

# Journal of Contemporary Health Law & Policy (1985-2015)

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Volume 14 | Issue 1

Article 8

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1997

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### Recommended Citation

Frank Morgan, *Babe the Magnificent Organ Donor? The Perils and Promises Surrounding Xenotransplantation*, 14 J. Contemp. Health L. & Pol'y 127 (1998).

Available at: <https://scholarship.law.edu/jchlp/vol14/iss1/8>

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## COMMENTS

### **BABE THE MAGNIFICENT ORGAN DONOR? THE PERILS AND PROMISES SURROUNDING XENOTRANSPLANTATION**

God watches over us, cats look down on us, dogs look up to us,  
and pigs look us right in the eye.<sup>1</sup>

In the United States alone, over 40,000 people remain on the organ recipient waiting list each year.<sup>2</sup> Several approaches have been taken to increase the supply of human organs, but currently the demand far outstrips the supply.<sup>3</sup> Xenotransplantation, the use of animal organs for transplants into humans, is a response to the human organ shortage.<sup>4</sup> On September 23, 1996, the Public Health Service (PHS) issued draft guidelines (Guidelines) in the Federal Register governing xenotransplantation.<sup>5</sup> The proposed Guidelines were open for a ninety-day comment period, after which a final draft was to be issued.<sup>6</sup> Working together, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Food and Drug Administration (FDA), through a series of public meetings and submissions, created the Guide-

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1. Attributed to Sir Winston Churchill.

2. Charles Marwick, *British American Reports on Xenotransplantation*, 276 JAMA 589, 589 (1994).

3. *Id.*; COMMITTEE ON XENOGRAFT TRANSPLANTATION: ETHICAL ISSUES AND PUB. POL'Y, INSTITUTE OF MEDICINE, XENOTRANSPLANTATION: SCIENCE, ETHICS, AND PUBLIC POLICY 10-12 (1996) [hereinafter INSTITUTE OF MEDICINE].

4. INSTITUTE OF MEDICINE, *supra* note 3, at 6. See Louisa E. Chapman et al., *Sounding Board: Xenotransplantation and Xenogenic Infections*, 33 NEW ENG. J. MED. 1498, 1498 (1995). See also S. S. Kalter & R. L. Heberling, *Xenotransplantation: and Infectious Diseases*, 37 INST. OF LABORATORY ANIMAL RESOURCES J. 31, 31, 35 (1995).

5. Xenotransplantation is a procedure to transplant animal organs, tissues and cells into humans. *Xenos* is "the Greek word for strange or foreign." See John Travis, *The Xeno-Solution*, SCI. NEWS, Nov. 4, 1995, at 298.

See also Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. 49,920, 49,920 (1996).

6. Draft Public Health Service Guidelines on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. at 49,920-21 (1996). As of this writing, no subsequent draft has been issued.

lines and made them available for public comment.<sup>7</sup>

Xenotransplantation is not a new science, but it remains a largely unproven scientific endeavor, raising a host of questions.<sup>8</sup> Among the traditional concerns, xenotransplantation trials raise concerns regarding adequate informed consent,<sup>9</sup> acceptance of the donor organ by the donee,<sup>10</sup> and the availability of suitable organs for transplantation.<sup>11</sup> Additionally, xenotransplantation raises several non-traditional concerns, which are in part the impetus for the Guidelines.<sup>12</sup> Transplanting non-human organs into a human introduces potential zoonoses, diseases transmitted from animals to humans,<sup>13</sup> in the organ recipient. While not as common in allotransplantation (the transplantation of organs, tissues, and cells between humans), xenotransplantation creates an environment where an infection can be transmitted to a "close contact" of the organ recipient.<sup>14</sup>

Cross-species transmission of diseases has led to some spectacular

7. *Id.*

8. INSTITUTE OF MEDICINE, *supra* note 3, at 15-16.

9. *Id.* at 62.

10. See NUFFIELD COUNCIL ON BIOETHICS, ANIMAL TO HUMAN TRANSPLANTS: THE ETHICS OF XENOTRANSPLANTATION, para. 1.3 (1996) [hereinafter NUFFIELD COUNCIL ON BIOETHICS]. Because of the need to facilitate acceptance of the animal organ, doctors employ immunosuppressive drugs. *Id.*

[I]n patients with xenotransplants the diagnosis and management of familiar zoonoses may be complicated by immunologic manipulations that alter the clinical presentation of illness, the reliability of antibody testing, and the response to therapy. Infusions of bone marrow from the animal and other new strategies proposed for manipulating the immune response of the host undergoing xenotransplantation may also raise the risk of infectious disease. The intense immunosuppression of patients undergoing xenotransplantation may facilitate both the amplification and the epidemic potential of pathogens.

*Id.*; see also Chapman, et al., *supra* note 4, at 1500.

11. Marian G. Michaels & Richard L. Simmons, *Xenotransplant Associated Zoonoses*, 57 *TRANSPLANTATION* 1, 4-5 (1994). Although xenotransplantation and xenografts are measures to circumvent human organ shortage problems, some evidence suggests that the use of non-human primates would be prohibitive at the onset because of the relatively low numbers of primates that would be suitable as donors. *Id.* There is additional concern that even the existing supply of baboons taken together would not fill the demand. See Rachel Nowak, *Xenotransplants Set to Resume*, 266 *SCIENCE* 1148, 1148 (1994). Finally, "there is a realistic concern that only the rich will be able to afford lifesaving animal organs." See Joseph Palca, *Animal Organs for Human Patients?* 25 *HASTINGS CENTER REP.* 4, 4 (1995).

12. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 *Fed. Reg.* at 49,920.

13. See Michaels & Simmons, *supra* note 11, at 1. INSTITUTE OF MEDICINE, *supra* note 3, at 8.

14. See Chapman et al., *supra* note 4, at 1498-99.

images in recent movies and books.<sup>15</sup> Unlike scenes depicted in these movies and books, however, it is highly unlikely that xenotransplantation's greatest danger would come from a viral strain like Ebola, whose short latency period, generally less than two weeks, makes it a poor candidate for a major outbreak. Ebola can be contained before it spreads because it quickly causes death, giving the carrier little chance to infect others.<sup>16</sup> In contrast, the danger in a cross-species transmission would involve a virus with a long latency period, like Human Immune Deficiency Syndrome Virus (HIV), which goes undetected in the donor animal and could remain undetected in the host.<sup>17</sup> Moreover, xenotransplantation raises new ethical issues regarding the breeding of animals solely for their organs,<sup>18</sup> some psychological issues for the recipient not encountered in allotransplantations,<sup>19</sup> and its possible negative impact on human organ donation.<sup>20</sup>

Part I of this Comment establishes the context of xenotransplantation by describing the current state of human organ transplantation. Part II examines several of the relevant statutory provisions under which the first clinical trials will be governed. This Comment then assesses xenotransplantation, detailing the science, the early and recent cases, and probing the ethics. It also discusses the differences between the British approach and the American approach.

Part V concludes that xenotransplantation clinical trials should proceed, if at all, only with great caution and subject to several restraints.

15. Movies like *Outbreak* and the recent Tom Clancy book *EXECUTIVE ORDERS* are two examples from a long list.

16. See Chapman et al., *supra* note 4, at 1498-99. Ebola's latency period is five to twelve days. Containment procedures can be initiated quickly because the host will begin to exhibit symptoms, 80% of the time ending in death. In a virus with a lengthier latency period, it is able to spread more broadly because the host has not begun to show symptoms and will continue to spread the virus unknowingly. *Id.*

17. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 6.14. The specter of a virus with a lengthy latency period like HIV is a controverted topic. *Id.* See also Palca, *supra* note 11, at 4.

18. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 4.1-4.54.

19. See INSTITUTE OF MEDICINE, *supra* note 3, at 16. Many transplant recipients feel sadness associated with their gain because of the death of another. But the families of the organ donor sometimes are solaced by the fact that the death of a loved one gave another an opportunity to live. How xenotransplantation may affect these emotions and the emotions of recipients who know that they have a non-human organ are still to be determined. *Id.*

20. See *id.* at 16. For example, "[p]eople who have received human organ transplants often report having deep and complex emotions about having another person's organ in their bodies." *Id.*

Risk to third parties cannot be discounted, and until reliable methods for providing organs free of potential pathogens<sup>21</sup> are established, the initial recipients need to be monitored closely. They should be required to submit names of all sexual and close contacts,<sup>22</sup> including past, present, and future contacts. Moreover, when the patient is notified that xenotransplantation may be an option, she must consent to the necessary restrictions after being informed of them. Informed consent should include a waiver of the right to withdraw from the clinical trial. Finally, early xenotransplantations should be conducted only when no other alternatives are available.

## I. FAILURE TO MEET THE DEMAND: THE HUMAN ORGAN DONOR SHORTAGE

### A. *Tragic Shortages*<sup>23</sup>

Demand for xenotransplantation arises from the undersupply of human organs for transplantation.<sup>24</sup> Currently, over 40,000 people each year are on waiting lists for organs.<sup>25</sup> The greatest successes in allotransplantations are kidney transplants, with heart and other organ transplants on the rise.<sup>26</sup> Increased success rates are largely the result of improved immunosuppression,<sup>27</sup> which prevents the donor organ from being re-

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21. A pathogen is: "Any virus, microorganism, or other substance causing disease." *STEDMAN'S MEDICAL DICTIONARY* 1312 (26th ed. 1995).

22. A "close contact" is defined as "household members and others with whom the recipient participates in activities that could result in exchanges of body fluids." See Draft Public Health Service Guidelines on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. 49,920, 49,923 (1996).

23. This subheading is borrowed, in part, from Guido Calabresi and Phillip Bobbitt's book, *TRAGIC CHOICES*, which provides an excellent discussion of the choices people confront when supply of an important good is limited. GUIDO CALABRESI & PHILLIP BOBBITT, *TRAGIC CHOICES* (1978).

24. PHS in its Guidelines, succinctly described this shortage.

The demand for human cells, tissues, and organs for clinical transplantation continues to exceed the supply. The resultant limited availability of human allografts, coupled with recent scientific and biotechnical advances, has prompted the development of new investigational therapeutic approaches that use cells, tissues, and organs of animal origin (xenografts) in human recipients.

Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. at 49,921.

25. See Marwick, *supra* note 2, at 589.

26. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 1.3-1.9. See also INSTITUTE OF MEDICINE, *supra* note 3, at 11.

27. See Joan Stephenson, *Xenotransplantation Workshop Ponders Science, Safety of Animal Tissue Grafts*, 274 JAMA 285, 285 (1995). Xenotransplantation has only become viable due to the "revolution in techniques for immunosuppression." *Id.*

jected by the recipient's immune system. National registries also have facilitated better matches between organ donors and recipients.<sup>28</sup> Despite the progress of the medical and scientific communities in allotransplantations, their continued success hinges on access to an adequate supply of human organs, which is currently lacking.<sup>29</sup> Notwithstanding national campaigns<sup>30</sup> to increase public awareness of the need to donate, organ donation has not increased sufficiently. In fact, donation may even decrease depending on the type of campaign that is launched.<sup>31</sup> This phenomenon occurs because people feel that no need exists for them to register to donate; the necessary organs can or will be obtained elsewhere.

### B. *The National Organ Transplant Act*<sup>32</sup>

The history of the National Organ Transplant Act (NOTA) identifies some issues posed by xenotransplantation. Congress enacted NOTA to address several areas of concern, including: establishing national registries; ensuring organs were not allocated on the basis of wealth; and, providing uniform regulations to be followed in organ procurement.<sup>33</sup> Congress was particularly concerned not only with the lack of organ donors, but also with issues of equity.<sup>34</sup> These issues need to be dealt with in xenotransplantations. One future critic, then Representative Albert Gore, was quite optimistic about NOTA's prospects when it was passed, only to be disappointed by its subsequent implementation.<sup>35</sup> This suggests the necessity of carefully reviewing xenotransplantation decisions to ensure that such decisions are insulated, to the greatest extent possible,

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28. See National Organ Transplant Act, 42 U.S.C. § 274b(2)(i)-(ii) (1996) (establishing a national list to match donors to recipients).

29. See Fred H. Cate, *Human Organ Transplantation: The Role of Law*, 20 J. CORP. L. 69, 70 (1994).

30. See INSTITUTE OF MEDICINE, *supra* note 3, at 13.

31. See *id.* at 16.

32. 42 U.S.C. §§ 273-74g (1994).

33. See *id.*

34. See 136 CONG. REC. S13625, S13626 (daily ed. Oct. 4, 1984) (statement of Sen. Quayle). Both sides of the aisle were concerned with putting an equitable system into place. Senator Dan Quayle felt NOTA would "help us provide what has been lacking — a national, equitable policy related to transplantation." *Id.* On the other side, Senator Kennedy felt NOTA was "the most equitable and effective way of distributing organs, and the best methods of financing the cost of organ procurement and transplantation." 136 CONG. REC. S13625, S13627 (daily ed. Oct. 4, 1984) (statement of Sen. Kennedy).

35. Representative Gore had "every hope and expectation that this legislation [would] save many thousands of lives. It represents a true compromise." 136 CONG. REC. H11087-88 (daily ed. Oct. 3, 1984) (statement of Rep. Gore).

from any political partisanship. Partisan politics should not determine what action to take on xenotransplantation; the stakes are too high.

Partisan politics spilled over into the debate concerning why organ donor numbers had plateaued as early as 1990.<sup>36</sup> Each political party criticized the effectiveness of NOTA for opposite reasons. On one side, then Senator Albert Gore of Tennessee criticized both the Reagan and Bush administrations for actively failing to execute NOTA's policies.<sup>37</sup> On the other side, Senator Orrin Hatch of Utah was critical of the amount of congressional abdication that was taking place with respect to NOTA's implementation.<sup>38</sup> Hatch argued that allowing the United Network for Organ Sharing (UNOS) to implement guidelines without any executive action violated a long line of United States Supreme Court decisions.<sup>39</sup>

In essence, the Guidelines represent the opposite situation NOTA presented, almost total executive control and no Congressional action. Congress has failed to take any action on xenotransplantation issues, thereby leaving the policy solely within the control of the executive branch. This control issue may need to be examined if the Guidelines would allow independent contractors to act on behalf of the federal government.<sup>40</sup> Furthermore, because of the possible negative impact xenotransplantation could have on the public health, Congress, as the most politically accountable branch, should exercise a greater degree of oversight.

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36. See 136 CONG. REC. S18236, S18240 (daily ed. Oct. 25, 1990) (statement of Sen. Kennedy). Speaking on the Senate Floor, Senator Ted Kennedy pointed to a two-year gap between the enactment of NOTA and its effective implementation. The system has gradually improved donation rates, but, "[t]he number of organ donors has reached a plateau; the national focus of the referral system needs to be strengthened; and performance standards for organ procurement organizations must be developed." *Id.*

37. Senator Albert Gore accused the Reagan Administration of "footdragging" and more generally criticizing the Bush Administration. 136 CONG. REC. S18236, S18240 (daily ed. Oct. 25, 1990) (statement of Sen. Gore). Senator Gore stated that since 1986 the public's focus on NOTA related issues was drawn away by several things, but "none is more frustrating or disheartening than the miserable job the President and his administration are doing to implement the laws we have enacted." *Id.*

38. See 136 CONG. REC. S18236, S18242 (daily ed. Oct. 25, 1990) (statement of Sen. Hatch). Senator Orrin Hatch argued that Congress was unconstitutionally delegating its power by allowing the United Network for Organ Sharing (UNOS), to take on executive functions. *Id.*

39. *Id.*

40. See *infra* notes 239-54 (discussing the potential for biotechnology companies to monitor xenotransplant recipients and close contacts and provide informed consent).

### C. Ethical Considerations in Allografts

One of the primary ethical concerns in human organ donation is separating the dire need of a person waiting to receive an organ from the potential donor's life interests.<sup>41</sup> Included in these concerns is the potential donor's family, who also has an interest in maintaining the dignity of the dying individual.<sup>42</sup> In some cases, time can pressure decisions because a medical team may be preparing the individual for the transplant while the organ is being harvested from the donor.<sup>43</sup>

Another ethical consideration surrounds live donors giving an organ, tissue, or bone marrow to a recipient.<sup>44</sup> The danger of coercion may exist in these situations, particularly when a family member is involved, with the live donor possibly feeling obligated to provide the necessary organ or tissue for the recipient.<sup>45</sup> Although a national registry exists for bone marrow donors, maintaining lists of individuals willing to donate, the number of suitable donors is, as with organs, below the demand.<sup>46</sup> This leaves open the possibility of coercion where a family member is able, but unwilling, to donate.

### D. Alternatives to Increase the Supply of Organs

#### 1. Changing the Law

One proposal to increase the supply of human organs is the enactment of legislation to call for presumed consent.<sup>47</sup> Presumed consent would permit the removal of organs for donation where no express wish to the

41. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 2.9.

42. *Id.* at 82. Often, the potential donor has expressed no interest in donation. This leaves the family with the decision of whether organs should be removed for donation. Even if the dying individual expressed a wish to donate, emergency room physicians find it difficult to overrule the wishes of the family if it disallows removal of the organs. *Id.*

43. See, e.g., Steve Reinbrecht, *Visitors His Salvation in Long Wait for Heart*, *READING TIMES*, Nov. 1, 1995, at B1; see also Marla K. Clark, Note, *Solving the Kidney Shortage Crisis Through the Use of Non-Heart-Beating Cadaveric Organs: Legal Endorsement of Perfusion as a Standard Procedure*, 70 *IND. L.J.* 929, 935 (1995).

44. See INSTITUTE OF MEDICINE, *supra* note 3, at 11. Several types of live donor transplants occur where the donor only needs one of a paired organ set to live, as in the case of a kidney. Bone marrow is another example of a procedure that is performed with a live donor. *Id.*

45. See Joel D. Kallich & Jon F. Merz, *The Transplant Imperative: Protecting Living Donors from the Pressure to Donate*, 20 *J. CORP. LAW* 139, 145 (1995).

46. See National Bone Marrow Registry, 42 U.S.C. § 274k(a)(1994) (establishing a nationwide registry of bone marrow donors).

47. See Cate, *supra* note 29, at 83-84.



contrary has been provided.<sup>48</sup> Currently, even though public support for donation is high, the legal presumption is that consent to donate does not exist.<sup>49</sup> Only two ways of bypassing this presumption exist: first, to sign an organ donor card; and second, to gain the consent of the next-of-kin.<sup>50</sup> Both of these alternatives seem to be ineffective methods of circumventing the legal presumption against consent.<sup>51</sup> While changing the laws simply to reflect public opinion polls may not be justified, it is an indication that legislation in this area would receive public support.

Another proposal would allow for compensation of those agreeing to donate organs.<sup>52</sup> While this is statutorily prohibited,<sup>53</sup> it can be argued that since all others involved in the process are compensated in some form, so too should the donor.<sup>54</sup> However, selling organs for transplantation could adversely affect the number of individuals willing to donate for purely altruistic reasons<sup>55</sup> and may well defeat the purpose by actually decreasing the overall numbers of organs donated. Because donation rates are fragile, the decrease in donation by non-paid donors may offset the additional organs made available by compensating donors.<sup>56</sup> In other words, to pay donors for their organs might actually decrease the number of available organs below current levels.

## 2. Changing the Oil

Technological innovations are moving toward increasing the availabil-

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48. *Id.* In practice, this could be difficult to implement because in some cases it could conflict with the wishes of the family. Further, whether this approach would raise the level of available organs enough to meet the demand is not clear. *Id.*

49. *See id.* at 81.

[D]espite overwhelming public support for transplantation, current law assumes that no one wishes to donate organs or tissues upon death. According to a 1990 Gallup poll, ninety-four percent of Americans report having heard or read about organ transplants; eighty-four percent believe that transplants are successful in prolonging and improving the quality of life; eighty-nine percent said that they were likely to honor loved ones' requests that their organs be donated after their death.

*Id.*

50. *Id.* at 81-82.

51. *Id.* at 82-83.

52. *Id.* at 84-85.

53. *See* National Organ Transplant Act, 42 U.S.C. § 274e(a) (1996).

54. *See* Cate, *supra* note 29, at 85. The transplant removal team, the implanting team, hospitals, among many others, all receive compensation. *Id.*

55. *See* Sheldon F. Kurtz & Michael J. Saks, *The Transplant Paradox: Overwhelming Public Support for Organ Donation vs. Under-Supply of Organs: The Iowa Organ Procurement Study*, 21 J. CORP. L. 767, 792 (1996).

56. *Id.*

ity of mechanical devices that can perform functions of human organs.<sup>57</sup> These efforts have included attempts to make mechanical hearts, lungs and kidneys.<sup>58</sup> Although mechanical devices are more readily available now, the preference is still for an organic source.<sup>59</sup>

## II. EXISTING REGULATIONS GOVERNING XENOTRANSPLANTATION TRIALS

### A. *Basic Health and Human Services Policy for the Protection of Human Subjects*<sup>60</sup>

The Department of Health and Human Services (HHS) requires that "all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency . . .",<sup>61</sup> must comply with several requirements. Xenotransplantation trials would fall under federal regulation in several respects.

To begin with, any institution engaging in research subject to regulation must submit written assurances that it will comply with the regulations.<sup>62</sup> The regulations require that at least one institutional review board (IRB) be established. IRBs must also meet membership requirements, including minimum membership numbers,<sup>63</sup> and background requirements for members.<sup>64</sup> IRBs can review proposed research, provided a majority of

57. See Cate, *supra* note 29, at 69.

58. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 2.11-2.32.

59. This would include either a human or an animal organ.

60. See Basic HHS Policy for Protection of Human Research Subjects, 45 C.F.R. § 46 (1996).

61. 45 C.F.R. § 46.101(a).

62. These assurances:

shall at a minimum include: (1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. . . . (2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties. (3) A list of IRB members identified. . . . (4) Written procedures which the IRB will follow. . . . (5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

45 C.F.R. § 46.103(b).

63. The minimum number is five. 45 C.F.R. § 46.107(a).

64. At least one member must be unaffiliated with the institution in any respect; one

the members of the IRB board are present, including at least one member with a nonscientific background.<sup>65</sup>

IRBs ensure that adequate informed consent is given to participants.<sup>66</sup> Because participation is voluntary and may be discontinued at any time, the current policy would need to be addressed for xenotransplant recipients.<sup>67</sup> For reasons discussed below, IRBs should be required to inform xenotransplant recipients of several other factors.<sup>68</sup>

HHS regulations also require maintenance of records by the IRBs for a minimum three-year period.<sup>69</sup> This minimum provision would need to be extended to provide for the potential latency periods of as-yet-undiagnosed pathogens.<sup>70</sup> The HHS regulations require that the “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”<sup>71</sup> This provision may be problematic because, to date, there have been no tremendous successes for xenotransplantations.<sup>72</sup> Additional

must be a scientist; one must be something other than a scientist; and no member may have a conflicting interest. See 45 C.F.R. § 46.107(b)-(e).

65. See 45 C.F.R. § 46.108(b).

66. The following information is required:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained; . . .

(1) A statement that participation is *voluntary . . . and the subject may discontinue participation at any time . . .*

45 C.F.R. § 46.116(a) (emphasis added). The IRB may provide additional information if it will help to protect the welfare of the patient. See 45 C.F.R. § 46.109(b).

67. *Id.* Continuing participation in xenotransplant trials should be made mandatory, with no possibility of discontinuing, thereby recognizing the public health considerations. See *infra* text accompanying notes 258-60.

68. See *infra* text accompanying notes 154-58.

69. See 45 C.F.R. § 46.115(b). The minimum requirement would need to be extended to provide adequate monitoring of xenotransplant recipients and their close contacts.

70. See INSTITUTE OF MEDICINE, *supra* note 3, at 44. Because viruses with unknown latency periods exist, xenotransplantation poses special risks. *Id.*

71. 45 C.F.R. § 46.111(a)(2).

72. For a discussion of the Baby Fae case, see Joanne Silberner, *Postmortem in Baby Fae*, 128 SCI. NEWS, Dec. 21, 1985, at 390; for a discussion of the recent Jeff Getty case, see

regulations are set forth to protect activities involving fetuses, pregnant women, *in vitro* fertilizations, prisoners, and children.<sup>73</sup> Due to the uncertainty surrounding xenotransplantation, applying the ethical advisory board approach<sup>74</sup> to xenotransplantation procedures is appropriate.

### III. XENOTRANSPLANTATION: READY OR NOT, HERE IT COMES<sup>75</sup>

#### A. *The Science*

##### 1. *Xenotransplantation*

Xenotransplantation involves placing a non-human organ into a human recipient. Early trials will use the non-human organ as a bridge until a suitable human organ is available.<sup>76</sup> Researchers hope that eventually the procedure will work well enough so that animal organs can be used interchangeably with human organs.<sup>77</sup> The first step in the process is to find a suitable animal donor. This is similar to the matching process employed in allotransplantations.<sup>78</sup> Much like allotransplants, the recipient must receive drugs, following the transplant, to decrease the response of the immune system which recognizes the organ as foreign.<sup>79</sup> Ordinarily, the body's immune system fights infections by recognizing foreign protein strains.<sup>80</sup> When an organ is transplanted, no matter how closely it is matched, rejection at some level will occur. This is because the body's immune system is extremely effective at recognizing foreign surface pro-

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*Baboon Cells Fail to Join With AIDS Patient's Cells*, AIDS WKLY., Feb. 19, 1996, at 40; for a discussion of the earlier cases see *infra* text accompanying notes 132-153.

73. See 45 C.F.R. § 46.202-46.409.

74. See 45 C.F.R. § 46.204. "One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues . . ." *Id.* § 46.204(a).

75. Jonathan Allan continues to be the most vocal opponent of the Draft Guidelines. "Jonathan S. Allan, D.V.M. is a scientist in the Department of Virology and Immunology, Southwest Foundation for Biomedical Research, San Antonio, Texas." See Jonathan S. Allan, *Xenograft Transplantation and the Infectious Disease Conundrum*, 37 INST. OF LABORATORY ANIMAL RESOURCES J. 37, 37n. (1995). Regarding the commencement of clinical trials Allan states, "[t]ransplant specialists are determined to proceed with studies directed toward xenogeneic transplantation. Over 30 years have gone into its development . . ." *Id.* at 45.

76. See INSTITUTE OF MEDICINE, *supra* note 3, at 8; see also Kalter & Heberling, *supra* note 4, at 31, 35.

77. See INSTITUTE OF MEDICINE, *supra* note 3, at 44.

78. *Id.* at 17-18.

79. *Id.* at 17-26.

80. *Id.* at 26.

teins, which will be present in the tissue from the donor.<sup>81</sup> The only exception occurs in donations from one identical twin to another.<sup>82</sup> To promote the success of the transplant, the recipient ingests drugs to suppress the immune system, which also makes the recipient more susceptible to ordinary diseases.<sup>83</sup> Arguably, recipients from an animal donor are likely to become carriers for a variety of pathogens, both zoonoses and human diseases.<sup>84</sup> Another reason why there is increased likelihood that humans will become carriers is that as phylogenetic distance, or the measure of the genetic distance between species,<sup>85</sup> increases, so too does the level of the immune system's rejection.<sup>86</sup> As the phylogenetic distance increases between the animal donor and the human recipient, the strength of immunosuppressive drugs must be increased to accommodate the body's more virulent rejection.<sup>87</sup> Hyperacute rejection,<sup>88</sup> or total rejection of the organ almost immediately, is a danger inherent in xenotransplantation. This danger increases the further away phylogenetically the donor moves from a human organ. Thus, transplanting a non-human primate organ into a human recipient will require a greater level of immunosuppression in the recipient than the same procedure involving a human organ,<sup>89</sup> and a pig organ will involve an even greater level of immunosuppression in the recipient than the organ from the non-human primate.<sup>90</sup>

## 2. *Transgenesis*<sup>91</sup>

One method of addressing the problem of hyperacute rejection by the recipient's immune system would be to alter the genetic make-up of the material to be transplanted to prevent the recipient's immune system

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81. *Id.*

82. *Id.*

83. See Stephenson, *supra* note 27, at 285. Xenotransplantation has become viable due to the "revolution in techniques for immunosuppression." *Id.*

84. See Chapman et al., *supra* note 4, at 1498-99. Not only may a human carry the animal disease but recombination of viral strains may occur with nascent strains in the recipient. *Id.*

85. See INSTITUTE OF MEDICINE, *supra* note 3, at 17. The closest animal to humans phylogenetically is the chimpanzee. *Id.*

86. *Id.* at 17-18.

87. *Id.*

88. *Id.* at 18-20.

89. *Id.* at 18.

90. *Id.* at 17.

91. "In transgenic modification, either all cells of the animal contain the foreign gene (transgene) which is incorporated stably into their genome expressing the protein, or only selected cells contain it." *Id.* at 30.

from recognizing it as foreign.<sup>92</sup> This would avoid the problem of excessive doses of immunosuppression therapy where an opportunistic infection could invade the host's weakened immune system and cause more severe illness or death.<sup>93</sup> Transgenesis would require that one or two genes<sup>94</sup> from the recipient be incorporated into the donor animal tissue prior to the transplantation.<sup>95</sup> The donor animal organ would then be transplanted into the human recipient with the modified genetic material.<sup>96</sup> If this procedure works as expected, the modified organ would be accepted through identification of genetic markers as "self" thus averting rejection.<sup>97</sup>

### 3. Bone Marrow Chimerism

Another method of avoiding high levels of immunosuppression is to achieve a bone marrow chimerism. First, as in transgenesis, portions of the donor bone marrow are implanted into the recipient before transplanting the organ.<sup>98</sup> Next, radiation would be used to decrease the levels of the recipient's own bone marrow to prevent the recipient's immune system from recognizing the donor's marrow as foreign.<sup>99</sup> Finally, the donor organ would be transplanted into the recipient.<sup>100</sup> Doctors/scientists expect that the donor marrow will begin to work with the recipient's own bone marrow to form a hybrid or chimera which would reject neither the recipient's own organs nor the organ transplanted from the donor.<sup>101</sup>

### 4. Other Alternatives

More modest examples of xeno-technology already are employed in allotransplants.<sup>102</sup> Pig heart valves are used in human heart transplants but they are modified to prevent rejection by the immune system.<sup>103</sup> One

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92. *Id.*

93. *Id.* at 30.

94. *Id.* at 30-32.

95. *Id.* at 30. The genes would be transplanted into the nucleus of a fertilized egg. Only the mature adult would be modified. *Id.*

96. *Id.* at 31.

97. See Stephenson, *supra* note 27, at 285.

98. See INSTITUTE OF MEDICINE, *supra* note 3, at 33-34.

99. See Stephenson, *supra* note 27, at 285; see also INSTITUTE OF MEDICINE, *supra* note 3, at 33-34.

100. See INSTITUTE OF MEDICINE, *supra* note 3, at 36.

101. *Id.* at 33.

102. For example, "pig heart valves have been transplanted into human beings for more than 30 years." See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10 at para. 6.12.

103. *Id.* But the process that the pig heart valves undergo before transplantation ren-

alternative to a complete organ transplantation entails transplanting cells and tissues from a non-human donor into a human, so as to replicate the function of faulty cells.<sup>104</sup>

### 5. *The Pig as Donor*

Using pigs as alternative donors to non-human primates offers several advantages. One such consideration is the availability of gnotobiotic, or germ free pigs.<sup>105</sup> Another is that objections to the use of pigs would be less fierce because, unlike non-human primates, pigs are a common source of food and other items.<sup>106</sup> The Nuffield Bioethics Committee, along these lines, concluded in its second report that using pigs was ethically acceptable, while using primates was unacceptable.<sup>107</sup> Several problems would still need to be overcome before the pig could be considered a viable alternative, including preventing the recipient's rejection of the organ.<sup>108</sup> Pigs are further from humans phylogenetically, and this is problematic because less is known about the possible diseases they may carry. Researchers in Britain discovered the possibility for transmission of retroviruses from pigs to humans which was, in part, the reason for Great Britain's moratorium on clinical trials.<sup>109</sup> When scientists announced the cloning of Dolly the sheep, cloning pigs for use in xenotransplantations became a stronger possibility.<sup>110</sup> Because cloned pigs would be identical in all respects, once a specific-pathogen-free pig was developed it could be cloned and quarantined, which avoids the risk of viral or disease transmission from mother to offspring.<sup>111</sup> The recent discovery of porcine endogenous retroviruses, however, may stall, indefinitely, the use of pigs in clinical trials.<sup>112</sup>

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ders them unlikely candidates for spreading disease because they are so substantially altered and chemically treated. This modification is not viable for most other organs and tissues. *Id.*

104. See INSTITUTE OF MEDICINE, *supra* note 3, at 13-15.

105. See D. K. C. Cooper, *The Pig as Potential Organ Donor for Man*, in XENOTRANSPLANTATION, THE TRANSPLANTATION OF ORGANS AND TISSUES BETWEEN SPECIES 481, 482 (D. K. C. Cooper et al. eds., 1991).

106. *Id.* at 481.

107. See Peter J. Morris, *Pig Transplants Postponed Until We Know More About Graft Rejection, Physiology, and Ineffectivity*, 314 BRITISH MED. J. 242 (1997).

108. *Id.*

109. See Jacqui Wise, *Pig Virus Transfer Threatens Xenotransplantation*, 314 BRITISH MED. J. 623 (1997).

110. See Robert Winston, *The Promise of Cloning for Human Medicine: Not a Moral Threat But an Exciting Challenge*, 314 BRITISH MED. J. 913 (1997).

111. See *infra* text accompanying note 113 and notes 178-80 and accompanying text.

112. See Rick Weiss, *Viruses in Pig Organs Could Infect Humans*, WASH. POST, Oct. 16,

## B. The Viruses

### 1. Endogenous Infection and Exogenous Infection

Viral infections may take two primary routes. Endogenous infection occurs when genes are passed from mother to offspring; this is called a vertical transmission.<sup>113</sup> An exogenous infection is the most common route and comes from another animal.<sup>114</sup> In nature, this can occur from contact with an animal, from insect to human, or from contact with another non-human primate.<sup>115</sup> Other routes, which are not common, involve a latent or chronic infection integrating a host cell.<sup>116</sup>

### 2. Herpesviruses

These viruses "are of greatest concern and probably present the greatest challenge in terms of xenotransplants."<sup>117</sup> While some viruses are thought to be "species specific,"<sup>118</sup> others are benign in the host but become malevolent when they cross species.<sup>119</sup> Macaque monkeys are known to be carriers of the B virus which causes symptoms similar to herpes in human beings. When human beings are introduced to this virus, and not treated, it is fatal.<sup>120</sup> Herpesviruses are the most common viruses associated with allotransplantations and, therefore, necessitate a great deal of attention and concern for xenotransplantations.<sup>121</sup> A plethora of herpesviruses found in different species of monkeys raise concerns when they are isolated and then cross into a different species. Some of these herpesviruses can be oncogenic;<sup>122</sup> others can cause infectious mononucleosis;<sup>123</sup> and others can cause more common forms of

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1997, at A8. Jonathan P. Stoye and Robin Weiss, virologists at the National Institute for Medical Research in London, announced the discovery of the viruses, which belong to the same family as the human immunodeficiency syndrome. *Id.* For a discussion of endogenous retroviruses, see *infra* text accompanying notes 113-16, 125-29.

113. S. S. Kalter, *The Nonhuman Primate as Potential Organ Donor for Man: Virological Considerations*, in *XENOTRANSPLANTATION, THE TRANSPLANTATION OF ORGANS AND TISSUES BETWEEN SPECIES* 457, 459 (D. K. C. Cooper et al. eds., 1991).

114. *Id.* at 459.

115. *Id.*

116. *Id.* at 460.

117. *Id.* at 461.

118. Michaels & Simmons, *supra* note 11, at 1-2.

119. *Id.* at 2-3.

120. *Id.* at 3.

121. *Id.*, See also Kalter, *supra* note 113, at 461.

122. H. saimiri and H. tamarinus are examples of natural infections in one species, but oncogenic in another. Kalter, *supra* note 113, at 462.

123. Epstein-Barr virus. *Id.* at 462.



disease.<sup>124</sup>

### 3. *Retroviruses*

Retroviruses are named for reverse transcriptase, an enzyme that transcribes the viral RNA into the DNA.<sup>125</sup> In non-human primates, a retrovirus of particular interest is the simian immunodeficiency virus (SIV), which causes symptoms similar to HIV-2 in non-human primates.<sup>126</sup> Combining the symptoms of SIV with its genetic similarities to HIV, suggests HIV may be of primate origin.<sup>127</sup> This demonstrates to researchers the possibility that SIV, like HIV, may have a lengthy latency period which would have a great deal of significance for xenotransplantation procedures.<sup>128</sup> Additionally, retroviruses are associated with cancers and other human and non-human diseases.<sup>129</sup>

### 4. *Filoviruses*

Perhaps the most spectacular and least understood of the viruses discussed herein are the filoviruses. Examples of filoviruses include the much publicized strains of Ebola. The source(s) of these viruses remains unknown.<sup>130</sup> These viruses are generally short lived and result in acute outbreaks because of their short latency periods. As such, they do not present much risk to xenotransplantation recipients, provided proper isolation of the donor animal occurs prior to the procedure.<sup>131</sup>

## C. *The Early Cases*

The earliest case of a xenotransplantation to receive notoriety involved the transplantation of a baboon heart into a fifteen-day-old infant.<sup>132</sup> The infant, known only as Baby Fae, survived twenty days with the baboon heart.<sup>133</sup> Baby Fae, however, was not the first human to receive a

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124. *Id.* at 462-464.

125. Michaels & Simmons, *supra* note 11, at 3.

126. *Id.* at 3.

127. *Id.*

128. *Id.* at 3-4.

129. See Kalter, *supra* note 113, at 468.

130. Michaels & Simmons, *supra* note 11, at 4.

131. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. 49,920, 49,925-26 (1996).

132. See Dan Chu, *Helped by a Baboon's Heart, An Imperiled Infant, Baby Fae, Beat the Medical Odds*, PEOPLE WKLY., Nov. 19, 1994, at 71; *Medicines Brave New Babies*, LIFE, Jan. 1985, at 40; Joanne Silberner, *Postmortem in Baby Fae*, SCI. NEWS, Dec. 21, 1985, at 390.

133. See Silberner, *supra* note 72, at 390.

xenotransplant.

In 1964, six patients received chimpanzee kidneys, with the longest recipient surviving nine months.<sup>134</sup> Interestingly, as early as 1969, researchers proposed that “[t]he establishment of breeding programs for chimpanzees and other non-human primates should receive the highest priority.”<sup>135</sup> However, since chimpanzees are now an endangered species, they are not considered as possible donors. The next xenotransplantation also took place in 1964 using baboon kidneys, and again, six patients underwent the operation.<sup>136</sup> Four of the patients lived for a period ranging from nineteen to forty-nine days.<sup>137</sup> The remaining two patients received allotransplants after forty-nine and sixty days but died after thirty-nine and forty-four days, respectively, following the allotransplantations.<sup>138</sup> In all but one of the patients, the procedure failed due to a failure to control rejection.<sup>139</sup> Physicians noted that, “the vigor of the immunologic reaction has seemed to be much less with chimpanzee tissue, in contrast to baboon and rhesus monkey heterotransplants which evoke a fierce response on the part of the human host.”<sup>140</sup>

Aside from a sheep heart being transplanted into a patient who died instantly, no more significant trials, using non-human primates as donors, were attempted until Baby Fae.<sup>141</sup> The procedure was criticized for failing to consider alternatives, including waiting for a suitable human organ<sup>142</sup> and using an infant as a guinea pig for a procedure doomed from the beginning.<sup>143</sup> Yet, Dr. Leonard Bailey, who performed the Baby Fae procedure, defends the transplantation, saying “the compassionate effort to save an infant’s life got lost in a quagmire of professional and public

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134. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at table 3.1; see also Keith Reemsta, *Renal Heterotransplantation from Nonhuman Primates to Man*, 162 ANNALS N.Y. ACAD. OF SCI. 412 (1969).

135. Reemsta, *supra* note 134, at 417; see also Michaels & Simmons, *supra* note 11, at 4-5.

136. See T. E. Starzl et al., *Renal Heterotransplantation from Baboon to Man: Experience With 6 Cases*, 2 TRANSPLANTATION 752 (1964).

137. *Id.*

138. *Id.*

139. *Id.* at 772.

140. *Id.* at 773-774.

141. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at table 3.1.

142. See *Human Heart Not Sought for Baby Fae*, SAN DIEGO TRIB., Oct. 29, 1984, at A4.

143. For a harsh criticism of the procedure by Dr. Bailey and for overall doubts about xenotransplantation’s prospects for success, see Jerold M. Lowenstein, *The Transplant Gap*, DISCOVER, June, 1993, at 25.

rhetoric.”<sup>144</sup> Dr. Bailey notes that Baby Fae did not die from a rejection of the baboon heart, but instead from an incompatible blood type.<sup>145</sup> He contends Baby Fae would have survived the operation if a baboon donor with a compatible blood type had been used.<sup>146</sup>

Attracting a great deal of attention recently was the plight of a thirty-seven year old AIDS patient in the final stages of the disease.<sup>147</sup> Jeff Getty petitioned the FDA for permission to pursue a xenotransplant procedure, in which he would receive bone marrow from a baboon, because they are inherently resistant to HIV.<sup>148</sup> Following the introduction of the baboon bone marrow, Getty was given radiation treatment to promote chimerism between the donor marrow and his own.<sup>149</sup> After receiving the approval of both the University of Pittsburgh’s IRB and the University of California, San Francisco’s IRB, the FDA agreed to allow the procedure to go forward for the limited purpose of establishing the safety of the procedure, not the effectiveness.<sup>150</sup> Getty’s improved health was attributed to radiation treatment rather than the xenotransplant.<sup>151</sup> In fact, it appears that the baboon marrow failed to engraft at all, so that from a xenotransplantation perspective, the operation was not a success.<sup>152</sup> The only encouraging aspect, to proponents of xenotransplantation, is that no evidence of viral transmissions from the donor to the recipient exists.<sup>153</sup> It remains too early to judge the procedure a total success from the viral aspect because Getty could be a carrier of a virus with a long latency period.

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144. Leonard L. Bailey, *Organ Transplantation: A Paradigm of Medical Progress*, THE HASTINGS CENTER REP., Jan.-Feb., 1990, at 24.

145. *Id.* This incompatibility of blood type would cause problems in an allotransplantation as well. *Id.*

146. *Id.*

147. See Clare Thompson, *No Cheers for Baboon to AIDS Patient Xenotransplant*, 346 THE LANCET 369 (1995); *Animal-to-Human Transplants Raise Concerns*, AIDS WKLY. PLUS, Mar. 18, 1996, at 32.

148. There are, however, “several doubts as to whether baboon cells are truly resistant to HIV.” See Thompson, *supra* note 147, at 369.

149. See *supra* text accompanying notes 98-101.

150. See Lawrence K. Altman, *AIDS Test Involving Baboon is Approved*, N.Y. TIMES, July 15, 1995, at § 1, page 7, col. 1.

151. See Janet Fricker, *Barrier to Transplacental Exchange; Baboon Xenotransplant Fails But Patient Improves*, 347 THE LANCET 457 (1996); *Baboon Cells Fail to Join With AIDS Patient’s Cells*, AIDS WKLY. PLUS, Feb. 19, 1996, at 40; *Animal-to-Human Transplants Raise Concerns*, AIDS WKLY. PLUS, Mar. 18, 1996, at 32.

152. *Id.*

153. See Fricker, *supra* note 151, at 457. “The Center for Disease Control and Prevention have been monitoring Getty for baboon-derived infections and have as yet found no evidence that baboon viruses or other infections have been transmitted.” *Id.*

### D. *The Ethics*

#### 1. *Informed Consent*

In addition to informed consent requirements found in the HHS regulations,<sup>154</sup> the Guidelines propose that several new elements be disclosed to the potential subject. These would include:

The potential for infection from zoonotic agents known to be associated with the donor species. The potential for transmission of unknown xenogeneic infectious agents to the recipient. . . . The potential risk of transmission of xenogeneic infectious agents to the recipient's family or close contacts, especially sexual contacts. . . . Any need for isolation procedures during hospitalization . . . and any specialized precautions (e.g., dietary, travel) following hospital discharge. . . . The need to comply with long-term or potentially life-long surveillance necessitating routine physical evaluations. . . . The need for the subject to inform the investigator or his/her designee of any change in address or telephone number in order to maintain accurate data for long-term health surveillance. . . . [and] Access by the appropriate health agencies to all medical records. . . .<sup>155</sup>

These informed consent requirements point to several of the difficulties that could be encountered in an attempt to enforce a restrictive informed consent requirement. The United States Supreme Court generally regards restrictions on travel and one's right to privacy as constitutionally suspect.<sup>156</sup> Yet, the Guidelines would require subjects to agree to restrictions on those rights to be eligible for the xenotransplant procedure. Should an unhappy xenotransplant recipient subsequently file suit, a judicial decision overturning the restrictions as unconstitutional would erode the public safety measures. Should an individual successfully petition a court to overturn restrictions imposed by the IRB, all efforts to monitor the recipient's close contacts would fail. In the event that the recipient decides to suspend his or her compliance with the program, and carries a latent virus, a way to contain the damage may not exist.

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154. See *supra* notes 66 and 71 and accompanying text.

155. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. 49,920, 49,923 (1996).

156. See *Roe v. Wade*, 410 U.S. 113 (1973) (holding that the Fourteenth Amendment to the United States Constitution guarantees a fundamental right to privacy); see *Shapiro v. Thompson*, 394 U.S. 618 (1969) (holding that a residency requirement to obtain welfare aid violated an individual's right to interstate travel).

## 2. Risk to Third Parties

Unlike risks associated with allotransplantation, xenotransplantation presents an unidentifiable and unquantifiable risk to third parties.<sup>157</sup> The risk to the recipient is real and swift because the organ might be rejected or a zoonotic infection could result in death. Nonetheless, the recipient probably is undergoing the procedure as a last alternative.<sup>158</sup> The question that must be asked is whether it is ethically justifiable to hold one person's life more heavily in the balance than that of another. This is a difficult question to resolve. When coupled with the potential infection of significant numbers of people, the balance begins to tip more heavily in favor of erring on the side of caution.

### E. The Nuffield Council Report

The Nuffield Council Report (Nuffield Report), which preceded the IOM report, responded to an announcement by Imutran, Ltd. that it would begin xenotransplantation trials in 1996.<sup>159</sup> The Nuffield Report stresses that the presentation of such issues is urgent due to "the continuing shortfall of human donation to meet the growing demand for organ transplantation; growing uncertainty about the risk of potential transmission of diseases by xenografts; public concern about the proper use of genetic modification of animals; [and] wide and increasing concern about animal welfare."<sup>160</sup>

Before considering measures to safeguard xenotransplantation procedures, the Nuffield Report considers more traditional alternatives. First on this list is an attempt to decrease the demand for organs by increasing the level of public health. For example, "the major causes of liver failure in the UK are alcoholism, infection with hepatitis viruses and drug intoxication."<sup>161</sup> Many hope that by decreasing the number of people needing

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157. The Institute of Medicine (IOM) committee concluded, "although the degree of risk cannot be quantified, it is unequivocally greater than zero." (emphasis in original). See INSTITUTE OF MEDICINE, *supra* note 3, at 2.

158. "If the risk of xenotransplant-associated infections is restricted to the recipient, it simply constitutes one more factor affecting the risks and benefits of transplantation. However, there may be wider implications for the human community." See Chapman et al., *supra* note 4, at 1498-99.

159. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at Preface. "[T]hese concerns have been highlighted by the announcement in September 1995 by the UK company Imutran, Ltd. that, in the light of its research with pigs and monkeys, it envisaged the first xenografts of transgenic pig hearts into human patients taking place in 1996." *Id.*

160. *Id.*

161. *Id.* at para. 2.2.

organ transplants from self-inflicted causes, the supply of human organs will go to truly needy recipients, and far fewer people will be in need. Another, more traditional approach would be to increase the supply of organs by increasing the number of intensive care units, the primary source of most organ donations.<sup>162</sup>

The United Kingdom faces problems similar to the United States concerning the legal approach to organ donation.<sup>163</sup> While polls in the U.K., like those in the U.S., show that organ donation is widely supported by the population, still relatives are able to withhold consent.<sup>164</sup> Placing patients who will inevitably die on elective ventilation to preserve organs for transplantation is controversial; not only is it currently illegal, but conflicts with the underlying premise of medical treatment being in the best interests of the patient.<sup>165</sup> Regardless of a possible increase in the number of organs made available by the aforementioned procedures, the report concludes that an undersupply is unavoidable.<sup>166</sup> Based on the inability to bridge the gap between organ demand and organ supply, even taking into account the use of artificial mechanical devices, the report concludes that xenotransplants must be considered.<sup>167</sup> Due to the highly speculative possibilities for success of xenotransplants, the Nuffield Report argues it would be ethically impermissible to proceed with human trials until an Advisory Committee on Xenotransplantation is formed by the U.K. Department of Health.<sup>168</sup> Any experiments done with human subjects would be under the review of Local Research Ethics Committees,<sup>169</sup> which are similar to Institutional Review Boards in the United States.

In addition, animal rights issues will be raised. One consideration is whether widespread breeding of animals explicitly for use as organ donors is ethical. The Nuffield Report "accepts the principle that in some cases, the saving of human life or of significantly enhancing its quality may justify a certain amount of animal suffering, provided this is kept to a minimum."<sup>170</sup> Arguments of speciesism were addressed in the report along with conscientious objectors who, for religious or other reasons,

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162. *Id.* at para. 2.3.

163. *See supra* text accompanying notes 47-51.

164. *See* NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 2.7.

165. *Id.* at para. 2.9.

166. *Id.* at para. 2.10.

167. *Id.* at para. 2.32.

168. *Id.* at para. 10.31.

169. *Id.* at para. 10.33.

170. *Id.* at para. 4.7.

would object to procedures involving transplantation of animal organs or tissues.<sup>171</sup> On this issue, the Nuffield Report concludes that non-human primates should be excluded from xenotransplantation studies to the greatest extent possible and if other alternatives, such as the use of pigs, prove workable, then non-human primates should be excluded altogether.<sup>172</sup>

#### F. *The IOM Report*

In 1995, a workshop was held by the Institute of Medicine to discuss the various considerations raised by xenotransplantation. The result was a report (IOM Report), which was a compilation of the various presentations. It is less comprehensive in many respects than the Nuffield Report, but its importance lies in the fact that it serves as part of the basis on which the Guidelines were drafted. Because the public health concerns are real, the IOM Report recommends instituting a program consisting of the following four parts: research, risk assessment, risk management, and risk communication.<sup>173</sup> Risk assessment and communication of that risk present problems because of the uncertain nature of the risk.<sup>174</sup> Risk management would be available before the procedure by conducting a careful pretransplant screening of the animal and the material to be transplanted. After the procedure, a post-transplant screening of the recipient and the transplant would be conducted.<sup>175</sup> Further risk management tools include lifetime surveillance of the recipient and careful archiving of tissue from both the animal and the recipient.<sup>176</sup> Also surveillance would have to cover the health care workers involved and the family of the recipient.<sup>177</sup>

Another method of decreasing the risks of disease transmission is to develop specific-pathogen-free (SPF) animals to be used as donors of both organs and tissues.<sup>178</sup> Expense and time impede the effectiveness of developing SPFs, and even an SPF animal is only free of those pathogens specified.<sup>179</sup> For instance, a significant amount of time would be required

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171. "Speciesism" is the belief that singling out humans is a form of discrimination based on ones species. See *id.* at para. 4.13, 4.23.

172. *Id.* at para. 4.40.

173. INSTITUTE OF MEDICINE, *supra* note 3, at 45.

174. *Id.* at 46-47.

175. *Id.* at 47.

176. *Id.*

177. *Id.*

178. *Id.* at 49.

179. *Id.* at 49-50.

to develop an SPF baboon colony. Baboons take five to seven years to reach sexual maturity and, like human births, are usually single.<sup>180</sup>

A national registry would be an important component of a successful strategy to minimize the impact, if any, on the public health, should a zoonotic infection occur.<sup>181</sup> But a concentrated number of illnesses, as opposed to several scattered ones, is usually required before an outbreak can be detected.<sup>182</sup> A national registry alongside an archive of tissue samples hopefully would be able to provide an ability to investigate the event and hasten the response time.<sup>183</sup>

The IOM Report also notes several concerns surrounding the procurement of organs for transplantation. Many people are distrustful of the current organ procurement system, fearing that this “could easily lead to the perception that animal organs as experimental therapies will be offered to desperately sick people who lack the financial resources or are members of racial or ethnic minorities.”<sup>184</sup> Also some critics express a concern that because the organ donation system is so fragile, early reports, which may be over-enthusiastic regarding the success of xenotransplants, will diminish the overall number of human organs donated.<sup>185</sup>

#### G. *Comparing the Nuffield Council Approach to the Institute of Medicine Approach*<sup>186</sup>

Perhaps the most noticeable difference in these two approaches is with respect to using non-human primates as donors. The IOM Report recommends that SPF animals be used as donors,<sup>187</sup> but says nothing about restricting non-human primates from the donor pool. The Nuffield Report, however, recommends that early trials should exclude non-human primates for both ethical and virulogical reasons.<sup>188</sup> This difference is

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180. *Id.* at 49.

181. *Id.* at 54.

182. *Id.* at 55.

183. *Id.* at 56.

184. *Id.* at 67.

185. *Id.* at 69.

186. *Id.*

187. *Id.* at 2.

188. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 10.11

The routine use of higher primates to supply organs for xenotransplantation on a scale sufficient to meet the organ shortage would represent a new use of primates in the UK. . . . The potential risk of extinction, even to a species like the baboon that is not currently endangered, must be taken seriously. Xenotransplantation using primate organs or tissues may pose particular risks of disease transmission. *Id.* at para. 10.11 (citations omitted).



partly a result of the varying degrees of emphasis that the two groups placed on the rights of the donor animals. The Nuffield Report emphasized maintaining the dignity of the animals in the process.<sup>189</sup> After a brief overview of the two competing philosophical views towards animal rights, the utilitarian against the Kantian rights approach, the IOM Report concluded that, "although no philosophical or ethical consensus has emerged, most people would favor proceeding with well-designed xenotransplantation experiments that begin with baboons, but would favor the use of swine if these animals prove to be a viable source of organs for humans."<sup>190</sup> An interesting proposal in the Nuffield Report is to lower the demand for organs by increasing overall public health and awareness.<sup>191</sup> The recommendation section of the IOM Report includes no such suggestion.

#### *H. The Guidelines*

While not binding, the Guidelines are intended to present information. Issuance of the Guidelines was not intended to be an endorsement of beginning clinical xenotransplantation trials, nor was it intended to suggest that funds would be routed to institutions pursuing the procedure.<sup>192</sup> Advocates call for periodic review and modification of the Guidelines as scientific advances are made.<sup>193</sup> The Guidelines' objective is to "present measures that can be used to minimize the risk to the public of human disease due to known zoonoses and emerging xenogeneic infectious agents arising from xenotransplantation."<sup>194</sup> The Guidelines break down into four main sections: xenotransplantation protocol issues, animal sources, clinical issues, and public health needs.

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189. See *id.* at para. 4.13. In fact, the Council reprinted a submission that maintained xenotransplantation was nothing more than speciesism, and that the procedure was a new form of slavery. *Id.*

190. INSTITUTE OF MEDICINE, *supra* note 3, at 78. The data suggests that baboons would not be ideal donors because of the long gestation period, the fact that most baboons give singular birth, and their relatively small numbers in captivity.

191. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 10, at para. 2.2. "One possible way of bridging the gap between supply and demand is to reduce the demand for human organs and tissue by introducing public health measures to prevent the conditions that currently require treatment by transplantation." *Id.* "[T]he major causes of liver failure in the UK are alcoholism, infection with hepatitis viruses and drug intoxication." *Id.*

192. Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. 49,920, 49,921 (1996).

193. *Id.* at 49,922.

194. *Id.*

### 1. Protocol Issues

Xenotransplantation protocol issues include the composition of the transplant team, the maintenance of the site at which the procedure is performed, surveillance plans, and informed consent proposals.<sup>195</sup> Proposals recommend but do not require, that the xenotransplant team be composed of at least one epidemiologist, one transplant immunologist, one member with a veterinary medicine background, and another with an infectious disease specialty.<sup>196</sup> Clinical site suggestions include requiring that the institution participate with accredited virology and microbiology laboratories.<sup>197</sup>

### 2. Animal Sources

In the animal sources section, the Guidelines deal with the procurement of animals, screening of animals, and maintenance facilities, including both record maintenance and animal surveillance. These records should include details of the animal's contacts and lineage.<sup>198</sup> Although the Guidelines propose that SPF animals be the sole xenotransplant donors, like the IOM report does, the regimen is fairly exacting.<sup>199</sup> Specifically excluded from animal housing facilities should be any animal with any documented illness including, but not limited to: bovine spongiform ecephalopathy (BSE), the so-called "mad cow disease;" wild-caught animals; imported or first generation animals; and, any slaughterhouse animals.<sup>200</sup> Animal activity will be monitored and restricted so that anything from the outside environment that could potentially transmit a pathogen is kept out of contact with the animals in the facility. This includes monitoring the feed given to the animals and animal contact with human caretakers.<sup>201</sup> After an animal has reached the appropriate age and is deemed suitable as a donor, the animal is placed in quarantine. This occurs, though, only if a period of greater than three months has elapsed from the time when the animal was initially deemed suitable as a donor.<sup>202</sup> Once tissues are selected for use in a xenotransplantation, they

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195. *Id.* at 49,922-23.

196. *Id.* at 49,920, 49,922.

197. *Id.*

198. *Id.* at 49,923-49,926.

199. *See id.* at 49,923.

200. *Id.* at 49,923.

201. *Id.* at 49,924.

202. *Id.* at 49,925.

should undergo further tests for the presence of any pathogens.<sup>203</sup> A full necropsy will be performed on the animal, and appropriate quantities of tissue and biologic samples will be archived.<sup>204</sup>

### 3. *Clinical Issues*

The clinical issues section more thoroughly discusses surveillance of the recipient, including his/her contacts and clinical records. The recipient will be informed that any unexplained illnesses should be reported to the clinical center immediately and that the recipient should inform his/her close contacts of the need to do the same if they should experience any unexplained illnesses.<sup>205</sup> The clinical center also is responsible for maintaining certain levels of biologic specimens including safeguarding the samples' continued storage.<sup>206</sup>

### 4. *Public Health*

Finally, in the section dealing with public health needs, the Guidelines recommend the establishment of a national registry to "allow the accurate linkage of these events to exposures on a national level . . . ." <sup>207</sup> Additionally, tissue, plasma, and leukocytes are recommended as materials to be archived.<sup>208</sup> The location of the specimens and the nature of the archived specimens should be placed in the health care records to allow access as required.<sup>209</sup>

#### *I. The Guidelines' Variances From the IOM Recommendations*

One critical area where the Guidelines differ from the recommendations of the IOM Report is whether the Guidelines are mandatory or precatory. The IOM Report recommends that "adherence to specific national guidelines be required of all experimenters and institutions that undertake xenotransplantation trials in humans."<sup>210</sup> But, "[t]he draft guideline is intended to provide information and does not set forth requirements."<sup>211</sup> Following the ninety day comment period, the PHS will

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203. *Id.* at 49,926.

204. A necropsy is a post-mortem examination of the animal's cells. *Id.* at 49,926.

205. *Id.* at 49,926-49,927.

206. *Id.* at 49,926.

207. *Id.* at 49,928.

208. *Id.* at 49,929.

209. *Id.*

210. INSTITUTE OF MEDICINE, *supra* note 3, at 3.

211. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. at 49,921.

issue a revised draft guideline.<sup>212</sup> Thus, whether the final guidelines will demand adherence is unclear.

The IOM Report also recommends that HHS coordinate the various entities developing, overseeing, and evaluating the Guidelines.<sup>213</sup> However, the Guidelines do not provide for an administrative oversight body.<sup>214</sup> Additionally, the IOM Report warns that “a real danger exists that the commercial applications of xenotransplant technology will outstrip both the research base and the national capacity to address special issues raised by xenotransplantation, including the risk of disease transmission.”<sup>215</sup> It, therefore, recommends that “funding, by federal agencies, private industry, and other sources, of research and other programs (e.g., tissue banks and patient registries) necessary to minimize the risk of disease transmission”<sup>216</sup> is justified. Again, the Guidelines do not include this recommendation.<sup>217</sup>

### *J. Scientific Concerns*

One prominent virologist, Jonathan Allan,<sup>218</sup> is quite reticent about beginning xenotransplantation trials.<sup>219</sup> Allan argues that “[d]espite all the best efforts to provide [a] ‘clean’ baboon for donating organs or cells to humans, the best strategy for preventing xenotransmission is still not to do them.”<sup>220</sup> Allan points to the AIDS epidemic as an example of a zoonotic disease that continues to plague modern medicine.<sup>221</sup> This is not to say that AIDS is in any way related to a xenotransplant, merely that zoonoses are neither an unknown phenomenon, nor an abstract danger. Instances of zoonotic agents being transmitted from poliovirus vaccines are well documented.<sup>222</sup> SV40, a monkey DNA virus inadvertently transmitted to humans through a vaccination, “suggest[s] that monkey viruses

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212. *Id.*

213. See INSTITUTE OF MEDICINE, *supra* note 3, at 4.

214. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. at 49,920.

215. See INSTITUTE OF MEDICINE, *supra* note 3, at 4.

216. *Id.*

217. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. at 49,920.

218. Dr. Allan participated in the panels that authored the IOM Report. See INSTITUTE OF MEDICINE, *supra* note 3, at List of Participants.

219. See generally, Allan, *supra* note 75.

220. *Id.* at 45.

221. *Id.* at 38.

222. *Id.* at 39.

may play a role in human cancer . . . .”<sup>223</sup> Allan also notes that human organ shortage is not the only reason for proposing baboons as donors, but rather because baboons are resistant to infection with several human viruses, and could serve additional curative purposes.<sup>224</sup> If this is correct, several additional questions are raised about the propriety of undergoing xenotransplantation trials before proper safeguards are enacted to prevent transmission to third parties.

It has been suggested that, because evolution is a continual process of changing DNA, xenotransplantation is not unnatural. Allan disputes this assertion noting that “[a]ll major natural barriers to viral infections that have evolved during the millennia will have been circumvented by a single surgical procedure.”<sup>225</sup> Rather than being a natural process, according to Allan’s view, xenotransplantation would destroy evolutionary trends geared towards fighting off viruses. Bone marrow chimerism hopefully will minimize this danger to the recipient.<sup>226</sup> Even though the recipient may, through chimerism, fight off the infection, the danger is transferred to the close contacts of the recipient, whose immune system is not similarly prepared by a chimerism.<sup>227</sup> Spread of an infection to a third party is dangerous because “the more difficult viruses to detect and eliminate will be sexually transmitted or blood borne, similar to AIDS.”<sup>228</sup> Success in controlling infections has not been with slow methodical diseases like AIDS and hepatitis, but with diseases that kill quickly.<sup>229</sup> Once xenotransplantations begin, according to Allan, it will no longer be a question of whether baboon and other donor animal viruses will enter the population, but how serious the effects will be.<sup>230</sup>

#### IV. SHOULD XENOTRANSPLANTATION TRIALS PROCEED?

To this question the U.K. answered a resounding “maybe” on January 16, 1997.<sup>231</sup> U.K. Secretary of State for Health, Stephen Dorrell, cited insufficient medical information and a corresponding risk to the public

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223. *Id.*

224. *Id.* at 40.

225. *Id.* at 45.

226. *See supra* notes accompanying text 98-101.

227. Allan, *supra* note 75, at 44-45.

228. *Id.* at 44.

229. *Id.*

230. *Id.* at 45.

231. *UK to Ban Pig Transplants to Humans, Says Dorrell*, MARKET LETTER, Jan. 20, 1997, available in 1997 WL 7972243.

health as reasons for delaying the approval of clinical trials.<sup>232</sup> Imutran, the British biotech company, was ready to proceed with clinical trials using genetically modified pigs, but a discovery of a hitherto unknown virus by Professor David Onions raised severe concerns.<sup>233</sup> Further, the British decided to appoint Lord Hapgood of Calverton<sup>234</sup> to chair the U.K. Xenotransplantation Interim Regulatory Authority.<sup>235</sup> Finally, Parliament is expected to enact legislation pertaining to xenotransplantation, and will, if necessary, enact emergency legislation to prohibit human trials.<sup>236</sup> The U.S. Congress should follow the British lead by taking an active role in the formulation of U.S. policy on xenotransplantations; otherwise, it will be abdicating its responsibility to the executive branch with painfully slow results. Finally, it is important to note that xenotransplantation presents an international problem, as well as a domestic one, because viruses are not restricted by national boundaries. Accordingly, the World Health Organization is preparing international guidelines on xenotransplantation.<sup>237</sup>

#### A. *The Comments*<sup>238</sup>

A wide range of comments were submitted ranging from exuberant praise<sup>239</sup> to sharp criticism.<sup>240</sup> Several companies in the biotechnology industry filed a joint comment, agreeing with certain portions of the regu-

232. *Id.*

233. Onions, of Glasgow Veterinary School, found a pig retrovirus and is currently conducting more tests in an effort to determine whether it is capable of causing harm to humans. See Charles Arthur, *Transplants? Pigs Might Fly*, THE INDEP.-LONDON, Jan. 20, 1997, at 20.

234. Lord Hapgood's choice was criticized because he is not "an expert on the safety of transplant procedures, but . . . a former archbishop who, 40 years ago, was a pharmacologist." Editorial, *Have A Pig's Heart*, 349 THE LANCET 219, 257 (1997).

235. *UK to Ban Pig Transplants to Humans, Says Dorrell*, *supra* note 231, at 1997 WL 7972243.

236. Charles Arthur, *Study Will Be Key to Pig Transplants*, THE INDEP.-LONDON, Jan. 17, 1997, at 4.

237. See David Shapiro, *The Wrong Issue for a Moral Panic*, THE FINANCIAL TIMES, June 13, 1997, at 14.

238. Pursuant to the Draft Guidelines' call for Comments, several organizations and individuals submitted comments on the proposed Guidelines in an effort to influence the final Guidelines. See Comments Submitted to the Food and Drug Administration, Docket No. 96M-0311. (on file with the Food and Drug Administration's Dockets Management Branch).

239. See Comments of Ava D. Lancaster, President, Association for Professionals in Infection Control and Epidemiology, Inc., submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment 86), at 1 (Dec. 20, 1996).

240. See Comments of Richard E. Kruger, Director, Regulatory Affairs, Grace Bi-

lations, provided they remain flexible and non-mandatory.<sup>241</sup> In contrast, groups wholly opposed to any effort to begin xenotransplantation clinical trials submitted comments.<sup>242</sup>

An interesting, but not surprising, breakdown can be seen by looking at the respondent's financial stake in the commencement of clinical trials. Biotechnology firms were the most adamant to downplay the risks of clinical trials.<sup>243</sup> One company felt that access by appropriate health agencies to the records would violate an individual's right to privacy, and requiring autopsies to be performed would violate religious freedom.<sup>244</sup> Still another company argued that only direct testing of the sample would provide the safest alternative to justify clinical trials.<sup>245</sup> According to this company, it alone possessed the technology to test the needed tissue.<sup>246</sup>

A high level of self-interest surrounds the comments submitted, especially those from the biotechnology companies, because to the winners go the spoils, to the tune of some six billion dollars a year.<sup>247</sup> This is not to say that those with a smaller financial stake are not interested in the final guidelines. Even a nurses' association submitted comments to ensure their members would not be left without financial reward in the final guidelines.<sup>248</sup>

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omedical, submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 93), at 9 (Dec. 20, 1996).

241. See Comment of Allan Goldhammer, Director of Technical Affairs, Biotechnology Industry Organization, submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 75), at 1 (Dec. 20, 1996).

242. See Comments of Jonathan S. Allan, et al., Southwest Foundation for Biomedical Research, submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 83), at 1 (Dec. 20, 1996); see Comments of Neal D. Barnard, President, Physician's Committee for Responsible Medicine, submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 73), at 1 (Dec. 19, 1996).

243. See Comments of Mathias Hukkelhoven, et al., Sandoz Pharmaceuticals Corp., submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 85), at 1 (Dec. 20, 1996). Sandoz Pharmaceuticals is a conglomeration of three corporations working together on developing xenogeneic pigs. These corporations are: Sandoz, Imutran, Ltd., and Biotransplant, Inc. Commenting on the informed consent requirements, Sandoz recommends that "[i]t should be made clear that there is an undefined but probably small risk of infection." *Id.* at 3.

244. See Comments of Richard E. Kruger, *supra* note 240, at 2-3.

245. See Comments of Anton-Lewis Usala, Chairman and Chief Technical Officer, Encelle, Inc., submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 84), at 1 (Dec. 20, 1996).

246. *Id.*

247. See Comments of the Medical Modernization Committee, submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 91), at 16 (Dec. 20, 1996).

248. See Comments of Christy A. Price, President, American Nephrology Nurses'

Not all of the comments, however, were generated out of financial self-interest. One group that staunchly opposes beginning clinical trials submitted a comment based on its ethical position against animal experimentation.<sup>249</sup> Furthermore, per the solicitation in the preamble of the Guidelines, comments were submitted by interested parties, and the fact that they were self-interested is readily evident. Nevertheless, the degree of self-interest from the biotechnology companies recalls the warnings of the IOM's Report concerning the danger of commercial applications outstripping the scientific base.<sup>250</sup>

If there is any general consensus among the comments, it would appear to address the informed consent requirement section of the Guidelines. For example, although one group called the Guidelines excellent and another called for more regulation, if not an outright prohibition of clinical trials, both agreed that informed consent requirements need to be improved.<sup>251</sup> The groups differ on whether the transplant team must be required to provide the information concerning risks to close contacts.<sup>252</sup>

Another area of consensus, which appears amongst the submissions of biotechnology companies, concerns maintenance of archive samples. Most of the companies agreed that the responsibility to maintain archives, and to track donors, should be left to them.<sup>253</sup> Essentially, the argument is that only the companies have the requisite expertise to perform maintenance of samples and tracking of individuals.<sup>254</sup>

## V. CONCLUSION

Ample scientific evidence indicates that the risks of xenotransplanta-

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Ass'n, submitted to the Food and Drug Admin. (Dkt. No. 96M-0311) (Comment No. 81), at 1 (Dec. 20, 1996).

249. See Comments of the Medical Modernization Committee, *supra* note 247, at 1.

250. See INSTITUTE OF MEDICINE, *supra* note 3, at 96. Another illustration of this is the PPL Therapeutic Company's decision to begin cloning pigs for use in xenotransplantation despite concerns surrounding the two technologies. *Scientists Serve Up the Prospect of Cloned Pigs*, THE INDEP.-LONDON, Mar. 25, 1997, at 5.

251. See Comments of Ava D. Lancaster, *supra* note 239, at 4; Comments of Jonathan S. Allan, et al., *supra* note 242, at 2.

252. See Comments of Ava D. Lancaster, *supra* note 239, at 4, saying, "The consent form should state that counseling is available for close contacts." *Id.* Compare Comments of Jonathan S. Allan, et al., *supra* note 242, at 2 saying, "Leaving the responsibility for educating contacts as to potential infections with the recipient is inappropriate and has been generally ineffective for other known human infectious diseases." *Id.*

253. See Comments of Allan Goldhammer, *supra* note 241, at 5; see also Comments of Mathias Hukkelhoven, et al., *supra* note 243, at 2.

254. "[M]uch of this expertise can and should be provided by the company's experts." Comments of Mathias Hukkelhoven, *supra* note 243, at 2.



tion are real and unquantifiable. Correspondingly, there is also a real shortage of human organs available for transplantation. Herein lies the dilemma. Every year, real people, not just statistical figures, die because of an inability to find a compatible organ; the pleas by these people and their families are well documented and difficult to ignore.<sup>255</sup> What must be balanced against this is the abstract risk associated with xenotransplantation. It is difficult to quantify the potential risks that exist and for this reason, if for no other, it seems likely that xenotransplantation trials will eventually begin. The recent procedure, which placed bone marrow from a baboon into a human, points to the likelihood that a slow pragmatic approach is unlikely to be taken when human beings are in dire need.

Nevertheless, throwing caution to the wind is not a desirable approach,<sup>256</sup> nor is it advocated by anyone. A more prudent approach, especially at the beginning, is necessary because the risks are tremendously uncertain.<sup>257</sup> Early recipients who are presented with no alternatives short of a xenotransplantation are likely to agree to a great many restrictions that seem reasonable at the time.<sup>258</sup> If the early procedures are successful enough to allow recipients to restore a degree of normalcy to their lives, then enforcement mechanisms will be required. It will be necessary to ensure that surveillance is complied with and that any close contacts of the recipient are adequately identified. Assuring confidentiality in this regard will be crucial in gaining the recipient's trust, thereby increasing the likelihood of total disclosure. Modifying human behavior has proven to be a daunting task, and a largely undesirable one, so the problem becomes enforcing the surveillance requirements if compliance is not provided voluntarily. Another troubling aspect is that if something occurs it is only possible to react in the hope that enough preventive measures were taken. All of the measures taken to establish a national registry, archive tissue samples, and monitor close contacts and health care workers are proactive; but, they can only be implemented reactively. Once an infection has occurred, and if it is passed from the recipient to a

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255. See INSTITUTE OF MEDICINE, *supra* note 3, at 58-61.

256. *Id.* at 45-46.

257. See Stephenson, *supra* note 27, at 285. "[M]any scientists and public health experts, citing potential infectious disease risks in grafting animal organs into the human body, say that xenotransplantation efforts should move slowly until such hazards can be properly assessed." *Id.*

258. Jeff Getty himself said in response to a question about public health risks, "[I] am more than willing to be quarantined, isolated or whatever it takes to satisfy the safety requirements." See CNN Transcript No. 996-3, July 14, 1995.

third party, the only thing to do is to prevent the infection from spreading further.<sup>259</sup>

While the Guidelines address the surveillance requirements and travel restrictions the recipient must observe, they are only suggestions and are not mandatory. Even if they were mandatory, the Guidelines did not discuss whether failure to agree to comply will disqualify the potential recipient for the xenotransplantation.<sup>260</sup> If a recipient agrees to comply before the procedure but ignores the requirements after the procedure, what can be done is an area which needs to be addressed.

Prior to the procedure going forward, an IRB should be required to approve the transplant after heavily weighing the alternatives. In balancing alternatives, there should be a presumption of foregoing the procedure. An equivalent to a *guardian ad litem* should be appointed by the IRB to argue on behalf of third parties' interests. If the IRB determines to move forward with the procedure, the recipient should be informed of all risks involved, both known and unknown, and of the danger of transmission to third parties. When this information is presented to the patient it should be done by a party not otherwise involved in the procedure, and it should be in the presence of the potential recipient's next of kin. Doctors should disclose, to recipients, the mandatory requirements of xenotransplantation including compliance with surveillance, restrictions on travel and other restrictions, which may arise dependent on varying circumstances. A list of sanctions for failure to comply also should be presented at this time. Only if the recipient agrees to comply should the procedure go forward. If the recipient does not agree, no prejudice should be made in their course of treatment, except with regard to xenotransplantations.

Following the procedure, the clinical institution should be required to monitor the recipient, and any deviation by the recipient should be reported immediately to the IRB and to a committee within HHS formed to coordinate the policies of the various federal agencies respecting xenotransplantation. Holding recipients responsible prior to the procedure may not be possible, and draconian enforcement measures against the individual recipient may not be desirable. Therefore, it would be reasonable to levy sanctions against a clinical institution if any irregularities following the procedure were to occur. These sanctions could range from

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259. Allan, *supra* note 75, at 45.

260. See Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, 61 Fed. Reg. 49,920, 49,923 (1996).

suspension of accreditation, monetary fines, to federal investigation. It is preferable to levy the sanctions against the institution because the incentive to comply with the requirements lies with them and not the recipient.

## VI. SUMMARY

The number of xenotransplantations may increase despite the many concerns about the likelihood of spreading known and unknown infectious diseases. Regardless of the safety precautions employed in the early trials, the risks remain unknown. Zoonotic and even xenozoonotic diseases are not remote possibilities; they exist in various forms and come from various sources. The nature of transplantation requires the suppression of the immune system to levels where opportunistic infections may take route. Even if procedures to avoid increased levels of immunosuppression to the recipient were successful, risk to third parties, whose immune systems would not be equipped to fight off the infection, would remain.

In this context, the PHS Guidelines provide a useful starting point, but they do not go far enough. First, the Guidelines are merely suggestions; this needs to be changed to require institutions undertaking xenotransplantation research and clinical trials to comply with the Guidelines. Second, every possible effort should be made to protect third parties from disease transmission. This requires and justifies placing restrictions on recipients that, in an ordinary context, would be unacceptable. Third, xenotransplantations should occur only after all other medical measures have been exhausted. Until the time when disease transmission risks are scientifically insignificant or cures for the transmitted diseases are found, mandatory guidelines with stringent requirements are the best means of balancing the interests of society against the potential beneficiaries of xenotransplantation.

*Frank Morgan*