



THE XENOME PROJECT



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D138 CRITICAL UPDATED REPORT ON LEGAL, ETHICAL AND REGULATORY BIBLIOGRAPHY AND DOCUMENTS

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1. Introduction

This report highlights briefly and in general terms a number of issues which have generated both interest in and concern about xenotransplantation. The comments are based on the bibliographic references, legal framework and links which are included in the legal and ethical issues area of the Xenome web site and where it is possible to elaborate in more detail the general ideas described here.

It is true that there is considerable interest in the transplantation of animal organs or tissue as a means of reducing the shortage of human organs and tissue for transplantation. 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. Debate continues about how to reduce the gap between the demand for transplantation and the shortage of human organs and tissue. The benefits of preventive measures to improve health and prevent the diseases requiring treatment by transplantation are likely to be long-term ones. Some of the suggested measures for increasing the supply of human organs, such as changing the consent requirements, are not without ethical and practical difficulties. Even radically innovate measures to increase rates of human organ donation are likely to be insufficient to bridge the gap between supply and demand. Thus, there is interest in alternative ways of meeting the organ shortage.

Xenotransplantation of animal organs and tissues is an alternative option following for reducing the shortage of human organs and tissue for transplantation. The strong immune response to animal organs or tissue, however, means that transplant rejection is a major problem and, to date, xenotransplantation involving human recipients has not been successful. An exception is the routine transplantation of pig heart valves. These can be treated so they do not cause such a strong immune response.

In many documents it is pointed out that ethical concerns about the use of primates for xenotransplantation have led to attempts to develop non-primates as sources of organs and tissue. 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. Since pigs are less closely related to human beings than primates, the immune response to pig xenografts is rapid and severe.

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

Given the recent developments in overcoming the problems associated with xenotransplantation, the moves by some 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 principal ethical concerns arising from xenotransplantation are discussed in many of the documents which are uploaded on the aforementioned area of the Xenome web site and some general ideas will be described in the next paragraph.

2. Ethical concerns

- Is using animals to provide organs and tissue for transplantation into human beings acceptable? Certainly some of the documents deal with this important issue: whether there is anything inherently unethical or unacceptable about using animal organs, tissues and cells for transplantation to humans. For instance, the Nuffield Council on Bioethics has published a report, “the ethics of research involving animals”, which seeks to clarify the debate and aims to help people think through the scientific and ethical issues that are raised. It also makes practical recommendations for future policy and practice. The report was produced by a Working Party comprised of academic and industry scientists, philosophers, members of animal protection groups, and a lawyer. In the report are described, amongst other issues, the following ones: the number of animals used annually in research; the different species of animals which are used in research; the main reasons for using animals in research; the main criteria used to describe how the research involving animals is regulated; the main criteria used to explain how to assess pain, distress and suffering in animals; the meaning of the “Three Rs” as the crucial principle to reduce animal suffering; etc¹.

- Are there special concerns about the use of higher primates, or of genetically modified animals? And if some use of animals for xenotransplantation is considered ethically acceptable, how can the welfare of the animals be adequately

¹ See: <http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction>

protected? With regard to this issue, there is a line of thought that holds the following idea: 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. In the aforementioned report of the Nuffield Council is suggested that there are five features that have the potential to give rise to moral concern: sentience; higher cognitive capacities; capability for flourishing; sociability; and possession of a life². It is pointed out that the most controversial is the last one. It is also explored how to consider these features in moral reasoning. With regard to the feature of being self-aware, this requires a high degree of intelligence, the capacity to make comparisons and judgments, and a language with which to articulate them. It has been argued that suffering and death are uniquely painful to a self-aware being that not only senses pain but can also perceive the damage being done to his or her self and future.

There is, somehow, a consensus about the idea 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 health and alleviate the suffering of human beings. Not every benefit to human beings 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.

However, with regard to the use of animals, their use for xenotransplantation raises specific issues that need further consideration. Particular concerns are raised by the use of primates. The potential risk of extinction, apart from other ethical aspects, must be taken seriously. In addition, xenotransplantation using primate organs or tissue may pose particular risks of disease transmission.

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 has been said, the use of pigs for xenotransplantation raises fewer ethical concerns.

² See: <http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction>, “The ethics of research involving animals”, 2005, pages 41-48.

To develop the use of primates for xenotransplantation, when there is an ethically acceptable alternative, would not be justifiable. 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.

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. It is also 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.

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. 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. In this respect, there is, somehow, a consensus about the use of transgenic pigs that have been genetically modified to reduce the human immune response to pig organs as an ethically acceptable criterion. Of course, monitoring the welfare of transgenic animals is regarded as a principle of high importance. In this regard, it is also very important to take the aforementioned principle of “Three Rs” into account³. In general terms, it can be defined as follows: **-Refinement:** improvement of all aspects of the lifetime experience of animals to reduce suffering and improve welfare; **Reduction:** the use of fewer animals in each experiment without compromising scientific output and the quality of biomedical research and testing, and without compromising animal welfare; **Replacement:** the use of methods that permit a given scientific purpose to be achieved without conducting experiments or other scientific procedures on living animals.

³ A definition of this principle and examples of all three Rs, as well as a description of the barriers to its implementation and ways in which this could be overcome, can be explored in the mentioned report of the Nuffield Council (Chapters 11-12)

It is necessary to point out that **other key principles in addition to the 3Rs** include **Justification** and **Responsibility**: • **Justification**—it requires projects using animals to be performed only after they are justified, weighing the predicted scientific or educational value of the project against the potential effects on the wellbeing of the animals. Thus, the justification must take into account all aspects of the project that may have an adverse impact on the animals; • **Responsibility**—it states that investigators who use animals for scientific purposes have personal responsibility for all matters relating to the wellbeing of the animals. They have an obligation to treat the animals with respect and to consider their wellbeing as an essential factor when planning or conducting projects. To meet these responsibilities, it is essential that investigators are knowledgeable about all factors associated with the project that may affect the wellbeing of the animals they use, mechanisms to minimize these effects, the monitoring and assessment of adverse effects on animal wellbeing, and appropriate actions to take if adverse effects are observed.

- Xenotransplantation raises the possibility that infectious diseases of animals will be transmitted into the human population. How can this risk be assessed and managed? Certainly, 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. 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. 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 organism of primates, notably viruses, can pass into the human population and cause disease. This supports the recommendation, as has been said, 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. Therefore, it would not be ethical to begin clinical trials of xenotransplantation involving human beings if some measures have not previously taken into account. In this respect, strict efforts should be made to collect 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. In the documents related to these questions there are described some cautious measures. For instance, 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. Researchers are required to follow the regulatory mechanism that would cover the safety and quality of animal organs and tissue. On the other hand, there should be methodical monitoring of early recipients, with regular testing for signs and symptoms of disease. In this respect, 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 addition, it is necessary, in order to facilitate the recording and analysis of information concerning possible disease transmission, that a xenotransplantation register is created and maintained by an independent body. Suitably anonymised data should be reviewed for evidence of the possible emergence of new diseases. Since, 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.

- When should clinical trials of xenotransplantation start and how can the welfare and interests of early patients be protected? As has been said, 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 as to whether the current data using

animal recipients justifies progressing to clinical trials. As has been also seen above, 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. But, with regard to this question, there are several difficulties which do not have an easy solution. In any case, the consent of patients to participation in xenotransplantation trials is required by appropriately trained professionals. The information given to prospective recipients should include an estimation of likely success, attendant risks and subsequent quality of life. In addition, 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, as has been seen, consent to this monitoring. In this respect, it is necessary 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 also included in any scientific publication.

- What are the implications for the financing of the health service, if xenotransplantation is successful 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 health service. There are some reasons for introducing new and potentially expensive specialist services in a controlled way. Restricting xenotransplantation to designated centers for the foreseeable future would ensure adequate monitoring of its cost and effectiveness.

3. International and European Initiatives

With regard to the legal framework, there are on the Xenome web site numerous references which have been divided as follows: International; Council of Europe; European Union; National legislation; and a summary of the main regulatory developments in xenotransplantation by country. We do not have the purpose in this report to make a detailed analysis of all these references. We only want to point out some general ideas about the international and European initiatives. We consider important that a review of international responses to the issues raised by xenotransplantation has an important role to play in the ethico-legal assessment of the procedure, particularly because efforts to address the issues, –particularly surrounding infectious disease-, associated with xenotransplantation require some form of international co-operation. We will review very briefly some of the work of some of international and European agencies on xenotransplantation. This examination will assess the contributions of the World Health Organization (WHO), the Organization for Economic Co-operation and Development (OECD), the European Parliament and the Council of Europe to debates on animal to human transplants.

- *World Health Organization (WHO)*

The WHO's work on xenotransplantation is influenced by its responsibility to public health, or in the words of Article 1 of the WHO Constitution, to support the "attainment by all peoples of the highest possible level of health". This interest in protection the health of "all peoples" means that the WHO is concerned with the health of individuals who may be helped by a form of xenotransplantation, as well as with the health of those who could experience the negative consequences of zoonoses. The WHO endeavours to discern the characteristics of a surveillance system that would be able to perform this dual task. In this respect, WHO suggests that the protection of individual recipients can be based on traditional bioethical principles. It holds that these principles will support the life-long monitoring of transplant recipients and require them to adapt their behaviour to protect public health. The reliance on traditional ethical principles also means that the WHO maintains that participants in clinical trials must be able to withdraw from them at any time. This may seem to suggest that the WHO underestimates the novel challenges presented by xenotransplantation. Yet it also suggests that the requirement of life-long monitoring may have to take place without

what can be regarded as truly free and informed consent. This leads the WHO to suggest that it may be necessary to re-evaluate this traditional ethical and legal concept. Finally, the WHO gives considerable importance to the need to establish and maintain international surveillance measures. In this, it concurs with other European and international agencies. In this respect, WHO points out the concern that xenotransplantation research and clinical trials take place in countries where there is no regulatory procedures. In response to this, it recommends that Member States should “give urgent attention” to ensuring that they have procedures in place to regulate all forms of organ and tissue transplantation. It also recommends that Member States should only permit xenotransplantation when regulatory procedures are in place containing measures to prevent secondary infection and to support international collaboration on the safety measures that are required⁴.

- *Organization for Economic Co-operation and Development (OECD)*

The OECD presents xenotransplantation as an issue that raises difficult socio-ethical and ethico-legal issues. It emphasizes that these require the same level of international co-operation as the technical issues. The OECD’s interest in the socio-ethical issues raised by xenotransplantation leads it to consider the possible impact of the procedure on resource-poor countries. The joint OECD/WHO consultation moves away from the WHO suggestion that the recipients of animal organs would have to be free to leave trials at anytime. Instead the consultation notes ways in which it may be possible to bind individuals to treatment regimes. In addition, its joint consultation with the WHO notes that the traditional understanding of consent may need to develop in order to incorporate third parties. The involvement of the OECD in discussions on xenotransplantation has helped to broaden the scope of international debates, because its remit means that it places socio-economic and ethico-legal issues at the centre of its analysis⁵.

⁴ World Health Assembly, *Human Organ and Tissue Transplantation*, WHA57.18, 22 May 2004. Available at: http://www.who.int/transplantation/en/A57_R18-en.pdf; Human Organ and Tissue Transplantation, Report by the Secretariat, 27 November 2003, EB113/14.

⁵ OECD (1999), *Xenotransplantation: International Policy Issues*, OECD: Paris.

- *The European Commission (EC)*

The European Commission published its Opinion on the State of the Art Concerning Xenotransplantation in October 2001⁶. The document was intended to inform the EC of issues that are important in the area of xenotransplantation and “to identify issues that may require community-wide action”. The report gives considerable importance to the infection risks posed by xenotransplantation. It identifies the pig as the animal most likely to be used as source for tissue and organs because it is easier to breed than non-human primates and presents less chance of transmitting infections to humans. However, it is acknowledged that even raising pigs under specific conditions will not completely eliminate the risk that they will transmit animal viruses to the human population. Furthermore, transplanting animal tissue into individual patients who have suppressed immune systems may prove particularly risky.

In respect of surveillance measures, the report highlights that although various supranational organizations, including the council of Europe, have examined the issues raised by xenotransplantation, no mechanism have been created to collate and share information between Member States and no Europe-wide legislation or regulation have been formulated. This is despite the fact that the infection risk posed by xenotransplantation could be more successfully treated by a Europe-wide approach that unites the efforts of individual Member States. Given this shortcoming the EC suggests that it is important that there should be some form of registration of the clinical trials, and collation and exchange of information. An agency like the WHO seems a likely candidate to function as office for the distribution of information to local governments.

It has been also acknowledged that there are ethical questions concerning humans and animals that must be addressed. In respect of humans, it has been stated that: xenotransplantation raises ethical as well as scientific considerations for all those involved. Whilst these will not be discussed in detail they include practical consideration such as obtaining informed consent from the early clinical trial patients, the gaining of consent from non-transplanted persons in contact with the patient for surveillance purposes... archiving of samples, data protection of personal details, dissemination of results, confidentiality conditions by contributing commercial companies, and even, perhaps, how to handle breaches of agreed contracts when others may be put at risk.

⁶ European Commission (2001), *State of the Art Concerning Xenotransplantation*, European Commission: Brussels.

On the ethical issues that concern the treatment of animals, the EC underlines that animals that are used in xenotransplantation would not be caused “avoidable suffering”. It also suggest that the European Parliament’s Directive 2001/20/EC, which outlines standards for maintaining good clinical practice in clinical trials, might provide a suitable legal framework for regulating xenotransplantation trials. In addition, its recommendations include:

- The establishment of a centralized regulatory body;
- An iterative risk analysis by the EC;
- That specific measures for clinical trials dealing with authorization, informed consent, registration, surveillance of patients and those at risk should be defined on the basis of directive 2001/20/EC;
- The maintenance of appropriate standards in animal welfare and the procurement of organs,
- Additional research by the European Commission to determine the risks of viral infection and the risks associated with severe immunosuppression,
- The need to implement surveillance measures for source animals.

In summary, the document published by the EC is not intended to analyze or advance the debate on animal to human transplantation, but rather to inform the Commission of the current standing of research in the area. Thus, while the document notes the ethical issues that exist, it does not examine them in any detail. However, in terms of regulation the Commission does emphasize that, despite much discussion about the value of having some form of Europe-wide or international regulation of xenotransplantation, nothing of this nature exists. The Commission adds its voice to the calls for such a framework to be established.

- *The Council of Europe*

Since 1999, when the Parliamentary Assembly called for a legally binding moratorium on clinical xenotransplantation to be adopted, the attitude of the Council of Europe towards the development of animal to human transplantation has become more permissive. The Working Party on xenotransplantation that was formed as a response to the call for a moratorium has recommended that animal to human transplantation can proceed providing certain preconditions are fulfilled. These preconditions include the

need for nation states to have a regulatory framework in place and a greater amount of certainty on the risks posed by the procedure. To provide such confidence in the procedure, the Working Group suggests that more research is required on all forms of xenotransplantation. The *State of the Art Report* gives considerable attention to the ethical and legal issues raised by xenotransplantation⁷. Like the WHO and the OECD, the Council of Europe affords special attention to consent, because it is an ethico-legal principle that has the potential to be an important element in an effective and appropriate xenotransplantation surveillance system. However, in its State of the Art Report the Working Party suggests that the consent of transplant recipients and their close contacts to life-long surveillance is highly desirable, but concedes that no mechanisms exist to deal with a subsequent failure to abide by the terms of that consent. However, should participants and their contacts not comply with surveillance measures, the Committee of Ministers suggests that constraints could be used.

- The review of *different national regulatory approaches to xenotransplantation* is beyond the scope of this report, but we can underline both continuity and diversity. Many States were concerned with similar ethical and regulatory issues. For instance, much attention is given to the measures that are needed to protect public health, the ethical legitimacy or restrictive surveillance strategies and the need to protect the welfare of animals as much as possible. However, it is evident from the initiatives of the different countries that there is no agreement between States over how, when and in what circumstances to proceed with xenotransplantation. In this regard, most States hold that more research in animal models is required before clinical trials should be permitted. Other countries have deemed it acceptable to proceed to clinical trials. In this respect, the cautious approach of countries which have not proceeded to clinical trials –despite their interest in the technique- is arguably negated by those which have begun trials of xenotransplantation in humans using extra-corporeal devices and animal tissue. The potential public health risk associated with xenotransplantation makes this uncoordinated approach problematic. In respect of legislation, the Council of Europe survey has reported that while a minority of countries

⁷ Council of Europe (2003), *Report on the State of the Art in the Field of Xenotransplantation*, Council of Europe: Strasbourg. The full report is available at: [http://www.coe.int/T/E/Legal_Affairs/Legal_cooperation/Bioethics/Activities/Xenotransplantation/XENO\(2003\)1_SAR.pdf](http://www.coe.int/T/E/Legal_Affairs/Legal_cooperation/Bioethics/Activities/Xenotransplantation/XENO(2003)1_SAR.pdf).

has legislation in place that applies specifically to xenotransplantation, others rely on non-statutory chances; still others have called for a moratorium.

As has been seen above, the work of European and international agencies on xenotransplantation is united by calls for international co-operation and national regulation. This has not been met in some countries at a national level by the necessary action or commitment. In fact the lack of consensus within and between nation States over the essential elements of an ethically acceptable xenotransplantation surveillance program suggests that more attention must be given to the fundamental issues the procedure raises. Thus, it is of concern that the ethical issues presented by xenotransplantation are rarely discussed in detail by national or international bodies. Rather, ethical issues are frequently deemed too lie outside the remit of the body concerned. The following sections will briefly review a general examination of the ethical and legal issues raised by animal to human transplantation.

4. The ethical dimensions of xenotransplantation: General aspects

In the modern era clinical efforts to transplant animal organs into humans have driven by a desire to treat critically ill patients for whom no other treatment options have been available. Dedicated researchers and programs have sought to develop animal to human transplantation into a technique able to overcome the shortfall of organs. To be adopted as treatment options, xenogeneic therapies must be ethically accepted as well as scientifically and medically viable. There are a number of ethical issues based on the use and treatment of animals and the potential impact of xenotransplantation on individuals and wider society.

- With regard to **the use of animals**, it has been noted by some authors that the use of animals –for research and clinical purposes- is ethically problematic. In this respect, problems have been identified with the main approaches that have been used to support the use of animals in biomedical procedures like animal to human transplantation cost-benefit analysis and the assessment of animal capacities. In respect of cost-benefit assessment it has been underlined that lack of information on the nature of animal experience, the incommensurability of human and animal experience and

concerns over what constitutes a cost to animals are all areas which problematize this method of assessment.

As has been seen, arguments based on capacities are undermined by the fact that it is difficult to find a criterion which justifies the use of certain animals –such as pigs- and excludes the use of other animals, or for that matter the use of certain humans. In addition, there is disagreement over the level of capacities of different species. Of particular concern is that judgements using such criteria are often assertions of pre-existing social assumptions rather than the product of critical reflection. Finally, the fact that arguments from capacities are unable to present a clear, morally relevant distinction between animals and humans, or between different animal species, serves further to problematize cost-benefit analysis. This is because cost-benefit assessments are based on the notion that animals are in some way different from humans. However, if we cannot consistently identify why humans have a higher moral status than non-human animals, then justification for the moral segregation which exists between humans and animals crumbles. In this respect, the Nuffield Council on Bioethics, for instance, has explored how to consider the five aforementioned features in moral reasoning. A consequentialist view weighs all costs against all benefits. A deontological view lays down particular prohibitions. A hybrid view contains some prohibitions and some weighing. It also concludes that the ethical positions that with the current UK regulations are hybrid. It appears that, in practice, the positions of most people, except perhaps those of animal protection groups, are hybrid too, allowing some weighing of factors, and accepting absolute prohibitions in other areas.

- The **public health issues** raised by xenotransplantation have become a central feature in the ethical assessment of the procedure. An ethical assessment of xenotransplantation which prioritizes public health requires that clinical trials pose a minimal risk to the human community. The primary strategy for reducing the risks which biomedical procedures present to humans is to test such techniques on animals before commencing clinical trials. Thus, a major ramification of the suggestion that research on xenotransplantation should continue until it is safer is that it will increase the burden on animals; a concern that is heightened by the fact that the arguments which are used to justify even the current use of animals do not stand up to scrutiny. This, as has been seen, is because the costs to animals are likely to be substantial; to date these costs are not clearly outweighed by large benefits for humans. In addition it is unclear

that there is an unambiguous distinction between the capacities of humans, non-human primates and pigs which justifies the distinct moral value and treatment which is afforded to these species.

Given these concerns, if other less costly ways of addressing the shortage of organs exist, or could be developed within a time-scale similar to that of animal to human transplantation, society would have a moral obligation to re-double its efforts to develop these alternative strategies. The availability of treatment options which are thought to carry less risk for the human community and impose less of a burden on animals would mean that xenotransplantation would cease to have any claim to be ethically justifiable. In this respect, stem cell therapies and artificial organs may well provide preferable treatment options to xenotransplantation.

It could appear that a risk adverse public health ethic might also have a negative attitude towards other avant-garde treatments. Thus, it is important to stress that this cautious approach is specifically concerned with the degree of risk that it is genuinely thought may be associated with transplanting animal tissue into humans. It must be emphasized that it is not medical progress per se which a public health ethic seeks to prevent, but the harm which may inadvertently be suffered by the human community as a result of such untried therapies. This means that if safer innovative treatment options were available this form of ethical assessment would certainly encourage their development.

A public health ethic has a number of other positive contributions to make to the issues xenogeneic therapies are intended to address. Because public health ethics is driven by the general aim to protect and improve human health, it must conduct a comprehensive assessment of the best way in which to remedy particular concerns. In the context of organ shortage a public health ethic is able to perceive this issue as one which is multi-faceted. Its starting-point is the need to minimize the number of organs that are required and find ways to increase the number of human organs which are donated. While such initiatives would certainly not solve the problem of the shortage of organs, they have the ability to save many lives. It is also true that some of the responsibility for alleviating the current shortage of organs must be taken by community-centred initiatives.

5. Legal issues in xenotransplantation: General aspects

Although many of the commentaries on xenotransplantation have focused on what might broadly be called ethical issues, there are a number of legal questions which have considerable importance, but have often only been minimally treated. On the other hand, there are a number of areas in which law and ethics overlap, or complement each other. The concept of consent, for instance, can be seen both as a legal and an ethical issue, as indeed might the question of the allocation of resources.

The review of each legal issue surrounding xenotransplantation is beyond the scope of this report, but with regard to **consent considerations** it is clear that moving to clinical trials of xenotransplantation strong efforts would be focused on the challenges to the current law of consent. Not only do we doubt the capacity of the individual to agree to participation in clinical trials of xenotransplantation given the current state of knowledge, but the interests of third parties are given an unusual significance. If xenotransplantation is to proceed, therefore, either to clinical trials or beyond them into part of the medical treatment, arguably a new model of consent which engages third parties and the public, as well as the patient, would need to be developed. How this would be achieved is, however, every bit as problematic as whether it should be, and its impact on the general rules about consent to medical treatment can only be guessed at. On the other hand, a point in the research scale must be reached where the questions remaining to be answered about xenotransplantation are considerably less critical than they currently seem to be. Even then, concern remains about freedoms which would be required to be surrendered by recipients and their relatives/close contacts, and the standing of any supposed agreement to participation. If it is impossible to bind the patient or immediate family members, then it is even more difficult to imagine how one could bind the community. Equally, it is very difficult to imagine a mechanism whereby community involvement could be sufficiently robust as to guarantee or reassure that the community is in fact willing to take the kind of risks xenotransplantation might present.

Another concern is referred to the impact which xenotransplantation trials may have on future generations. The concept of **intergenerational justice** is gaining credibility in biomedical discourse, particularly in light of the so-called genetics revolution. Indeed, UNESCO has formulated a code on the responsibilities of current

generations to future generations⁸, and it is clear that, if the risk of the transmission of unknown or untreatable viruses is a potential consequence of xenotransplantation, then both moral and legal liability may lie.

The complexities surrounding agreement to participate in clinical trials of xenotransplantation are such that there remain more questions than there are answers. Further, even if the requirement to provide potential recipients with adequate information becomes a reality, concerns remain about the impact of an individual's choice for therapy on third parties; not just their contacts, who will be required to adopt a constrained lifestyle in perpetuity, but also the wider community.

However, the legal matters which are relevant to xenotransplantation do not end with the issue of consent. The risks, -the scale of which we do not yet know which-, provoke dubiety about the validity of any purported consent will potentially place incalculable liability on states, challenge the medical profession's commitment to confidentiality and may be in danger of conflicting with internationally agreed norms of behaviour. These issues are referred to **monitoring and surveillance, confidentiality, resource issue, legal liability for harm**, etc.

Certainly, in addition to the issue of consent, there is a range of other additional legal matters which also impact on xenotransplantation. The detailed analysis of these issues is, as has been said, beyond the scope of this report. In general terms, we can say that, certainly, there are a number of legal questions which arise directly or indirectly from xenotransplantation. Unarguably, the major problems will be those which relate to consent issues in either clinical trials or the use of xenografting as standard medical treatment in the future. There must, therefore, remain a question as to whether or not the practice of xenotransplantation, given the current state of knowledge, allows potential recipients the protection of the general rules of consent, and whether harm caused will be compensated under any of the legal regimes in place. Additionally, there are consent-based questions which go beyond the individual, and which severely test the accepted legal understanding of consent. Not only would individuals be expected to submit to unusual limitations on their basic freedoms, but others would have a direct impact on the availability of the treatment, and would also be required to make significant modifications to their lifestyles. As we have said, difficult issues arise not only from the question of consent. Wider accountability issues must also be recognized, and relevant

⁸ UNESCO (1997), *Declaration of the Responsibilities of the Present Generations towards future generations*, UNESCO: Paris.

problems addressed. Many of these raise direct challenges to fundamental concepts such as confidentiality. The impact of human rights legislation and international humanitarian law must also be taken into account in any evaluation of xenotransplantation. Additionally, the internationally agreed standards to which healthcare professionals subscribe, for example the Declaration of Helsinki, also pose some problems in respect of clinical trials of xenotransplantation.

On the other hand, resource allocation decisions will require careful scrutiny, both at macro and at micro level. Liability will also devolve onto those who produce the organs for xenotransplantation or associated products. Either under sale of goods or consumer protection legislation, where there is a defect of inherent danger in the product, either the National Health System or the producer will have liability.

Nations states must take seriously their responsibility for global safety, as required by international law. They must also be alert to the possibility of liability devolving on them for harm caused elsewhere, for example by the spread into the world's population of hitherto unknown infections resulting from xenotransplantation. They must take seriously their obligations under international humanitarian and human rights law, as well as their commitments to future generations. Xenotransplantation could be an enormously expensive procedure for health service, especially for as long as it is market driven, and matters of the just allocation of health resources must be given attention both at the macro and the micro level.

6. General considerations

The need to consider xenotransplantation as a viable treatment option in the future remains clearly grounded in the possibility that, even were less controversial sources of organ transplantation to be maximized, there would still remain a shortage of organs for transplantation. On the plus side, xenotransplantation has a number of immediate attractions; not least that, were it possible to breed sufficient numbers of transgenic animals, and were we able to overcome immunological and physiological problems, it would provide a ready supply of organs, permit the planning of surgery and perhaps reduce the need for expensive immunosuppressive regimes. Equally, the development of cellular xenografting is potentially of benefit in respect of certain degenerative conditions, such as Parkinson's disease. As has been seen, the promise of

xenotransplantation, even if established, would not be without costs, both ethical and legal. In general terms, the **ethical acceptability of xenotransplantation** is dominated, as has been discussed above, by two issues in general: whether it is use of animals is acceptable and whether it is contribution to public health is likely to outweigh any harm it may cause. The public health issues raised by animal to human transplantation are not easily addressed within a framework that is primarily concerned with the interests and rights of individuals. Thus, it has been suggested that it is preferable to utilize an ethical approach which gives priority to the interests of the whole community and which will also respect the autonomy of individuals, unless public health issues make this impossible. This led to the conclusion that although individual patients are able to consent to some treatments which may pose a risk to them, the public health implications of xenotransplantation appear sufficiently serious to make it necessary for public health to trump individual choice on this issue. At present time, a public health ethic would support a moratorium on xenotransplantation clinical trials until more information is available on the procedure⁹.

With regard to the use of animals, there is not enough information concerning animal experience to identify the costs to animals accurately. Additionally, the use of capacities (animal and human) to determine the ethical legitimacy of xenotransplantation procedures is also problematic. This is because it is not possible to forge a consensus on the intellectual and social abilities of different non-human species. Apart from this criterion it is necessary to take practical considerations into account. What is needed is a model that takes both theory and practice into account. From the point of view of animal ethics, the main claim is that all experiencing beings must be considered equally, and that their welfare is the bases for decision-making. In this respect, interest conflicts ought to be solved so as to best serve the welfare of those involved in each context. This has radical implications for the use of animals, as many practices ranging from dairy farming to animal experimentation are difficult to justify. In this regard, researchers are required to meet animals' behavioral needs as well as their biological needs, in order to ensure that animal wellbeing is maintained during scientific experiments. In some studies, animal behavior is modified or manipulated to

⁹ The legal, ethical and scientific problems associated with xenotransplantation might make the notion of calling a halt appealing, either in the short or indeed permanently. In fact a moratorium might permit an extensive analysis of the view of the public to be conducted in an atmosphere free from pressure and would presumably allow time for some of the ethical and legal problems to at least move towards resolution.

achieve an experimental outcome, and pain or distress may result. A number of behavioral modifications do cause an animal pain, distress and suffering, and all steps must be taken to ensure that this is minimized. Even those modifications that do not necessarily result in pain, distress and suffering may have that result if inappropriately administered. All steps must be taken to ensure that pain and distress are minimized. Therefore, research involving behavior modifications must be scientifically justified, approved by the relevant animal ethics committee and conducted in a way that minimizes any adverse effects for the animals.

In general terms, we have also seen that one of the most problematic legal issues is the question of consent to involvement in xenotransplants. This can be considered in two stages. The question of consent should xenotransplantation become part of standard therapy is less important than is the question of consent to clinical trials. In the research phase, issues surrounding the selection of patients, the capacity of those selected to provide a valid consent and the general questions as to whether or not it is either possible to agree to surrender basic human rights or to enforce the recommended surveillance and monitoring requirements are of considerable importance. Compliance with the surveillance and monitoring regimes cannot be enforced under the present legal fundamental rights. Equally, research concerning the social and psychological potential of xenotransplantation would need to be undertaken before proceeding to trials so that, in as much as this is possible in any experimental situation, the fullest possible information can be made available to potential recipients. Moreover, it is internationally accepted that involvement in clinical trials must be subject to the right to withdraw at any stage. It is, however, inherent in the surveillance requirements of xenotransplantation that such withdrawal should be actively discouraged, if not enforced. Also, the need for third party agreement and involvement in life restricting surveillance is of highly dubious legal standing and is certainly unenforceable. In this respect, there is wide agreement about the idea that no trials should take place until the community as a whole has agree to this, because of the potential effect on other members of society should the infection risk manifest itself in reality. Identifying public opinion –particularly as this might involve a global consensus- is likely to be difficult to achieve. Consultation is a common characteristic of law reform, but it is unclear how widely different opinions can be married. For the moment, it seems difficult to identify any consensus on the development of xenotransplantation. Given fears that infection may spread following xenotransplantation, it is clear that “community” cannot be

conceived of as only including those within boundaries. The entire population of the world is potentially threatened should infections follow xenotransplants, but if it is difficult to gauge the views of the immediate community, how much more difficult will it be to engage with the whole world?

7. Conclusions

Given the general review of the ethical and legal issues involved in xenotransplantation, it seems clear that appropriate regulation, with a clear ethical and legal remit is necessary in order to develop a different or similar approach from that usually taken in the evaluation of new medical technologies. It can be deduced from that general review that the ethical analysis of xenotransplantation is poorly strong if based exclusively on a cost-benefit analysis which has no way of accurately measuring costs, particularly costs to animals. It is also necessary that the review of ethical and legal issues must be iterative if it is to be useful. Furthermore, public engagement is critical and must also be iterative and up to date, and should expose the public not simply to the science but also to the ethical and legal dilemmas. Indeed, article 30 (–Public debate–) of the Council of Europe’s 2003 Recommendations states: “In accordance with the principles stated in Article 28 of the Convention on Human Rights and Biomedicine, member states should take active steps to ensure that the fundamental questions raised by xenotransplantation are the subject of appropriate public discussion particularly in light of relevant medical, psychological, cultural, ethical, legal, social and economic implications”.

The regulatory framework in this field must be designed to assure the respect for the fundamental rights of the people that undergo this kind of treatment. This requires that ethical and legal analysis is firmly built into the design of the regulator, as has occurred, for example, in Sweden¹⁰.

¹⁰ Two xenotransplantation trials did take place in Sweden in 1995, when it had no legislation on animal to human transplants in place. To fill this void the Swedish Committee on Xenotransplantation was established in 1997, and began its work in January 1998. The Committee’s terms of reference include the “medical, ethical, legal and animal protection aspects’ of xenotransplantation” –(The Swedish Committee on Xenotransplantation (1999), *From One Species to Another*, Swedish Committee on Xenotransplantation, Stockholm)-. Under its terms of reference it has a responsibility to: establish the conditions under which clinical trials could take place; identify the authority that should be responsible for implementing these standards; propose safety guidelines for animal to human transplants; ensure the

Caution in simply following science to its logical conclusion is not unique to xenotransplantation, but it is of vital importance in this field. The main reason makes reference to this idea: xenotransplantation involves decision making in a medical and scientific context with many uncertainties at all stages of the process. Here, the problems relating to risks are more important than in other fields not simply because they involve both human and animal life, but also because they are not limited to the present and extend to future generations. It is no longer the individual or society that may be at risk but the human species itself. In this respect, we need to carry out the moral groundwork very carefully, and especially we need to continue to find ways of allocating moral values to the complexity of our origins as humans.

Additionally, as has been also mentioned, there is a risk to the welfare of the animals upon which research and genetic modification are undertaken. That welfare is not limited, as has been seen, to physical harm. Indeed, the need to consider other matters is enshrined in the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposed, which declares that: “Any restriction on the extent to which an animal can satisfy its physiological and ethological needs shall be limited as far as practicable”¹¹.

Moreover, the same Convention states that “a procedure shall not be performed for any of the purposes referred to in Article 2, if another scientifically satisfactory method, not entailing the use of an animal, is reasonably and practicably available”¹².

quality control of organs and tissue from source animals; and report on any necessary statutory changes. Furthermore, the Committee has sought to determine public opinion on xenotransplantation by commissioning a survey of attitudes. The survey found a generally positive attitude towards xenotransplantation, providing the risks involved are minimal. The main topic addressed in *From One Species to Another*, the report of the Swedish Committee on Xenotransplantation, is how clinical trials should be monitored. A number of ethical principles underpin the Committee’s evaluations. This places an ethical framework at the heart of the Committee’s work, and integrates ethico-social concerns with the practical interests of the report. Having identified the relevant principles, the report then highlights the issues that must be addressed in order for policy decisions on xenotransplantation to make a positive contribution to human wellbeing and avoid causing harm. Given its philosophical foundations, to be internally consistent the Committee deems it necessary to recommend that: the system should involve a procedure to evaluate applications to carry out clinical trials, a register of recipients and a tissue bank. In addition, among the proposals in the report are those for a special Act, the Xeno Licensing and Control Ordinance, to regulate clinical trials. It also recommends that a special authority, the Xenotransplantation Board, be established to regulate xenotransplantation. The report ends with recommendations for new legislation and an amendment to current law. These statutory proposals concern the regulation of clinical trials, proposals for a biobank, an amendment to the Secrecy Act and instructions to the Xenotransplantation Board.

¹¹ Strasbourg, 18.III.1986, ETS: 123.

¹² See article 6.1.

This latter requirement leads to a brief, but necessary, consideration in the analysis of this field. It has been proposed that, were alternatives available, xenotransplantation should not be contemplated, given the range of ethical, legal and welfare issues raised by it. Although these other alternatives have not been mentioned in detail, it is possible to say that researchers are now exploring, in turn, other new therapies to overcome the shortage of donated organs and tissues and treat an increasing range of diseases and conditions that have not been treated before. For instance, one such area of work is on **human stem cells**. Stem cells are early, unspecialized cells that can, under certain conditions, be induced to mature into specialized cell types (such as heart, liver, brain and pancreas). It is hoped that these cells will have the potential to repair human organs and to treat a similar range of diseases to those proposed for animal cell therapies. However, human stem cell technology raises a number of ethical issues of its own, and its development will require the use of animals in preclinical studies that are similar to those required for xenotransplantation research (including nonhuman primates). Also, some stem cell techniques cannot be regarded as an ‘alternative’ to xenotransplantation because the stem cell lines are grown on a layer of animal cells, so they come within the definition of animal external therapies. A second area of research is into the use of mechanical or artificial organs, either for short-term ‘bridging’ procedures for people waiting for an organ to become available or for longer term replacement or repair. The development of artificial devices may provide solutions to some conditions and diseases that currently require transplants, but not all.

Like xenotransplantation, research in both these areas is in the early stages and it is not clear whether they will be more or less successful than animal therapies across the wide range of diseases and conditions involved. Only further research will determine the best form of therapy for each condition. It has been pointed out that stem cell research appears in this regard as a crucial alternative. Certainly, according to the predictions of some scientists, there is considerable reason to believe that an alternative is on the scientific horizon, namely stem cell research. For those scientists, few could doubt about the amazing potential for human benefit that implies this line of research¹³.

¹³ An evaluation of the potential of stem cells in the future is clearly beyond the scope of this report, but its possibilities should be borne in mind when considering the ethics of pursuing and investing in xenotransplantation.

Given this general analysis of the ethics and law surrounding xenotransplantation, it seems clear that there are good reasons to require adequate regulation of xenotransplantation. Until we can adequately address the benefits and drawbacks of xenotransplantation, the state's obligation is the protection of the general public's health and safety.