The Public Health Risk of Animal Organ and Tissue Transplantation into Humans

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The many ethical, societal, and public policy issues surrounding animal organ and tissue transplantation into humans (xenotransplantation) have been expounded in a variety of settings over the past decade, but in the past year one particular issue has taken center stage—that of risk to the public health posed by novel viral diseases stemming from unique opportunities for species jumping. Underlying the issue is the shortage of human organs for transplantation and advances in immunological and surgical sciences that now promise the means to overcome cross-species rejection phenomena (*1*). The argument over the level of societal risk presented by xenotransplantation has been intense and is far from being resolved. In hindsight the argument seems to have followed a roller-coaster course, alternating between a sense that the risk might be acceptable and a sense that it might not. For example, in 1994 the Food and Drug Administration (FDA) seemed headed toward approval of clinical trial protocols, but in 1995 such plans were suspended. In the past year two oversight groups, encouraged by FDA approval of a clinical trial involving the xenotransplantation of baboon bone marrow cells into a patient with acquired immunodeficiency syndrome (AIDS), have suggested that, with substantial safeguards in place, clinical trials should proceed (*2*, *3*).

Focus is now turning to policy development to ensure that (i) the best scientific approaches are used to evaluate and quantify specific risks; (ii) comprehensive surveillance and virus screening, discovery, detection, and diagnostics systems are established; (iii) national clinical trial guidelines are made available to local institutional review boards; (iv) ample communication takes place among involved professionals; (v) ethical concerns of patients and society are melded with scientific issues; and (vi) a permanent national oversight body is chartered. In this Policy Forum, factors pertaining to risk assessment are presented as bases for the kind of comprehensive policy development that must evolve over the next few years—hence this is a "work in progress," where new data will continually drive societal attitudes.

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The viruses of xenograft donor species. There are about 4000 known virus species and about 30,000 strains and variants that infect humans, animals, plants, invertebrates, and microorganisms (*4*). Although the risk posed by many viruses will require further evaluation, attention must be concentrated on viruses that are known to be pathogenic in donors or recipients and viruses with other suspected risk potential.

Known pathogenic viruses that might pose a risk in xenotransplantation include many adenoviruses, papovaviruses, papillomaviruses, parvoviruses, hepadnaviruses, morbilliviruses, filoviruses, hantaviruses, arenaviruses, arteriviruses, flaviviruses, and togaviruses. In evaluating the pathogenic potential of specific viruses, rather than whole categories such as the ones described, it will not be easy to determine which viruses represent a risk to the xenograft recipient alone, which represent a risk to society as a whole as a result of species jumping, and which may be dismissed as representing a minimal risk. An important aspect of policy development should be the construction of a list of the viruses of concern and an evaluation of the relative risk each poses in various xenotransplantation settings—this is a task that has not yet been done in a comprehensive way.

In particular, the risk associated with the presence in donor animals of certain retroviruses (including endogenous retroviruses, mammalian type C and D retroviruses, lentiviruses, and human T cell leukemia virus/bovine leukemia virus–like viruses) and certain animal herpesviruses (including herpes simplex–like viruses, Epstein-Barr–like viruses, cytomegaloviruses, and HHV6-, 7-, and 8-like viruses) must be considered further. Every potential donor species carries one or more herpesvirus, usually silently by a high proportion of individuals in the population and often capable of causing severe disease when infecting a heterologous species.

Sources of xenograft organs and tissues. Various sources have been used to obtain organs, tissues, and cells for xenotransplantation, including abattoirs, open colonies, closed colonies, specific pathogen–free (SPF) colonies, and gnotobiotic colonies. It is easy to say, "the 'cleaner' the donor animal the better," but there is need for data on the relative risk posed by various animal sources. Meanwhile, the commercial production of swine raised under SPF conditions and genetically engineered to lessen rejection when their organs are grafted into humans has been initiated by at least six biotechnology firms, and in the United Kingdom a national committee has been formed to draft a code of practice for using transgenically modified SPF swine (*5*). Proposals for the development of SPF baboons are far less advanced, partly because of the time and cost involved in developing special rearing programs and facilities, and partly because of objections over the use of this species for this purpose.

What about the immunosuppression induced in xenograft recipients? Pathologically and pharmaceutically induced immunosuppression affects the escape from immune control of viruses already present in the body, such as cytomegaloviruses, papovaviruses, and papillomaviruses, and also favors persistent virus carriage and shedding. In such circumstances, mutations may continue to accumulate so that the virus population found late in the course of infection may be quite different from the original infecting virus. In most observations of this phenomenon, the virus shed late has been attenuated in pathogenic properties, but who is to say that this will always be the case? This is one of the most important issues facing policy developers and requires further research in animal models and in immunocompromised human patients.

What is the difference between a xenograft and an unsterilized biologic product derived from an animal and injected into a human? There are many examples of biologic materials derived from animals for use in humans; a number of these are subjected to viral-inactivation procedures, and many are regulated by the FDA, including porcine insulin (treated with HCl and ethyl alcohol), bovine thyroxin (treated with acid), porcine heart valves (treated with glutaraldehyde), bovine lung lipids (for treating hyaline membrane disease; treated with solvents), bovine adrenal cells (experimental, as a source of endorphins for long-term intractable pain relief; no treatment), and porcine skin (for burn repair; no treatment). In addition, fetal calf serum, calf serum, and horse serum are used in cell culture substrates for vaccine production and for many in vitro autologous cell manipulations. Such sera are heat-treated or γ-irradiated, but viruses occasionally survive such treatment. So, there may not be much difference between xenografts and unsterilized biologic products derived from animals. In fact, we have for many years

been parenterally transferring some of the same kinds of viruses into humans that might now be considered a risk in the xenotransplantation setting. Such parenteral transfers, which to a large extent have proceeded without apparent harm, should nevertheless be reviewed in regard to lessons for policy development and should also be compared with experiences involving transfers of whole organs (allografts and xenografts, where cell-cell interfaces and microvasculature remain intact and eventually unite host and transplant).

Systems for viral discovery, detection, and diagnostics. One imperative of xenotransplantation policy development is the design of a national system for virus screening, discovery, detection, and diagnostics. This system could be applied to potential xenograft donor animals as well as to xenograft recipients and surgical staff. Despite our incredible power to diagnose viral diseases and detect viruses, it would be a mistake to think that methods in common use are all that sensitive and specific for the purposes at hand. This failing is mostly a result of the extreme compartmentalization of diagnostics technology and shortcomings in technology transfer and training. An infrastructural change, driven by national policy, is crucial to the development of the kind of laboratory resources that would meet public expectations.

In a national virology laboratory supporting leading clinical xenotransplantation centers, (i) the list of tests available for known viruses of concern would be comprehensive; (ii) the sensitivity of tests would be maximized; (iii) the specificity of tests would be adjusted to the purpose at hand (not too narrowly specific, such that variant viruses might be missed); (iv) the sampling of donor materials would be expansive and statistically sound; and (v) there would be a seamless cloth from standard methods through to avant-garde investigational methods. Of course, there are wide gaps between standard and investigational methods; the former are subject to quality control and are usually supported by reference laboratories and state and national reference centers, whereas the latter are research-driven and not subject to independent oversight. Tests for many viruses in xenograft donors would for some time have to be seen as investigational, in need of careful interpretation (6).

There is a big difference between diagnostics and etiologic-agent searching. In the latter, many nonspecific approaches are used in complementary fashion (such as electron microscopy and evidence of viral growth in cell cultures inoculated with donor materials). Overall, despite the introduction of powerful molecular biologic methods (such as shotgun cloning, amplification by the polymerase chain reaction, representational difference analysis, and sequence-independent single-primer amplification), nonspecific methods are often poorly predictive of the presence of many kinds of viruses. Moreover, every application of such methods represents a major research project. The matter of how best to detect unknown viruses of potential concern in xenotransplantation must be regarded as a new field, open-ended and in need of greater research. This issue will be one of the linchpins of comprehensive policy development.

Understanding risk. One element that has helped bring about the national decision to allow further clinical trials has been an increasing public understanding of the concept of risk. In dealing with infectious diseases, the reality is that our best efforts may decrease but will never eliminate risk (7). There is also a need to better understand the fundamental nature of the viral infection risks involved in xenotransplantation. Each virus of concern must be evaluated independently and quantitatively. Ultimately, risk may be revealed only through ongoing surveillance and clinical observation, but in complementary fashion, animal model studies may provide our best opportunity for understanding the mechanistic bases for species jumping. In such studies endogenous viral recombinants, complemented escape mutants, and other exotic, theoretical risks can be experimentally tested. Policy development must include a fundamental biomedical research base for clinical xenotransplantation sciences—a need that has not yet been comprehensively described.

The need for national leadership, coordination, and guidelines. At first, the question of risk associated with xenotransplantation focused on the individual recipient. This focus led to a consideration of many topics, including the nature of the virus, its pathogenesis, its pattern of transmission, and its stability. Prions—the agents of the spongiform encephalopathies—being so physically stable (for example, resistant to boiling, formaldehyde, and ultraviolet- and γ-irradiation), so insidious and persistent, and so difficult to detect in donors, seemed to represent the ultimate test of various risk management proposals and policy ideas.

In the past year, however, the question of risk has been expanded to cover the whole population that might come into contact with the xenograft recipient. The questions now asked include: What is the risk of novel viral diseases stemming from unique opportunities for species jumping? Will xenotransplantation be the cause of the epidemic emergence of "new" viruses? Will the immunosuppression induced in xenograft patients amplify this risk? Here, another HIV-like virus/AIDS-like epidemic replaces prion diseases as the ultimate threat.

The answers to these population-based questions will come from many sources of expertise; however, to a greater extent than with individual health questions, the scientists at the national public health agencies—the Centers for Disease Control (CDC), FDA, and National Institutes of Health (NIH)—bear particular responsibility for providing direction. Their special expertise must be complemented with that from other areas, such as basic biomedicine, academic clinical medicine, veterinary medicine, laboratory animal medicine, and primatology.

At a recent workshop sponsored by the Institute of Medicine's Committee on Xenograft Transplantation, a strategy was developed to achieve national leadership, coordination, and guidance (2). The strategy avoids regulation per se, calling instead for national guidelines to help local institutional review boards oversee clinical investigators. In keeping with a recommendation that the CDC, NIH, and FDA play the lead role in developing these guidelines, an interagency xenotransplantation working group has been formed, and draft guidelines are expected to be published in the Federal Register soon (8). These guidelines will call for a national registry of patients and will describe in detail the kind of national surveillance and laboratory resources needed. The guidelines will reaffirm the principle that the issues at hand are societal in nature—they concern not just individual physicians, scientists, and patients—and will also reaffirm the need to continue to assess, manage, and communicate the risks involved.

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