Xenotransplantation continues to present daunting scientific hurdles but there is now a genuine prospect for clinical application. There are also significant and unknown risks. We call for a moratorium on all human xenotransplantation and offer a strategy for balancing the ethical, medical, scientific and societal demands of xenotransplantation prior to human clinical trials.

Uncertainty in xenotransplantation: Individual benefit versus collective risk

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Clinical xenotransplantation, the transplantation of cells, tissues or organs from non-humans to humans, crosses a species barrier that has evolved over millions of years. In doing so, it promises a great benefit to some patients, but it creates the possibility of new disease entering the human population. The ethical issues posed by this dramatic tradeoff of individual benefit against societal risk is the subject of this paper. These ethical issues demand an approach different from that usually taken in the evaluation of new medical technologies. We advocate a process of education in which public discussion and iterative evaluations are used to define the ethical concerns, the potential risks and the benefits of clinical xenotransplantation at the societal level.

Clinical interest in xenotransplantation is prompted by the shortage of human donor organs for allotransplantation. Successful xenotransplantation would provide unlimited numbers of organs, making transplantation available to a greater number of patients. We focus on xenografts from pigs throughout, noting that grafts from evolutionarily more proximate species, such as non-human primates, likely pose even greater risks of infection.

The problems of rejection of a porcine organ by a primate are formidable. However, advances made in the past decade have allowed us to overcome some aspects of these problems and develop promising therapeutic approaches to others, making it conceivable that transplantation of porcine organs to humans will become a clinical reality[1–8]. Porcine cells are already being transplanted into the brain of patients with neurological diseases[9], and the Food and Drug Administration has tentatively approved "bridge transplant" protocols to perfuse the blood of patients with liver failure through porcine livers.

Four ethical considerations guide our thinking. First, a risk to the public requires a public mechanism for determining the acceptability of, and method of consent to, the risk. Second, since the risk to the public is not a "one time only" event, its assessment and regulation must be iterative. Third, the standard model of individual informed consent to medical interventions must be modified, since risks involve third parties, requiring that patients and close contacts be carefully monitored. Fourth, the possibility that a new infectious agent with altered pathogenicity will arise within the xenograft recipient may represent a danger to the pig population. Because of these four considerations, xenotransplantation requires a novel process of evaluation at the national level with novel institutional guidelines, responsibilities and resources.

Although a number of lengthy reports have been published dealing with xenotransplantation[10–13], no organized method has been developed that addresses how to deal with the assessment and decision-making regarding this infectious risk to the public. A recent report of the U.S. National Research Council outlines an approach to assess and manage such risk-laden situations through an iterative process of analysis and deliberation involving public officials, scientists, and interested and affected parties[14]. We propose such an approach for xenotransplantation.

The Food and Drug Administration (FDA) has already established a broadly constituted advisory committee, including both expert scientists and lay representatives to examine xenotransplantation. However, due to the unique aspects of public risk associated with xenotransplantation, initial discussions must be focused on the ethical issues. It is essential that the larger public interest, reflected in the ethical considerations we note above, be adequately aired and developed prior to developing a regulatory framework driven by technical considerations, and prior to making a commitment to proceed. A publicly constituted national advisory committee would be one vehicle to accomplish this type of broad public discussion.

Such a national committee should be comprised of individuals who are open-minded, sensible and broadly concerned citizens from many walks of life, thus representing a range of philosophical backgrounds and disciplines. Ethicists must be actively involved. Physicians and scientists familiar with technical aspects of the problem should also be included. As part of their own educational process, the committee would invite experts in relevant disciplines to answer questions and give advice. These should include, but not be limited to, those involved in the science of xenotransplantation, epidemiology, ethical aspects of the problem, animal welfare and rights, the medical profession, commercial efforts in transplantation, as well as the law and economics. Transplant recipients should be consulted. It will be important for the committee to have input from experts from the U.S. Food and Drug Administration and the Centers for Disease Control and Prevention.

Education of the members of the national committee is only a preliminary to their participating in decision-making about the future of xenotransplantation. The fundamental aim is to develop a consensus about the risks posed by present clinical trials, whether these efforts in xenotransplantation should be abandoned or expanded and if so, under what conditions. These efforts in the United States must be coordinated internationally with similar efforts, such as those of the Interim Regulatory Authority in the United Kingdom[10], in countries and with organizations that are likely to become involved in xenotransplantation. Whatever safeguards are needed to avoid infectious spread to the population must be adhered to in all countries concerned.

There are some historical precedents to deal with concerns about risks to the public of infection from novel procedures, such as agents produced by genetic engineering. The Asilomar proposals set standards dealing with recombinant DNA research[15,16]. The fact that worst-case scenarios that underlay that caution did not materialize is no reason to suspend caution in this case.

Xenosis

The term xenosis was coined to describe the transfer of infections by transplantation of xenogeneic tissues or organs. Xenosis, or xenozoonosis, potentially poses unique epidemiological hazards due to the efficiency of transmission of pathogens, particularly viruses, with viable, cellular grafts. Transplantation in general enhances the risk of infection for a variety of reasons: (i) the graft itself serves as a nidus or "culture plate" from which organisms can spread in the human host, avoiding the need for a vector to achieve disease transmission; (ii) migration of cells from the graft throughout the host may carry cell-associated infection, and (iii) administration of immunosuppressants leads to a diminished host response to infection, allowing infection to proceed in the absence of the usual manifestations of inflammation, often causing a delay in diagnosis.

The risks associated with xenotransplantation may be greater than those of allotransplantation for a variety of reasons (see box).

Whereas any type of organism can become a pathogen in the immunocompromised human host, viruses transferred with viable cellular grafts have been a major source of concern with both allotransplantation and xenotransplantation. Recent molecular data suggest that there is a family of closely related porcine endogenous retroviruses (PERV), some of which appear to be infective for human cells *in vitro*[20]. *In vitro* infection is not always predictive of *in vivo* infectivity and does not predict the ability of an agent to cause disease in the host. However, the possibility that a porcine retrovirus might be xenotropic, might have altered biological behavior in the human hosts, or might recombine with genetic material from the host (either in the germ line or from exogenous infection) raises the specter of a new disease entity developing. Such pathogens might spread undetected to the general population.

The level of risk for such infections to the recipient and the likelihood that such infection will spread to others is unknown.

A three-tiered approach to policy development and decisions

The potential that xenotransplantation could introduce new infectious diseases into the population is the inverse of immunization. Immunization is intended to protect the population at the risk of having occasional individuals experience adverse reactions to the immunization. Xenotransplantation, on the other hand, offers potential benefit to the individual while putting the population at risk. Because the risk is societal and not merely individual, the decision whether to undertake the procedure involves more than ensuring the ability of the surgeon and the transplant team, the capacity of the institution, and the willingness of the patient. Where the risks are collective, the public must not only be educated about the risk but must also be involved in decision-making. The first level of decision-making must therefore occur at the level of social policy; the second at the level of the institutions performing the xenografts; and the third at the level of individual patients and physicians, affecting especially the processes of informed consent and of medical confidentiality.

Risks associated with xenotransplantation

- the level of immune suppression and/or rejection may be greater in xenograft recipients enhancing the activation of latent pathogens, including viruses;
- organisms carried by the graft may not be known human pathogens and/or may include "xenotropic" organisms, that is organisms that are not pathogens in the native host species but cause disease in other species, in this case the human recipient;
- microbiologic assays may not exist for some organisms derived from non-human species;
- novel, animal-derived, organisms may cause novel and thus unrecognized clinical syndromes;
- genetic modification of the donor animals (one xenotransplantation strategy) or treatment of the recipient with, for example, tolerance induction or antibody removal, may alter the host's susceptibility to organisms[17–19].

Societal level

Our focus on the risk of infection that can spread to the general population, while the most urgent ethical problem in xenotransplantation, should not diminish concerns about ethical issues related to the use of organs in humans from genetically-manipulated donor animals, and the risk to pigs of infection, among others. All the major reports on xenotransplantation released to date have recommended comprehensive monitoring and surveillance of xenograft recipients because of the risk of xenosis. The legal and ethical problems associated with imposing such surveillance on recipients, and perhaps their sexual partners, for what will likely be many years or for life, as well as details about the nature and frequency of monitoring, require further discussion. It is not inconceivable that patients manifesting signs of a possible xenosis after transplantation would have to be quarantined. The maintenance of patient confidentiality, as in all areas of medicine, remains paramount and further complicates the need for adequate monitoring of recipients.

Neither the degree of risk nor the capacity of the medical community to deal with xenosis are known. Hence, perception of uncertain risk becomes key. In general, perceptions of the public about risk are quite different from those of experts. Public views are affected by the degree to which risk is familiar or mysterious, controllable or uncontrollable, and whether it evokes feelings of dread or suggests the potential for catastrophe[14]. While news reports of breakthroughs in the use of animal tissue are appearing frequently, many in the lay community still fear the idea of organ farming and regard the exchange of body parts between animals and humans as macabre and the stuff of horror films. Fears and values play a key role in the way humans view risk[14].

Experts tend to focus more directly on the degree of likelihood that mortality may result from the practice in question. With respect to the risk of transmission of infection from an animal donor to a human recipient, there are essentially no data which could be used accurately to assess the level of such risk. The range of uncertainty is large, with the possibility of devastating cross-species infection looming in the background.

Because of this uncertainty and because risk can mean very different things to different constituencies, the framing of statements about risk is particularly important[14]. First, the

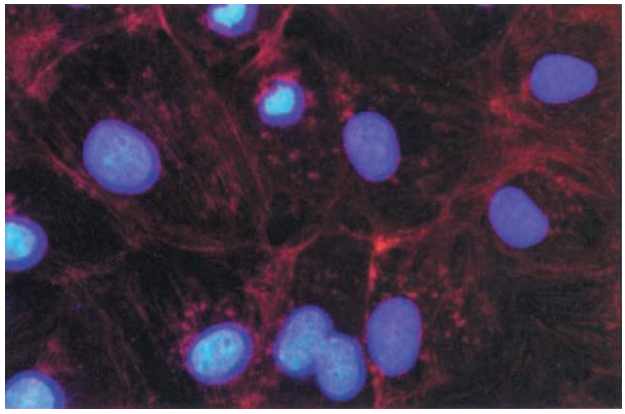
life-saving potential and enormous impact on the practice of medicine that successful xenotransplantation would have needs to be made clear. Second, the public must be informed of any risk that could arise from xenotransplantation, whether or not the extent of that risk and the degree to which that risk is controllable can be precisely defined. Finally, it would be helpful for the public to have a better understanding of the process by which decisions are made in situations of uncertainty.

The problem cannot be dismissed by talking about education as if the experts have to eliminate ignorance and persuade the public; the public has its own concerns, rooted in quite diverse moral beliefs. There is a needed deliberative task: how do we coalesce the different ethical and factual considerations that merit consideration? A public deliberative process is key with the ultimate control over risk management vested in the public. Decisions as to how xenotransplantation will best proceed, and how risk will be handled at different stages of technological development, must emerge from such societal deliberations.

At the outset, there are two alternative, default positions. Either something has to happen to allow moving forward, or something has to happen to prevent moving forward. If the decision is to proceed, then the generally accepted policy in situations of uncertainty is to begin a limited series of experiments proceeding only to the point where risk reaches a certain pre-defined level. The committee would therefore serve to define the milestones for subsequent re-evaluations at each stage of the process.

Because it is impossible for all of the necessary evidence about risk to be available before xenotransplants begin to be performed, an appropriate approach might be to have a controlled initial trial involving a limited number of human recipients, and have those patients followed for a specified period of time. This approach has the advantage of allowing the refinement of regulatory and institutional mechanisms for evaluation of approaches to microbiological testing and other factors. This first phase would ideally last for as long as there is any risk of infectious transmission, which would mean waiting for some number of years. The length of this observation period is one appropriate issue for the committee to discuss and resolve. Society would then be presented with outcomes which could be used to revise the initial risk assessment, allowing reassessment of the safety and advantage of further experimentation. It may then be necessary to modify or extend the monitoring system in order to justify proceeding to the next phase of testing. Such a stepwise approach could be repeated and would require specifying in advance the points of reassessment with the assurance of regulatory controls as the process unfolds.

There will be great pressure on the committee to yield to the reality of "identified victims" who will die without an organ transplant. The central challenge to the committee will be to sustain in balance the uncertain societal risks against the palpable risks to individuals dying of organ failure.



Aortic endothelial cell activation in a pig-primate model of xenograft rejection

In addition, the national committee must concern itself with at least two other problem areas: the financial commitments that must be made to allow monitoring for a period long enough to cover possible late-occurring xenosis, and the use of transgenic animals (in this case transgenic donor animals) and risks to the pig population of infections arising from xenotransplantation.

The cost of monitoring patients and others for signs of infection would likely be very expensive and must be addressed prior to starting xenotransplantation. There must be discussion with national funding agencies, insurance companies, pharmaceutical and biotechnology companies interested in xenotransplantation, and other health care financing institutions regarding a commitment to meet the required costs of the monitoring procedures for whatever period is deemed necessary.

Xenotransplantation has stimulated renewed interest in the use of animals in research. The use of pigs as a donor species has generally been viewed as reasonable. Some additional concerns have emerged as herds of swine are developed for possible use in xenotransplantation. First, pigs that are quarantined for the purpose of minimizing disease transmission must be assured of appropriate social interactions, which are important for general health and development. Second, xenotransplantation presents the possibility that an infectious organism that did not previously exist might arise in humans that would be devastating to pigs. Transmission to a human recipient of a porcine retrovirus that did not cause disease in pigs could result in modification of the nucleic acid sequences of that virus via recombination or mutation. Such a novel viral strain could cause disease in swine with devastating consequences for pig animal husbandry.

The report of a national advisory committee will provide guidelines for decisions that must be made at the institutional and patient-doctor levels. A supra-institutional public authority will need to be responsible for the regulation and management of xenotransplantation. In that role, the authority would define the conditions under which an institution would be authorized to proceed, and would fix the nature of the commitment that the patient and relevant contacts must make before xenotransplantation can take place. Regulations would likely be aimed at offering a uniform measure of protection to patients, to society and to animals.

As such, decisions at the institutional and individual levels should be guided by the deliberations at the societal level and should not be undertaken before the societal process has taken place. Because the societal discussions are likely to take some time, it is critical that these be started as soon as possible to avoid the unnecessary withholding of therapies from patients in need. Despite the fact that lives of patients needing transplantation may be lost with delay, we believe that the risks are sufficient to warrant refraining from human xenotransplantation until public deliberations on the ethical issues have occurred. Research in xenotransplantation should be strongly encouraged, including studies to define the potential risks of inter-species transplantation.

Institutional policy

At the level of the hospital or research center, institutions must be responsible for establishing and enforcing standards for quality of care, management of risk, monitoring of patients and their contacts, and evaluation of the effectiveness of the procedure in accordance with public guidelines and regulations. Institutions should avoid a situation in which individuals proceed with xenotransplantation in advance of adequate safeguards and should curtail clinical trials until societal guidelines are available.

Patient-Physician Interactions: Consent and Confidentiality.

A new approach to informed consent as it relates to xenotransplantation is called for. A patient's agreement to participate in xenotransplantation must be premised on perceptions of both individual risk, as is the case with any experimental or extreme procedure, and the risk of new disease to family, friends, close contacts, and society at large. Because of the need for monitoring for signs of infection, the patient and others will have to commit to participate in such monitoring for a period of time that is considered to be longer than the potential time it might take for an infection to become manifest. Patients would not only have to agree to the risks attendant to a transplant procedure, but also to a contract binding the patient and others to carry out future obligations, including the patient's possible quarantine, as well as modification of the guarantees of confidentiality and surrender of the right to "drop out" of the study[21]. Whether such a contract could be enforced is an issues that the national committee will need to debate. In theory, xenotransplantation might not be allowed unless the patient and family members and sexual partners agree to some onerous conditions for monitoring. For instance, should there be a requirement that the some persons be informed of the fact that the patient is a xenotransplant recipient. Thus, the xenotransplant patient undertakes a social obligation to submit to close monitoring and frequent follow-up, even if this means relinquishing certain freedoms in order to gain the potential benefits of participation.

Concluding comment

We offer a strategy for handling the ethical issues related to xenotransplantation based on the optimistic perspective that xenotransplantation could become a clinically useful procedure, and our strong support of the science being performed. We propose a moratorium on xenotransplantation including those procedures that could be practiced at any time, such as using a pig organ as a temporary "bridge" until an allogeneic organ is found, or as support for patients with hepatic failure. We have a feeling of urgency for a national review to be undertaken given the need of patients who might benefit from xenotransplantation, the impact on the field of the already-arrayed commercial interests, and the present and impending use of xenotransplantation procedures that could cause spread of disease. Past experience with problems involving uncertain public risks that are hard to quantify has shown that individuals and groups with various interests and concerns will have to work together in an interactive manner if appropriate decisions are to be made, and effective and responsible policy is to be generated[14].

The history of medical innovation has shown us unwilling to resist tangible individual benefit even in the face of unknown risks. It is incumbent upon us now to prepare for the moment when the decision to begin organ xenotransplantation will be well-nigh irresistible.

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