four Parkinson's disease sufferers have already received xenografts of pig fetal neural cells.[10] It is hoped that the cells of the xenograft will produce the neurotransmitter dopamine that is deficient in Parkinson's sufferers. If successful, this would cause a very specific pharmacological change in the brain. Consequently, the Working Party considers that neural tissue xenografts should be regarded in the same way as any other xenograft intended to restore the body's physical function. Xenotransplantation with the intention of changing aspects of someone's personality is almost certain to remain technically impossible, and would certainly be ethically unacceptable.[11] The unlikely prospect of attempts to alter the germline by xenotransplantation would be equally unacceptable.[12]

7.13 If xenotransplantation of neural tissue were to be successful, it might reduce or eliminate the current use of human fetal neural tissue for transplantation. This material comes from aborted human fetuses and many would see a reduction in its use as desirable. In this respect, some would argue that xenotransplantation would reduce the ethical difficulties associated with neural transplantation. As set out in Chapter 4, however, there is a contrary view that using animals to treat human beings is equally, if not more, unacceptable (paragraph 4.13).

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[9] A point made by Professor John Polkinghorne in his submission to the Working Party.

[10] Parkinson's pig cure. **The Times**, 15 December 1995.

[11] A view expressed in several submissions to the Working Party including those from the Christian Medical Fellowship, the Church of England and the Methodist Church.

[12] A view expressed in submissions from the Joint Ethico-Medical Committee of The Catholic Union of Great Britain and Guild of Catholic Doctors, the Methodist Church, the Royal College of Obstetricians and Gynaecologists.

Consent considerations

7.14 It will be ethically acceptable to offer xenotransplantation to individual patients only when it has been decided, by the procedures set out above, that the results using animal recipients merit starting human trials. At this stage, the question becomes how best to protect early patients' welfare and interests. The principal problems that may arise with the early use of xenografts in human beings include: possible suffering for perhaps limited, if any, therapeutic benefit; the raising of unjustified expectations even when every effort is made to explain honestly the low likelihood of success in early cases; poor quality of life that might follow only a semi-successful use of xenografts; the possibilities of disease transfer across species, which would be an unknowable risk for early patients; and the consequences of the need for health monitoring for those who are recipients. It is likely that the first xenografts will be offered only to those with little chance of surviving without it. But these people, who are facing death, require particular protection from over-optimistic or reckless experiments.

7.15 It is a paramount principle of contemporary medicine that patients should give properly informed consent to any treatment or therapeutic research, and that human volunteers should give properly informed consent to participation in research. People should be in a position to make a decision on the basis of proper information and without pressure, so that participation can truly be said to be voluntary. Where possible, people should make decisions for themselves. Alternative safeguards to protect people who are not considered capable of consenting on their own behalf are considered below (paragraphs 7.22 - 7.26). The Department of Health's 1990 circular, **A guide to consent for examination or treatment**, defines the patient's right to information in the following way:

> "*Patients are entitled to receive sufficient information in a way that they can understand about the proposed treatments, the possible alternatives and any substantial risks, so that they can make a balanced judgement. Patients must be allowed to decide whether they will agree to the treatment, and they may refuse or withdraw consent at any time.*" [13]

7.16 As with any other procedure, 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 foresees the following problems with regard to consent to xenotransplantation. First, the risk/benefit ratio of the procedure will be hard to assess in the early stages, because of its novelty. There may be good reason to believe on the basis of experiments using animal recipients that using transgenic animal organs will allow successful xenotransplantation. But

[13] NHS Management Executive (1990) **A guide to consent for examination or treatment**. London: Department of Health. p 2.

researchers will only know the risks of the procedure after a considerable number of operations have been carried out in human beings.

7.17 Second, some researchers, keen to discover whether xenografts are a viable alternative to human transplants, might be inclined to overestimate the chance of success. Even with well-established procedures to protect the human subjects of research, innovators may be more dismissive of the risks, and the pains and stresses, of a particular procedure than may be their patients. One North American research programme, for example, discovered that, when men with benign enlargement of the prostate were shown an interactive video, explaining the risks and benefits of surgery, a higher proportion of them chose to postpone surgery (the 'watchful waiting' option) than the surgeons anticipated.[14] If a research team is over-eager to carry out a xenotransplant, its members may naturally find it difficult to present the risk/benefit ratio to the patient in an unbiased way. Subtle changes in the manner of presentation may influence the perception of risk and a patient's decision. For example, one study found that if two treatments are put forward, of equal effectiveness and risk, the alternative presented in terms of the survival rate, rather than the mortality rate, will be consistently preferred by patients and doctors alike, even though both terms describe the same risk, and in this example, the risks of each treatment were the same.[15]

7.18 Thus "*patients must be made aware, whenever possible, of the extent to which they are 'experimental subjects', involved in unpredictable clinical trials of techniques that are largely in the developmental stages.*" [16] To ensure that a patient is given a balanced view, an independent and trained person with appropriate counselling skills, not on the research team wishing to carry out the xenografts, should be given the duty of discussing with the patient the proposed treatment, the possible alternatives and the risks. These discussions should be held as early as is reasonably possible. In order to ensure that consent is properly informed and freely given, **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.**

7.19 As discussed in Chapter 6, it will be extremely important to monitor early xenograft recipients for any evidence that diseases are being transmitted from animals to the early human recipients (paragraphs 6.33 - 6.37). This need to monitor closely the

[14] Barry M J *et al.* (1988) Watchful waiting versus immediate transurethral resection for symptomatic prostatism: the importance of patients' preferences. **Journal of the American Medical Association,** 259:3010-17.

[15] McNeil B J *et al.* (1982) On the elicitation of preferences for alternative therapies. **New England Journal of Medicine**, 306:1259-62.

[16] Mepham T and Moore C: submission to the Working Party.

outcomes associated with all early patients brings its own ethical problems, most notably that of how far respect for privacy is consistent with the practice of adequate monitoring. 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 (paragraph 6.36).

7.20 One piece of information of great importance to patients concerns their expected quality of life. The speed of the body's rejection of xenografts to date has, in most cases, been so fast that quality of life considerations have not arisen (Table 3.1). If xenotransplantation is successful, however, and the patient survives and the xenograft functions properly, quality of life will become important. 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.

7.21 Since xenotransplantation will be an experimental procedure on every occasion on which it is undertaken in the near to medium term, it is essential that those carrying out the procedure report fully on all the important consequences. This will ensure the maximum benefit is obtained from these major and risky procedures. It will improve the information upon which subsequent potential recipients can make a decision. Finally, it will provide more information for public debate on the acceptability of xenotransplantation.

Children

7.22 Special issues arise in the case of children. There is an especially acute shortage of hearts for transplanting into newborn babies with congenital heart defects and of heart-lungs for transplanting into children suffering from cystic fibrosis. It has been suggested that this might justify early xenotransplantation trials involving babies or children: indeed, in 1984 in the US, a baboon heart was transplanted into Baby Fae.[17] She survived 20 days.

[17] Baily L L *et al.* (1985) Baboon-to-human cardiac xenotransplantation in a neonate. **Journal of the American Medical Association,** 254:3321.

7.23 As discussed above, therapeutic research must offer some benefit to the patient (paragraph 7.6). Since, by its nature, however, therapeutic research involves greater uncertainties than treatment, 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.[18, 19] In the case of early xenotransplantation trials, the main problem is likely to be overcoming organ rejection, which will be a problem in both adults and children. Thus, it would be difficult to justify the involvement of children in major and risky trials as recipients of heart xenografts, for example, 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.**

7.24 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.[20, 21] The agreement of any child to participation in therapeutic research such as xenotransplantation should always be obtained.

Adults who cannot consent on their own behalf

7.25 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.[22] In its study of the law relating to mental incapacity, the Law Commission recommended that therapeutic research should be

[18] British Paediatric Association (1992) **Guidelines for the Ethical Conduct of Medical Research Involving Children**.

[19] Medical Research Council (1991) **MRC Ethics Series: The Ethical Conduct of Research on Children**. London.

[20] Kennedy I and Grubb A (1994) **Medical Law: Text with Materials** Second edition. London: Butterworths, p 1043.

[21] Department of Health (1991) **Local research ethics committees**, London. p 16.

[22] Kennedy I and Grubb A (1994) **Medical Law: Text with Materials** Second edition. London: Butterworths, pp 1052-4.

lawful *"if it is in all the circumstances reasonable"*.[23] It would be difficult to justify, by this standard, 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.**

7.26 The Medical Research Council has recommended that the participation of incapacitated adults in therapeutic research may be justified if, in addition to evidence that the procedure will benefit the individual, it relates to their incapacitating condition and the relevant knowledge could not be gained by research in adults able to consent.[24] One situation in which this might justify xenotransplantation trials involving the mentally incapacitated is the proposed transplantation of pig fetal neural tissue to treat people suffering from Huntington's disease, a neurodegenerative disorder which affects mental capacity. Such trials should only take place, however, if there is evidence to support progressing from animal research to human trials and to indicate that the procedure will benefit the individuals involved.

Conscientious objections

7.27 One of the starting points for this report was that public policy must reflect the ethical pluralism that characterises this and many other societies (paragraph 1.29). In Chapter 4, the Working Party concluded that xenotransplantation using organs and tissue from transgenic pigs would be ethically acceptable (paragraphs 4.42 and 4.49). Some people, however, will conscientiously hold the opinion that xenotransplantation is wrong in principle. Some of these people will themselves turn out to be eligible for xenotransplantation should the technology turn out to be feasible. By the principle of consent, they would be quite entitled to refuse a xenograft for this or any other reason such as religious, cultural or ethical grounds or, indeed, because they do not think the benefits of xenotransplantation outweigh the risks.

7.28 What are the implications for people who refuse xenografts? This may become an important issue if xenotransplantation develops into a successful procedure. Xenotransplantation might then offer a cheaper form of treatment than, say, dialysis for patients with kidney failure. There might, then, be pressure on individuals to accept xenografts. Certainly, patients must always be told the sources of the organ

[23] Law Commission Report No 231 (1995) **Mental Incapacity** London: HMSO. See in particular pp 49-51.
[24] Medical Research Council (1991) **MRC Ethics Series: The Ethical Conduct of Research on the Mentally Incapacitated**. London.

or tissue they might receive: withholding such information would amount to deception. Another issue is how refusal of a xenograft might affect an individual's consideration for human organ transplantation.

7.29 Consider the situation in which refusing a xenograft reduced a person's priority for receiving a human organ, presumably on the grounds that they had been offered, and refused, an appropriate form of treatment. In this case, consent to xenotransplantation certainly would not be freely given. Rather, an element of coercion would be involved. The principle of respect for conscientious objection would be compromised if people who objected had to accept greater harm than others.

7.30 Should people who refuse xenografts be given some priority in access to human organs, in order not to jeopardise their freedom of conscience? In some cases, such as the refusal of blood transfusion by a Jehovah's Witness, refusal of treatment will result in a greater risk to the patient and so there can be little doubt of the patient's sincerity. But objection to xenotransplantation might be seen as self-interested if, by refusing a xenograft, that person were given priority for a human organ transplant. **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.**

7.31 A question then arises about what should happen to the status of a person who has accepted a xenograft, but for whom a human transplant 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. At least initially, xenotransplantation might be used as a bridging procedure to keep a patient alive until a human organ became available.[25] This suggests that, in principle, accepting a xenograft should not affect the recipient's entitlement should a suitable human organ become available. It is true that, in practice, receiving a xenograft might affect the suitability of the person for a subsequent human organ transplantation, in terms of their physical fitness, for example. This does not, however, seem unfair. Other factors, such as the degree of tissue matching, being equal, human organs are made available on the basis of clinical need. All patients would have the opportunity to accept or to refuse a xenograft, fully informed of the consequences of so doing. **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

[25] Steele D and Auchincloss H (1995) The application of xenotransplantation in humans - reasons to delay. **Institute of Laboratory Animal Resources Journal**, 37:13-5.

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.

Health care workers

7.32 It is not only patients who may have conscientious objections to involvement with xenografts. The right of conscientious objection should also be extended to health care personnel. In this case, the right cannot be understood to be absolute. Rather, it must be seen as a consideration which should always be taken seriously by other medical and managerial personnel in individual cases. Problems are unlikely to arise in the early stages of xenografts, since they will be carried out in special centres, staffed, presumably, by people who do not object to xenotransplantation. But in later stages it may be considered reasonable, perhaps, for a nurse to refuse to participate in the actual xenograft, but not, say, to refuse to take food to a recipient of a xenograft. As set out in Chapter 6, there is a case for monitoring health care workers involved in xenotransplantation for the possible transmission of animal diseases (paragraph 6.34). This requirement should be made clear to all involved.

7.33 The question also arises of what responsibilities medical personnel would have were it to become clear that involvement with xenografts was dangerous for them, perhaps because of the risk of infection. In entering the profession, health care workers assume a duty to accept certain reasonable risks, especially when efficient protective measures are available. Thus, health care workers are expected to care for people infected with the HIV virus, and, similarly, they might be expected to care for people suffering from diseases transmitted via xenotransplantation. In extreme cases, however, it cannot be demanded of any member of staff that they place themselves at severe risk. In the unlikely event that xenotransplantation leads to the emergence of a highly infectious disease, the only solution would be to call for volunteers.

Conclusion

7.34 This chapter has set out the following ethical issues that need to be taken into account in the regulation of xenotransplantation involving human recipients:

- the timing of the first trials
- consent considerations
- conscientious objection

These concerns will best be taken account of if clinical trials of xenotransplantation are restricted initially to a small number of approved centres. The decision to

proceed with clinical trials involving human beings will also require an assessment of whether concerns about infectious organisms have been addressed adequately (paragraph 6.41). This is an important concern both for individual patients, and for the wider population. The Working Party considers that it would not be ethical to undertake clinical trials of xenotransplantation until a regulatory structure is in place that can take account of all these concerns. This reinforces the argument for an Advisory Committee on Xenotransplantation.