

Chapter 3

Xenotransplantation : progress and prospects

- 3.1 A key question raised by xenotransplantation is whether or not the technique will work. In this chapter the scientific background to xenotransplantation is set out to provide a basis for the discussion of the ethical issues that follows in subsequent chapters.
- 3.2 Table 3.1 gives examples of the main xenotransplantation procedures involving human recipients that have occurred to date. A wide range of procedures has been used. Some of them are now routine, such as the use of pig heart valves to replace the patient's own defective valves. Far more ambitious and, to date, unsuccessful are attempts to replace defective human organs, such as the heart, liver or kidneys, with transplanted animal organs. There are two major practical problems that have to be faced.
- 3.3 First, there is the problem of organ rejection. When a human organ is transplanted from one individual into another, the recipient's immune system attacks the organ because it is seen as foreign (the sole exception is transplantation between identical twins). If the immune response is extreme, the organ will be rejected and the transplant will fail. This is why human donor organs are matched with those of transplant patients as closely as possible. Even with closely matched organs, however, immunosuppressive drugs have to be used to subdue the response of the patient's immune system to the transplanted organ.
- 3.4 Organ rejection becomes much more of a problem with xenografting, because of the greater difference between human and animal tissues. The more distantly related, in a biological sense, the human recipient and the source animal, the stronger the immune reaction. For this reason, attempts have been made in the US to use organs from primates, such as baboons, for xenotransplantation. Biologically speaking, primates are closely related to human beings so that problems of organ rejection may not be much more severe than those seen with human transplants. As discussed in Chapter 4, however, ethical concerns are raised by the use of primates for xenotransplantation. So efforts have been made to develop animals other than primates for use in xenografting. Attention has focused in particular on the pig for several reasons. Pig organs are comparable in size and, to a lesser degree, physiology to those of human beings, and they reproduce quickly and produce large numbers of offspring. The use of pigs as a domestic animal that is farmed and eaten is long established and many would have fewer concerns about their use for xenotransplantation as compared with the use of primates (discussed further in Chapter 4).

- 3.5 Pigs, however, are less closely related to human beings than primates. The human immune response to pig organs is rapid and severe, resulting in complete destruction of the transplanted organ. This is called **hyperacute rejection**.¹ Hyperacute rejection is so extreme that it cannot be controlled with immunosuppressive drugs. The success of pig heart valve transplantation lies in the fact that they can be treated with a preservative (glutaraldehyde) that reduces the strength of the immune response they induce.² This cannot be done with organs because they must be fully viable when they are transplanted. Instead, one promising approach for preventing organ rejection involves modifying the pig organs so that they do not cause such a strong immune response when transplanted into human beings. This is done by altering the genetic make-up of the pig by introducing human genetic material, producing **transgenic** pigs.³ There is evidence from experiments with animal recipients that the immune response is reduced when transgenic pig organ or tissue is transplanted.
- 3.6 The second problem raised by xenotransplantation is whether an animal organ will be able to perform the functions that a healthy human organ does. The heart is a relatively simple mechanical pump, so an animal heart, in principle, should be able to perform the same function. It is clearly important, however, that the animal organs are about same size as human ones. Other organs, notably the liver, have complicated biochemical functions that may differ between species. Proteins produced by an animal liver may be functionally incompatible with those of a human recipient. It is simply not known whether an animal liver will support human life. Finally, differences in life span must be considered. The natural life span of the pig is about 20 years.⁴ Would a transplanted pig organ age more rapidly than the human recipient? If so, this might lead to the need for successive transplants throughout the lifetime of the recipient.
- 3.7 The next sections describe the scope of the report and provide some background about the immune response and organ rejection. Experience with the use of primates for xenotransplantation is described. Then, the problem of reducing the immune response to xenografted pig organs is discussed, and the different approaches for overcoming hyperacute rejection are described.

¹ Reviewed in Rowe P M (January 1996) Xenotransplantation: from animal facility to the clinic? **Molecular Medicine Today**, pp 10-15, and Fabre J W (1995) Nudging xenotransplantation towards humans. **Nature Medicine**, 1:403-4.

² Marks C and Marks P (1993) **Fundamentals of cardiac surgery**. London: Chapman & Hall Medical, pp 105-9.

³ Cozzi E and White D J G (1995) The generation of transgenic pigs as potential organ donors for humans. **Nature Medicine**, 1:964-6.

⁴ Holliday R (1995) Letter to **Nature**, 378:434.

Table 3.1 Examples of the major xenotransplantation procedures involving human recipients that have occurred to date

Primates	
All operations took place in the US.	
1964	Six patients received chimpanzee kidneys. Most died within days. One survived nine months. ⁵
1964	Six patients received baboon kidneys. All died within two months. ⁶
1984	Baby Fae received a baboon heart. She survived 20 days. ⁷
1992	Patient received a baboon liver and survived 70 days. ⁸
1993	Patient received a baboon liver and survived 26 days. ⁹
1995	AIDS patient received a baboon bone marrow transplant in December. He left hospital in January 1996, at which point it was not known whether the transplant had been successful. ^{10, 11}
Other animals	
1964	The first UK pig heart valve transplant took place. Now a routine operation. ¹²
1968	Patient received sheep heart and died instantly. ¹³
1992	Patient received pig heart and survived less than 24 hours. ¹³
1994	Ten Swedish diabetic patients received pig fetal islet cells. In four patients, the pig cells survived for up to 14 months. Insulin produced at extremely low levels. ^{14, 15}
1995	Four Parkinson's patients received pig fetal neural tissue in the US. ¹⁶

⁵ Reemtsma K B *et al.* (1964) Renal heterotransplantation in man. **Annals of Surgery**, 160:384.

⁶ Starzl T E *et al.* (1964) Renal heterotransplantation from baboon to man: experience with 6 cases. **Transplantation**, 2:752-76.

⁷ Bailey L L *et al.* (1985) Baboon-to-human cardiac xenotransplantation in a neonate. **Journal of the American Medical Association**, 254:3321-9.

⁸ Starzl T E *et al.* (1993) Baboon-to-human liver transplantation. **Lancet**, 341:65-71.

⁹ Starzl T E *et al.* (1994) Clinical xenotransplantation. **Xenotransplant**, 1:3-7.

¹⁰ AIDS patient given baboon bone marrow (1995) **Nature**, 378:756.

¹¹ Baboon man leaves hospital (1996) **New Scientist**, 13 January 1996, p 6.

¹² Marks C and Marks P (1993) **Fundamentals of cardiac surgery**. London: Chapman & Hall Medical, pp 105-9.

¹³ Mentioned in Dunning J, White D and Wallwork J (1994) The rationale for xenotransplantation as a solution to the donor organ shortage. **Pathologie Biologie**, 42:231-5.

¹⁴ Groth C G *et al.* (1994) Transplantation of porcine fetal pancreas to diabetic patients. **Lancet**, 344:1402-4.

¹⁵ Nowak R (1994) Pig transplants offer hope in diabetes. **Science**, 266:1323.

¹⁶ Parkinson's pig cure. **The Times**, 15 December 1995.

Definition and scope of xenotransplantation

3.8 **Transplantation** involves the removal of cells, tissue or organs from one organism and their implantation into another organism. **Xenotransplantation** or **xenografting** refers to transplantation between different species. The scope of this report is restricted to the relatively new developments in xenotransplantation of **organs, tissue or cells**. The transfer of **molecules** between species, as in the use of pig insulin for treating human diabetics, is not normally thought of as xenotransplantation, and lies outside the scope of this report. If xenotransplantation involving organs, tissue and cells is found to be ethically acceptable, however, then it is unlikely that there will be objections to the transfer of molecules from one species to another. Conversely, even if it is considered ethically acceptable to use animals to provide molecules for human benefit, there may well be objections to the use of their organs, tissue or cells. The transfer of **genetic material** between species is also not usually thought of as xenotransplantation. It is discussed in this report in the context of the production of transgenic animals for xenografting (paragraphs 4.45 - 4.54 and 5.9 - 5.17).

The immune response

3.9 The function of the immune system is to protect the body from disease. The immune response is divided into two: the **antibody response** and the **cell-mediated response**. Both responses depend on white blood cells, the main component of the immune system.¹⁷

3.10 Any infectious organisms entering the body, such as bacteria or viruses, have molecules called **antigens** on their surface. These antigens are recognised as foreign by the immune system and an immune response is mounted to protect the body from infection. Unfortunately, an immune response is also induced by transplantation. This is because organs and tissues also have antigens on their surface. Some of these antigens vary between individuals. When an organ is transplanted from a human donor into a patient, the patient's immune system recognises the antigens on the transplanted organ as different, or foreign, and an immune response is triggered. If the immune response is very strong, the transplanted organ or tissue may be rejected. Whether the immune response occurs in response to infectious organisms or to a transplant, the basic elements are as described below.

3.11 An important element of the immune response is due to **antibodies**. Antibodies are produced by a type of white blood cell, called B-cells. Antibodies are molecules that circulate in the blood and stick to foreign antigens. This may inactivate the foreign organisms or the cells of the transplant directly, or it may enable other white blood

¹⁷ Roitt I (1994) **Essential Immunology** Eighth Edition. Oxford: Blackwell Scientific Publications.

cells to destroy them. One important consequence of antibodies sticking to antigens is the activation of a complicated reaction called the **complement** reaction.

- 3.12 Complement is a system of more than twenty different blood proteins. When antibodies stick to antigens, a reaction is triggered, with one complement protein activating the next, and so on. Ultimately, the complement proteins at the end of the chain attack the foreign organisms or the cells of a transplanted organ, punching holes in them and thus destroying them.
- 3.13 Clearly, it is important that the complement proteins do not attack the body's own cells. In order to prevent this, human cells have on their surface **complement regulating proteins** that prevent the activation of complement proteins. The most important of these molecules are called DAF, CD59 and MCP.¹⁸
- 3.14 The cell-mediated immune response depends on another class of white blood cell, called T-cells. Killer T-cells directly attack cells bearing foreign antigens, including the cells of transplanted organs, ultimately killing them. For the transplantation of human organs, the cell-mediated response of the T-cells is more important for organ rejection than the antibody response.

Preventing organ rejection

- 3.15 While the immune response is beneficial when directed towards foreign organisms, it is clearly undesirable when directed towards a transplanted organ. Such is the strength of the human immune response that transplantation of human organs between unrelated individuals was a dangerous and experimental procedure until the 1970s. There are two main approaches for reducing the immune response and preventing organ rejection.
- 3.16 First, the antigens on the transplanted organ are matched with the recipient's antigens as closely as possible in order to reduce the immune response. There are many different antigens, and each one varies widely between individuals. This means that it is almost impossible to get a perfect tissue match between individuals (except between identical twins).
- 3.17 Second, the patient's immune system can be suppressed with immunosuppressive drugs to help prevent rejection of mismatched transplants. The major drawback of immunosuppression is that it interferes with the operation of the immune system as a whole. This means that the patient has increased susceptibility to infections and to certain types of cancer. Immunosuppressive drugs work in different ways. Some,

¹⁸ DAF stands for 'decay accelerating factor' and MCP for 'membrane co-factor protein'. CD59 is a member of a group of cell surface molecules called CD antigens.

such as cyclosporin A, inhibit T-cell activity. Other drugs, for example azathioprine, reduce the numbers of T-cells. Another drug, cyclophosphamide, inhibits the production of antibodies, and prednisone reduces inflammation.¹⁹

Xenotransplantation of primate organs and tissue

- 3.18 The more closely related two species are, the more antigens they will have in common, and the weaker the recipient's immune response will be. Genetically, the higher primates are remarkably similar to human beings: the genetic material of our closest relative, the chimpanzee, differs from that of human beings by just 2 per cent.²⁰ Accordingly, many antigens are shared, and few differ. Thus, the immune response when a human receives a primate xenograft is broadly similar to the response to a poorly matched human organ.²¹ However, very close tissue matching when donor and recipient are from different species is impossible and rejection is therefore correspondingly stronger than that seen with human transplants.
- 3.19 Xenotransplantation between closely related species, where the immune response is not too extreme, is called **concordant xenografting**. Rejection of concordant xenografts, as of human transplants, is usually because of the action of T-cells. In practice, organs transplanted from concordant species are handled in a broadly similar way to human transplants where donor and recipient tissues are poorly matched. Immunosuppressive drugs are used to prevent rejection of concordant xenografts although so far with less success than for human transplants. With continuing advances in the effectiveness of immunosuppressive drugs, however, it may become possible to control the immune response to concordant xenografts.
- 3.20 Of the several attempts made in the United States to transplant primate organs into human beings, none has been successful (Table 3.1). In a series of experiments in the 1960s, patients were transplanted with chimpanzee or baboon kidneys. Most of these patients died within days but one recipient of a chimpanzee kidney survived nine months. This is remarkable, given the limitations of the immunosuppressive drugs available at that time. Due to the endangered status of chimpanzees, their use as a source of organs is no longer acceptable (Chapter 4), and attention has turned to the use of baboons. Much interest was raised by the case of Baby Fae, born with a defective heart, who received a transplanted baboon heart in 1984. Baby Fae survived 20 days. More recently, there have been two attempts to transplant a baboon liver into patients suffering from liver failure. One of these recipients survived 26 days, the other 70 days.

¹⁹ Roitt I (1994) **Essential Immunology** Eighth Edition. Oxford: Blackwell Scientific Publications, pp 348-50.

²⁰ Diamond J (1993) The Third Chimpanzee, Chapter 8 of Cavalieri P and Singer P, eds. **The Great Ape Project**. London: Fourth Estate.

²¹ Starzl T E *et al.* (1993) Baboon-to-human liver transplantation. **Lancet**, 341:65-71.

Baboon bone marrow transplants for treating AIDS patients

- 3.21 Another rather different use has been proposed for baboon xenografts. This stems from the observation that baboons, unlike most other primates, are resistant to infection with the HIV virus that causes AIDS. It has been proposed to transplant baboon bone marrow into patients suffering from the advanced stages of AIDS, in an attempt to restore the function of the immune system. This proposal has been approved by the Food and Drug Administration of the United States.²² There are, however, several difficulties with the procedure. It is not clear that baboon bone marrow will transplant successfully into human beings. There is a risk that the baboon bone marrow will attack the patient's body in what is called graft versus host disease. Moreover, it is not known whether baboon bone marrow will be able to restore the functions lacking in the patient's immune system. In addition, as described in Chapter 6, there are serious concerns about the risk that xenotransplantation of baboon tissue will enable primate diseases to pass into the human population. Nevertheless, an AIDS patient received a bone marrow xenograft in the US in December 1995.²³

Will primate organs function properly in human beings?

- 3.22 One problem in xenotransplantation is caused by the disparity in size of human and primate organs. An adult male baboon, for example, weighs only about 22–30 kg,²⁴ less than half the average weight of an adult human being, and the organs are correspondingly smaller than human organs. This means that a baboon heart would not be powerful enough to pump blood around the body of an adult human being. There is an acute shortage, however, of very small human organs for transplantation into babies suffering from heart malformations. This has led to the suggestion that primate organs might be transplanted into children as a temporary solution, or bridge, while they wait for a suitable human organ to become available. This suggestion is discussed further in Chapter 7 (paragraphs 7.22 – 7.24). Consideration must also be given to whether primate organs will be able to perform the biochemical and physiological functions required in human beings.

²² Pennisi E (1995) FDA Panel OKs baboon marrow transplant. **Science**, 269:293–4.

²³ AIDS patient given baboon bone marrow (1995) **Nature**, 378:756.

²⁴ 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.

Xenotransplantation of pig organs and tissue

3.23 The ethical and scientific difficulties in using primate organs and tissue for xenotransplantation have led to interest in using pigs, but the immune response if a pig organ is transplanted into a human being is extremely strong. Xenotransplantation of this type, between distantly related species in which the immune response is rapid and extreme, is called **discordant xenografting**. The immediate effect seen after transplantation of a discordant xenograft is called **hyperacute rejection**. This is a fast, violent reaction in which a discordant xenograft can be destroyed within minutes.

Hyperacute rejection

3.24 Hyperacute rejection occurs because human beings have antibodies in their circulation which recognise antigens on the cells of pigs and all other distantly related species, triggering a rapid immune response.²⁵ As blood flows through the animal organ, antibodies bind to the antigens on the endothelial cells lining the blood vessels of the organ. The complement system is activated and the xenograft is attacked. Complement proteins also activate the immune system's white blood cells which then attack the xenograft. Within minutes the xenograft is reduced to a black, swollen mass. Unlike solid organs, tissues such as bone marrow do not have major blood vessels passing through them. This means that hyperacute rejection is not such a problem.

3.25 For pig organs, however, preventing hyperacute rejection will be a crucial first step towards successful xenotransplantation. One promising method for achieving this is to modify the pigs genetically so that they carry human complement regulating proteins (DAF, CD59 or MCP) on the surface of their cells.^{26, 27} These are the proteins that prevent complement being activated (paragraph 3.13). The idea is that when an organ from a modified pig is transplanted into a human being, the human complement regulating proteins on the cells of the pig organ will inhibit the activation of complement. The method of modification involves introducing the human gene that produces the complement regulating protein into the pig.

²⁵ Reviewed in Rowe P M (January 1996) Xenotransplantation: from animal facility to the clinic? **Molecular Medicine Today**, pp 10-15, and Fabre J W (1995) Nudging xenotransplantation towards humans. **Nature Medicine**, 1:403-4.

²⁶ Cozzi E and White D J G (1995) The generation of transgenic pigs as potential organ donors for humans. **Nature Medicine**, 1:964-6.

²⁷ McCurry K R *et al.* (1995) Human complement regulatory proteins protect swine-to-primate cardiac xenografts from humoral injury. **Nature Medicine**, 1:423-7.

- 3.26 The process of introducing a gene into an animal is called transgenesis. It has been possible to produce transgenic animals for more than ten years. These are mostly transgenic mice used for research purposes. Transgenic farm animals are now in existence which can produce human proteins for therapeutic purposes. For example, sheep have been transgenically modified to produce a human protein called AAT (α 1-antitrypsin) which protects the lungs. Ultimately, this protein will be used to treat people who cannot produce their own AAT and who suffer from emphysema.²⁸
- 3.27 The first step is to induce mature female pigs to produce many eggs by treatment with hormones. The sows are then mated and the fertilised eggs are removed. The human gene is introduced into each egg by use of a very fine glass needle guided by a microscope. A gene transferred in this manner is known as a **transgene**. In a small percentage of animals the transgene will be incorporated into the pig's genetic material and will be expressed in every cell of the body, including the cells of the germline, so that if these animals are subsequently bred, their offspring will also carry the transgene and inherit the modification.
- 3.28 The treated fertilised eggs or early embryos are implanted into a surrogate mother, which may need to be treated with hormones to accept the implant. When the offspring are born, techniques are used to identify which ones are transgenic, and carry the desired gene. These animals usually have the transgene in only one of a pair of chromosomes (they are heterozygotes). By selective breeding, transgenic animals can be produced in which both chromosomes of a pair have copies of the transgene (homozygotes).
- 3.29 The UK company Imutran Ltd has produced transgenic pigs that contain the human complement regulating protein, DAF.²⁹ Hearts from these pigs have been transplanted into ten cynomolgus monkeys. In two of the monkeys the hearts were still beating after 60 days. In comparison, unmodified pig hearts lasted just under an hour after transplantation before they were destroyed by hyperacute rejection.³⁰ In the US, transgenic pigs containing human CD59 have been produced.³¹ Hearts transplanted into baboons lasted up to 30 hours whereas unmodified pig hearts lasted about an hour.

²⁸ Sheep to produce α 1-antitrypsin (1992) **British Medical Journal**, 304:527.

²⁹ Cozzi E and White D J G (1995) The generation of transgenic pigs as potential organ donors for humans. **Nature Medicine**, 1:964-6.

³⁰ Thompson C (1995) Humanised pigs hearts boost xenotransplantation. **Lancet**, 346:766.

³¹ McCurry K R *et al.* (1995) Human complement regulatory proteins protect swine-to-primate cardiac xenografts from humoral injury. **Nature Medicine**, 1:423-7.

- 3.30 A slightly different approach is to modify pigs so that they no longer have the pig antigens that mark them as different from human beings. The most important pig antigen is the sugar molecule galactosyl α -1,3-galactose (here called α -gal).³² This is recognised by the human antibodies which trigger hyperacute rejection. One strategy would be to remove the pig gene which produces α -gal so it was no longer present on the pig's cells. Deleting a gene from an animal requires embryonic stem cells which can be grown in the laboratory. This allows the appropriate gene to be deleted from the cells, after which the cells are placed into developing embryos. The resulting offspring will contain some tissue that developed from the embryonic stem cells and which does not contain the gene. Suitable pig embryonic stem cells are not yet available, although this approach has been used successfully in mice.
- 3.31 Since genes cannot be deleted from pigs at the moment, a different strategy has to be used in order to reduce the levels of α -gal pig antigen. This involves making transgenic pigs containing a human gene which has the effect of reducing the levels of α -gal antigen. The transgenic pigs contain the human α -1,2-fucosyltransferase gene. This gene makes the pigs produce a different antigen and a competition is set up: in producing the new antigen, the pigs produce less of the α -gal antigen that causes hyperacute rejection.³³
- 3.32 It would, in principle, be possible to breed animals containing two or more different transgenes. For example, if an animal with the DAF transgene were mated with an animal with the α -1,2-fucosyltransferase transgene, some of the offspring would have both transgenes. The hope would be that the presence of two complement regulating proteins might allow more effective complement inhibition if the organs were transplanted into human beings.

Other methods for reducing hyperacute rejection

- 3.33 A different approach is to try and make the human recipient tolerant of the xenografted organ or tissue so that an immune response is not induced. There is evidence that if an animal receives a bone marrow transplant from an animal of a different, but closely related, species, the recipient can subsequently receive other transplants from the same source animal without mounting a strong immune response.³⁴ Attempts to transplant pig bone marrow into primates have not yet been successful. In principle, however, it might prove easier to transplant pig bone marrow than pig organs since, like other tissue, it is not susceptible to hyperacute rejection (paragraph 3.24), although graft versus host disease can be a problem

³² Platt J L and Parker W (1995) Another step towards xenotransplantation. **Nature Medicine**, 1:1248-50.

³³ Sandrin M S *et al.* (1995) Enzymatic remodelling of the carbohydrate surface of a xenogenic cell substantially reduces human antibody binding and complement-mediated cytotoxicity. **Nature Medicine**, 1:1261-7.

³⁴ Sachs D H *et al.* (1995) Tolerance and xenograft survival. **Nature Medicine**, 1:969.

(paragraph 3.21). The eventual aim would be to give people bone marrow transplants from a source animal. Once tolerance was induced, other organs could be transplanted.

- 3.34 A number of other methods have been used to try and prevent, or reduce, hyperacute rejection.³⁵ One approach is to remove the antibodies that recognise pig antigens from the blood of the human recipient. In principle this could be done by passing the person's blood through a filter that contains the pig antigen. The antibodies would stick to the antigen in the filter and thus be removed from the blood. This would allow a xenograft to take place. The human recipient would eventually make more antibodies but it is possible that the pig tissue would not be destroyed at that stage. Another approach is to treat the pig organ with fragments of antibody before transplantation which cover up the antigens and stop the body's antibodies sticking to them. Finally, it is possible to try and treat the recipient with substances that inhibit the complement system.³⁶ Cobra venom factor acts as a complement inhibitor. Alternatively, one of the body's natural complement inhibitors, soluble complement receptor type 1, can be made artificially and used to try and prevent hyperacute rejection. It is not yet clear whether these methods will be useful for clinical xenotransplantation.

Other obstacles to xenotransplantation using pig organs

- 3.35 Thus, a number of methods for preventing, or reducing, hyperacute rejection are being developed. If hyperacute rejection can indeed be controlled, there will be other elements of the immune system to overcome.³⁷ Since most discordant xenografts are destroyed by hyperacute rejection, little is known about these other elements but they may have a significant role in organ rejection. First, there is likely to be an additional antibody response, less vigorous than hyperacute rejection and similar to the antibody response seen in human organ transplantation. Second, there will be a cell-mediated response, in which T-cells attack the xenograft. T-cells, however, must interact with the cells they are attacking. Since the cells of a pig xenograft are very different to human cells, the T-cells may not be able to interact with them very effectively and so it is possible that the cell-mediated response to a xenograft may be less severe, in some respects, than the response to a human transplant. Finally, xenografts, like human transplants, may be susceptible to chronic rejection. This slow process happens over months or years, and leads to damage to the blood vessels of the transplant. Even in human organ transplantation, this process is not

³⁵ Reviewed in Rowe P M (January 1996) Xenotransplantation: from animal facility to the clinic? **Molecular Medicine Today**, pp 10-15, and Fabre J W (1995) Nudging xenotransplantation towards humans. **Nature Medicine**, 1:403-4.

³⁶ Ryan U S (1995) Complement inhibitory therapeutics and xenotransplantation. **Nature Medicine**, 1:967-8.

³⁷ Bachs F H *et al.* (1995) Barriers to xenotransplantation. **Nature Medicine**, 1:869-73.

understood. Nevertheless, the UK company Imutran Ltd have announced their intention to start trials transplanting transgenic pig organs into human patients in 1996.³⁸ Xenotransplantation of pig fetal neural tissue is currently taking place in the US.³⁹

Conclusion

- 3.36 To date, attempts to treat people by xenotransplantation have not been successful. There has been recent progress in overcoming some of the difficulties in preventing xenograft rejection, but many obstacles remain. Despite advances in the effectiveness of immunosuppressive drugs, the levels of immunosuppression required to prevent rejection of primate xenografts leave patients susceptible to lethal infections.⁴⁰ The small size of primate organs is also likely to cause problems. Where xenotransplantation of pig organs is concerned, the first problem is to control hyperacute rejection. The most promising approach is the development of transgenic pigs containing human proteins that inhibit the complement reaction to a xenografted organ. Even if hyperacute rejection can be controlled, there will be other immunological barriers to acceptance of the xenograft by the recipient. There may also be biochemical and physiological incompatibilities between pig organs and human beings.
- 3.37 The current attempts to develop xenotransplantation raise the questions whether the use of animals to provide organs and tissue for transplantation is acceptable and, if so, how their welfare can best be taken into account. These questions are discussed in Chapters 4 and 5.

³⁸ Pig-to-human heart transplant slated to begin in 1996 (1995) **Nature Medicine**, 1:987.

³⁹ Parkinson's pig cure. **The Times**, 15 December 1995.

⁴⁰ Starzl T *et al.* (1994) Clinical xenotransplantation. **Xenotransplant**, 1:3-7.