Choosing Risk-Benefit Analysis or Precautionary Principle as Our Approach to Clinical Xenotransplantation

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A 1999 editorial on xenotransplantation in the *Lancet*, interpretable as the profession's viewpoint, concluded "It is time to let clinicians begin the slow and painstaking journey of translating experiment into practice."[1] However, a recent article by an eminent Canadian science reporter, based on extensive international visits and interviews, concluded that xenotransplantation "is the most potentially explosive issue of the biotechnology revolution, easily eclipsing the troubling scientific and ethical questions that surround genetically modified food."[2]

Why the divergence of opinion? Clinicians are comfortable evaluating the risk-benefit ratio for their individual patients. They were not trained to worry about the public. Xenotransplantation, by raising the issue of xenozoonoses spreading from recipients to the general public, extends the risk-benefit calculus to the public, which does not benefit directly from this experimental therapy but may be put at risk. At issue also is the fact that different constituencies approach and perceive the same scientific data on public risk in two very different ways.

Those who would base their public policy decisions on traditional risk-benefit analysis would tend to favor patients, perhaps at the expense of the public. Many clinicians and scientists in the transplant community do this instinctively for xenotransplantation, emphasizing the benefits in terms of ameliorating suffering and saving lives.[3] On the other hand, those who would base decisions on the "precautionary principle" (of which there are many flavors) would tend to pay more attention to the public interest and perhaps burden needy patients.[3,4] The media, regulators (remembering "mad cow disease" and HIV-tainted blood), the few amongst the public and others interested in this debate tend to look at the limited risk data from this latter perspective.

The public generally, as a result of these divergent opinions, is becoming aware of the existence of potential problems that may arise if human beings were to be transplanted with animal organs, but has little sense of the details. There is another confounding factor: heavy industry investment and potential investigator conflicts of interest mean that we must try to find acceptable ways[5] to balance opportunity with possible opportunism.

So, how do we move forward, given the imperative to explore potentially important therapeutic options in the face of some as yet unquantified level of public risk? Based on my experience with the World Health Organization (WHO)[6] and other international xenotransplantation-related groups,[7] I believe we now need to ask three key questions:

How Do We Engage the Public in a Meaningful Way to Inform, Educate and Consult?

Several recent xenotransplant guidelines, including the World Health Organization (WHO)[8] report, have recognized the need to engage the public. Fritz Bach and his colleagues, including prominent ethicists, argued that, since the public was going to be exposed to some level of risk (of xenozoonoses mainly), the public must be consulted, and in the meantime it would be prudent to have a moratorium on clinical trials.[9] Responding to that need, a small group of experts met at Meech Lake in Canada last summer to begin exploring the difficult question of how actually to engage the public. We came to realize that there were no real answers yet. To move forward, the multidisciplinary International Meech Lake

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Initiative on Science and Ethics will explore in much greater depth than in the past the various ways in which the public could be identified, informed, educated, and meaningfully consulted. It has commissioned white papers from internationally recognized experts, established a website,[7] and is forming national consultative committees and converting skeptics.

At the same time, we have formed a WHO electronic discussion group (EDG) on the Internet,[10] with the help of Health Canada and OECD. The *Lancet* commented in the same editorial that "WHO has, for once, led imaginatively with an Electronic Discussion Group on International Xenotransplantation Policy Considerations. . . with an international panel of moderators with precisely defined questions and objectives on concerns ranging from animal welfare to risk assessment."[1] The EDG is about to finish the first round of discussions based upon the recommendations from the WHO report. It is our hope that more people will become involved in these kinds of "practical ethics" endeavors.

What Kind of Consent Process Is Appropriate for Potential Xenotransplant Recipients?

This is a subject of immediate concern and the United Kingdom Xenotransplant Interim Regulatory Authority is to be congratulated for taking the lead in producing a discussion document addressing it.[11] Dying and very sick patients can easily be convinced to accept experimental therapy, but will they and their contacts and sexual partners agree to the kinds of invasive investigations, limits to freedom and very real dangers to confidentiality that the proposed surveillance guidelines entail? Will they refuse to cooperate once they are well, or if the graft fails? What are the implications in local and international law?

As a start, we have proposed a kind of "Ulysses contract" model that might be applicable, with suitable modification, to address this issue.[12] In Greek mythology, Ulysses was a strong, good man. On his epic voyage, he knew he would sail near the Sirens, whose enchanting songs would overcome him and cause his ship to be destroyed, with loss of all lives. He instructed his sailors to plug their ears with wax but, as he wished to hear the songs himself, he had himself tied to the mast and ordered his companions not to release him under any circumstances, even if he implored them to do so. A contract loosely based on the Ulysses-Siren myth has been recommended, for example, in relation to psychiatric patients experiencing alternating periods of competence and incompetence. While in a competent state, they would specify what treatment they desire if they lapse into an incompetent state in the future. They would agree to be bound by this contract even if they later, in their incompetent state, wished to renege on it. This kind of binding, enduring advanced directive could theoretically be used to forcibly investigate, treat or even confine a patient who had signed it. With suitable modification, such a binding contract, made in advance, could be relevant to patients about to undergo xenotransplantation. The potential xenotransplant recipient would have to sign it before the transplant, and would be required to abide by it for the remainder of his/her life, even in the event that the xenograft was rejected (and the patient returned to dialysis or received an allograft).

Are There Any Types of Limited Clinical Studies That Can Answer Important Scientific Questions While Substantially Minimizing the Risk to the Public?

It is necessary to consider moving forward very cautiously because moratoria, by removing the subject from consideration, can be harmful, and also because of the substantial danger that, because of financial considerations and desire for primacy, clinical experiments may be performed in countries or centers incapable of ensuring safety or ethics.[13,14] Were this to occur, with disastrous results, xenotransplantation and its potential to alleviate suffering would be set back for a long time.[15]

There is, for example, a need to see if tissues/organs from "humanized," transgenic pigs will indeed be protected from hyperacute rejection in human recipients, as they seem to be in primates. Extracorporeal perfusion of transgenic pig livers will go some way towards answering this question, and it may soon be time to allow this in a very few "centers of excellence" under rigidly controlled safety conditions and where experienced investigators have declared any competing interests, are willing to let the public know what they seek, and are willing to submit results, whether positive or negative, for peer review and publication as soon as they become available.

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Similarly, transgenic pig islets enclosed in immunoisolating biomaterials that would allow egress of insulin but not of viruses, may be considered when the necessary animal experiments have succeeded. If the results are negative or indicate significant infectious risk, the pressure to move forward more aggressively will be diminished, i.e., this is not necessarily the first step on a slippery slope.

There seems to be some consensus that this is the way to proceed in the United States and in Australia, but in Europe and the rest of the world there is some confusion as to what is the next course of action. In this regard it is essential that we continue to monitor all evidence implying either reduced[16] or increased[17,18] infectious risk for potential human recipients.

We are certainly not ready to proceed to large-scale clinical trials, particularly of vascularized whole organs. We are still learning how to assess the infection risks. We certainly have to be cautious, but by asking nuanced, action-oriented questions, we may be able to proceed cautiously[19] and reassess the situation at every stage.

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