Regulation of Xenotransplantation: Are we asking the right questions?

*Animal-to-Human Transplants: the ethics of xenotransplantation*

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Xenotransplantation, as both a therapeutic modality and an answer to the chronic shortage of organs for transplantation, has been richly discussed from the perspectives of a variety of governmental and quasi-governmental organizations. All of these discussions have focused on the risks of interspecies transplantation, largely due to the potential spread of non-human animal-derived infectious diseases to humans. Recent reports, guidelines, and articles have emanated from the United States Department of Health and Human Services (Centers for Disease Control and Prevention – CDC; National Institutes of Health – NIH; Food and Drug Administration – FDA). These agencies have focused on the prospective monitoring of known and possibly unknown or unrecognized infectious agents transmitted by xenotransplantation (called “xenosis” or xenozoonosis or xenogeneic infection) by the CDC; establishing a registry for experimental human research protocols at the NIH; and on developing guidelines to enhance the safety (e.g., animal breeding) and review of xenotransplantation protocols by the FDA. The World Health Organization (WHO), which would seem to have little direct role in these discussions, has focused on outlining the potential problems and listing (nonselectively) the potential pathogens which might be transmitted by nonhuman primates and swine source animals. This report is flawed in regard to discussions about viral pathogenesis in the compromised host (section 3.2) and about the interpretation of microbiological testing. For example, not all live viruses transplanted with tissues will establish infection outside the xenograft — many will lack the receptors and metabolic systems needed to survive in the alien (human) environment. “Resolved viral infection” can often be reactivated from latency, contrary to the WHO statement, and pose a risk as great as active infection to the organ recipient. The United States’ Institute of Medicine (IOM) has produced a report that introduces thoughtful discussions of the current scientific basis of interspecies transplantation and of the ethical issues posed by the new technology. While omitting primary data, this report introduced a detailed discussion of ethical issues, and addresses the rights of those individuals requiring organ transplantation to receive the potential benefits of experimental technologies. However, the report does not strike a clear balance between the rights of the potential transplantation recipient and the potential risk to the community at large, including family, medical staff, and social contacts. The report of the British Nuffield Council on Bioethics (NCB) has the most complete outline of the problems posed by experimental technologies, addressing the alternatives, risks, patient selection criteria, ethics, and scientific basis of xenotransplants into humans. This report is the first to suggest, on ethical and microbiological grounds, the exclusion of nonhuman primates as source animals for
xenografts but accepts the importance of primate recipients in ongoing technological development. The breadth of the NCB discussion reflects the input of a large spectrum of interested individuals.

**Infection, Xenotransplantation, and Informed Consent**

The prevention and recognition of infectious disease syndrome in xenograft recipients is central to the success of xenotransplantation and, ultimately, to the public’s acceptance of this procedure. It should be noted that a number of important benefits may accrue to xenotransplantation. Not only would there be an adequate supply of organs of the correct size for each individual, but these organs may well be resistant to common infectious agents of humans (Hepatitis viruses, Herpes viruses, HIV). Further, they will be free of many of the pathogens which may be acquired by a donor during hospitalization prior to donation.

Immunosuppressive drugs which are needed to maintain graft function also contribute to the risk of “opportunistic infections” — infections due to organisms which do not cause infection in immunologically normal hosts or which are of greater severity than in normal individuals. Many of the factors capable of activating infection in transplanted tissues, especially due to viruses, will be present in the xenograft recipient. In general, appropriate microbiological tests for the presence of animal derived pathogens do not exist. For example, tests which measure antibodies in the blood of individuals exposed to infectious organisms (serologies) are often useless in immunosuppressed transplant patients who cannot develop such an immune response. Thus, new tests must be developed to detect the organism rather than the host response to the organism.

When the first candidates are chosen for xenotransplantation, informed consent is to be obtained prior to the procedure, as for any major intervention. The likelihood of graft rejection can be assessed and the likely technical and immunological problems described. However, in the absence of relevant scientific data, what do we tell our patients about the infectious risks posed by xenotransplantation, both to the individual xenograft recipient and to the community? Further, how can the “rights” of transplant candidates to the use of potentially lifesaving, new technology be balanced against the unknown risks to the community?

All of the available data suggest that elimination of infection from the donor animals is a key to the safety of the procedure. The IOM report (chapter 3) and others recognize the importance of the potential emergence of infection in the xenograft recipient, but do not detail mechanisms by which the potential risks of xenotransplantation can be assessed. The Nuffield report takes up this concern (sections 6.24-26) to identify specific areas of research needed to identify the hazards of infection derived from the donor species. In particular, the NCB Working Group recognized the value of studying infectious disease transmission in the appropriate animal (i.e. xenograft) models.

Many new pathogens (parasites, bacteria, fungi and viruses) or new presentations of infections have been recognized only in immunocompromised human hosts (e.g. with AIDS or organ transplants). Thus xenograft-derived infections may be