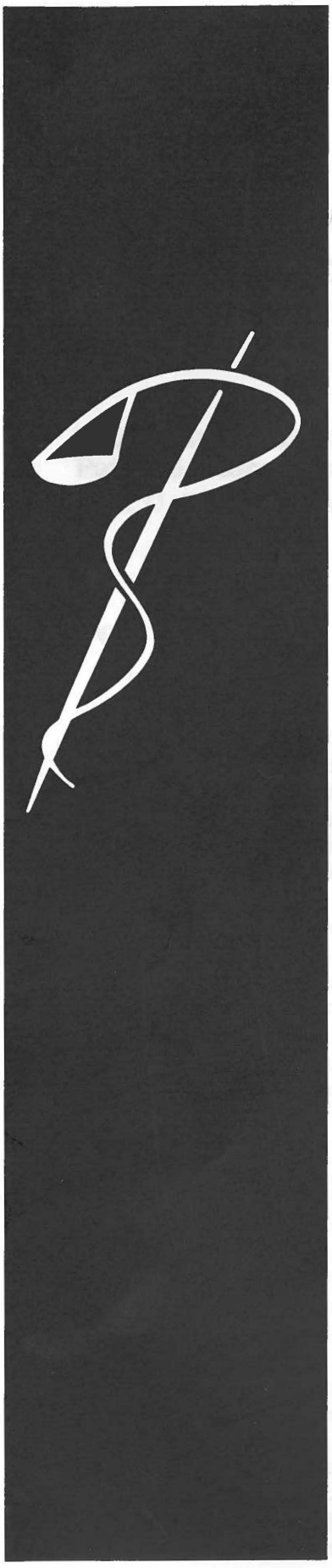

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Xenotransplantation is any transplantation, implantation, or infusion of either live cells, tissues, or organs from a nonhuman animal source, or human bodily fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs into a human recipient.[1] Most scientists agree that clinical xenotransplantation should not be performed in the absence of accompanying public health safeguards.[2] The science upon which that consensus is based has been extensively described in the literature.[3] By and large the most compelling reason for public health safeguards is the possible introduction of new infectious agents into the human life cycle as a result of xenotransplantation.

The most frequent source of new infectious diseases in human populations is the transfer of agents, such as viruses, bacteria, or prions, from animals to man.[4] Human diseases and infectious agents that are thought to have originated from animals include influenza,[5] rabies,[6] malaria,[7] lassa fever,[8] lyme disease,[9] AIDS,[10] yellow fever,[11] tuberculosis,[12] the human t-cell lymphotropic virus,[13] the herpes B virus,[14] the hantavirus,[15] and even the bubonic and pneumonic plagues.[16] The risk inherent with xenotransplantation is that infectious agents in the xenotransplant product could be transmitted to xenotransplant recipients and ultimately to the general public. Agents that are non-pathogenic in the animal host could cause disease in humans, and lead to significant morbidity and mortality.

What makes predicting the likelihood of disease transmission in xenotransplantation so difficult is that the medical community does not possess the diagnostic instrumentation to test for every agent that could be endogenous to the xenotransplant product. Thus, even if we test for all known infectious agents, many others may escape detection by virtue of lying on the periphery of our diagnostic reach. Additionally, animal agents could recombine with human agents to form novel chimeric agents, a feature that is not uncommon in cells infected with retroviruses.[17] It is this mechanism, for example, that is thought to account for the pandemics caused by modified influenza viruses in 1957 and 1968.[18] As with the human immunodeficiency virus (HIV), some of these infectious agents may remain dormant for many years before expressing themselves pathogenically in human tissues. For this reason, surveillance efforts must be long-term.

In response to the scientific consensus regarding public health safeguards, the regulatory agencies of those nations preparing for clinical trials of xenotransplantation have developed public safety measures intended to restrict the propagation of infectious diseases that could emerge as a result of xenotransplantation.[19] These public safety measures call for the establishment of a system of surveillance — the ongoing systematic collection, analysis, and interpretation of relevant data (such as tissue and body fluid specimens to be taken from xenotransplant recipients), closely integrated with the timely dissemination of these data to those responsible for the control of infection — that may permit the early detection of, and rapid response to, any emerging epidemics. On the assumption that robust public safeguards will accompany the clinical trials, many within the scientific community have voiced their readiness to proceed with xenotransplantation.[20] While trials of whole organ xenotransplantation are not yet feasible due to physiological and immunological barriers, trials of cellular and tissue xenotransplantation are already underway in the United States and Europe.

Yet, the policy question of whether, and if so under what circumstances, we should proceed with

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xenotransplantation cannot be answered by scientists alone. The issue involves numerous ethical, social, and legal questions lying beyond what Stephen Jay Gould has termed the "magisterium of science."[21] Relatively little attention has been paid to the important questions that may be raised by these other fields of study, including the legal uncertainties associated with the enforcement of the public safety measures.[22] Some concerned scientists have suggested that the law of contracts might be used to bind xenotransplant recipients to the public safeguards.[23] For the most part, however, debate about the infectious disease risks associated with xenotransplantation appears to presume that the law will be able to enforce whatever safeguards the scientific community deems necessary for the protection of the public health. The reality is that there are limits to the enforcement measures that the law will be prepared to accommodate.

We recently assessed the legal enforceability of what is, at least from an epidemiological perspective, probably the most important of the available public safety measures—the obligation of xenotransplant recipients to provide periodic tissue and body fluid specimens to the health authorities responsible for disease surveillance. In the United States, for example, the Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation ("PHS Guidelines") characterizes the surveillance of xenotransplant recipients as being "critical" to the detection of infectious agents prior to their dissemination in the general public.[24] The importance of the safeguards lies not in their ability to altogether prevent the emergence of infectious diseases — because they are incapable of doing so — but in their ability to provide the foundation for a rapid response to emerging infectious diseases. Without the epidemiological information provided by the tissue and body fluid samples of recipients, scientists will be handicapped in detecting and isolating any disease-producing infectious microbes that could emerge as a result of xenotransplantation.

According to the PHS Guidelines, tissue and body fluid specimens must be collected by the sponsor of any clinical trial involving xenotransplantation, and maintained by both the sponsor and the Public Health Service.[25] Specifically, tissue and body fluid specimens must be collected both prior to as well as after the xenotransplantation procedure, and for the remainder of the recipient's lifetime.[26] Specimens must be maintained for at least 50 years beyond the date of the xenotransplantation operation.[27]

We are concerned that the legal infrastructure necessary to enforce the public surveillance system is not currently in place. In our recent assessment of this infrastructure in the United States and Canada, we concluded that public health legislation — requiring either the amendment of existing legislation or, better yet, the enactment of specific xenotransplantation legislation — would be the only legally effective means of enforcing compliance with the lifelong obligation of providing tissue and body fluid specimens.[28] To date, no xenotransplantation legislation has been enacted. It is therefore doubtful whether the obligation of periodically providing tissue and body fluid specimens could be enforced against noncompliant recipients. Moreover, even if xenotransplantation legislation were enacted, its enforceability would ultimately depend on the ability to defend it against legal challenges. Should such legislation be declared unconstitutional or otherwise unenforceable by the judiciary, the capacity of the surveillance system to generate the data required for the protection of the public health would depend entirely on the willingness of recipients voluntarily to comply with the safeguards. In the absence of such willingness, the surveillance system would collapse and society could be left defenseless in the face of an epidemic.

In this article, we review various sources of legal authority that might be used to enforce compliance with the public safeguards in the United States and Canada. These include the law of informed consent, the law of contracts, and public health legislation. We also briefly comment on the likely outcome of constitutional scrutiny of xenotransplantation legislation, concluding that it should be feasible to craft legislation that is both effective and constitutional.

Could Informed Consent or Contract Law Bind Recipients to the Safeguards?

All that is normally required by law prior to the provision of medical treatment is that the physician obtains the patient's informed consent. The doctrine of informed consent was designed specifically to protect the patient's right to self-determination.[29] Importantly, this doctrine in no way binds the patient to a legal course of action, whether contractual or otherwise. The consent speaks not to the patient's promise to undertake future obligations in consideration of having access to medical care, but to the patient's acquiescence in having a particular intervention performed upon his or her person. In the case of xenotransplantation, the recipient's consent to the xenotransplantation procedure, even with full understanding of the accompanying public health safeguards, would not legally bind the recipient to comply with the safeguards. This is because the recipient's right to self-determination continues after the initial consent has been given and the treatment has begun. Recipients could withdraw their consent, written or otherwise, at any time.[30] The right to withdraw consent exists even in the context of life-sustaining interventions.[31] Because the recipient's consent is insufficient under both American and Canadian law to guarantee that the public safety measures will be followed, some other legal mechanism must be relied upon.

Some scientists have suggested that the law of contracts might be used to bind the recipients to the safeguards.[32]

However, under most contracts, the obligated party under contract has the option of delegating performance of his or her obligations to a third party, such as an agent or an employee. The nature of the contractual undertaking in the case of xenotransplantation is such that it would be essential for the transplant recipient to perform the obligations — that is, comply with the safeguards — himself or herself. It has long been recognized that the enforcement of such "personal service contracts" leads to a conflict between two competing legal values — those of holding the debtor to his or her word and of respect for individual liberty. In light of this conflict, American[33] and Canadian[34] common law generally will not enforce the specific performance of personal service contracts.[35] Therefore, a contract between a recipient and a xenotransplant center, in which the recipient promises to comply with the public safeguards, is unlikely to be legally enforceable against the recipient. Nor would it be either practicable or fair for xenotransplant centers to be charged with the responsibility for enforcing compliance with the public health safeguards by pursuing legal action against every non-compliant recipient.

A related impediment to the use of contract law as an enforcement mechanism is that compulsory compliance with the safeguards would require the relinquishment of certain civil liberties that likely could not be contracted away as a matter of public policy or human rights. Although recipients may initially agree to bind themselves to contracts calling for, among other things, the periodic provision of tissue and bodily fluid samples, if they later break their promise, the enforcement of these contracts would be incompatible with fundamental legal instruments upholding civil liberties such as the inviolability of the body.[36] To be lawful, an invasion of civil liberties would have to be expressly authorized by legislation and the legislation would itself be subject to constitutional scrutiny.

Could Public Health Legislation Bind Recipients to the Safeguards?

Unlike the law of contracts, public health law encompasses the authority to demand the specific performance of human conduct that is deemed necessary to protect society from the spread of infectious diseases. As currently formulated, however, the generally applicable public health law provisions in most jurisdictions in the United States and Canada are inadequate to enforce xenotransplantation surveillance. For example, because the infectious disease risks associated with xenotransplantation, even if foreseeable, are theoretical, there would probably be insufficient grounds for invoking and applying general public health law provisions to recipients for as long as they remained asymptomatic.[37]

Nor could the Model State Emergency Health Powers Act[38] — granting broad powers to public health authorities to effectively respond to potential or actual public health emergencies — be used to bind recipients to the safeguards. Even if uniformly enacted across all states and provinces in the United States and Canada, so that recipients could not evade compliance with the safeguards by moving to a state or province with weaker laws, the provisions of the Model Act authorizing mandatory medical examinations become activated only after the governor of the state or province has declared a state of public health emergency.[39] The ground for declaring a public health emergency that is most relevant to the circumstances of xenotransplantation requires the existence of an imminent threat of illness caused by a novel infectious agent that both is highly fatal and poses a substantial risk of a significant number of human fatalities.[40] Given that there is no evidence to date establishing the existence of an imminent, substantial, and highly fatal infectious disease risk associated with xenotransplantation, the standard for declaring a public health emergency under the Model Act could probably not be satisfied at this time. Consequently, the Model Act could not be used to compel compliance with the xenotransplantation safeguards.

The viability of a xenotransplantation surveillance system depends upon its ability to collect epidemiological data in the absence of such compelling evidence, regardless of whether the recipients appear to be symptomatic or not. For this reason, we have stressed the need either to amend existing public health legislation such that it can accommodate the unique risks associated with xenotransplantation or to enact specific xenotransplantation legislation.[41]

While xenotransplantation legislation could not be used to physically compel recipients to provide tissue and body fluid samples — such a stipulation would almost certainly be struck down as unconstitutional — the legislation could nevertheless provide for the issuance of monetary fines against those recipients who, having benefited from the life saving intervention, refuse to accept responsibility for conforming to the public safety measures.

While one might expect xenotransplant recipients to be a highly motivated group, treatment noncompliance rates for patients with chronic diseases are generally very high.[42] Allotransplant recipients have proven to be no exception, with overall noncompliance rates reported between 20 and 50 percent.[43] With xenotransplantation, there is the further complication that surveillance may need to be performed at different timepoints and locations than follow-up medical care, and we might therefore expect an even lower compliance rate since surveillance has a far less tangible impact on the individual patient's well-being than follow-up care in general.

Another possible means of enforcing observance of the public health safeguards would be to condition any follow-up medical care required by recipients on their

compliance with the safeguards and, in particular, on the provision of tissue and body fluid specimens. The problems with this approach are practical, ethical, and legal. The practical difficulty is that while animal-to-human organ transplantations will likely be available only through formally designated xenotransplant centers, it will be difficult to guarantee that recipients also obtain all of their post-xenotransplantation follow-up care from these centers, rather than receiving some or most of such care from other providers. Conditioning follow-up medical services received at xenotransplant centers on compliance with safeguard obligations could act as a disincentive to comply with surveillance measures by making recipients less likely to present themselves to xenotransplant centers, and more likely to present themselves to other providers, for follow-up health care. Moreover, both ethically and legally, it would be impermissible for xenotransplant centers to provide only recipients who submit to serum and tissue extractions with follow-up health-sustaining care, while denying such care to noncompliant recipients. It is much more defensible to link noncompliance to monetary fines than to make follow-up health care inaccessible to noncompliant recipients.

Xenotransplantation legislation could also provide for the detention and isolation of those recipients who persistently refuse to comply with the safeguards, and for whom monetary penalties are an insufficient means of coercion. While detention in combination with directly observed therapy is one of the public health enforcement methodologies that was adopted to deal with persistently noncompliant individuals with active tuberculosis,[44] the detention of noncompliant but asymptomatic xenotransplant recipients is probably unjustified, and may be unconstitutional by virtue of being disproportionately intrusive. Detention is defensible in the case of tuberculosis because detained individuals can be tested for a known and readily identifiable infectious agent, and because any prolonged detention is premised on proof of infection with active tuberculosis as well as repeated failure to comply with treatment regimens, and because detention is necessary to prevent a known infectious disease risk. Similarly, evidence of an infectious and pathogenic agent in xenotransplant recipients may be necessary before the detention of asymptomatic individuals suspected of being carriers of the infectious agent — that is, recipients and their close contacts — becomes a legally acceptable means of enforcing compliance with the safeguards. In the meantime, monetary fines, if uniformly enacted and diligently enforced, could be a sufficiently persuasive means of ensuring compliance with the public health safeguards.

It is worth noting that, just like the common law grants patients with the right to withdraw their consent to conventional medical treatment at any time, the Common Rule likewise affords research subjects participating in clinical trials with the right to discontinue such participation at any time.[45] Thus, under the Common Rule, recipients would have the right to withdraw from the trial, and from the public health safeguards associated with the trial, at any time. Assuming that xenotransplantation legislation would be federal, a federal preemption issue would therefore be generated from the conflict between the Common Rule right to withdraw and the obligation that would be imposed by xenotransplantation legislation to comply with the safeguards.[46] As a general rule, conflicts between federal laws are resolved in favor of the more explicit and particularized law.[47] Thus, in the circumscribed case of xenotransplantation, xenotransplantation legislation would preempt the Common Rule to the extent that conflicts arise between the two laws. To avoid confusion regarding this issue, xenotransplantation legislation could expressly state that the Common Rule right to withdraw is inapplicable to post-xenotransplantation surveillance of clinical trial participants because monetary fines attach to noncompliance.

Can Specific Legislation Withstand Constitutional Scrutiny?

Legislation authorizing the issuance of monetary fines against those recipients who fail periodically to provide tissue and body fluid specimens could be challenged on the basis that it is in violation of a number of constitutionally protected freedoms. Such legislation could be viewed as intruding upon the right of transplant recipients to maintain the liberty, privacy and security of their persons[48] as well as the right of recipients to be protected from discrimination.[49] If xenotransplantation legislation were to be struck down on constitutional grounds, xenotransplant recipients in the relevant jurisdiction would be under no legal obligation to comply with the public health safeguards.

Although a full constitutional analysis is beyond the scope of this article, we believe that a statutory post-xenotransplantation surveillance system based on monetary penalties would not be discriminatory and that, although it would constitute a violation of the rights of recipients to liberty or security of their persons, this violation would be justified under existing constitutional doctrines.[50] Governments would have a compelling interest in enforcing such a surveillance system, the objective of which would be the acquisition of epidemiological data permitting the rapid identification and containment of infectious agents that could arise from xenotransplantation, thereby serving the fundamental interest of protecting the public health.[51] The implementation of a narrowly tailored surveillance system offers an important means of protecting the public health while avoiding alternative security measures, such as denying recipients the right to take advantage of xenobiotechnology or restricting their freedom of movement and association within society.[52]

Societal Consent to Clinical Xenotransplantation?

Some commentators have opined that while basic research in xenotransplantation ought to proceed unimpeded, clinical trials of xenotransplantation ought not to proceed in the absence of some form of public consultation and consent.[53] Societal consent is not suggested as an alternative to xenotransplantation legislation, the purpose of which is to enforce the public health measures that must necessarily accompany this biotechnology. Rather, it is suggested as a mechanism of ascertaining societal consensus regarding the acceptability of the risks intrinsic to clinical xenotransplantation. Societal consent may be advisable in the case of xenotransplantation because, unlike most clinical trials where the biological risks and benefits are confined to the subjects participating in the research, the most significant risk associated with clinical xenotransplantation — infection with a disease-producing agent — is shared by society as a whole. Proceeding without societal consent to the shared risk could be viewed as subjecting society to involuntary experimentation.

The principal challenge to securing meaningful societal consent is how to convey the esoteric science of xenotransplantation, and the sophisticated issues surrounding its implementation, to the public. To be truly informed, society's consent to, or rejection of, clinical xenotransplantation would need to be based on more than a vague awareness or apprehension of the infectious disease risks. Rather, an informed consent would need to be supported by an understanding of some of the important nuances inherent to xenobiotechnology, such as the fact that xenotransplantation carries with it an unquantifiable infectious disease risk. The public may not fully comprehend or know how to assess their willingness to proceed with a real, yet unquantifiable risk. Further debate and scholarship regarding the necessity and appropriateness of requiring societal consent to xenotransplantation would be valuable, as insufficient attention has been paid to this novel approach to bioethical evaluation.[54]

Conclusion

We must resolve to put into place a legal framework that is capable of enforcing compliance with the necessary xenotransplantation public health safeguards, particularly the collection of tissue and body fluid specimens required for epidemiological surveillance purposes. Establishing an enforceable legal framework is important to the preservation of the public health, to those government agencies charged with protecting the public health, to the sponsors of clinical trials of xenotransplantation, and ultimately to the development of science and biotechnology. If for political or legal reasons it is impossible to enact a legal framework capable of enforcing the public health safeguards, then that impossibility must be communicated to the scientific community forthwith, so that this vital information may be considered in the ongoing debate regarding whether to proceed with xenotransplantation. In our view, while xenotransplantation legislation would impose intrusive obligations on recipients, it nevertheless represents a fair compromise between outright prohibition of clinical xenotransplantation and unduly jeopardizing the public's health through non-existent or ineffective regulation. In exchange for an opportunity to save and prolong their lives, xenotransplant recipients would undertake to provide society with the minimum level of epidemiological data that it requires to protect itself. This data will hopefully enable us to ensure that, should an epidemic result from xenotransplantation, medicine will not be crippled as it was at the height of the bubonic plague: "[...] the plague defied all medicine; the very physicians were seized with it, with their preservatives in their mouths; and men went about prescribing to others and telling them what to do, till the tokens were upon them, and they dropt down dead, destroyed by that very enemy, they directed others to oppose."[55]

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52. *Id.*

53. Bach et al., *supra* note 23; M. Somerville, *The Ethical Canary: Science, Society and the Human Spirit* (Toronto: Penguin, 2000): at 104.

54. In addition to the issue of how to assure that societal consent is informed, other issues needing further erudition include how to effectively disseminate information to the public (e.g., mailed information packages, televised debate); how to collect consent (e.g., referendum, online polls); quorum requirement — what percentage of a nation's citizenry must vote for the societal consent or refusal to be considered effective and binding (e.g., 15%; 30%; 50%); level of consent required (e.g., regular majority; two thirds majority); scope of the research to which consent is being provided (e.g., cell and tissue xenotransplantation, whole organ xenotransplantation); effect of societal refusal (i.e., particularly in countries already engaged in clinical trials of cell and tissue xenotransplantation).

55. D. Defoe, *A Journal of the Plague Year* (Oxford: Oxford University Press, 1990): at 35–36.