

XENOTRANSPLANTATION

Should We Add “Xeno” to “Transplantation”?

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Abstract. Proponents of xenotransplantation hope that it will provide organs to fill the gap between the demand for and supply of organs for transplant. The scientific obstacles to transplanting animal organs into humans are daunting, as are the moral, political, and policy issues. Among them are concerns about animal rights and welfare, patient acceptance and informed consent, and broader public health issues, such as the cost-efficient deployment of scarce resources and the risk of disease in third parties. The latter is, in my view, the most immediately urgent issue. Pigs, the current animal of choice, carry many bacterial and viral pathogens, and it is currently impossible to assess the risk of disease to human populations. Because of this risk, a moratorium on xenotransplantation is necessary to protect public health; it is also questionable whether the technology, if successful, would be the most cost-effective way to promote health.

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One of the hottest new issues in bioethics is the prospect of “xenotransplantation,” using non-human tissue and organs to treat human disease. Spurred on by the possibility that animal materials could be used to promote human health and save lives, research on animal materials has been steadily increasing. Moreover, with the spectacular advances in other fields of medicine—such as immunology, genetics, and cloning—the prospect of success in xenotransplantation seems tantalizingly close. Yet, xenotransplantation also raises serious ethical questions. Among them are animal rights issues, patient acceptance and informed consent, and risk to patients and to other members of society.¹ Although these questions are receiving some consideration, experimentation with xenotransplantation—as with other exciting new medical technologies—threatens to outpace thoughtful responses to them.

Experiments with animal materials appear to have started in 1628, when animal blood was reportedly given to a human (Cooper and Lanza, 2000:27). In 1682, part of a dog’s skull was used to repair a Russian’s damaged skull (Cooper and Lanza, 2000: 28). In the late nineteenth century, transplants were attempted with a rabbit eyeball, a sheep’s urethra, and skin flaps from lambs (Cooper and Lanza, 2000:29). Attempts at whole organ transplants followed in the early twentieth century, when a monkey kidney was implanted into a patient who survived for two days (Canadian Public Health Association, 2000).

A new spate of attempts to use animal organs began in the 1960s, using monkey, chimpanzee, baboon, and pig hearts, livers, and kidneys. One patient who received a chimpanzee kidney in 1963 survived for nine months (Canadian Public Health Association, 2000). In 1984, in the much-publicized Baby Fae case, a baboon heart was implanted into a newborn with a severe heart defect; the baby lived for twenty days before the heart was rejected (Cooper and Lanza, 2000:38).

The 1990s saw renewed interest both in whole organs and cells and tissue. Surgeons in Poland and India attempted to transplant animal hearts into humans, and in 1992, two Americans received baboon livers. One lived seventy days (Cooper and Lanza, 2000:40). More recently, pig neural

cells have been transplanted into patients with Parkinson's disease (Bosch, 2000), and fetal pig islet cells have been transplanted into diabetic patients. In one islet cell trial, six patients rejected the cells within days, while in four others, the cells survived up to fourteen months (Beddard and Lyons, 1996:17). In other trials, the blood of patients with liver failure is successfully being circulated externally through pig livers on a temporary basis; apparently, some patients have been helped (Cooper and Lanza, 2000:41-43; Health Canada, 1999b). In 1995, baboon bone marrow stem cells were transplanted into an AIDS patient; however, the cell transplant did not engraft. Other experiments with corneas and blood have also failed (Beddard and Lyons, 1996:18).

A variety of other possibilities are also being tried, such as thymus transplants for AIDS patients (Henderson, 1998). However, it is now apparent that significant scientific obstacles to successful use of animal materials, whole organs in particular, remain. Recipients of whole organ transplants have, with only a couple of exceptions, survived no more than seventy days, often much less. Organs from nonhuman primates have been the most successful; no transplants with organs from other animals have lasted more than one day. Patients receiving tissues and cells have survived, but there is little evidence of long-term benefit (Cooper and Lanza, 2000:43; United Kingdom Xenotransplantation Interim Regulatory Authority, 2001:6.19).

Transplantation of whole organs, rather than cells or tissue, has been the focus of much of the debate about xenotransplantation so far. It has generally been assumed that whole organ transplants would provide the most dramatic medical progress, but that they would also pose the greatest risk and danger. It is not clear whether these are tenable assumptions. However, this discussion, too, will center on whole organ transplants.

Why Xenotransplant?

Why is the possibility of using animal materials so attractive? The reason is simple: thousands of individuals who could benefit from transplants die every year because not enough human organs are available.

Rates of organ donation vary enormously (Butler, 1998a),² but nowhere are there enough organs available to meet the demand. At the end of 1997, the waiting lists in the United States included more than 55,000 names (Organ Transplant, 2001). This figure does not include the thousands of patients who now fail to qualify for waiting lists (Butler, 1998a:325).³ In addition, as Western populations age and more individuals experience organ failures due to underlying diseases such as diabetes, the demand for organs can be expected to grow (Butler, 1998a:325). At the same time—at least in the United States—fewer organs are becoming available because of new traffic safety measures (Butler, 1998a:325).

Xenotransplantation promises other benefits as well. Organs could be ready and waiting when people need them (Butler, 1998a:325). In theory, these organs would come from healthy animals raised in clean conditions. In addition, the characteristics of these animals could be known ahead of time, and they could be engineered to provide a uniform and optimum product.⁴ The complex arrangements now required for matching donors to recipients would be unnecessary. Painful and difficult discussions about donation with families of dying patients who are potential donors could be avoided. Less than optimal practices (transplanting hepatitis-C livers, for example) could also be avoided. There would also be much less pressure for such morally troubling innovations as taking organs from patients in persistent vegetative states, anencephalic infants, or living donors.

In short, given the potentially huge demand for organs, xenotransplantation could open up new frontiers and resolve a host of serious problems. There is both fame and—in this age of commercial medicine—enormous fortune to be made (Butler, 1998a:320).⁵

Worries about Xenotransplantation

Is there any reason not to push forward with clinical research? A number of considerations ought to give us moral pause.

Animal Rights and Welfare

First, what about animal welfare and animal rights? Views about animal rights range from the belief that it is morally permissible for humans to exploit them to the belief that it is wrong to interfere with their lives. For example, Michael Fox argues that because animals are not autonomous beings, and therefore do not have valuable lives of their own, humans may use them for their own ends (Fox, 1986:50).⁶ At the other end of the spectrum, ecofeminists such as Josephine Donovan stress the connections between the oppression of women and animals, arguing that “we should not kill, eat, torture, and exploit animals because they do not want to be so treated, and we know that” (Donovan, 1993:185). Proponents of the first view have no qualms about killing animals for their organs and tissues; proponents of the second hold that animals' lives are as worthwhile as ours are and so it is wrong to kill them even to save human lives. I proceed here with a middle-of-the-road view that, other things being equal, it is morally permissible to use animal bodies for human benefit, so long as they live and die comfortably.⁷ According to this view, the primary moral challenge is ensuring that animals truly are well treated and painlessly killed when necessary.

The practical difficulties of assuring animal welfare are underlined by the recent allegation that research activities

causing indefensible animal suffering took place at Imutran's United Kingdom laboratory, Huntingdon Life Science. Documents describing these activities were leaked to Dan Lyons (director of the anti-vivisectionist organization, Uncaged Campaigns), who published them as *Diaries of Despair* (see *Uncaged Campaigns*, 2001). In September 2000, descriptions of the experiments and their consequences for the animals were published in the *Daily Express* (Johnston and Calvert, 2000a,b). Shortly afterwards, the *Express* announced that Imutran was closing its lab and moving the research to the United States to collaborate with another xeno lab, BioTransplant ("Animal Lab Shuts Down," 2000). However, Imutran, a subsidiary of Novartis, then obtained an injunction preventing dissemination of the leaked materials on the grounds that they were confidential and that publication violated copyright law. In defense of his January 11, 2001 ruling in Imutran's favor, the judge argued that "many of those documents are of a specialist and technical nature suitable for consideration by specialists in the field but not by the public generally" (Imutran, 2001).

Thus, it may be difficult in practice to ensure animal welfare. One might, therefore, reasonably place the burden of proof on any medical use of animals to show that they do not suffer. In any case, there has so far been little discussion of how the procedures necessary for xenotransplantation would affect the current animal of choice, pigs, and it is unclear whether medical researchers would take these moral constraints seriously without stringently enforced regulations (Langley and D'Silva, 1998:55-66).

Animals who might be moral beings, such as baboons, require a still higher standard of concern. Until recently, baboons have been xenotransplanters' favorite source of organs (Bailey et al., 1985). Yet, as James Nelson writes, "we're at a loss to say what it is about baboons that makes their livers fair game, when we wouldn't dare take vital organs from those of our own species whose abilities to live rich, full lives are no greater than those of the nonhumans we seem so willing to prey upon" (Nelson, 1992:6). Attention has recently turned away from baboons and their cousins, but not, alas, because of moral worries, but because of concerns about cost, availability, and the possible transmission of disease. But it might be as immoral to use pigs as to use baboons, and for the same reason. Although pigs look a lot less like us than baboons, psychological characteristics are paramount, not looks. Pigs are considered intelligent animals, and intelligence is associated with the kind of self-awareness that many philosophers see as the basis for the right to life.⁸

Using pigs is worrisome on other grounds as well. Although it *may* be safer to use animals that are phylogenetically more distant from us—because it may be more difficult for the viruses they harbor to latch onto us successfully—

the tradeoff in using more genetically distant animals is that the immunology is trickier (Stephenson, 1995).

Organs from animals genetically less like us trigger "hyperacute rejection" (HAR), an immune system reaction that can cause organs to fail in just a few minutes (Stephenson, 1995:286). Attempts to circumvent HAR are underway, and some researchers believe that the problem has been solved.⁹ However, once HAR has been vanquished, patients are at risk from at least two additional types of rejection, delayed graft rejection and T-cell-mediated rejection (Collignon, 1998:516). These other types of rejection need to be resolved before going forward with xenotransplantation.¹⁰

Breeding relevant human genes into pigs is one method through which researchers are attempting to circumvent HAR. For example, researchers have successfully inserted genes into pig embryos that cause them to make the human complement regulatory proteins that protect us from foreign materials. The hope is that if pig organs also contain complement, human bodies will not attack them, staving off HAR (Stephenson, 1995:287). Successfully breeding transgenic animals might eventually allow us to avoid immunosuppressive drugs altogether, the most serious drawback to transplantation.¹¹

Is there anything wrong with breeding transgenic pigs? We have been shaping pigs (and other animals) to suit our needs for years, of course: wild pigs have less meat than contemporary, domestic pigs. A recent editorial in *The Lancet* comments approvingly that "transgenic pigs are acceptable sources providing 'the pig neither suffers unduly nor ceases recognizably to be a pig'" (*The Lancet*, 1997:219). Even if pigs are primitive moral beings, why might it be intrinsically wrong to alter them substantially? The position that it would be wrong to reshape pigs seems to be based on creationism and its corollary that God's handiwork should not be changed. Consequentialism would counter that such change is permissible so long as pigs are not harmed. So, increasing pigs' potential bacon content is immoral only if it leads to their living worse lives (as in factory farming), and the same is true for more fundamental changes. However, although genetic manipulation may not itself be immoral, it may be the case that it requires morally dubious means to achieve. These "details" need scrutiny to ensure that otherwise acceptable measures do not cause serious suffering (Langley and D'Silva, 1998).

Acceptability and Informed Consent

A second worry about xenotransplantation is whether humans will be open to accepting animal organs. In one study, some two-thirds of a group of 1,728 acute care nurses in 59 Australian hospitals said that they would refuse organs from primates, pigs, or sheep; another 15-19% were unsure (Mohacsi et al., 1995:434). A smaller study of 113 patients with end-stage organ failure showed that only 42% were

willing to accept animal organs (Mohacsi et al., 1997:1031). However, another, and larger study, suggested more openness to the idea, with 78% of dialysis patients saying they would be willing to accept a pig kidney (Ward, 1997:1775). Clearly, additional research on this topic would be useful.

Paradoxically, another concern about xenotransplantation is the fear that, as with other potentially life-saving innovations, it may be impossible to obtain anything but the most superficial kind of informed consent from patients who know that they will die without the treatment. Informed consent is intended to protect patients from unwanted care. It helps them choose treatment that is consonant with their values. Informed consent in transplantation—even when the organs are of human origin—is morally required, because patients may experience significant post-transplant health problems, with their quality of life being lower than they expected (Littlefield et al., 1996).

This problem would be especially acute for early xenotransplant patients, for whom the procedure would be experimental and the outcome precarious. On one hand, it would be difficult for providers to give patients anything like an accurate account of what could go wrong. On the other hand, it would be especially difficult for the very sick patients for whom such transplants might be appropriate to judge whether they are likely to benefit, or whether xenotransplantation would only make their dying more painful (Vanderpool, 1998:1348; Welin, 2000). As Vanderpool points out,

If their autonomy is to be respected, they will need to hear, understand, weigh, and make decisions about a host of complex concerns. These concerns include: the stage of xenotransplant research (incorporating discussions about data from previous experiments on mortality and quality of life); the likelihood of media attention and compromised confidentiality; the risks and discomforts of opportunistic infections; information about the risk of development of animal-mediated (zoonotic) and genetically innovative (xenogeneic) infections, and of transmission of these infections to others (1998:1348)

They will also need to understand how they will have to live the rest of their lives:

adherence to a schedule of frequent, long-term, or life-long medical surveillance; the granting of permission to public-health agencies to examine private medical records; the granting of consent to a complete necropsy at time of death; the responsibility to educate close contacts about the risks and control of infections; and detailed information about

the trying, sometimes traumatic psychological effects of immunosuppressive drugs, (1998:1348)

The demands on patients may go beyond this; in October of 1999, the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) proposed a list of possible precautions, including a promise that recipients will not have children, that they will always use barrier contraceptive devices, and that they will provide the names of sexual partners so that they can be monitored (Connor, 1999). As exposure to animal materials may confer risk even when the transplant fails, such survivors might reasonably be expected to adhere to the same infection control measures (UKXIRA, 2001:5.9). Society must also face hard questions about how to deal with organ recipients who fail to follow these procedures or who develop new, perhaps infectious diseases. Are we prepared—physically and morally—to quarantine them?¹²

Unfortunately, current informed consent procedures in general are inadequate, partly because of the way health care is delivered (especially the time constraints on physicians), and partly because it is very difficult for individuals in pain and fearful for their lives to reason well about alternative treatments.

What follows from this situation for xenotransplantation? One might argue that it does not make sense to ban it on ground that it is impossible for patients to make truly autonomous decisions, for this point is also true for many other treatments now offered to patients. As with other procedures, patients inevitably rely on researchers and physicians to protect their interests. Given the unknowns here, that means the scientific community has a particularly stringent duty to subject xenotransplantation to rigorous scrutiny before trying it on patients. Animal work must be pursued until every foreseeable problem has been resolved and only human experimentation will reveal further problems. International authorities (with no personal or financial stake in the outcome) should judge when, if ever, clinical trials with humans would be scientifically and morally tenable. The alternative would be to argue that the unknowns in xenotransplantation so significantly magnify patient risk that it cannot go forward until more effective methods of achieving informed consent are developed.

Last, but not least, xenotransplantation raises troubling new questions about third-party consent. Because of the risk of infection, patients' health care providers and intimates must be made aware of potential dangers to themselves and the ways they could put others in danger. What sort of informed consent procedures are possible and appropriate under these circumstances? Society has not yet had to grapple with this issue, or the related compliance issues in case of infection.

These considerations suggest that if we were to go forward with clinical trials, the as-yet undealt-with matter of

third-party informed consent would have to be taken very seriously. Vanderpool asserts that although the draft guidelines of the U.S. Public Health Service emphasize education of third parties rather than consent, there are still good reasons for thinking in terms of consent (Vanderpool, 1998:1348). He argues, first, that patients' loved ones may be affected by, and themselves affect, the outcome. They may be required to refrain from certain sexual practices, and to agree to testing and monitoring. Second, researchers and medical institutions may be protected from lawsuits by third-party informed consent. Finally, medical personnel connected with xenotransplantation would need to provide baseline serum samples that would be stored and subject to surveillance by federal agencies. They surely should be informed about (and consent to) the handling of their materials (Vanderpool, 1998:1348).¹³

However, even this kind of consent fails to address the issue of how society at large might provide informed consent.

Risk to Society at Large

The last major concern about xenotransplantation is its potential effect on society at large. At issue is the possible risk of transmission of diseases from animals to humans via transplant patients. In this respect, xenotransplantation is different from previous experimental treatments, from which patients have both stood to gain and undertaken most or all of the risk. As Jonathan Hughes urges,

the fact that xenotransplantation carries risks not just for the xenograft recipient but for the population generally is important because it takes the ethics of xenotransplantation outside the realm of individual consent and into the realm of *justice*, raising questions about the extent to which it is permissible for an individual to impose risks on others for his own benefit. (Hughes, 1998:21)

This point has been reinforced by a number of writers recently, including Fritz Bach et al., who argue for a moratorium on clinical experimentation until the public can be educated about the risks and benefits. The authors argue that because of this feature of xenotransplantation, the ethical issues must be addressed and resolved before a regulatory framework is developed and before any commitment to proceed is made. They also propose a new process for evaluating technologies of this kind (Bach et al., 1998).

Why might such an appeal be reasonable? Philosophers are not scientists and therefore cannot make authoritative claims about the potential dangers here. However, educated laypersons can find worrisome information in the most well respected journals, such as *Nature*, *Journal of the Ameri-*

can Medical Association (JAMA), *New England Journal of Medicine (NEJM)*, *The Lancet*, and *The Annals of Internal Medicine*.

Primates and Infection. It is now well established that primates can transmit disease to us. Ebola and the other hemorrhagic diseases are thought to have come from our primate cousins. In addition, animal handlers in primate research labs have developed a variety of frightening and sometimes lethal diseases (Garrett, 1994:573-74). HIV-1 now turns out to have come to us from chimpanzees (Gao et al., 1999:436); HIV-2 appears to have been transmitted to us by sooty mangabey monkeys (Chapman et al., 1995: 1499).

Some of these primate diseases are so virulent that they kill humans before others can be infected. Yet diseases do not have to be virulent or easily transmissible to wreak havoc among humans—consider the 30 million or so HIV-positive humans, most of whom will probably die of AIDS.

Some primate species harbor viruses known to cause lethal diseases in other primate species. In 1968, it was discovered that captive *Saimiri* squirrel monkeys at the New England Primate Research Center passed a herpes virus, *Herpesvirus saimiri*, to members of other monkey species housed with them. Although the virus is harmless in squirrel monkeys, its new hosts rapidly developed lethal lymphatic cancers. Shortly afterwards, it was discovered that another herpes virus, *H. Ateles*, harmless in spider monkeys, causes almost 100% lethal leukemias and lymphomas in members of other monkey species living near them. Because we are so closely related to the higher primates, it is reasonable to wonder whether we are vulnerable to these herpesviruses (Garrett, 1994:573). Furthermore, viruses engage in intensive mutation and gene swapping. An initially harmless virus could quickly change character once safely inside a human being. This danger might be enhanced in immunosuppressed transplant patients whose bodies are less able to restrict viral proliferation (Garrett, 1994:573). It might be magnified still further if such patients later became infected with other microbes, as they could engage in reassortment (Garrett, 1994:657).¹⁴

Given these dangers, it seems doubtful that researchers should have attempted to transplant baboon livers into humans, as they did in 1992-93. At least one of the livers was known to be infected with SIV (the simian AIDS virus), CMV (the simian cytomegalovirus), EBV (the simian Epstein-Barr virus), and Simian Agent 8 (the baboon form of B virus) (Garrett, 1994:575). The patient died soon after the transplant, and post-mortem exam showed no evidence of viral transmission.¹⁵ However, we do not know what might have happened had the patient lived longer.

The possible development of an easily transmissible lethal virus suggests that it would be imprudent to use primates for xenotransplantation. Would it be any safer to use other animals? Not necessarily.

Pigs and Other Animals. Diseases may well have traveled from other species to us in the more distant past, but we did not have the science to understand what was going on. We suspect that the devastating 1918 influenza that killed more than 20 million people came from birds via pigs; a more recent dangerous flu came from birds, as well (Larson, 1998).¹⁶ It also now looks as though the lethal Bovine Spongiform Encephalopathy (BSE) was transmitted to humans from sheep via cows; still more frightening, it may involve entirely new and poorly understood infectious agents, prions. In short, phylogenetic distance does not appear to guarantee immunity (Chapman et al., 1998:1498).

Current xenotransplantation hopes are focused on pigs. Pigs, like other animals, carry bacteria and “exogenous” viruses (viruses that happen to infect particular animals). It would be premature to presume that we already know everything about pig viruses; for instance, a new virus related to human hepatitis E was reported in pigs in 1998 (Weiss, 1998:328). Many bacteria infect both pigs and humans, and human recipients of pig heart valves have been infected by *Myocardium fortuitum* complex (Conly, 1998:263). Pigs also harbor many viruses that could be transmitted to humans, some of which might be far more damaging to us than to their usual hosts (Conly, 1998:263).

Pigs also carry endogenous retroviruses (PERV), retroviruses whose DNA has become part of the pig genome (Chapman et al., 1998:1499). These are worrisome because retroviruses have exceptionally high mutation rates; they would also be difficult or impossible to eradicate. Pigs are also infected by many parasites (Conly, 1998:263).

Developing transgenic pigs in the attempt to circumvent HAR may magnify the danger of infection. Robin Weiss argues that some pig viruses may be inactivated by the same mechanism as HAR. So, transgenic pigs designed to eradicate HAR may also render the lipid envelopes containing potentially dangerous viruses resistant to destruction inside the human body and thus more likely to flourish (Weiss, 1998:327-328). Transgenic pigs might therefore provide ideal conditions for helping animal viruses adapt to humans (Collignon, 1998; Collignon and Purdy, 2001).

In short, several factors—DNA mutation and reassortment, the alteration of risk when infectious organisms jump species, patient immunosuppression, and the unknowns created by the development of transgenic animals—render calculations of risk even less reliable than usual. These factors together could generate a catastrophic scenario in which a pig microorganism mutated into an easily transmissible, lethal, human disease (Collignon and Purdy, 2001). Such a microorganism might turn out to be unstoppable by any known treatment, and could, conceivably, threaten human existence altogether.

It is tempting to reject this vision as apocalyptic, the product of a fevered bioethicist’s mind. After all, humans and other animals have lived together for millennia; the

appearance of dangerous new microbes might therefore seem unlikely. But, as Weiss points out, xenotransplantation breaks down existing barriers to transmission, and both immunosuppression in patients and the existence of transgenic pigs may facilitate the adaptation of viruses to humans (Weiss, 1998).¹⁷ Thus, appeals to past experience may have limited utility, especially when we face the fact that dangerous new diseases (AIDS, for example) can appear at any time. Suppose, after all, that AIDS had turned out to be much more easily transmissible? It seems clear that we should be cautious in estimating our ability to recognize and control new diseases.

Proponents of xenotransplantation also argue that many animal-derived products are currently being used to treat disease or do research. Among them are insulin, heart valves, and skin from pigs; thyroxin, lung lipids, and adrenal cells from cows; and sera from horses and calves. All are being used in the production of vaccines. However, all are treated to try to stop the transmission of disease-causing organisms or viruses (Collignon, 1998:517). Whole cells are generally not used, and the contact usually involves smaller volumes of material (Collignon, 1998:517). It is known that SV40 contaminated polio vaccine in the 50s and 60s, and for many years it was thought to be harmless. However, there is recent evidence that it may play a causative role in certain cancers, especially tumors of the central nervous system. Furthermore, it appears that the virus can be transmitted between humans (Butel and Lednicki, 1999). Although the virus in question is simian, these developments would suggest the need for renewed caution about putting humans in close contact with any animal organisms.

There are, in addition, serious epistemological problems in making judgments about risk here. As Fred Murphy cautions, methods commonly used to detect viruses are not sufficient to rule out their existence (Murphy, 1996:747). Apparently healthy animals can still carry disease-causing organisms (Collignon, 1998:517). Furthermore, it is likely that many undiscovered microorganisms still lurk in both humans and animals. Several significant disease-causing organisms—such as HIV, *Helicobacter pylori*, *Chlamidia pneumoniae*, herpesviruses 6-8, *Bartonella*, and hepatitis C—have been discovered only in the last twenty years or so (Collignon, 1998:517). One might reasonably conclude that there may yet be many more to learn about.

Nor does the absence of evidence of harm necessarily mean that no harm is being done. A recent study of some 160 recipients of pig materials apparently shows no evidence of active infection with PERV (Paradis et al., 1999). However, Collignon suggests that that the study does not demonstrate that there is no danger (Collignon, 1999:1853).¹⁸ It seems reasonable to hold out for completely unambiguous evidence about this matter, given that PERV-A and PERV-B are similar to leukemia viruses in other ani-

mal species (Collignon, 1998:517). Collignon comments, "Xenotransplants . . . represent one of the best experiments we could devise to 'create' new infectious agents" (Collignon, 1998:519).

Such examination of the existing evidence must clearly continue. However, it is also important to keep in mind that judgments about risk are inductive. For that reason, no matter how much evidence accumulates that a procedure is safe, the very next example might contradict this judgment. So, the key question is when, if ever, it might be reasonable to go forward with clinical trials.

More generally, the appropriate criteria for concluding that there is no danger are far from clear. C.P. Snow's two cultures are alive and well (Snow, 1993). As a philosopher encountering the culture of medicine, I am struck by the divergent conceptions of good evidence in the two worlds, particularly with respect to time and sample size. In medicine, drugs and procedures are routinely declared safe after periods that look frighteningly inadequate to many philosophers. A striking example of these divergent attitudes toward risk is a recent statement by James Watson. Because worries about recombinant DNA research failed to materialize (so far), Watson focuses on the delays in cutting-edge research caused by such worries, and concludes: "The moral I draw from this painful episode is this: Never postpone experiments that have clearly defined future benefits for fear of dangers that can't be quantified" (Watson, 1999:71). But surely such a sweeping conclusion from a single (ongoing) situation constitutes the fallacy of hasty generalization and cannot be justified.

This difference in outlook is not surprising. Medical scientists are, after all, practical folks geared to improving and saving life, and they are accustomed to having to make decisions with insufficient evidence. Philosophers, with no such stake in practice, can afford to be more conservative. However, the lessons of the DES children, as well as our newly acquired suspicions about SV40, suggest reasons why medicine needs to seriously consider more demanding standards of evidence.¹⁹ Further debate about the extent of the required change is critical here, since the possibilities are especially chilling in light of evidence accumulating in the last twenty years that infectious agents might be implicated in a wide range of diseases. Among them may be certain forms of ulcers, renal failure, arthritis, vasculitis, inflammatory bowel disease, diabetes, coronary artery disease, and cancer (Lorber, 1996).

Current Policy and Regulation

Because of all these concerns, xenotransplantation research has been the focus of a good deal of attention on the part of advisory and regulatory bodies. Thus, in Great Britain, the Nuffield Council on Bioethics produced a report, *Animal to Human Transplants: The Ethics of Xenotransplantation*

(1996). It argued that the risk of infection calls for a precautionary approach, avoiding risks even if their nature is uncertain, and putting the burden of proof on proponents of the technology to show that it will not cause serious harm (1996:chap. 6). In 1997, the government-mandated Advisory Committee on Xenotransplantation published a report, *Animal Tissue into Humans*, that called for legislation to regulate xenotransplants; it concluded that xenotransplantation could be acceptable under certain conditions, and that a national committee should be established (1997:Section 5.4). Since then, the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) has been given oversight of trials or procedures involving xenotransplantation.²⁰

In the United States, the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the National Institutes of Health (NIH), and the Health Resources and Services Administration of the Department of Health and Human Services (DHHS) joined together in 1996 to publish *Guidelines on Infectious Disease Issues in Xenotransplantation* (Clark, 1999). The document provides multiple regulations under the FDA's investigational new drug (IND) regulations, Institutional Review Board regulations, and informed consent regulations (Clark, 1999). Several xenotransplantation trials are currently under FDA oversight, and there is a Xenotransplantation Product Reviewer Working Group that meets regularly to discuss issues relevant to xenotransplantation. The Xeno-Transplantation Subcommittee of the Biological Response Modifiers Advisory Committee (BRMAC) holds open meetings to update the committee and the public on issues associated with xenotransplantation and the development of FDA policy. The DHHS also has a Xenotransplantation Committee (USFDA, 2001).²¹ On January 11, 2001, the Public Health Service issued a revision of its previous guidelines, *Guidelines on Infectious Disease Issues In Xenotransplantation* (U.S. Public Health Service, 2001).

In Canada, an Expert Working Group on Xenotransplantation is writing a *Canadian Standard for Xenotransplantation* under the aegis of the Therapeutic Products Programme of the Health Protection Branch of Health Canada; Draft 14 was issued in July 1999. It recommends that a National Review Board be established to which local Research Ethics Boards would refer clinical xenotransplantation trials; the National Review Board should also advise on measures for monitoring compliance to ethical commitments at the local level.²²

In January 1999, the Parliamentary Assembly of the Council of Europe passed Recommendation 1399 on xenotransplantation, calling for a legally binding moratorium on xenotransplantation (including clinical trials). The Council of Ministers of the Council of Europe then set up a working party on the subject, which is to set up draft guidelines within three years (www.crt-online.org/090099.html).

The Assembly also asked the Council of Europe's Public Health and Bioethics Committees to work with the World Health Organization to develop a position that balances ethical, medical, scientific, legal, social, and public health issues before going forward with clinical trials (Health Canada, 1999b).²³

The World Health Organization produced the *Report of the WHO Consultation on Xenotransplantation* in 1997 (WHO, 1997). The report is intended to call attention to the issues that must be taken into account before adopting the technology.

What Should be Done?

Each of these official bodies counsels caution. However, in my view, a decision to proceed to clinical trials—even with caution—must ignore the fact that implanting animal materials into humans, especially whole organs, might create an infection that humans would be unable to control. Even if this risk were known to be minimal (which we have no way of knowing at present), I believe it would be unwise to proceed until we have a better idea of how to resolve this new kind of problem in medical research, in which experimentation puts not only patients, but society, at risk.²⁴

Is this an entirely new problem? Probably not. In retrospect, it may very well be that other decisions of this general kind have faced medical scientists. They may, in fact, unknowingly have engaged in innovative practices that had risks for third parties. Or they may knowingly have done so, but the larger community was unaware of the risk.²⁵ Certainly, related kinds of decisions have had this effect, and society, as a whole is only now realizing it. For instance, given the scarcity of medical resources and the organization of health care delivery, decisions to pursue innovative high-tech medicine by medical leaders has certainly affected population health in the United States.

But xenotransplantation seems to pose this problem in an exceptionally stark way. Although it now seems unlikely that each of the long series of steps required for the worst case scenario would occur, we do not know this now; nor can we forecast the consequences if just a few of those steps occurred. Because of the possibility of risk to third parties, the scientific community must be able to point to clear evidence of safety before proceeding. However, because evidence of risk is inductive, it will be difficult to know when, if ever, it would be safe to proceed. Considerable ingenuity will be required to develop criteria that, if satisfied, would quell reasonable doubt. Moreover, before proceeding with clinical trials, plans for dealing with infectious diseases should be developed. Included should be plans for cooperation between and among government agencies and private organizations, as well as anticipated responses to the inevitable legal challenges to quarantines.

Do these hard questions and demands ignore the claims of those dying for lack of organs now? Is the Institute of Medicine right that “our own humanity is diminished if we turn away from others whose suffering is visible; as members of society we can't run away from the risks that may be involved in helping those in need”? (Marwick, 1996:90). Deciding that we must proceed with xenotransplantation on these grounds would be to succumb to the fallacy of false dilemma: either we turn callously away from suffering or undertake any and all risks to save lives. Of course, we need to try to find ways to prevent or end human suffering. And, of course, it is reasonable to take some risks as we attempt to do these things. But not every risk can be justified, even in the face of great need.

Deciding how to address any particular source of suffering is a moral and political issue, not solely a medical one. Yet the scientific discourse regarding this issue often attempts to frame the question primarily as a medical one, downplaying even the issues in epistemology and philosophy of science that it raises, not to mention the moral and political issues. Although the medical proponents of xenotransplantation define their stance as cautious, the underlying premise seems to be that we must proceed, and that only by proceeding will we know what the risks are.²⁶ Yet every step forward takes us further along on a slippery slope.

Is there a theoretical perspective that would help elucidate this perspective?

The Precautionary Principle

A promising approach for social decision-making about public health and the environment is provided by the Precautionary Principle (PP). The PP constitutes a framework for decision-making in the absence of certainty (Santillo et al., 1999:46). Although versions of the PP have long been incorporated in some national and international law (Geiser, 1999:xxiii), it was first fully articulated as Principle 15 at the United Nations Conference on Environment and Development in 1992.²⁷ In 1998, a group of scientists, government officials, lawyers, and environmentalists met at Wingspread to further develop the concept. According to the Wingspread group, the PP makes three demands. First, it shifts the burden of proof to those who propose technological innovation. Second, it calls for full analysis of alternatives to potentially harmful activities. Third, it emphasizes democratic decision-making (Raffensperger and Ticknor, 1999:350). This approach does not ban potentially harmful innovations, but it requires that their proponents provide an “assurance bond,” like those now often posted for government construction jobs (Costanza and Cornwell, 1999:16-18). The amount of the bond would be equal to an estimate of the cost of remedying the worst-case scenario that could be caused by the innovation.

This conception of the Precautionary Principle has been accused of being “unscientific” and “dangerous,” but this criticism misses the point that decisions about potentially harmful innovations are inherently political and moral, not merely “scientific.” Such decisions are political because they must be made in the political arena, and conflicting positions about the best decision will reflect entrenched interests. Such decisions are moral because they will distribute benefits and burdens among individuals, and such distributions can either be fair or unfair. In general, distributions are fair when every member of society has an equal opportunity to benefit from innovation, and equal risk of bearing its burdens.

The Precautionary Principle attempts to protect those who would be put at risk by innovation; the price is lost benefits by those who would gain from innovation. The PP’s rival, cost-benefit analysis, tends in practice to do the reverse when there is uncertainty about risk.²⁸ However, the PP’s emphasis on scrutinizing alternative approaches suggests other paths that provide similar benefits with less risk.

Xenotransplantation would have a hard time proceeding if this version of the Precautionary Principle were applied to it. First, the PP would require estimating the cost of treating widespread serious disease; it would also require some valuation for lost lives. Posting the resulting sums as bond would clearly be prohibitive. Second, xenotransplantation puts everyone at risk, but given its probable expense, most people in need of new organs would be unable to afford it. Third, a deeper look at the problem to which xenotransplantation is allegedly the solution suggests promising alternative paths.

Discussions of the need for xenotransplantation generally start from the premise that there is a shortage of organs for transplant. Starting instead from the premise that there is a gap between the supply and need for organs reframes the issue, encouraging us to consider both ways to increase the supply and reduce the need for organs.

The supply could be increased by widespread implementation of the most successful programs for increasing donation (McArdle, 1998:6-9), thorough exploration of creative new ways to encourage donation, and making the most of innovations such as split liver donation. Research on mechanical organs is also advancing. Research is showing that Left Ventricle Assist Devices can already sometimes buy time for people to heal sufficiently to avoid the need for heart transplant altogether; it is reasonable to expect further progress in the near future (Ueno et al 2000; Mussivand, 1999). In addition, promising new work on stem cells and tissue engineering may lead to the development of a wide range of therapeutic tissue and organs for transplant not requiring immunosuppressants and free of the risk of zoonoses (Lorenz and Schaefer, 1999; Chen et al., 2000). Other things being equal, investment in such alter-

natives would clearly be preferable, given that they are not accompanied by the catastrophic possibilities of infection inherent in xenotransplantation. Although such work is still in beginning stages, it might overtake xenotransplantation if the remaining forms of rejection prove significant hurdles.²⁹ Even if it took somewhat longer, avoiding the risk of infection is a crucial objective. Although some additional lives of seriously ill patients would be lost, it would be morally questionable to conclude that to save them it would be reasonable to put so many other lives at risk.

There are also promising ways to reduce the need for organs in the future. Some diseases that lead to the need for organs are preventable by means of wide-ranging behavioral and public health measures. Although more research is needed on how to help people make healthier choices on a daily basis, much is already known about the conditions that help people do so.³⁰ In addition, intriguing research suggests a significant relationship between social equality and population health, both for those who might otherwise have been in poverty, but also for those who are better off. Such approaches are less sexy than high-tech alternatives, and they won’t make fortunes for biotech companies. However, they are preferable for a variety of reasons. First, focusing on them would reduce the need for transplantation, which is expensive and does not necessarily increase quality or length of life (Littlefield, 1996). Second, they are desirable on independent grounds, as they would improve general health, not just reduce the need for transplantation.³¹ Third, the benefits would be distributed more broadly and in more egalitarian ways. Fourth, this approach could help us rethink our narrowly technological orientation toward medicine and the reluctance to face our mortality (Kurtz, 1998).

These considerations suggest that although substantial work remains to be done on the Precautionary Principle as a decision-making tool (Jordan and O’Riordan, 1999), it can stimulate fruitful new ways of approaching questions about the conditions for proceeding with new technologies such as xenotransplantation. In addition, its emphasis on democratic decision-making promotes salutary public education and discussion. Although there have been public meetings, and an electronic discussion list has even been opened for the public, it is far from clear that the average citizen (in any country) is aware of xenotransplantation or the threat it may pose.³² It also broadens the scope of debate to include citizens of less developed countries. Inclusivity is morally and politically appropriate because xenotransplantation puts citizens of developing countries doubly at risk. On one hand, if xenotransplantation takes place in developed countries, persons in the Third World will share the risk, even though its predicted high cost will preclude access to its benefits for most. On the other hand, if developed nations were to

implement moratoria, research might well proceed in less regulated areas of the world (Daar, 1998:229).³³

Conclusion

I believe that the foregoing discussion provides excellent grounds for a moratorium on clinical trials of xenotransplantation. It is true that many individuals are now dying of end-stage organ failure. However, that fact alone does not by itself justify such trials. After all, many lives could be saved if we killed some healthy individuals in order to distribute their organs to others who would die without them. Acknowledging that this would be wrong recognizes that using such simple equations in moral decision-making is untenable. Of course we ought to save lives, other things being equal. But opponents of xenotransplantation recognize that the *ceteris paribus* condition fails to hold, whereas proponents believe that opponents are instead simply blind to the ongoing loss of life from organ failure. In addition, given the unresolved immunological problems, there are good theoretical reasons for believing that no clinical trial in humans could be successful; it would therefore be immoral to subject any patient to the procedure in any case.

The real question now facing us is whether there should be continued investment in research on xenotransplantation.³⁴ The bulk of the discussion about risk has focused on the possible risk of clinical trials, not research activities; yet there is some reason for concern as researchers move between the bench and the bedside.³⁵ In addition, as I have argued, it would be morally preferable to direct resources instead to other measures, especially those that confer protection against conditions that undermine life quality or kill. It is true that such an emphasis would not save patients now waiting for organs, but neither will xenotransplantation. Moreover, even if investing in xenotransplantation would save some who would otherwise die, its potentially catastrophic risk is too high a cost. Proponents of xenotransplantation research will perhaps suggest that those who favor a moratorium are guilty of callous disregard for human misery. But if what is truly at stake here is saving lives,³⁶ then there is a morally compelling argument for focusing instead on the millions who die every year for want of remedies that cost pennies and put no one else at risk.³⁷

In sum, “xeno” should not be added to “transplantation.”

Notes

1. Not considered in depth is the larger issue of resource allocation. The introduction of new, expensive technologies always raises the question of whether people would be better off if the required expenditures were deployed in other ways. For some estimates of what widespread use of

- xenotransplantation might cost, see Berger and Lamont, 1999; Kochlin, 1996.
2. The rate varies from 27 organ donations per million inhabitants in Spain, to 21 per million in the United States, to 5 per million in Greece (Butler, 1998).
3. According to David Sachs, more than 400,000 Americans could benefit from heart transplants, but only 3,698 people were on the waiting list at the time he gave this estimate (Butler, 1998: 325).
4. Thanks to Megan Sykes for this point (personal communication).
5. A Swiss firm, Novartis, may invest as much as US\$1 billion in the new technology. Peter Laing (an analyst at Society General Strausse Turnbull, in London) suggests that there could be a \$6 billion market in transplant by 2010 (Butler, 1998a:325).
6. Interestingly, Fox rejected his own thesis shortly after his book appeared. See Gruen, 1994:283.
7. This position is probably closest to the views of Peter Singer (1990).
8. I would therefore be equally wary about using dolphins, elephants, or even octopi.
9. Personal communication from Gary Levy.
10. Collignon argues that “conventional immunosuppressive agents may . . . be less effective than they are against allografts, and more potent agents may need to be developed” (Collignon, 1998: 516). See also Stephenson, 1995: 287 and Butler, 1998a: 323.
11. Immunosuppressive drugs are powerful, don’t always work, and, like AIDS, lay patients open to an array of diseases that their immune systems might not be able to fight off.
12. Thanks to Medard Hilhorst for pressing this point.
13. For additional discussion of these issues, see Welin, 2000:231-236.
14. Recent studies by Colwell, Epstein, and Ford have been looking at mutation patterns. It appears that under favorable circumstances, bacteria and viruses can freely exchange plasmids with antibiotic-resistant factors or virulence factors (Garrett, 1994:657).
15. Personal communication from Gary Levy.
16. There is evidence that the deadly 1918 flu resulted from gene reassortment between flu viruses. Likewise, the transition between mild and deadly avian flu herpes viruses appears to result from the mutation of a single nucleotide (Larson, 1998).
17. The exchange of genetic material and microbes might well put pigs at risk, too (Weiss, 1998).
18. Collignon points out that most of the patients were exposed to pig tissue for less than 60 minutes, that PERV may have been transmitted to all the patients, that pig cells persisted in 23 recipients for up to 8.5 years, that 4 patients with positive antibodies to PERV and 4 more with unexplained symptoms may be infected, and that lack of antibodies to PERV may not exclude the existence of infection (Collignon 1999; Paradis and Langford respond on the same page).
19. Correspondingly, philosophers need to come to grips with the fact that their approach may entail more short-term deaths.
20. UKXIRA’s website, www.doh.gov.uk/ukxann3.htm, contains its most recent annual report, September 1999–November 2000. The report gives information about conferences and meetings on xenotransplantation during this period. It concludes that progress on whole-organ transplantation is advancing more slowly than expected (6.8–6.15), and that “the likelihood of whole-organ xenotransplantation (particularly for heart transplantation) being available within a clinically worthwhile time frame may be starting to recede” (6.15). It also states that uncertainty about safety is still “a significant obstacle” (6.23). However, it does not support a moratorium on clinical trials, asserting that “until clear evidence becomes available on the infection risks posed by xenotransplantation, the UKXIRA will assess the risk posed by particular proce-

- dures individually" (6.28), although it provides no information about how that might be possible, and concedes that risk to patients and the population as a whole "remains unquantifiable" (6.30).
21. The website of the USFDA Center for Biologics Evaluation and Research (www.fda.gov/cber) is an excellent source of information and links to government documents.
 22. This report can be found online at www.hc-sc.gc.ca/hpb-dggs/thereput/htmleng.
 23. The Organization for Economic Cooperation and Development maintains an excellent website with regulatory updates by OECD member countries, and other resources, at www.oecd.org/dsti/sti/s_t/biotech/xenosite/country.htm.
 24. This formulation of the problem was suggested to me by Peter Singer, M.D. It would also be unwise to proceed with so much unresolved about animals and about informed consent, even if there were good reason for believing the risks of disease transmission to be minimal.
 25. Sachs et al. suggest that "similar decisions are made routinely in the use of new antibiotics. Each such agent has a clear impact on bacterial flora and poses a risk to the general public through the potential for emergence of new, drug resistant bacterial strains" (Sachs et al. 1998).
 26. The exceptions that I am aware of are Fritz Bach and Peter Collignon. However, the few bioethicists who have thus far turned their attention to the question have tended to conclude that it would be wrong to go forward with clinical trials given what we know now. See Nelson, 1992; Hughes, 1998; and Clark, 1999.
 27. "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." (United Nations, 1992).
 28. For further discussion of related issues here, see Cranor, 1999.
 29. Lack of progress in the last few years suggests that this slower timetable for xenotransplantation (if it can be made to work at all) is the most realistic scenario (UKXIRA, 2001).
 30. The common sense judgment that long work hours steal time from the preparation of healthy foods and exercise is clear. Recent studies provide additional evidence that long work hours can harm health. For example, longer hours of work can increase the probability of weight gain, or increase in tobacco or alcohol consumption. Research in other countries, such as Japan, bears out these findings linking long work hours to cardiovascular disease (Shields, 1999).
 31. For example, helping people to quit smoking will not only reduce their chance of developing heart disease (and thus needing a heart transplant), it will also reduce their chances of developing a variety of cancers, including, it now turns out, breast cancer (see, for example, Davis et al., 1997).
 32. Further support for this claim comes from a 1999 Canadian survey, "Survey on Human Organ Donation and Xenotransplantation." A majority of respondents had heard of xenotransplantation, but only 45% had any knowledge of the potential risk of infection to patients, and only 18% of the risk to those who come into contact with the patient (Health Canada, 1999a).
 33. Daar adds: "Another relevant issue is that there is little discussion about animal rights in developing countries and I know of institutions that have used this as a selling point to outside funding sources to attract research funds. Could xenotransplantation of solid organs first take place in a relatively developing country because of this lack of sensitivity to animal rights/welfare and because of lax or absent regulations? This is one of the arguments used in the U.S. to proceed soon to major clinical trials because any infections from these countries could subsequently easily enter the United States. The counterargument could be made, of course, that the infection could as easily go the other way" (Daar, 1998).
 34. Private companies have invested substantial sums in xenotransplantation research, and it may be argued that it would be inappropriate to regulate such expenditures. However, the potential for harm to society at large undermines this claim; furthermore, considerable public resources are also being devoted to xenotransplantation.
 35. For example, Johnston and Calvert state that the Ministry of Agriculture, Fisheries, and Food warned Imutran that its researchers at the Huntingdon Life Sciences lab might be putting their human surgery patients at risk from Simian Herpes B, an easily transmissible and potentially fatal virus (Johnston and Calvert, 2000b).
 36. It should be noted that quality of life, rather than saving life, may often be at issue with kidney transplantation.
 37. Examples of such remedies are prenatal care for pregnant women, food for starving children, and generic AIDS drugs.

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