Chapter 6

Transmission of infectious diseases

6.1 In principle, xenografts, if successful, would offer huge benefits to individual patients. Xenografting, however, may also involve certain risks. This chapter discusses the risk that using animals to supply organs will result in the transmission of infectious diseases from animals to the human population. As discussed in Chapter 4, the Working Party recommends that the development of xenotransplantation should involve pigs, not primates as source animals (paragraph 4.40). One important reason contributing to that decision is the greater concern about disease transmission from primates. The evidence for that concern is presented in this chapter. The fact that xenotransplantation of baboon organs and tissue into human beings is proposed and, indeed, already occurring in the US[1] is a further reason for discussing the risks that diseases will pass from primates to xenograft recipients and thereby into the wider population.

6.2 Many disease-causing organisms (pathogens) are common to human beings and other animals.[2] For example, the bacterium causing tuberculosis infects both human beings and baboons, and human beings and pigs both carry the virus that causes influenza. Clearly it would be important to make sure that any animal used to supply organs was free from infectious organisms that cause disease in human beings, just as it is important to make sure that human organ donors are free from infections that might be transmitted to a transplant recipient. The use of animals as a source of organs, it is argued, would allow for more thorough screening than is possible with human organ donors, and so the risk of such diseases might be reduced.

6.3 In addition to organisms that can infect both human beings and other animals, any animal species will be infected with organisms that do not usually infect other species. Xenotransplantation, however, may allow such organisms to infect xenograft recipients who may, consequently, contract previously unknown diseases. There is also a risk that the infectious organisms might cause disease in and destroy the transplanted organ, even if they do not harm the human recipient. Even if not infected with disease-causing organisms when transplanted, the xenografted organ may remain susceptible to infectious organisms of animals. This is most likely to be a problem with lung transplants, where infectious organisms of animals would easily get access to the transplanted animal tissue. Any person thinking about volunteering

[1] Aids patient given baboon bone marrow. (1995) **Lancet**, 378:756.

[2] The word 'organisms' should be taken to include viruses and prions. While not strictly correct, the Working Party adopted this convention in the interests of accessibility and brevity.

for a xenograft would have to be made aware of, and to consider these risks, about which very little is known at present, along with all the other factors that would need to be taken into account (paragraphs 7.14 - 7.21).

6.4 The possibility must also be considered that should an animal organism infect a xenograft recipient the resultant disease might then be passed on to the public at large. In this way, xenografting may pose a risk to public health as well as to individual health. Many of those who responded to the public consultation emphasised the importance of addressing the risks of disease transmission associated with xenotransplantation.[3] This chapter considers, first, the possibility that new diseases will be transmitted from animals to xenograft recipients. It then considers the risks that such diseases might spread from xenograft recipients into the general population. Finally, the principles by which these risks might be assessed and managed are discussed.

The risk that infectious organisms will be transmitted from animals to human beings

6.5 There is evidence that human beings are susceptible to some animal diseases. Such diseases are called zoonoses. For example:

- human beings in contact with monkeys can become infected with monkeypox virus, which is related to the smallpox virus;
- contact with macaque monkeys can lead to infection with a macaque form of herpes B virus which causes encephalitis in human beings which is rapidly fatal;
- the human immunodeficiency virus (HIV) virus that causes AIDS is very similar to the simian immunodeficiency viruses (SIV) found in primates. One view attributes the emergence of the HIV virus and the disease AIDS in human beings to the transmission of SIV viruses from primates to human beings. There is evidence that the SIV virus can, indeed, be transmitted from primates to human beings although, as yet, there is no evidence of disease symptoms in SIV infected human beings.[4, 5]

[3] These included Animal Aid, the British Union for the Abolition of Vivisection, the Christian Medical Fellowship, the Church of England, the Church of Scotland, the Church in Wales, Professor David Onions, the Genetics Forum, the Jain Academy, Professor John Polkinghorne and PPL Therapeutics.

[4] Chapman L E *et al.* (1995) Xenotransplantation and xenogeneic infections. **New England Journal of Medicine**, 333:1498-501.

[5] Thanks, but no thanks. **The Economist**, 21 October 1995, pp 17, 137-9.

6.6 Xenotransplantation is one way by which disease-causing organisms could be transferred from animals to human beings. Because xenotransplantation involves the direct introduction of animal organs or tissue into the human body, many of the natural barriers to infection are by-passed. Xenograft recipients are also likely to require immunosuppression to prevent transplant rejection. Since immunosuppression lowers the body's resistance to disease, the possibility of infection of a recipient with animal diseases may be increased further.

6.7 It is sometimes argued that the risk of transmission of animal diseases is overestimated, since immunosuppressed recipients of human organ transplants who are in contact with pets or farm animals, do not contract animal diseases. This argument, however, ignores the major difference between close contact with animals and the transfer of animal organs or tissue directly into the human body. The potential importance of this difference is illustrated by the following example. Cats are susceptible to infection by feline leukaemia virus. Dogs or human beings, in contact with cats, do not become infected with the virus. But if young, immunosuppressed dogs are transplanted with infected cat tissue, the dogs become infected with the virus and develop tumours.[6]

Infectious organisms

6.8 Xenografting provides a potential route for the transmission of disease. So it is necessary to consider the organisms that infect possible source animals and to assess whether they are likely to cause disease in human beings. Important categories of infectious organisms include viruses, bacteria and fungi. Prion proteins are another type of infectious agent that are thought to cause diseases such as bovine spongiform encephalopathy (BSE, or 'mad cow disease') and human Creutzfeldt-Jakob Disease (CJD). There is evidence that prion diseases can pass from one species to another.[7] Thus, prion disease transmission is another risk that needs to be considered when contemplating xenografting.

6.9 Most concern about the risks of infection from xenotransplantation focuses on viruses. This is because:

1 viral infections are difficult to treat with drugs;

2 viral infections may have a long latent period during which the person has no symptoms of the disease. This is the case with HIV infection: it may take 10 years for an infected person to develop AIDS. If a new disease were to

[6] Onions D (1995) Comments made at an Institute of Medicine conference on Xenograft transplantation: science, ethics and public policy, Washington DC.

[7] Prusiner S (1995) The prion diseases. **Scientific American**, 272(1):30-7.

emerge as a consequence of xenotransplantation, it might be several years before the problem was identified. During this time the infection might be spreading throughout the population;

3 viruses can mutate rapidly and thereby change their characteristics.[8] Mutation might allow animal viruses to infect human beings more readily; to resist attack by the human immune system; or to become drug-resistant;

4 one type of mutation occurs when viruses from different species recombine with each other and form new and possibly more dangerous viruses. It is thought that influenza epidemics are caused when new types of influenza virus are formed by recombination of two viruses, sometimes from different species. Xenotransplantation would provide increased opportunities for recombination between animal and human viruses;

5 one group of viruses, known as endogenous retroviruses, are inserted into the genetic material of the host animal and can be passed in this way from parent to offspring. This makes endogenous retroviruses almost impossible to eliminate from any animals that might be used as a source of organs for xenografting. It is possible that, after xenotransplantation, the endogenous retroviruses would move from the transplanted organs and become inserted into the genetic material of the human cells. Such insertion may cause mutations in the human genetic material and lead to an increased risk of cancer.[9]

Comparison of the risks to human beings from infectious organisms of primates and pigs

6.10 The high degree of genetic relatedness of human beings and other primates means that infectious organisms from primates may have a good chance of surviving in, and causing disease in, human beings. Baboons, for example, carry several viruses with the potential to infect human beings including several herpes viruses (SA8, simian cytomegalovirus, and herpes papio) and several retroviruses (STLV-1, baboon endogenous retrovirus and foamy virus).[10] As mentioned above, there is considerable evidence that primates do indeed carry viruses that infect and cause disease in human beings (paragraph 6.5). These risks are reflected in the safety

[8] This is especially likely for RNA viruses, including retroviruses, which replicate less faithfully than DNA viruses.
[9] Stoye J P and Coffin J M (1995) The dangers of xenotransplantation. Letter to **Nature Medicine,** 1:1100.
[10] Allan J S (1995) Xenotransplantation at a crossroads: Prevention versus progress. **Nature Medicine**, 2:18-21.

precautions taken by people handling primates.[11] There is also experimental evidence that endogenous retroviruses from baboons can infect human cells.[12] Because the viruses from human beings and other primates are often closely related, the risk of recombination to form new harmful viruses, may be high (paragraph 6.9.4). Another problem is that to breed primates free from known viruses, in so far as this is possible, would require a long-term programme because of their relatively slow breeding rates (paragraph 4.34). As discussed below, there are certain to be primate viruses that are currently unidentified and which may have the potential to cause disease in human beings (paragraph 6.14).

6.11 In contrast, the more marked biological differences between pigs and human beings, and between their infectious organisms, may make it more difficult for infectious organisms from pigs to cause disease in human beings. Moreover, pigs have been domesticated and used by human beings for centuries, yet there is no evidence for transmission of viral diseases into the human population on the scale seen with viral diseases of other primates. Although the risks are likely to be lower, however, they cannot be ignored. Imutran Ltd, the UK firm developing transgenic pigs for xenotransplantation have pointed out that "*the particular concern that xenografting raises is the risk of transmitting a pig pathogen to a human*."[13] Pig viruses with the potential to infect human beings include those causing porcine influenza, parainfluenza, swine vesicular disease, encephalomyocarditis and, possibly, pseudorabies.[14] Pigs, like primates, contain endogenous retroviruses and studies are needed to assess whether they can infect human cells.[15] Since they have a shorter generation time than primates, breeding pigs free of known viruses should prove more feasible. Pigs, however, will also contain viruses and other infectious organisms that have not yet been identified. Moreover, at least initially, recipients of pig xenografts might require high levels of immunosuppression which would render them very susceptible to infections. However, the hope is that, eventually, relatively low levels of immunosuppression could be used if organs are taken from transgenic pigs that have been genetically modified to reduce the immune response after transplantation.[16]

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[11] Whitney R A and Wickings E J (1987) Macaques and other old world simians, Chapter 40 of **The UFAW Handbook on the Care and Management of Laboratory Animals** Sixth Edition. UK: Longman Scientific & Technical.

[12] Benveniste R *et al.* (1974) Infectious type-C virus isolated from baboon placenta. **Nature** (London), 248:17-20.

[13] Imutran Ltd: submission to the Working Party.

[14] Onions D: submission to the Working Party.

[15] Stoye J P and Coffin J M (1995) The dangers of xenotransplantation. Letter to **Nature Medicine,** 1:1100.

[16] Cozzi E and White D J G (1995) The generation of transgenic pigs as potential organ donors for humans. **Nature Medicine,** 1:964-6.

6.12 The evidence suggests that the risk of disease transmission from primates will be greater than that from pigs. This conclusion supports the Working Party's recommendation that non-primate species should be regarded as the source animals of choice for xenotransplantation. Nevertheless, the risks of disease transmission from pigs also need careful consideration. It is sometimes argued that pig heart valves have been transplanted into human beings for more than 30 years without any evidence of disease transmission. Pig heart valves, however, are fixed in glutaraldehyde, a process that renders them non-viable and which would reduce, if not eliminate, all infectious organisms.[17] This treatment would not be possible for organs and tissue that are to be transplanted whilst still viable.

Assessing the risks of infection

6.13 It is important to know as much as possible about the infectious organisms present in the animal species that are most likely to be developed as sources for xenografts, namely baboons and pigs. It is, however, very difficult to determine whether organisms that cause disease in animals will also infect and cause disease in human beings. Another difficulty is that it is not uncommon for infectious organisms, that are harmless or cause relatively mild symptoms in their natural host, to cause more severe disease in a different species. One example is macaque herpes B virus which causes severe human encephalitis in human beings (paragraph 6.5).

6.14 Another problem is that there are undoubtedly infectious organisms of both primates and pigs that are currently unknown. This is true even of human beings: in the last few years, three new herpes viruses have been identified (herpes viruses 6, 7 and 8).[18] It will be very difficult to identify organisms that do not cause any symptoms in the animal from which they come. Previous experience indicates that infectious organisms are normally identified only after the emergence of the disease they cause. The HIV virus, for example, was only identified after the emergence of the disease AIDS. Put bluntly, it may be possible to identify any infectious organism transmitted by xenografting only if it causes disease in human beings, and after it has started to do so. Even this may be difficult if, as with AIDS, there is a long latent period between infection and development of the disease. Animal Aid pointed out in their submission that "*cross species transplants carry a further, potentially devastating risk in that a currently unknown (and therefore unscreened for) animal virus could trigger a new plague when it crossed the species barrier.*"

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[17] Marks C and Marks P (1993) **Fundamentals of cardiac surgery.** London: Chapman & Hall Medical, pp 105-9.

[18] Herpes virus 6: Salahuddin S *et al.* (1986) Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. **Science**, 234:596-601. Herpes virus 7: Frenkel N *et al.* (1990) Isolation of a new herpesvirus from human CD4+ T-cells. **Proceedings of the National Academy of Sciences, USA**, 87:748-52. Herpes virus 8: Chang Y *et al.* (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. **Science**, 266:1865-9.

6.15 Just as with any other medical advance, it is impossible to eliminate all risk or, even, to be able to predict and quantify all the risks associated with xenotransplantation. But it is important to make a clear distinction between the unquantifiable risks and the risks that can be usefully investigated. It is necessary to be sure that all the research that can usefully be done has been completed before clinical trials involving human beings are contemplated. A variety of experimental approaches will help identify, quantify and eliminate some of the risks of infection associated with xenografting (paragraphs 6.24 - 6.26).

The risk of animal diseases spreading from xenograft recipients into the general population

6.16 While some infectious organisms of animals may cause disease if they are transferred directly into a xenograft recipient, they may not be able to pass from person to person. Infectious organisms may need to change their characteristics before they can spread into the human population. It is known that disease-causing organisms of one animal species can undergo changes enabling them to infect different animals. One example is the feline parvovirus, that has infected at least two new hosts, mink and dogs, in the last 40 years.[19] On the whole, however, changes of this kind are more likely to occur within a large number of organisms, that is, amongst the organisms found in the animals they normally infect. Such changes are less likely to arise within the small number of organisms that would be found in xenograft recipients. An exception to this would be the retroviruses since xenotransplantation would increase the risk of recombination between animal and human viruses (paragraph 6.9.4). This might produce a new virus that was able to pass efficiently from human being to human being. Conversely, prion diseases are unlikely to pass into the wider population, even if they infect individual recipients (paragraph 6.8). This is because transmission of prion diseases is normally by transplantation or by eating infected material.

6.17 It is extremely difficult to assess the level of risk that an animal disease will be transmitted to the human population as a result of xenotransplantation. Experts in the field vary widely in their opinions.[20] The conclusion would seem to be that, when considering the possibility of xenografting leading to the transmission of disease into the human population, the risk is unquantifiable and it may be extremely small. But it cannot be ruled out.

[19] Parrish C (1990) Emergence, natural history, and variation of canine, mink and feline parvoviruses. **Advances in Virus Research**, 38:404-50.

[20] Allan J S (1995) Xenotransplantation at a crossroads: Prevention versus progress. **Nature Medicine**, 2:18-21.

6.18 Someone who required a life-saving operation would probably be prepared to accept a risk of infection which is greater than that thought to be acceptable for the whole population. The ethical question is how to balance the needs of individual transplant recipients, and the potential benefits to them of xenotransplantation, against the uncertainties associated with the possible transmission of a new infectious disease to the general population. Even allowing that xenografts might bring benefits to patients in terms of increased quality and length of life, the potential public health risks nevertheless counsel caution. The consent of individuals to take these risks does not justify their imposition upon the public.

6.19 In other areas of medical and scientific developments, it has been found appropriate to limit the associated risks by establishing regulatory mechanisms. Examples are the regulations controlling the development of new medicines, and of gene therapy techniques. Where there is a perceived risk to public health, or the environment, there is further increased rigour, as seen in the area of genetically modified organisms (paragraphs 4.50 - 4.52). This suggests the urgent need in the field of xenografting to establish agreement on best practice and the appropriate regulation of xenografting procedures.

The principle of precaution

6.20 As set out above, the development of xenotransplantation is associated with the potential risk of transmission of new diseases to the human population. It is not possible to predict or quantify this risk but, in the worst case, the consequences could be far-reaching and difficult to control. In this type of situation, a cost/benefit approach to dealing with risk analysis has limitations because the costs (and, indeed, the benefits) are not known and cannot be predicted. Since the possible consequences of developing xenotransplantation are potentially very serious, it is hardly wise to use a method of risk analysis that cannot address such consequences until they start to be seen.

6.21 The principle of precaution offers an alternative method of risk analysis and assessment.[21] This has been developed within the field of environmental policy and applied to the control of pollution and the release of genetically modified organisms. The principle of precaution requires that action should be taken to avoid risks **in advance of** certainty about their nature. This challenges the view that, until there is evidence that a new technology is harmful, it is acceptable to proceed with its development. It suggests that the burden of proof should lie with those developing the technology to demonstrate that it will not cause serious harm.

[21] O'Riordan T and Jordan A (1995) The Precautionary Principle in Contemporary Environmental Politics. **Environmental Values**, 4:191-212.

6.22 An implication of the principle of precaution is that the development of some technologies simply should not be pursued. Since any innovation must by definition carry some unknowable risks, however, it would be unacceptably conservative to restrict innovation merely by appeal to the possibility of risk. For each technology, an attempt must be made to identify and define the risks and to decide on a course of action. It may be that, for some technologies, the principle of precaution would argue that they should not be pursued. For others, it will be possible to identify safeguards that will reduce the risks of the technology.

6.23 What are the implications of the principle of precaution when applied to the uncertainties associated with disease transmission via xenotransplantation? The discussion above has set out the potential risk from infectious organisms of animals and highlighted the difficulties in identifying these organisms, determining whether they will cause disease in human beings and predicting whether the diseases will spread to the wider population. **The Working Party concluded that the risks associated with possible transmission of infectious diseases as a consequence of xenotransplantation have not been adequately dealt with. It would not be ethical, therefore to begin clinical trials of xenotransplantation involving human beings.** In order to address the risks of disease transmission associated with xenotransplantation, the Working Party suggests that the following measures should be taken:

- stringent efforts should be made to assemble as much information as possible about the risks of disease transmission **before** further xenotransplantation goes ahead. This would involve reviewing existing research and undertaking new research where necessary on the infectious organisms of primates and pigs and the possibility of transmission of disease to human beings (paragraphs 6.24 - 6.26);

- 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 that can be eliminated (paragraphs 6.27 - 6.32);

- there should be thorough monitoring of early recipients, with regular testing for signs and symptoms of disease (paragraphs 6.33 - 6.37);

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

The next sections discuss these requirements in more detail.

Assembling information about the risks of disease transmission

6.24 Experimental studies can be used to try to identify unknown infectious agents in animal tissue.[22] Transplantation of pig or baboon tissue into immunocompromised mice might allow the identification of previously unknown infectious organisms. It is also possible to test whether animal viruses will infect human cells grown in the laboratory, using co-cultivation techniques in which human cells and infected animal cells are grown in the same container. This technique has shown that baboon retroviruses can infect human cells. New molecular techniques allow virologists to search for the genetic material of previously unknown viruses.[23]

6.25 Such research is not without its difficulties. Results obtained using human cells in tissue culture may not always be applicable to human recipients. But there is no doubt that much useful laboratory research can be done, particularly in the area of endogenous retroviruses which may present particular risks. Useful research could be done to identify the different retroviruses present in source animals, to assess whether the viruses are activated by transplantation, and to examine the rate of mutation shown by the viruses. Research involving animal xenograft recipients could be useful in this respect. Primate recipients of pig organs, for example, could be assessed in order to determine whether porcine retroviruses are activated after transplantation, and whether the viruses then infect the primate tissue.

6.26 Another area where research is needed is in improving the diagnostic tests used to identify infectious organisms. Many of the tests used to identify infectious organisms in animals were originally developed as tests for closely related organisms that infect human beings. When the tests are used with animals, the results are often less reliable, increasing the risk that an animal with a negative test result may in fact be infected with the organism. The technology is now available to develop tests which analyse the genetic material of infectious organisms. Such DNA-based analysis is often more reliable than tests which measure the antibody levels in the human or animal. Antibody tests have the drawback that they do not work well in patients who are immunosuppressed and therefore have low levels of antibody. Reliable, accurate and more sensitive methods of diagnosing infection in animals and human beings should be available and regularly used before clinical xenotransplantation trials go ahead.

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[22] Onions D and Lees G, Human herpesviruses and retroviruses: problems and solutions in the safety testing of biologicals in Horaud F and Brown F eds. (1990) **Developments in Biological Standardisation**, 75:145-158.

[23] Representational difference analysis, for example, basically involves comparing the genetic material of uninfected organisms with that of potentially infected organisms: any extra material may be due to the presence of an infectious organism (Lisitsyn N *et al.* (1993) Cloning the difference between two complex genomes. **Science**, 259:946-51). Organisms can also be identified using polymerase chain reaction techniques with primers based on the sequence of organisms potentially related to the unknown organism (Compton T, Degenerate primers for DNA amplification. Chapter in Innis M A *et al.* eds. (1990) **PCR Protocols: A guide to methods and applications**. Academic Press).

Producing animals free from known infectious organisms

6.27 Because of the potential dangers of disease transmission, xenotransplant teams have sought to produce source animals free from known infectious organisms. The animals are reared in captivity and maintained in a clean environment. Individual animals are tested regularly to check levels of infection. Precautions are also taken to ensure that human beings rearing the animals do not inadvertently infect them with human diseases, such as influenza. In order to eliminate other viruses, a long-term breeding programme and intensive screening would be required. This would be a particularly lengthy process for primates.[24] In addition, it might be necessary to use methods such as delivery of animals by Caesarean section, and rearing of animals in isolation. This would have implications for the welfare of the animals (Chapter 5). Moreover, it is essentially impossible to eliminate retroviruses that have become inserted into the genetic material of the host animal (paragraph 6.9.5).

6.28 There is currently no general agreement amongst xenograft teams as to precisely which organisms should be excluded from animal sources. Thus, some xenografts have already taken place which have used animals infected with known organisms. For example, the baboons used as sources for the two liver xenotransplant recipients in Pittsburgh were known to be infected with foamy virus, a member of the retrovirus family.[25] Neither patient showed evidence of foamy virus infection during the short time they lived after their operations. Baboon foamy virus is not known to infect human beings, but some foamy viruses have the ability to infect several species. For example, some mouse foamy viruses can infect human cells. While there is no evidence to date that foamy viruses cause diseases in their hosts, some virologists nevertheless hold the view that foamy viruses should be eliminated from animals used to provide xenografts.[26]

6.29 The term **specified-pathogen free** is used to describe animals from which specified infectious organisms (pathogens) have been excluded. But, as the example above makes clear, there is no consensus about which organisms should be excluded from specified-pathogen free animals. **The Working Party recommends that a code of practice should be drawn up specifying which organisms should be excluded from specified-pathogen free animals. Xenotransplantation teams should be required to exclude from source animals all the pathogens listed in the code of practice.** Mechanisms should be in place to allow the list of organisms to be updated in the light of experience. The code of practice should recommend the diagnostic tests to be performed by accredited test centres.

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[24] Allan J S (1995) Xenotransplantation at a crossroads: Prevention versus progress. **Nature Medicine**, 2:18-21.

[25] Michaels M (1995) Presentation at an Institute of Medicine conference on Xenograft transplantation: science, ethics and public policy, Washington DC.

[26] Allan J (1995) Xenotransplantation and the infectious disease conundrum. **Institute of Laboratory Animal Resources Journal**, 37:37-48; Onions D (1995) Comments made at an Institute of Medicine conference on Xenograft transplantation: science, ethics and public policy, Washington DC.

6.30 It must be borne in mind that specified-pathogen free status can apply only to known infectious organisms. Specified-pathogen free animals may still be infected with unidentified infectious organisms about which nothing is known (paragraph 6.14).

6.31 In addition to the elimination of pathogens from the whole animal, it may also be necessary to perform tests on the organ or tissue intended for xenotransplantation to ensure that it is free from infectious organisms and, more generally, that it is of a high quality. In the case of transgenic pigs, for example, it will be necessary to ensure that the organ or tissue does indeed carry the correct genetic modification.

6.32 A regulatory framework will be needed to ensure the quality and safety of xenografts. How far would current regulations cover xenografts? The Medical Devices Directive regulates the use of some, but not all, products used for medical treatment. The Directive excludes "*transplants or tissues or cells of animal origin, unless a device is manufactured utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue.*" [27] Since most animal organs and tissue used for xenotransplantation will be viable, they will be excluded from the Directive. Human organs and tissue are also excluded from the Directive.[28] A previous report of the Nuffield Council on Bioethics has highlighted the lack of a coherent regulatory structure for controlling the quality and safety of human organs and tissue.[29] This means that there is no regulatory mechanism which could be adapted for animal organs and tissue. **The Working Party recommends that a regulatory framework is devised to control the safety and quality of animal organs and tissue for xenotransplantation.** Such regulation should require the development of protocols describing the production of organs and documentation of the production process. This would enable every stage of the production of an individual organ to be controlled and checked, from preparation of the DNA required for production of the transgenic animal to screening of the source animal and transplantation of the organ. The protocols should include archiving of serum and/or tissue samples from the source animal.

Follow-up of xenograft recipients

6.33 There is a need for thorough monitoring and surveillance of early recipients of xenografts. As described earlier, a number of xenografts involving human beings have already taken place (Table 3.1). In some cases, the life of the recipient did not

[27] Council Directive 93/42/EEC of 14 June concerning medical devices, Article 1.5(g). **Official Journal of the European Communities**, **L 169**,Vol 36, 12 July 1993.

[28] Council Directive 93/42/EEC of 14 June concerning medical devices, Article 1.5(f). **Official Journal of the European Communities**, **L 169**,Vol 36, 12 July 1993.

[29] Nuffield council on Bioethics (1995) Safety and Quality, Chapter 12 in **Human Tissue: Ethical and Legal Issues**.

depend on the success of the transplant. Thus, in one study, fetal pig pancreatic islets were transplanted into eight diabetic patients.[30] The surviving recipients of these, and other, xenografts represent good subjects for further follow-up in order to assess whether there has been any transmission of infection from the source animal to the recipient.

6.34 It is equally important to establish procedures for monitoring any future recipients of xenografts. What level of monitoring and follow-up would ensure that any signs of infectious disease are picked up early, but at the same time would not constitute too much of an imposition? It is possible to highlight a number of important features of any follow-up. Regular physical examinations with archiving of serum and, where appropriate, tissue samples should continue throughout the lifetime of the recipient. Serum samples taken from health care workers caring for the xenograft recipients should also be archived. The recipient should be required to report any serious unexplained illness. Close contacts, that is, family members, household members, sexual contacts and others with whom bodily fluids may be shared, should also be encouraged to report unexplained illnesses. Recipients should be asked to agree to an autopsy on their death.

6.35 In addition, xenograft recipients should be asked to take routine precautions to minimise the transmission of any infectious disease. They should not donate blood, tissue or organs. They should be counselled on methods of minimising the transmission of diseases, for example, by sexual contact.

6.36 The most difficult question is what procedures should be followed if it is found that a disease has indeed been transmitted from the animals used to provide organs or tissue to human xenograft recipients? In principle, steps should be taken to prevent transmission of the disease to other people. In practice, this is a very difficult issue. For a start, it is very unlikely that, at the outset, the mode of transmission of the disease will be understood. The appropriate response will depend on the mode of transmission and on how infectious the disease is. It would hardly be acceptable to isolate xenograft recipients suffering from an infectious disease, or to ask them to refrain from sexual intercourse or, in the case of a virus transmitted from parent to offspring, from having children. This highlights how difficult it would be to prevent the transmission of an infectious disease originating from xenotransplantation. It is sobering to reflect on the difficulty, despite globally coordinated attempts, of controlling and eliminating infectious diseases such as malaria, hepatitis and AIDS. This demonstrates the importance of taking steps to reduce as far as possible the risk that a new disease will emerge before trials involving human beings take place. **The Working Party recommends that standards and mechanisms for monitoring xenograft recipients and for the action to be taken in case of disease transmission should be in place before human trials begin. It should be a requirement of**

[30] Groth C G *et al.* (1994) Transplantation of porcine fetal pancreas to diabetic patients. **Lancet**, 344:1402-4.

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.

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

Conclusion

6.38 Xenotransplantation of animal organs and tissue carries with it the potential risk of transmission of disease to xenograft recipients and to the wider human population. Since the possible consequences of developing xenotransplantation are potentially very serious, the principle of precaution should apply. This requires that action is taken to avoid risks in advance of certainty about their nature. This chapter has set out what action would be required by the serious application of the principle of precaution to the development of xenotransplantation. To arrive at the necessary consensus about good practice, and the mechanisms to ensure that such good practice is adhered to, a body of expertise, of authority and of independence from the research teams at work on xenotransplantation is required. In view of the seriousness of the issues and of the public concerns about the technique, **the Working Party recommends that the Department of Health should establish an Advisory Committee on Xenotransplantation.**

6.39 One possible model for the proposed Advisory Committee on Xenotransplantation is the Gene Therapy Advisory Committee (GTAC). GTAC is a non-statutory Committee that was established in 1993 to "*consider and advise on the acceptability of proposals for gene therapy research on human subjects*".[31] Like GTAC, the proposed Advisory Committee on Xenotransplantation should combine the necessary scientific and medical expertise to examine early protocols with broader expertise to ensure that the Committee keeps in mind the wide range of issues raised by xenotransplantation. The proposed Committee should be open and accountable: qualities valued by many of those who made submissions to the Working Party. The Methodist Church wrote: *"the management and oversight of [xenotransplantation] can best be achieved through a regulatory and licensing body which is also charged with the*

[31] Gene Therapy Advisory Committee (March 1995) **First Annual Report November 1993-December 1994**, Health Departments of the United Kingdom. p 6.

task of examining the ethical dimensions of xenografts in the light of structured public discussion."

6.40 The Working Party accepts that there will be reluctance to create another Advisory Committee. But the UK Government has a good record in establishing stringent controls to monitor developments in genetic engineering. It has been possible to reduce these controls where developments have proved satisfactory over a term of years.

6.41 **The Working Party recommends that the proposed Advisory Committee on Xenotransplantation should produce guidance on best practice and revise that guidance in the light of experience. The responsibilities of the Advisory Committee should include:**

- **assembling and assessing information about the possible risks of disease transmission and, on that basis, making recommendations (paragraphs 6.24 - 6.26);**
- **establishing a regulatory mechanism to ensure that the appropriate infectious organisms are eliminated from source animals (paragraphs 6.27 - 6.32); and**
- **developing guidance on the monitoring of future recipients of xenografts and maintaining a register of xenograft recipients (paragraph 6.33 - 6.37).**

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

6.42 Animals used for xenotransplantation, the Working Party has recommended, should be protected by a system whereby the Animal Procedures Committee examines all applications to use animals for this purpose (paragraph 5.5). There will be a need for close liaison between the proposed Advisory Committee on Xenotransplantation and the Animal Procedures Committee. The Advisory Committee will be in a position to advise the Animal Procedures Committee on the expected benefits of xenotransplantation which would need to be weighed against the harm to the animals. The Animal Procedures Committee will be able to advise the Advisory Committee on the welfare implications of measures to eliminate infectious organisms from source animals.