Xenotransplantation – the transplantation, implantation, or infusion of live cells, tissues or organs from a nonhuman animal source into humans – has been suggested as the most imminent strategy to alleviate the shortage of human grafts. The pursuit of this technology is nonetheless restricted by an unquantifiable risk that the use of animal grafts will unleash new zoonoses that may affect the public at large. This paper is concerned with what the proper response to this public health threat should be. We will demonstrate that the regulatory measures taken to prevent secondary infections currently do not warrant full-blown protection of public health. That reality forces us to reconsider the extent to which the public should be guaranteed protection from a xenotransplant-related health hazard. In pondering that question, we will suggest that the permissibility of health hazards posed by emerging (bio)technologies is dependent on the perception that the benefits are both substantive and attainable and on the duty to account for foreseeable risks. In that sense, there is both good and bad news for the acceptability of xenotransplantation. An increased understanding of the infectious agents that are known to pose a health risk, relates the man-made health threat to risks that have a natural origin.

1 The risk of a xenogeneic pandemic

On 18 January 2006, 90,628 patients were enlisted on waiting lists for an organ transplant across the US (OPTN 2006). Between January and October 2005 a 'mere' total of 23,511 solid organ transplants were conducted from 12,090 (both living and cadaveric) donors nationwide (UNOS 2006). The gap between supply and demand creates a considerable annual death toll. For instance, in 2003, the US Organ Procurement and Transplantation Network reported a national total of 7,147 deaths among the 114,442 patients then on the waiting list (UNOS 2004). That amounts to an average of 19 to 20 deaths a day.

Researchers are developing new technologies that yield the outlook of virtually limitless supplies of transplantable grafts. One of those possibilities is the use of organs, cells and tissues from specially bred, genetically modified pigs, a procedure named xenotransplantation. According to the proponents of this emerging biotechnology, the use of porcine grafts will alleviate the burden of organ disease sooner than alternative strategies, such as the use of artificial replacements or regenerative medicine (Cascalho and Platt, 2005). Specially engineered pigs could also provide suitable organs for infants, for whom the organ shortage is the most devastating, and for individuals who do not accept human organ donation for ethical or cultural reasons. Moreover, safe and effective xenotransplantation should annul many of the practical and emotional burdens related to the long waiting times for an available cadaveric donor organ (Groth 2005). With a source of grafts readily available, the transplantation procedure can be scheduled and prepared well in advance. Recipient pre-treatment can be conducted and the quality of organs can be screened in detail. Xenotransplantation may also widen the indications for transplantation. Applications of unlimited sources of animal-derived cells and tissues could potentially address currently unmet medical needs such as incurable neurological diseases, epilepsy, chronic intractable pain syndromes, paraplegia due to spinal cord lesions and insulin dependent diabetes.

The development of xenotransplantation over the past century has defined many challenges in terms of cross-species immunology and physiology that remain to be met before xenotransplantation, of organs in particular, will be a viable routine therapy. However, the *major* brake on clinical use of xenotransplantation procedures relates to the possibility that the use of animal grafts may facilitate adverse effects to third parties not involved with the potential clinical benefits. Theoretically, xenotransplantation could allow transmission of either recognized or novel infectious agents along with the xenograft and contaminate the xenotransplant recipient, his/or her intimate contacts and health care workers, and, at worse, the public at large.

It is well established – and topically illustrated by the recent outbreak of H5N1 Avian Influenza – that most of the infectious diseases that have emerged over the past decades can be traced to animal-derived viruses, bacteria, or prions that have passed onto or adapted in human hosts (Murphy 2002, 2). Xenotransplantation appears to pose a particularly pertinent health hazard. That is due to the fact that transplantation bypasses most of the patient's usual protective physical and immunological barriers. There is also lack of knowledge about the behavior of source animal-derived infectious agents in immunosuppressed humans. Moreover, the risk of xenogeneic virus transfer materialized with evidence that a family of porcine endogenous retroviruses (PERVs) can infect human primary cells and cell lines *in vitro* and can adapt to those cells by serial transmission on uninfected cells (Patience et. al. 1997; Le Tissier et. al. 1997). In contrast to exogenous retroviruses, endogenous retroviruses are deemed particularly problematic because they are resident as proviruses in the DNA of the host, and thus difficult to exclude. This paper is concerned with what the proper response to this public health threat should be.

2 Xenotransplant regulation

In a cautious, initial attempt to define and determine the seriousness of the risk posed by use of pigs as xenograft source animals, Patience et. al. (1998a, 539) identified several questions that needed answering before we can decide whether xenotransplantation experiments on humans should proceed. More knowledge was required in terms of the micro-organisms present in the donor animals, the likeliness of cross-species microbe transfer to cause disease in humans, and the likeliness of and

capacity for potential cross-species microbe transfer to elicit a human pandemic. In the absence of full scientific certainty, several pleas for a moratorium were made (Bach et. al. 1998; Butler 1998; COECM 1999), preferring to circumvent the risk altogether. In most regulatory authorities, however, *de facto* moratoria in name of the Precautionary Principle were soon replaced by stringent national oversight of adherence to detailed safety protocols for xenotransplantation research and clinical trials. The suggested protocols (see for instance US FDA 1999; US PHS 2001; UKXIRA 1999; COECM 1999, 2003; EMEA 2003; OECD 1999; Working Party on Biotechnology 2001; WHO 2001, 2004a) apply to the procurement and screening of source animals, the clinical and pre-clinical testing of xenotransplantation products and the post-xenotransplant monitoring of recipients. Perhaps the most essential, and certainly the most problematic aspect of the recommended safety measures is the requirement of long-term (possibly lifelong) surveillance of the prospective recipients. In order for a clinical trial to be accepted, xenotransplant guidelines require ensured traceability of the prospective recipients' whereabouts. To facilitate the tracking process in event of an infection, various nations are developing computerized registers for all xenotransplant product recipients. Prospective recipients must also consent to the potential need for confinement or specialized medical housing. The recipients' current and future close contacts, too, must be notified of the infection risk and asked to take appropriate measures to restrict exposure to others. The prospective recipients will be responsible for taking appropriate precautions for sexual and non-sexual contact. Among the more stringent requirements, it has been suggested that the prospective trial recipients should refrain from having children. These monitoring requirements will be applicable even if the clinical trial fails to obtain sufficient graft survival ('imposed extended compliance').

It is highly questionable whether such recommendations are the appropriate response to the threat of xenogeneic infectious diseases. The need for long-term monitoring will undoubtedly have an effect on the freedom and privacy of prospective xenograft recipients (and their close contacts). It is particularly unclear whether that is something we may demand from patients who aim to improve their quality of life (Ravelingien and Braeckman 2005). Moreover, and given the high rates of non-compliance to health recommendations after an allotransplantation (Hilbrands et. al. 1995), it is unclear whether the consenting recipients would be continuously willing and able to adhere to the extensive and stringent supervision. In order to protect public health, then, it will be necessary to *enforce* adherence to a person's prior consent against his or her later wishes. Most crucially, however, even if it can be argued that such enforcement is ethical, the legal means by which compliance can (and should) be enforced prior to a *demonstrable* state of public health emergency have not yet been set in place (Florencio and Ramanathan 2001; Florencio and Ramanathan 2004). Although forcible isolation of infected individuals goes back (at least) to cases of leprosy in the Middle Ages (Lachmann 1998, 297), enforcement of public health measures is dependent on evidence that the individual has in fact contracted an infectious disease and poses a public health hazard. Current public health law provisions cannot enforce long-term surveillance when the recipients are asymptomatic and the nature and communicability of possible pathogens are undetermined.

Another problem for current xenotransplant regulation is the difficulty of ensuring adherence to the (costly) surveillance measures by the transplant centers themselves, particularly in nations that do not have appropriate national oversight in place. In the understanding that the risks of xenogeneic virus are not confined to the nation in which an outbreak initially occurs, great effort has been put to establish international cooperation for the protection of public health on a *global* scale. The Council of

Europe Committee of Ministers (COECM 2003), the Organization for Economic Co-operation and Development (OECD 1999, 46), the World Health Organization (WHO 2004a, 2), the European Agency for the Evaluation of Medical Products (EAEM 2003) and the International Xenotransplantation Association (Sykes et. al. 2003, 194) have urged international collaboration to develop universal standards of good practice. Those institutes recommend that clinical applications of xenotransplantation should not be carried out without effective national regulatory control and surveillance mechanisms and/or without specific authorization. Nonetheless, there are verbal reports that pig-to-human transplant experiments are currently being conducted in countries without proper oversight (Cooper 2005; Rood and Cooper 2006). Those reports indicate that at least 400 islet transplants and 2,000 bovine cell transplants for pain relief have been conducted in China so far. In Russia, allegedly hundreds (possibly more than 800) of rabbit islet transplants have been done. That opens the door for the risks of 'xenotourism', in which case a patient may seek a xeno-'therapy' in those specific nations where they are available. The xenotourist may perhaps mistakenly assume that established oversight is in place, or be kept unaware of the potential dangers inherent in the unconventional procedures. It is therefore unlikely that such a patient will attune to appropriate precautions (SACX 2004). There is currently an agreement that the results of trials that breach xenotransplantation guidelines should not be accepted for publication in high-ranked peer-reviewed journals. Apart from that, however, there is currently no international sanction for non-compliance to international xenotransplant guidelines, nor, for that matter, an authority to impose the sanction.

In light of these difficulties in preventing xenozoonosis, the current regulations can be regarded as flawed attempts to address the Precautionary Principle. They raise false expectations that the risks will be eliminated altogether. That reality forces us to *reconsider* to what extent the public should be guaranteed protection from a xenotransplant-related health hazard. As a response, we will suggest that a more feasible and acceptable control of xenotransplantation research and trials is attainable when a distinction is made between the relevant social norms for different types of risk.

3 Do as you wish, but do not make a nuisance of yourself to others

Xenotransplantation involves the conflict of two intuitively felt moral duties. By not pursuing xenotransplantation trials, we are refraining from helping waiting-list patients who currently have no alternative to life-saving treatment. In other words, we are potentially allowing preventable deaths. By pursuing xenotransplantation trials, on the other hand, we could help some individuals at the cost of harming (possibly many) others, with harm broadly defined as affecting someone's interests adversely.

The above-mentioned xenotransplant protocols suggest that the duty not to harm others is the weightiest principle. This appears to be in keeping with the maxim "Above all [or first] do no harm" (*Primum non nocere*), which is sometimes (although incorrectly) deemed the essential principle underlying the Hippocratic tradition of medical ethics (Beauchamp and Childress 2001, 113). Within a purely medical ethics context, however, the duty not to harm would not necessarily enjoy priority over the duty to provide benefit. The principles serve as a guide for good clinical practice to patients and have a *prima facie* character rather than a definite hierarchy. Whether or not in a given situation the principle of nonmaleficence overrules the principle of beneficence is co-dependent upon two other principles: respect for persons and equitable distribution of benefits and burdens. In considering the role of those principles, it seems to matter whether the person to be harmed is the very same person who is to be the beneficiary or some other person.

In Kantian ethics, acknowledging a person's autonomy implies viewing persons as ends in themselves and not merely as a means to the ends of others. Each person merits respect for his or her 'private sphere', in which he or she is sovereign and free to determine his or her own destiny. As a moral notion to guide our acts, that implies that an individual with the necessary critical mental capacities to act as an autonomous agent may not be restrained by controlling interferences from others. Strong defense of personal sovereignty will grant autonomous beings the right to act in such a way that is of harm to them – even when the decisions are unreasonable or when they imply an alienation rather than fulfillment of autonomy – as long as the act is done voluntarily and knowingly of the effects (Feinberg 1986, 52-97). Within the medical ethical context, milder trends towards anti-paternalism are more prevalent. As such, a patient is generally assigned a right to consent to medical research or therapies that are potentially harmful to his or her health on the additionally specified condition that the risks are reasonable in relation to the potential benefits. From that perspective, we can imagine that a recipient will be willing to accept a xenotransplant, fully knowing of the potential of xenogeneic virus transmission. For the patient, that risk may to a certain extent and in severe cases be counterbalanced by the potential benefits. Nevertheless, the least stringent and most basic limit of personal sovereignty is set to those harms that are only other-regarding (ibid., 58).

> This is the 'harm principle' as introduced by John Stuart Mill.
> The only part of the conduct of any one, for which he is amenable to society, is that which concerns others. In the part which merely concerns himself, his independence is, of right, absolute. (Mill 1859)

The duty to respect the autonomy of others makes a strong case against the moral permissibility of secondary xenogeneic virus transfer. The case could also be made in reference to the fact that, for the general population, the harm of a xenogeneic epidemic will not be counterbalanced by the benefits. That is particularly compelling when placing the notion of just health distribution in a global context. The developing world, most parts of which lack even the most minimal health care, will not have access to the benefits of that expensive technology (in effect, a critique against most high-tech medical therapies) but will rather be confronted with yet another health burden.

In principle, the conflict between the autonomy of the beneficiary and the autonomy of others could be resolved if those others were to consent to the acceptability of the harm involved in xenotransplantation (perhaps, in the belief that they themselves may one day benefit from the therapy). However, consent of all those potentially involved in the harm at stake is virtually impossible. In practice, seeking collective consent would apply to public consultations on a national level. The important role of public input in the decision whether or not to proceed with xenotransplantation has indeed been emphasized (Bach et. al. 1998, 141; Sykes et. al. 2003, 198), but so far, the various national efforts have not yielded unanimously positive acceptance rates. Rather to the contrary: public consultations in Canada, the Netherlands and Australia rendered overall recommendations not to proceed with clinical trials until the risks were better understood and could be better managed (Einsiedel 2004, 1110-1). However, when such nations decide not to engage in further trials, they have no assurance that they will be protected from the harm they do not wish to accept. The harms of infectious disease will not be restricted to the country in which the transplant is performed. With an imperfect guarantee of recipient compliance to the safety measures, the chance that they can be identified and confined at those nation's borders are inherently uncertain.

The moral weight of the harm principle is deeply engrained in our common sense morality. In fact, we will generally conclude that duties not to injure others are more compelling than duties to prevent harm or to provide benefit. A classic thought experiment often used to illustrate this is one in which we are asked to consider saving the lives of five patients on the waiting list by killing an innocent person in order to retrieve his or her vital organs (Kagan 1998, 70). While that act would bring about the best consequences in terms of lives saved, most of us would object to the means by which the lives are saved. The moral impermissibility of such harm is not necessarily grounded in deontological principles: it can be supported on consequentialist grounds as well. The consequentialist could maintain that, although initially most lives are saved, killing a person for his or her organs would render the results worse overall. For instance, if the transplants were unsuccessful, the lives of all six people rather than five would go lost. Alternatively, if the killing were brought to light, the distress that could cause among the public would diminish the overall welfare. Moreover, if the public were to lose trust in the medical community and refrain from seeking medical help, that could result in the unnecessary loss of many more lives.

Notwithstanding this, even the duty not to harm others is not a moral absolute. Where the outcomes are clearly favorable in terms of overall results, this is a consideration to which even some deontic theories would not be entirely insensitive (Ibid., 79). In other words, the constraint against doing harm has a threshold at which point the harm can be outweighed. The problem, however, is that opinions may vary regarding the level of that threshold. There is no clear amount of benefit that must be at stake before the constraint against doing harm can be forsaken. Kagan indicates that the threshold is rather a function of the size and nature of the harm that has to be done to bring about the good results (Ibid., 82). The difficulty of balancing benefit and harm is further complicated in those cases in which we are not asked to consider the permissibility of doing harm, but only a *risk* of doing harm. The nature of the problem is highlighted by the fact that few of our everyday acts involve *no risk* of harming someone else. Some of those everyday acts – Kagan gives the example of driving cars (Ibid.) – imply risks of serious, life-threatening harm. That suggests that the permissibility of imposing risk of harm to others is not solely dependent on the nature and size of harm at risk; the probability that the harm will occur is also taken into account. The higher the risk, so it would seem, the higher the threshold.

Establishing the permissibility of risk seems all the more intangible in the case of xenotransplantation. The number of people at stake in both the benefits and harms is potentially large-scale, while the size and nature of the harm – whether it be a harmless influenza or a fatal pandemic, the range in between, or neither – and the probability that any of those scenarios will occur are essentially *uncertain* and *unquantifiable*. Given that the 'scientific-descriptive' component of risk assessment is thereby lacking, we are compelled to make do with a second component, which involves an individual and social normative basis (Engels 2000, 185). In what follows, we borrow two analogies in an attempt to provide additional factors which play a role in the perception and acceptance of xenotransplant public health hazards.

4 The ethics of man-made public health hazards

4.1 Analogies

In her account of the conflict of individual and public interests inherent in xenotransplantation, Martine Rothblatt compares the situation to the prior development of two similarly risky biotechnologies (Rothblatt 2004). In both cases, the technologies harbored a great potential benefit and imposed risks of equally grave harm to the public. Nevertheless, the situations deviate in terms of tolerance of the

risks. In what follows, we hope to shed light upon the permissibility of the risk of xenogeneic infections by investigating the factors that might have led to the different risk perceptions.

The first analogy is drawn in reference to the emergence of antibiotics, which became a treatment option for a range of bacterial infections in the 1940s (Ibid., 115-122). Rothblatt notes that the antibiotics were administered with knowledge that improper use could lead to a generation of resistant forms of bacteria, which in turn could form a major public health hazard. Indeed, within a few decades, excessive use of antibiotics has rendered entire new species of antibiotic resistant bacteria which cause an increasing death toll. The widespread use of antibiotics in both animals and humans has given rise to new human-borne pathogens as well as new antibiotic-resistant zoonoses and constitutes an enduring risk of creating an antibiotic-resistant pandemic. Rothblatt observes that, in contrast to the current attitude towards xenotransplantation, there is no mention of banning or severely restricting the practice. The public is willing to accept the risks, as well as the existing harms, in light of the life-saving benefits provided and in the confidence that public health regulations can timely manage the severe harms.

The second analogy is drawn in reference to the development and study of recombinant DNA technology (Ibid., 122-133). In that case, the potential scientific and social benefits were not a sufficient justification and the development of the research went hand-in-hand with efforts to control and contain public health hazards. Here too, the potential hazards related to infections from bacteria and viruses. They were taken seriously from the start and some of the world's prime molecular biologists voluntarily implemented a temporary moratorium on the research. In February 1975 stringent requirements were set for the continuation of genetic experimentation. During the Asilomar meeting, the scientific expert invitees were confronted with ultimate uncertainty whether or not cancers or new infectious diseases could result from the splicing of genes and transfer of chromosomes. Consequently, they decided rather to be on the safe side and protective measures were established in accordance with a classification of risk. Experiments that were clearly safe were permitted on the bench top; (possibly) dangerous experiments were restricted to confined areas. Those recommendations have since been adopted by governmental agencies worldwide.

Rothblatt uses the above-mentioned analogies to demonstrate the way forward for xenotransplantation experimentation and clinical practice. The antibiotics analogy highlights certain conditions, which render public health hazards acceptable. The permissibility is a function of the perception that the potential benefits are both significant and attainable and of the trust that the harm can be effectively controlled once it occurs (Ibid., 120). The emergence of recombinant DNA research regulation teaches us that mechanisms can be put in place beforehand to constrain the risks to public health while not necessarily quashing the potentially beneficial research itself (Ibid., 123). Rothblatt concludes that xenotransplantation can be ethically pursued if similar measures are put in place in advance to detect and restrict related infectious outbreaks globally (Ibid., 129). Her suggestion is to halt xenotransplant trials until the detection, treatment and follow-up measures as proposed by xenotransplant regulation authorities are 'geoethically' implemented in all nations. This requires a global buy-in to ensure that even those parts of the developing world are given the resources to perform effective xenozoonosis surveillance. The buy-in should include establishing basic health care support in exchange for randomized blood sampling.

The focus of Rothblatt is on a just distribution of health benefits and burdens and on means to enhance global security. Again, however, this conclusion is a flawed response to the Precautionary Principle. She cannot ensure that the global safety

measures will be universally adhered to. Nonetheless, the analogies she brings forward are useful. In our view, the distinctions between the two case studies reveal extra factors that are relevant when questioning the permissibility of man-made public health hazards. These extra factors do not necessarily require full-proof adherence to xenotransplant regulation.

4.2 Foreseeable risk

A first relevant distinction between the analogies relates to the perception that the potential benefits are significant and attainable. Arguably, such a perception was more apparent in the advent of antibiotics than in the emergence of recombinant DNA technology. The potency of antibiotics to decrease the high percentages of mortality and complications due to infectious diseases was apparent upon its discovery in 1928: pre-clinical data demonstrated the ability to destroy a common bacterium that was associated with sometimes fatal infections (*Staphylococcus aureus*) (Bass et. al. 2001). A decade after that discovery, during which diverse technical difficulties were overcome, Howard Florey, Ernst Chain and Norman Heatley were able to show penicillin's capability to provide cures for a wide variety of conditions. By contrast, the advances in therapeutic applications of recombinant DNA technology have been slower and the importance of its potential much more contested.

The recombinant DNA analogy also shows evidence of less public trust that the risks will be manageable at the moment they occur. Instead, it is indicative of an increased demand to prevent the risks beforehand. That may very well be a partial effect of the various time frames. Rothblatt indicates that the invention of new antibiotics in the 1950s and 1960s convinced society that the emergence of sub-types of antibiotic-resistant bacteria should not pose a great problem (Rothblatt 2004, 116). Arguably, that trust echoed the confidence and public support of medical and other scientific research at a time when laboratory efforts had successfully been mobilized for war (Frederickson 1991, 259-260). The fruits of those experiments were reaped in the scientific boom years of the 1950s. Asilomar, by contrast, is indicative of a turning point in the ethics of science. It marked the first time that scientists engaged a social contract with society. The moral impermissibility of *knowingly* exposing a population to manufactured risks appears to have increased in significance during the past century. That may relate to the fact that many risks associated with contemporary technology transgress former spatial and temporary limits (Welsh and Evans 1999; 202). The greater focus on accounting for foreseeable adverse effects in recombinant DNA research may also partly be due to a greater advance in indications of the risks. In the case of antibiotics, the first warnings of the risks arose well after applications on soldiers and only one year prior to widespread clinical use. Antibiotic resistance was marked as a real threat only after two cases of lethal resistant bacterial infections in patients occurred in the 1970s (Bass et. al. 2001). That was well after the scientists were in the position to exclude that kind of harm beforehand. By contrast, the controversy surrounding recombinant DNA started with evidence of successful insertion of hybrid genes into *E. coli* (Rothblatt 2004, 125), of which the adverse effects were evident before they occurred. In that case, the scientists were in the position to exclude them from occurring altogether.

In our view, the increased significance of accounting for foreseeable adverse effects is particularly relevant in understanding the reluctance to accept the public hazard posed by xenotransplantation. The case can be further clarified in reference to HIV. Although the current, real impact of the HIV pandemic relates to the *worst*-case harms of xenotransplantation, much more stringent monitoring and surveillance measures are imposed on the xenograft recipient than on a patient affected by HIV.

It has been proposed that the crucial distinction lies in the fact that xenotransplantation will be introduced *purposely* as a clinical experiment, whereas HIV is an 'experiment' of nature (Cooper and Lanza 2000, 216). It appears to make a difference to us whether harm was due to natural causes or knowingly brought about by the action of another person. That difference is tied to notions of individual responsibility and human agency (Teuber 1990). This is not to say that moral responsibility is attributed to only those effects that were purposely pursued. Rather, the underlying reasoning would seem to be that we are in the position *now* to annul foreseeable adverse consequences and thus have a particular moral responsibility to do so. Indeed, the freedom and autonomy of HIV/AIDS subjects is respected to the extent that their acts exclude foreseeable events of virus transmission.

If the permissibility of health hazards posed by emerging (bio)technologies is dependent on (1) a favorable perception of the feasibility and significance of the potential benefits and (2) on the duty to account for foreseeable risks, there is both good and bad news with regard to the development of xenotransplantation.

5 Foreseen risk and benefit

5.1 The bad news

Proponents of xenotransplantation have long defended the added values of applying solid organ xenotransplants to resolve the organ shortage problem. An unlimited source of animal grafts could help not only those patients who currently die while on the waiting lists, but also the individuals who are not enlisted on the transplant waiting lists, who are withdrawn from a list prior to their death or who have not accepted human organ donation for ethical or cultural reasons. Moreover, if a sufficient supply of xenografts were readily available, the transplant procedure could be precisely scheduled and preparatory measures could be facilitated (Groth 2000, 833). As such, both the graft and the recipient could be thoroughly screened prior to the transplant and the diverse patho-physiological effects of brain death on the organ quality could be avoided.

Nevertheless, xenotransplantation is not a heaven-sent timely solution to the limits of allotransplantation. While attempts to transplant nonhuman animal organs to humans go back to the beginning of last century, xenotransplantation has not been able to live up to its promises to this day (Deschamps et. al. 2005). After the failures of early experiments, interest in xenotransplantation was rekindled in the 1960s, motivated by a first wave of human donor shortages (prior to the implementation of the brain death criterion) and by increased knowledge of immunology. During that period, several xenotransplant trials were conducted parallel to some of the first non-related human-to-human allotransplants. In terms of the results achieved within both experimental fields at that time, Keith Reemtsma achieved outstanding survival rates of 63 days and 9 months after the xenotransplantation of nonhuman primate kidneys (Reemstma et. al. 1964). Those survival rates remain by far the longest ever achieved in animal-to-human organ transplantation, whereas allotransplantation has since made great strides forward.

It appears unlikely that xenogeneic organs will survive and function in humans for prolonged periods in the near future. Sir Roy Calne, one of the pioneers of the xenotransplantation enterprise, recently pictured that negative outlook. In a commentary entitled 'Xenografting – the future of transplantation, and always will be?', Calne doubts that therapeutic xenografts will be obtained within the next five to ten years (Calne 2005, 6). The prospect of using xenotransplantation as the

medium to avert the waiting list death toll is currently based more on rhetorical promise than on feasible potential. Indeed, due to the failure to materialize significant progress to the clinic, private industry has increasingly withdrawn or suspended commitment in this area (Pierson 2004, 391). The success of xenotransplantation is obstructed mainly by immunological incompatibilities. Due to the short survival rates obtained to date, the impact of subsequent rejection phases is not yet entirely manifest. The many physiological and biochemical incompatibilities between swine and humans form yet another source of factors that stand in the way of effective and successful use of xenogeneic organs.

Currently, most hope and effort are dedicated to various cellular xenotransplants and extracorporeal perfusion therapies. The transplantation of animal-derived cells is also very promising in terms of treating a wide variety of diseases, among which are: diabetes, liver failure, neurodegenerative disease, anaemia, spinal cord injuries, haemophilia, amyotrophic lateral sclerosis, AIDS, hypocalcaemia, hypercholesterolernia, lyposomal storage disease and dwarfism (Lanza and Cooper 1998, 40). Nevertheless, many of the cellular therapies differ in terms of urgency and life-sustaining benefit when compared to the need for whole organ replacement. Furthermore, the results of most cellular xenotransplants have thus far not provided compelling indications of progress in graft survival and clinical utility. A review of the clinical experience with both extracorporeal pig liver perfusion and bioartificial devices containing pig hepatocytes does not demonstrate a significant benefit for hepatic assist in acute liver failure (Pascher et. al. 2002; Wigg and Padbury 2005). The most imminent contribution of xenotransplantation to the clinic is likely to lie in the transplantation of porcine islets of Langerhans. That could provide an alternative to injections of human or porcine insulin, which are ineffective in fully restoring proper glucose homeostasis. Islet cell xenotransplantation may eliminate the need for daily insulin injections and obtain better glucose control. It could thereby avoid or retard development of the various ills and co-morbidity related to deficient treatment of chronic diabetes. Islet cells from cadaveric sources have been shown to provide at least 1-year insulin-independence in patients with very unstable diabetes (n=7) (Shapiro et. al. 2000). Two recent reports of more than 6 months of insulin independence in pig-to-monkey transplants provided promising indications of the feasibility of using islets from porcine sources too (Hering et. al. 2006; Cardona et. al. 2006). A recent report of a islet xenotransplant trial in humans suggests that combining porcine islet cells with Sertoli cells and encasing them in a semi-permeable encapsulation device is a promising means to eliminate the immune barrier to cell xenotransplants (Valdes-Gonzalez et. al. 2005).

Although the latter study is encouraging, the fact remains that xenotransplantation is overall still "very much in its infancy" (SACX 2004, 2). It is likely that there will be a long lead time between clinical trials and the commercial availability of significant numbers of transplantable genetically modified organs (Welsh and Evans 1999, 210). In effect, given the high costs and difficulties of breeding appropriate source animals, the question is whether xenotransplantation will *ever* be able to alleviate the waiting list death toll considerably.

Aside of these concerns, it is also questionable whether the potential benefits of xenotransplantation are perceived as significant enough to be regarded a health care delivery priority. Currently, there is reason to be skeptical about the favorable attitude of the public in this regard. In Canada, an extensive public consultation on xenotransplantation was conducted, consisting of citizen forums and mail-in/telephone/website surveys. Among the results of that consultation, only 30 per cent of the forum, 35 per cent of the mail-in, 22 per cent of the website and 35 per cent of the telephone survey respondents supported a redirection of health care resources to xenotransplantation (Canadian Public Health Association 2001, 24). The main

objections were based on scarce funds, high costs and other health care priorities. It can be expected that clinical xenotransplantation will result in a high rise of health care expenditure. It is possible that other claims for the limited health care budgets are regarded as more effective and efficient expenditures of the health care budgets. Oregon has led the way in rationing allotransplants on the basis of such considerations. In 1987, the state legislature decided to stop solid organ allotransplant coverage from Medicaid (Golenski 1990). It was determined that cutting expenditure on transplants would better meet the needs of the least well-off by reducing infant mortality through greater investments in prenatal maternal care. Against this, it must be noted that, at least in developed regions, the proportion of people with chronic diseases potentially treatable by transplantation – such as cardiovascular disease, cancer and diabetes – is enormous and expected to grow. Furthermore, allotransplantation of solid organs often provides the best overall anticipated health gains at lower costs in comparison with non-transplantation or alternative treatments. Nonetheless, these justifications do not necessarily apply for xenotransplantation. The ongoing costs of post-transplant care constitute the limiting factor of allotransplant cost-effectiveness against other existing treatment options. If xenotransplantation requires more aggressive and expensive immunosuppression, the investment in follow-up will be even greater. Moreover (and in light of the known effects of immunosuppression following an allotransplantation) it is conceivable that the immunosuppression will have adverse effects on the functioning of other organs, thereby undermining the therapeutic potential of the xenotransplant.

5.2 The good news

In questioning the attainability of xenotransplant benefits, we must also take note of the progress that has been made in the understanding of the level of infectious risk during the past decade. Indeed, we currently seem relatively well equipped to identify and define the infectious potential of most known porcine pathogens (Fishman and Patience 2004).

Broad exclusion lists have been generated which provide guidance to breeding out organisms particular to the source animal species, organisms that commonly cause infection in transplant recipients and organisms that have a high inclination for recombination. Those lists also facilitate the screening and studying of those organisms and the development of possible infection-suppressive measures. Various potential human pathogens can now be identified in advance, including porcine circovirus types 1 and 2, porcine reproductive and respiratory syndrome virus, porcine encephalomyocarditis virus, hepatitis E-like virus, pseudorabies virus, parvovirus and polyomaviruses of swine (Ibid., 1386). None of these have been shown to cause disease in humans. Recent research suggests that porcine cytomegalovirus, which has been shown to cause severe disease even in immunosuppressed host pigs (Mueller et. al. 2002), can be screened and excluded from herds of swine by early weaning of newborns (SACX 2004, 22). Conversely, failed attempts to wean out porcine lymphotropic virus (Mueller et. al. 2005) and the recent identification of hepatitis E virus (Van der Poel et. al. 2001) subject those viruses to further risk defining.

Significant progress has also been made in identifying and excluding the infection or recombination potential of PERV. Archived samples from past recipients of porcine insulin and clotting factors, temporary skin grafts, islet and neural cell xenotransplants, and extracorporeal porcine liver or spleen support have not shown any transmission of PERV or other porcine virus in patients treated with pig tissues thus far (Heneine et. al. 1998; Patience et. al. 1998b; Paradis et. al. 1999; Dinsmore et. al. 2000; Levy et. al.

2000; Cunningham 2001). Nor is there a clear relation between PERV production and illness in pigs, although PERV-C was originally cloned from a malignant lymphoma cell line (Suzuka et. al. 1986). Some authors have expressed concern that the promising results merely reflect the small numbers of patients studied so far, their brief exposure to the porcine grafts, the poor graft survival and an exclusive focus on known PERV strains during follow-up. Although the large-scale follow-up study of 160 patients after transplantation or exposure to pig tissue (Paradis et. al. 1999) is generally viewed as the most compelling demonstration of absence of PERV transmission, Collignon and Purdy drew attention to the more negative outcomes of the study (Collignon and Purdy 2001, 342-3). PERV was in effect detected in the blood of 30 patients. In 23 patients, pig cells were still detected up to 8.5 years after exposure. The authors suggest that at least the first two of four crucial conditions in terms of the potential for secondary infection have been fulfilled: the virus (or its genome) was present in the animal's cells or tissue and remained viable in people after transmission of the virus. Furthermore, studies have recently established the presence of natural immunity against PERV in human serum, showing that human serum with anti-Gal antibody can inhibit human cell infectivity of PERV *in vitro* and *in vivo* (Bucher et. al. 2005). That implies that the use of 'knockout' pigs that lack the anti-Gal antibody would entail additional risks. Notwithstanding this, significant knowledge has been gained on PERV infectivity. Previous findings had already suggested that only PERV-A and -B can infect human and pig cells *in vitro*, while the third subgroup, PERV-C, only infects porcine cells (Takeuchi et. al. 1998). The other PERV families are unlikely to encode infectious virus owing to disruptions in open-reading frames. Certain inbred lines of miniature swine appear to be incapable of producing replication-competent PERV (Oldmixon et. al. 2002, 3045), and progress in the science of PERV infection of human cells raises the possibility that the relevant PERV could be genetically engineered out of a source animal herd (Secretary's Advisory Committee on Xenotransplantation 2004, 21). Moreover, evidence suggests that PERV is susceptible to currently available antiviral agents (Wilhelm et. al. 2002). More worrisome are indications suggesting that, while PERV-C does not infect human cells, it is involved in extra harmful human-tropic PERV recombinants (Bartosch et. al. 2004). A recombinant isolate, PERV-A 14/220, has been shown to infect human cells with a significantly higher titer than previous PERV-A and –B families. Studies of its genome suggest that it is an A/C recombinant PERV and that therefore replication-competent PERV-C should best be excluded from the source animal's genome. Breeds of miniature swine have been identified which do not possess replication-competent PERV-C (Wood et. al. 2004).

Alongside the growing potency to recognize and exclude infection risks, a significant distinction must be made with regard to the different types of porcine grafts (Aebischer et. al. 1999, 252). The infection risk is directly related to the degree of recipient immunosuppression and the nature and intensity of the epidemiological exposure of the recipient. Cell-based xenotransplantation products imply a significantly smaller risk of virus transmission than xenotransplants of vascularized organs (although at this stage, it could be maintained that vascularized xenogeneic organ grafts pose the least public health threat due to the limited survival rates of the recipients (Allan 1999, 63)). Cells can also be best screened for a spectrum of infectious agents in advance. Moreover, xenogeneic cell transplant barriers to immunology, such as the above mentioned encapsulation techniques, may control viral transmission as well.

Finally, it should not be left unsaid that immunosuppressed allograft recipients too bear a significant, well-documented virus risk, often with an accelerated course of accidentally-transmitted infection (for instance, transmission of HIV-1 has been shown to manifest AIDS within six months (Fishman 2003a)). Over the past two years, six organ transplant recipients were reported to have died after graft-mediated infection of lymphocytic choriomeningitis virus, a zoonosis transmitted by rodents (Anonymous

2005, 340). Use of xenografts may be advantageous in this respect if resistant to human pathogens such as HIV, HTLV, hepatitis and herpes viruses. Moreover, if a ready source of xenografts allows scheduling the transplants at the time of greatest clinical need, exposure to pathogens related to lengthy hospitalizations of donor and recipient will be reduced (Fishman and Patience 2004, 1388).

6 Implications of revised risk: an optimistic note

In the following, we wish to interpret the development of findings related to the virus risk in an optimistic note. We will consider the possibility that all foreseeable factors that contribute to the risks of a xenogeneic epidemic *can* be excluded via current pre-clinical methods of porcine infectious agent detection and exclusion.

6.1 Theoretical risk

While the advanced xenogeneic virus research suggests that the probability of harm is less great than once feared, it does nothing to change concerns regarding the nature of the risk. Various screening methods may eventually exclude all pathogens identifiable in pre-clinical models. Caesarian section and suitable containment of the source animals may even help to exclude the unknown (Takeuchi and Weiss 2000, 504). *Nonetheless, none of those approaches guarantee that the theoretical possibility of latent, asymptomatic infection by unknown or recombined exogenous and endogenous agents is eliminated.* Indeed, undetectable organisms constitute the greatest concern of all, particularly if they can remain in a latent state within the source animal and recipient for indefinite time. In contrast to viruses that induce acute symptomatic viral infections, latent viruses can potentially spread easily between immunocompetent individuals and manifest long after the initial recipient is released from hospital containment practices.

In questioning the permissibility of risky technologies, the moral duty to account for foreseeable adverse effects is left undoubted. That moral duty explains why less stringent control measures are required to preclude risks from 'natural' causes, such as AIDS, in comparison with risks from man-made causes, such as xenotransplantation and recombinant DNA research. Nevertheless, a focus on optimal risk assessment to cover all theoretical consequences provokes the reproach that 'one cannot prove something that is not there'. Granted that sufficient pre-clinical detection and exclusion of known viruses and mutations in the source animals may one day be feasible, it would be asking too much of those involved in developing a new technology to guarantee the exclusion of *all* risks. Indeed, in comparison with the rationale that underlies our attitude towards the emergence of other theoretical epidemics/pandemics, it is questionable why the xenotransplantation enterprise should be answerable to risks of introducing a novel epidemic or pandemic beyond the degree to which such risks are constituted by predictable factors.

6.2 Natural and man-made pandemics

If we were able to reduce the infectious risks related to xenotransplantation to a merely *theoretical* risk – one in which all predicable effects have been eliminated – it would be ambiguous whether we should persist in treating xenotransplantation as a 'special case' and in subjecting it to severe advance public health protection measures. The only thing that would distinguish the risk of xenogeneic virus contamination from the contamination of a nature-borne virus, would be the fact that the xenogeneic virus resulted from human agency. It is not clear why the fact

that the harm results from a man-made technology demands for unequal consideration over nature-derived harm. The argument works both as a means to put the 'unique harm' of this man-made technology into perspective and as a reminder of our duty to take 'natural' health hazards at least as seriously.

First, the distinction between a natural epidemic/pandemic and a man-made one is not a relevant factor for those in the medical community concerned with treating the effects (Fishman 2003b, 911). Also, that distinction is not always clear-cut. In the emergence of certain pandemics of so-called natural origin, humans have also played an inflicting role. Notions of moral responsibility and blame do not apply in such cases, because the effects were unforeseen. Explanations for the spread of Human Immunodeficiency Virus (HIV) are illustrative in that respect. There is compelling evidence that HIV (-2 and some types of -1) is a derivative of Simian Immunodeficiency Virus (SIV) and was transferred to the human population from sooty mangabeys and chimpanzees in Africa (Chakrabarti 2002, 61). Most probably, SIV was transmitted to humans through blood contact during hunting and field dressing of the animals. Nevertheless, secondary viral transmission may not result in an epidemic unless certain conditions are met. A sporadic HIV infection in a small, remote African village could have been restricted to the infected person and his or her sexual partner(s) and close contacts. Their resulting deaths would have prevented further contaminations. The rapid spread of the virus among larger proportions of society was interdependent upon certain demographic and social conditions. They are said to include the massive emigration from rural areas for employment opportunities, the separation of family units that resulted from that migration and the increased rate of extramarital relations and sexual promiscuity (Fauci 2003, 672). An alternative description of the origin of the HIV pandemic, argued for by Louis Pascal (1991) and recently brought to our attention again (Martin 2003), ascribes an even greater function to human agency. According to this theory, SIV was transmitted to humans through the world's first mass polio vaccination campaign in central Africa during the late 1950s. Those polio vaccines were cultured on monkey kidneys, which would have allowed for the transfer of SIV. Whether or not that is the better theory, it is generally agreed that those involved in the African polio vaccination campaign cannot be held responsible for AIDS (Pascal 1991). The reason why no one is to blame is that SIVs had not been discovered at the time and the contamination, when it occurred, was inadvertent.

Most of the contemporary naturally-caused infections, such as the annual variants of type A and B influenza, also arise at least in part due to human agency. The ways we alter the ecology of the world in which we live – through technology, industry, agriculture, international travel, etc – and the interdependence of humans and animals are particularly conducive to the emergence of new zoonotic pathogens (Fishman 2003, 910; Lederberg 2002, 114). In a cautious approach to xenotransplantation, the claim is made that:

> Of course, animals have transmitted viruses and other infectious pathogens to humans ever since we learnt to hunt or husband them, yet we continue to meet nasty surprises. (Weiss et.al. 2000, 21)

This does not necessarily serve to demonstrate the unacceptability of the *theoretical* risk of xenogeneic infections that are beyond our control beforehand. Rather, it shows us the urgency to deal with the persistent manifestation of new epidemics, regardless of their cause. We are constantly confronted with theoretical risks of epidemics, and xenotransplantation is not per se our greatest concern. If the risk of xenozoonosis is merely theoretical, we should rather invest our energy and resources in the battle

against all types of zoonosis, rather than focus on ways to eliminate just this one, man-made xenozoonosis.

Against that, it may be argued that xenotransplantation would not be accessible for all those in need of it and could still increase the health burden of those who are arguably the worst-off in terms of health care. The worst-off are indeed those in the developing world, which bears more than 90 per cent of the global disease burden (Benatar 2001, 333) and has neither the financial means nor the infrastructure to provide large-scale basic health care, let alone expensive technologies to alleviate organ shortage. Nevertheless, an unjust distribution of the health burdens would not be alleviated significantly by avoiding the risks of xenogeneic infections altogether. A much greater balance of health benefits over burdens would be achieved if theoretical xenogeneic infections were regarded as one of the many global pandemic threats that face all of us today – and in the future – and that call for rapid response. In thinking of those who are amongst the most disadvantaged in terms of basic health care, a strong emphasis should be placed on an estimated 34 to 46 million people affected with HIV/AIDS (WHO 2004b, xii), and on many other infections, such as malaria, which are among the leading causes of death worldwide. AIDS is particularly illustrative of the gross discrepancies between the industrialized and the developing world in terms of infectious health burdens (Boyd et. al. 2000, 68). Sub-Saharan Africa accounts for 75 per cent of the global AIDS-related mortality (Woloschak 2003, 166). If we are in fact worried about the unjust distribution of health harms worldwide, then those patient populations ought to be the subject of further investigation and intense efforts to constrain the risks and manage the effects. In light of the fact that zoonoses currently constitute one of the major threats to human health, the systems for studying, controlling and preventing zoonotic diseases on a global basis must be further expanded. Others have voiced the opinion that the looming threat of bioterrorism is an extra motivation to invest more in a bio-defense plan (Relman 2006, 114; Franz 2002, 15-17).

In any case, the optimistic account of the permissibility of a xenogeneic virus risk is dependent on whether or not we can exclude predictable factors of the infectious risk beforehand. Even if that is feasible, still other factors may impede permissibility of xenotransplantation. On the societal level, the question remains whether this biotechnology must be granted a priority in the distribution of health care funding. On the individual level, the onus for those wishing to implement the various xenotransplantation procedures in the clinic still lies in demonstrating greater proof of the benefits they promise to provide. That is of importance in terms of outweighing the remaining risks of physical harm to the future recipients.

7 Conclusion

In attempts to balance the benefits and harms potentially involved in xenotransplantation, the benefits for the prospective patients have been subordinated to the risks of unleashing a xenogeneic pandemic. National and international restrictions on clinical research and trials have been set in place in order to exclude the risks for the public. However, for both practical and ethical reasons, these restrictions are inadequate. Indeed, they are a flawed response to the Precautionary Principle. In this paper, we suggested a different approach, which does not require that the risk for others is entirely eliminated. Rather, the most pressing condition for enhancing the permissibility of xenotransplant public health hazards is further identification and exclusion of the infection or recombination potential of *detectable* organisms. Of equal importance is the public perception that the promised benefits of this biotechnology are both attainable and significant. The permissibility of harm-doing is then rendered an issue of medical ethics, in which

doctor and patient can consider a weighing of harms against the benefits of the procedure. While this is the proper direction for further xenotransplant research, the road ahead is still long.

References

Aebischer, P., A.F. Hottinger, and N. Deglon. 1999. Cellular xenotransplantation. *Nature Medicine* 5(8): 852.

Allan, J.S. 1999. Nonhuman primates as organ donors? *Bulletin of the World Health Organization* 77(1): 62-3.

Anonymous. 2005. Xenotransplant News: Six organ transplant recipient deaths from rodent virus. *Xenotransplantation* 12(2): 340.

Bach, F.H., J.A. Fishman, N. Daniels, J. Proimos, B. Anderson, C.B. Carpenter, L. Forrow, S.C. Robson, and H.V. Fineberg. 1998. Uncertainty in xenotransplantation: Individual benefit versus collective risk. *Nature Medicine* 4(2): 141-4.

Bartosch, B., D. Stefanidis, R. Myers, R. Weiss, C. Patience, and Y. Takeuchi. 2004. Evidence and consequence of porcine endogenous retrovirus recombination. *Journal of Virology* 78(24): 13880-90.

http://www.molbio.princeton.edu/courses/mb427/2001/projects/02/antibiotics.htm.

Beauchamp, T.L. and J.F. Childress. 2001. *Principles of biomedical ethics (fifth Edition)*. Oxford: Oxford University Press.

Bass, S.E., S.S. Joshi, D. Nuttal, S.L. Sozinsky, T. Tharschmidt, and R. B. Spence. 2001. *History of antibiotics*. Retrieved online at:

Benatar, S.R. 2001. Commentary: Justice and medical research: A global perspective. *Bioethics* 15(4): 333-40.

Boyd, K.M., R. Higgs, and A.J. Pinching. 2000. An AIDS lexicon. *Journal of Medical Ethics* 26(1): 66-76.

Bucher, P., P. Morel, and L.H. Bühler. 2005. Xenotransplantation: An update on recent progress and future perspectives. *Transplant International* 18(8): 894-901.

Butler, D. 1998. Last chance to stop and think on risks of xenotransplants. *Nature* 391(6665): 320-4.

Calne, R. 2005. Xenografting--the future of transplantation, and always will be? *Xenotransplantation* 12(1): 5-6.

Canadian Public Health Association. 2001. *Animal-to-human transplantation: Should Canada proceed? A public consultation on xenotransplantation*. Ottowa, Ontario: Canadian Public Health Association. Retrieved online at: http://www.xeno.cpha.ca/english/finalrep/reporte.pdf.

Cardona, K., G.S. Korblitt, Z. Milas, J. Lyon, J. Cano, W. Jiang, H. Bello-Laborn, B. Hacquoil, E. Strobert, S. Gangappa, C.J. Weber, T.C. Pearson, R.V. Rajotte, and C.P. Larsen. 2006. Long-term survival of neonatal porcine islets in nonhuman primates by targeting costimulation pathways. *Nature Medicine* 12(3): 304-306.

Cascalho, M., and J.L. Platt. 2005. New technologies for organ replacement and augmentation. *Mayo Clinic Proceedings* 80(3): 374.

Chakrabarti, L. 2002. Natural history of simian immunodeficiency viruses: Clues to the emergence and virulence of AIDS viruses. In *The emergence of zoonotic diseases: Understanding the impact on animal and human health*, ed. T. Burroughs, S. Knobler and J. Lederberg. Washington, DC: National Academy Press.

Collignon, P., and L. Purdy. 2001. Xenografts: Are the risks so great that we should not proceed? *Microbes and Infection* 3(4): 341-8.

Committee for Proprietary Medicinal Products. 2003. *Points to consider on xenogeneic cell therapy medicinal products*. London: European Agency for the Evaluation of Medicinal Products. Retrieved online at: http://www.emea.eu.int/pdfs/human/regaffair/119902en.pdf.

Cooper, D.K.C. 2005. 8th International Xenotransplantation Association. Göteborg, Sweden. Verbal communication.

Cooper, D.K.C., and R.P. Lanza. 2000. *Xeno: The promise of transplanting animal organs into humans*. Oxford: Oxford University Press.

Council of Europe Committee of Ministers (COECM). 1999. Xenotransplantation. Recommendation n° 1399 (1999) on xenotransplantation. Adopted by the Parliamentary Assembly of the Council of Europe on 29 January, 1999. Retrieved online at: https://wcd.coe.int/ViewDoc.jsp?id=409609&BackColorInternet=9999CC&BackColorIntranet=FFBB55&BackColorLogged=FFAC75.

Council of Europe Committee of Ministers (COECM). 2003. Recommendation Rec n° 10 (2003) of the Committee of Ministers to member states on xenotransplantation *and explanatory memorandum*. Adopted by the Committee of Ministers on 19 June 2003. Retrieved online at: http://www.coe.int/t/e/social%5Fcohesion/health/Recommendations/Rec%282003%2910.asp#TopOfPage.

Cunningham, D.A., C. Herring, X.M., Fernandez-Suarez, A.J. Whittam, K. Paradis, and G.A. Langford. 2001. Analysis of patients treated with living pig tissue for evidence of infection by porcine endogenous retroviruses. *Trends in Cardiovascular Medicine* 11(5): 190-6.

Deschamps, J.Y., F.A. Roux, P. Sai, and E. Gouin. 2005. History of xenotransplantation. *Xenotransplantation* 12(2): 91-109.

Dinsmore, J.H., C. Manhart, R. Raineri, D.B. Jacoby, and A. Moore. 2000. No evidence of infection of human cells with porcine endogenous retrovirus (PERV) after exposure to porcine fetal neuronal cells. *Transplantation* 70(9): 1382-9.

Einsiedel, E.F. 2004. Commentary: On the position paper of the Ethics Committee of the International Xenotransplantation Association. *Transplantation* 78(8): 1110-1.

European Agency for the Evaluation of Medicinal Products (EMEA). 2003. *Points to consider on xenogeneic cell therapy medicinal products*. London: EMEA. Retrieved online at: http://www.emea.eu.int/pdfs/human/regaffair/119902en.pdf.

Engels, E.M. 2000. The moral status of animals in the discussions on xenotransplantation (Part I). Law Hum Genome Rev H 13: 165-81.

Fauci, A.S. 2003. The AIDS epidemic: Considerations for the 21st century. In *Contemporary issues in bioethics (Sixth edition)*, ed. T.L. Beauchamp TL and L. Walters. Belmont, CA: Thomson-Wadsworth.

Feinberg, J. 1986. Harm to self. Oxford: Oxford University Press.

Fishman, J., and C. Patience. 2004. Xenotransplantation: Infectious risks revisited. *American Journal of Transplantation* 4(9): 1383-90.

Fishman, J.A. 2003a. Transplantation for patients infected with human immunodeficiency virus: No longer experimental but not yet routine. *Journal of Infectious Diseases* 188(10): 1405-1411.

Fishman, J.A. 2003b. SARS, xenotransplantation, and bioterrorism: Preventing the next epidemic. *American Journal of Transplantation* 3(8): 909-12.

Florencio, P.S., and E.D. Ramanathan. 2001. Are xenotransplantation safeguards legally viable? *Berkely Technology Law Journal* 16(Suppl): 937-77.

Florencio, P.S., and E.D. Ramanathan. 2004. Legal enforcement of xenotransplantation public health safeguards. *Journal of Law, Medicine & Ethics* 32(1): 117-23.

Food and Drug Administration (FDA). 1999. *Guidance for Industry: Public Health Issues posed by the use of non-human primate xenografts in humans.* Washington, DC: US Department of Health and Human Services. Retrieved online at: http://www.fda.gov/cber/gdlns/xenoprim.htm.

Franz, D.R. 2002. The potential "bioweaponization" of zoonotic diseases. In *The emergence of zoonotic diseases: Understanding the impact on animal and human health*, ed. T. Burroughs, S. Knobler and J. Lederberg. Washington, DC: National Academy Press.

Frederickson, D.S. 1991. *Biomedical Politics.* Washington, DC: National Academy Press.

Golenski, J. 1990. *A report on the Oregon medicaid priority setting project*. Berkely, CA: Bioethics Consultation Group.

Groth, C. 2000. Presidential address: Why xenotransplantation? *Transplantation Proceedings* 32(5): 833.

Groth, C. 2005. Honouree member lecture: why xenotransplantation? Plenary at the 8th International Xenotransplanation Congress. Göteborg, Sweden. Verbal communication.

Heneine, W., A. Tibell, W.M. Switzer, P. Sandstrom, G.V. Rosales, A. mathews, O. Korsgren, L.E. Chapman, T.M. Folks, and C.G. Groth. 1998. No evidence of infection with porcine endogenous retrovirus in recipients of porcine islet-cell xenografts. *Lancet* 352(9129): 695-9.

Hering, B.J., M. Wijkstrom, M.L. Graham, M. Hardstedt, T.C. Aasheim, T. Jie, J.D. Ansite, M. Nakano, J. Cheng, W. Li, K. Moran, U. Christians, C. Finnegan, C.D. Mills, D.E. Sutherland, P. Bansal-Pakala, M.P. Murtaugh, N. Kirchhof, and H.J. Schuurman. 2006. Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates. *Nature Medicine* 12(3): 301-3.

Hilbrands, L.B., A.J. Hoitsma, and R.A. Koene. 1995. Medication compliance after renal transplantation. *Transplantation* 60(9): 914-20.

Kagan, S. 1998. Normative Ethics. Boulder, CO: Westview Press.

Lachmann, P.J. 1998. Public health and bioethics. *Journal of Medicine and Philosophy* 23(3): 297.

Lanza, R.P., and D.K.C. Cooper. 1998. Xenotransplantation of cells and tissues: Applications to a range of diseases, from diabetes to Alzheimer's. *Molecular Medicine Today* 4(1): 39-45.

Le Tissier, P., J.P. Stoye, Y. Takeuchi, C. Patience, and R.A. Weiss. 1997. Two sets of human-tropic pig retrovirus. *Nature* 389(6652): 681-2.

Lederberg, J. 2002. Summary and assessment. In *The emergence of zoonotic diseases: Understanding the impact on animal and human health*, ed. T. Burroughs, S. Knobler and J. Lederberg. Washington, DC: National Academy Press.

Levy, M.F., J. Crippin, S. Sutton, G. Netto, J. McCormack, T. Curiel, R.M. Goldstein, J.Y. Newman, T.A. Gonwa, J. Bancherau, L.E. Diamond, G. Byrne, J. Logan, and G.B. Klintmalm. 2000. Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD55/hCD59) porcine livers: Clinical results and lack of pig-to-human transmission of the porcine endogenous retrovirus. *Transplantation* 69(2): 272-80.

Martin, B. 2003. Investigating the origin of AIDS: Some ethical dimensions. *Journal of Medical Ethics* 29: 253-6.

Mill, J.S. 1859. *On Liberty.* Text retrieved online at: http://www.utilitarianism.com/ol/one.html.

Mueller, N.J., K. Kuwaki, C. Knosalla, F.J. Dor, B. Gollackner, R.A. Wilkinson, S. Arn, D.H. Sachs, D.K. Cooper, and J.A. Fishman. 2005. Early weaning of piglets fails to exclude porcine lymphotropic herpesvirus. *Xenotransplantation* 12(1): 59-62.

Mueller, N.J., R.N. Barth, S. Yamamoto, H. Kitamura, C. Patience, K. Yamada, D.K. Cooper, D.H. Sachs, A. Kaur, and J.A. Fishman. 2002. Activation of cytomegalovirus in pig-to-primate organ xenotransplantation. *Journal of Virology* 76(10): 4734-40.

Murphy, F.A. 2002. A perspective on emerging zoonoses. In *The emergence of zoonotic diseases: Understanding the impact on animal and human* health, ed. T. Burroughs, S. Knobler S, J. Lederberg. Washington, DC: National Academy Press.

Oldmixon, B.A., J.C. Wood, T.A. Ericsson, C.A. Wilson, M.E. White-Scharf, G. Andersson, J.L. Greenstein, H.J. Schuurman, and C. Patience. 2002. Porcine endogenous retrovirus transmission characteristics of an inbred herd of miniature swine. *Journal of Virology* 76(6): 3045-8.

Organ Procurement and Transplantation Network (OPTN). 2006. Current US waiting list – overall by organ. Retrieved online at: http://www.optn.org/latestData/rptData.asp.

Organisation for Economic Co-operation and Development (OECD). 1999. *Xenotransplantation: International policy issues.* Paris: OECD.

Paradis, K., G. Langford, Z. Long, W. Heneine, P. Sandstrom, W. M. Switzer, L.E. Chapman, C. Lockey, D. Onions, and E. Otto. 1999. Search for cross-species

transmission of porcine endogenous retrovirus in patients treated with living pig tissue. *Science* 285(5431): 1236-41.

Pascher, A., I. Sauer, C. Hammer, J.C. Gerlach, and P. Neuhaus. 2002. Extracorporeal liver perfusion as hepatic assist in acute liver failure: A review of world experience. *Xenotransplantation* 9 (5): 309-24.

Pascal, J. 1991. What happens when science goes bad. The corruption of science and the origin of AIDS: A study in spontaneous generation. *Wollongong Science and Technology Analysis Research Programme* Working Paper 9. Retrieved online at: http://www.uow.edu.au/arts/sts/bmartin/dissent/documents/AIDS/Pascal91.html.

Patience, C., Y. Takeuchi, and R.A. Weiss. 1997. Infection of human cells by an endogenous retrovirus of pigs. *Nature Medicine* 3(3): 282-6.

Patience, C., Y. Takeuchi, and R.A. Weiss. 1998a. Zoonosis in xenotransplantation. *Current Opinion in Immunology* 10(5): 539-42.

Patience, C., G.S. Patton, Y. Takeuchi, R.A. Weiss, M.O. McClure, L. Rydberg, and M.E. Breimer. 1998b. No evidence of pig DNA or retroviral infection in patients with short-term extracorporeal connection with pig kidneys. *Lancet* 352(9129): 699-701.

Pierson, R.N. 3rd. 2004. Xenotransplantation at the crossroads. *Xenotransplantation* 11(5): 391-3.

Public Health Service (PHS). 2001. *Guideline on infectious disease issues in xenotransplantation*. Retrieved online at: http://www.fda.gov/cber/guidelines.htm.

Ravelingien, A., and J. Braeckman. 2005. The patients' perspective: Comments on 'Reluctance of French patients with type 1 diabetes to undergo pig pancreatic islet xenotransplantation. *Xenotransplantation* 12(3): 173-4.

Reemtsma, K., B.H. McCracken, J.U. Schlegel, and M. Pearl. 1964. Heterotransplantation of the kidney: Two clinical experiences. *Science* 143: 700-2.

Relman, D.A. 2006. Bioterrorism – Preparing to fight the next war. *New England Journal of Medicine* 354(2): 113-5.

Rood, P.P.M., D.K.C. Cooper. 2006. Islet xenotransplantation: Are we really ready for clinical trials? *American Journal of Transplantation* 6(6): 1269-74.

Rothblatt, M. 2004. Your life or mine: How geoethics can resolve the conflict between public and private interests in xenotransplantation. Aldershot, UK: Ashgate Publishing.

Secretary's Advisory Committee on Xenotransplantation (SACX). 2004. *Report on the state of the science in xenotransplantation (Draft)*. Bethesda: US Department of Human Health Services. Retrieved online at: http://www4.od.nih.gov/oba/SACX/reports/Sci_draft_030905.pdf: 26.

Shapiro, A., J. Lakey, E. Ryan, G.S. Korbutt, E. Toth, G.L. Warnock, N.M. Kneteman, and R.V. Rajotte. 2000. Islet transplantation in 7 patients with type 1 diabetes melitus using gluocorticoid-free immunosuppressive regimen. *New England Journal of Medicine* 343(4): 230-8.

Suzuka, I, N. Shimizu, K. Sekiguchi, H. Hoshino, M. Kodama, K. Shimotohno. 1986. Molecular cloning of unintegrated closed circular DNA of porcine retrovirus. *FEBS Letters* 198(2): 339-43.

Sykes, M., A. D'Apice, M. Sandrin, and IXA Ethics Committee. 2003. IXA Ethics Committee: Position paper of the Ethics Committee for the International Xenotransplantation Association. *Xenotransplantation* 10(3): 194-203.

Takeuchi, Y., and R. Weiss. 2000. Xenotransplantation: Reappraising the risk of retroviral zoonosis. *Current Opinion in Immunology* 12(5): 504-7.

Takeuchi, Y., C. Patience, S. Magre, R.A. Weiss, P.T. Banjeree, P. Le Tissier, and J.P. Stoye. 1998. Host range and interference studies of three classes of pig endogenous retrovirus. *Journal of Virology* 72(12): 9986-91.

Teuber, A. 1990. Justifying risk. *Proceedings of the American Academy of Arts and Science* 119(4). Retrieved online at: http://people.brandeis.edu/~teuber/paperrisk.html.

United Network for Organ Sharing (UNOS). 2004. Reported deaths and annual death rates per 1000 patient–years at risks. Waiting list 1994 to 2003. OPTN/SRTR data as of May 3, 2004. Retrieved online at: http://www.optn.org/AR2004/106_dh.htm.

United Network for Organ Sharing (UNOS). 2006. Retrieved online at: http://www.optn.org/latestData/step2.asp?

United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). 1999. *Draft report of the Infection Surveillance Steering Group of the UKXIRA*. London: UKXIRA.

Valdes-Gonzales, R.A., L.M. Dorantes, G.N. Garibay, E. Bracho-Blanchet, A.J. Mendez, R. Davila-Perez, R.B. Elliott, L. Teran, and D.J. White. 2005. Xenotransplantation of porcine neonatal islets of Langerhans and Sertoli cells: A 4-year study. *European Journal of Endocrinology* 153(2): 419-27.

van der Poel, W.H., F. Verschoor, R. van der Heide, M.I. Herrera, A. Vivo, M. Kooreman, and A.M. de Roda Husman. 2001. Hepatitis E virus sequences in swine related to sequences in humans, The Netherlands. *Emerging Infectious Diseases* 7(6): 970-6.

Weiss, R.A., S. Magre, and Y. Takeuchi. 2000. Infection hazards of xenotransplantation. *Journal of Infection* 40(1): 21-5.

Welsh, I., and R. Evans. 1999. Xenotransplantation, risk, regulation and surveillance: Social and technological dimensions of change. *New Genetics and Society* 18(2/3): 197-217.

Wigg, A.J., and R.T. Padbury. 2005. Liver support systems: Promise and reality. *Journal of Gastroenterology and Hepatology* 20(12): 1807-16.

Wilhelm, M., J.A. Fishman, R. Pontikis, A.M. Aubertin, and F.X. Wilhelm. 2002. Susceptibility of recombinant porcine endogenous retrovirus reverse transcriptase to nucleoside and non-nucleoside inhibitors. *Cellular and Molecular Life Sciences* 59(12): 2184-90.

Woloschak, G.E. 2003. HIV: How science shaped the ethics. *Zygon* 38(1): 163-7.

http://www.oecd.org/document/10/0,2340,en_2649_34537_1902986_1_1_1_1,00.html.

World Health Organization (WHO). 2001. *WHO Guidance on xenogeneic infection/disease surveillance and response: A strategy for international cooperation and coordination.* Geneva: WHO.

World Health Organization (WHO). 2004a. *Report of the 57th World Health Assembly. Human organ and tissue transplantation (WHA57.18, 22).* Geneva: WHO. Retrieved online at: http://www.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf.

World Health Organization (WHO). 2004b. *The World Health Report 2004: Changing history.* Geneva: WHO.