Round Table Discussion

Nonhuman primates as organ donors?

Jonathan S. Allan[1]

Baboons and pigs are potential source animals for human xenotransplantation. For practical reasons, baboons have been proposed by only a handful of US surgeons to demonstrate "proof of concept". The Loma Linda paediatric heart transplant performed by Leonard Bailey in 1986 received a lot of negative publicity because of ethical concerns about "experimenting" on a newborn baby. Nevertheless, further paediatric xenografts using baboon hearts are being planned (*1*). Two baboon liver transplants were performed in 1993 and they also failed for unknown reasons. This has precluded further liver transplant studies (*2*).

AIDS activists helped to accelerate human xenograft trials in the case of an AIDS patient who received a baboon bone marrow in a high risk attempt at immune constitution (*3*). The monkey bone marrow failed to grow but the patient derived some benefit from the conditioning regimen used in preparing him for the procedure. This was not an ablative bone marrow procedure, so the patient's own marrow remained fully functional. Strong criticism of the experiment, based on a lack of significant scientific merit and the potential infectious disease risks, was voiced by many researchers, but in this case public health policy was determined by pressure from special interests. Some of these pioneering studies have done more harm than good to the xenotransplantation field because of negative publicity. On the other hand, they have made the transplant community more aware of the problems, and steered them towards using nonprimate species. There will always be a handful of individuals who want to be the first to succeed using primates, however, and this is where strict regulations can prevent new pandemics caused by cross-species infections.

Widespread use of nonhuman primates is no longer foreseen, mainly because of serious risks caused by infectious diseases naturally carried by baboons (*4*). It is also unlikely that sufficient numbers of baboons could be made available even with tremendous commitments of time and money. Currently, the largest breeding colony of baboons is at the Southwest Foundation for Biomedical Research, where there are over 3200 baboons bred for use in research. Unfortunately, breeding practices there have not been developed with zoonotic infections in mind. For example, virtually all adult baboons in this colony carry simian foamy virus (SFV) a persistent retroviral infection that has recently been found in humans who work with primates (*5*,*6*). A novel retroviral infection that can be transmitted to humans via wounds or needlesticks is not a good sign. Transplantation of tissues along with a cocktail of immunosuppressive agents would be an ideal way of transferring simian viruses to humans.

Most baboons also harbour simian T-cell lymphotropic virus (STLV), another retroviral infection that causes leukaemia and T-cell lymphomas in baboons (*7*). The human form (HTLV) probably arose from cross-species transmission from nonhuman primates (*8*). Higher rates of infection for both retroviruses and herpesviruses are found in captive colonies than in the wild, indicating that intensive breeding may adversely affect the pool of nonhuman primates. Given the breadth of persistent infections, selecting baboons in this milieu would not be good public health practice. In addition, wild-caught baboons are occasionally introduced into the breeding programme, which could seed the established colony with new infections.

Furthermore, many viral infections remain nonpathogenic in their existing hosts only to become pandemics when transmitted to new ones, as was the case with AIDS. We are currently unable to predict the outcome of such zoonotic infections in xenograft recipients, or to predict *in vivo* pathogenicity on the basis of *in vitro* studies. Most problematically, novel agents transmitted by xenotransplantation might circulate into the population for some time before evidence of new clinical syndromes comes to light through changes in disease prevalence. For retroviruses the time between infection and disease can span decades, and many thousands of people could be infected before a change in disease patterns is detected.

Preventing even some of the known infections can be expensive. The cost of developing a specific-pathogen-free (SPF) baboon colony, for instance, has been estimated at US$ 20 million, with the first 50 animals ready for donation in five to ten years.

Infectious disease risks are not equal

Most of the effort and enthusiasm for xenotransplantation has centred on pig cells and tissues for use in humans. Attempts are being made to overcome hyperacute and later rejection, but the ultimate goal of such efforts has not yet been defined. Injection of cells or tissues as a temporary measure or for use in bridging studies represents a significant risk: if the patient survives, the viral passenger can survive too, and thus transmission can occur later on.

As has been the case with most whole organ

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xenografts, human patients rarely survive for long enough to get back to a way of life that would enhance transmission. With the advent of cellular therapies, however, such as those used to treat patients with Parkinson disease, comes the prospect of long-term survival. Still, here the risk is to some extent limited by the fact that these patients are usually elderly and thus less likely than others to have a lifestyle that fosters the spread of sexually transmitted pathogens. Also, the infusion of only several million fetal porcine cells reduces the risk of viral transmission to the patient and the establishment of infection. Increasing the "dose" of foreign cells increases viral load and might result in a persistent infection. Studies are in progress on the risk to the population from pig endogenous viruses, and there is some evidence that these may not be expressed in the peripheral blood of human recipients of porcine cells (*9,10*). The same may not be true for immunosuppressed recipients of whole organs, however.

Are we creating chimeric humans?

The possibility that xenotransplantation could change human evolution in some profound way has received little attention. The interplay of species genomes through recombinational events stemming from xenotransplantation is a theoretical reality. Retroviruses are in vogue as vectors for shuttling genes into patients to treat a variety of genetic diseases. More than 200 gene transfer human clinical protocols have been registered by the Office of Recombinant DNA Activities and approved by the Food and Drug Administration. The admixture of porcine cells and retroviruses produces a favourable environment for the transduction of porcine genes by a pig endogenous retrovirus. Several studies support the notion that this retrovirus is infectious in human cells (*9,10*). Theoretically, transduced porcine cell genes might then be spliced into the human genome when the xenograft recipient is infected with a porcine endogenous retrovirus. If thousands of xenotransplants were to be carried out, this might favour the evolution of porcine-human chimeras.

Science fiction may meet reality if a selective advantage arises from some porcine gene such as a chemokine, enzyme, oncogene, or chaperone. The issue of chimerism has been discussed in the context of transferring donor lymphoid cells either as part of the xenograft (leukocyte passengers) or by bone marrow transplantation in an attempt at tolerance induction (*11*). Several proposed xenotransplants have been designed specifically to incorporate microchimerism as an adjunct to the induction of tolerance (*12*). The use of bone marrow may help xenotransplantation to succeed, but long-lived foreign lymphocytes derived from the donor marrow are likely to harbour long-lived viruses, increasing the chances of cross-species infection (*13*). If public health is to be protected, these concerns must be at the forefront of any discussions on animal species and therapeutic modality.

History has taught us that we should restrict animal transplants to lower nonprimate animals. Even if one were to screen baboons for the known pathogens, emotionally charged situations, such as the one that led to the Getty baboon transplant, would be sure to arise. For these reasons, and to avoid the danger of rogue transplanters dumping primate organs into humans, we should restrict our efforts in xenotransplantation to safer and more economical donor resources. At a recent meeting sponsored by the Organisation for Economic Co-operation and Development (OECD) in conjunction with the New York Academy of Sciences, there was a clear international consensus in favour of the use of porcine tissues and cells (*14*). From everyone except a few United States officials, there was strong opposition to the use of primates for transplants. Since viruses do not respect national borders, we must hope that the US will decide to take a leadership role in placing public health first in this burgeoning field. ■

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2. **Starzl TE et al**. Baboon-to-human liver transplantation. *Lancet*, 1993, **341**: 65–71.
3. **Exner BG, Neipp M, Edstad ST**. Baboon bone marrow transplantation in humans: application of cross-species disease resistance. *World journal of surgery*, 1997, **21**:962–967.
4. **Allan LS**. Xenotransplantation and possible emerging infectious diseases. *Molecular diagnosis*, 1996, **1**(3): 1–8.
5. **Broussard SK et al**. Characterization of new simian foamy viruses (SFV) from African nonhuman primates. *Virology*, 1997, **237**:349–359.
6. **Heneine W et al**. (1998). Identification of a human population infected with simian foamy viruses. *Nature medicine*, 1998, **4**:403–407.
7. **Moné J et al**. (1992) Simian T-cell leukemia virus type 1 infection in captive baboons. *AIDS research and human retroviruses*, 1992, **8**(9): 1667–1675.
8. **Koralnik LL et al**. A wide spectrum of simian T-cell leukemia/lymphotropic virus type 1 variants in nature: evidence for interspecies transmission in Equatorial Africa. *Journal of virology.* , 1994, **68**:2693–2707.
9. **Patience C, Takeuchi Y, Weiss RA**. Infection of human cells by an endogenous retrovirus of pigs. *Nature medicine*, 1997, **3**:282–286.
10. **Wilson CA et al**. Type C retrovirus released from porcine primary peripheral blood mononuclear cells infects human cells. *Journal of virology*, 1998, **72**:3082–3087.
11. **Starzl TE et al**. Chimerism and donor-specific nonreactivity 27 to 29 years after kidney allotransplantation. *Transplantation,* 1993, **55**:1272–1277.
12. **Greenstein JL, Sachs DH**. The use of tolerance for transplantation across xenogeneic barriers. *Nature biotechnology*, 1997, **15**:235–238.
13. **Allan JS et al**. Amplification of simian retroviral sequences from human recipients of baboon liver transplants. *AIDS research and human retroviruses*, 1998, **14**:821–824.
14. **Allan JS**. The risk of using baboons as transplant donors: exogenous and endogenous viruses. *Annals of the New York Academy of Sciences*, 1998 (in press).

New problems beget new solutions

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Professor Daar has made an excellent survey of the various issues that arise. Acceptability of the concept of xenotransplantation and the sources used in different cultural and religious systems is an important part of the discussion. The right of recipients to proper information about the risks and the opportunity involved does not overrule the right of communities to information on the risks involved for them, and to the security of knowing that reasonable precautions have been taken. The animals used also must be treated in a humane manner. The other ethical problems of priorities surrounding transplantation in general also apply. Now that rapid progress is being achieved in dealing with the immune system problems associated with xenotransplantation, and that assurance of the functional capability of suitable organs is closer, the many other issues need continuing and urgent consideration in a pragmatic manner.

Source of organs

The patient has a right to know where an organ was obtained. However, this might cease to be a religious or moral issue after a time. Although catgut is of animal intestine origin and requires the death of the animal for its production, it is so ubiquitous that no one objects to its use, and the matter does not even come up for discussion with patients. Heart valves of porcine origin, tissues of nonhuman origin stored in tissue banks for use in humans, and hormones and enzymes of porcine origin are acceptable in many societies. In others they are still not acceptable on religious grounds, but if no alternative were available the reaction might be different. A potential justification for acceptance may be that the complex preparatory process would "elevate" the material into the domain of a therapeutic device, and it would cease to be porcine. It would have been interesting to know Professor Daar's views on whether the reactions to transplants other than those of whole organs might indicate less long-term opposition to xenotransplantation than one might have anticipated. "Pseudo-rationalization" by societies is not new. Even where organs are concerned, especially those whose antigenic potential is altered by genetic manipulation, an argument could develop to facilitate their use on the lines that the organ is no longer porcine but human as it will "take" in a human. A strong middle-class demand could both facilitate and necessitate the use of such rationalizations. It is apposite to mention that there are now many patents for transgenic animals and animal materials.

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The major religions

Professor Daar has mentioned some issues arising out of religious beliefs; my comments are aimed at supplementing his.

- In Buddhism where there is belief in reincarnation, there could be conflicting views on whether the use of a nonhuman organ confers disadvantage on the human or advantage on the animal as regards the next birth. This matter has not come up for discussion, and it is unlikely that any debate would have an adverse effect on the use of animal organs.
- In Hinduism also, the pantheistic philosophies do not have any direct comment on the concept of xenotransplantation; the use of organs of bovine origin could raise a problem similar to the use of porcine organs in Islam and Judaism. However, here again demand from the middle class is likely to lead to a rationalization of use in the absence of other alternatives.
- In the philosophies and religious systems of other societies such as China and Japan, where the extraction of organs from the brain-dead may be thought by some to be dehumanizing, it is possible that implantation of a nonhuman organ may be viewed similarly.

Basic ethics

The basic principles of biomedical ethics such as beneficence, non-maleficence, autonomy and justice (among others) must apply in this field, both to the individual and to the community. There is a potential conflict, for example, between the right of a dying patient to the only available treatment and the right of the community to avoid being exposed to an unknown and possibly nonexistent threat of infection. Such arguments arose in the case of the Getty marrow transplant described by Professor Daar.

Infection

It is not necessary to debate here the whole vitally important issue of the possibility of infection and its avoidance, prevention, monitoring, diagnosis, and control in the individual or community. Suffice it to point out that host-to-donor infection or disease transmission has to be and is considered even when blood transfusion is done and homografts of any kind used. Individual patients and the community have a right to expect that all reasonable precautions are taken to ensure that such risks are lower than the risks of the illnesses for which the xenotransplants are being done. That is to say, it is choice of the lesser risk that is required here, rather than absence of risk.

The non-maleficence principle when applied to individuals and communities does call for rigour in looking for possible infections. The exposure of the widest possible range of human tissue and cell cultures to the cells and extracts from the donor animal would seem an essential step in such an evalu-

ation. It might be argued that if no infection or infestation in such tissue or cell culture (neither of which has any immune competence) occurs, then infection of the general population, whose immune systems are normal, is much less likely than infection in a host whose immune system is suppressed. The xenotransplant also has to be protected from infection by the host's organisms; in this respect grafts from gnotobiotic animals may be more susceptible (as the whole animals are) to such infection than grafts from normal animals.

Issues of rights and resources

The question of priority of rights arises when determining how health resources are used, and weighing the need for community services against that of expensive therapeutic procedures. Xenotransplantation would be very expensive, and involve the diversion of resources from activities with a much higher cost–benefit ratio. Diversion even from efforts at increasing the availability of cadaver organs might occur. It would be appropriate for the work to be done only in a few centres until reduction of costs as a result of better methodology or economies of scale is anticipated. In the transplant field the choice of patients in a situation of donor shortage is done by various methods, including the ability to pay for the organ or for the procedure. The choice may be between xenotransplantation or nothing initially. The category of treatment a patient would be offered would require the same kind of ethical balancing act doctors face at present. It would be unfortunate if xenotransplants were regarded as available only to "the poor" (who would ironically also be the least able to afford them) and the alternative of live donor or cadaver organs were reserved for the rich because it was perceived as "better".

Restrictions

The restrictions imposed on a patient fall into two categories. In the first they would be to protect the patient. The ethics and rights of this are no different from those that apply in the case of, say, patients who need total body radiotherapy or have had massive chemotherapy or immune suppression. In the second they would be to protect the community. Such restrictions might be justified, or they may be terribly wrong – as was the way in which those with leprosy were ostracized in the recent past. In the event of an unforeseen epidemic it is conceivable that quarantine of a community could be required. Action of this kind is not new, but has not been used for decades. It would have to be taken at government level. In the matter of transplant ethics it is imperative that each country be allowed to make its own ethical decisions – guided by other countries' experience. In the case of organ procurement from other animals, international codes regarding some aspects of preventing the risk of infection would have to apply. The "mad cow" problem provides a good illustration of the need for thoughtfully and imaginatively formulated stringent controls.

Rights of disadvantaged patients

From historical precedent we can expect that terminally ill prisoners or poor people, who need transplantation but have no hope of access to the best currently available, may be asked to be guinea pigs for xenotransplantation. However, the quantity and types of drugs needed, the kinds of suffering that may occur, the kinds of restrictions it may be necessary to impose on patients, as well as many other parameters, remain unknown. The rewards for the patient, even if health were restored, may be small. Are the rights of the community to have access to new treatments such that the rights of these individuals can be overlooked? Or should such experiments be seen rather as fulfilling the individual's right to any treatment that might offer some hope? ■

Putting the public at risk

Fritz H. Bach[1]

Of the many important points discussed by Daar, I shall address only one: the ethical issues raised by the fact that xenotransplantation will put the public at risk of an infectious epidemic. My emphasis on this one point should not detract from other ethical concerns related to xenotransplantation. I have been and continue to be in general agreement with Daar's writings and comments regarding xenotransplantation. This one area I shall discuss from my own perspective.

The possibility that xenotransplantation, such as from pigs to humans, could lead to an infection that spreads to the human population, possibly not unlike the AIDS epidemic, is generally accepted. Earlier in 1998, we wrote an article suggesting that a moratorium be declared on clinical trials involving xenogeneic organs, tissues and cells that involve such a risk *(1)*. That moratorium, we felt, should be in place until the public has been informed about the risk to which it will be exposed if xenotransplantation proceeds, and has had an opportunity to participate in a meaningful way in making the decision on whether and how to proceed.

This is not different from Daar's view. He states "Since the community is in a sense being put at risk, there is a real argument to consider some form of community consent." The suggestion for public involvement in the decision-making process is analogous to "informed consent" as it is obtained from individual patients undergoing an experimental procedure. We urged that research on xenotransplantation should continue actively *(1)*. In that article, we discussed the question of how the "public" might be involved in the decision-making. I return to that topic below.

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While supporting the desirability of community consent, Daar wonders whether we should "push this point", in view of two factors: first, "our inability to quantify the…risk", and second, the fact that "there is little experience in obtaining such community consent". I would like to take up both of these points.

Our lack of knowledge about the quantitative aspects of the risk of xenotransplantation does not detract from the pressing ethical need to involve the public now. One of the most important steps in our progress regarding the ethics of medical experimentation was to insist that informed consent be obtained from the patient undergoing a procedure. Our proposal that the public must have a voice in deciding under which conditions one could proceed with xenotransplantation essentially extends this concept of informed consent. Such an approach attempts to ensure that the public is truly represented on this ethical issue.

Daar's argument that we should not push public discussion now, given our uncertainty about the risk, will achieve the same result as the approach proposed by some who are against a moratorium. They have argued that since we do not know the extent of the risk of xenotransplantation, we must do a number of xenotransplants so that it can be assessed. This argument repudiates one of the most sacred tenets of informed consent: that consent must be obtained before any part of the procedure is performed. We often do not know how much risk we impose on an individual patient when asking for informed consent, and we make that fact clear to the patient in the process of obtaining informed consent. We do not say to the first patients undergoing a new procedure that we have to go ahead without informed consent so that we can assess the degree of the risk. By that logic, we would only ask patients undergoing the new procedure for informed consent after we had performed the procedure on a sufficient number of patients without such consent, in order to understand the extent of the risk. The fact that the magnitude of the risk is not known does not justify proceeding in order to find out. The decision by the individual patient, and in the case of xenotransplantation by the public, must be made while realizing that the risk exists, even though we cannot quantify it.

The argument that we must proceed with xenotransplantation in order to assess the risk has profound implications. If an infection related to xenotransplantation occurs in the human population, we will have determined that there is a risk, and we will also have created a potentially devastatingly dangerous scenario. If there is no infection in the first several years, it still does not mean that there will be no problems later. Thus, the argument that we should proceed to assess the risk in this way is proposing a potential *fait accompli*, an approach that some criticize as the general insensitivity of medicine to the public (*2*).

Ethically, can we put the public at risk in order to help individual patients? If it is not the public that decides, who should? The individuals who make such a decision cannot be those who are stakeholders in xenotransplantation, in the sense that they have a conflict of interests in this regard. As we have previously discussed (*1*), they must be involved in the decision-making but the decision should not rest with them. Nor should others who come under pressure from the stakeholders make the decision. The Food and Drug Administration (FDA) properly deals, and has dealt, with the technical issues of safety. However, that body too is under pressure from many interests.

I would thus reject arguments that our lack of knowledge about the extent of risk should reduce our insistence that there be public involvement in the decision-making prior to putting the public at risk.

There is a logical inconsistency in the rules currently governing xenotransplantation. As Daar points out, the FDA has issued guidelines that essentially exclude the baboon as a donor. This has been done on the basis, at least in part, of the perceived higher risk of infection if baboons rather than pigs are used as donors. The baboon as a donor may well pose a higher infectious risk than the pig, but in fact we do not know the extent of the risk presented by either animal. Given this ignorance, is it not somewhat incongruous to conclude that the risk of using baboons is too great while the risk of using the pig is acceptable? From the ethical point of view, both pose a risk to society and it must be society that decides under which conditions it is willing to accept that risk.

Daar's second point is that there is little experience in obtaining public opinion or consent. It is correct that public consultation is a difficult task. However, in some countries such as Switzerland, the public is consulted by referendum. There was such a referendum in Switzerland on the use of genetic engineering very recently. Many expected the public to forbid the use of such techniques. However, probably because of the excellent effort that was made to educate the public, the referendum resulted in a solid endorsement of continued use of genetic techniques. In the United States it is hard to imagine holding a national referendum, although doing it at the local level is not inconceivable. For this reason we proposed that for the United States there should be a national committee composed of individuals from a variety of disciplines, including ethics, who would try to reach a consensus on how to proceed, on behalf of the public. We have previously discussed such a national committee in detail (*1*). In fact, there is a committee not unlike the one we suggested now functioning: the President's Ethics Committee, which recently issued a report dealing with human cloning. As discussed above, the decisions of the committee should not be made by individuals with conflicts of interest or by those who are under pressure from interest groups.

The fact that we do not have much experience with polling the public in such situations should not dissuade us from developing appropriate procedures in this regard, or from proceeding in the best possible way. We face a time in which there will be increasing numbers of technologies that offer great benefit in medicine while having potential dangers that might affect the public. We will need mechanisms for handling such situations from the ethical standpoint. Xenotransplantation is a clear example of such a problem; we should use this opportunity to develop an approach to decision-making that is both responsible and ethical.

The suggestion of a moratorium to allow us to inform the public and gauge the response of society is not anti-xenotransplantation. As we wrote in a letter answering a critique of our suggestion for a moratorium: "our call for a moratorium on clinical work is not anti-science; rather it is a way of respecting the rights of the public, thus preserving the trust of the public in science" (*3*). ■

1. **Bach FH et al.** Uncertainty in xenotransplantation: individual benefit versus collective risk. *Nature medicine*, 1998, **4**: 141–144 .
2. **Beck U**. *Risk society*. London, Sage Publications, 1992.
3. **Bach FH, Daniels N, Fineberg HV.** Letter. *Nature medicine,* 1998, **4**: 372–3.

The case for using pigs

Arthur Caplan[1]

The question of whether or not to use pigs, genetically altered to minimize the likelihood of organ rejection, as sources for transplantable organs seems to hinge only on whether xenografting poses an intolerable danger to public health. As Dr Daar accurately notes in his comprehensive review of the state of xenografting, recent debates about the morality of xenografting in the United States and Europe, especially the United Kingdom, have arrived at different answers to the question based on their assessment of the public health risk posed. The decision in Europe has been that the threat to public health of disease transmission is too great, given the limited knowledge available, to justify clinical trials of any xenografts at the present time. Expert panels in the US are not so convinced of the dangers, and see the science as more promising.

In one way the differences between the American and European assessment of the morality of xenografting reflect deep cultural differences in attitudes toward biomedicine and science. Americans tend to be more positive toward the promise of science then do Europeans, who tend toward caution in their assessment of risk when it derives from scientific activities.

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Strangely, it is also the case that for all the difficulty that surrounds the computation of the risks posed by transmission of viruses and microorganisms to people from animals, questions of safety provide a framework within which scientists and policy-makers are comfortable. Attitudes and answers may differ from country to country, but there are no sticky, complex or ineffable ethical issues to tackle if the debate about xenografting can be reduced to a question of safety.

Public safety surely must be a primary consideration in deciding whether or not genetically modified animals ought be used as sources of organs for people in need of transplants. The threat of a public health catastrophe caused by a lethal virus transmitted from a pig or primate to a human transplant recipient and thence to a large segment of the human population is small but real. It is a risk that cannot be justified simply by the possibility of saving a comparatively small number of lives by means of transplants. But, as Daar correctly and insightfully perceives, the ethics of xenografting involves more than an analysis of the safety question.

Equally important questions in assessing the morality of xenografting are whether it is ethical to breed and kill pigs or other animals for this purpose; whether it is ethical to ask a human subject to face the risks, emotional as well as physical, that will attend any attempt to xenograft; or whether the psychosocial issues raised for recipients are too great to bear. Each of these issues must be answered in a way that the public finds convincing. I suspect this will require clinical research in xenografting to follow very specific protocols if it is to be an option for solving the problem of scarce supply in the field of organ transplantation.

There should be no doubt that serious risks are posed when organs from any animal are placed inside a human body. It is a well-established fact that many viral and prion agents are capable of moving from animal vectors to humans. The natural defences of the human body against viruses and other microorganisms that can be carried along in an animal organ may well be compromised when that organ comes into direct contact with the body's own internal organs and fluids.

It might be supposed that the danger posed is greatest with the earliest experiments, but this is not true. It may well be easier to manage the danger of transmission and infection by animal-borne viruses and microorganisms in the earliest stages of xenografting than later in the development of the technology. The first experiments can be done under very carefully controlled conditions. Those involved in the first xenografts can be closely monitored. Recipients can be rigorously isolated and those who come into close contact with them can be required to wear appropriate protective clothing and equipment. Animal organ recipients must understand that they will have to be under biological surveillance, undergo restrictions in living and hu-

man contact possibly for the rest of their lives and that a postmortem will be required when they die.

It will be very difficult for the first recipients to endure the safety precautions that must accompany this surgery. Still, the safety measures needed are not unprecedented, having been used in a number of other situations in which infection from human to human with dangerous agents is a real possibility. The isolation of David the so-called "bubble boy", the carefully controlled environments in which persons live after bone marrow transplants, and the special facilities used to handle persons believed to be carrying tuberculosis and other highly infectious agents all provide examples.

It is only if xenografting should prove clinically feasible that the real question of public health safety will loom large as a possible stumbling block. The same exacting monitoring and environmental control standards used for a small series of experimental subjects, chosen in part for their capacity to deal with them, will be difficult, costly and far more prone to failure when put to use in larger numbers of patients. The need for safety is not a barrier to the conduct of a small number of clinical experiments to show the feasibility of using genetically modified animals as sources of organs.

If safety can be reasonably assured for an initial series of experiments, the ethical focus on the use of animals as sources of organs shifts to the question of whether it is ethical to raise and kill them for this purpose. For many, including some prospective recipients, xenografting will only be morally acceptable if the animals do not suffer, are not rare or on the verge of extinction, and are as distant as possible phylogenetically from human beings, so that concerns about the moral standing of the animal to be sacrificed are minimized. In addition, there would need to be no other plausible alternative source of transplantable organs.

Happily, the animals to be used for xenografting at present are pigs, not primates. The fact that hundreds of millions of these animals are killed for food each year makes it difficult to muster moral outrage over their sacrifice to save lives. True, pigs are capable of suffering, and it might be argued that if pigs are genetically altered to improve the chances of transplantation success some wrong or harm is being done to them. But changes to the immune system of a small number of pigs hardly threaten to undermine the dignity or individuality of that species. To serve as sources of healthy organs, the pigs that will be sacrificed must be very carefully raised in safe and clean environments. So although pigs will be killed, the standard of their treatment and the quality of their lives will be very high prior to their deaths. Unless one believes that a human life and a pig life have absolutely equal value – a moral position that is exceedingly implausible – and once it is understood that the pigs will be very well treated and killed in a humane manner, concerns about the welfare of these animals are not sufficient grounds for prohibiting their sacrifice (*1*).

In examining the ethics of xenografting it is easy to overlook the issue of how much a subject can be asked to do. Since prospective subjects face death without a transplant and since there will be competition to gain access to a clinical trial of xenografting, there is a danger of overlooking the burden that xenografting can place upon subjects in such research.

Subjects in proposed xenografting trials will face death, but there is a real danger that the surgery could lead to more suffering and an earlier death than they would have had if they had not received an organ from a pig. In addition, the conditions required for ensuring public safety will require great sacrifice from subjects, who would not be able to preserve their confidentiality or the privacy of their loved ones in an experiment of this nature. Subjects would need to understand that in becoming subjects they may suffer more if the research fails or find themselves treated as subjects for the rest of their lives if it succeeds.

This is not to say that the risks of pig xenografting are so onerous that the experiment ought not be done, but the psychosocial issues of living with an animal organ may prove too burdensome for some to bear. Extraordinary care must be taken in subject selection, informed consent must be thorough, independent sources of information must be available to those considering serving as subjects, and persons who wish to be candidates must understand that the experiment is likely to fail.

Public health can best be protected if only a small number of experiments are conducted, and those in a rigorous manner. The ethical case against xenografting, while compelling and worthy of more public and expert debate and discussion, is not persuasive. Genetically altered pigs may not be able to save human lives but the time has come to take a tentative step to see whether they can. ■

1. **Caplan AL.** *Am I my brother's keeper?* Indianapolis, Indiana University Press, 1998.

Speculation, stringent reasoning, and science

Louisa Chapman[1]

Dr Daar has provided a cogent review of recent developments in xenotransplantation that have attracted public concern. In 1993, the US Centers for Disease Control and Prevention (CDC) began to assess such concerns in response to requests for leadership in developing a national consensus on xenotransplantation. Those chairing academic human subject review committees, struggling to adopt responsible local positions on xenotransplantation

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clinical trials, were foremost among the petitioners. By 1995, at the initiative of the US Food and Drug Administration (FDA), the agencies of the US Public Health Service (USPHS) were working together to draw up national guidelines. An initial assessment of the issues, published in 1995 (*1*), can be summarized as follows.

Infectious agents already endemic in human populations have been transmitted from donors to recipients through allotransplantation. Xenotransplantation carries a risk of transmitting infectious agents not recognized as classic zoonoses (and perhaps not capable of infecting humans under normal circumstances) from source animals to human recipients. The unusual circumstances of xenotransplantation, in which normally intact barriers are breached and the living xenograft serves as a persistent source of exposure to infectious agents, may permit transmission of xenogeneic infectious agents that do not pose a threat under normal circumstances. Once infected, the xenograft recipient may become a source patient, introducing new infections into the larger human community. Historic pandemics of zoonotic human disease, including the 1918 influenza pandemic attributed to swine influenza and the current HIV/AIDS pandemic, are precedents for these concerns.

By September 1996 a draft *USPHS guideline on infectious disease issues in xenotransplantation* had been jointly drawn up by the FDA, the CDC, the National Institutes of Health (NIH) and the Health Resources Service Administrations, and published for public comment (*2*). As noted by Dr Daar, this draft provoked an extensive critical response. A revision of the guideline, based on this public response and the interim advances in science and public policy development, should be published in the near future. Foremost among the significant changes between the draft and the revised document is the requirement that all clinical xenotransplantation trials in the United States proceed under FDA regulation. Plans have also been made for forming a National Xenotransplantation Advisory Committee, which will have, among other responsibilities, that of providing a forum for the consideration of persistently contentious issues (such as concerns about the use of nonhuman primates as sources of xenografts).

In the absence of hard data, attempts to assess risks and develop a rational policy are exercises in reasoned speculation. Prudence requires that one neither understate nor exaggerate risk when attempting to generate public discussion of these issues. As long as hypotheses remain untested, there will be a wide divergence of opinion among responsible scientists. These conditions provide an open field for sensationalism or unrealistically imaginative concerns by less responsible or less knowledgeable discussants. Responsible dialogue requires stringent reasoning with the available information. In this regard, Dr Daar has done an admirable job of walking a cautious line while attempting to facilitate public discussion of this topic.

Dr Daar refers to the assumption that xenografts procured from nonhuman primates pose more risk of transmitting infections to humans than do those procured from pigs. This issue has generated much concern among both scientists and lay people and is an area in which science at present offers inexact guidance. While the simplest solution is to call for an absolute moratorium on the use of nonhuman primates, the wisdom of imposing one on the basis of fear rather than science is questionable. A moratorium would prevent the reckless use of nonhuman primate xenografts when alternative solutions are available, but it would also prevent the use of such xenografts for selected "niche" applications that may become desirable in the future.

The assumptions implicit in the statement that "xenografts procured from nonhuman primates are more dangerous than porcine xenografts" become clearer if the statement is reversed. Can we confidently base public policy on the assumption that xenografts procured from pigs are safer (pose less risk of transmitting infection) than xenografts procured form nonhuman primates? Familiarity can lead to complacency. Prudence again argues that we recognize the limitations in our knowledge in this area. It is true that domesticated pigs have coexisted with humans for centuries while captive nonhuman primates are only a generation or two removed from the wild. It seems reasonable to deduce that the microbial flora of pigs, whose husbandry has been the subject of industrial development, is more throughly explored than that of nonhuman primates. However, the description of a newly recognized persistent hepatitis E virus infection of pigs suggests that our knowledge in this area is less than comprehensive (*3*). Likewise, it seems reasonable to argue that the phylogenetic proximity of human and nonhuman primates increases the probability that cross-species infections will be facilitated by shared cellular machinery, and epitopes retained despite evolutionary divergence. However, available data from which one may infer the evolutionary history of existing retroviruses suggest a more complex reality. Despite the phylogenetic divergence of primates, cats, and mice, gibbon ape leukaemia virus and feline leukaemia virus both appear to have evolved through the cross-species transmission of an ancestral C-type murine retrovirus (*4*).

The Swedish diabetic recipients of porcine pancreatic islet xenografts, to whom Dr Daar refers, have been carefully investigated for evidence of infection with porcine endogenous virus. No evidence of infection was found in these patients or in an additional two who underwent short-term extracorporeal connection to pig kidneys (*5, 6*). This initial investigation is a promising first step, but only the first step in what must be a laboriously developed multiphase process. The risk of xenogeneic infection will be influenced by the species from which

the xenograft is procured, the lifelong exposure history of the individual animal, the tissue used in the xenograft, and the specific application employed. The development of clinical trials employing immunoprotected cellular xenotransplants can be expected to result in longer post-hospital survival of larger numbers of xenograft recipients. These survivors are likely to have retained functioning xenograft tissue for months or years rather than days or weeks. The presence or absence of endogenous retrovirus infection in larger numbers of these recipients must be explored to develop a database with which to quantify the risk of xenogeneic infections. Existing public policies can then be refined in light of new knowledge.

We often have to choose an initial course of action based on reasoned assumptions. There is a danger, in the face of laboriously established policy, of becoming intellectually bound by early precedents. The comfort of having established policy can obscure the need to test the hypotheses and assumptions underlying that policy. For this reason, adversaries who push us to refine our reasoning, examine our prejudices, and be uncomfortable with conclusions not yet supported by science may be more valuable than allies.

Dr Daar's closing paragraph discusses the risk of expatriate experiments and introduces another important caveat. We cannot protect communities in the industrialized world by driving renegade experiments into the developing world where fewer regulatory protections may exist. Infectious diseases intermittently remind us that we are all citizens of an increasingly global community. Many recent events warn us against the illusion of being protected by geopolitical boundaries. They include:

- the importation of Lassa fever from Nigeria to Chicago in 1988 by an infected person (*6*);
- the importation of Ebola Reston fever from the Philippines to Reston, Virginia, in 1989 and 1990 by infected nonhuman primates (*7*);
- the importation of malaria into the United Kingdom and the United States with subsequent secondary transmission (*8*, *9*);
- the establishment of endemicity after the introduction of HIV/AIDS initially in Africa, subsequently in the United States and Europe, and most recently in Asia (*10*).

For residents of industrialized countries, the prevention of renegade experiments in the developing world is as much enlightened self-interest as benevolent regard for our fellow residents on this planet. ■

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Legal and regulatory issues

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The review of developments and key issues so admirably presented by Professor Daar raises concerns of appropriate legal and regulatory responses at three levels, namely governmental, clinical and social.

Governmental approaches

Developments in medical technology need not necessarily induce a legislative or regulatory response. Professor Daar notes that the field of xenotransplantation is moving very rapidly. This may caution governments against rushing to legislation that risks being overtaken by events, thus denying benefits to those whose interests governments claim to serve. Such a rush could, for instance, freeze governments into ill-considered positions, shaped perhaps by misguided stereotypes or imaginary horrors that are irrational and become increasingly indefensible. We have recently seen how moral panic over prospects of human cloning has resulted in demands for prohibitive laws that would endanger respect for values such as the right to freedom of therapeutic and academic enquiry, the right to reproductive choice and the right to benefit from scientific advances.

Nevertheless, the concerns Professor Daar raises include risks to recipients of animal organs and cells, as well as to their companions and the public at large, that justify governmental scrutiny. The contrast is presented between the regulatory approach recommended in the United Kingdom by the Kennedy Report (*1*) and the advisory approach favoured by the United States Institute of Medicine (*2*). The regulatory approach depends on legislation that empowers a regulatory agency to approve or reject prospective xenotransplants. It protects potential recipients against their own and others' disre-

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gard of dangers arising from xenotransplantation, and it protects family members and others whom patients might expose to animal-derived infections, and the wider public. This approach may be criticized for being paternalistic, but people who in other regards are competent adults may feel that they have only an infantile understanding of the scientific implications of xenotransplantation, and appreciate informed regulation of this technology. This is particularly so if they see the technology as being promoted by commercial rather than therapeutic interests.

The advisory approach favours informed, autonomous choice rather than governmental direction. An advisory council can often be legally constituted under existing governmental powers, but legislation may be required for payment of council members and administrators. If public health authorities or public clinics incorporate advisory council recommendations into their practices, principles of administrative law may apply. If their decisions affect patients' or staff members' legal rights or legitimate expectations, for instance to receive or render appropriate treatment, the persons concerned may be entitled to contradict advice and oppose recommendations before final decisions are made. Public authorities whose decisions affect others' legal interests cannot voluntarily surrender their duty of judgement to another agency like an advisory council.

Though not directly legally binding, advisory council recommendations can have legal effects through the professional licensing of health care providers, and through private service contracts. Professional licensing authorities may consider disregard of such advice to constitute professional misconduct, and impose disciplinary sanctions such as the withdrawal or suspension of a licence. Similarly, it may be a written or implied term of a service contract that performance will follow such advice, and disregard may amount to breach of contract and justify its termination. Accordingly, advisory council recommendations on xenotransplantation can have serious but indirect legal consequences.

Clinical approaches

Professor Daar refers to the controversy over whether we are ready to embark on large-scale clinical trials of vascularized whole organs. It has become common to expect that new medical technologies will be introduced through "clinical trials", and proceed only with caution and due ethical reflection. In the United Kingdom, for instance, the Clothier Committee on gene therapy recommended that, at least initially, somatic cell therapy should be regarded not as ordinary medical practice but as clinical research (*3*). Many procedures that are undertaken only for research purposes are performed in clinical settings. So also, however, are many innovative therapies designed primarily to offer seriously ill patients perhaps their only chance of survival. Xenotransplantation itself will probably initially be offered only to patients close to death. Professor Daar describes Dr Thomas Starzl's 1992 baboon-to-human kidney transplants, and observes that "the experimental nature of these attempts naturally leads to the selection of very sick persons; thus the first recipient was a patient with advanced AIDS and near-terminal hepatitis."

A legal and regulatory concern is whether clinical trials of proposed life-saving innovations are governed as research or as therapy. A proposed distinction between "therapeutic research" and "nontherapeutic research" has been condemned as illogical and harmfully confusing (*4*). Research and therapy are usually distinguishable in law and in regulatory provisions. Research is undertaken for development of generalizable knowledge *on* people rather than *for* people who may be patients. It requires preliminary approval by committees that review proposals on ethical grounds (*5*). Some procedures may require additional approval. For instance, Professor Daar describes the detailed review undertaken in 1995 by the US Food and Drug Administration (FDA) before an experimental baboon-to-human bone marrow transplant was performed, with apparent success.

In contrast, therapy, including innovative therapy, is practised upon adequately informed patients for their personal benefit. Its outcome, whether successful or not, may be of considerable interest to other therapists and the research and wider scientific communities, but its primary purpose is to advance the health interests of the sick patient whose attending clinician judges it to be clinically appropriate. The proposal and performance of procedures intended as therapy constitute the practice of medicine. Those legally unqualified for this within a jurisdiction, including lay members of research ethics review committees, are entitled neither to practise medicine nor to veto the proposals made to their patients by those who are qualified.

Innovative proposals to desperately ill patients do indeed often require ethical review, and this is what the FDA may have accomplished in 1995 in the baboon bone marrow case. There is a tendency to describe proposed innovations such as gene therapy, as "research" in order to bring them before research ethics review committees, in the absence of alternative means of ethical review. However, such committees have no authority over therapy. Where laws or regulations govern therapeutic procedures, for instance because they are innovative or controversial, health care providers are expected to comply. However, when patients are facing death with no alternative means of relief, disregard of such laws or regulations may be found legally excusable. There is a long history, for instance, of physicians being acquitted of serious criminal charges for disregarding the legal prohibition of abortion on the grounds that their procedures were necessary to save their patients' lives (*6*).

In this context excusable conduct is unlawful even when held not to warrant judicial sanction.

Professional licensing authorities may therefore impose disciplinary sanctions, since their mandate is not to punish but to protect the public against unethical conduct. Performing xenotransplantation in breach of the law and without prior ethical consideration may be classed as medical professional misconduct. Lawyers cannot advise unlawful conduct, and must inform clients of its illegality. They may also inform clients, however, that a court of law might find a certain action excusable although licensing authorities might not. Accordingly, whether initial instances of xenotransplantation are characterized as research or as attempts at life-preserving therapy is a matter of legal and regulatory concern.

Social approaches

Xenotransplantation may be presented as a means to reduce the serious gap between the supply of transplantable organs of human origin and the demand for them. Some legal or regulatory oversight of this biotechnology may be required, however, to ensure that use of animal organs does not cause prejudice to patients on waiting lists for human organs, and that the potential benefits of xenotransplantation are fairly assessed. Prejudice may arise when patients who agree to receive xenotransplants as therapy suffer organ rejection, and thereby move into a category of need that affords them priority over other patients on the same waiting list. Rules governing assignment of patients to priority status on the list should be developed to counter strategies by a patient or physician that prejudice the patients who are pre-empted on the waiting list for therapeutic transplantation by one who has accepted xenotransplantation.

It has been seen that more experimental procedures, such as Dr Starzl's baboon kidney transplants, may be considered acceptable and natural only for patients close to death. The modern history of transplantations of artificial hearts and human hearts, for instance, shows their justification as means of last resort offered to patients nearing death (*7*). Necessity may explain resort to desperate and unproven medical interventions. However, there is a risk of inadequate assessment of new medical technologies when their initial use in research is limited to patients in whom alternative means have failed, and whose health is so compromised that they are liable to succumb even if the novel intervention were otherwise able to succeed. "Last chance" interventions limited to treatment only of the most severe or hopeless cases, involving patients least likely to be helped, do not test a research intervention adequately. Social interests in acquisition of scientific knowledge about the potential of xenotransplantation require that the procedure should not risk being discredited by regulations or practices that confine its use to patients at the most advanced stage of deterioration. Laws or regulations should allow patients to approve xenotransplantation research at earlier stages in their illness.

Professor Daar discusses the risk of infection that explains why organs from non-human primates such as baboons and chimpanzees may be contraindicated for transplantation into humans, but elsewhere he has also reviewed the cultural considerations that underlie discomfort with use of organs from sources so close to the human species (*8*). He writes of the part played by "the emotional attachment that human beings have to them" that leads to rejection of non-human primates as sources of organs for human recipients. This emotional attachment may be parallelled by a need for detachment. We can perhaps accept transplantation of pigs' organs into humans because we know we are not pigs, but the prospect of non-human primates as organ sources raises the issue of uncomfortable similarities between all of the walking apes (*9*). Sigmund Freud once explained that the smaller the real difference between two peoples, the larger it looms in their imagination. This may explain why a group's capacity to esteem itself is dependent on an ability to emphasize trivial distinctions from others (*10*), which Freud described as the narcissism of minor difference (*11*).

In Canada, research ethics boards constituted under a new joint policy statement of the three federal research councils concerned will increase the number of representatives of social sciences participating in the ethical review of medical research (*10*). Further, the Industrial Biotechnology Association has established an ethics committee (*11*) to examine ethical aspects of biotechnology in a broad context. Exposing xenotransplantation to widely reflective review offers a prospect of biomedical advance that is consistent with social values and conscience. ■

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The process of discovery

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Questions about xenotransplantation are often posed philosophically, in terms of right and wrong. This approach contrasts with the rest of evidence-based biomedicine, which rarely provides absolute answers to questions of merit. Should xenotransplants be performed? Do the potential benefits outweigh the theoretical risks? In general, such questions are examined in the light of current biological knowledge, and are subject to revision over time. As our database develops, hypotheses are reformulated. Certainty does not exist. Thus, when allotransplantation was introduced, knowledge of the infectious risks associated with immune suppression was rudimentary. Data about infection in allotransplantation has grown rapidly with basic science and clinical experience (*1*). This relatively recent information was central to the discussions on the risk to the individual (potentially great) and to society (thought to be small) when the transplantation of baboon marrow into a human with AIDS was reviewed for the Public Health Service in the United States. Those discussions were coloured by passions about science, AIDS and individual rights, but they resulted in a far safer experiment in terms of risks of infection. They were also of benefit for more general considerations of clinical xenotransplantation.

The term "xenosis" was coined to reflect not only the experience in allotransplantation, but also the unique epidemiological aspects of interspecies transplantation – the potential transfer into the general human population of novel or unknown pathogens derived from animal donors (*2–6*). In terms of basic science, the search for such novel organisms has already had a beneficial effect on studies of the microbiology of transplantation, for example the isolation and sequencing of the first full-length porcine endogenous retrovirus (*7*) and to virological studies which suggest the ability of such organisms to infect human cells *in vitro* (*8–10*). Such data have been used by the US Public Health Service, and by corporate interests, to develop testing strategies for pigs raised as potential xenograft donors. Such studies and discussions have also made it clearer to most investigators that infection is a critical consideration in the development of clinical xenotransplantation.

Further studies are likely to find additional new, and possibly pathogenic, organisms in xenograft donor species, and the potential for human infection can be assessed for each. This discovery process adds to our understanding of the risks of xenotransplantation, and of the microbiology of immunocompromised hosts in general. It is a part of the evolution of the science of xenotransplantation. Microbiological guidelines for xenotransplantation should therefore be devised, to indicate what is currently known about infection for such procedures, and serve as a basis for future scientific investigations.

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Benefits of xenotransplantation

The benefits of xenotransplantation must be seen in the light of the limitations of currently available technologies. Many patients die while awaiting cadaver donor organs. Cadaveric donors provide life-saving opportunities for a small number of fortunate recipients, but the organs have often been subjected to hypoperfusion, infectious contamination, or injury during surgical procurement. All of these are problems which may be eliminated by the use of planned xenotransplants. Allograft recipients may suffer from chronic infection or debilitation but these problems could be reduced if elective transplantation could be scheduled, as it is currently for living donor transplants. In addition to their potentially unlimited availability and correct size, xenogenic organs may be resistant to infection with viral pathogens of humans, including HIV (1 and 2), HTLV, hepatitis viruses, and herpes viruses – including human cytomegalovirus (CMV), which has been shown in our laboratory to be unable to infect porcine cells *in vitro* (*11*). Further, human hepatitis B virus does not appear to infect baboon *in vivo* (*12*). While such protection is unlikely to be observed for all potential pathogens, it may provide a significant advantage to patients with organ failure due to viral infection.

Assessing the risks

The central goal of infectious disease physicians in transplantation is disease prevention, given the poor clinical response of the immunocompromised host to established infections. What types of organisms should we be concerned about in xenotransplantation? As in the case of allotransplantation, the following points are fundamental to the assessment of the risks of infection in xenograft recipients.

- All organisms are a potential cause of infection in any species, but the organisms most likely to cause infection are the ones that are similar or identical to those that do so in the immunosuppressed human allograft recipient, in addition to species-specific organisms not associated with human tissues.
- The risk of infection is a direct function of the overall level of immune suppression needed to maintain allograft function and the nature and intensity of the epidemiological exposure of the recipient. The minimization of immune suppression (for instance by tolerance induction strategies such as bone marrow transplantation) may significantly reduce the risk of infection if it does not increase the exposure of the recipient to donor-derived organisms or reduce the immune response to such organisms.
- The manifestations of infection in the xenograft recipient will also be modified by the type (such

as corticosteroids, antilymphocyte therapy or ciclosporin), intensity and duration of the immune suppression needed to sustain organ function, and by the clinical status of the recipient following transplantation.

A number of additional factors conspire to increase the risk of infection in xenotransplantation:

- the xenograft itself serves as a nidus or "culture plate" from which such organisms can spread in the human host without needing a "vector" to achieve disease transmission;
- clinical laboratory tests for most organisms derived from non-human species (e.g., antibodies, molecular probes, culture systems for species-specific organisms, or serological tests for human antibodies against animal pathogens) are not generally available;
- the migration of cells from the graft to other sites in the host may carry cell-associated infection throughout the host;
- clinical syndromes caused by new pathogens are not necessarily recognizable;
- little is known about the behaviour of potential pathogens from the donor species in humans;
- graft rejection and immune suppression are strong stimuli for the activation of many organisms from latency;
- genetic recombination, mutation, or interactions between exogenous and/or endogenous organisms may mask or alter the common manifestations of infection;
- the absence of pre-existing immunity in the recipient to novel, animal-derived organisms may render the host more susceptible to infection;
- species disparity of histocompatibility antigens may be associated with diminished cellular immune function by the host against organisms within the xenograft (*4*).

Which organisms should we fear?

The organisms of greatest concern to the general public are those which spread easily between immunocompetent individuals, which can attach to and enter human cells, which can replicate within these cells or tissues, and which can spread with few clinical signs or symptoms. The ideal "stealth organism" takes on surface antigens from the host so as to reduce the capacity of the host's immune system to attack the pathogen. The organism must also cause disease (injury) directly or must develop pathogenic characteristics in the xenograft recipient so as to justify concern about its spread in the general population.

The endogenous retroviruses, like the betaherpesviruses, are almost perfect transplantation pathogens. The endogenous retroviruses are carried in the genome of every cell, acquire host antigens while budding off from infected host cells, and require cell-mediated immunity for clearance, which is diminished by immune suppression of the transplant recipient. However, there is no clear association of the porcine retroviruses, as yet, with clinical disease, infection of normal or immunocompromised individuals, or spread between individuals. All retroviral assays to date (unfortunately largely based on anecdotal reports) have been negative in terms of infection of humans exposed to porcine tissues (*12–14*). Preclinical studies of xenotransplantation will be important in defining the risk of spread of infection between species and the factors which control viral replication. However, preclinical models (e.g. pig-to-primate) may not predict the infectivity or all the manifestations of disease which may occur in human xenograft recipients.

The available data have not demonstrated risks which should impede measured progress towards further studies of clinical xenotransplantation. However, further microbiological studies of xenograft tissues or cells from human recipients may be very revealing, and are of critical importance. To this end, new molecular or antigen detection assays for known organisms of donor species are needed. Each approved clinical trial must also be designed to optimize the possible recovery of novel organisms and should not be limited to searching for previously identified organisms. Therefore, biopsies and blood samples must be collected from xenograft donors and recipients not only for archiving but for use in an active programme of microbiological investigation, including the search for unknown organisms (for instance by representational difference analysis) and studies of the biology of such potential pathogens. It seems likely that new organisms will be discovered in association with the transfer of animal tissues into immunocompromised or otherwise modified human hosts, just as novel infections have been described in association with the immune deficits of AIDS and cancer chemotherapy. Rather than being guided by fear of the unknown, we must not squander a unique opportunity for discovery. ■

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Xenotransplantation in Sweden

C.G. Groth[1] & M. E. Breimer[2]

Several Swedish research groups are working actively in the field of xenotransplantation. Recently, these efforts have resulted in two clinical pilot trials: 10 diabetic patients have been transplanted with porcine pancreatic islets, and two patients have had pig kidneys connected to their blood circulation and perfused extracorporeally.

Transplantation of porcine islets

Transplantation of isolated pancreatic islets offers a simple and safe method to provide the diabetic patient with insulin-producing tissue. If such transplantation is to be widely applied, the supply of human pancreases will not suffice. Transplantation of pig islets could then serve as an alternative. Porcine insulin differs from human insulin only in regard to one amino acid, and glucose homoeostasis and the regulation of insulin secretion are similar in pig and man. Furthermore, porcine insulin has been used for decades to treat diabetic patients. Since the transplanted islets will become vascularized by host vessels, hyperacute rejection should not occur.

Fetal porcine islets can be prepared in large quantities by tissue digestion and culture. After transplantation, the fetal cells mature and differentiate into insulin-producing cells. Microbiological screening revealed no infectious agents in the material, and, when the material was injected intraportally in dogs, no adverse effects were noted.

On the basis of the above findings, a clinical pilot trial was conducted in the years 1990–1993 in 10 diabetic renal transplant patients. All patients were given immunsuppressive treatment because of their renal transplant (*1*). Eight patients who had previously undergone kidney transplantation had the porcine islets injected into the portal vein. Four of the patients excreted small amounts of porcine C-peptide for 100–400 days after transplantation, indicating porcine insulin production. In two patients, the islets were placed under the capsule of their renal graft just after the graft had been revascularized. In one of the patients, a kidney biopsy specimen taken three weeks after transplantation revealed morphologically intact epithelial cells under the kidney capsule. These cells stained positively for insulin and glucagon. Ultrastructural and immunocytochemical features were typical of pancreatic islet cells; the appearance of the cells indicated that they were viable (*2*).

All patients had preformed xenoantibodies against the Gal 1,3Gal, an antigen epitope present on porcine but not on human cells. After transplantation there was a pronounced increase in the antibody titres (*3*). The finding that the porcine islets did not function at all in some patients, and only for a limited time in the others, probably indicates rejection. The role of the xenoantibodies in this process remains obscure.

The patients derived no clinical benefit from the transplantation in that their insulin requirements remained unaffected. A larger and longer-lasting insulin production will be required to accomplish a clinical benefit. Recently, we have isolated adult pig islets which provide immediate function. When such islets were transplanted into unmodified rats, rejection occurred in 4–5 days. However, when the rats were treated with novel immunosuppressive drug regimens, rejection was prevented for several weeks (*4*). These encouraging findings will provide the basis for further trials with pig-to-human islet transplantation.

Extracorporeal (ex vivo) perfusion of pig kidneys in two patients

Removal of the preformed xenoantibodies by immunoadsorption, or plasmapheresis should facilitate xenograft survival. In order to test this concept, we performed a clinical trial in 1995 where pig kidneys were extracorporeally connected to the blood circulation of two volunteer dialysis patients. The procedure was similar to an ordinary dialysis, except that the dialysis filter was replaced by a pig kidney. Prior to the procedure, the patients underwent plasmapheresis with a subsequent reduction in xenoantibody titres. No immunosuppressive drugs were given (*5–7*).

Initially both the pig kidneys perfused well, and produced urine. However, after 65 minutes of perfusion, the first kidney underwent rejection as evidenced by discoloration and a reduction in blood flow, and the experiment was discontinued. The second patient developed symptoms of anaphylaxis after 15 minutes of perfusion. The pig kidney appeared normal at this time but the perfusion was terminated for safety reasons. Histopathological examination of the first kidney confirmed the diagnosis of rejection,

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while there was no histological evidence of rejection in the second case. In both kidneys, there was a pronounced entrapment of platelets. In the second patient, analyses revealed an activation of the complement cascade, this presumably contributing to the symptoms that appeared. Both patients developed a marked increase in their anti-pig antibody titres, the antibodies displayed specific patterns regarding class and subclass (*6*). Further pertinent scientific questions are currently being examined using material from these two experiments.

The aim was to proceed with perfusion experiments, using kidneys from transgenic pigs carrying the human complement regulator, h-DAF, which counteracts hyperacute rejection. However, a United Kingdom Government report published in 1996, outlining the possible risks of viral transmission from pig to humans, led to a moratorium on further trials with pig organs in Europe. Of particular concern was the possibility that porcine endogenous retroviruses (PERV) would be transmitted.

In the meantime, blood samples from the 12 Swedish patients who had participated in the clinical xenotransplantation trials have been examined for evidence of PERV infection by using polymerase chain reaction (PCR) and transcriptase assays. The findings were negative in all patients (*8, 9*).

In conclusion, the two pilot trials conducted in Sweden have provided important information concerning immunological and physiological consequences of transplanting porcine tissue to humans. Furthermore, they have provided a unique opportunity to assess the risk for transmission of PERV in the context of xenografting. ■

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Stop now before it's too late

André Menache[1]

Animal-to-human organ transplantation (xenotransplantation) did not originate in a vacuum. It is the net result of a fundamental assumption by the medical establishment that the solution to most of society's health problems lies in the development of ever more expensive, complex and sometimes risky technologies. Thus, historically, the first transplant of a human heart in 1967 was widely hailed as modern medicine's supreme achievement, despite the fact that the patient died not long afterwards.

Today, human-to-human organ transplants are becoming more routine but they are far from being a perfect solution to the health problems they are supposed to solve. Many patients still die as a direct result of complications from the transplant, and others describe their lives as a living hell due to the polypharmacy regime and lifestyle restrictions that are forced upon them (C. Ray Greek, personal communication).

If human-to-human organ transplants are still fraught with complications, animal-to-human organ transplants are taboo, or they should be. Transgenic transplants actually represent one experimental technique (the production of transgenic animals) superimposed on another (the transplantation of transgenic animal organs into human beings). Attempts to analyse the possible outcomes of this situation lead to a statistical nightmare, since there is an exponential increase in unknown risks.

Although the consequences of xenotransplantation are far from being well understood, the public is being led to believe that the main obstacle – foreign organ rejection – can be overcome on the basis of earlier experiments in which monkeys receiving transgenic pig hearts survived for 60 days. Modern medicine still has great difficulty matching human tissue types, let alone animal tissue types.

However, a more serious public health consideration is that of disease transmission from animal to human, and subsequently to the general population. A worst-case scenario could mean another AIDS-like epidemic, with little promise of containment, given the difficulty of carrying out environmental impact studies beforehand. Overwhelming scientific evidence is now available to show that xenotransplants represent an *unquantifiable* risk to the health and well-being of the general public (*1*).

As Murphy put it, "It will not be easy to determine which viruses represent a risk to the xenograft recipient alone, which represent a risk to society as a whole as a result of species-jumping, and which may be dismissed as representing a minimal risk" (*2*). Equally disturbing is the well-publicized statement made by another US veterinary virologist, Jonathan Allan: "This is a serious mistake…it only

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takes one transmission from one baboon to a human to start an epidemic. There's no way you can make it safe" (*3*).

Despite these and other clear warnings not to proceed with xenotransplants, the United Kingdom health authorities have decided, nevertheless, to "proceed with caution" with pig-to-human organ transplants (*4*). It is truly ironic that these health authorities, which go to extremes to protect the public from importing the rabies virus are now prepared to expose that same public to an "unquantifiable" risk by transplanting known and unknown pig viruses into people (*2*).

The situation in the US is actually far worse, since xenotransplants have already taken place, unopposed by either the Food and Drug Administration (FDA) or the Centers for Disease Control and Prevention (CDC), the very bodies whose stated policies are to protect the health of the public. Despite the fact that almost all of the patients who received animal organs died soon after their operation, and despite the fact that FDA public health policies have always been "risk averse" (i.e. against research methods that are not well understood), the US Government continues to allow xenotransplants to proceed. In 1984, Leonard Bailey transplanted a baboon heart into newborn "Baby Fae" at Loma Linda University, despite the fact that a proven surgical repair technique could have been used instead of the high-risk baboon heart. In addition, a human heart was available at the time. Also, the majority of medical opinion at the time was against the idea of using a baboon heart at all (*5*).

Should society condone such unethical behaviour? The public has been presented with a dilemma by the medical establishment: organ transplants can save lives, but there is a shortage of suitable human organs. Clearly, the idea of using animal organs is tempting, but on the basis of its abysmal track record, plus the Pandora's box of unquantifiable risks involved, xenotransplants cannot be the answer.

Then there are legal questions which have so far not been answered. For example, who would be responsible for paying compensation to persons who are damaged as a result of the animal organ inside them, or to secondary victims exposed to the viruses xeno-recipients transmit? A further major obstacle, which must be overcome before xenotransplants can proceed, is how to obtain the "informed consent" of the general population, since xenotransplantation puts not only the recipient at risk, but also the general public.

The best long-term solution to organ transplants in general is preventive medicine, in the widest possible meaning of the term (obviously, this does not apply to those in need of an immediate organ transplant). Several alternatives exist, although none provides a complete solution. There is an urgent need for governments to invest more in preventive measures (such as improved diet and lifestyle patterns, anti-smoking campaigns, and the like) in order to reduce future waiting lists to the point where supply meets demand.

Allotransplantation (human-to-human organ transplantation) is still the best that modern medicine can offer the end-stage organ failure patient. From a purist medical perspective, however, organ transplants with a few exceptions are an admission of failure, on three counts:

- failure to diagnose a disease condition correctly in the early stages;
- failure to provide the correct therapeutic regimen despite a correct diagnosis;
- failure to implement corrective preventive measures (*6*).

The result of all these failures is a serious shortfall in the number of suitable human organs available for transplantation. Several schemes exist to increase the number of human organs available. For instance, so-called "opt-out" schemes as practised in Austria and Belgium, can increase the availability of human donors. However, any organ-donation scheme must be accompanied by strict hospital protocols to fulfil all the criteria of "brainstem" death, and the necessary written informed consent, before a donor's organs are removed.

Even where these schemes are used, the demand for organs still far outweighs the supply. However, before rushing for animal organs, there are other options well worth considering. Artificial organs are still in their infancy, but they can provide a temporary substitute, or "bridge", until a suitable human organ is found. In some cases, artificial organs already provide a permanent solution (e.g. part-hearts). From a public health perspective, artificial organs are far superior to animal organs, because they are essentially disease-free. Indeed, research funding would be better spent on developing these more promising technologies than on xenotransplantation. There are also other alternatives to xenotransplants available today, some of which are already in use, such as the successful transplant of a liver lobe from a mother to her child in need of a total liver transplant. Similarly, cells from a particular organ can now be cultured into cell aggregates in the laboratory, to provide a "part-organ" as a substitute, in some cases, for a conventional organ transplant. Also, cell injection may help some liver diseases, as recently reported in the *New England journal of medicine*.

Viable alternatives to animal organ transplants do exist, but they need to be explored in much greater depth. The present situation, whereby xenotransplantation is being allowed to proceed despite alarm bells ringing, is both untenable and intolerable and should be challenged on several fronts: in the media, in court, and in scientific debate. "Seldom, if ever, have we had as much knowledge to prevent a future epidemic. What is lacking is the wisdom to act upon that knowledge" (*7*).

Xenotransplantation is still a dangerous and highly experimental technique, about to be unleashed on an uninformed, and possibly also misinformed public, against its will. ■

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Current obstacles

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I read Professor Daar's article with considerable interest. He adopts a conservative stance on the question of clinical trials of animal organs in humans at this point in time, and I must say that I would join him in this stance.

There is no question about the demand for more organ transplants as the numbers of patients with end-stage organ failure awaiting kidney, liver, and heart/lung transplants grow all over the world. Indeed many patients are dying while waiting for liver and intrathoracic transplants. Furthermore, if type 1 diabetes could be cured either by whole organ pancreas transplantation or pancreatic islet transplantation using minimal and safe immunosuppression, there is no way that the supply of human organs could meet the demand. Hence there is no doubt about the attraction of transplanting organs from animals into man. Nevertheless, there are major barriers to be overcome before this is possible, and some people would consider some of these barriers to be insuperable.

The obstacles to successful xenotransplantation are immunological, physiological, infectious, anatomical and ethical. The pig, at the moment, is the animal of choice as a donor, for, as Professor Daar points out, anatomically its organs are of a size appropriate for the human, physiologically they do not appear too dissimilar, and as much of the world's population eats pork there are relatively few ethical or cultural objections to the pig as a potential organ donor.

Among the immunological problems the first major barrier is the problem of hyperacute rejection mediated by natural cytotoxic antibodies in the presence of complement to a xenoantigen (known simply as the Gal antigen). These cytotoxic antibodies are present in man and in Old World monkeys (from Europe, Asia and Africa), as the Gal antigen is not expressed in these species. Thus a pig organ transplanted into man would undergo rejection within minutes. Major advances have been made in attempts to overcome hyperacute rejection such as the production of pigs expressing a human complement inhibitor on endothelial surfaces. Other molecular biological approaches to this problem have also been developed which suggest that the problem of hyperacute rejection of a pig organ may have been essentially resolved. However, less immediate but no less severe degrees of rejection, such as accelerated vascular rejection, conventional cellular rejection, and chronic rejection, will undoubtedly prove to be a problem, which may require heavy immunosuppression to overcome.

On the anatomical and physiological side there is a question of the size of the organ and its work capacity, its behaviour in an upright human compared to a quadruped, and of course whether proteins produced by the pig organ (e.g. erythropoeitin by the pig kidney) will react with human receptors. These latter problems are likely to make xenotransplantation of a pig liver impossible, in view of the fact that the liver produces some 1000 proteins, all of which would be foreign to man.

With respect to the transmission of infection, a major concern is the possible transfer of porcine endogenous retroviruses, and although there is no evidence yet that this has occurred in humans exposed to pig tissues, such as islets, it is by no means excluded, and indeed transfer of the virus of porcine endogenous retroviruses to human cells has been demonstrated *in vitro*. The transfer of potential pathogens represents a danger not only to the immunosuppressed recipient, which might well be justifiable in the case of liver or heart transplants carried out to save life, but also to the public at large if a pathogenic retrovirus is introduced into the human species.

Finally, there are ethical problems which certainly apply to the use of higher order primates as donors, bearing in mind their similarity to humans, poor breeding in captivity and their status as endangered species. But many people would also see, I suspect, an ethical problem with the use of pigs as organ donors, and recipients might find this to be either an ethical or a cultural issue. Nevertheless there does not appear to be a strong body of opinion representing this latter view.

In conclusion, although we have made very important strides in finding out about the problems that have to be overcome to attempt xenotransplantation, and indeed solving some of these problems, there still does not seem to me to be sufficient knowledge to advocate clinical trials at this point in time. Nevertheless, if one could be as certain as possible that the risk of introducing a pathogenic virus into man was highly unlikely to occur, one could consider trials, in the first place of certain organs as a bridge to transplantation. In this scenario the heart, being the simplest of them all, would be the organ of choice for the initial trials. Needless to say, there would be tremendous potential for the transplantation of tissues, particularly pancreatic islet tissue from

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the pig, if this could be achieved successfully without risk of infection. Furthermore the transplantation of tissues, in contrast to organs, offers the possibility of transplanting tissues encapsulated so as to allow egress of hormones such as insulin from pancreatic islets, but prevent entry of antibodies and immunologically reactive cells which would destroy the foreign tissue. ■

The view of the Health Council of the Netherlands

Eric van Rongen[1]

In the past decade, great progress has been made in finding solutions to rejection problems associated with xenotransplantation. In 1995 the first clinical experiment with genetically modified animal organs seemed close at hand. This prompted the Netherlands Minister of Health, Welfare and Sport to request the Health Council of the Netherlands to summarize the present scientific status of xenotransplantation and advise her on the prospects of the technology for the future. The Council was also asked to consider ethical issues in relation to the desirability and acceptability of research on xenotransplantation, and of its possible clinical application. An inventory of the relevant legislation in the Netherlands was also requested, together with an evaluation of its applicability in this field. A committee of the Health Council of the Netherlands drafted the report entitled *Xenotransplantation*, the main conclusions of which are presented here (*1*).

Viability of xenotransplantation

Several major biotechnological problems still prevent the successful long-term use of xenotransplantation. The first is immunological rejection of the transplanted material. Especially when discordant animals such as pigs are used as the source of organs, hyperacute rejection is the main obstacle. Since the molecular processes associated with this type of rejection nowadays seem to be quite well understood, the Committee felt that this problem could in due course be solved by using animals made adequately transgenic (*2–4*). However, for the other forms of rejection, which become manifest within days or weeks after transplantation, the only method of prevention is to use immunosuppressive agents in doses which are not acceptable for humans, because of the associated high risk of many serious complications (*5*,*6*). There is no obvious solution to this problem at present.

Another question that needs to be answered is how the transplanted organ functions in the recipient's body. Certain considerations and some data indicate that xenotransplants might not always take over the function of the replaced organ properly (*7*, and C. Hammer, personal communication).

At present, a further major obstacle to the use of xenotransplantation is the risk of infection – for the individual recipient and, more importantly, for the human population as a whole. The Committee feels that the use of non-human primates as source animals constitutes a much larger infection risk than that of discordant species and therefore advises against clinical experiments using primate organs. Scientific developments suggest the (transgenic) pig to be currently the most suitable source animal for xenotransplantation. However, since rejection problems with primate organs are much smaller than with pig organs, the use of primates as source animals is not *a priori* rejected. The technical and ethical problems associated with the necessary breeding of specific-pathogen-free (SPF) primates should not be underestimated, however.

Recent research suggests that viruses could make the transition from pig to man, but it is not yet clear whether they would then cause disease (*8–10*). In any case this means that xenotransplantation of pig organs to humans is also not without risks of infection. Much more understanding about the processes involved is required for an assessment of these risks.

The Committee felt that it was not possible as yet to reach any conclusion regarding the future viability of xenotransplantation as a clinical technique. Clinical experiments, whether with whole organs, tissues or cells, would not be appropriate until (a) there is a good chance of operative success; (b) the rejection problems have been reduced to a level comparable to that currently associated with the transplantation of organs from human donors; and (c) the risk of infection is reduced to an acceptable level, for the safety of both the recipient and the population at large. For the same safety reasons, other applications where intimate contact occurs between an animal organ and a human being, such as extracorporeal pig liver perfusion (*11*), should also not be performed until the associated infection risks have been better determined.

Ethics

The Committee agrees with the conclusions of the elaborate ethical considerations of the Nuffield Council of Bioethics and the Advisory Group on the Ethics of Xenotransplantation, both from the United Kingdom (*12, 13*). If, under the conditions outlined above, xenotransplantation becomes clinically viable, the technique will be capable of alleviating the suffering of people with certain medical conditions and in many cases of prolonging life. The Committee therefore believes that, from a human point of view, xenotransplantation is ethically acceptable. Furthermore, the Committee feels that the interests of the people who might benefit from the technique are sufficient to justify the possible inconvenience to or infringement upon the integrity

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of the animals concerned and that the breeding of genetically modified (SPF) animals for xenotransplantation purposes is therefore acceptable.

The Committee recognizes that some people may, for cultural, religious or other reasons, disagree with these conclusions. It would consequently like to see more education of the public on xenotransplantation and more public debate on these matters.

Legislation

The use of animals is regulated in the Netherlands by the Animal Health and Welfare Act, which stipulates, among other things, that performing biotechnological procedures, including genetic modification, is subject to licensing based on an ethical judgement of the Biotechnology in Animals Committee. However, the Act does not control experimentation with animals or animal material genetically modified in other countries. The Committee therefore proposes to modify the Act in such a way that the use for xenotransplantation purposes of organs, tissues and cells from animals genetically modified outside the Netherlands should also be licensed and brought before the Biotechnology in Animals Committee.

Organs from genetically modified source animals and the recipients of such organs are covered by the legislation on genetically modified organisms (GMOs). This legislation, based on European regulations, is designed to protect the environment and human health from any adverse effects which the production or use of GMOs might have. Any recipient of a genetically modified animal organ would be regarded under this legislation as the carrier of a GMO. As such, the recipient would be subject to the requirements of the Environmentally Hazardous Substances Act and associated regulations. This is considered undesirable.

The Committee recommends strongly that agreement should be sought within the European Union regarding the application of GMO regulations in a way which deals specifically with the issues surrounding xenotransplantation.

According to the Committee, the government should act before clinical experimentation begins, to protect individual patients and public health against the risks associated with xenotransplantation, particularly the risk of possible pathogen transfer. Requirements for organ quality and for all aspects of treatment associated with transplantation should be introduced, in order to limit the risk of infection from unknown pathogens.

As animal organs for xenotransplantation will be supplied on a commercial basis, it is important that quality requirements applicable to such organs are included in product regulations. Given that the trade in organs will in all probability be international, the Committee strongly favours uniform product quality standards, at the least within Europe, but preferably worldwide.

In the Committee's judgement, the Netherlands' existing medical product regulations, which are based on European guidelines, are not adequate to regulate the trade in organs for xenotransplantation, mainly because they do not contain the desired quality standards or quality control requirements. The Committee therefore wishes to see new legislation introduced, covering medical products that consist at least partly of living material (biologicals). This legislation should include quality standards both for biological products in general and for particular product types. The quality standards included in any such legislation should be internationally agreed.

While recognizing that new legislation of the kind described cannot be introduced in the short term, the Committee would like to see regulations brought in quickly to cover xenotransplantation involving human beings. Accordingly, it suggests that, as an interim solution, organs for xenotransplantation should be brought within the scope of the legislation on medicines. Until the introduction of European (or global) quality standards, this move should be agreed with other member states of the European Union.

The forthcoming Medical Research Involving Human Subjects Act will cover clinical xenotransplantation experiments and appears to provide a sound basis for the supervision of such activities. The Act provides for local Medical Ethical Committees that should give permission for clinical experiments. However, it is suggested that only the central ethical review committee, whose establishment is also provided for by the Act, should have the authority to review protocols for research involving human xenotransplantation. As a national body, the central ethical review committee would be well placed to monitor developments in this field.

The new Exceptional Medical Procedures Act makes it possible to ban xenotransplantation or to introduce compulsory licensing. The Act could also be used to impose a moratorium.

Informed consent

Any patient offered an animal organ should be properly informed about the proposed procedure. The possibility of pathogen transfer, and the consequent need for continuous and extensive monitoring following the operation, should be clearly explained. Since an infection could be passed on to people with whom the transplant patient has contact, the health of such individuals would also have to be monitored. The voluntary and informed cooperation of these people is therefore needed. Registration of the data collected during the postoperative checks is essential. There may, however, be problems in reconciling public health interests with the individual's right to privacy. It should be made clear that direct contact between the patient and anyone who declines to cooperate in this regard would not be possible. Furthermore, during the clinical experimentation phase at least, it will be necessary to restrict the number of people with whom a patient has contact following a transplant operation, so as to keep the

postoperative monitoring programme within tolerable proportions. As a result, the organ recipient's freedom of movement would need to be restricted. Xenotransplant operations should not be made generally available until these problems become manageable. ■

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