Overcoming the Risks of "EthicalRejection"?

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Graft 2001; 4; 140

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Beginning with attempts to transfuse animal blood into humans in the 17th century, the success of animal-to-human xenotransplantation has depended upon overcoming rejection.[1] Extensive research over the last 20 years has shown that viable xenotransplantation is also dependent upon overcoming complex barriers pertaining to immunological tolerance, physiological compatibility, and risks of infectious disease.

In like manner, the acceptability of animal-to-human transplants is conditioned upon identifying, understanding, and responsibly dealing with a number of ethical barriers. What are the key ethical barriers to xenotransplantation? Are some of these serious enough to cause xenotransplantation to be rejected? Are the key ethical issues being seriously considered and handled responsibly?

A Potpourri-of-Problems Approach

The first authors and committees that addressed the ethics of xenotransplantation identified a potpourri of problems, most or all of which were viewed as issues that should be investigated before clinical trials resume. This still-utilized potpourri approach[2] identifies xenotransplantation with:

1. violations of the laws of nature,
2. cruelty and disrespect toward animals,
3. physical harms to desperately sick patients,
4. problems over informed consent from research subjects,
5. disputes over the review and oversight of clinical trials,
6. psychological harms to patients,
7. offenses to religious traditions,
8. threats to public health,
9. unjust allocation of medical resources, and
10. the risk of undermining human organ donation.[3]

In spite of its heuristic value, this mode of analysis does not provide a way to determine which of these concerns are pivotal or more or less serious. Regarding three of the items above, recent surveys indicate that xenotransplantation is acceptable to between 70 and 75 per cent of groups that were surveyed—clear indications that initial fears over the psychological trauma of living with an animal organ were overblown.[4] Authors also have convincingly argued that the same religious traditions that forbid pigs as food condone their use in order to save life.[5] And opposition to xenotransplants based on violations of the laws of nature are, arguably, illogical and misleading.[6]

What are the pivotal issues that must be addressed and sufficiently resolved before animal-to-human transplants are reinitiated? These are set forth in the following two topic headings, which address items 3, 4, 5, and 8 listed above.

Threats to Public Health

Far beyond the risk of infection to individual transplant recipients, the transplanting of animal organs into human beings could create new human pathogens with epidemic potential. The infectious potential of xenotransplantation is derived from experience with allotransplantation, numerous examples of cross-species zoonotic infections, and discoveries over the likely causes of HIV infection.[1,3,7] In addition, discoveries in 1997 and 1998 that porcine endogenous retroviruses (PERV) could infect human cells in vitro led the US Food and

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Drug Administration (FDA) in October of 1997 to place a hold on new clinical trials of cellular xenotransplantation. Alarm over the infectious disease risks of non-human primate organs in humans led to a virtual prohibition of their use in clinical trials in the US in 1999. Outcries for a moratorium on all clinical research with xenotransplantation cells, tissues, and organs accompanied these developments. In short, the possibility that xenotransplantation might create grave, but non-quantifiable, harms to the public threatened xenotransplantation with "rejection".

Several developments have significantly eased, but not fully resolved, this serious ethical concern. The US Public Health Service published detailed guidelines for screening and safety monitoring of infectious disease. Regulatory agencies proved that they would take strong and timely action to control for newly-discovered risks. More sensitive tests for detecting PERV were required of, and developed by, researchers. And studies of patients who had been exposed to porcine cells and tissues found no evidence of PERV infection, which suggests that "very few xenotransplant recipients are likely to become infected."[8]

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Nevertheless, worries over the infectious disease risks of xenotransplantation have not been fully resolved, in part because the genetic modification of pigs for the sake of preventing organ rejection might facilitate the development of "humagenic-PERV infectivity.[8] While threats to the public's health remains as an ever-present ethical concern, it is being handled responsibly and resolutely and is less worrisome now than in the recent past.

Greater Harms than Benefits for Critically Ill Patients

Chronologically, the first major moral objection to animal-to-human transplants arose over the way they appeared to betray an historic tenet of the ethics of the medical profession: the duty to see that the benefits of medical interventions should outweigh their harms. The turmoil over the transplanting of a baboon's heart into "Baby Fae" in 1984 indicated how xenotransplantation became readily associated with premature, harmful, and even deceitful medical experimentation. Below the surface of these criticisms lie haunting literary images of H.G. Well's Dr. Moreau.

Unless the public is assured that xenotransplantation clinical trials are viable and beneficial for patients and their families, distrust over the harms of animal-to-human transplants may result in long delays and possibly even the rejection of xenotransplantation as a clinical modality.

For several reasons, however, this ethical concern is dormant at the present time. First, the benefits of allotransplants, combined with an increasingly dire shortage of human organs, fuels guarded enthusiasm for the possibly enormous benefits of xenotransplantation.[1] Second, scientists, surgeons, veterinarians, ethicists, and others in the US and abroad have convened at conferences, on commissions, and in regulatory agencies to control the development, timing, and beneficial outcomes of animal-to-human clinical trials.

Discussion and policy formation include:

1. identifying the populations of patients who stand to benefit from these trials,
2. predicating the initiation of human trials on explicit and agreed-upon success rates in pig-to-primate preclinical studies,
3. a thorough understanding and honoring of fully-informed consent as a condition for clinical trial acceptability,[9] and
4. thorough scientific and ethical review of clinical trials by respective national and local review committees.

Ethical analysis and decision-making are implicit in each of these areas, and analysis will be sharpened if it is explicit. Consider the second area above. This topic construes the balance between benefits and risks (or probable harms) to research subjects in terms of success rates. This presses us to specify and defend why some "balance" of risks and benefits is chosen over another.

In June of 1999, a majority of the FDA Subcommittee on Xenotransplantation recommended that, before clinical trials resume, the success rate of experimental pig-to-nonhuman primate transplants should be 90% survival for 2 months and 50% for 3 months. To many scientists and clinical researchers who are familiar with the daunting barriers to xenotransplantation and the dire circumstances of critically ill patients in need of organ transplants, these success rates seem rational and moral. They promise to extend the lives and, hopefully, improve the quality of life of patient/subjects with no other treatment alternatives. The ethical acceptability of experimental xenotransplants with the above pre-

clinical success rates is also predicated on the process of informed consent, whereby subjects would voluntarily agree to accept porcine organs after being fully informed about preclinical outcomes.

Does the above "balance" of risks and probable benefits that is acceptable to a majority of researchers and, presumably, to a number of willing subjects enable us to conclude that these trials would be ethical? An answer to this question depends upon what risks and probable benefits are kept in mind and how they ought to be balanced.

To return to the history of xenotransplantation and the public's response to "Baby Fae," the way to maximize the benefits of xenotransplantation rests in part on assuring the public that xenotransplants will be viable and beneficial. If this concern is viewed as an essential component of risk/benefit calculations, the success rates recommended by the FDA subcommittee may not satisfy the ethical demands of newly initiated clinical trials. Indeed, a negative and distrustful public response to news stories about the subjects of clinical trials based on the FDA committee's recommendation could conceivably undermine the foreseeable benefits of xenotransplantation for several years.

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This point about the consequences of choosing a success rate for newly-initiated clinical trials illustrates how this and other decisions pertaining to these trials rest on ethical assumptions that may prove to be pivotal. Ethically-responsible decision-making is predicated upon making these assumptions explicit, thoroughly debating their merits, and reaching decisions that are as rational and convincing as possible.

The phrase "as rational and convincing as possible" does not mean that the decisions that are reached are something other than well-informed and aired "judgment calls." The decision over the choice of some preclinical success rate should be based on a combination of identified topics, including:

1. solid data (pig-to-primate survival rates),
2. clinical experience (with patients experiencing organ failure),
3. historical precedent (knowledge about the history of allo- and xeno-transplantation), and
4. incomplete data (about, for example, public attitudes toward animal transplants in humans)[10] by
5. a diverse group of persons known for their knowledge and discretion.

This analysis of ethical issues inherent to one of the important decisions pertaining to clinical trials with animal-to human transplants should not detract from the way the duty to benefit subjects and future patients has been, and is being, responsibly recognized and acted upon at the present time.

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