Xenotransplantation: A Rational Choice?

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Abstract

There are many potential benefits that xenotransplantation (cross-species transplantation) might afford us, but there are also many weighty biological hurdles which must be surmounted if this procedure is ever to become a clinical reality. Many of these biological concerns are being addressed by specific and novel therapies; however, we must still determine the point at which xenotransplantation could be considered safe enough for clinical implementation. Many members of the scientific community believe that we should strive to make xenotransplantation products as safe and effective as possible, whereas others argue that we should not need to optimize the safety and efficaciousness of xenotransplantation products for them to be deemed acceptable for human use. In this paper I take the latter position, I argue that "the scientific community should move from the paradigm of…trying to indicate to society optimal solutions to that of…trying to help society in finding 'satisficing' solutions" which, although not necessarily optimal, are, nevertheless, good enough (Giampietro, 2002, p. 466).

The Case for Xenotransplantation

Although organ transplantation saves thousands of lives every year, the worldwide demand for organs has always exceeded the supply. As a result, in 2005, over 6000 patients died while on the waiting list for an organ transplant. Tens of thousands died before they could even be placed on the donor waiting list. In the coming years, this organ shortage is only expected to worsen (USPHS guideline, 2001). In light of these dismal statistics, scientists are once again exploring xenotransplantation, defined here as the transplantation, implantation or infusion of cells, tissues, organs, or body fluids from animals (primarily pigs) into humans.

Xenotransplantation products (e.g. hearts, valves, kidneys, livers, and bone marrow) are able to support and sustain human life for extended periods of time (Deschamps et al., 2005; Michler, 1996; Mollnes and Fiane, 1999, p. 269-276; Reemtsma et al., 1964, p. 384-410). For instance, in 1998, Autumn Tate, a dying 16-year-old girl from Lincoln, Nebraska, received an extracorporeal perfusion through a pig liver before a human liver could be found (Reeves, 1998). If properly developed, xenotransplantation promises to be one of the most revolutionary medical technologies of the twenty-first century. To be sure, its scope of potentially-treatable conditions is noticeably wide, ranging from organ failure, to diabetes mellitus, to Parkinson's disease, to Huntington's disease, and many others.

However, despite its potential benefits, xenotransplantation also carries many risks, the most critical being the possible transmittance of infectious diseases across species lines. Several potentially pathogenic infections have been detected in and eliminated from source animals through diagnostic testing and selective breeding (Chmielewicz et al., 2003, p. 349-356). Yet, virologists are still concerned with diseases that have not been identified or characterized, which may escape the screening process. Of particular concern are endogenous retroviruses (viruses embedded within DNA), which may recombine and/or sustain prolonged incubation periods before disease symptoms appear. Meanwhile, if the virus could evade detection, the patient might inadvertently transmit the disease(s) through sexual contact or to those who have come into "transient but close contact with the carrier of the agent" such as doctors, nurses and family members (Cooper, 2003, p. 557). If this were to continue in an uncontrolled manner an epidemic—or possibly a pandemic—could result. To minimize this danger, the U.S. Public Health Service requires that xenograft recipients, as well as those who come in contact with the recipient, consent to frequent clinical examinations, postmortem autopsies, travel restrictions, and the use of barrier contraception, just to name a few precautions (see USDHHS/FDA/CBER report, 2003).

Xenotransplantation and Rational Choice Theory

At present, the scientific community believes that the risks of disease transmittance are low; however, many commentators assert that laboratory work should continue until we have learned more about the pathogenic potential of xenotransplantation products. Indeed, researchers and ethicists generally agree that, prior to a clinical trial of xenotransplantation, preclinical experimentation in animal models (e.g., pig-to-primate) should offer compelling evidence that xenotransplantation products are both safe and effective. At what point, though, can we justifiably say "that [the physician-investigator's] work with laboratory animals has solved the conceptual, empirical, and technical problems presented by a therapeutic innovation sufficiently to warrant trying it on human subjects?" (Fox and Swazey,

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1974, p. 67-68). The relevant ethical question at work here is, "How much safety is enough safety?" Or put another way, "How much risk are we, as a society, willing to tolerate in order to reap the benefits of this technology?"

On the one hand, many commentators believe that we should strive to make xenotransplantation products as safe and effective as possible; on the other hand, several individuals argue that we should not need to optimize the safety and efficaciousness of xenotransplantation products for them to be deemed acceptable for human use. In this paper I take the latter position, I will argue that "the scientific community should move from the paradigm of…trying to indicate to society optimal solutions to that of…trying to help society in finding 'satisficing' solutions" which, although not necessarily optimal, are, nevertheless, good enough (Giampietro, 2002, p. 466).

As a first step in theorizing about safety and efficacy, it is necessary that we recognize the point at which we have successfully achieved an acceptable degree of safety and efficacy. Without specifically outlined expectations for safety and survival time, for instance, safe will never be safe enough, survival time will never be long enough.

But how should we go about defining this notion of safe enough? When dealing with decisions that involve evaluations of safety, researchers typically utilize formal-analytical decision theories such as risk analysis. "[T]he central question in risk…analysis is determining the point at which risk has been sufficiently reduced" (Rowe, 1977, p. 962). In risk analysis, the relationship between an act and the probability and utility of its intended consequences are subjected to a risk calculus and the resulting assessment is expressed in a formal and quantitative manner. This approach to risk is preferable insofar as it is fairly straightforward, standardized, and non-arbitrary. Unfortunately, xenotransplantation is not amenable to any formal method of risk assessment (Tackaberry and Ganz, 1998, p. 41-43). In order to estimate and assign expected utility values to potential consequences, one needs empirical data. This requisite places us in a somewhat perplexing and ironic position: In order to proceed with clinical trials we must first establish that xenotransplantation is safe enough. And in order to determine when safe is safe enough we must first have empirical data, which would ultimately come from clinical trials. Thus, it appears that formal risk assessment is bankrupt when dealing with xenotransplantation. We must find another way to justifiably establish an acceptable level of safety. I suggest we turn to rational choice theory.

Rational choice theory has been used in economics, political science, and cognitive psychology for decades. Rational choice theory suggests that our decisions, for the most part, are rational, ordered, and predictable to some degree (Etzioni, 1988). Most readers will be acquainted with rationality and rational behavior, so I will not dwell on the topic. Briefly, classical and neoclassical economists hold that the actions of all rational agents are aimed at a particular end and our goal as rational actors is to choose the action that maximizes the expected utility of that end (Gibbard, 1990). Rational choice theorists regard this choice strategy as an optimizing/maximizing strategy. With regard to ethics and moral agents, this is tantamount to the statement: the right action is the best action, that is, the one that maximizes the good or expected good (Schmidtz, 1995). If applied to xenotransplantation, we would have to submit that our desired level of safety ought to be optimized, and only an optimal level of safety ought to be tolerated and deemed ethically acceptable. This sounds all well and good, but perhaps we should analyze this position a bit further. When considering scientific innovations like xenotransplantation, what constitutes optimal safety? Should we require that xenografts survive indefinitely? Transplanted human organs cannot survive indefinitely and require the indefinite use of aggressive immunosuppressant drugs. Should we require that no casualties result from xenotransplantation? Casualties occur in the development of many novel technologies, especially invasive procedures such as this. Furthermore, the patients generally selected for transplants are individuals who are in such dire need for a treatment that they have no reasonable alternative but to seek a xenograft. These often include patients who are not eligible for the donor waiting list (e.g., patients with autoimmune disorders like AIDS). Correspondingly, it does not come as a surprise that these patients frequently suffer from numerous health-related problems. Should we require that xenogeneic organs pose no threat of cross-species infection? We can excise viral genes directly from the germ line – a very non-trivial task – but there still might exist undiscovered infections. In short, xenotransplanation will never be considered risk-free. In fact, no medical intervention (especially an experimental one such as this) is ever risk free

We in the scientific and philosophical community are going to have to come to the realization that risk will be an unavoidable artifact of xenotransplantation research. We cannot be rid of it and neither can we minimize it in order to optimize a xenotransplantation product's level of safety. If we place the burden of safety optimization on xenotransplantation, we will never reap any of its potential benefits. From a traditionally rational perspective, laboratory research would continue ad infinitum because increasing safety will always be the more rational choice procedure. However, what immediately strikes me as irrational in this behavior is the lack of any clearly defined stopping point for one's inquiry, the incessant insistence on the better option. This method of decision-making offers no point at which laboratory research can cease and clinical trials may commence, and is thus of no pragmatic use to us.

Optimization is, nonetheless, our prevailing mode of thinking with respect to xenotransplantation. This mindset is, in part, due to advances in the science of public health and, in part, a result of changes in the social climate of many Western societies. In the case of the former, the rise of the precautionary principle in the last few decades has placed more pressure on the developers of technology to explore the potential adverse effects of using the technology before entering the market. In the case of the latter, medical technologies like stem cell research, for instance, are increasingly touted by the media along with many physicians-investigators as "miracle therapies" with seemingly endless therapeutic potential. Thus, there is an increasing pressure to live up to those expectations.

So where are we to go from here? How are we to proceed with xenotransplantation? Characteristic of ethical situations like this is the moral dilemma, the fact that there are several alternative answers to a moral question. In situations that involve uncertainty, like scientific innovation, it may not be feasible to obtain sufficient information in order to optimize a decision. Also, the decision climate may be dynamic, with new options constantly emerging. These are some of the problems that are inherent to xenotransplantation. The extent to which animal models can mimic the human condition is uncertain. High doses of the immunosuppressant cyclosporine A do not elicit adverse effects in non-human primates, but are toxic in humans (Deschamps et al., 2005, p. 91-109). No one knows the disease-causing potential of porcine endogenous retroviruses, if any; or if an unknown infection might unprecedently rear its ugly head. And it is impossible to predict how and to what extent xenotransplantation technology will improve in the future. We must, nonetheless, find a way by which we can make decisions in the face of such uncertainties. In my opinion, we should appeal to "bounded rationality."

Bounded rationality was initially described by the Nobel laureate, Herbert A. Simon, and employs a satisficing strategy rather than an optimizing/maximizing strategy. Satisficing states that it is at times permissible and necessary to make decisions that deliberately do not maximize expected utility; particularly, in situations where there is no clearly-defined right answer, where there is limited time, knowledge, or technical capacity (Simon, 1957). Satisficers pre-establish an aspiration level or threshold level for expected utility, such that the first option that equals or exceeds that level is immediately selected. This option is considered the right option inasmuch as it is good enough to satisfy one's expectations. However, at the same time, the option may not maximize expected utility (Simon, 1979, p. 493-513). Therefore, moral actors, in some situations, need not maximize the good of their actions in order for their actions to be considered morally right. The moral satisficer need only choose options that s/he deems good enough (Slote, 1984, p. 139-163, 1989).

In keeping with the bounded rationality model, it follows that xenotransplantation should not need to maximize safety to be considered morally permissible. I even go as far as saying maximizing safety is an irrational and impracticable decision procedure for this technology. Researchers merely need to establish that the technology is safe enough. In order to determine this safety level, researchers, ethicists, and other representative members of the scientific community must outline an acceptable aspiration level for safety, such that a therapeutic option that equals or surpasses this level would immediately be chosen. In my view, the decision process would likely resemble the following scheme:

(1) Investigators initially specify an aspiration level for safety which identifies
  (a) The number of days a xenograft should be able to support a non-human primate
  (b) The identity of viral genes that need to be removed, if any
  (c) Expectations for the absence of infections during these experiments
  (d) How reproducible the experiments should be
(2) With these safety expectations put in place, laboratory research is conducted in non-human primate models
(3) Once the contingencies of the aspiration level have been satisfied, proceed to clinical trials

Clinical trials could only be justified if a decision stratagem such as the one put forth above is employed. Moral satisficing is the only method of ethical justification by which laboratory experiments can be compared to an acceptable standard.

In conclusion, xenotransplantation is a technique burdened by a specter of risk. Therefore, divorcing risk from this technique is a practical impossibility. However, the mere presence of risk should not automatically deter us from making decisions. Indeed, decisions must often be made in the face of uncertain risks. I submit that Simon's theory of satisficing could be adopted in order to facilitate decision making with regard to xenotransplantation research. Satisficing acceptable risk is not a novel concept in and of itself, and it may not be the most appropriate decision strategy in every instance. However, many cognitive psychologists believe that satisficing closely resembles how most individuals deal with life's complexities. And its usefulness to the field of cross-species organ transplantation is evident.

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